FORMULATION AND STATISTICAL OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE & AMBROXOL HYDROCHLORIDE

A THESIS SUBMITTED TO
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IN THE PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF DEGREE OF

MASTER OF PHARMACY (M.PHARM)
IN
(PHARMACEUTICS)

SUBMITTED BY

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Dedicated to my beloved family who sacrifice their present to shape my future….

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This is to certified that the topic incorporated in this dissertation **"FORMULATION AND STATISTICAL OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE& AMBROXOL HYDROCHLORIDE"** being submitted by **PRIYANKA CHOUDHURY**, Roll no:**1405211007**,Regd no:**098805214**,in partial fulfilment of the requirement for the award of Degree of Master of Pharmacy (M. Pharm) of department of Pharmaceutics laboratory, **Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to Assam Science And Technical University, Guwahati, Assam** during the academic session 2015-2016.

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DECLARATION

I hereby declare that the topic incorporated in this dissertation entitled **"FORMULATION AND STATISTICAL OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE& AMBROXOL HYDROCHLORIDE"** ,final project report being submitted in partial fulfillment of the requirement for the award of Degree of Master in Pharmacy (M.Pharm)in Pharmaceutics of **Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to Assam science and Technology university, Guwahati, Assam** is a bonafied assignment which has been carried out by me under the guidance and supervision of Dr.Pulak Deb,Assistant professor, Department of Pharmaceutics(GIPS) & Principal Dr.Suvakanta Dash (GIPS).No any part of this thesis has been submitted by any other research persons or any student.

DATE-

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Date

Place

Priyanka Choudhury

PUBLICATION AND POSTER PRESENTATION

- The manuscript AJPCR/11453/16 entitled "Formulation and statiscal optimization of fast dissolving tablets of Levocetrizine hydrochloride" has accepted to publish in upcoming issue Vol 9 Issue 4_2016 July-August in Asian Journal of Pharmaceutical and clinical research (AJPCR).
- The manuscript, *RJPT*-3700/11-5-2016 entitled "Formulation and statiscal optimization of fast dissolving tablets of Ambroxol hydrochloride**",** has been accepted to publish in upcoming issue *(Vol.9, Issue-10, and October2016) in* Research Journal of Pharmacy and Technology (RJPT).
- Poster presentation in one day national seminar on "Emerging trends in Pharmaceutical Education and Research" and 1st prize winner of poster presentation in M.Pharm scholar and Research category ("Formulation and Statistical optimization of Fast dissolving tablets of Levocetrizine Hydrochloride").

FORMULATION AND STASTICAL OPTIMISATION OF FAST DISSOLVING TABLETS OF LEVOCETRIZINE HYDROCHLORIDE

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INTRODUCTION

The oral route is always most ideal routes of drug administration as it is more suitable, cost effective, and ease of administration lead to high level of patient compliance. Also sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels by passes the hepatic first-pass metabolic processes (1).

Levocetrizine hydrochloride is an orally active H1-receptor antagonist, a racemic compound with antihistaminic properties (2). Buccal absorption of Levocetrizine hydrochloride is quite high and in general recommended for mild to moderate disease as first line therapy, but not effective in nasal congestions. Fast dissolving tablets of Levocetrizine hydrochloride prepared using direct compression have been optimized successfully using a face-centered Central Composite Design. (3).

METHODS

Formulation of Fast dissolving tablets of Levocetrizine Hydrochloride

Fast dissolving tablets of Levocetrizine hydrochloride were prepared by direct compression method.The indivisual weight was found to be 120mg(3).

Experimental design

A Central Composite Design using Design Expert Software (Version 10.0, Stat- Ease Inc, and Minneapolis, MN) was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the disintegration time, wetting time, water absorption ratio and in vitro release of Levocetrizine hydrochloride. A 2-factor, 3-level design was observed to be most suitable for exploring quadratic response surfaces and constructing second-order polynomial models(5)

A 2-factor, 3-level design was observed to be most suitable for exploring quadratic response surfaces and constructing second-order polynomial models(10,11) The amount of Crosscarmellose sodium (X1) and Sodium starch glycolate (X2) were selected as the factors, studied at 3 levels each were selected based on the results from preliminary experimentation (3).

Various pre compression and Post compression parameters were also calculated(4,5).

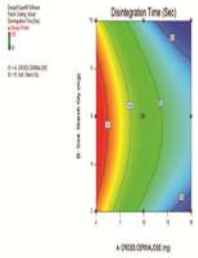
RESULT

The results of pre-compression studies reveal that the bulk density is in limit of both bulk density and tapped density. Also in case of Carr's index it was found in between 10-11.2 and Hausner ratio in between 1.06-1.99 which holds the assumption of good compressibility(4,5)

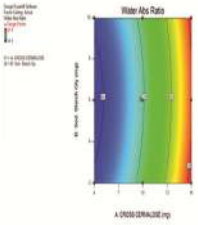
•The prepared tablets were evaluated for different post-compression parameters like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits.Disintegration time of various prepared fast dissolving tablets of Levocetrizine hydrochloride was found to be within the range of 50 to 120 seconds(3).

Response Surface Analysis

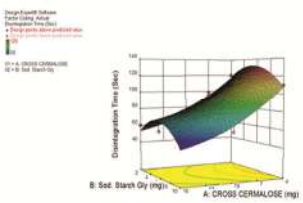
•Effect of variable in Disintegration Time-



•Effect of Variables in Water absorption ratio



3D-Response surface plot showing the influence of two different super disintegrants on disintegration time



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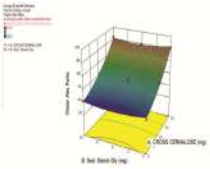

Composition of the Optimized Formulation, the Predicted and Experimental values of Response Variables, and Percentage Prediction Error.

Composition Crosscarmellose sodium :Sodium Starch glycolate	Responses variable	Experimental Value	Predicted Value	Percentage Error
16:10	Disintegration Time(sec)	61	45.28	3.47
	Water Absorption ratio	69.67	91.21	2.36

CONCLUSION

The response surface methodology (RSM) using Central Composite Design (Design Expert Software ,Version 10.0.Stat- Ease Inc, Minneapolis, MN) with 2-factor, 3-level Central Composite design with different ratio of super disintegrants - Crosscarmellose sodium and sodium starch glycolate was employed for optimization of fast dissolving tablets of Levocetrizine hydrochloride. The direct compression method in this study is relatively simple and safe and a stable, effective and pleasant tasting fast dissolving tablets, which has a good balance over disintegration time and water absorption ratio, was formulated.

