DEVELOPEMENT AND EVALUATION OF FIXED DOSE COMBINATION (FDC) OF A CEPHALOSPORIN AND A FLUOROQUINOLONE DERIVATIVE IN TABLET DOSAGE FORM

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I wish him all the success in life.

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I wish him all success in life.

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STATEMENT BY THE CANDIDATE

As required by university regulation, I wish to state that this work embodied in this pre-thesis titled ***"Development and Evaluation of Fixed Dose Combination (FDC) of a Cephalosporin and a Fluoroquinolone derivative in tablet dosage form"*** *from my own contribution to the research work carried out under the guidance of* ***Mr. Bhupen Kalita*** *(Assistant professor, Dept. of Pharmaceutics, Girijananda Choudhury Institute of Pharmaceutical Science, Azara, Ghy-17) and* ***Dr. Kapileswar Swain*** *(Vice President, Research & Development Centre, G-2, Mahakali Caves Road, Shanti Nagar, Andheri (E), Mumbai- 400093). This work has not been submitted for any other degree of this or any other university. Whenever references have been made to previous work of others, it has been clearly indicated as such and included in the bibliography.*

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(Tapash Chakraborty)

Dedicated to
My beloved family

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LIST OF ABBREVIATIONS

Sl. No.	Abbreviations	Remarks
1	API	Active Pharmaceutical Ingredient
2	AUC	Area Under Curve
3	ASTM	American Society for Testing and Materials
4	BD	Bulk Density
5	CI	Compressibility Index
6	DT	Disintegration Time
7	FDC	Fixed Dose Combination
8	FDA	Food & Drug Administration
9	HPMC	Hydroxy Propyl Methyl Cellulose
10	HR	Housner's Ratio
11	IPQC	In-Process Quality Control
12	MCC	Micro Crystalline Cellulose
13	mg	Milli gram
14	PVP	Polyvinyl Pyrrolidone
15	RH	Relative Humidity
16	RTI	Respiratory Tract Infection
17	SLS	Sodium Louryl Sulphate
18	TD	Tapped Density
19	USP	United States Pharmacopoeia
20	UTI	Urinary Tract Infection
21	WHO	World Health Organization

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Chapter 1

INTRODUCTION

1. TABLETS
2. FIXED DOSE DRUG COMBINATIONS (FDCS)
3. IMMEDIATE RELEASE DOSAGE FORMS
4. MANUFACTURING METHODS FOR A TABLET DOSAGE FORM
5. CEPHALOSPORINES
6. FLUOROQUINOLONES

1. TABLETS:

1.1. TABLET DOSAGE FORM:

Tablets are solid preparations each of which contains a single dose of one or more active ingredients. They are obtained by compressing uniform volumes of particles, and are almost always intended for oral administration. The most common method of drug delivery is the oral solid dosage form, of which tablets and capsules are predominant. The tablet is more widely accepted and used compared to capsules for a number of reasons, such as cost, tamper resistance, ease of handling and packaging, ease of identification, and manufacturing efficiency.[1] The tablet is a dry dosage form promotes stability, and in general, tablets have shelf lives measured in years. They are also convenient to transport in bulk, since they contain relatively small proportions of excipients unlike, for example, oral liquids. The compressed tablet is by far the most widely used dosage form, having advantages for both producer and user. The tablet is the most popular dosage form because it provides advantages for all concerned in the production and consumption of medicinal products. [2]

1.2. HISTORY OF TABLETS:

It is likely that the term ‘‘TABLET’’ for this dosage form was first used in the United States in the 1870s. The earliest reference to a dosage form resembling the tablet is to be found in tenth century Arabic medical literature. Drug particles were compressed between the ends of engraved ebony rods, force being applied by means of a hammer. Details of the tabletting process, as it is now known, were first published in 1843 when William Brockedon was granted British Patent “9977” for ‘‘manufacturing pills and medicinal lozenges, by causing materials, when in a state of granulation, dust or powder, to be made into form and solidified by pressure in dies.’’

In this case, too, force was applied by a hammer. Potassium bicarbonate was the first pharmaceutical substance to be so treated. [3]

A monograph for Glyceryl Trinitrate Tablets was included in the British Pharmacopoeia of 1885, but no other tablet monograph appeared there until 1945. This was not due to lack of popularity of the dosage form itself, but rather the absence of suitable methods of quality control that were applicable to tablets. [3]

The tablet did not meet with universal approval. In 1895 an editorial in the Pharmaceutical Journal in the United Kingdom described the tablet as ‘‘one of the evils suffered by legitimate pharmacy,’’ and predicted that tablets ‘‘have had their day.’ Notwithstanding such a prediction, the usage of tablets has continued to increase. The 2000 edition of the British Pharmacopoeia contains 320 monographs for tablets, far in excess of any other dosage form. [4]

During the 1950s, much research was devoted to the physics of compression. Since that time, the pharmaceutical industry has attained a much greater understanding of the compression process, which resulted in the development of more robust pharmaceutical formulations. This has been achieved by the use of instrumented tablet presses and sophisticated data collection systems combined with the development of mathematical models. [5]

1.3. RECENT ADVANCES:

Recent advances in the design of tablet compression equipment has resulted in higher-efficiency machines designed to optimize compression efficiency, minimize tablet weight variation, and provide greater flexibility, allowing the production of a greater range of products. However, the modern sophisticated machines still employ the same general concepts of operation: die fill, tablet compression, tablet ejection, and tablet scrape-off. Therefore, studies conducted on older equipment designed to

evaluate the compression characteristics of materials, can offer significant insight into material behavior. [2], [3]

However, modern machines provide greater accuracy and efficiency as follows: [1]

- Improved material feed systems.
- Improved cam design and material of construction.
- Multistage compression.
- Isolated design for quick cleaning and changeover. Improved force-measurement techniques.
- Introduction of electronics to provide force control.
- Integration of on-line weight, thickness, and hardness test units providing weight feedback control to the force control unit, and
- High-speed single-tablet sorting to reject out-of-specification tablets.
- Modern tablet presses that are capable of producing about one million tablets per hour being available.

2. FIXED DOSE DRUG COMBINATIONS (FDCS):

A fixed dose combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed dose combination drug products may improve medication compliance of patients. Fixed dose combination drugs are also developed to target a single disease like AIDS, TB and malaria, RTI, UTI, burning etc. [6]

According to WHO expert committee on specifications for pharmaceutical preparations (39th report, 2005) a FDC can be defined as follows…

"A combination of two or more actives in a fixed ratio of doses."

This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product. [7]

Some of the FDCs are reviewed by the FDA and the active ingredients used therein are not expected to interact adversely with each other, but may interact with other drugs that a patient is taking. Though FDCs may reduce burden of consuming more pills, there are some disadvantages. [6]

Like, if a patient needs dosage adjustment, the existing FDC may not suit the most appropriate strength for the patient. Further, after using an FDC if an adverse drug reaction occurs, it may be difficult to identify the active ingredient responsible for causing the reaction. [8]

A pharmaceutical company may develop a FDC with the sole aim of marketing advantage of exclusive rights to sell the FDC, even though the individual active ingredients may be off-patent. When more than two drugs are combined, the cumulative toxicity and risk-benefits of the new product need to be examined before marketing such products. [8]

Combination pharmaceutical products are also defined as being able to treat the same disease state, multiple disease states, or counteract the negative side-effects. [7]

2.1. NEED FOR FIXED DOSE DRUG COMBINATIONS:

There is drug-drug interaction when the effect of a drug is modified by another drug. So that this interaction appears, it is necessary for the 2 drugs to be simultaneously present in the body or that the effects of one of them still persist at the time of the administration of the second. The interactions between drugs are observed in general when the drugs are taken simultaneously or with a short time interval, a few hours to one day. But interactions are possible with much longer intervals separating

their intake, a few days to two weeks. In this last case, one at least of drugs has long lasting effects resulting for example from sustained-release or an irreversible enzyme inhibition necessitating a new synthesis of the enzyme. The consequences of this interaction can be described as synergy, potentiation or antagonism. [9], [10]

- ***'Additive'*** is combining two or more drugs with complementary modes of action to gain the desired therapeutic effect without the side-effects. When the effect of two drugs having similar action are additives the net effect of two drugs used together is equal to the sum of the individual drug effect, [10] i.e.

1+1=2

Example: Thiazide diuretics + Beta blocker have an additive antihypertensive action.

- ***'Potentiation'*** is the synergistic effect on drug "A" by adding a dose of drug "B" with or without a therapeutic effect. When the net effect of two drugs used together is greater than the sum of the individual drug effects, [10] i.e.

1 + 1 > 2 or 1 + 0 > 2

Example:

i. When one drug increases the action of other drug, i.e. 1+1>2

   e. g. Sulphamethoxazole + Trimethoprim → Cotrimoxazole (bactericidal)

ii. When one drug has no effect of its own but increases the effect of the other drug, [10] i.e. 1+0>2

   e. g. Levodopa + Carbidopa

- ***'Cancellation'*** or ***'Antagonism'*** is when effects of one drug are nullified by the addition of a second one, i.e. the effect of one drug is decreased or abolished by the administration of another one. [10]

2.2. GENERAL CONTENTS OF A FIXED DOSE COMBINATION:

A combination product may contain pharmaceuticals, biopharmaceuticals, or nutraceuticals. They can also incorporate several, different controlled-release profiles, such as immediate, pulse, chronotherapy, targeted and sustained. [6]

The pharmaceutical industry is placing a greater emphasis on combination products and commercializing poorly-soluble compounds due to their limited pipelines of soluble compounds. [7]

With the successful evolution of combination products, companies will continue to place increasing resources on developing new, innovative and beneficial combination products. Layered tablets have provided a successful approach in delivering combination products, primarily consisting of compatible, soluble compounds. Some of these layered tablets have included different release profiles for each compound in order to achieve the most beneficial release profile for each active. [6], [7]

2.3. RATIONAL FOR COMBINATION THERAPY:

All drugs have unwanted side effects in addition to the desired therapeutic effect. The idea of combining two or more drugs with complementary modes of action is to produce additivity of the desired therapeutic effect but not of the side effects. [6]

Fixed dose combinations are valuable only when they have been developed based on sound pharmacokinetic and pharmacodynamic criteria. As an example, at least five classes of drugs are commonly used to treat hypertension: diuretics, beta-blockers, ACE-inhibitors, Angiotensin receptor blockers, and calcium-channel blockers. [7]

The antihypertensive effects of an ACE-inhibitor and a calcium channel blocker, for instance, are additive, but these drug classes have different spectra of side effects, none of which are additive (although the spectrum can be broadened in a combination

drug). Because the combination produces the same antihypertensive effect as higher doses of either constituent, the exposure to side effects is reduced and the therapeutic ratio is increased. [11]

The therapeutic ratio can be increased in certain instances by the phenomena of potentiation and cancellation. Potentiation is the synergistic effect on drug "A" by adding a dose of drug "B" with or without a therapeutic effect. An example is the combination of Bisprolol or Enalapril with a low dose of hydrochlorothiazide itself without antihypertensive effect. [10]

Cancellation is a phenomenon in which the adverse effects of one drug are nullified by the addition of a second (e.g., the hypokalemic effects of Thiazide diuretics are counteracted by the slight hyperkalemic effect of an ACE-inhibitor). [8]

2.4. ADVANTAGES AND DISADVANTAGES OF FIXED-DOSE COMBINATIONS:

Advantages: [6], [7], [9], [11]

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes.
- Reduces inadvertent medication errors.
- Prevents and/or slows attainment of antimicrobial resistance by eliminating mono-therapy (i.e., one drug is never by itself in circulation).
- Allows for synergistic combinations (i.e., trimethoprim/ sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms.
- Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being "out of stock".

- Only 1 expiry date simplifies dosing (single products may have different expiry dates).
- Procurement, management and handling of drugs are simplified.
- Lower packing and shipping costs.
- Less expensive than single ingredient drugs.
- Side effects are reduced by using one drug of the combination for this purpose.
- Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheal narcotic diphenoxylate is discouraged by side effects of atropine in the FDC atropine + diphenoxylate).
- Combination therapy by combining two drugs targeted for same indication.
- Reduction in the number of prescriptions and the attendant administrative costs.
- Allow to treat the different aliments (co-morbidity) in the same patient at same time with single pill.
- Side effects of one drug can be reduced by using one of the drugs in combination for this purpose. For e.g. Amiloride used in combination with Hydrochlorothiazide to prevent hypokalemic caused by hydrochlorothiazide.
- Reduction in number of pills to be taken by patients.
- Reducing the number of pills diminishes the complexity of the regimen, so that improved patient adherence is expected with combination products.
- Increasing patient compliance with therapy.
- Increasing efficacy by optimizing timings of medicaments.
- Minimization of side-effects and adverse effects.
- Enhancement of pharmacokinetic characteristics of each compound.
- Increased patient quality of life.
- Optimization of institutional resources by minimizing.

- Reduces impact of generic competition.
- Less financial risk than developing a new compound.

Disadvantages: [6], [7], [9], [11]

- FDCs are (possibly) more expensive than separate tablets.
- Potential quality problems, especially with Rifampicin in FDCs for TB, requiring bioavailability testing.
- If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets.
- Dosing is inflexible and cannot be regulated to patient's needs (each patient has unique characteristics such as weight, age, pharmacogenetics, co-morbidity, that may alter drug metabolism and effect).
- Incompatible pharmacokinetics is irrational because of different elimination ½ lives of individual components.
- Reaction of one of the components (e.g., a rash to sulfamethoxazole in cotrimoxazole) may result in patient avoiding the "innocent" trimethoprim in the future.
- Drug interactions may lead to alteration of the therapeutic effect.
- Dose of one ingredient cannot be altered.
- Different pharmacokinetic properties can pose difficulty in frequency of administration and in case of development of an ADR.
- It is difficult to withdraw the suspected drug alone.
- The greater are the number of ingredients, the less likely the prescriber or the physician is to know what FDCs are and what their adverse reactions are.
- Another drawback with FDCs is that they may lead to an ineffective dosage. In certain cases like heart failure, it becomes necessary to determine the strength of

the dose against the appropriate end point. It is better to handle individual drugs rather than combinations in such life threatening conditions.

- Some FDCs when combined lead to increased toxicity. For instance, the anti-TB drugs, streptomycin, Kanamycin and Capreomycin cannot be combined, as they have the same side effects (Oto and nephrotoxicity).

2.5. EXAMPLES OF FIXED DOSE COMBINATION PRODUCT:

There are currently at least twelve combination drug products in the top selling pharmaceutical products. Several new ethical combination products have been approved by the FDA recently, such as Pfizer's Caduet, Merck/Schering-Plough's Vytorin and Gilead Sciences' Truvada. [2]

Pfizer's Caduet was unique in being the first product that combined two drugs to treat two different, but concomitant disease states. In the consumer sector, there are over 200 combination products that are the best selling products in areas such as cough/cold and analgesics. [4]

Table 1: Examples of FDC candidates in clinical development and recent launches [12]

Compound	Phase	Company	Indication (s)
Symbicort (Budesonide/ Formoterol)	Approved (US)	AstraZeneca	Asthma/COPD
Montelukast/Loratidine	Phase III	Merck/ Schering Plough	Seasonal allergic rhinitis
Flutiform (Fluticasone/ Formoterol)	Phase III	SkyePharma/ Abbott	Asthma/COPD
Super Advair (Undisclosed)	Phase II	GlaxoSmithKline	Asthma/COPD
Exforge (Amlodipine/ Valsartan)	Approved (US)	Novertis	Hypertension
ABT 335/ Rosuvastatin	Phase III	Abbott/ AstraZeneca	Hyperlipidaemia
Coreg CR (Carvediol)/ ACE inhibitor	PhaseIII	GlaxoSmithKline	Hypertension
MK 0524A (Laropiprant/ Niacin)	Phase III	Merck	Hyperlipidaemia
Zetia/ Lipitor (Ezetimibe/Atorvastatin)	Undisclosed	Merck/ Schering Plough, Joint venture	Hyperlipidaemia

Atripla (Efavirenz/ Emtricitabine/ Tenovir)	Launched July 2006 (US)	Gilead/ Bristol Myers Squibb	HIV
Lamivudine/ Zidovudine/ Nevirapine	FDA tentative approval	Generics	HIV

2.6. DRUG DELIVERY SYSTEMS FOR FIXED DOSE COMBINATION PRODUCT:

Fixed dose combination products are generally formulated by following technology:

- ♠ Multilayered tablets
- ♠ Compression coated tablets
- ♠ Inlay technology
- ♠ Multicompartment capsules:
  - α. Capsule within capsule
  - β. Tab in capsule
  - χ. Capsule coated

2.6.1. Multilayered tablets: [13]

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet.

It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different color to produce a distinctive looking tablet. Each layer is fed from separate feed frame with individual weight control. Dust extraction is essential during compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates.

It makes possible sustained release preparation with the immediate release quantity in one layer and the slow release portion in the second. A third layer with an immediate release might be added.

Example: Combination of Phenylephedrine HCL and Ascorbic Acid with Paracetamol.

Paracetamol + Phenyl-ephedrine Hydrochloride →one layer.

Paracetamol + Ascorbic acid → another layer.

i. Advantages of multilayered system: [14]

- Best option for incompatible drugs.
- The maximum flexibility in drug release patterns.
- Ease of manufacturing.
- Improved patient convenience.
- Increase in safety margin of high potency drug.
- Maximum utilization and reduction in health care cost etc.

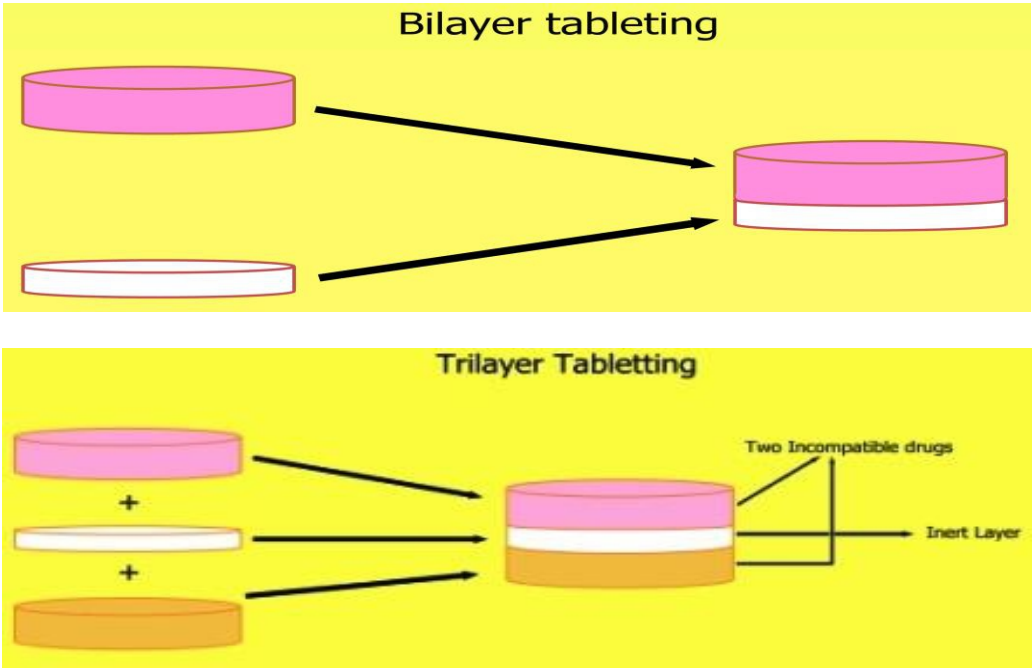


Figure 1: Bi-layer and Tri-layer Tableting

ii. Reason for Multilayered Tablets:[15]

a. Physical/Chemical Separation: It is possible to avoid the incompatibility in between active-active; excipient - excipient and active-excipients by mean of physical separation. Well known example of such an interaction is a Millard reactions occurring during tablet compression.

b. Multiple release profile: Such drug delivery systems are able to provide multiple release kinetics of same/different drugs of same or different physicochemical properties by application of multiple layers. Each monolith was formulated in order to parcel out the delivery of drug dose by means of different release control mechanisms.

c. Immediate Release (Disintegrating monolith): Disintegrating monolith deliver the initial quick release required to achieve peak plasma concentration. Introduction of initial loading dose in conventional dosage form were neglected by application of such technique.

d. Delay Release (Erodible monolith): Delay release achieved by application of erodible monolith, which deliver the second installment of actives in the latter part of gastrointestinal tract (GIT).

e. Controlled Release (Swelling monolith): Swelling monolith perform by both swelling as well as eroding mechanism in which drug were continuously released throughout the GIT.

f. To produce repeat action: Multilayered tablets readily lend themselves to repeat-action products, wherein one layer of the layered tablet or the outer tablet of the compression coated tablet provides the initial dose, rapidly disintegrating in the stomach. The inner tablet is formulated with components that are insoluble in gastric media but release in the intestinal environment.

iii. Problems during manufacturing of multilayered systems: [15]

- Lack of proper bonding of two layers which may result into the separation of two layers.
- Degradation of certain drugs because of the high pressure due to compression of tablets. E.g. Ramipril.
- There might be the chances of increase in impurities because of crystal lattice of the structure of drugs may rupture due to high compression force.

2.6.2. Compression coated tablets: [13]

This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied.

This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity.

To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.

Figure 2: Cross sectional view of compression coated tablet

2.6.3. Inlay technology: [13]

A type of layered tablet, in which instead the core tablet being completely surrounded by coating, top surface remains completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.

This form can be useful in sustained release preparation to reduce the size and weight of the tablet. The slow release portion which contains 2-3 times the amount of active ingredient becomes the coating and the immediate release portion becomes the core.

It has some advantages over compression coated tablets:

- Less coating material is required. Only 25-50% of more than the weight of the core.
- Core is visible, so coreless tablets can be easily detected.
- Reduction in coating forms a thinner tablet and thus freedom from capping of top coating.
- There is no concern with the capping of the top coating.

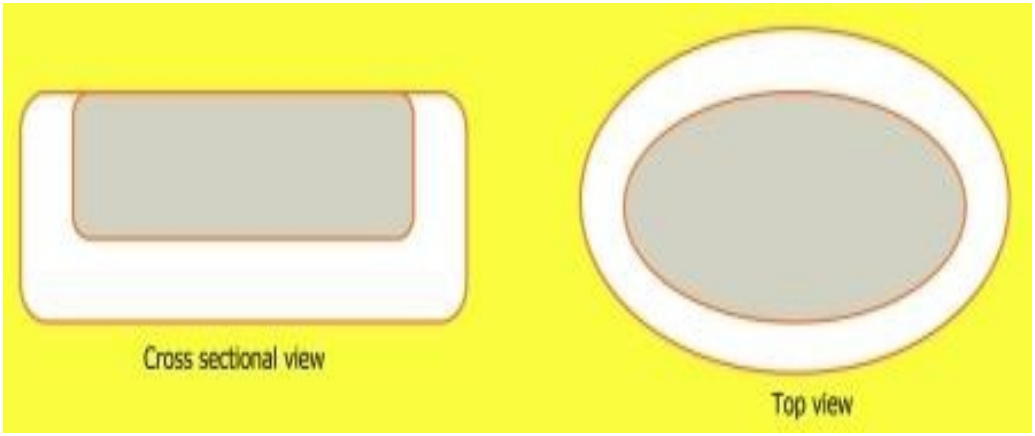


Figure 3: Cross sectional and top view of Inlay Tablet

2.6.4. Multi-compartment capsules: [16]

INNERCAP Technologies has developed a proprietary multi-phase, multi-compartment capsule-based delivery system that can deliver incompatible and compatible drugs using different physical phases.