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INTRODUCTION

1. INTRODUCTION

1.1 Oral Drug delivery system

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient(1)

Fig no-1.1 Oral Drug delivery

However, the potential for oral dosage form development is sometimes limited for therapeutic agents that are poorly absorbed in the gastrointestinal (GI) tract and unstable to various enzymes, in particular, to proteolytic enzymes, such as peptide and protein drugs. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions, such as pH, presence of food, transit times, expression of P-Glycoprotein (P-Gp) and CYP3A, as well as enzymatic activity in the

alimentary canal. Manipulation of these problems and challenges is considered an important strategy for improving oral drug delivery, and requires thorough understanding and appropriate integration of physicochemical principles, GI physiology and biochemistry, polymer science, pharmacokinetics, and pharmacodynamic. Over the last 3 decades, much research effort has been made in this area to address various biological and technological issues. Research has opened many novel avenues for the more effective, sustained, or rate-controlled oral delivery of both existing and new therapeutic agents, including peptide and protein drugs emerging from the biotechnology arena. Furthermore, the oral route offers an attractive approach of drug targeting at the specific sites within GI tract for the treatment of certain pathological conditions, such as gastro esophageal reflux disorder, gastro duodenal ulcers and inflammatory bowel disease, and stomach and colon cancers. Oral drug delivery systems (DDS) can be classified into three categories: immediate-release (IR) preparations, controlled-release (CR) preparations, and targeted-release preparations (2).

1.1.1. Physicochemical Barriers to Oral Drug Delivery

1.1.1.1 Aqueous solubility

It has long been recognized that before an orally administered drug becomes available for absorption at specific sites within the GI tract, it must be dissolved in the GI fluid. Since both the dissolution rate and the maximum amount of a drug that can be dissolved are dictated by the solubility of the drug in the medium, aqueous solubility of a drug could be regarded as a key factor responsible for low oral bioavailability of poorly water-soluble drugs, thereby limiting their therapeutic potential. Other issues related to low bioavailability for a sparingly soluble drug are lack of dose proportionality, substantial food effect and high intra- and inter subject variability, gastric irritancy, and slow onset of action.

1.1.1.2. Lipophilicity

The lipid solubility or lipophilicity of drugs has long been recognized as a prerequisite for transcellular diffusion across the intestinal membrane. Traditionally, the lipophilicity of drug substances is expressed as the apparent partition coefficient or distribution coefficient (log P)

between n-octanol and an aqueous buffer (pH 7.4), which is pH-dependent in the case of ionizable compounds. In general, compounds with low log P are poorly absorbed, whereas compounds with log P > _1 offer satisfactory absorption. Biological Barriers to oral Drug delivery is Intestinal epithelial barrier. The intestinal epithelial layer that lines the GI tract represents the major physical barrier to oral drug absorption. Structurally, it is made up of a single layer of columnar epithelial cells, primarily enterocytes and intercalated goblet cells (mucus secreting cells) joined at their apical surfaces by tight junctions or zonulaoccludens. These tight junctions are formed by the interaction of membrane proteins at the contact surfaces between cells and are responsible for restricting the passage of hydrophilic molecules during the paracellular transport. In fact, electrophysiological studies have suggested that epithelium gets tighter as it progresses distally, which has been implicated in a reduced paracellular absorption in the colon (3).

1.1.1.3. Gastrointestinal transit

Advanced CR dosage forms can provide a precise control over release rates or release patterns for most drugs, which is attractive from a clinical point of view, particularly minimization of peak and trough variations in plasma drug concentration, and chronotherapy. For example, the GI therapeutic system can provide zero-order drug absorption, in which the rate of drug absorption from the GI tract is constant and not determined by the amount of drug available in the GI tract. However, none of the CR systems can control the extent of drug absorption from the GI tract. This is mainly attributed to the fact that the extent of drug absorption from different regions of the GI tract is different, which in fact partly constitutes a basis for the biopharmaceutical classification scheme for drugs administered as extended-release (ER) products.

1.1.1.4. Food effect

The co-administration of drugs with food is known to result in decreased, delayed, increased, or accelerated drug absorption, which may have pharmacokinetic and pharmacodynamic implications. Most often, the food effect is non-specific and manifested as interplay between physiological effects of food (such as delayed gastric emptying, stimulated bile secretion, increased liver blood flow, and alterations in gastric and duodenal pH), physicochemical characteristics of the drug (e.g., water solubility), or its formulation (e.g., size, structural

organization, and dissolution profiles). In general, drugs those are most influenced are those that are primarily absorbed from the upper regions of the GI tract and/or are poorly water-soluble. Apparently, food does not have a clinically significant effect on the absorption of moderately soluble drugs having a pH-independent solubility, and those that are completely absorbed (e.g., glipizide, isosorbide-5- mononitrate, felodipine, and nifedipine) from the GI tract. Furthermore, food may indirectly influence the drug absorption by affecting drug release from both hydrophilic matrix as well as lipid matrix formulations. Tablets and capsules are the most popular solid dosage forms. However, many people face difficulty in swallowing tablets and hard gelatin capsules. This difficulty in swallowing is called dysphasia. It has been found that this problem has been encountered in all groups of patient, but especially with pediatric and geriatric populations. Thus, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes(4).

Pioneering developments in manufacturing equipment, capsule design, excipients and coating technologies have propelled liquid-fill encapsulation up the list of oral drug delivery options for the formulation development scientist. Together with an increasing number of poorly water soluble drugs, highly potent APIs, probiotics and biological within drug company pipelines, the potential applications for liquid-fill encapsulation has grown substantially in recent years. These drivers have served to reduce costs such that liquid-fill encapsulation is able to compete economically with soft gelatin capsule manufacturing (3, 4).

1.2. Fast dissolving tablets

Many patients find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with the prescription which results in noncompliance and ineffective therapy. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration to achieve better patient compliance. Rapidly disintegrating tablet are appreciated by significant segment of the population, particularly pediatric, geriatric, unconscious and bed-ridden patients who have difficulty swallowing conventional tablet and capsule . To provide the patient with the most convenient mode of administration, there is need to develop a fast-disintegrating dosage

form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without water, anywhere, anytime. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. FDTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies (5).

Orodispersible tablets are also called as orally disintegrating tablets, mouth dissolving tablets, rapid-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing. United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without and difficulty of swallowing. The concept of bilayer has been introduced to attain sustain release of drug which refers to tablet containing subunits that either may be same (Homogeneous) or different (Heterogeneous) (6). Bilayer tablet allows for designing and modulating the dissolution and release characteristics. Bilayer tablet are prepared for one layer for immediate release while second layer is designed to release drug, later as second dose or in an extended release pattern. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablet are preferred when the release profiles of the drugs are different from each other. The basic approach in development of ODT is the use of superdisintegrants like cross linked carboxy methyl cellulose (Crosscarmellose), Indion 414, crosspovidone etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva (7).

1.3. BILAYER TABLETS

The concept of bilayer has been introduced to attain sustain release of drug which refers to tablet containing subunits that either may be same (Homogeneous) or different (Heterogeneous). Bilayer tablet allows for designing and modulating the dissolution and release characteristics. Bilayer tablet are prepared for one layer for immediate release while second layer is designed to release drug, later as second dose or in an extended release

pattern. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablet are preferred when the release profiles of the drugs are different from each other (6).

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The problems of repetitive dosing and unpredictable absorption of the dosage form led to the concept of controlled drug delivery systems. The goal behind these delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization of the drug at the site of action which in turn reduces the dose requirement and thus providing uniform drug delivery. The rational of sustained release drug delivery is to ensure safety and to improve effectiveness of drugs as well as patient compliance (8).

Fig no-1.2. Bilayer tablets

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM

1. Bi-Layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odor and bitter taste can be masked by coating technique.
5. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
6. Easy to swallowing with least tendency for hang-up.
7. Suitable for large scale production.

DISADVANTAGES OF BILAYER TABLET DOSAGE FORM

1. Some drugs resist compression into dense compacts due to their amorphous nature and low density character.
2. Bitter tasting drugs, drugs with an objectionable odors or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients because the size of bilayer tablet is large as compared with normal conventional tablet.
4. Drugs with poor wetting, slow dissolution rate, highly absorptive in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability(9).

IDEAL CHARACTERSTICS OF BILAYER TABLETS

1. A bi-layer tablet should have elegant product identity while free of defects like chipping, cracking, mottling and contamination.
2. It should have sufficient strength to withstand mechanical shock during its manufacturing, packaging, shipping and dispensing.
3. It should have the chemical and physical stability to maintain its physical appearance over time. The bi-layer tablet must be able to release the pharmaceutical agents in a predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so that it may not alter the medicinal agents because of chemical instability (8, 9).

TYPES OF BILAYER TABLET PRESS

A. Single sided tablet press
B. Double sided tablet press
C. Bilayer tablet press with displacement monitoring.

A. Single sided press

The simplest design is a single-sided press with both chamber of the double feeder separated from each other. Two individual layer of the tablet produced as each chamber have gravity or forced fed with a different powder. When the die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two (pre and main compression) steps. The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer separation occurs when the tablet is produced (10).

Fig.1.3: Single Sided Tablet Press (Accura ATX –I model).

Limitation of single sided press

- No weight control of the individual layer.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in
- Poor de-aeration, capping and hardness problem.

Dwell time

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are major factor in producing a quality tablet, especially when we compress a difficult formulation (11).

B. Double sided tablet press

A double sided press has an individual fill station, pre compression and main compression for each layer. Most of the double sided presses with automate production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main

compression of that layer. Measured peak compression force is the signal used by the control system to reject out-of-tolerance tablet and correct the die fills depth when required.

Fig. 1.4: Double sided press (stokes model 720).

Limitation of double sided press

- Capping and separation of two layers during final compression of bilayer tablet.
- Most of the double sided press is provided with automated controller for monitoring compression fore and control tablet weight, but compression force control system is always based on measurement of compression but not at pre compression.
- At higher production speed, the risk of separation and capping increases.

C. Bilayer tablet press with displacement monitoring

The principle of bilayer tablet press is fundamentally different from the principle of compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. In this case the accuracy increase with reduced compression force. At higher production speed the risk of capping and separation of layer increase but can be reduced by sufficient dwell time at all four compression stages.

Fig no-1.5.Bilayer tablet press with displacement monitoring

Advantages

- Displacement weight monitoring for accurate independent weight control of individual layers.

- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Maximum prevention of cross contamination between the layers.
- A clear visual separation of the layers.
- Maximized yield (10, 11).

PREPARATION OF BILAYER TABLET

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layer of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included. To produced adequate tablet formulation certain requirement such as sufficient mechanical strength and desired drug profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and lamination. The compaction of material involved both the compressibility and consolidation.

Compression

It is defined as reducing in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation

It is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). The compression force on layer was found to be major factor influencing tablet delaminating.

Various steps involved in bilayer tablet formulation are as follow

- Filling of first layer.
- Compression of first layer.
- Ejection of upper punch.
- Filling of second layer.
- Compression of second layer.
- Ejected fully bilayer tablet (12).

CHALLENGES IN THE MANUFACTURING OF BILAYER TABLET

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice there are some manufacturing challenges.

Delamination

Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross contamination

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross contamination occurs. Proper dust collection goes a long way toward preventing cross contamination.

Production yield

To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single layer tablets.

Cost

Bilayer tablet is more expensive than single layer tablet for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must which means more time spent on formulation development, analysis and validation. Therefore, it is critical to obtain an insight into the root causes to enable deign of a robust product and process (11, 12)

EVALUATION OF BILAYER TABLET

1. **Tablet Thickness and Size**

Thickness and diameter were important for uniformity of tablet size. Thickness and diameter was measured using Vernier caliper.

2. **Tablet Hardness**

The resistance of tablets to shipping or breakage under conditions of storage. Transportation and handling before usage depends on its hardness. The hardness of the tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in **kg/cm2.** Other tester used to check tablet hardness is strong-cub tester, Pfizer tester, the Erweka tester and schleuniger tester.

3. **Friability**

Friability is the measure of tablet strength. Roche friabilator was used to determine friability using the following procedure. Weighed accurately twenty tablets and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablet through a distance six inches with each

revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined

% friability = [(initial wt. of tablet-final wt of tablet)/initial wt. of tablets]*100

4. **Uniformity of weight/weight variation**

Twenty tablets were selected random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation as per IP and none deviates by more than twice the percentage.