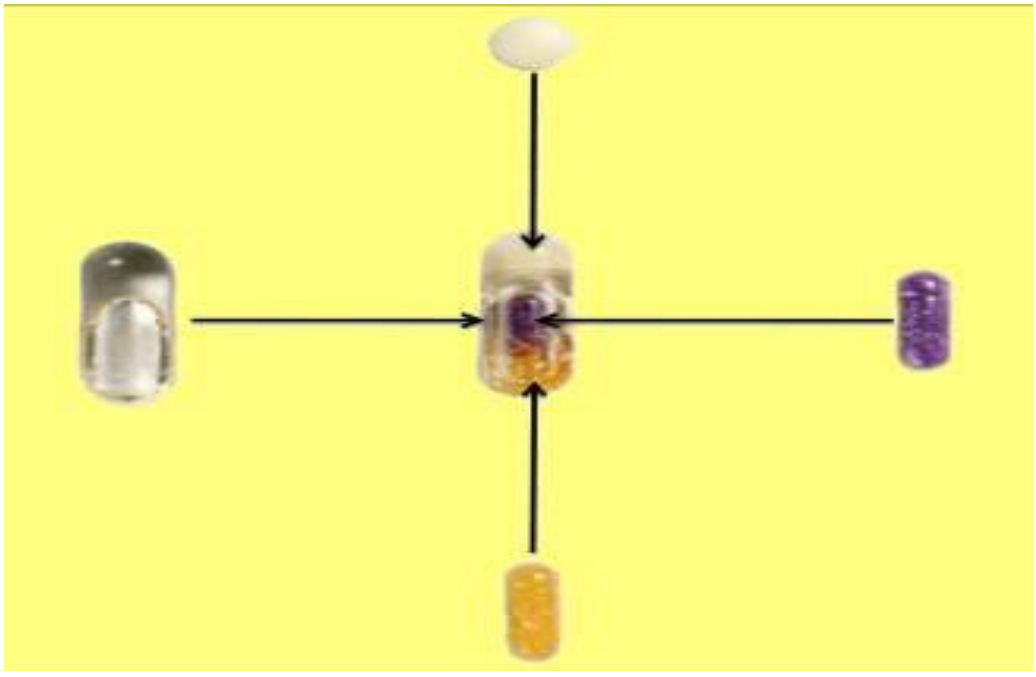


Figure 4: Multi-Phase, Multi-Compartment Dosage form

Each compartment is sealed to prevent the medicaments from escaping and coming into contact with one another. If a compound is currently stable within a capsule, stability problems are precluded in a multi-capsule application.

As with any new combination drug project, a combination drug may not work in a specific dosage form due to incompatibility or other formulation issues and an alternative delivery system will have to be identified. For instance, both bi-layer tablets and multi-compartment capsules have specific benefits associated with the dosage form.

If the combination product will contain incompatible or multi-phase compounds, multi-compartment capsules can make a project possible that may otherwise fail in a bi-layer tablet. This new development may make viable projects that may have failed in the past and it dramatically increases the possibilities when working with different combinations.

Furthermore, multi-compartment capsules can accelerate the development of a combination product and facilitate to clinical trials by bypassing the formulation development of a combination tablet project. This allows a combination product to enter clinical trials and expedites the process to determine if the new product achieves the desired therapeutic effects in the trial group.

This approach can save millions of dollars in development costs, and a first-to market advantage can mean the success or failure of a multi-million dollar product in the marketplace.

Typically, the technology is not restrained by the use of a specific capsule material. The outer walls of the compartments are formed of an acceptable soluble ingredient, such as gelatin, starch, hydrophilic polymers or hydroxypropyl methyl-cellulose (HPMC). These provide a barrier for containing the active ingredient or medicament within the internal periphery of the walls.

The most appropriate chamber material is determined by the medicaments that will come into contact with the shell material; a single capsule could use

combinations of acceptable shell materials. The release profiles can be incorporated into the shell materials, or coatings can be applied to target or control the release of the medicaments from the compartments.

Also, release profiles can be applied to the active compounds filled into each capsule in a number of ways. One example would be the use of enteric-coated pellets with different release profiles to by-pass the stomach.

Marketing departments seek new drug delivery systems as well, especially if it gives them an opportunity for a unique marketing campaign. For example, Wyeth's liquid filled Advil capsules and McNeil's recently introduced Tylenol Rapid Release Gel Capsules have been very successful products because consumers perceive from visual images and marketing benefits how they can benefit from using these new products.

i. Benefits of multiphase compartment capsules: [16]

- Allows incompatible compounds to be delivered in a single dosage form.
- Allows different release profiles for each compound.
- Reduces development time to start clinical trials.
- Allows multiphase excipients for greatest pharmacokinetic profile.
- Requires less active pharmaceutical ingredients to work with during development.
- Heat and pressure sensitive drugs can be delivered by this formulation.
- Increase in patient compliance.
- Provides unique marketing and brand opportunities.
- Reduce counterfeiting.
- Reduce the time line for product to hit the market.

3. IMMEDIATE RELEASE DOSAGE FORMS:

The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes: First- the disintegration of tablet into granules and second-dissolution of these granules through the GIT into the blood. Disintegration is the rate limiting step in case of highly soluble drugs where as dissolution is the rate limiting step in case of drugs with low solubility. [12]

The release of drug from an immediate release dosage form can be achieved by...

- Placing the drug in a layer or coating that is sufficiently thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a rapid rate.
- Incorporating the drug in a mixture that includes a supporting binder or other inert material that dissolves readily in gastrointestinal fluid, releasing the drug as the material dissolves.
- Using a supporting binder or other inert material that rapidly disintegrates intofine particles upon contact with gastrointestinal fluid, with both the binder particles and the drug quickly dispersing into the fluid.

Conventional dosage forms can be considered to release their active ingredients into an absorption pool immediately. The absorption pool represents a solution of the drug at the site of absorption, and the terms K_r, K_a and K_e are first-order rate constants for drug release, absorption and overall elimination, respectively. [12]

Immediate release from a conventional dosage form implies that $k_r >>> k_a$ or alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in the delivery of drug to its target area. [12]

4. MANUFACTURING METHODS FOR A TABLET DOSAGE FORM:[17-21]

The product development stages for immediate release dosage forms may follow three processes, either direct compression or wet granulation or dry granulation.

4.1. DIRECT COMPRESSION:

It is a process in which tablets are compressed directly from the powder blend of active ingredient and suitable excipients, which will flow uniformly into a die cavity and form into a firm compact. [17]

Dosage strengths with 1 to 10 mg per 100 or 150 mg tablet are considered suitable drug candidates for direct compression development route. Low tablet fill weight variations are easily obtained. To keep the direct compression formulation simple and elegant, the following factors have to consider:

a. Proper selection of excipients:

Particle size and granulometric parameters of the powder including active pharmaceutical ingredient are significant parameters in DC formulation. Selection of DC excipients depends upon these factors. The most commonly used tablet diluent is spray dried lactose which is having direct compression and good flow properties. Another widely used diluent for the same purpose is microcrystalline cellulose which will produce marginally harder tablet at the same compression strength. It is generally used with moisture sensitive material because of its property of lower hygroscopicity and lower moisture up take. [17]

Avicel pH 101/102 is having superior disintegrating abilities. Sodium starch glycolate in the concentration of 2-4% and dried starch NF in concentration of 3-5%

are used as DC disintegrants which promote rapid disintegration of tablets and faster dissolution.

Magnesium stearate is the most commonly used lubricant in the range of 0.5-1% in DC tablet formulations. In active materials with low bulk density (< 0.4 g/ml), talc (1-2%) may be used as a glidant and densifier. [18]

b. Weight of the tablet: [17]

It depends upon the strength of the tablet and the excipients used. Variation in the tablet weight should be qualified for each formulation. Film coating for better elegance or to mask the taste of active ingredient will add on an additional 2-3% of the overall tablet weight.

Steps involved in manufacturing of tablets by direct compression process:

a) Milling of drugs and excipients.

b) Mixing of all the materials.

c) Compression in to a tablet.

Advantages of Direct Compression process: [17]

- ❖ Fewer manufacturing steps, less processing time thereby less laborious work make this process more economical with fewer validation steps.
- ❖ It helps in faster disintegration of the tablet and dissolution of drug as each particle of the tablet is rapidly liberated from the tablet mass and is available for dissolution.
- ❖ Preferable method for moisture sensitive materials.

Disadvantages of Direct compression method: [17]

- ❖ There might be the chances of segregation or non-homogeneous distribution of very low dose drug.

- ❖ It is not suitable for high-dose drugs that have poor compression and flow properties.
- ❖ There is a problem of air entrapment with drugs or excipients having very low bulk density.
- ❖ It is sensitive to over-lubrication and there is a limit to color variation.

4.2. WET GRANULATION: [19], [20]

The most widely used method of granulation for low as well as high strength tablet is wet granulation method. Dosage strengths with 0.5 to 850 mg or more per tablet are considered suitable drug candidates for the high shear development route. It involves aqueous or non-aqueous granulation techniques.

A. Non- aqueous granulation:

Many active materials do not produce satisfactory stability profiles when granulated solely with purified water. Active degradation and overall impurity growth is often accelerated during wet granulation or during the shelf life period due to presence of residual water in compressed tablets. Hydrous or anhydrous alcohol is the solvent of choice in aqueous sensitive active materials. E.g. of drugs undergoing alcoholic granulation include Bupropion, Metoprolol, Glipizide, Mesalamine, Omeprazole etc.

B. Alcohol/ Water granulation:

Occasionally an appropriate ratio of alcohol/water mixtures from 60:40 (Nabumetone) to 95:5 (Mesalamine) is appropriate and can produce stable granulated material.

C. Aqueous granulation:

Water is commonly used for economical and ecological reasons. Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of

susceptible products and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment need not be taken. E.g. of drugs undergoing aqueous granulation include Clonazepam, Losartan, Enalapril etc.

4.2.1. Excipients for wet granulation process: [18]

- **Diluents:** MCC, Tricalcium Phosphate, Maltose, Lactose, Maize Starch.
- **Disintegrants:** Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate. Avicel PH102/105 as an extra granular disintegrants.
- **Granulating agents:** PVP K-30/90, HPC, HPMC, Pregelatinized starch/starch paste.
- **Stabilizers:** Sodium bicarbonate, Citric acid, Meglumine.
- **Lubricant:** Magnesium stearate.

4.2.2. Methods used for wet granulation: [17]

The active materials particle size and bulk/tapped density are significant parameters in wet granulation. Generally rapid mixture granulator (high shear) or fluid bed granulator are used for wet granulation process. Processing by high shear granulators produce high density granules as opposed to moderate density granules produced in FBG. Adequate mixing and blending steps are very important for proper granulation of the blend. The selection of granulator type has a major influence on the characteristic of the final product.

a. EXTRA and INTRA granular addition: [17]

Placing MCC, disintegrants and/or starch either extra or intra granular may have a marked impact on granular formation and flow characteristics, as well as the

dissolution profiles. Both intra and extra granular addition are sometimes preferred to fine tune the dissolution profile.

b. Order of Addition:

Dry glidants are added and blended immediately before the lubricant(s) is added. Addition of lubricant in the prior stage may result in the coating of granules by the hydrophobic lubricant resulting in the retardation of drug release. Homogeneity testing prior to addition of lubricant is omitted in routine commercial production once this content uniformity step has been adequately qualified and validated.

4.2.3. Steps involved in wet granulation: [17]

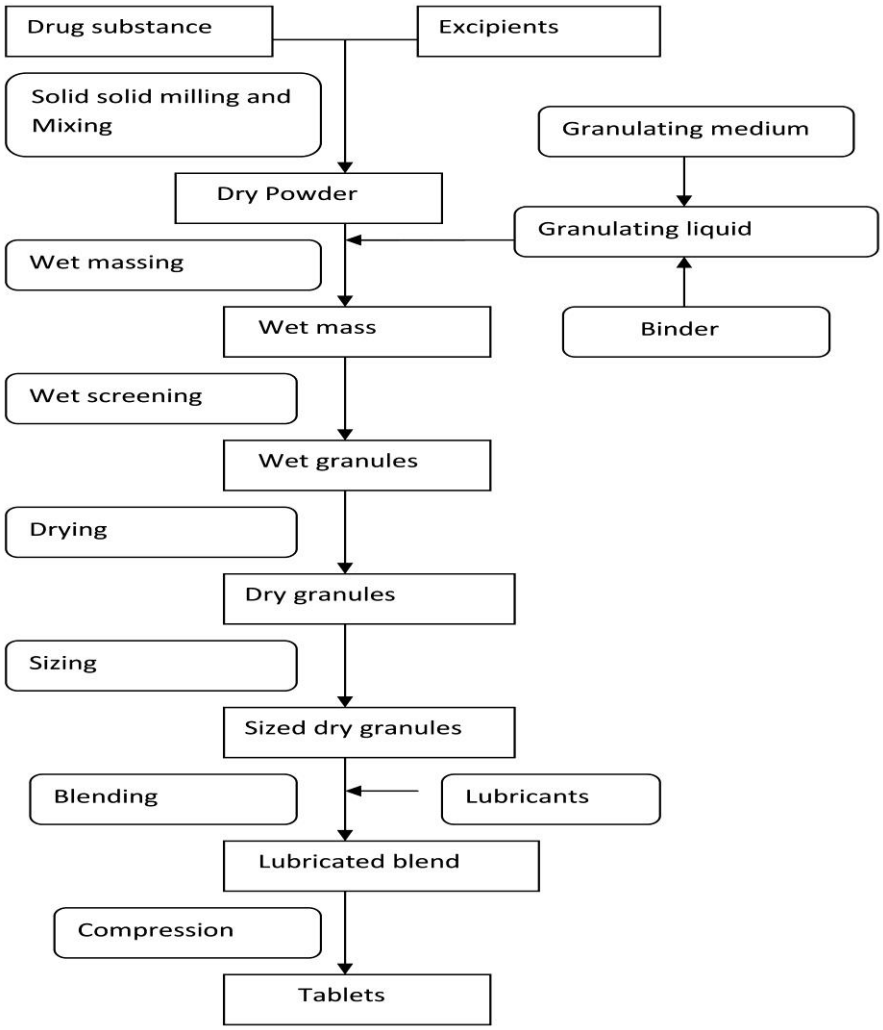


Figure 5: Flow chart of wet granulation process

Advantages of Wet granulation method: [19], [20]

- ❖ It increases formulation compressibility and content uniformity of the dosage form.
- ❖ Useful for fluffy powders that don't flow well or mix well, thus improving uniformity important for potent (low dose) drugs.
- ❖ Binder increases particle strength, and particle size and shape are optimized for flow.
- ❖ Wide range of available excipients.
- ❖ Dustiness is decreased which improves powder handling; the tablet can be dried to low final moisture content and segregation of fines can be prevented.

Disadvantages with Wet granulation method: [17]

- ❖ Not useful for moisture sensitive and heat labile materials.
- ❖ Large number of process steps—making it more expensive (labor/time) and complicated than other methods.
- ❖ There is some material loss during processing because of the involvement of more unit operations.
- ❖ Assay and dissolution problems can occur if the drug (especially low dose) forms complex with the binder, or are adsorbed onto one of the other excipients.

4.3. DRY GRANULATION: [17]

Slugs are prepared by compacting powder of drug and excipients in a roller compactor and resulting slugs are milled to yield granules. Granules are compressed into tablets.

Advantages:

- ❖ Fewer processing steps compare to wet granulation.
- ❖ Less expensive as well as less time consuming.

- Useful for moisture sensitive drugs.
- Less loss of materials because of less involvement of unit operations.

Disadvantages:

- Dry granulation may require recycling or reprocessing and therefore may adversely affect batch control.
- There is also possibility of color variation and segregation during finished mixing.

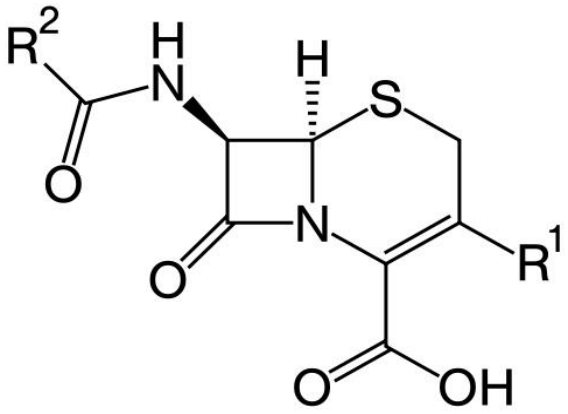
5. CEPHALOSPORINES:

Cephalosporins are beta-lactam compounds in which the beta-lactam ring is fused to a 6-membered dihydrothiazine ring, thus forming the cephem nucleus. Side chain modifications to the cephem nucleus confer 1) an improved spectrum of antibacterial activity, 2) pharmacokinetic advantages, and 3) additional side effects. Based on their spectrum of activity, cephalosporins can be broadly categorized into five generations. [22]

5.1. MECHANISM OF ACTION:

Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins) but are less susceptible to penicillinases. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic the D-Ala-D-Ala site, thereby competitively inhibiting PBP cross linking of peptidoglycan. Cephalosporins show a Concentration-independent bactericidal activity, with maximal killing at 4-5 times the

MIC of the organism and clinically significant post-antibiotic effect is not observed. [22]



Cephalosporin core structure

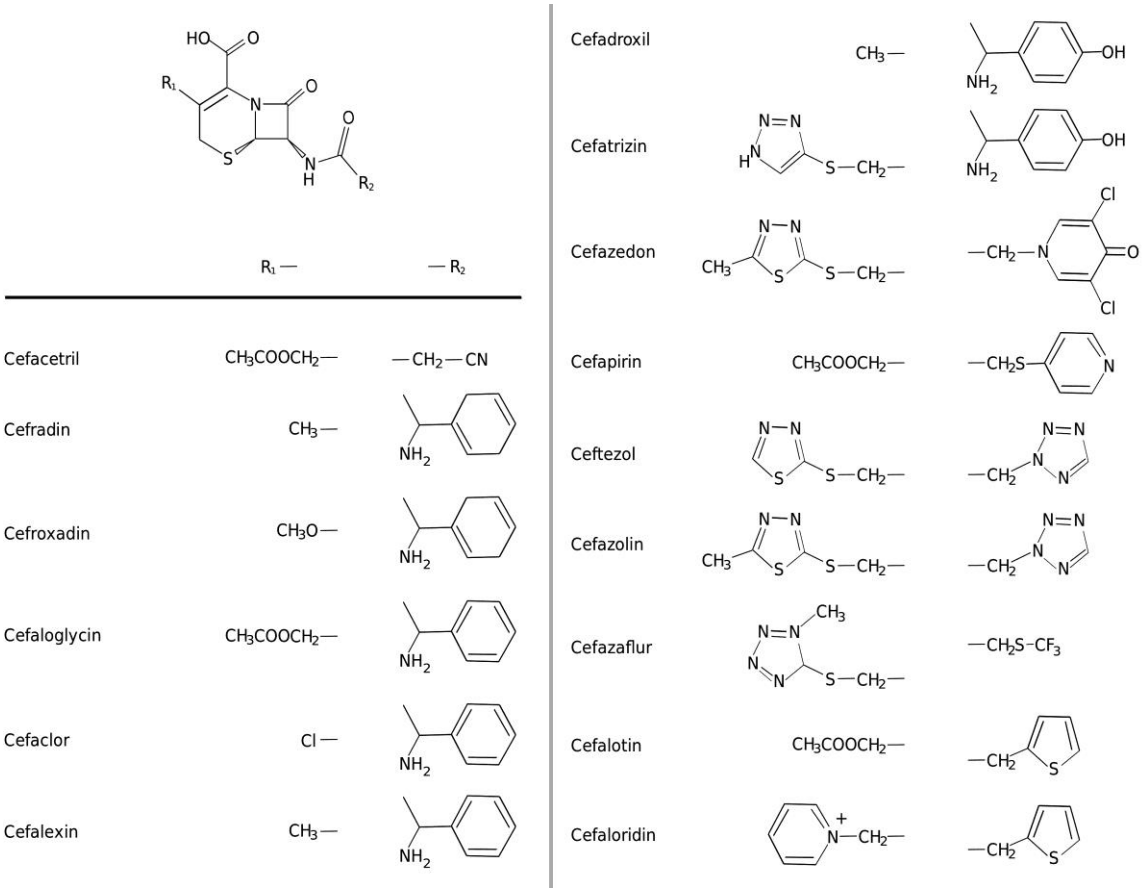


Figure 6: Cephalosporin Antibiotics

5.2. SPECTRUM OF ACTIVITY: [23]

In general, 1st generation cephalosporins have better activity against gram-positive bacteria and less gram-negative activity, while 3rd generation agents, with a

few exceptions, have better gram-negative activity and less gram-positive activity. The only fourth generation agent has both gram-positive and gram-negative activity.

5.3. MECHANISMS OF BACTERIAL RESISTANCE: [24]

It is not uncommon for several resistance mechanisms to be operating simultaneously.

a. Destruction of beta-lactam ring by beta-lactamases; an intact beta-lactam ring is essential for antibacterial activity.
b. Altered affinity of cephalosporins for their target site, the penicillin binding proteins.
c. Decreased penetration of antibiotic to the target site, the PBPs. This is only applicable to gram-negative bacteria because gram-positive bacteria lack an outer cell membrane, and therefore penetration to the target site is not a problem.

Table 2: Generations of Cephalosporin Antibiotics [25]

Generation	Cephalosporin	Dose	Route	Dosing Interval	Renal
1st	Cefazolin	1-2gm	IV/IM	8	yes
	Cephalothin	1-2gm	IV/IM	4-6	yes
	Cephapirin	0.5-1gm	IV/IM	4-6	yes
	Cephalexin	250-500mg	PO	6	yes
	Cefadroxil	500mg	PO	12	yes
	Cephradine	250mg <500mg>	PO PO	6 12	yes
2nd	Cefamandole	1-2gm	IV/IM	4-6	yes
	Cefuroxime	0.75-1.5gm 250-500mg	IV/IM PO	8 12	yes
	Cefoxitin	1-2gm	IV/IM	4-6	yes
	Cefmetazole	2gm	IV	6-12	yes
	Cefaclor	250-500mg	PO	8	yes
	Cefprozil	250-500mg	PO	12-24	yes

	Cefpodoxime	200-400mg	PO	12	yes
3rd	Cefotaxime	1-2gm	IV/IM	6-8	yes
	Ceftriaxone	1-2gm	IV/IM	12-24	
	Ceftizoxime	1-2gm	IV/IM	8-12	yes
	Ceftazidime	1-2gm	IV/IM	8	yes
	Cefoperazone	1-2gm	IV/IM	12	
	Cefixime	400mg 200mg	PO PO	24 12	yes
4th	Cefipime	---	---	---	Yes
5th	Ceftaroline	400/600 mg	IV	12	yes
	Ceftobiprole	---	---	---	---

5.4. PHARMACOKINETICS: [26]

Generally distributes well into the lung; kidney; urine; synovial, pleural, and pericardial fluids. Penetration into the cerebral spinal fluid (CSF) of some 3rd generation cephalosporins (Cefotaxime, Ceftriaxone, and Ceftazidime) is adequate to effectively treat bacterial meningitis. Elimination is primarily via the kidneys, though a few exceptions include Cefoperazone and Ceftriaxone which have significant biliary elimination.

5.5. GENERAL SIDE EFFECTS/ PRECAUTIONS: [27]

Hypersensitivity reactions manifested by rashes, eosinophilia, fever (1-3%); interstitial nephritis. Given the structural similarity of cephalosporins and penicillins, an estimated 1-7% of patients with penicillin allergies will also be hypersensitive to cephalosporins. Cephalosporins should be avoided in patients with immediate allergic reactions to penicillins (e.g.: anaphylaxis, bronchospasm, hypotension, etc.). Cephalosporins may be tried with caution in patients with delayed or mild reactions to penicillin.

Medical attention should be sought immediately if any of these symptoms develop while taking cephalosporins: shortness of breath; pounding heartbeat; skin rash or hives; severe cramps or pain in the stomach or abdomen; fever; Severe watery or bloody diarrhea (may occur up to several weeks after stopping the drug); unusual bleeding or bruising.

5.6. INTERACTIONS: [22], [25]

Some cephalosporins cause diarrhea. Certain diarrhea medicines, such as diphenoxylate-atropine, may make the problem worse. Birth control pills may not work properly when taken at the same time as cephalosporins. To prevent pregnancy, other methods of birth control should be used in addition to the pills while taking cephalosporins.

Taking cephalosporins with certain other drugs may increase the risk of excess bleeding. Among the drugs that may have this effect when taken with cephalosporins are:

- ♠ blood thinning drugs (anticoagulants) such as Warfarin
- ♠ blood viscosity reducing medicines such as Pentoxifylline
- ♠ the anti-seizure medicines Divalproex and Valproic acid

5.7. USE: [23], [25], [27]

Cephalosporins are used to treat infections in different parts of the body—the ears, nose, throat, lungs, sinuses, and skin, for example. Physicians may prescribe these drugs to treat pneumonia, strep throat, staph infections, tonsillitis, bronchitis, and gonorrhea. These drugs will *not* work for colds, flu, and other infections caused by viruses.

Parenteral 1st generation agents are used for surgical wound prophylaxis, uncomplicated, community-acquired infections of the skin and soft tissue and urinary

tract. Useful for respiratory tract infections caused by penicillin-sensitive *Streptococcus pneumoniae* but not for *Haemophilus influenzae* and *Moraxella catarrhalis*. While effective for these infections, other less expensive alternatives should be used when appropriate because of their efficacy and narrower spectrum of activity (e.g.: penicillins, trimethoprim/sulfamethoxazole).

The 2nd generation agents are useful for community-acquired infections of the respiratory tract (*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*) and uncomplicated urinary tract infections (*Escherichia coli*). The Cephamycin group is useful for mixed aerobic/anaerobic infections of the skin and soft tissues, intra-abdominal, and gynecologic infections, and surgical prophylaxis.