5. **Dissolution studies**

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery.\ Drug release studies were carried out using USP dissolution apparatus at 100 rpm, 37-+ 0.5oc, and pH1.2 buffer (900ml) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH6.8 buffer (900ml) and experiment continued for another 10 hours. At different time intervals 5 ml of the samples were withdrawn and replaced with 5 ml of drug free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis (12).

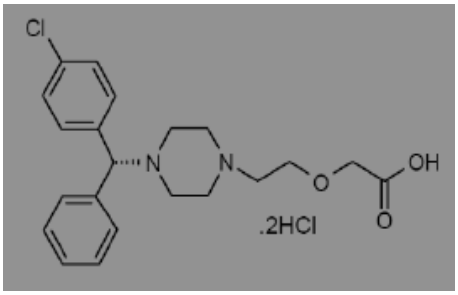
1.4. DRUG PROFILE

1.4.1. Levocetrizine Hydrochloride

Levocetrizine, the active isomer of its parent compound, cetirizine, is one of the newest second-generation antihistamines. After only 1 dose, it has been found to suppress the cutaneous allergic response to a significantly greater extent than similar drugs in its class. In addition, Levocetrizine is effective in the treatment of nasal congestion. Levocetrizine hydrochloride, have low oral bioavailability due to high first pass metabolism. To minimize such problems Levocetrizine hydrochloride is formulated in the form of fast dissolving tablets where the drug is rapidly disintegrated in mouth within fraction of seconds and improves the oral drug bioavailability (13).

Levocetrizine hydrochloride is a third generation non-sedative antihistamine, developed from the second-generation antihistamine, cetirizine. Levocetrizine works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to receptors. In addition, it is an important drug in the treatment of allergies and idiopathic urticaria. Levocetrizine is called a non sedating antihistamine as it does not enter the brain in significant amounts, and is therefore unlikely to cause drowsiness. Levocetrizine has several pharmacokinetic properties that are desirable for an antihistamine providing a combination of both potency and safety (14). Its clinical advantages are derived from its rapid and extensive absorption, limited distribution and its very low degree of metabolism. The incorporation of Levocetrizine in an extended-release of oral dosage form would have many disadvantages such as aiding in enhancement of bioavailability. Hydrogels are one of the upcoming classes of polymer-based controlled-release drug delivery systems. Besides exhibiting swelling-controlled drug release, hydrogels also show stimuli-responsive changes in their structural network and hence, the drug releases (15).

It's having following **physicochemical properties**-



Systematic (IUPAC) name : 2-[2-[4-[(R)-(4-chlorophenyl)-phenyl-methyl] piperazin-1-yl]ethoxy]acetic acid

- **Dose**- 5mg orally for adults
- **Storage**-Store at 68-70˚c
- **Class**-Antihistaminic
- **Pharmacology**-Inhibition of H_1 receptor

1.4.1.1. Physicochemical properties of Levocetrizine hydrochloride

- **Molecular formula**- $C_{21}H_{25}ClN_2O_3$
- **Molecular weight**-388.15g/mol
- **Boiling point**-542.1˚c at 760 mm of Hg
- **Solubility**- Water soluble
- **Color**-white, crystalline powder
- **Drug interection**-Advair,Discus,Aspirin,Crestor(Rosuvastatin)

1.4.1.2. Pharmacokinetic properties of Ambroxol hydrochloride

- **Absorption-**rapidly absorbed
- **Tmax-**0.9 hour
- **C max-**270 and 308 mg/ml
- **Distribution-**Plasma protein binding 92%
- **Metabolism**-14%
- **Elimination-**Elimination by urine (85.4%)
- **Bioavailability**- Greater than 70%

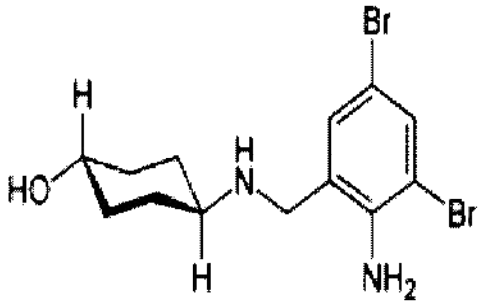
1.4.2. Ambroxol Hydrochloride

Ambroxol Hydrochloride is a potent mucolytic & mucokinetic, capable of inducing bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes network of fibres in tenacious sputum is broken. It is used as expectorant and variety of respiratory disorders including asthma, bronchitis and used in the treatment of cough. It is particularly useful if mucus plugs are present. In pediatrics, the most common triggers are viral illnesses such as those that cause the common cold. Due to sore throat conditions, the pediatrics patient experiences difficulty in swallowing a tablet type of dosage form. Liquid dosage forms are having their own limitation from stability and dose measurement perspectives. Thus, fast disintegrating tablets would serve as an ideal dosage form for pediatric patients. Ambroxol is a metabolite of bromohexine with similar matrix following exposure to aqueous fluid [2, 3].It is chemically described as Trans-4- Controlled-release (CR) formulations have been [(2-Amino-3, 5-dibromobenzyl) amino]-cyclohexanol. It is introduced into drug therapy with two main purposes: to an expectoration improver and a mucolytic agent used in reduce the number of single doses per day improving the treatment

of acute and chronic disorders characterized patient compliance of treatments and to decrease the by the production of excess of thick mucus. It has been fluctuations of plasma levels, in order to obtain better successfully used for decades in the form of its therapeutic efficacy and lower toxicity. There are many hydrochloride as a secretion-releasing expectorant in a controlled-release pharmaceutical systems currently variety of respiratory disorders (16).

Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus. The drug is a mucoactive drug with several properties including secretolytic and secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract, which play an important role in the body's natural defense mechanisms. It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall, in improving its transport and in providing protection against infection and irritating agents. Ambroxol also provides pain relief in acute sore throat. Pain in sore throat is the hallmark of acute pharyngitis (17).

It has following physicochemical properties-



Systematic (IUPAC) name:4-[(2-Amino-3,5-dibromophenyl)methyl amino]cyclohexan-1-ol hydrochloride

- **Dose-** 30 mg,75 mg daily
- **Storage-**store below 15˚c
- **Category-**Mucolytic agent
- **Pharmacology-**Active mucolytic agent
- **Uses-**Respiratory diseases like Emphysema with bronchitis, Pneumoconiosis, COPD**.**

1.5.1. Physicochemical properties of Ambroxol Hydrochloride

- **Category-**Mucolytic agent
- **Melting point-**235-240˚c
- **Onset of action-**30 mins after administration
- **Side effects-** Allergic reaction, mild GI effects

1.5.2. Pharmacokinetic properties of Ambroxol hydrochloride

- **Metabolism-** by liver
- **Plasma half life-** 1-3 hours
- **Excretion-** hepatic

1.5. Optimization techniques

Optimization with factorial designs is a powerful, efficient and systemic tool that shortens the time required for the development of pharmaceutical dosage forms and improves research and development work. The response surface method has been applied to dosage form design for various kinds of drugs by many researchers.

The computer software have been used almost at every step during the entire optimization cycle ranging from selection of design, screening of factors, use of response surface designs, generation of the design matrix, plotting of 3-D response surfaces and 2-D contour plots, application of optimum search methods, interpretation of the results, and finally the validation of the methodology (Potter, 1994). Verily, many software packages lead the user through the data analysis even without a mathematical model or statistical equations in sight. Use of pertinent software can make the DoE optimization task a lot easier, faster, more elegant and economical. Specifically, the erstwhile impossible task of generating varied kinds of 3-D response surfaces manually is accomplished with phenomenal ease using appropriate software (Bolton, 1987; Potter, 1994).Various types of computer softwares are used like-Design Expert MINITAB,JMP, CARD,MATREX,Cornerstone™,ECHIP,GRG2,DoE PC IV,STATISTICA etc(18).

Experimental designs

The designs used for simultaneous methods are frequently referred to as response surface designs. Various experimental designs frequently involved in the execution of RSM can broadly be classified as:

A Factorial design and modifications

B Central Composite design and modifications

C Mixture designs

D D-optimal designs (19)

A. Factorial design and modifications

Factorial designs (FDs; full or fractional) are the most frequently used response surface designs. These are generally based upon first-degree mathematical models. Full FDs involve studying the effect of all the factors (n) at various levels (x), including the interactions amongst them, with the total number of experiments as xn(12). The simplest FD involves study of two factors at two levels, with each level coded suitably. FDs are said to be symmetric, if each factor has same number of levels, and asymmetric, if the number of levels differs for each factor . Besides RSM, the design is also used for screening of influential variables and factor influence studies. The mathematical model associated with the design consists of the main effects of each variable plus all the possible interaction effects, i.e., interactions between the two variables, and in fact, between as many factors as are there in the model (20).

The mathematical model generally postulated for FDs is given as Equation 4.

$Y = b0 + b1X1... + b12X1X2... + b123X1X2X3... + e$ **… (4)**

Where, bi, bij and e represent the coefficients of the variables and the interaction terms, and the random experimental error, respectively. The effects (coefficients) in the model are estimated usually by multiple linear regression analysis (MLRA).

B Central composite design and its modifications

Also known as Box-Wilson design, it is the most often used design for second-order models (Box & Wilson, 1951). Central composite design (CCD) is comprised of the combination of a two-level factorial point (2n), axial or star points (2n) and a central point. Thus the total number of factor combinations in a CCD is given by 2n +2n + 1. The axial points for a two-factor problem include, (± a, 0) and (0, ± a), where a is the distance of the axial points from the center. A two factor CCD is identical to a 32 FD with square experimental domain (a is ± 1), as shown in Fig. 10. 6 (a). On the other hand, when a is Ö2 = 1.414, the experimental domain is spherical in shape, as shown in Fig. 10. 6 (b). A face centered cube design (FCCD)

results when the same positive and negative distance is taken from the center in a CCD. A rotatable CCD (RCCD) is identical to FCCD except that the points defined for the star design are changed to [± (2n)1/4,… 0] and those generated by the FD remain unchanged. In this way, the design generates information equally well in all the directions, e.g., the variance of the estimated response is same at all the points on a sphere centered at the origin (21).

C. Mixture designs

In FDs and the CCDs, all the factors under consideration can simultaneously be varied and evaluated at all the levels. This may not be possible under many situations. Particularly, in pharmaceutical formulations with multiple excipients, the characteristics of the finished product usually depend not so much on the quantity of each substance present but on their proportions. Here, the sum total of the proportions of all excipients is unity and none of the fractions can be negative. Therefore, the levels of the various components can be varied with the restriction that the sum total should not exceed one. Mixture designs are highly recommended in such cases . In a two-component mixture, only one factor level can be independently varied, while in a three-component mixture only two factor levels, and so on. The remaining factor level is chosen to complete the sum to one. Hence, they have often been described as experimental designs for the formulation optimization .For process optimization; however, the designs like FDs and CCDs are preferred (22).

D. D-optimal designs

If the experimental domain is of a definite shape, e.g., cubic or spherical, the standard experimental designs are normally used. However, in case the domain is irregular in shape, D-optimal designs can be used. These are non-classical experimental designs based on the D-optimum criterion, and on the principle of minimization of variance and covariance of parameters. The optimal design method requires that a correct model is postulated, the variable space defined and the number of design points fixed in such a way that will determine the model coefficients with maximum possible efficiency. One of the ways of obtaining such a design is by the use of exchange algorithms using computers. These designs can be continuous, i.e., more design points can be added to it subsequently, and the experimentation can be carried out in stages. D-optimal designs are also used for screening of factors. Depending upon the problem, these designs can also be used along with factorial, central composite and mixture designs (21, 22)