3rd generation Cephalosporins are used For infections involving gram-negative bacteria, particularly hospital-acquired infections or complicated community-acquired infections of the respiratory tract, blood, intra-abdominal, skin and soft tissue, and urinary tract. Because of their activity includes the aerobic gram-negative bacteria covered by Aminoglycosides, they may be an alternative to Aminoglycosides in some patients with renal dysfunction.

The clinical situations requiring use of 3rd generation cephalosporins are likely to be encountered in patients who are hospitalized, have recently received antibiotics, or are immunocompromised.

Use of 4th and 5th generation Cephalosporins are similar with 3rd generation cephalosporins.

6. FLUOROQUINOLONES:[28-33]

The fluoroquinolones are a family of synthetic broad-spectrum antibiotics, which eradicate bacteria by interfering with DNA replication. However, the fluoroquinolones are relatively ineffective against intracellular pathogens. Quinolones

and fluoroquinolones are a relatively new class of synthetic antibiotics with potent bactericidal, broad spectrum activity against many clinically important pathogens which are responsible for variety of infections including urinary tract infections (UTI), gastrointestinal infections, respiratory tract infections (RTI), sexually transmitted diseases (STD) and skin infections. They are primarily used against urinary tract infections and are also clinically useful against prostatitis, infections of skin and bones and penicillin resistant sexually transmitted diseases. These agents are also employed against bacterial enteric infections, prophylaxis in the immunocompromised neutropenic host. New quinolones provide a valid alternative antibacterial therapy, especially in areas where the prevalence of penicillin resistant and macrolide resistant organisms exists. [28]

Table 3: Generations of Fluoroquinolone antibiotics: [29]

Generations		**Microbiological activity**	**Administration and characteristics**	**Indications**
1st	Nalidixic Acid Cinoxacin	*Enterobacteriaceae*	Oral administration , low serum and tissue drug concentrations, narrow gram-negative coverage	uncomplicated urinary tract infections , not for use in systemic infections
2nd	Class I Lomefloxacin Norfloxacin Enoxacin	*Enterobacteriaceae*	Oral administration , low serum and tissue drug concentrations , improved gram negative coverage compared to first generation quinolones , limited gram positive coverage	uncomplicated urinary tract infections , Not for use in systemic infections
	Class II Ofloxacin Ciprofloxacin	*Enterobacteriaceae, atypical pathogens; Pseudomonas aeruginosa (ciprofloxacin only)*	Oral and intravenous administration, higher serum , tissue and intracellular drug concentrations compared with class I agents coverage of atypical pathogens	Complicated urinary tract and catheter-related infections, Gastroenteritis with severe diarrhea, Prostatitis, Nosocomial infections, STD's
3rd	Levofloxacin	*Enterobacteriaceae,*	Oral and intravenous	Similar indications

	Sparfloxacin Gatifloxacin Moxifloxacin	*atypical pathogens, streptococci*	administration , similar to class II second generation quinolones but with modest streptococcal coverage	as for second generation quinolones, community acquired pneumonia in hospitalized patients.
4th	Trovafloxacin	*Enterobacteriaceae, atypical pathogens, Pseudomonas aeruginosa, methicilli susceptible Staphylococcus aureus, streptococci, anaerobes*	Oral and intravenous administration, similar to third generation quinolones but with improved gram-positive coverage and added anaerobic coverage	Consider for treatment of intra-abdominal infections.

6.1. MECHANISM OF ACTION: [30]

Fluoroquinolones inhibit the replication and transcription of bacterial DNA, which eventually culminate in cell death. They either inhibit the activity of DNA gyrase, an essential adenosine tri-phosphate hydrolyzing topoisomerase II enzyme or/and prevent the detachment of gyrase from DNA.

The topoisomerases exert their bactericidal activity by interacting with the DNA. During the processes of replication and transcription, enzymes called helicases unwind/uncoil the DNA double helix leading to excess supercoiling of the remaining DNA double helix. A tension is created in this remaining double helix which must be relived in order to continue the process. The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of DNA chain, crossing them over, and then resealing them. Bacterial gyrase is different enough from mammalian topoisomerase so that quinolones and fluoroquinolones show about 1000 fold selectivity towards bacteria over the corresponding enzyme in humans.

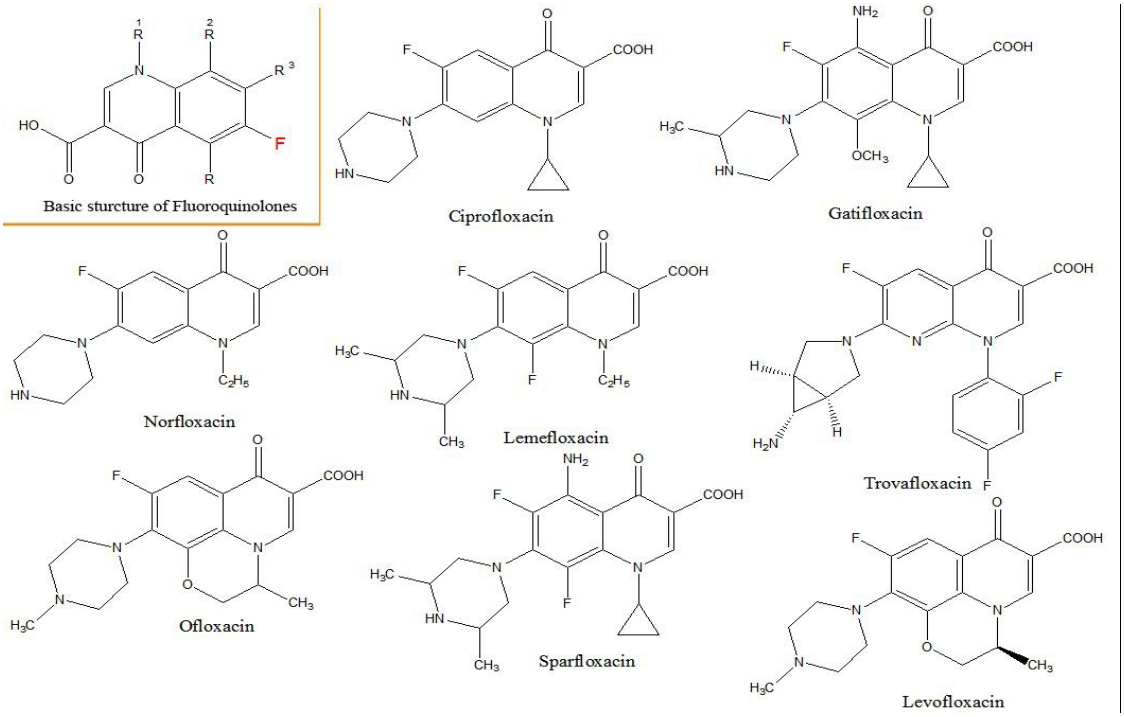


Figure 7: Fluoroquinolone Antibiotics

Fluoroquinolones have also been found to inhibit the in vitro activities of topoisomerase IV, having structure similar to DNA gyrase. This enzyme has an important role in partitioning of chromosomal DNA during bacterial cell division and may be the primary target of Fluoroquinolone activity in Gram positive bacteria. This mechanism is consistent with apoptosis rather than necrosis.

6.2. ANTIMICROBIAL ACTIVITY: [30]

The older fluoroquinolones, Ciprofloxacin and Ofloxacin, have minimal gram positive activity, but they are the most active against aerobic gram-negative bacilli. Limited microbial susceptibility and acquired resistance limit the usefulness of older agents in the treatment of staphylococcal, streptococcal, and enterococcal infections. Ciprofloxacin remains the most potent of the fluoroquinolones against some strains of *Pseudomonas aeruginosa*. Norfloxacin has a primarily gram-negative spectrum of activity.

Newer fluoroquinolones, Gemifloxacin, Levofloxacin and Moxifloxacin, have improved gram-positive coverage as compared to older agents. Newer agents have in vitro activity against S. *pneumoniae*. Gemifloxacin, Levofloxacin, and Moxifloxacin provide coverage for penicillin-resistant and multi-drug resistant strains of S. *pneumoniae*. However, Levofloxacin and Fluoroquinolone-resistant S. *pneumoniae* isolates have been reported. Compared with Levofloxacin, Moxifloxacin is four to eight times more active against S. *pneumoniae* in vitro. Moxifloxacin also has shown greater in vitro activity against Staphylococcus aureus and some enterococcal strains.

6.3. MECHANISMS OF BACTERIAL RESISTANCE: [31]

Resistance to fluoroquinolones can evolve rapidly, even during a course of treatment. Numerous pathogens, including *Staphylococcus aureus*, enterococci, and *Streptococcus pyogenes* now exhibit resistance worldwide. Resistance to this class of agents occurs primarily via two fundamental processes. First, by spontaneous mutations at various locations on the gyrase enzymes subunit A, which lower the affinity of the drug at the gyrase DNA complex? Mutations of subunit A are found in both Gram negative and Gram positive strains and involve amino acid alterations. These alterations are clustered between amino acid 67 and 106 in the amino terminus of subunit A, which is near the active binding site of the enzyme. For example, the substitution of leucine or tryptophan at the place of serine 83 is the most commonly observed alteration and causes a largest increase in resistance. Similar alterations have been seen in topoisomerase IV. Combination of both alterations results in Fluoroquinolone resistance in *S. pneumoniae*.

Second mechanism that entails resistance to the fluoroquinolones is slow to appear, but when it appears it is mainly due to the efflux mechanism, which pumps the drug back to the cell. This is due to the mutation in the genes that code for porins,

which are membrane proteins by which quinolones enter Gram negative cells. These mutations raise tolerance limit of antibiotics to four folds and result in either reduced production of outer membrane proteins or stimulated cell efflux system, which lead to active drug expulsion. This type of resistance has been described in both *E. coli* and *P. aeruginosa*. Similar evidence of enhanced quinolone efflux has been found in *S. aureus*, which lacks an outer cell membrane.

6.4. PHARMACOKINETICS: [32]

a. Oral dosing equivalent to intravenous.

b. Tissue penetration

I. High tissue concentrations

1. Stool and bile
2. Prostate
3. Lung
4. White Blood Cells: Neutrophils, Macrophages
5. Kidney and urine

II. Low tissue concentrations (poor penetration)

1. Poor cerebrospinal fluid penetration

c. Excretion

I. Renal excretion: Most Fluoroquinolones

II. Hepatic excretion

1. Sparfloxacin
2. Moxifloxacin
3. Trovafloxacin

6.5. GENERAL SIDE EFFECTS/ PRECAUTIONS: [33]

A. Interferes with cartilage growth in animals

1. Avoid in children under age 18 years

B. Nausea

C. Taste disturbance

D. Diarrhea

E. Photosensitivity

F. Pruritus or dermatitis

G. Tendinopathy (black box warning)

1. Onset at approximately day 13 of therapy
2. Achilles Tendon Rupture increased risk (3.2 cases per 1000 patient treatment years)
3. Higher risk patients
    1. Age over 60
    2. Concurrent Corticosteroid use
    3. Athletes
    4. Transplant recipients

H. QTc Prolongation (risk of Torsade de Pointes)

1. Grepafloxacin pulled from U.S. market in 1999
2. Also may occur with Sparfloxacin and Moxifloxacin

I. Neurologic effects

1. Seizures (especially if concurrent NSAID use)
2. Confusion
3. Headache
4. Dizziness
5. Tremors

6.6. INTERACTIONS: [33]

1. Antiarrhythmic or Cisapride (risk QTc prolongation)
2. NSAIDs (risk of Seizure)
3. Increases level of other medications
    1. Increased Anticoagulation effect with Coumadin
    2. Increased Cyclosporine (also risks nephrotoxicity)
    3. Increased Caffeine level
    4. Increased Theophylline levels
    5. Increased Riluzole levels
4. Chelates with Cations (decreased Quinolone absorption)
    1. Avoid these agents within 2 hours of Quinolone
    2. Antacids containing Magnesium, Aluminum or Calcium
    3. Iron Sulfate
    4. Zinc
    5. Calcium
    6. Didanosine
    7. Sucralfate
5. Decreases Norfloxacin activity
    1. Chloramphenicol
    2. Nitrofurantoin
    3. Rifampin
    4. Tetracycline

6.7. USE: [32], [33]

1. Cystic Fibrosis
2. Complicated Urinary Tract Infection
3. Enteric Fever
4. Chronic Suppurative Otitis Media
5. Multi-drug resistant Gram Negative Sepsis
6. Multi-drug resistant Mycobacterium infection
7. Skeletal infection caused by Gram Negatives
8. Febrile neutropenic patients
9. Bacterial Meningitis with resistant organisms
10. *Neisseria Meningitidis* prophylaxis

Chapter 2

REVIEW OF LITERATURE

1. **Burgess D S *et. al.* evaluated the activity of two doses of Levofloxacin alone and in combination with other agents against *Pseudomonas aeruginosa, in vitro.*** [34]

They says that *P. aeruginosa* is one of the most difficult to treat pathogens that generally requires combination therapy to prevent the development of resistance. In their study, they evaluated the in vitro activity of two concentrations of Levofloxacin (modeled for the 500 mg and 750 mg daily dose) in combination with Ceftazidime, Cefepime, Piperacillin/ Tazobactam, Imipenem, and Tobramycin against *P. aeruginosa*. MICs and time-kill studies were performed against 12 non-duplicate clinical isolates of *P. aeruginosa* in the study. The percent susceptible for Levofloxacin, Ceftazidime, Cefepime, Piperacillin/ Tazobactam, Imipenem, and Tobramycin were 67%, 58%, 58%, 67%, 75%, and 100%, respectively. Tobramycin was found to be the most active single agent, killing and maintaining 99.9% killing over a 24 h period against all isolates. Levofloxacin 4µg/mL (750 mg/day) alone reached 99.9% killing and maintain this killing over the time period more often than Levofloxacin 2µg/mL (500 mg/day). No combination was antagonistic and all combinations with Tobramycin were indifferent. Overall, Levofloxacin 2µg/mL plus a β-lactam was synergistic (65%) more often than Levofloxacin 4µg/mL combinations (46%). As per them, this was not unexpected due to the increased activity of Levofloxacin 4µg/mL However, Levofloxacin 4µg/mL combinations maintained a 99.9% killing over the entire 24 h period more often than Levofloxacin 2µg/mL combinations (94% vs. 83%). From the findings of their work, they suggests that Levofloxacin 750 mg/day in combination with another agent active against *P. aeruginosa* may prove to be clinically beneficial and superior to combinations using lower doses of Levofloxacin.

2. **Zullo A *et. al.* studied about A third-line Levofloxacin-based rescue therapy for *Helicobacter pylori* eradication.**[35]

In the report of the study, they say that *Helicobacter pylori* infection persists in a considerable proportion of patients after both first- and second-line current treatments. A standard therapy for re-treatment in such refractory patients is still lacking. Their study aimed to evaluate the efficacy of a Levofloxacin– Amoxicillin combination in patients who previously failed two or more therapeutic attempts. In the study consecutive patients with persistent *Helicobacter pylori* infection were enrolled. Bacterial infection was assessed by rapid urease test and histology on gastric biopsies at endoscopy. Patients were assigned to receive a 10-day triple therapy, comprising rabeprazole 20 mg BD, Levofloxacin 250 mg BD, and Amoxicillin 1 g BD 4 to 6 weeks after therapy, *Helicobacter pylori* eradication was assessed by a further endoscopy or ^{13}C urea breath test. They enrolled overall 36 patients, but two patients were lost to follow-up. *Helicobacter pylori* was successfully cured in 30 patients, giving an 83.3% (95% CI571.2–95.5) and 88.2% (95% CI577.4–99) eradication rate at intention-to-treat and per protocol analysis, respectively. Compliance was good in all but two patients, who discontinued the treatment at 8 and 6 days, respectively, on account of glossitis. No major side-effects were reported in the study, whilst 7 (20.1%) patients complained of mild side-effects. This study demonstrates that a 10-day Levofloxacin– Amoxicillin triple therapy is a safe and successful third-line therapeutic approach for *Helicobacter pylori* eradication.

3. **Reid G *et. al.* studied the efficacy of Ofloxacin for the treatment of urinary tract infections and bio films in spinal cord injury.**[36]

Forty two paraplegic and quadriplegic hospitalized spinal cord injured patients with urinary tract infections (UTI) were included in a double blind, randomized treatment study comparing 7 days Ofloxacin (300 mg BD) with trimethoprim-sulphamethoxazole (TMPSMX; 160 – 800 mg BD) or an alternative, chosen because of resistance to TMPSMX. The 4-day clinical cure rate, defined as an asymptomatic patient with sterile urine, was 90% (19:21) with Ofloxacin, significantly greater than 48% (10:21) for the comparison group (P-0.003) and the rate at end of therapy was 90% (19:21) with Ofloxacin, against 57% (12:21) (P-0.015). Bacterial bio films were detected on bladder epithelial cells in 39:41 (95%) patients. The bio film score fell significantly following Ofloxacin therapy (PB0.001) or alternative therapy (PB0.001). Ofloxacin treatment led to significantly more bio film eradication than the other antibiotic group on day 4 (62 vs. 24%) (P-0.005) and day 7 (67 vs. 35%) (P-0.014). The study showed that Ofloxacin was better than TMPSMX and alternatives at relieving clinical infection and eradicating bladder cell bio films.

4. **Muratani T *et. al.* studied the resistance of bacteria towards antimicrobial agents of urinary isolates.**[37]

They saw that *Escherichia coli* accounted for about 80% of organisms in uncomplicated urinary tract infections (UTIs), followed by Staphylococcus spp. Especially *Staphylococcus saprophyticus*, and *Proteus mirabilis*. Against *E. coli* isolates from patients with uncomplicated UTI, Faropenem was the most effective. They have mentioned that Up to 1999, Fluoroquinolone-resistant isolates were not observed in patients with uncomplicated UTI, but in 2001 Fluoroquinolone-resistant *E. coli* isolates emerged and accounted for about 8%. They isolated various types of organisms in patients with complicated UTI. *Enterococcus faecalis*, *E. coli*, and

Pseudomonas aeruginosa were the three most frequent organisms isolated. These three organisms accounted for 44.6%.

Amongst oral agents, Faropenem showed the lowest rate of resistance against *E. coli* followed by Cephems. According to them the rates of highly Fluoroquinolone-resistant and cefpodoxime-resistant *E. coli* isolates increased rapidly from 1998 to 2001. Fluoroquinolone-resistant *P. aeruginosa* isolates accounted for about 40% in 2001. Against this species, Amikacin was the most effective antimicrobials among all agents tested. About 17% of Pseudomonas were resistant to Carbapenem. Eight milligram per liter of Ampicillin inhibited all *E. faecalis* isolates; about 60% of *Enterococcus faecium* were resistant to Ampicillin. The rates of Levofloxacin-resistant isolates of *E. faecalis* and *E. faecium* were 38 and 97% respectively.

5. **Hooton T M studied about the Fluoroquinolones and resistance in the treatment of uncomplicated urinary tract infection.**[38]

In his report he says that acute uncomplicated cystitis is one of the most common problems for which young women seek medical attention. Most of these infections are caused by *Escherichia coli* which are susceptible to many oral antimicrobials, although resistance is increasing to some of the commonly used agents, especially trimethoprim/sulphamethoxazole (TMP/SMX). In his report he says that in women with risk factors for infection with resistant bacteria, or in the setting of a high prevalence of TMP/SMX resistance, a Fluoroquinolone or Nitrofurantoin should be considered for empirical treatment. Use of Nitrofurantoin does not share cross-resistance with more commonly prescribed antimicrobials and its more widespread use is justified from a public health perspective as a Fluoroquinolone-sparing agent. β-lactams and Fosfomycin should be considered second-line agents for empirical

treatment of cystitis. From his study he found that for acute uncomplicated pyelonephritis, fluoroquinolones are superior to TMP/SMX for empirical therapy due to the relatively high prevalence of TMP/ SMX resistance among uro-pathogens causing pyelonephritis. TMP/SMX, effective for patients with mild to moderate disease, is an appropriate drug if the uro-pathogen is known to be susceptible. It is reasonable to use a 7/10 day oral Fluoroquinolone regimen for outpatient management of mild to moderate pyelonephritis in the setting of a susceptible causative pathogen and rapid clinical response to therapy. Finally he concludes that most women with acute uncomplicated pyelonephritis are now managed safely and effectively as outpatients.

6. **Gehanno P *et. al.* studied and reported the effect of Levofloxacin in the treatment of acute and bacteriologically documented sinusitis with high risk of complications.**[39]

The authors aimed to evaluate the efficacy and tolerance of oral Levofloxacin (500 mg once a day during ten days), as a treatment for acute bacterial sinusitis at risk for complications in adult patients. They performed a prospective, multicenter, open, non-comparative, efficacy and tolerance study of Levofloxacin in acute sinusitis at risk for complications, radiologically confirmed, and with documentation of the bacterial origin by fiberoptic rhinoscopy. They included two hundred and thirty-one patients and 174 patients had an X-ray confirmed sinusitis. The localization was frontal in 81% patients, sphenoidal in 9.2%, ethmoido-sphenoidal in 2.3%, and 7.5% patients had a pansinusitis. 133 patients had a probable or proven bacterial infection, involving: *Streptococcus pneumoniae*(26.0%), Enterobacteriaceae (19.7%), *Haemophilus influenzae*(17.3%), *Staphylococcus aureus*(15.0%), streptococci other than *S. pneumoniae*(7.9%), and *Branhamella catarrhalis*(5.5%). 101 patients

constituted the per protocol population. They got clinical success in 94.1 % patients (95/101), and 85.1% (86/101), respectively 7 to 14 days and three to four weeks after the end of treatment, with consistent success rate according to the localization of the infection, and the various pathogens involved. The tolerance data was as expected for Levofloxacin. The results of their study show that Levofloxacin, (one 500 mg tablet QD during ten days) is efficient in over 94% patients with bacteriologically documented sinusitis at risk for complications.

7. **Naber K G *et. al.* observed and reported about the Antibiotic treatment of uncomplicated urinary tract infection in premenopausal women.**[40]

According to them uncomplicated urinary tract infections (UTIs) in otherwise healthy premenopausal women are one of the most frequent infections in the community. Therefore any improvement in management will have a high impact not only on the quality of life of the individual patient but also on the health system. They saw that in placebo-controlled studies antimicrobial treatment was significantly more effective than placebo, but on the other hand showed more adverse events. They reported that the choice of antibiotic for the treatment of uncomplicated urinary tract infection in premenopausal women depends on the spectrum and susceptibility patterns of the uro-pathogens, its effectiveness for this indication, its tolerability, its collateral effects and cost. After a systematic literature search, they have given recommendations for empiric treatment of acute uncomplicated cystitis and acute uncomplicated pyelonephritis and for follow-up strategies.

8. **Goldblatt E L *et. al.* compared the efficacy of topical Ofloxacin formulation with systemic Amoxicillin/ Clavulanate in purulent otorrhea in children with tympanostomy tubes.**[41]

In this study they compared the safety and efficacy of Ofloxacin otic solution, 0.3% (OFLX) with that of Augmentin® oral suspension (AUG) in pediatric subjects 1 – 12 years of age with tympanostomy tubes and acute purulent otorrhea. Subjects were randomized to receive 10 days of OFLX, 0.25 ml topically BID, or of AUG, 40 mg/kg/day. Audiometry was performed in subjects of 4 years of age. Overall cure rate for clinically evaluable subjects was 76% with OFLX and 69% with AUG. Overall eradication rates for OFLX and AUG were similar for *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* and were superior with OFLX for *Staphylococcus aureus* and. OFLX had a greater overall pathogen eradication rate (96% vs. 67%). Treatment-related adverse event rates were 31% for AUG and 6% for OFLX. Neither treatment significantly altered hearing acuity. Topical Ofloxacin 0.3% otic solution 0.25 ml bid was as effective and better tolerated than systemic therapy with Augmentin® oral suspension 40 mg/kg/day in treating AOM in children with tympanostomy tubes.

9. **Bundrick W *et. al.*, in a randomized double-blind multicenter study, compared the safety and efficacy Levofloxacin with that of Ciprofloxacin in the treatment of chronic bacterial prostatitis.**[42]

They performed the study in a multicenter, double-blind, active-control trial, with 377 men with a history of chronic bacterial prostatitis, current clinical signs and symptoms, and laboratory evidence of prostatitis. Patients were randomized to treat with Levofloxacin 500 mg once daily or Ciprofloxacin 500 mg twice daily for 28

days. The primary endpoint was microbiologic efficacy in the microbiologically assessable population. They used Meares-Stamey "four-glass" procedure to obtain prostatic secretions and urine for culture. The clinical success rates, including cured plus improved patients, were similar (75% for Levofloxacin and 72.8% for Ciprofloxacin; 95% confidence interval for the difference in the success rates: 13.27 to 8.87), as were the microbiologic eradication rates (75% for Levofloxacin and 76.8% for Ciprofloxacin; 95% confidence interval for the difference 8.98 to 12.58). they found *Enterococcus faecalis* and *Escherichia coli* as the most common isolates. The 6-month relapse rates were similar for both regimens. Both Levofloxacin and ciprofloxacin were well tolerated, with similar rates of adverse events.

10. **Richard G A *et. al.* compared Levofloxacin with Ciprofloxacin and Lomefloxacin for efficacy and safety in treating acute pyelonephritis in their study.**[43]

They enrolled a total of 186 patients with bacteriologically proved infection. Of those, 89 patients in both trials combined received Levofloxacin 250 mg once daily; 58 received Ciprofloxacin 500 mg twice daily in the first trial (double blind); and 39 received lomefloxacin 400 mg once daily in the second trial (open label). Microbiologic response of patients evaluable for microbiologic efficacy was the primary efficacy variable, and clinical response of microbiologically evaluable patients was the secondary efficacy variable in both studies. They also found *Escherichia coli* as the most prevalent pathogen. At 5 to 9 days after the end of treatment, 95% of uro-pathogens were eradicated in patients who received Levofloxacin compared with 94% in the Ciprofloxacin-treated group and 95% in the lomefloxacin-treated group. The clinical cure rate was 92% for Levofloxacin in both studies combined, 88% for Ciprofloxacin, and 80% for Lomefloxacin. Drug-related

adverse events were reported by 2% of Levofloxacin-treated patients, 8% of Ciprofloxacin-treated patients, and 5% of Lomefloxacin-treated patients. From the study they concluded that once-daily oral administration, proven efficacy, and good tolerability make Levofloxacin an excellent choice for empiric treatment of acute pyelonephritis.

11. Mora R *et. al.* did a detailed study over the Efficacy of cefpodoxime in the prophylaxis of recurrent pharyngotonsillitis.[44]

In their study report, recurrent acute pharyngotonsillitis has been mentioned as a common illness in children and young adults and which may lead to serious complications if not treated. They evaluated the efficacy of second-generation cephalosporins in the prophylaxis of recurrent pharyngotonsillitis in children. For the study, 180 children aged between 4 and 14 years with recurrent pharyngotonsillitis were randomized to receive either cefpodoxime proxetil (100 mg twice a day, 6 days a month for 6 months) or placebo (at the same dosage). Their study results show that treatment with Cefpodoxime proxetil may be effective in reducing symptoms of recurrent pharyngotonsillitis and preventing recurrences without causing side effects or developing bacterial resistance.

12. Hadley J A *et. al.* studied about the efficacy of Oral β-lactams in the treatment of acute bacterial rhinosinusitis.[45]

According to them, acute bacterial rhinosinusitis (ABRS) is a well-known complication of viral upper respiratory tract infection and is associated with a significant socioeconomic burden. Difficulties in diagnosis, a substantial spontaneous resolution rate, and growing concerns regarding antimicrobial resistance make the proper management of ABRS quite challenging. Different treatment guidelines have

been developed, taking into account the major bacterial pathogens, rates of antimicrobial resistance, spontaneous resolution rates, and pharmacokinetic and pharmacodynamic considerations, by different authors. They also says that optimal choices for initial treatment of ABRS in patients without prior antibacterial exposure include the oral β-lactam agents Amoxicillin/ Clavulanate, Cefdinir, Cefpodoxime, and Cefuroxime. They want to encourage the clinicians to consider the local pathogen distribution and rates of antibacterial resistance in selecting therapy for ABRS.

13. Gibb A P *et. al.* screened *Escherichia coli* and *Klebsiella* spp. for Cefpodoxime by VITEK for detection of organisms producing extended-spectrum β-lactamases.[46]

They used a VITEK custom card to detect cefpodoxime MIC (minimum inhibitory concentration) of — 2 mg/L as a screen for extended-spectrum β-lactamase (ESBL) production in *E. coli* and *Klebsiella* spp. Of 2873 organisms tested, 60 were screen positive, but only 3 were confirmed to be ESBL producers. Cefpodoxime is believed to be a sensitive screen for ESBL production, but they suggested a more specific test.

14. Zyl L V *et. al.* studied the efficacy of Cefditoren pivoxil with that of Cefpodoxime Proxetil for Community-Acquired Pneumonia in a Multicenter, Prospective, Randomized, Double-Blind Study.[47]

This was a multicenter, prospective, randomized, double-blind study conducted in the United States and South Africa. They randomized ambulatory patients with a diagnosis of CAP were to 14 days of treatment with Cefditoren 200 or 400 mg BID or Cefpodoxime 200 mg BID.

From the results, they suggested that Cefditoren may have a role in the treatment of CAP in ambulatory patients.

15. Aronovitz G H reviewed about the antimicrobial therapy of Acute Otitis Media (AOM).[48]

From the literature search, he recommended Amoxicillin as the first-line agent to treat uncomplicated AOM. For clinical treatment failures after 3 days of amoxicillin, his recommended antimicrobial agents include oral Amoxicillin+ Clavulanate, Cefuroxime axetil, Cefprozil, Cefpodoxime proxetil, and intramuscular (IM) Ceftriaxone. According to him, IM Ceftriaxone should be reserved for severe cases or patients in whom noncompliance is expected. He also recommended Tympanocentesis for identification of pathogens and susceptibility to antimicrobial agents, for selection of third-line agents.

Chapter 3

RATIONALE AND PLANE OF WORK

1. RATIONALE BEHIND THE STUDY
2. RECOMMENDED USE OF THE FORMULATION
3. OBJECTIVES OF THE STUDY
4. PLAN OF WORK

1. RATIONALE BEHIND THE STUDY:

From different independent studies, the combined administration of the drugs under discussion [A Cephalosporin (Drug "A") & A Fluoroquinolone (Drug "B")] has already been proved to be effective in the management and treatment of different complicated and mixed infections, especially in resistant *Pseudomonas aeruginosa* infections, *Helicobacter pylori* eradication, sinusitis, UTI, RTI, pyelonephritis, pharyngotonsillitis, burns, hospital acquired infections etc. [34]

Each antimicrobial agent (AMA) has a specific effect on a limited number of microbes. Successful chemotherapy must be rational and demands a diagnosis. However, most of the time, definitive bacteriological diagnosis is not available before initiating treatment. Bacteriological testing is time consuming, expensive and appropriate samples of infected material for bacteriology may not be obtainable. [11]

A clinical diagnosis should first be made, at least tentatively, and the likely pathogen guessed.

No guess can be made about the infecting organism or its sensitivity, e.g. bronchopneumonia, empyema/ meningitis, osteomyelitis, urinary tract infection, wound infection, burns etc. In these situations, an AMA should be selected on the basis of culture and sensitivity testing; but this may not be always possible. [11]

More than one AMA is frequently used concurrently. This should be done only with a specific purpose and not blindly in the hope that if one is good, two should be better and three should cure almost any infection.

The objectives of using antimicrobial combinations are:

1.1.TO ACHIEVE SYNERGISM:

Every AMA has a specific effect on selected microorganisms. Depending on the drug pair as well as the organism involved: synergism (supra-additive effect), additive action, indifference or antagonism may be observed when two AMAs belonging to different classes are used together. [10]

Synergism may manifest in terms of decrease in the MIC of one AMA in the presence of another, or the MICs of both may be lowered. If the MIC of each AMA is reduced to 25% or less, the pair is considered synergistic, 25-50% of each is considered additive and more than 50% of each indicates antagonism. Thus, a synergistic drug sensitizes the organisms to the action of the other member of the pair. This may also manifest as a more rapid lethal action of the combination than either of the individual members. Synergistic prolongation of post antibiotic effect has also been demonstrated for combinations of β-lactams with Aminoglycoside and by addition of Rifampin to a variety of antibiotics. [10]

1.2.TO REDUCE SEVERITY OR INCIDENCE OF ADVERSE EFFECTS:

This is possible only if the combination is synergistic so that the doses can be reduced. This is needed for AMAs with low safety margin, which when used alone in effective doses, produce unacceptable toxicity. [35]

1.3.TO PREVENT EMERGENCE OF RESISTANCE:

Mutation conferring resistance to one AMA is independent of that conferring resistance to another. If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12}

bacilli will be resistant to both. The chances of its surviving host defence and causing a relapse would be meagre. [10]

This principle of using two or more AMAs together is valid primarily for chronic infections needing prolonged therapy; has been widely employed in tuberculosis, leprosy and now adopted for *H. pylori*, HIV as well. It is of little value in most acute and short-lived infections.

However, Rifampin given with ciprofloxacin prevents *S. aureus* resistance to the latter. [10]

1.4.TO BROADEN THE SPECTRUM OF ANTIMICROBIAL ACTION:

Broadening of the spectrum of antimicrobial action is needed in:

A. ***Treatment of mixed infection*:** Bronchiectasis, peritonitis, certain urinary tract infections, brain abscesses, diabetic foot infection, bedsores, gynaecological infections are mostly mixed infections. Often, aerobic and anaerobic organisms sensitive to different drugs are involved. Obviously two or more AMAs have to be used to cover the pathogens. Drugs should be chosen on the basis of bacteriological diagnosis and sensitivity pattern (known or presumed), and should be employed in full doses. Clindamycin or metronidazole is generally included to cover anaerobes. It may sometimes be possible to find a single agent effective against all the causative organisms. [36]

B. ***Initial treatment of severe infections:*** For empirical therapy, since bacterial diagnosis is not known; drugs covering gram-positive and gram-negative (in certain situations anaerobes as well). e.g. penicillin + streptomycin; cephalosporin or erythromycin + an Aminoglycoside ± metronidazole or

clindamycin, may be given together. Rational combinations improve the certainty of curing the infection in the first attempt, but should be continued only till bacteriological data becomes available. When the organism and its sensitivities has been determined, severity of infection is in itself not an indication for combination therapy. Combinations should not be used as a substitute for accurate diagnosis. [37]

C. Topically: Generally, AMAs which are not used systemically, are poorly absorbed from the local site and cover a broad range of gram-positive and gram-negative bacteria are combined for topical application, e.g. bacitracin, neomycin, polymyxin B. [35]

2. RECOMMENDED USE OF THE FORMULATION:

The fixed dose combination product of drug "A" & "B" is normally recommended for various reasons like....

2.1.SYNERGISTIC EFFECT:

Though both the drugs of discussion are having broad spectrum of activity, but drug "A" has better effect upon Gram positive bacteria while drug "B" has better activity on Gram negative bacteria. So, when both of them are given at the same time, the spectrum of activity is more extensive then the individual drugs. [34]

2.2.REDUCED SIDE EFFECT:

When single drug "A" or "B" is used, the dose required for optimum activity is quite high. For drug "A", the dose is 800 mg/day and for drug "B", the dose is 500 mg BD/ OD. In these high doses they show various side effects. But when given concurrently, to get the same antimicrobial efficacy, reduced dose of drug "A" (200 mg) and drug

"B" (250 mg) for one time in a day is required. It also reduces the duration of treatment. [35]

2.3.REDUCED INCIDENCE OF RESISTANCE FORMATION:

Studies have shown that when the two drugs are given concurrently, the chance of resistance formation is reduced to a great extent. [35]

3. OBJECTIVES OF THE STUDY:

3.1.AIM OF THE PRESENT DEVELOPMENT:

The basic aim of present development is to provide a stable pharmaceutical formulation of two broad spectrum antibiotics (Drug "A" and Drug "B") for the treatment of various complicated infections occurred from both Gram positive and Gram negative bacteria.

Another objective of the study is to develop an immediate release 'tablet dosage' form, containing a fixed dose of the antibiotics 'in a single tablet' for convenience of use by the physician as well as patient and for rapid onset of action.

3.2.OBJECTIVES OF THE STUDY:

The main objectives of the project are:

- ✓ To develop physically and chemically compatible, stable and bioequivalent fixed dose combination product.
- ✓ To perform the Pre-formulation studies for:
  - ❖ For characterization of active pharmaceutical ingredients (API).
  - ❖ For compatibility studies with different excipients.
- ✓ To perform the complete evaluation of physicochemical parameters of tablets during development.

- ✓ To observe dissolution profiles of both drugs in formulated tablets.
- ✓ To perform the stability studies of reproducible batch.

4. PLAN OF WORK:

i. Review of literature

ii. Selection of excipients

iii. Physical and chemical characterization APIs and excipients

iv. Formulation of dosage form

v. Optimization of excipients concentration to achieve desired profile of drug

vi. Optimization of process parameters

vii. Evaluation and characterization of prepared tablets

a. Drug content

b. Content uniformity test

c. In-vitro dissolution study

viii. Selection of optimized formulation, and

ix. Stability study of the optimized formulation.

Chapter 4

DRUG EXCIPIENT PROFILE

1. DRUG PROFILE: DRUG “A”
2. DRUG PROFILE: DRUG “B”
3. EXCIPIENT PROFILE

1. DRUG PROFILE: DRUG “A”:

1.1. PHYSICAL PROPERTIES:

Table 4: Physical properties of drug "A"

Molecular weight	557.6
State:	White to yellowish powder (solid)
Water solubility	400 µg/ ml (1.85e-01 g/l)
Log P	0.05
pKa	11.09
Polarizability	39.9
Refractivity	100.71
Melting point	111-113°C
BCS Class	Class IV
Polar surface area	156.44
Hydrogen acceptor count	9
Hydrogen donor count	3

1.2. PHARMACOKINETICS:

1.2.1. Absorption: [26]

Drug “A” is de-esterified in the intestinal epithelium after oral doses, to release active metabolite in the bloodstream. Bioavailability is about 50% in fasting subjects and may be increased in the presence of food. Absorption is decreased in conditions of low gastric acidity. Peak plasma concentrations of about 1.5, 2.5, and 4.0 micrograms/ml have been achieved 2 to 3 hours after oral doses of 100, 200, and 400 mg of Drug “A” respectively. About 20 to 30% of Drug “A” is bound to plasma proteins. The plasma half-life is about 2 to 3 hours and is prolonged in patients with renal impairment.

1.2.2. Distribution: [26]

Drug “A” gets widely distributed throughout the body and reaches therapeutic concentrations in most of the tissues and body fluids, including synovial, pericardial, pleural, and peritoneal fluids, bile, sputum and urine. It also gets distributed into bone, gallbladder, myocardium, skin and soft tissue. Most of the cephalosporin cross the placenta and are distributed into breast milk. Normally Drug “A” is 22-33% protein bound in serum and 21-29% in plasma.

1.2.3. Elimination: [26]

Drug “A” undergoes minimal metabolism & almost 33% of the dose is excreted unchanged renally. Elimination half life is about 2.09-2.84 hours.

1.3. PHARMACODYNAMICS:

1.3.1. Mechanism of Action: [22]

Drug “A” is active against a wide spectrum of Gram-positive and Gram-negative bacteria. Drug “A” is stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillin and cephalosporins, due to their production of beta-lactamase, may be susceptible to Drug “A”. Drug “A” is inactivated by certain extended spectrum beta-lactamases. The bactericidal activity of Drug “A” results from its inhibition of cell wall synthesis. The active metabolite of Drug “A” binds preferentially to penicillin binding protein 3, which inhibits production of peptidoglycan, the primary constituent of bacterial cell walls.

1.3.2. Indication: [23], [25], [27]

Drug “A” is prescribed in Pneumonia, Pyelonephritis, Sinusitis, Skin or Soft Tissue Infection, Tonsillitis/Pharyngitis, Upper Respiratory Tract Infection, Bronchitis, Cystitis, Gonococcal Infection, Otitis Media etc.

1.3.3. Dosage: [22]

Table 5: Normally Prescribed Doses of Drug "A"

Disease	Adult dose	Pediatric dose
Bronchitis	200 mg orally every 12 hours for 10 days.	≥12years: 200 mg orally every 12 hours for 10 days
Cystitis	100 mg orally every 12 hours for 7 days.	≥12years: 100 mg orally every 12 hours for 7 days.
Gonococcal Infection Uncomplicated	200 mg orally one time.	≥12years: 200 mg orally one time.
Gonococcal Infection Disseminated	400 mg orally twice a day.	≥12years: 400 mg orally twice a day
Pneumonia	200 mg orally every 12 hours for 14 days	≥12years: 200 mg orally every 12 hours for 14 days.
Pyelonephritis	100 mg orally every 12 hours	---
Otitis Media	---	2 months to 12 years: 5 mg/kg/dose (maximum 200 mg) orally every 12 hours for 5 days.
Sinusitis	---	2 months to12 years: 5 mg/kg/dose (maximum 200 mg) orally every 12 hours for 10 days.
Skin or Soft Tissue Infection	---	≥12 years: 400 mg orally every 12 hours for 7 to 14 days.
Tonsillitis/Pharyngitis		2 months to 12 years: 5 mg/kg/dose (maximum 100 mg) orally every 12 hours for 5 to 10 days

1.3.4. Contraindications:

Drug "A" is contraindicated in patients with a known allergy to the cephalosporin group of antibiotics.

1.4. WARNINGS/ PRECAUTIONS: [22], [25]

Before therapy with Drug "A" is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to Drug "A", other cephalosporins, penicillin, or other drugs. If Drug "A" is to be administered to penicillin sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Drug "A" occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, and airway management, as clinically indicated. *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Drug "A", and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. Difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. [22]

In patients with transient or persistent reduction in urinary output due to renal insufficiency, the total daily dose of Drug "A" should be reduced because high and

prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Drug “A”, like other cephalosporins, should be administered with caution to patients receiving concurrent treatment with potent diuretics. [25]

As with other antibiotics, prolonged use of Drug “A” may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient’s condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. [22]

Prescribing Drug “A” in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. [22]

Drug “A” is in Pregnancy Category: B.

Drug “A” is excreted in human milk.

Safety and efficacy in infants less than 2 months of age have not been established.

Drug “A” was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m2) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m2). [25]

There are, however, no adequate and well-controlled studies of Drug “A” use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. [25]

1.5. COMMON ADVERSE EFFECTS: [27]

Significant laboratory changes that have been reported in adult and paediatric patients in clinical trials of Drug "A" without regard to drug relationship were:

Hepatic: Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH.

Hematologic: Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, decreased hematocrit, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocythemia, positive Coombs' test, and prolonged PT, and PTT.

Serum Chemistry: Hyperglycaemia, hypoglycaemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia.

Renal: Increases in BUN and creatinine.

Body: Localized abdominal pain, abdominal cramp, headache, monilia, generalized abdominal pain, asthenia, fever, fungal infection.

Digestive: Nausea, monilia, anorexia, dry mouth, stomatitis, pseudo membranous colitis.

Musculo-Skeletal: Myalgia.

Nervous: Hallucination, hyperkinesia, nervousness, somnolence.

Respiratory: Epistaxis, rhinitis.

Skin: Skin moniliasis, urticaria, fungal dermatitis, acne, exfoliative dermatitis, maculopapular rash.

Special Senses: Taste perversion.

1.6. INTERACTIONS FOR DRUG "A":

1.6.1. Antacids: [27]

Concomitant administration of high doses of antacids (sodium bicarbonate and aluminium hydroxide) or H_2 blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate of absorption is not altered by these concomitant medications. Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in T_{max}), but do not affect the extent of absorption (AUC).

1.6.2. Probenecid: [27]

As with other beta-lactam antibiotics, renal excretion of Drug "A" was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 20% increase in peak Drug "A" plasma levels.

1.6.3. Nephrotoxic drugs: [27]

Although nephrotoxicity has not been noted when Drug "A" was given alone, close monitoring of renal function is advised when Drug "A" is administered concomitantly with compounds of known Nephrotoxic potential.

2. DRUG PROFILE: DRUG “B”:

2.1. PHYSICAL PROPERTIES:

Table 6: Physical properties of Drug "B"

Molecular weight	361.37
State:	Off-white to yellow crystals (Solid)
Water solubility	25 mg/ml
Log P	1.49 ±0.79
pKa	6.8±0.3
Polarizability	34.82
Refractivity	62.34
Melting point	218°C
BCS Class	Class I
Polar surface area	73.3
Hydrogen acceptor count	5
Hydrogen donor count	1

2.2. PHARMACOKINETICS:

2.2.1. Absorption: [32]

Drug “B” is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one or two hours after dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of Drug “B” are both approximately 99%, demonstrating complete oral absorption of Drug “B”. Drug “B” pharmacokinetics is linear and predictable after single and multiple oral dosing regimens. Steady state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentration attained following multiple once-daily oral dosage regimens were approximately 5.7±1.4 and 0.5±0.2µg/ml after the 500mg doses, and 8.6±1.9

and 1.1±0.4 µg/ml after the 750 mg doses respectively. Oral administration of 500mg Drug "B" with food prolongs the time to peak concentration by approximately 1 hour & decreases the peak concentration by around 14%.

2.2.2. Distribution: [32]

The mean volume of distribution of Drug "B" generally ranges from 74 to 112L after single and multiple 500 mg and 750 mg doses, indicating widespread distribution into body tissues. Drug "B" reaches its peak level in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg Drug "B", respectively, to healthy subjects. Drug "B" also penetrates well into lung tissues. In vitro, over a clinically relevant range (1 to 10 µg/ml) of serum/plasma Drug "B" concentrations, Drug "B" is approximately 24 to 38% bound to serum proteins across all species studied, as determined by equilibrium dialysis method. Drug "B" is mainly bound to serum albumin in humans. Drug "B" binding to serum proteins is independent of the drug concentration.

2.2.3. Elimination: [32]

Drug "B" undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of the administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. The mean terminal plasma elimination half life of Drug "B" ranges from approximately 6 to 8 hours following single or multiple doses of Drug "B" orally or intravenously. The

mean apparent total body clearance and renal clearance range from approximately 144 to 226 ml/min and 96 to 142ml/min, respectively.

Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of Drug "B" occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximate 24% and 35% reduction in the Drug "B" renal clearance, respectively, indicating that excretion of Drug "B" occurs in the renal proximal tubule.

2.3. PHARMACODYNAMICS:

2.3.1. Mechanism of Action: [30]

Drug "B" inhibits bacterial type II topoisomerases, topoisomerase IV and DNA gyrase. Drug "B", like other fluoroquinolones, inhibits the A subunits of DNA gyrase, two subunits encoded by the gyrA gene. This results in strand breakage on a bacterial chromosome, supercoiling, and resealing; DNA replication and transcription are inhibited.

2.3.2. Indication: [32], [33]

Drug "B" is prescribed in Sinus infections, Bronchitis, Pneumonia, Skin infections, Urinary tract infections, Kidney infections, Prostate infections, Plague infections etc.

Table 7: Normally Prescribed Doses of Drug "B"

Type of Infection	Dose Every 24 hours	Duration (Days)
Nosocomial Pneumonia	750 mg	7-14
Community Acquired Pneumonia	500 mg/ 750 mg	7-14/5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10-14
Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7-14
Uncomplicated SSSI	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection or Acute Pyelonephritis	750 mg	5
Complicated Urinary Tract Infection or Acute Pyelonephritis	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Pediatric Patients < 50 kg and ≥ 6 months of age	(not to exceed 250 mg per dose)	60
Inhalational Anthrax (Post-Exposure)	500 mg	60
Adults and Pediatric Patients > 50 kg and ≥ 6 months of age	8 mg/kg BID	

2.3.3. Contraindications:

Drug “B” is contraindicated in persons with a history of hypersensitivity to Drug “B”, quinolone antimicrobial agents, and any other components of this product.

2.4. WARNINGS/ PRECAUTIONS:

2.4.1. Pregnancy: Category - C. [34]

Drug “B” was not teratogenic in rats at oral doses as high as 10 mg/kg/day, which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area.

There are however, no adequate and well-controlled studies in pregnant women. Drug "B" should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2.4.2. Nursing Mothers: [34]

Drug "B" has not been measured in human milk. Based upon data from Ofloxacin, it can be presumed that Drug "B" may be excreted in human milk. Hence, Drug "B" should be used if most necessary.

2.4.3. Paediatric Use: [34]

Safety and effectiveness on paediatric patients and adolescents < age of 18 years have not been established.

2.4.4. Geriatric Use: [34]

Elderly patients may even more susceptible to drug associated effects on the QT interval. Therefore, precaution should be taken when using Drug "B" with concomitant drugs that can result in prolongation of the QT interval (e.g. class A or class II antiarrhythmics) or in patients with risk factors for Torsades de pointes (e.g. known QT prolongation, uncorrected hypokalemia)**.**

2.5. COMMON ADVERSE EFFECTS: [33]

In clinical trials, the following events were considered likely to be drug elated in patients receiving Drug "B":

Nausea 1.5%, Diarrhoea 1.2%, Vaginitis 0.5%, Insomnia 0.4%, Abdominal pain 0.4%, Flatulence 0.2%, Pruritus 0.2%, Dizziness 0.3%, rash 0.3%, dyspepsia

0.3%, genital moniliasis 0.1%, moniliasis 0.2%, taste perversion 0.2%, vomiting 0.3%.