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LITERATURE REVIEWS

2. LITERATURE REVIEW

2.1. Literature Review of Fast dissolving tablets

- **Sharma A et.al** formulated the fast dissolving tablets of Aceclofenac to produce the intended benefits. Fast dissolving tablets of Aceclofenac were prepared using superdisintegrants crosspovidone, Crosscarmellose sodium and sodium starch glycolate and surfactant sodium lauryl sulfate, using the direct compression method. The tablets prepared were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, *in vitro* disintegration time and *in vitro* dissolution time. The tablets disintegrated within 18 to 49 seconds. Almost 90% of drug was released from all formulated ions within 15 min. Stability studies of the tablets at 40±2°/75%±5% RH for 3 months showed no significant drug loss. The formulation containing 6% of Crosscarmellose sodium was found to give the best results. Apart from fulfilling all official and other specifications, the tablets exhibited higher rate of release.
- **Saroha K et al.** In present study, the fast dissolving tablets of Amoxicillin Trihydrate were prepared by direct compression technique using microcrystalline cellulose (MCC) as direct compressible diluents. Sodium starch glycolate (SSG) and Crosscarmellose sodium (CCS) used as synthetic superdisintegrants. The swelling indices of the super disintegrants were also compared. Among both the superdisintegrants, crosscarmellose sodium showed the highest swelling index. The blends showed satisfactory flow properties. Eight formulations were prepared using different concentrations of Superdisintegrants and were investigated for their effect on the disintegration time and dissolution rate of the tablets. Tablets were also evaluated for weight variation, hardness, thickness, friability and drug content. All the tablets exhibited acceptable pharmaco-technical properties. Tablets prepared with the blend of CCS (60mg) exhibited quicker disintegration. According to the present study, it was found that tablets of batch F8 (blend containing CCS 60mg) showed better disintegrating property as well as % drug release (99.78% within 25 min.) than the most widely used synthetic superdisintegrants like SSG in the formulations of FDTs.

- **Kumare M M et.al.** Prepared Atenolol **tablets** were prepared by direct compression technique using two different superdisintegrants in combination by co-process mixing

and by physical mixing. Crosscarmellose sodium and Crosspovidone were used as superdisintegrants in combinations in the different ratio (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed excipients was found to be < 250, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.11-1.14. Fast dissolving tablets of Atenolol were prepared using the co-processed superdisintegrants and evaluated for pre-compression and post compression parameters. Based on *in-vitro* dispersion time (approximately 20sec) CP1 formulation was tested for *in-vitro* drug release pattern in pH 6.8 Phosphate buffer and drug excipients interaction were studied with DSC. Among the designed formulations, the formulation (CP1) containing 4% w/w of co-processed superdisintegrants (1:1 mixture of Crospovidone and Croscarmellose sodium) emerged as the overall best formulation based on drug release characteristics in pH 6.8 phosphate buffer.

- **Rane D R et al.** formulated fast dissolving tablets of Albendazole to achieve a better dissolution rate and further improving the bioavailability of the drug. Fast dissolving tablets prepared by direct compression and using super disintegrants in different concentration and evaluated for the pre-compression parameters. The prepared tablets were evaluated for post compressional evaluation. Among all, the formulation F3 containing 5%w/w superdisintegrant Crospovidone and 20%w/w Microcrystalline Cellulose was considered to be best formulation, which release up to99.097% in 40 min.
- **Patil B S et al. studied in** the present work fast dissolving tablets of Granisetron hydrochloride have been prepared by direct compression method. Formulations were evaluated for pre compressional parameters such as angle of repose, % compressibility and Hausner's ratio. The prepared tablets were evaluated for post compressional parameters such as hardness, friability, thickness, *in vitro* dispersion time, wetting time, and water absorption ratio. The prepared tablets were characterized by FTIR studies. Effect of superdisintegrants [such as croscarmellose sodium, sodium starch glycolate and crospovidone,] on wetting time, *in vitro* dispersion time and stability parameter has been studied. No chemical interaction between drug and excipients was confirmed by FTIR studies.

- **Behin Sundara Raj et al.** studied the fast Dissolving Tablet (FDT) was prepared using direct compression method using Crospovidone and Sodium starch glycolate as the super disintegrants. Amongst all formulations, formulation F3 prepared by a combination of both Crospovidone and Sodium starch glycolate showed least disintegrating time, and faster dissolution of 87%.Combination of super disintegrants was found to be better to formulate fast dissolving tablets of Amlodipine besylate.
- **Baddam Set al.** Ofloxacin is a broad-spectrum, synthetic fluoroquinolones antibacterial agent for oral administration. The bioavailability of ofloxacin in the tablet formulation is approximately 98 %. It is extremely bitter in taste, water insoluble drug. It is used to treat variety of infections. The purpose of the present research work was to formulate and evaluate the fast dissolving tablets of ofloxacin by direct compression method using different super disintegrants like PGS (pregelatinized starch), SSG (sodium starch glycolate), PVPP (ploy vinyl poly pyrrolidone) in different concentrations 5 %, 7.5 %, 10 %. FT-IR spectroscopy was used to investigate the physical characteristics of the complex. The blend was evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The tablets were evaluated for weight variation, hardness, and friability, and disintegration time, water absorption ratio, wetting time, drug content uniformity and *in vitro* dissolution. Tablet formulated with 10 % (F9) of PVPP showed low disintegration time (8 ± 2), wetting time (4.3 ± 0.3) and friability than the other batches. The % cumulative release of drug from tablet (F9) was found to be more than 87 % within 10 minutes. It was concluded from the study that ofloxacin may improve patient compliance especially pediatric and geriatric patients and increase the efficacy of drug for treating infections.
- **Panigrahi R et al. prepared the** fast dissolving tablets of Lisinopril were designed using combination of synthetic superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate in a ratio of 5:10 and 10:5 respectively by direct compression method. The blends of all formulations were evaluated for various pre-formulation factors. Tablets were evaluated for weight variation, hardness, disintegration time, drug content, friability and in vitro dissolution. The formulation of Lisinopril containing 10% crospovidone and 5% croscarmellose showed disintegration time of 145±0.502 secs respectively with 99% drug release within 30

mins. The results showed that super disintegrants used in combinations shows better disintegrating property. The FTIR spectra showed no interactions among them.

2.2. Literature Review of Bilayer Sublingual tablets-

- **Shashidhar K R et.al**. studied on attempt to formulate and evaluate fast dispersible tablets of a model antiemetic drug, prochlorperazine maleate using natural disintegrants prepared by direct compression method. The drug excipients compatibility studies were carried out using FTIR.

- **Swapna K et.al.** studied to develop and optimize sublingual tablets of Montelukast sodium and Levocetrizine di hydrochloride which are effective drugs in the treatment of asthma. They used the methods- sublingual tablets of Montelukast sodium and Levocetrizine di hydrochloride were prepared by direct compression method using sodium starch glycolate, crosspovidone (CP), and Crosscarmellose sodium (CCS) as superdisintegrants. From the study, it can be concluded that sublingual route has potential to improve the bioavailability of the drug by avoiding first pass metabolism, to provide quicker onset of action and to improve patient compliance in the management of asthma.