2.6. INTERACTIONS FOR DRUG "B": [33]

Antacid, Sucralfate, Metal Cations, Multivitamins may interfere with the gastrointestinal absorption of Drug "B", resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after Drug "B" administration.

2.6.1. Theophylline:

No significant effect of Drug "B" pharmacokinetics, however, concomitant administration of other quinolones with theophylline has ensured in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population.

2.6.2. Warfarin:

No significant effect of Drug "B" pharmacokinetics. But Drug "B" enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and Drug "B" use have been associated with episodes of bleeding.

2.6.3. Cyclosporine:

No significant effect of Drug "B" pharmacokinetics. But elevated serum levels of cyclosporine have been reported when co-administered with some other quinolone.

2.6.4. Digoxin:

No significant effect of Drug "B" pharmacokinetics.

2.6.5. Probenecid and Cimetidine:

No significant effect of Drug "B" pharmacokinetics.

2.6.6. NSAIDs:

The concomitant administration of a non-steroidal anti-inflammatory drug with Drug "B" may increase the risk of CNS stimulation and convulsive seizures.

2.6.7. Antidiabetic agents:

Disturbances of blood glucose, including hyperglycaemia and hypoglycaemia, have been reported in patients treated concomitantly with quinolone and an Antidiabetic agent.

3. EXCIPIENT PROFILE:

3.1. MICROCRYSTALLINE CELLULOSE: [49], [50]

- ***Non-proprietary Names:***

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

- ***Synonyms:***

Avicel PH; Cellets; Celex; Cellulose gel; Hellulosum microcristalli-num; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

- ***Chemical Name and CAS Registry Number:***

Cellulose [9004-34-6]

- ***Empirical Formula and Molecular Weight:***

$(C_6H_{10}O_5)$ n 36000 where n=220.

- ***Structural Formula:***

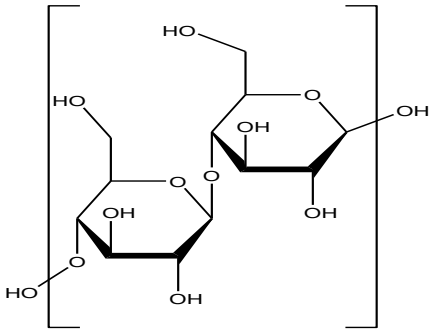


Figure 8: Structural formula of microcrystalline cellulose

- ***Functional Category:*** Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
- ***Applications in Pharmaceutical Formulation or Technology:*** Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, micro-crystalline cellulose also has some lubricant and disintegrant properties that make

it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 8: Uses of Microcrystalline Cellulose

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

- ***Typical Properties:***

Table 9: Typical properties of Microcrystalline Cellulose

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-102	100	60	⩽8.0	⩽5.0
		200	⩾45.0	
Avicel PH-103	50	60	⩽1.0	⩽3.0
		200	⩽30.0	
Avicel PH-105	20	400	⩽1.0	⩽5.0
Avicel PH-112	100	60	⩽8.0	⩽1.5
Avicel PH-113	50	60	⩽1.0	⩽1.5
		200	⩽30.0	
Avicel PH-200	180	60	⩾10.0	⩽5.0
		100	⩾50.0	
Avicel PH-301	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-302	100	60	⩽8.0	⩽5.0
		200	⩾45.0	

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

3.2. MAIZE STARCH: [49], [51]

- ***Non-proprietary Names:***

USP: Absorbable Dusting Powder

- ***Synonyms:***

Bio-sorb; double-dressed, white maize starch; Fluidamid R444P; Keoflo ADP; Meritena; modified starch dusting powder; Pure-Dent B851; starch-derivative dusting powder; Sterilizable corn starch.

- ***Chemical Name and CAS Registry Number:***

Sterilizable maize starch

- ***Empirical Formula and Molecular Weight:***

$(C_6H_{10}O_5)$ n where n= 300–1000

- ***Structural Formula:***

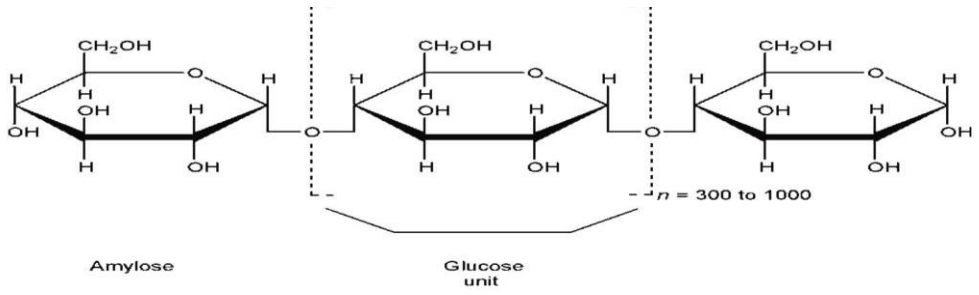


Figure 9: Structural formula of Starch

- ***Functional Category:*** Diluent; lubricant.

- ***Applications in Pharmaceutical Formulation or Technology:*** Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix, and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w; a typical concentration is 15%.

When using starch, a prior granulation step is required in most cases to avoid problems with insufficient flow and segregation. A starch–lactose compound has been introduced enabling the use of granular starch in direct compression, improving the tableting process and the disintegration time of the tablets. However, starch that is not pregelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations. Balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting.

Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerine. Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems. The retrogradation of starch can be used to modify the surface properties of drug particles. Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion, and they can improve the bioavailability of poorly soluble drugs.

Starch, particularly rice starch, has also been used in the treatment of children's diarrheal diseases. Specific starch varieties with high amylose content (resistant starches) are used as insoluble fibre in clinical nutrition, and also for colon-targeting applications. Due to their very high gelatinization temperature, these starches are used in extrusion/ spheronization processes. Starches with high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.

Native starches conforming to pharmacopeial specifications are used as the raw materials for the production of starch-based excipients and active pharmaceutical ingredients, frequently covered with their own pharmacopeial monographs.

- ***Description:*** Sterilizable maize starch occurs as an odourless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

- ***Typical Properties:***

Acidity/alkalinity: pH = 9.5–10.8 for a 10% w/v suspension at 258^0C.

Density: 1.48g/ cm^3

Density (bulk): 0.47–0.59g/cm^3

Density (tapped): 0.64–0.83g/cm^3

Flowability: 24–30% (Carr compressibility index)

Moisture content: 10–15%

Particle size distribution: 6–25mm; median diameter is 16mm.

Solubility: Very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.

Specific surface area: 0.50–1.15m^2/g

- ***Stability and Storage Conditions:*** Sterilizable maize starch may be sterilized by autoclaving at 121^0C for 20 minutes, by ethylene oxide, or by irradiation. Sterilizable maize starch should be stored in a well-closed container in a cool, dry place.

3.3. COLLOIDAL SILICON DIOXIDE: [49], [52]

- ***Non-proprietary Names:***

BP: Colloidal Anhydrous Silica

JP: Light Anhydrous Silicic Acid

PhEur: Silica, Colloidal Anhydrous

USP-NF: Colloidal Silicon Dioxide

- ***Synonyms:***

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica

sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

- ***Chemical Name and CAS Registry Number:***

Silica [7631-86-9]

- ***Empirical Formula and Molecular Weight:***

SiO_2 60.08

- ***Structural Formula:***

Figure 10: Structural formula of Silicon dioxide

- ***Functional Category:*** Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology: Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Table 10: Use of Silicon dioxide

Use	Concentration (%)
Aerosols	0.5–2.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–1.0
Suspending and thickening agent	2.0–10.0

- ***Description:*** Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15nm. It is a light, loose, bluish-white-colored, odourless, tasteless, amorphous powder.
- ***Typical Properties:***

Acidity/alkalinity: pH= 3.8–4.2 (4%w/v aqueous dispersion) and 3.5–4.0 (10% w/v aqueous dispersion) for Cab-O-Sil M-5P

Density (bulk): 0.029–0.042g/cm^3

Melting point: 1600^0C

Particle size distribution: Primary particle size is 7–16nm.Aerosil forms loose agglomerates of 10–200mm.

Refractive index: 1.46

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. It forms a colloidal dispersion with water. For Aerosil, solubility in water is 150mg/L at 25^0C (pH 7).

Specific gravity: 2.2

Specific surface area: 100–400m^2/g depending on grade.

Several grades of colloidal silicon dioxide are commercially available, which are produced by modifying the manufacturing process. The modifications do not affect the silica content, specific gravity, refractive index, colour, or amorphous form. However, particle size, surface areas, and densities are affected.

- ***Stability and Storage Conditions:***

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.

- ***Incompatibilities:*** Incompatible with diethylstilbestrol preparations.

3.4. CROSCARMELLOSE SODIUM: [49], [53]

- ***Non-proprietary Names:***

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

- ***Synonyms:*** Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium;Explocel; modified cellulose gum;Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

- ***Chemical Name and CAS Registry Number:***

Cellulose, carboxymethyl ether, sodium salt, cross linked [74811-65-7]

- ***Empirical Formula and Molecular Weight:***

Croscarmellose sodium is a cross linked polymer of carboxymethyl-cellulose sodium.

- ***Structural Formula:***

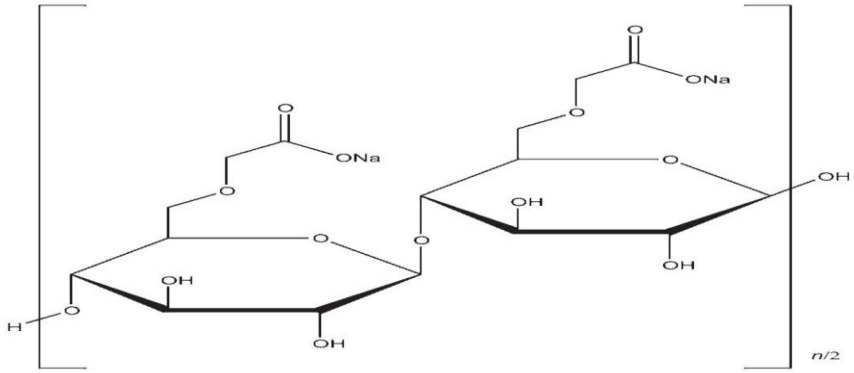


Figure 11: Structural formula of Croscarmellose Sodium

- ***Functional Category:*** Tablet and capsule disintegrant.

- ***Applications in Pharmaceutical Formulation or Technology:***

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table 11: Use of Croscarmellose Sodium

Use	Concentration (%)
Disintegrant in capsules	10–25
Disintegrant in tablets	0.5–5.0

- ***Description:***

Croscarmellose sodium occurs as an odourless, white or grayish-white powder.

- ***Typical Properties:***

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Bonding index: 0.0456

Brittle fracture index 0.1000

Density (bulk): 0.529g/cm^3 for Ac-Di-Sol

Density (tapped): 0.819 g/cm^3 for Ac-Di-Sol

Density (true): 1.543 g/ cm^3 for Ac-Di-Sol

Particle size distribution: Ac-Di-Sol: not more than 2% retained on#200 (73.7mm) mesh and not more than 10% retained on a #325 (44.5mm) mesh.

Solubility: Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. It is practically insoluble in acetone, ethanol and toluene.

Specific surface area: 0.81–0.83m^2/g

- ***Stability and Storage Conditions:***

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

- ***Incompatibilities:***

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminium, mercury, and zinc.

3.5. SODIUM LAURYL SULPHATE: [49], [54], [55]

- ***Non-proprietary Names:***

BP: Sodium Lauryl Sulphate

JP: Sodium Lauryl Sulfate

PhEur: Sodium Laurilsulfate

USP-NF: Sodium Lauryl Sulfate

- ***Synonyms:***

Dodecyl alcohol hydrogen sulfate, sodium salt; dodecyl sodium sulfate; dodecylsulfate sodium salt; Elfan 240; lauryl sodium sulfate; lauryl sulfate, sodium salt; monododecyl sodium sulfate; natrii laurilsulfas; sodium dodecyl sulfate; sodium n-dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; SDS; SLS; sulfuric acid monododecyl ester, sodium salt; Texapon K12P.

- ***Chemical Name and CAS Registry Number:***

Sulfuric acid monododecyl ester sodium salt (1: 1) [151-21-3]

- ***Empirical Formula and Molecular Weight:***

$C_{12}H_{25}NaO_4S$ 288.38

The USP32–NF27 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate [CH_3 $(CH_2)_{10}CH_2OSO_3Na$].

The PhEur 6.0 states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$.

- ***Structural Formula:***

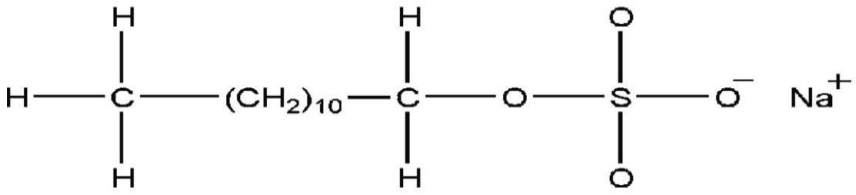


Figure 11: Structural formula of Sodium Lauryl Sulphate

- ***Functional Category:***

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

- ***Applications in Pharmaceutical Formulation or Technology:***

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non parenteral pharmaceutical formulations and cosmetics.

It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins; and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).

Table 12: Use of Sodium Lauryl Sulphate

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5–2.5
Detergent in medicated shampoos	≈10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0–2.0
Wetting agent in dentrifices	1.0–2.0

- ***Description:***

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odour of fatty substances.

- ***Typical Properties:***

Acidity/alkalinity: pH = 7.0–9.5 (1% w/v aqueous solution)

Acid value: 0

Antimicrobial activity: Sodium lauryl sulfate has some bacterio-static action against Gram-positive bacteria but is ineffective against many Gram-negative microorganisms. It potentiates the fungicidal activity of certain substances such as sulphanilamide and sulfathiazole.

Critical micelle concentration: 8.2mmol/L (2.365g/L) at 208C

Density: 1.07g/ cm^3 at 208C

HLB value: ≈40

Interfacial tension: 11.8mN/m (11.8dynes/cm) for a 0.05% w/v solution (unspecified nonaqueous liquid) at 308C.

Melting point: 204–2078C (for pure substance)

Moisture content: 45%; sodium lauryl sulfate is not hygroscopic.

Solubility: Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Spreading coefficient: -7.0 (0.05% w/v aqueous solution) at 30^0C

Surface tension: 25.2mN/m (25.2dynes/cm) for a 0.05% w/v aqueous solution at 308C

Wetting time (Draize test): 118 seconds (0.05% w/v aqueous solution) at 30^0C

- ***Stability and Storage Conditions:***

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e. pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

Incompatibilities:

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions. Sodium lauryl sulfate is incompatible with salts of polyvalent metal ions, such as aluminium, lead, tin or zinc, and precipitates with potassium salts. Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminium.

- ***Safety:***

Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop. Prolonged inhalation of sodium

lauryl sulfate will damage the lungs. Pulmonary sensitization is possible, resulting in hyperactive airway dysfunction and pulmonary allergy. Animal studies have shown intravenous administration to cause marked toxic effects to the lung, kidney, and liver. Mutagenic testing in bacterial systems has proved negative. Adverse reactions to sodium lauryl sulfate in cosmetics and pharmaceutical formulations mainly concern reports of irritation to the skin or eyes following topical application. Sodium lauryl sulfate should not be used in intravenous preparations for humans. The probable human lethal oral dose is 0.5–5.0g/kg body-weight.

- ***Handling Precautions:***

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation and contact with the skin and eyes should be avoided; eye protection, gloves, and other protective clothing, depending on the circumstances, are recommended. Adequate ventilation should be provided or a dust respirator should be worn. Prolonged or repeated exposure should be avoided. Sodium lauryl sulfate emits toxic fumes on combustion.

3.6. POLYVINYLPYRROLIDONE: [49], [56]

- ***Non-proprietary Names:***

BP: Povidone

JP: Povidone

PhEur: Povidone

USP: Povidone

- ***Synonyms:***

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; povidonum; Povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

- ***Chemical Name and CAS Registry Number:***

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

- ***Empirical Formula and Molecular Weight:***

(C6H9NO) n 2500–3000000

The USP 32 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, in the range 10–120. The K-value is calculated using Fikentscher's equation:

$$\log z = c\left[\frac{75k^2}{1+1.5kc}\right]+k$$

; Where z is the relative viscosity of the solution of concentration (in %w/v), and k is the K-value X 10^{-3}. Alternatively, the K-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c\log z\,(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

Where z is the relative viscosity of the solution of concentration "c" (in % w/v); approximate molecular weights for different povidone grades are shown in following table.

Table 13: K values and approximate molecular weight of different grade of Polyvinylpyrrolidone

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

- ***Structural Formula:***

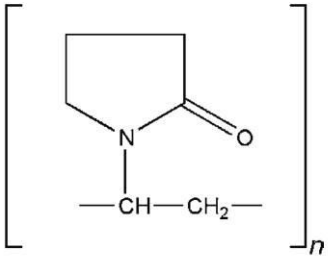


Figure 12: Structural formula of Polyvinylpyrrolidone

- ***Functional Category:*** Disintegrant; dissolution enhancer; suspending agent; tablet binder.

- ***Applications in Pharmaceutical Formulation or Technology:***

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.

Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads. Povidone

is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Table 14: Use of Polyvinylpyrrolidone

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

- ***Description:***

Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

- ***Typical Properties:***

Acidity/alkalinity: pH= 3.0–7.0 (5%w/v aqueous solution); pH= 4.0–7.0 (5% w/v aqueous solution) for Povipharm K90.

Density (bulk): 0.29–0.39g/cm^3 for Plasdone.

Density (tapped): 0.39–0.54g/$cm^3$for Plasdone.

Density (true): 1.180g/ cm^3

Melting point: Softens at 150^0C.

Moisture content: Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Particle size distribution:

Kollidon 25/30: 90% >50mm, 50%>100mm, 5%>200mm; Kollidon 90: 90% >200mm, 95%>250mm.

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic): The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Table 15: Dynamic viscosity of different grades of Polyvinylpyrrolidone

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

- ***Stability and Storage Conditions:***

Povidone darkens to some extent on heating at 150^0C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130^0C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

- ***Incompatibilities:***

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

- ***Safety:***

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone addition-ally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone. Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25mg/kg body-weight.

- ***Handling Precautions:***

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

3.7. MAGNESIUM STEARATE: [49], [57]

- ***Non-proprietary Names:***

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

- ***Synonyms:***

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

- ***Chemical Name and CAS Registry Number:***

Octadecanoic acid magnesium salt [557-04-0]

- ***Empirical Formula and Molecular Weight:***

$C_{36}H_{70}MgO_4$ 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

- ***Structural Formula:***

$[CH_3 (CH_2)_{16}COO]$ 2Mg

- ***Functional Category:*** Tablet and capsule lubricant.

- ***Applications in Pharmaceutical Formulation or Technology:***

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

- ***Description:***

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

- ***Typical Properties:***

Crystalline forms High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): $0.159 g/cm^3$

Density (tapped): $0.286 g/cm^3$

Density (true): $1.092 g/ cm^3$

Flash point: 250^0C

Flowability: Poorly flowing, cohesive powder.

Melting point range: $117^0C–150^0C$ (commercial samples).

$26–130^0C$ (high purity magnesium stearate).

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area: $1.6–14.8 m^2/g$

- ***Stability and Storage Conditions:***

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

- ***Incompatibilities:***

It is incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

- ***Safety:***

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition.

Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.

Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.

- ***Handling Precautions:***

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended. In the USA, the OSHA limit is $10mg/m^3$ TWA for magnesium stearate.

Chapter 5

PREFORMULATION STUDIES

1. DEFINITION AND OBJECTIVES
2. PROPERTIES OF API
3. DRUG SUBSTANCE AND EXCIPIENT COMPATIBILITY STUDIES

1. DEFINITION AND OBJECTIVES OF PRE-FORMULATION STUDIES:

1.1.DEFINITION: Pre-formulation is defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients.

1.2.OBJECTIVE: To generate information to the formulator in developing stable and bio-available dosage forms that can be mass-produced.

1.3.SCOPE: The use of Pre-formulation parameters maximizes the chance in formulating an acceptable, safe, efficacious and stable product.

For a drug substance to formulate into a dosage form it is necessary to study following:

- Physico-chemical parameters of the bulk drug
- Drug-Excipient compatibility study

A detailed understanding of the properties of the drug substances is essential for minimizing formulation problems in later stage of drug development which will ultimately help in reducing the drug development cost and in decreasing the product time to reach in market (i.e. , from drug substance to drug product).

The goal of the Pre-formulation study is to choose the correct form of the drug substance, to evaluate the physicochemical properties of drug, to check the compatibility of drug substances with various excipients and to generate a thorough understanding of the materials stability under the condition that will lead to development of an optimal drug delivery system.

2. PROPERTIES OF API:

2.1.DESCRIPTION:

Drug “A” a white to light brownish-white powder, odourless or having a faint odour.

Drug "B" is slight yellow crystalline powder, odourless and bitter in taste.

2.2.MELTING POINT:

"The melting point of a solid is the temperature at which the vapour pressure of the solid and the liquid are equal**"** i.e. "Temperature at which the material changes from a solid to a liquid state".

2.2.1. Rationale for melting point study: A pure substance melts at a precisely defined temperature, characteristic of every crystalline substance and dependent only on pressure (though the pressure dependency is generally considered insignificant). Determining the MP is a simple and fast method used in many diverse areas of chemistry to obtain a first impression of the purity of a substance. This is because even small quantities of impurities change the melting point, or at least clearly enlarge its melting range. The test is still an important technique for gauging purity of organic and pharmaceutical compounds.

2.2.2. **Types of melting point *apparatus*:** Four types of melting point apparatuses are:

- Thiele tube.
- Fisher-Johns apparatus
- Gallenkamp (Electronic) melting point apparatus and
- automatic melting point apparatus.

2.3.SOLUBILITY:

Solubility of a drug is a critical parameter deciding the ultimate dissolution rate of the active from the formulation.

Drug "A" is very slightly soluble in water; freely soluble in dehydrated alcohol; soluble in acetonitrile and in methyl alcohol; slightly soluble in ether.

Drug "B" is slightly soluble in methanol, sparingly soluble in acetic acid as well as in chloroform, soluble in dilute sodium hydroxide solution.

2.4.POWDER FLOW PROPERTIES:

- Bulk density
- Tapped density
- Compressibility Index (CI)
- Hausner's Ratio
- Angle of Repose
- Loss on Drying

***2.4.1. Bulk density*:** Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3. The bulk density of a powder primarily depends on particle size distribution, 'particle shape and the tendency of particles to adhere together. There are two types of bulk density. The particles are pack in such a way so as to leave large gaps between their surfaces 'resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important to choose the size of blending equipment.

$$\text{Bulk Density (BD)} = \frac{\text{Mass of Powder}}{\text{Bulk volume}}$$

It is determined by USP Bulk density Tapped density apparatus.

***2.4.2. Tapped density*:** It is defined as the ratio of mass of the powder taken to the volume occupied after specified tapping (500→ 750 →1250).

$$\text{Tapped Density (TD)} = \frac{\text{Mass of Powder}}{\text{Tapped volume}}$$

It is determined by USP Bulk density Tapped density apparatus.

2.4.3. Compressibility index (C.I): The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Compresibility Index (CI)} = \frac{\text{TD} - \text{BD}}{\text{TD}} \text{X100\%}$$

2.4.4. Hausner's ratio: The Hausner's ratio has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed Hausner's ratio.

$$\text{Hausner's ratio (HR)} = \frac{\text{TD}}{\text{BD}}$$

Table 16: USP limits for compressibility index & Housner's ratio

S. No.	CI (%)	Flow character	HR
1.	<10	Excellent	1.00-1.11
2.	11-15	Good	1.12-1.18
3.	16-20	Fair	1.19-1.25
4.	21-25	Passable	1.26-1.34
5.	26-31	Poor	1.35-1.45
6.	32-37	Very Poor	1.46-1.59
7.	>38	Very Very Poor	>1.60

2.4.6. Loss on drying: LOD is also an important property of blend because it influences the compaction and flow property, therefore hardness and disintegration has been also affected. Around 1g of blend examined in apparatus at temperature 60ºc, 80ºc, 105ºc etc. (depends on API melting point). Generally it should be <5%.

Procedure: This was determined by weighing 1gm of sample in LOD apparatus Sartorius-MA45 at 80°C.

Conclusion: From the above study, it was seen that both the drugs are having very poor flow properties.

3. DRUG SUBSTANCE AND EXCIPIENT COMPATIBILITY STUDIES:

3.1.PLAN FOR VISUAL OBSERVATION STUDY:

- ✓ API alone.
- ✓ API + individual excipients in proportion intended in the finished dosage form.
- ✓ API alone + water.
- ✓ API + Individual Excipients + water.

Based on the literature study, composition of API & Excipients in terms of w/w of the target wt. of tablet may be varied. Weight of API quantity + excipient quantity will be in the range of 100-500mg for compatibility study.

The following excipients were selected for the study: *Maize starch, MCC PH 112, Aerosil, SLS, Croscarmellose sodium, Monosodium citrate, PVP K30, Magnesium Stearate, HPMC, TiO_2, Purified Talc, Ferric oxide yellow.*

3.2.PROCEDURE:

API and excipients were thoroughly mixed in the predetermined ratio as given in tables and passed through 40# sieve and the blend was filled in the glass vials and were closed with the rubber stopper and further sealed with the aluminium seal and charged.

The blends of individual drug substance and excipients were subjected to various conditions of temperature and humidity like 40°C± 2°C/ 75% RH ± 5% RH; 55°C as shown in below Table, to evaluate the compatibility.

Mixtures were kept in dry condition in sealed clear glass vials. Initial observation of samples were taken and observed every week up to 2 weeks for change in their appearance, colour and odour.

The results of this test are given in Table No 30 to 35 in chapter 8.

Table 17: Drug excipient ratios for pre-formulation study

Sample ID	API	Excipient	API Excipient Ratios in mg
1	Drug "A"	Maize starch,	274:100
2	Drug "A"	MCC PH 112	274:400
3	Drug "A"	Aerosil	274:50
4	Drug "A"	SLS	274:50
5	Drug "A"	Croscarmellose sodium	274:100
6	Drug "A"	Monosodium citrate	274:50
7	Drug "A"	PVP K30	274:36
8	Drug "A"	Magnesium Stearate	274:20
9	Drug "A"	HPMC	274:40
10	Drug "A"	TiO_2	274:40
11	Drug "A"	Talc	274:20
12	Drug "A"	Ferric oxide yellow	274:10
13	Drug "B"	Maize starch,	259:100
14	Drug "B"	MCC PH 112	259:400
15	Drug "B"	Aerosil	259:50

16	Drug "B"	SLS	259:50
17	Drug "B"	Croscarmellose sodium	259:100
18	Drug "B"	Monosodium citrate	259:50
19	Drug "B"	PVP K30	259:36
20	Drug "B"	Magnesium Stearate	259:20
21	Drug "B"	HPMC	259:40
22	Drug "B"	TiO_2	259:40
23	Drug "B"	Talc	259:20
24	Drug "B"	Ferric oxide yellow	259:10
25	Drug "A" + Drug "B"	Maize starch,	274:259:100
26	Drug "A" + Drug "B"	MCC PH 112	274:259:400
27	Drug "A" + Drug "B"	Aerosil	274:259:50
28	Drug "A" + Drug "B"	SLS	274:259:50
29	Drug "A" + Drug "B"	Croscarmellose sodium	274:259:100
30	Drug "A" + Drug "B"	Monosodium citrate	274:259:50
31	Drug "A" + Drug "B"	PVP K30	274:259:36
32	Drug "A" + Drug "B"	Magnesium Stearate	274:259:20
33	Drug "A" + Drug "B"	HPMC	274:259:40
34	Drug "A" + Drug "B"	TiO_2	274:259:40
35	Drug "A" + Drug "B"	Talc	274:259:20
36	Drug "A" + Drug "B"	Ferric oxide yellow	274:259:10

3.3.EVALUATION CRITERIA:

3.3.1. Physical observation: (Visual)

- ✓ Caking
- ✓ Liquefaction
- ✓ Discoloration/Color Development

Any sample showing above physical observation on 55°C as well as lower temperatures, the sample combination will be not taken for further study.

Chapter 6

MATERIALS AND EQUIPMENTS USED

1. MATERIALS REQUIRED
2. EQUIPMENTS USED

1. MATERIALS REQUIRED:

Based on the above compatibility study we have selected the following materials for our further study:

Table 18: List of Excipient selected for Pre-formulation studies

Sl. No.	Name of Excipient	Function	Supplier/ Batch No.
1	Drug "A"	API	Covalent Labs Pvt. Ltd.
2	Drug "B"	API	Zhejiang Apeloa Kangyu Pharmaceutical Co.
3	Maize starch	Diluent/ lubricant	Roquette Freres
4	MCC	Disintegrant/ Diluent	Ranq Remedies Pvt. Ltd.
5	Aerosil	Glidant/ tablet disintegrant	Evonic Degussa Corporation
6	SLS	Lubricant/ wetting agent	Cognis GmbH
7	Croscarmellose sodium	Disintegrant	Maruti Fine chemicals
8	Monosodium Citrate	Buffering agent	Amijal Chemicals
9	PVP K30	Disintegrant/ dissolution enhancer/ suspending agent/ tablet binder	Nanhangh Industrial Co. Ltd.
10	Magnesium stearate	Lubricant	S. Kant Healthcare Ltd.
11	HPMC	Coating agent/ film-former	Dow Chemicals
12	Purified talc	Adsorbent	Vijay Minerals.
13	TiO_2	Coating agent/ opacifier/ pigment	Kronos International
14	Ferric Oxide Yellow	Coat Color	Neelikon Food Dye & Chemical Limited.

2. EQUIPMENTS USED:

In the study following equipments were used:

Table 19: List of equipments used

S. No.	EQUIPMENT	MANUFACTURER
1.	Electronic weighing balance	Afcoset
2.	B.D. / T.D. Test apparatus	Electrolab
3.	LOD Apparatus	Sartorius-MA45
4.	Rotary tablet Compression machine	Elliza Press (Mitsubishi)
5.	Hardness tester	Schleuniger
6.	Friabilator (USP)	Electrolab
7.	Dissolution apparatus	Electrolab
8.	Vernier caliper	Mitotoyu
9.	Tray Dryer	Alkemy
10.	Fluidized Bed Dryer	Alliance Engineering Co.
11.	RMG	Sainath / Gansons
12.	Stirrer	Remi motors
13.	Colloidal mill	Avon equipments
14.	Homogenizer	Remi motors
15.	Conventional coating Pan	GMI
16.	Melting point apparatus	Bellstone
17.	Humidity tester	Sartorius Ltd.
18.	Sonicator	Accurate labs
19.	Dehumidifier	Alkemy
20.	Strip packaging machine	Gansons Pvt. Ltd.
22.	HPLC	Agilant Technologies

Chapter 7

EXPERIMENTAL WORK

1. FEASIBILITY TRIAL 01
2. FEASIBILITY TRIAL 02
3. FEASIBILITY TRIAL 03
4. FEASIBILITY TRIAL 04
5. FEASIBILITY TRIAL 05
6. REPRODUCIBLE BATCH
7. PROCESS OPTIMIZATION BATCH
8. POST COMPRESSION PARAMETERS
9. ACCELERATED STABILITY STUDY

On the basis of review of literature and pre-formulation studies of API and excipients, the feasibility trials were initiated. The formulation trials were aimed to achieve a stable and reproducible formulation with good release profile of the APIs.

1. FEASIBILITY TRIAL 01:

Batch size: 300 Bi-layer Tablets.

Objective: To take a trial batch for method development to formulate bi-layer tablet.

Table 20: Batch plane for Feasibility Trial 1

TRIAL 1	Ingredients	mg/tab	%	g/300 tab
1st Layer	Drug "A"	290.08	32.23	87.02
	Maize starch	10	1.11	3.00
	MCC PH 112	117.92	13.10	35.38
	Aerosil	10	1.11	3.00
	SLS	10	1.11	3.00
	Croscarmellose sodium	25	2.78	7.50
	PVP K30	12	1.33	3.60
	Mag. Stearate	5	0.56	1.50
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	7.5	0.83	2.25
	MCC PH 112	13.5	1.50	4.05
	Aerosil	2	0.22	0.60
	Lubrication			
	Mag. Stearate	2	0.22	0.60
2nd Layer	Drug "B"	256.92	28.55	77.08
	Maize starch	15	1.67	4.50
	MCC PH101	60	6.67	18.00

	Aerosil	8	0.89	2.40
	Croscarmellose sodium	15.08	1.68	4.52
	Granulation			
	HPC-L	5	0.56	1.50
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	8	0.89	2.40
	MCC PH112	13	1.44	3.90
	Aerosil	2	0.22	0.60
	Lubrication			
	Mag. Stearate	2	0.22	0.60
	Wt. of uncoated tablet	**900**		270.00

1.1.GRANULATION PROCEDURE (AREA MAINTAINED AT RH BELLOW 35%):

Granulation of Drug "A" part was done by dry granulation (roll compaction) process and granulation Drug "B" part was done by wet granulation (non aqueous) process.

1.1.1. Granulation of Drug "A" part by roll compaction:

a) Drug "A" and all excipients were accurately weighed as per given formulae of trial 1.

b) Drug "A" was sifted through sieve #20 ASTM. All other ingredients except magnesium stearate were passed through #40 ASTM.

c) Aerosil was co-sifted with MCC PH112.

d) Magnesium stearate was sifted through sieve #60 ASTM.

e) All the sifted ingredients were thoroughly mixed in a polyethylene bag for 10min.

f) Then the powder mixer compacted to form compacts in a roll compactor at 3 ton pressure and 3-4 RPM.

g) The compacts were collected and crashed to form granules.

h) Sizing of the granules were done by passing the compacts through sieves kept in a series of #8→#12→#16→#20. Finally the granules were separated from fines by a #60 ASTM sieve.

i) Ratio between the #60 retained granule and #60 passed fines were determined.

j) The fine collected from the above step was again passed through the roll compactor and the whole process was repeated until a desirable ratio of granules and fines were obtained.

k) Then the granules and fines were mixed thoroughly for next processes.

1.1.2. Pre-lubrication of Granules of Drug "A" part:

l) All the ingredients of the pre-lubrication part of the formula were passed through #40 ASTM and were mixed for 10 min with the above prepared granules in the same polyethylene bag.

m) TD, BD, CI and HR of the pre-lubricated bland were determined.

1.1.3. Lubrication of Granules of Drug "A" part:

n) Magnesium stearate was sifted through #60 and was mixed with a little amount of the pre-lubricated blend.

o) Then the magnesium stearate containing blend was direct added to the rest of the blend and mixed for another 3 min.

p) TD, BD, CI and HR of the lubricated blend were determined.

1.1.4. Granulation of Drug "B" part by wet granulation:

a) Drug "B" and all excipients were accurately weighed as per given formulae of trial 1.

b) Drug "B" was sifted through sieve #20 ASTM. All other ingredients were passed through #40 ASTM.

c) Aerosil was co-sifted with MCC PH112.

d) All the sifted ingredients were thoroughly mixed in a polyethylene bag for 10min.

e) The powder mixture was taken in a stainless steel bowel.

f) HPC-L was dissolved in IPA with stirring.

g) HPC-L solution was gradually added to the above powder mixture to form a wet mass.

h) The wet mass was then passed through #8 ASTM sieve to obtain larger size granules.

i) Granules were dried in a fluidized bed dryer initially at room temperature and after 10min with hot (45°C) air.

1.1.5. Pre-lubrication of Granules of Drug "B" part:

j) All the ingredients of the pre-lubrication part of the formula were passed through #40 ASTM and were mixed for 10 min with the above prepared granules in the same polyethylene bag.

k) TD, BD, CI and HR of the pre-lubricated bland were determined.

1.1.6. Lubrication of Granules of Drug "B" part:

l) Magnesium stearate was sifted through #60 and was mixed with a little amount of the pre-lubricated blend.

m) Then the magnesium stearate containing blend was direct added to the rest of the blend and mixed for another 10 min.

n) TD, BD, CI and HR of the lubricated blend were determined.

1.2.Observations:

- ✓ The wet granulation of Drug "B" part becomes problematic as the #8 passed granules becomes agglomerated soon.
- ✓ The wet mass is too much sticky and loss is very high.

1.3.CONCLUSION:

Wet granulation of Drug "B" part with IPA and HPC-L was not satisfactory.

1.4.PLAN OF ACTION:

Wet granulation of Drug "B" part with IPA and PVP K30 was selected for the next trial.

2. FEASIBILITY TRIAL 02:

Batch size: 300 Bi-layer Tablets.

Objective: To take a trial batch with PVP K30 instead of HPC-L as binder.

Table 21: Batch plane for Feasibility Trial 2

TRIAL 2	Ingredients	mg/tab	%	g/300 tab
1st Layer	Drug "A"	290.08	32.23	87.024
	Maize starch	10	1.11	3
	MCC PH 112	117.92	13.10	35.376
	Aerosil	10	1.11	3
	SLS	10	1.11	3
	Croscarmellose sodium	25	2.78	7.5
	PVP K30	12	1.33	3.6
	Mag. Stearate	5	0.56	1.5
	Pre-lubrication			

	SLS	5	0.56	1.5
	Croscarmellose sodium	7.5	0.83	2.25
	MCC PH 112	13.5	1.50	4.05
	Aerosil	2	0.22	0.6
	Lubrication			
	Mag. Stearate	2	0.22	0.6
2nd Layer	Drug "B"	256.92	28.55	77.076
	Maize starch	15	1.67	4.5
	MCC PH101	60	6.67	18
	Aerosil	8	0.89	2.4
	Croscarmellose sodium	15.08	1.68	4.524
	Granulation			
	PVP K30	5	0.56	1.5
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	1.5
	Croscarmellose sodium	8	0.89	2.4
	MCC PH112	13	1.44	3.9
	Aerosil	2	0.22	0.6
	Lubrication			
	Mag. Stearate	2	0.22	0.6
	Wt. of uncoated tablet	**900**		270

2.1.GRANULATION PROCEDURE: Same steps of trial 1 were followed for the preparation of granules. The only difference was, PVP K30 was dissolved in IPA and was used as binder solution in the granulation process of the Drug "B".

2.2.COMPRESSION OF TABLETS:

With the lubricated granules of Drug "A" and Drug "B", bi-layer tablets were prepared with 19X9 mm, capsule shaped punches, having break-line on one surface, plain on the other in a bi-layer tablet compression machine.

The two feeding hoppers of the machine were filled with the prepared granules in each side. Only one punch was used for the compression. Compression RPM was kept between 4 and 6.

2.3.IPQC TESTS:

Following In Process Quality Control (IPQC) tests were performed with the compressed tablets.

2.3.1. **Weight Variation test:** Tablet weights were taken at a regular interval to determine the possible weight variation.

2.3.2. **Hardness:** Tablets were compressed in 3 harnesses, i.e. higher hardness, Optimum hardness and lower hardness. Hardness of the tablets was tested by UPS digital hardness testing apparatus.

2.3.3. **Disintegration time (DT):** 6 tablets, of all hardness were placed in the tubes of a USP DT apparatus with distilled water as the disintegration media, and the time required for the disintegration was observed.

2.3.4. **Friability:** 10tablets, of all hardness were weighed and its friability was tested in a USP friability apparatus for 100 rotations.

2.4.OBSERVATION:

- ✓ Sticking was observed.

✓ Weight variation was observed.

2.5.PLAN OF ACTION:

Tablets were not coated in this trial. Samples for long term stability study were also not submitted. It was decided that amount of Lubricant (Magnesium stearate) in lubrication step of both of the Drug granules to be increased in next trial.

3. FEASIBILITY TRIAL 03:

Batch size: 300 Bi-layer Tablets.

Objective: To take a trial batch with increased amount of Magnesium stearate in lubrication step.

Table 22: Batch plane for Feasibility Trial 3

TRIAL 3	Ingredients	mg/tab	%	g/300 tab
1st layer	Drug "A"	290.08	32.23	87.02
	Maize starch	10	1.11	3.00
	MCC PH 112	117.92	13.10	35.38
	Aerosil	10	1.11	3.00
	SLS	10	1.11	3.00
	Croscarmellose sodium	25	2.78	7.50
	PVP K30	12	1.33	3.60
	Mag. Stearate	5	0.56	1.50
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	7.5	0.83	2.25
	MCC PH 112	8.5	0.94	2.55
	Aerosil	4	0.44	1.20

	Lubrication			
	Mag. Stearate	5	0.56	1.50
2nd Layer	Drug "B"	256.92	28.55	77.08
	Maize starch	15	1.67	4.50
	MCC PH101	60	6.67	18.00
	Aerosil	8	0.89	2.40
	Croscarmellose sodium	15.08	1.68	4.52
	Granulation			
	PVP K30	5	0.56	1.50
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	8	0.89	2.40
	MCC PH112	8	0.89	2.40
	Aerosil	4	0.44	1.20
	Lubrication			
	Mag. Stearate	5	0.56	1.50
Wt. of uncoated tablet		**900**		270.00

3.1.GRANULATION PROCEDURE: Same steps of trial 1 were followed for the preparation of granules. The only difference was in the increased amount of Lubricant (Magnesium stearate) used in the lubrication step of the granules as given in the formula.

3.2.COMPRESSION OF TABLET: Tablets were compressed with the same specifications as trial 2.

3.3.IPQC TESTS: All the IPQC test mentioned in trial 2 were performed in this trial also.

3.4.OBSERVATION:

- ✓ Granule flow property was poor.
- ✓ Weight variation was observed.
- ✓ After few tablet compression, bridging effect was observed in the hopper.

3.5.PLAN OF WORK:

Tablets were not coated in this trial. Samples for long term stability study were also not submitted. It was decided that amount of Aerosil in pre-lubrication step of both of the Drug granules to be increased in next trial.

4. FEASIBILITY TRIAL 04:

Batch size: 300 Bi-layer Tablets.

Objective: To take a trial batch with increased amount of Aerosil in the pre-lubrication step.

Table 23: Batch plane for Feasibility Trial 4

TRIAL 4	Ingredients	mg/tab	%	g/300 tab
1st Layer	Drug "A"	290.08	32.23	87.02
	Maize starch	10	1.11	3.00
	MCC PH 112	117.92	13.10	35.38
	Aerosil	10	1.11	3.00
	SLS	10	1.11	3.00
	Croscarmellose sodium	25	2.78	7.50
	PVP K30	12	1.33	3.60
	Mag. Stearate	5	0.56	1.50

	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	7.5	0.83	2.25
	MCC PH 112	11.5	1.28	3.45
	Aerosil	4	0.44	1.20
	Lubrication			
	Mag. Stearate	2	0.22	0.60
2nd Layer	Drug "B"	256.92	28.55	77.08
	Maize starch	15	1.67	4.50
	MCC PH101	60	6.67	18.00
	Aerosil	8	0.89	2.40
	Croscarmellose sodium	15.08	1.68	4.52
	Granulation			
	PVP K30	5	0.56	1.50
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	8	0.89	2.40
	MCC PH112	11	1.22	3.30
	Aerosil	4	0.44	1.20
	Lubrication			
	Mag. Stearate	2	0.22	0.60
Wt. of uncoated tablet		**900**		270.00

4.1.GRANULATION PROCEDURE: Same steps of trial 1 were followed for the preparation of granules. The only difference was in the increased amount of Aerosil used in the pre-lubrication step of the granules as given in the formula.

4.2.COMPRESSION OF TABLETS: Tablets were compressed with the same specifications as trial 2.

4.3.IPQC TESTS: All the IPQC test mentioned in trial 2 were performed in this trial also.

4.4.OBSERVATION:

Disintegration time of the Drug "A" layer was out of the USP provided limit; Drug "A" layer fails the DT test. Tablets were not coated in this trial. Samples for long term stability study were also not submitted.

4.5.PLAN OF WORK: It was decided that incorporation of a super disintegrant intra-granularly in the Drug "A" part may be helpful to overcome the DT problem. In the next trial, Croscarmellose sodium (25 mg/tab) was used as a super disintegrant.

5. FEASIBILITY TRIAL 05:

Batch size: 300 Bi-layer Tablets.

Objective: To take a trial batch with increased incorporation of Croscarmellose sodium.

Table 24: Batch plane for Feasibility Trial 5

TRIAL 5	Ingredients	mg/tab	%	g/300 tab
1st Layer	Drug "A"	290.08	32.23	87.02
	Maize starch	10	1.11	3.00
	MCC PH 112	92.92	10.32	27.88
	Aerosil	10	1.11	3.00

	SLS	10	1.11	3.00
	Croscarmellose sodium	25	2.78	7.50
	PVP K30	12	1.33	3.60
	Mag. Stearate	5	0.56	1.50
	Monosodium Citrate	25	2.78	7.50
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	7.5	0.83	2.25
	MCC PH 112	8.5	0.94	2.55
	Aerosil	4	0.44	1.20
	Lubrication			
	Mag. Stearate	5	0.56	1.50
2nd Layer	Drug "B"	256.92	28.55	77.08
	Maize starch	15	1.67	4.50
	MCC PH101	60	6.67	18.00
	Aerosil	8	0.89	2.40
	Croscarmellose sodium	15.08	1.68	4.52
	Granulation			
	PVP K30	5	0.56	1.50
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	1.50
	Croscarmellose sodium	8	0.89	2.40
	MCC PH112	8	0.89	2.40

	Aerosil	4	0.44	1.20
	Lubrication			
	Mag. Stearate	5	0.56	1.50
Wt. of uncoated tablet		**900**		270.00

5.1.GRANULATION PROCEDURE: Same steps of trial 1 were followed for the preparation of granules. The only difference was in the incorporation of a super disintegrant, i.e. Croscarmellose sodium in the formula Croscarmellose sodium was sifted through #40 and was mixed thoroughly prior to roll compaction.

5.2.COMPRESSION OF TABLETS: Tablets were compressed with the same specifications as trial 2.

5.3.IPQC TESTS: All the IPQC test mentioned in trial 2 were performed in this trial also.

5.4.FILM COATING OF TABLETS:

Table 25: Formula for coating solution

Ingredients	**mg/tab**
HPMC 5 Cps	18.6
Purified Talc	2.65
Titanium Dioxide	9.3
PEG 4000	2.15
Ferric Oxide yellow	0.62
Propylene glycol	4.18
IPA	300
MDC	450

5.4.1. Procedure:

- All the ingredients of the formula were weighed accurately.
- IPA was divided into equal 2 parts and was taken in different beakers.
- In one part of IPA, HPMC was dispersed with stirring. PEG4000 was added to it gradually.
- MDC was added to it.
- In the other part, Talc, TiO_2 and ferric oxide yellow were dispersed and was homogenised for 20 min in a homogeniser.
- The two pats were then mixed with continuous stirring.
- Finally propylene glycol was added to the mixer.
- The coating solution was filtered through muslin cloth.
- Tablets were coated in an auto coater.

5.5.CONTENT UNIFORMITY TEST: Tablets were analysed for content uniformity of by HPLC.

5.6.DISSOLUTION: Dissolution study of the tablets was done with appropriate method and apparatus.

5.7.STABILITY STUDY: 20 coated tablets were packed in aluminium pouches and were installed in stability chambers at different conditions like 25^0C/60% RH, 30^0C/75% RH, 40^0C/ 75% RH for 1, 2 & 3 months.

5.8.OBSERVATION: Tablets of trial 5 gives satisfactory IPQC test results. Formula of trial 5 was considered as the optimised formula.

5.9.PLAN OF WORK: A reproducible batch of the formula of trial 5 would be taken in the next trial.

6. FEASIBILITY TRIAL 06 (REPRODUCIBLE BATCH):

Batch size: 1200 Bi-layer Tablets.

Objective: To take a reproducible batch with the formula generated in feasibility trial 5.

Table 26: Batch plane for Feasibility Trial 6

Reproducible Batch	Ingredients	mg/tab	%	g/1200 tab
1st Layer	Drug "A"	290.08	32.23	348.10
	Maize starch	10	1.11	12.00
	MCC PH 112	92.92	10.32	111.50
	Aerosil	10	1.11	12.00
	SLS	10	1.11	12.00
	Croscarmellose sodium	25	2.78	30.00
	PVP K30	12	1.33	14.40
	Mag. Stearate	5	0.56	6.00
	Monosodium Citrate	25	2.78	30.00
	Pre-lubrication			
	SLS	5	0.56	6.00
	Croscarmellose sodium	7.5	0.83	9.00
	MCC PH 112	8.5	0.94	10.20
	Aerosil	4	0.44	4.80
	Lubrication			
	Mag. Stearate	5	0.56	6.00
2nd Layer	Drug "B"	256.92	28.55	308.30
	Maize starch	15	1.67	18.00
	MCC PH101	60	6.67	72.00
	Aerosil	8	0.89	9.60

	Croscarmellose sodium	15.08	1.68	18.10
	Granulation			
	PVP K30	5	0.56	6.00
	IPA	q. s.		
	Pre-lubrication			
	SLS	5	0.56	6.00
	Croscarmellose sodium	8	0.89	9.60
	MCC PH112	8	0.89	9.60
	Aerosil	4	0.44	4.80
	Lubrication			
	Mag. Stearate	5	0.56	6.00
Wt. of uncoated tablet		**900**		1080.00

6.1.GRANULATION PROCEDURE: Steps which were followed in all above trials; were also followed for the preparation of granules in the reproducible batch. No change in formula was done and the formula of trial 5 was strictly followed.

6.2.COMPRESSION OF TABLETS: Tablets were compressed with the same specifications as trial 2.