- **Sathik J**et al. studied formulation and evaluation bilayer tablets of Levocetrizine and Montelukast for treating allergic rhinitis effectively. Anti-allergic medicines (eg, some antihistamines) can cause adverse events such as somnolence and sedation. The Combining Montelukast with Levocetrizine gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by persistent allergic rhinitis. Taking this into account different formulations were prepared by wet granulation method using natural Tamarind Seed Polysaccharide and synthetic HPMCK100, K15M and K4M release rate controlling hydrophilic polymers and evaluation tests are done.

- **Evneet K Bhatia et al.** discussed the therapeutic advantages of bilayer tablet by releasing the medicaments for the immediate relief and then maintaining the level of medicament for the certain time in order to get the sustain release of drug.

- **Bakka Aet.al.** studied bilayer tablets for treating respiratory tract infections. In present study Levofloxacin is selected as antibiotic to treat upper and lower respiratory tract infections, but antibiotic taking along with a mucolytic drug shows reduction of acute exacerbation and days of illness. So we selected Ambroxol hydrochloride as mucolytic drug along with antibiotic Levofloxacin. Bi-layered tablets were formulated consisting of Levofloxacin as immediate release layer and Ambroxol HCL as sustain release layer because its half-life is only 4 hours so it will not produce pharmacological effect along with Levofloxacin, so Ambroxol layer is sustained by using polymers. Levofloxacin IR layer was prepared, by using starch as disintegrants which shows sufficient hardness and friability and released the drug within one hour. Ambroxol HCL SR layer was prepared, by using HPMC K4M (11%) and HPMC K100M (12.5%) mixture, sustained the drug release upto 12th hour. Bilayer tablets prepared by wet granulation method were evaluated for thickness, hardness, weight variation, friability and drug content. FT-IR studies clearly indicated t ;hat there was no drug-polymer interaction

2.3. Literature review of Levocetrizine Hydrochloride tablets

- **Chaitanya Prasad MK et al.** studied a simple and rapid high-performance liquid chromatographic (HPLC) method for the determination Levocetrizine has been developed. The chromatographic system consisted of a Water2695 binary gradient pump, Water 2487 dual wavelength absorbance detector, and Empower 2software. Separation was achieved on the XTerra symmetry C18 column at room temperature. The sample was introduced through an injector valve with a 20 µL sample loop. The results obtained showed a good agreement with the declared content. Recovery values of Levocetrizine in tablets were from 99.57-100.48 %. The proposed method is rapid, accurate and selective; it may be used for the quantitative analysis of Levocetrizine from raw materials, in bulk drugs and other dosage formulations.

- **Mehul Dekivadia, Avinash Gudigennavar et.al.** studied about fast dissolving tablets of Levocetrizine HCl were prepared using sodium starch glycolate, Crosscarmellose sodium and Crosspovidone as superdisintegrants by direct compression method. The tablets prepared were evaluated for various parameters like weight variations, hardness, friability, in vitro dispersion time, drug content, wetting

time, in vitro drug release, FTIR and XRD. The formulation (MD6) contains Crosspovidone and Sodium Starch Glycolate shows better Disintegration time and 99% drug release within 20 min.

- **Patel Nilam K.1 and Pancholi S.** discussed the simple, accurate, and precise AUC curve spectrophotometric method was developed for simultaneous determination of Montelukast sodium (MTKT) and Levocetrizine dihydrochloride (LCTZ) in combined pharmaceutical dosage forms. The proposed methods can be successfully applied in routine work for the determination of MTKT and LCTZ in combined dosage form.
- **T. Raja et al.** discussed on simple, accurate, rapid and precise isocratic reversed-phase high-performance liquid chromatographic method has been developed and validated for simultaneous determination of Levocetrizine and Montelukast sodium in tablets.. The high recovery and low relative standard deviation confirm the suitability of the method for routine determination of Levocetrizine and Montelukast sodium in bulk and tablet dosage form.
- **Uddhav Bagul** et.al. studied on the objective of the current study was to develop and evaluate mouth dissolving tablets of Levocetrizine dihydrochloride by using sublimation technique. Mouth dissolving tablets of Levocetrizine dihydrochloride were prepared by direct compression method using different concentrations of spray dried mannitol (Perlitol SD 200), menthol and camphor. The sublimation technique is used to increase the porosity of the tablets in which menthol and camphor were used as subliming agents which in turn forms the porous structure on the surface of tablets after sublimation.
- **Subhakanta Kanungo** et al. studied on the basis of to formulate crosslink polyacrilic resin based, technologically optimized, melt-in-mouth tablet (MIMT) containing 5 mg of Levocetrizine Dihydrochloride that was intended to disintegrate rapidly in the oral cavity so as to form a stabilised dispersion and possessing adequate physicochemical stability. Different grades of crosslink polyacrilic resin were utilised to prepare MIMTs; employing complexation technique; and using additives like Mannitol DC, Ac-di-sol, Avicel-pH 112, Tusil pinapple, Saccharine sodium, Aerosil and Magnesium stearate.

2.4. Literature review of Ambroxol hydrochloride

- **Sharma D et al.** studied on the objective of the present study was to prepare the fast disintegrating tablet of Ambroxol Hydrochloride for respiratory disorders such as bronchitis, asthma and cough for pediatrics.
- **Gadireddy S. et.al**. studied on RP-HPLC method and validated as per ICH guidelines for the estimation of Ambroxol HCl and Levocetrizine. Simultaneous Estimation of Ambroxol HCl and Levocetirizine.2HCl were carried out by RP- HPLC using sodium phosphate buffer (PH 3.0): Methanol (30:70) and column Phenomenex Luna C-18 (250x4.6 mm, 5um) as a stationary phase and peak was observed at 230 nm which was selected as a wavelength for quantitative estimation. After the development of the method, it was validated for specificity, linearity, precision, accuracy, robustness and ruggedness studies.
- **Jayachandran D L** et.al. studied in the formulation and evaluation of Ambroxol hydrochloride using Eudragit RS100.the tablets are formulated by wet granulation methods and evaluated for various parameters including stability studies were done.
- **G. Ramana** et.al. discussed to develop oral controlled release matrix tablets of Ambroxol hydrochloride by melt granulation technique using hydrophilic meltable binders such as PEG 6000 and Gelucire 50/13(Stearoyl polyoxyl glycerides). The FT-IR and DSC analysis indicated the stability and compatibility of drug with excipients. The *in-vitro* dissolution studies of the matrix tablets prepared using only meltable binder released almost 90 % of the drug in the first 2 hours, which lead to the incorporation of HPMC K4M into the formulations as a release retardant to control the drug release for a prolonged period of time.
- **Sandhiya.K. M et.al.** formulated the oral sustained release matrix tablets of Ambroxol HCl in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Ambroxol Hydrochloride is a potent mucolytic agent capable of inducing bronchial secretions used in the treatment of respiratory disorders. Differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. Matrix tablets of Ambroxol Hydrochloride were formulated employing hydrophilic polymers HPMC K100M, Carbopol934P and hydrophobic polymer Ethyl cellulose as release retardant polymers.