6.3.IPQC TESTS: All the IPQC test mentioned in trial 2 were performed in the reproducible batch also.

6.4.COATING: Coating was done by the same procedure and formula as in 5th feasibility trial.

6.5.CONTENT UNIFORMITY TEST: Tablets were analysed for content uniformity of by HPLC.

6.6.DISSOLUTION: Dissolution study of the tablets was done with appropriate method and apparatus.

6.7.STABILITY STUDY: 20 coated tablets were packed in aluminium pouches and were installed in stability chambers at different conditions like 25^0C/60% RH, 30^0C/75% RH, 40^0C/ 75% RH for 1, 2 & 3 months.

6.8.OBSERVATION: Tablets of the reproducible batch gives satisfactory IPQC test results.

6.9.PLAN OF WORK: A process optimization (PO) batch of the formula of trial 5 would be taken in the next trial.

7. FEASIBILITY TRIAL 07 (PROCESS OPTIMIZATION BATCH):

Batch size: 3000 Bi-layer Tablets.

Objective: To take a Process Optimization Batch with the formula generated in feasibility trial 5.

Table 27: Batch plane for Feasibility Trial 7

PO Batch	Ingredients	mg/tab	%	g/3000 tab
1st Layer	Drug "A"	290.08	32.23	870.24
	Maize starch	10	1.11	30
	MCC PH 112	92.92	10.32	278.76
	Aerosil	10	1.11	30
	SLS	10	1.11	30
	Croscarmellose sodium	25	2.78	75
	PVP K30	12	1.33	36
	Mag. Stearate	5	0.56	15

	Monosodium Citrate	25	2.78	75
	Pre-lubrication			
	SLS	5	0.56	15
	Croscarmellose sodium	7.5	0.83	22.5
	MCC PH 112	8.5	0.94	25.5
	Aerosil	4	0.44	12
	Lubrication			
	Mag. Stearate	5	0.56	15
2nd Layer	Drug "B"	256.92	28.55	770.76
	Maize starch	15	1.67	45
	MCC PH101	60	6.67	180
	Aerosil	8	0.89	24
	Croscarmellose sodium	15.08	1.68	45.24
	Granulation			
	PVP K30	5	0.56	15
	IPA	q. s.		q. s.
	Pre-lubrication			
	SLS	5	0.56	15
	Croscarmellose sodium	8	0.89	24
	MCC PH112	8	0.89	24
	Aerosil	4	0.44	12
	Lubrication			
	Mag. Stearate	5	0.56	15
	Wt. of uncoated tablet	**900**		2700

7.1.GRANULATION PROCEDURE: (Area maintained at RH bellow 35%)

7.1.1. **Granulation of Drug "A" part by roll compaction:**

- Drug "A" and all excipients were accurately weighed as given in above PO batch formulae.
- Drug "A" was sifted through sieve #20 ASTM on a vibro sifter. All other ingredients except magnesium stearate were passed through #40 ASTM on the same vibro sifter.
- Aerosil was mixed well with MCC PH112 in a polyethylene bag and then co-sifted.
- Magnesium stearate was sifted through sieve #60 ASTM on vibro sifter.
- All the sifted ingredients were thoroughly mixed in a conta blender for 10min at 8 RPM.
- Then the powder mixer was compacted to form compacts in a roll compactor at 3 ton pressure and 3-4 RPM.
- The compacts were collected and crashed to form granules in a multi mill, at slow speed knife forward direction, fixed with 5 mm sieve in it.
- The larger compacts were again multi milled fitting 2mm sieve.
- Finally the granules were separated from fines by a #60 ASTM sieve.
- Ratio between the #60 retained granule and #60 passed fines were determined.
- The fine collected from the above step was again passed through the roll compactor and the whole process was repeated until a desirable ratio of granules and fines were obtained.
- Then the granules and fines were mixed thoroughly for next processes like determination of BD, TD, CI and HR.

7.1.2. Pre-lubrication of Granules of Drug "A" part:

- All the ingredients of the pre-lubrication part of the formula were passed through #40 ASTM on vibro sifter and were mixed with the above prepared granules in conta blender 10 min at 8 RPM.
- TD, BD, CI and HR of the pre-lubricated bland were determined.

7.1.3. Lubrication of Granules of Drug "A" part:

- Magnesium stearate was sifted through #60 on vibro sifter and was mixed with a little amount of the pre-lubricated blend.
- Then the magnesium stearate containing blend was direct added to the rest of the blend and mixed for another 3 min in the conta blender at 8 RPM.
- TD, BD, CI and HR of the lubricated blend were determined.

7.1.4. Granulation of Drug "B" part by wet granulation:

- Drug "B" and all other excipients were accurately weighed as given in PO Batch formulae.
- Drug "B" was sifted through sieve #20 ASTM on a vibro sifter. All other ingredients were passed through #40 ASTM on the same vibro sifter.
- Aerosil was mixed well with MCC PH112 in a polyethylene bag and then co-sifted.
- All the sifted ingredients were transferred to a Rapid Mixture Granulator (RMG).
- PVP K30 was dissolved in IPA with stirring.
- RMG was run and the propeller speed was kept at 200 RPM for 7 min for mixing.
- PVP K30 solution was gradually added to the above powder mixture carefully observing the current of the RMG machine for 2 min.
- After stopping RMG, the closer of the RMG was opened and binding property of the wet mass formed was observed.

- When desired mass consistency was attained, the wet mass was taken out and dried in a FBD.
- Initially air drying was done.
- Wet milling of the wet mass was done in a multi-mill with 5mm sieve, at slow speed knife forward direction.
- Loss on Drying (LOD) of the wet mass was examined occasionally.
- When desired drying was achieved, the mass was again milled in multi mill with 3 mm sieve attached in it.

7.1.5. Pre-lubrication of Granules of Drug "B" part:

- All the ingredients of the pre-lubrication part of the formula were passed through #40 ASTM on vibro sifter and were mixed with the above prepared granules in a conta blender for 10 min at 8 RPM.
- TD, BD, CI and HR of the pre-lubricated bland were determined.

7.1.6. Lubrication of Granules of Drug "B" part:

- Magnesium stearate was sifted through #60 on vibro sifter and was mixed with a little amount of the pre-lubricated blend.
- Then the magnesium stearate containing blend was directly added to the rest of the blend and mixed for another 3 min on the conta blender.
- TD, BD, CI and HR of the lubricated blend were determined.

7.2.COMPRESSION OF TABLETS:

With the lubricated granules of Drug "A" and Drug "B", bi-layer tablets were prepared with 19X9 mm, capsule shaped, standard concave punches, having break-line on one surface, plain on the other in a bi-layer tablet compression machine.

The two feeding hoppers of the machine were filled with the prepared granules in each side. Only one punch was used for the compression. Compression RPM was kept between 4 and 6.

7.3.IPQC TESTS: All the IPQC test mentioned in trial 2 were performed in the reproducible batch also.

7.4.CONTENT UNIFORMITY TEST: Tablets were analysed for content uniformity of by HPLC.

7.5.DISSOLUTION: Dissolution study of the tablets was done with appropriate method and apparatus.

7.6.STABILITY STUDY: 20 coated tablets were packed in aluminium pouches and were installed in stability chambers at different conditions like 25^0C/60% RH, 30^0C/75% RH, 40^0C/ 75% RH for 1, 2 & 3 months.

7.7.COATING: Coating was done by the same procedure and formula as in 5^{th} feasibility trial.

7.8.OBSERVATION: Tablets of the PO batch gives satisfactory IPQC test results.

8. POST COMPRESSION PARAMETERS:

8.1.SHAPE OF TABLET: Compressed tablets were examined under the magnifying lens for the shape of the tablet.

8.2.TABLET DIMENSIONS: Thickness and diameter were measured using calibrated Vernier callipers. Five tablets of each formulation were picked randomly and thickness and diameter was measured individually.

8.3.HARDNESS: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Schleuniger digital hardness tester. It is expressed in Neuton (N). Five tablets were randomly picked and hardness of the tablets was determined.

8.4.FRIABILITY TEST: The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Wt) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (WF). The % friability was then calculated by-

$$\%F = \frac{W\ (Initial) - W\ (Final)}{W\ (Initial)} X100$$

8.5.WEIGHT VARIATION TEST: Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed.

$$\%\ Deviation = \frac{Individual\ weight - Average\ weight}{Average\ weight} X\ 100$$

Table 28: USP permitted tablet weight variation with tablet weight

Average weight of a tablet	**Percentage deviation**
130 or less	± 10
>130 mg and <324 mg	± 7.5
324mg or more	± 5

8.6.DISINTEGRATION TEST: The disintegration time for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 900 ml of purified water maintained at 37 ± 2^0 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

8.7.ASSAY:

8.7.1. Chromatographic Conditions for Drug "A":

Apparatus: High Performance Liquid Chromatography system (HPLC).

Column: KROMASIL C18, (250 x 4.6) mm, 5µ BEQ-AC-261

Detector: UV/PDA

Wavelength: 235nm

Injection volume: 20µl.

Flow rate: 1.8ml/min

Column temperature: 30^0 C

Elution: Isocratic.

Mobile phase: Buffer + Acetonitrile (60:40 V/V).

Preparation of Buffer: Accurately weighed 1.54 gm of Ammonium acetate and was dissolved in 1L of water.

Diluent: Buffer + Acetonitrile (60:40 V/V).

Method of standard solution preparation: 40 mg of standard Drug "A" was accurately weighed and taken in a 50 ml volumetric flask. 25 ml of Methanol was added to it and was sonicated to dissolve. Volume was made up to 50 ml with diluent. Then 5 ml of the solution was again diluted to 50 ml with diluent, 5ml of which was further diluted to 10 ml with mobile phase.

Method for sample solution preparation: 3 intact tablets were taken in a 1000 ml volumetric flask. Then 800 ml of methanol was added to it and was sonicated for 30 min. Volume was made up to mark with methanol. The solution was filtered though glass fibre filter. 5 ml of the filtrate was diluted again 50 ml with methanol. 5 ml of which was further diluted to 10 ml with mobile phase.

8.7.2. Chromatographic Conditions for Drug "B":

Apparatus: High Performance Liquid Chromatography system (HPLC).

Column: COSMOSIL C18, (150 x 4.6) mm, 5µ (1968)

Detector: UV/PDA

Wavelength: 24nm

Injection volume: 20µl.

Flow rate: 1.0ml/min

Column temperature: Ambient

Elution: Isocratic.

Mobile phase: Buffer + Acetonitrile (82:18 V/V).

Preparation of Buffer: Accurately weighed 8.43 gm of Monohydrated sodium perchlorate and 3.8 gm of Ammonium acetate and was dissolved in 1L of water and adjust the pH with Ortho Phosphoric acid (OPA) to 2.2.

Diluent: 0.1 N HCl.

Method of standard solution preparation: 52 mg of standard Drug "B" was accurately weighed and taken in a 50 ml volumetric flask. 20 ml of diluent (0.1 N HCL) was added to it and was sonicated to dissolve. Volume was made up to 50 ml with diluent. Then 5 ml of the solution was a further diluted to 100 ml with diluent.

Method for sample solution preparation: Equivalent to 250 mg of Drug "B", sample was taken in a 250 ml volumetric flask. Then 170 ml of diluent was added to it and was sonicated for 15 min. Volume was made up to mark with diluent. The solution was filtered though glass fibre filter. 5 ml of the filtrate was further diluted to 100 ml with diluent.

The final concentrations of the standard solution of Drug "A" and Drug "B" were 30 ppm and 50 ppm respectively.

8.7.3. Procedure:

The HPLC column was equilibrated with mobile phase for sufficient time until stable baseline is obtained. Blank was injected in duplicate, standard preparation in five replicates and each test preparation in duplicate into the chromatographic system; the chromatogram was recorded and the response (Peak areas) for Drug "A" and Drug "B" was measured. The standard preparation was injected as bracketing after every six injections of test preparations.

8.7.4. System suitability parameters:

50 µ L volumes of standard solution were injected five times into the HPLC. The Chromatogram was recorded and the response (peak areas) for the CCB and SBB peaks were measured.

8.8.DISSOLUTION TEST:

8.8.1. Dissolution test for Drug "A":

Dissolution medium: Glycine buffer pH 3.0.

Medium volume: 900 ml

Apparatus type: USP type II (Paddle).

RPM: 75.

Time (min): 60.

Procedure for dissolution media preparation: Accurately 30.28 gm of glycie, 23.67 gm of Sodium chloride and 8 ml of HCL were weighed and mixed in water and made up the volume up to 10 litres with water. Adjust the pH to 3.0 with sodium hydroxide.

Standard solution preparation: Accurately 30 mg of Drug "A" was weighed at take in a 100 ml volumetric flask. 20 ml of methanol was added to it and sonicated to dissolve the drug. Finally volume was made up to mark with dissolution medium.

Sample preparation: In the dissolution apparatus, 1 tablet was inserted in each bowel. 10 ml of sample was collected at an interval of 10 min for 60 min which was compensated with 10 ml of fresh media. Collected samples were filtered and injected into HPLC column.

8.8.2. Dissolution test for Drug "B":

Dissolution medium: 0.1 N HCl.

Medium volume: 900 ml

Apparatus type: USP type I (Basket).

RPM: 100.

Time (min): 60.

Procedure for dissolution media preparation: Accurately 85 ml of HCL measured and was diluted to 10 litres with water.

Standard solution preparation: Accurately 55 mg of Drug "B" was weighed at taken in a 50 ml volumetric flask. 20 ml of 0.1 N HCl was added to it and sonicated to dissolve the drug. Volume was made up to mark with 0.1 N HCl. 5 ml of which was further diluted to 100 ml with 0.1 N HCl.

Sample preparation: In the dissolution apparatus, 1 tablet was inserted in each bowel. 10 ml of sample was collected at an interval of 10 min for 60 min which was compensated with 10 ml of fresh media. Collected samples were filtered and 5ml of the filtrate was diluted to 25 ml with dissolution media and was injected into HPLC column.

8.8.3. Assay of dissolution samples:

The sample were analysed for determination of the API content using the same analytical method as mentioned for assay of the APIs.

9. ACCELERATED STABILITY STUDY:

Samples of the PO batch was packed in Alu- Alu strip pack and was labelled to keep them in 40^0C/75% RH and in 55^0C for 1, 2 and 3 months respectively. The samples were then placed in stability chambers. Tablets were taken out of the stability chambers at different time intervals like 1, 2 and 3 months and was observed for physical and chemical changes taken place in the tablets. Assay and dissolution study were performed with the tablets.

Chapter 8

RESULT AND DISCUSSION

1. API CHARACTERIZATION
2. RESULTS OF COMPATIBILITY STUDIES
3. EVALUATION OF BLEND AND TABLET PROPERTIES
4. INITIAL DISSOLUTION STUDY RESULTS
5. RESULTS OF THE REPRODUCIBLE BATCHES
6. RESULTS FOR STABILITY SAMPLES OF PO BATCH
7. DISCUSSION OF THE STABILITY STUDY
8. DISCUSSION

1. API CHARACTERIZATION:

1.1.DESCRIPTION:

Drug "A" a white to light brownish-white powder, odourless or having a faint odour.

Drug "B" is slight yellow crystalline powder, odourless and bitter in taste.

1.2.MELTING POINT:

The melting point was determined by open capillary method. The reported melting point of drug A and Drug B is about 111-113ºC and 218°C respectively.

Table 29: Melting point of API

Sl. No.	Drug	Melting Point
1	Drug "A"	111-113°C
2	Drug "B"	218°C

1.3.SOLUBILITY:

Table 30: Solubility of API

SOLVENT	SOLUBILITY	
	Drug "A"	**Drug "B"**
Water	Very slightly soluble	Freely soluble
Acetonitrile	Soluble	---
Ethanol	Freely soluble	---
Methanol	Soluble	Slightly soluble
Ether	Slightly soluble	---
Acetic acid	---	Sparingly soluble
Chloroform	--	Sparingly soluble

1.4.POWDER FLOW PROPERTIES OF DRUGS:

Table 31: Powder flow property of API

PARAMETERS	Drug "A"	Drug "B"
Bulk density	0.51 gm./ml	0.302 gm./ml
Tapped density	0.75 gm./ml	0.597 gm./ml
Compressibility index	32%	49.41%
Housner's ratio	1.47	1.976

2. RESULTS OF COMPATIBILITY STUDIES:

2.1.INITIAL OBSERVATION FOR COMBINATIONS WITH DRUG "A":

Table 32: Initial observation for Drug "A"

Sl. No.	Combinations	Observations	
		Dry	Wet
1	Drug "A"	White to off white free flowing powder	Off white blend with some lumps adhered at the surface
2	Drug "B"	Pale yellow coloured free flowing powder	Pale yellow coloured blend with some lumps adhered at the surface
3	Drug "A"+ Drug "B"	White to off white free flowing powder	Buff coloured blend adhered at the surface
4	Drug "A"+ Maize starch	Off white coloured free flowing blend	White to off whit blend
5	Drug "A"+ MCC	Off white coloured free flowing blend	White to off whit blend
6	Drug "A"+ Aerosil	Off white coloured free flowing blend	White to off whit blend
7	Drug "A"+ SLS	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
8	Drug "A"+ Croscarmellose sodium	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
9	Drug "A"+ Monosodium Citrate	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
10	Drug "A"+ PVP K30	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface

11	Drug “A”+ Magnesium stearate	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
12	Drug “A”+ HPMC	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
13	Drug “A”+ Purified talc	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
14	Drug “A”+ TiO_2	Off white coloured free flowing blend	Buff coloured blend with some adhered lumps at the surface
15	Drug “A”+ Ferric Oxide Yellow	Pale yellow coloured free flowing powder	Buff coloured blend with some adhered lumps at the surface
16	Drug “A”+ All excipients	Buff coloured free flowing blend	Buff coloured free flowing blend

2.2. INITIAL OBSERVATION FOR COMBINATIONS WITH DRUG “B”:

Table 33: Initial observation for Drug "B"

Sl. No.	Combinations	Observations	
		Dry	Wet
1	Drug “B”+ Maize starch	Pale yellow coloured free flowing powder	Pale yellow coloured blend with some lumps adhered at the surface
2	Drug “B”+ MCC	Pale yellow coloured free flowing powder	Pale yellow coloured free flowing blend
3	Drug “B”+ Aerosil	Pale yellow coloured free flowing powder	Pale yellow coloured free flowing blend
4	Drug “B”+ SLS	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
5	Drug “B”+ Croscarmellose sodium	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
6	Drug “B”+ Monosodium Citrate	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
7	Drug “B”+ PVP K30	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
8	Drug “B”+ Magnesium stearate	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the

			surface
9	Drug “B”+ HPMC	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
10	Drug “B”+ Purified talc	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
11	Drug “B”+ TiO_2	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
12	Drug “B”+ Ferric Oxide Yellow	Pale yellow coloured free flowing powder	Yellow coloured blend with some lumps adhered at the surface
13	Drug “B”+ All excipients	Buff coloured free flowing blend	Buff coloured blend

2.3.INITIAL OBSERVATION FOR COMBINATIONS WITH DRUG “A” AND DRUG “B”:

Table 34: Initial observation for Drug "A" and Drug "B"

Sl. No.	Combinations	Observations	
		Dry	Wet
1	Drug “A”+ Drug “B”+ Maize starch	Off white coloured blend	Off white blend with some lumps adhered at the surface
2	Drug “A”+Drug “B”+ MCC	Off white coloured blend	Off white blend with some lumps adhered at the surface
3	Drug “A”+Drug “B”+ Aerosil	Off white coloured blend	Off white blend with some lumps adhered at the surface
4	Drug “A” + Drug “B”+ SLS	Off white coloured blend	Brown coloured lump
5	Drug “A”+ Drug “B”+ Croscarmellose sodium	Off white coloured blend	Off white coloured free flowing blend
6	Drug “A”+ Drug “B”+ Monosodium Citrate	Off white coloured blend	Off white coloured free flowing blend with some lumps adhered at the surface
7	Drug “A”+ Drug “B”+ PVP K30	Off white coloured blend	Off white coloured free flowing blend with some lumps adhered at the surface
8	Drug “A”+ Drug “B”+ Magnesium stearate	Off white coloured blend	Buff coloured blend
9	Drug “A”+ Drug “B”+ HPMC	Off white coloured blend	Off white coloured free flowing blend with some

			lumps adhered at the surface
10	Drug "A"+ Drug "B"+ Purified talc	Off white coloured blend	Off white coloured free flowing blend with some lumps adhered at the surface
11	Drug "A"+ Drug "B"+ TiO_2	Off white coloured blend	Off white coloured free flowing blend with some lumps adhered at the surface
12	Drug "A"+ Drug "B"+ Ferric Oxide Yellow	Off white coloured blend	Yellow coloured free flowing blend with some lumps adhered at the surface
13	Drug "A"+ Drug "B"+ All excipients	Buff coloured free flowing blend	Buff coloured free flowing blend

2.4.VISUAL OBSERVATIONS FOR DRUG-EXCIPIENT AND DRUG- DRUG COMPATIBILITY STUDY WITH DRUG "A":

Table 35: Visual Observations for Drug-Excipient and drug- drug compatibility study with Drug "A"

Sl. No	Combination	40^0C/ 75% RH; 7 Days		40^0C/ 75% RH; 15 Days		55^0C; 7 Days		55^0C; 15 Days	
		Dry	Wet	Dry	Wet	Dry	Wet	Dry	Wet
1	Drug "A"	NC	NC	NC	NC	Light brown blend	Dark yellow lump	Light brown blend	Light brown lump
2	Drug "B"	NC	NC	NC	NC	NC	Light yellow lump	NC	Light brown lump
3	Drug "A"+ Drug "B"	NC	Dark brown lump	NC	Dark brown lump	NC	Dark yellow lump	NC	Light brown lump
4	Drug "A"+ Maize starch	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
5	Drug "A"+ MCC	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
6	Drug "A"+ Aerosil	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
7	Drug "A"+ SLS	NC	NC	NC	Dark brown lump	Light brown lump	Dark yellow lump	Light brown lump	Light brown lump
8	Drug "A"+ Croscarmellose sodium	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
9	Drug "A"+ Monosodium Citrate	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump

10	Drug "A"+ PVP K30	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
11	Drug "A"+ Magnesium stearate	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
12	Drug "A"+ HPMC	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
13	Drug "A"+ Purified talc	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
14	Drug "A"+ TiO_2	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
15	Drug "A"+ Ferric Oxide Yellow	NC	NC	NC	NC	NC	Dark yellow lump	NC	Light brown lump
16	Drug "A"+ All excipients	NC	NC	NC	NC	NC	NC	NC	NC

NC = No Change

2.5.VISUAL OBSERVATIONS FOR DRUG-EXCIPIENT AND DRUG- DRUG COMPATIBILITY STUDY WITH DRUG "B":

Table 36: Visual Observations for Drug-Excipient compatibility study with Drug "B"

Sl. No	Combination	40^0C/ 75% RH; 7 Days		40^0C/ 75% RH; 15 Days		55^0C; 7 Days		55^0C; 15 Days	
		Dry	Wet	Dry	Wet	Dry	Wet	Dry	Wet
1	Drug "B"+ Maize starch	NC	NC	NC	NC	NC	NC	NC	NC
2	Drug "B"+ MCC	NC	NC	NC	NC	NC	NC	NC	NC
3	Drug "B"+ Aerosil	NC	NC	NC	NC	NC	NC	NC	NC
4	Drug "B"+ SLS	NC	NC	NC	NC	NC	NC	NC	NC
5	Drug "B"+ Croscarmellose sodium	NC	NC	NC	NC	NC	NC	NC	NC
6	Drug "B"+ Monosodium Citrate	NC	NC	NC	NC	NC	NC	NC	NC
7	Drug "B"+ PVP K30	NC	NC	NC	NC	NC	NC	NC	NC
8	Drug "B"+ Magnesium stearate	NC	NC	NC	NC	NC	NC	NC	NC
9	Drug "B"+ HPMC	NC	NC	NC	NC	NC	NC	NC	NC
10	Drug "B"+ Purified	NC	NC	NC	NC	NC	NC	NC	NC

	talc								
11	Drug "B"+ TiO_2	NC	NC	NC	NC	NC	NC	NC	NC
12	Drug "B"+ Ferric Oxide Yellow	NC	NC	NC	NC	NC	NC	NC	NC
13	Drug "B"+ All excipients	NC	NC	NC	NC	NC	NC	NC	NC

NC = No Change

2.6.VISUAL OBSERVATIONS FOR DRUG-EXCIPIENT AND DRUG- DRUG COMPATIBILITY STUDY WITH DRUG "A" AND DRUG "B":

Table 37: Visual Observations for Drug-Excipient compatibility study with Drug "A" and Drug "B"

Sl. No	Combination	40^0C/ 75% RH; 7 Days		40^0C/ 75% RH; 15 Days		55^0C; 7 Days		55^0C; 15 Days	
		Dry	Wet	Dry	Wet	Dry	Wet	Dry	Wet
1	Drug "A"+ Drug "B"+ Maize starch	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
2	Drug "A"+Drug "B"+ MCC	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
3	Drug "A"+Drug "B"+ Aerosil	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
4	Drug "A" + Drug "B"+ SLS	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
5	Drug "A"+ Drug "B"+ Croscarmellose sodium	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
6	Drug "A"+ Drug "B"+ Monosodium Citrate	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
7	Drug "A"+ Drug "B"+ PVP K30	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
8	Drug "A"+ Drug "B"+ Magnesium stearate	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
9	Drug "A"+ Drug "B"+ HPMC	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
10	Drug "A"+ Drug "B"+ Purified talc	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
11	Drug "A"+ Drug "B"+ TiO_2	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump

12	Drug "A"+ Drug "B"+ Ferric Oxide Yellow	NC	Dark brown lump	NC	Dark brown lump	NC	Brown coloured lump	NC	Dark brown lump
13	Drug "A"+ Drug "B"+ All excipients	NC	NC	NC	NC	NC	NC	NC	NC

NC = No Change

From the data obtained from pre-formulation study, it is clear that drug A is physically compatible with drug B and hence drug A and drug B can be given in combination. But Drug "A" shows reaction in wet conditions in lower temperature as well as in higher temperatures. Similarly combinations of the two APIs also show the reactions in the same conditions. Hence from discussion with guide, it was decided that Drug "A" will be granulated by dry granulation process (Roll-compaction) and Drug "B" will be granulated by non-aqueous granulation technique.

3. INITIAL EVALUATION OF BLEND AND TABLET PROPERTIES:

3.1.EVALUATION DATA OF BLEND AND TABLET PROPERTIES FROM F1- F7 (PO) BATCH:

Table 38: Evaluation Data of granules and Tablet Properties of Feasibility Trials (F1- F7).

Parameters	F1	F2	F3	F4	F5	R. B.	P.O.
Granule Study of Drug "A"							
Bulk density (g/ml)	0.64	0.642	0.644	0.645	0.644	0.648	0.648
Tapped density (g/ml)	0.84	0.838	0.832	0.832	0.83	0.834	0.834
Compressibility Index. (%)	30.12	30.53	29.19	28.99	28.88	28.70	28.70
Housner's ratio	1.30	1.31	1.29	1.29	1.29	1.29	1.29
Loss on drying (%)	0.85	0.78	0.96	0.65	0.61	0.58	0.6
Granule Study of Drug "B"							
Bulk density (g/ml)	----	0.55	0.554	0.548	0.549	0.55	0.55
Tapped density (g/ml)	----	0.732	0.73	0.729	0.732	0.733	0.733

Compressibility Index. (%)	----	24.86	24.11	24.83	25.00	24.97	24.97
Housner's ratio	----	1.33	1.32	1.33	1.33	1.33	1.33
Loss on drying (%)	----	1.83	1.86	1.83	1.8	1.83	1.831
Tablet Parameters							
Hardness(N)	--	130±8	130±6	130±5	130±5	130±5	130±5
Thickness(mm)	--	5.8±0.1	5.8±0.1	5.8±0.1	5.8±0.1	5.8±0.1	5.8±0.1
Friability (%)	--	0.03	0.03	0.04	0.01	0.01	0.15
Targeted weight(mg)	--	900	900	900	900	900	900
Average weight (uncoated) (mg)	--	900 ±9%	900 ±8%	900 ±6%	900 ±3%	900 ±2%	900 ±2%
Average weight (coated) (mg)	--	--	--	--	925 ±3%	925 ±2%	925 ±2%
Content uniformity for **Drug "A"** (%)	--	--	--	--	96.5	99.2	99.3
Content uniformity for **Drug "B"** (%)	--	--	--	--	101.5	99.8	99.8

4. INITIAL DISSOLUTION STUDY RESULTS:

4.1.DISSOLUTION STUDY OF FEASIBILITY TRIAL 5:

Table 39: Dissolution Study data of Feasibility Trial 5

Feasibility Trial 5		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	15	17
20	32	35
30	48	51
40	65	69
50	85	88
60	97	98

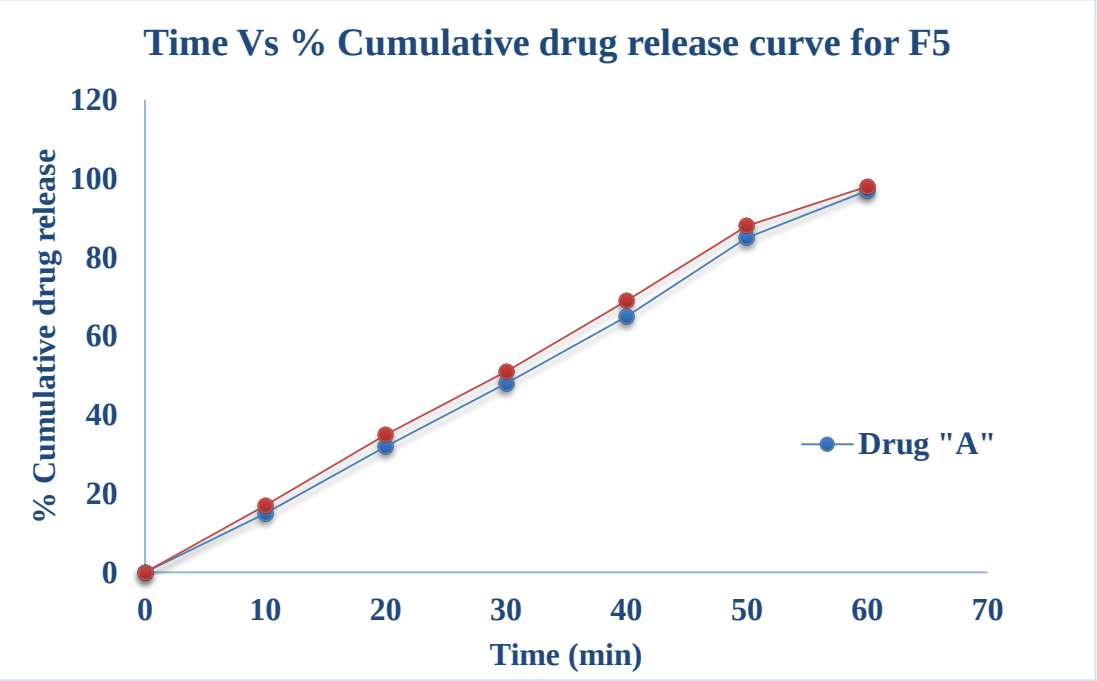


Figure 14: Time Vs. %Cumulative drug release curve for Feasibility trial 5

4.2.DISSOLUTION STUDY OF FEASIBILITY TRIAL 6:

Table 40: Dissolution Study data of Feasibility Trial 6

Feasibility Trial 6		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	14	18
20	33	37
30	51	54
40	69	71
50	88	89
60	98	99

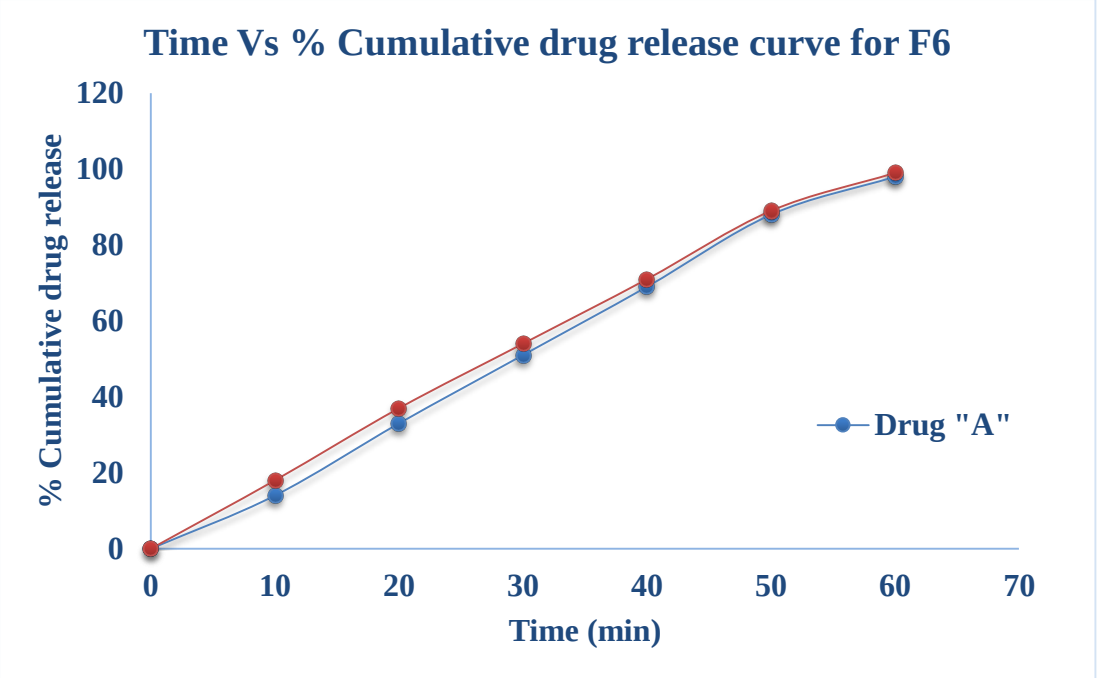


Figure 15: Time Vs. %Cumulative drug release curve for Feasibility Trial 6

4.3.DISSOLUTION STUDY OF FEASIBILITY TRIAL 7:

Table 41: Dissolution Study data of Feasibility Trial 7

Feasibility Trial 7		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	16	19
20	37	39
30	53	59
40	70	76
50	89	90
60	98	99

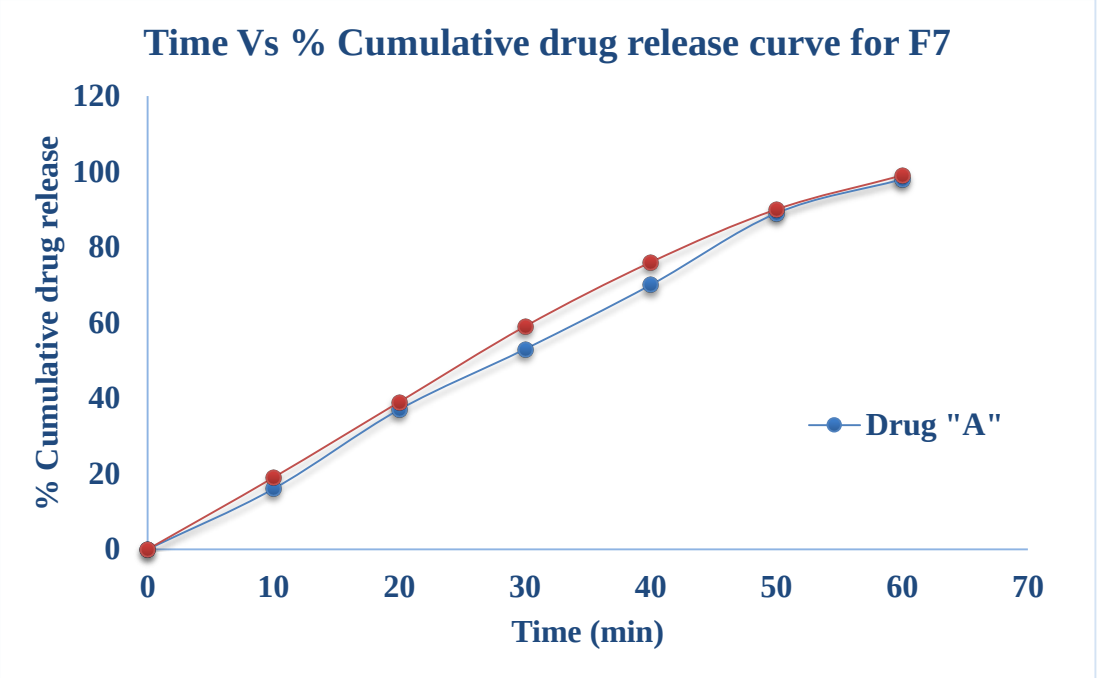


Figure 16: Time Vs. %Cumulative drug release curve for Feasibility Trial 7

5. RESULTS OF THE REPRODUCIBLE BATCHES:

No significant difference were observed in appearance, tablet weight, hardness, thickness, and disintegration time of the tablets of PO batch from the tablets of feasibility trials 5 & 6. All the parameters were found to be satisfactory.

Assay and content uniformity results were within the specification for both reproducible batches. The assay value for Drug “A” in feasibility trial 5, 6 and PO batch was found as 97%, 101% and 98% respectively and assay value for Drug “B” was found as 99%, 100% and 99.5% respectively.

As the tablets of reproducible batches were found to be stable, Bi-layer technology with finalized formula and manufacturing method had been selected for pilot batch production of Drug “A” + Drug “B” tablets of 200+250mg strength.

6. RESULTS FOR STABILITY SAMPLES OF PO BATCH:

6.1. PHYSICAL OBSERVATION:

Table 42: Physical observation of stability samples

PARAMETERS	INITIAL	1 month	2 month	3 month
Hardness	130±5N	132±5N	133±4N	134±4N
Thickness	5.8±0.1 mm	5.8±0.1 mm	5.8±0.1 mm	5.8±0.1 mm
Friability (%)	0.01	0.01	0.1	0.1
Avg. weight	925mg ±3%	925mg ±2%	925mg ±2%	925mg ±2%

6.2. ASSAY:

Table 43: Assay results of stability samples

	INITIAL		1 MONTH		2 MONTH		3 MONTH	
Assay	Drug "A"	Drug "B"	Drug "A"	Drug "B"	Drug "A"	Drug "B"	Drug "A"	Drug "B"
	97%	99%	96.5%	98%	96%	98%	95%	97%

6.3.DISSOLUTION STUDY RESULTS FOR SAMPLE AFTER 1 MONTH:

Table 44: Dissolution Study Data of Stability Sample after 1 Month

After 1 month of stability study		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	14	17
20	33	36
30	50	55
40	63	73
50	80	86
60	96	97

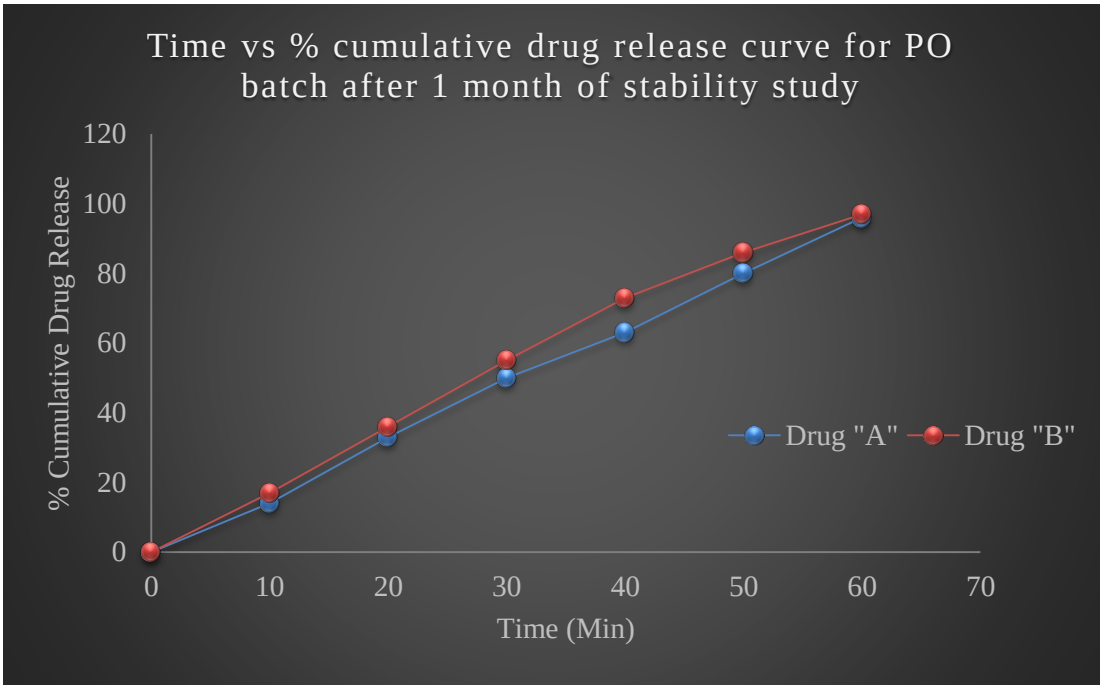


Figure 17: Time vs. % cumulative drug release curve for PO batch after 1 month of stability study.

6.4.DISSOLUTION STUDY RESULTS FOR SAMPLE AFTER 2 MONTH:

Table 45: Dissolution Study Data of Stability Sample after 2 Month

After 2 month of stability study		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	12	15
20	31	34
30	47	52
40	60	70
50	78	83
60	95	96

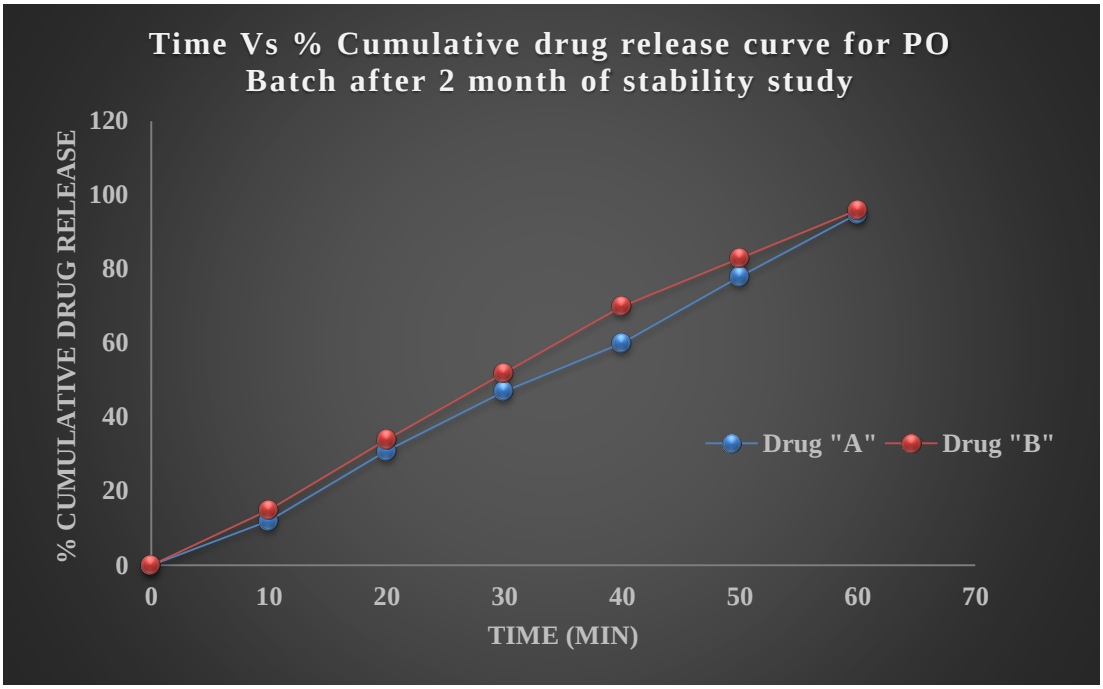


Figure 18: Time vs. % cumulative drug release curve for PO batch after 2 month of stability study.

6.5.DISSOLUTION STUDY RESULTS FOR SAMPLE AFTER 3 MONTH:

Table 46: Dissolution Study Data of Stability Sample after 3 Month

After 3 month of stability study		
Time (min)	**Drug "A"**	**Drug "B"**
0	0	0
10	11	13
20	29	31
30	44	50
40	57	68
50	75	80
60	93	94

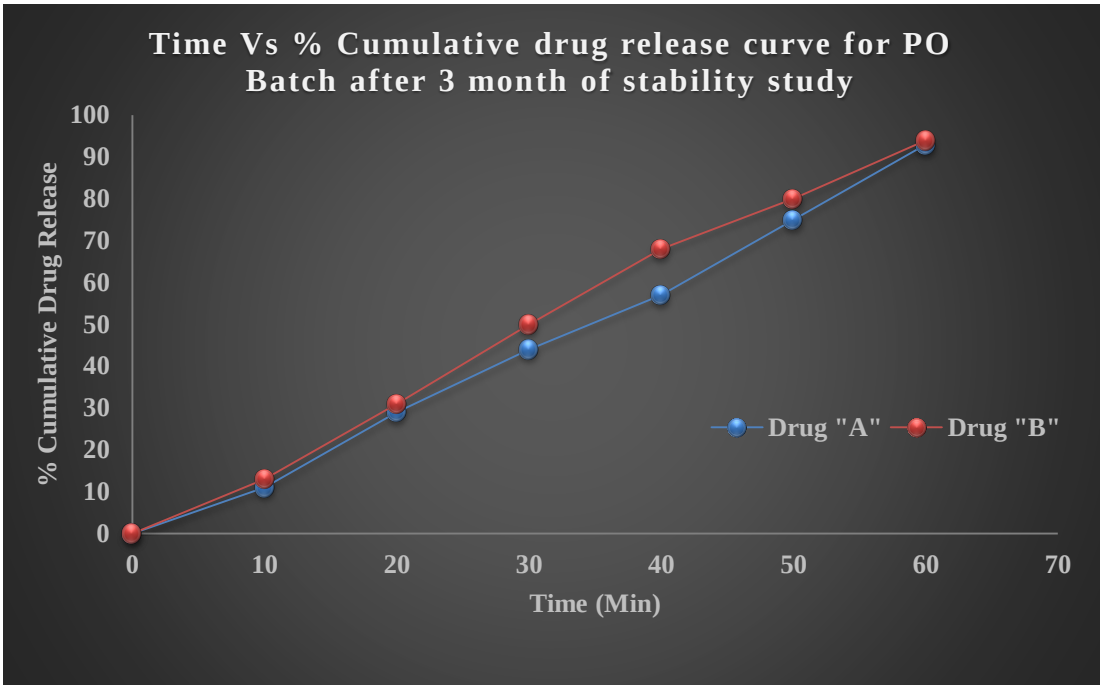


Figure 19: Time vs. % cumulative drug release curve for PO batch after 3 month of stability study.

7. DISCUSSION OF THE STABILITY STUDY:

Result of stability study shows that there is no significant changes observed in appearance of the tablets as well as in the values of assay and % drug release of tablet after 1st month, 2nd month and 3rd month.

Therefore it is concluded that the bi-layer tablet formulation is stable.

8. DISCUSSION:

The objective of the present research work was to formulate a non-infringing stable, physically- chemically compatible and bioequivalent fixed dose combination product of Drug “A” + Drug “B” tablets of 200+250mg strength.

From the literature survey, it was found that Drug “A” is having synergistic action with Drug “B” in controlling different complicated infections. So their combination is a rational approach for the management of community acquired

diseases along with various resistant bacteria causing different infections in human being.

From the pre-formulation experiments, Drug "A" was found to be highly unstable in presence of oxygen and humidity; having pH dependent solubility (lower in acidic pH and higher in alkaline pH) and highly incompatible with many excipients studied during drug-excipient compatibility studies at 40°C/75%RH in open as well closed conditions for 15 days.

Drug "B" was found to be stable with respect to environmental conditions like temperature, oxygen and humidity; having pH independent solubility and compatible with most of the excipients studied during drug-excipient compatibility studies at 40°C/75%RH and 55°C in open condition for 15 days.

Hence, based on the literature survey and pre-formulation studies excipients were selected and formulation trials were designed.

The formula and manufacturing method used for **Macleod's** inline project Drug "A" tablets (200 mg), and Drug "B" tablets (250 mg) were taken as a reference for the development of fixed dose combination product of Drug "A" + Drug "B" tablets.

Different stabilizers and alkalizing agents were used to stabilize the formulation and to control the *in vivo* solubility of the Drug "A" part.

Drug "B" part was formulated by non-aqueous wet granulation technique in Rapid mixture granulator (GMG). Dry granulation approach was tried for the addition of Drug "A" in the formulation to make a stable and bio available dosage form.

Bi-layer tablet technology was adopted which was having two separate layers in a tablet for both drugs. Drug "B" layer was formulated by wet granulation method in Rapid Mixture Granulator (RMG) and Drug "A" layer was formulated by dry

granulation (roll compaction) method. Both parts were compressed in Bi-layer tablet compression machine.

Initial analysis of the tablets shows excellent assay and dissolution profile. Analysis of the long term stability study samples reveals their long term stability. The tablets shows excellent stability profile in the accelerated stability study. The appearance, assay and dissolution profile shows that there is very minute change or negligible changes from that of initial study results.

From the results obtained from the above study in can be concluded that the prepared tablet is stable and can be used for treatment of various human diseases.

Chapter 9

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