- **Nilesh V. Ingle** formulated the matrix tablets of Ambroxol Hydrochloride for Sustained release.Hydroxy propyl Methyl Cellulose (HPMC) K4M and Guar Gum as the retardant polymers and studies the effect of various formulation factors such as polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. Matrix tablets were prepared by wet granulation method and prepared tablets were evaluated for weight variation, friability, hardness, thickness and in vitro dissolution studies.
- **S.Jayaprakash et al.** discussed the sustained release (SR) tablets of Ambroxol Hydrochloride were prepared by wet granulation method. The effect of hydrophilic matrices on the behavior of Ambroxol Hydrochloride using different polymers and their Combinations. The prepared tablets were evaluated for physical characteristics such as Hardness, Thickness, Friability, Weight variation, Content uniformity and In-vitro release behavior. The drug release from the optimized formulation was found to follow zero order kinetics. It was also found linear in Higuchi's plot. Thus the phenomenon of drug release showed that the release of optimized formulation is controlled by diffusion. It is concluded that as compare to other formulations, optimized formulation fulfilled all criteria for SR tablet dosage form.
- **Hemul V. Patel et.al.** studied on Oral sustained release matrix tablets of Ambroxol HCl were formulated in order to improve efficacy, reduce the frequency of administration, and better patient compliance. The overall objective of the present work was to develop an oral sustained release Ambroxol HCl tablets prepared by direct compression method, using hydrophilic hydroxyl propyl methylcellulose and hydrophobic ethyl cellulose polymer as a rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Mean dissolution time is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer.

2.5. Literature review of Bilayer sublingual tablets of Levocetrizine hydrochloride

- **Jahufar Sathik et al.** studied Bilayer tablet of Montelukast Sodium and Levocetrizine HCL was successfully developed. Immediate release of Montelukast was formulated with crosscaramellose sodium and Levocetrizine layer with starch

granules as disintegration. IR spectrum revealed that there is no disturbance in the principle peaks of pure drugs of Montelukast sodium and Levocetrizine HCL. This indicates there was no interaction between the drug and excipient.The formulation showed good flow property and compressibility index. The angle of repose was ranged from 25.0˚±1.40 to 31.4˚±0.97 for Montelukast sodium and 25.2˚±1.40 to 29.5˚± 0.68 for Levocetrizine HCL. The compressibility index was found range from 11.6 to 22.2 for Montelukast sodium and 14.1 to 27.8 Levocetrizine HCL. Hausner's ratio was found to be 1.143 to 1.287 for Montelukast sodium and 14.1 to 27.8 for Levocetrizine HCL. The result of the angle of repose indicates good flow property of the granules and the values of compressibility index further showed support for the flow property. The prepared tablets were evaluated for hardness, friability, weight variation, drug content uniformity. The results were found within the limits. Among the various formulations prepared, Formulation F8 with crosscarmellose sodium (20%) shows minimum disintegration time and improved dissolution properties compared to formulation F-1 to F-7.

- **Moiz Md et al.** formulating Montelukast in sustained release layer and Levocetrizine as immediate release layer as it improves and increases the stability by reducing the acid base interactions of both the drugs in combination there by increasing the bioavailability. Taking this into account different formulations were prepared by wet granulation method using natural Tamarind Seed Polysaccharide and synthetic HPMCK100, K15M and K4M release rate controlling hydrophilic polymers. The formulations were evaluated for hardness, weight variation, friability, swelling index and drug content uniformity. The in vitro release of drug from the formulations was studied in pH 1.2 acidic buffers and pH 7.4 phosphate buffer, and it was found that the prepared tablets were able to sustain the release of the drug upto 12hours. The release of Montelukast and Levocetrizine of both layers from the tablets was found to be diffusion controlled and the release mechanism was non-Fickian based on the n value of Korsmeyer-peppas plot. The FTIR studies were performed on three optimized formulations (F4, F12, F16) and the plain drug controls(Levocetrizine, Montelukast).From the observed peaks it is evident that the polymers used and the drugs were found to be mutually compatible chemically. The Pharmacokinetic Studies were performed in two groups of male wistar rats. One group was administered with the optimized formulation containing tamarind Seed Polysaccharide (F12) while Plain Montelukast oral suspension acted as control in the second group. The results indicate

that the formulation optimized with 1:4(drug:TSP) was able to sustain the release of Montelukast up to 12hours.Insrease in Tmax and AUC(0-á) also were also observed in the studies indicating efficient sustained action and improved bioavailability of the drug. The formulated bilayer tablets using natural polymers provided immediate release of Levocetrizine and sustained release of Montelukast and therefore hold promise as an alternative dosage form in the treatment of allergic rhinitis and bronchial asthma.

- **SwapnaK et.al.** studied to develop and optimize sublingual tablets of Montelukast sodium and Levocetrizine dihydrochloride which are effective drugs in the treatment of asthma. They used the methods- sublingual tablets of Montelukast sodium and Levocetrizine dihydrochloride were prepared by direct compression method using sodium starch glycolate, crospovidone (CP), and croscarmellose sodium (CCS) as superdisintegrants. From the study, it can be concluded that sublingual route has potential to improve the bioavailability of the drug by avoiding first pass metabolism, to provide quicker onset of action and to improve patient compliance in the management of asthma

2.6. Literature review of Bilayer sublingual tablets of Ambroxol hydrochloride

- **Kumar S et al.** made to design and develop of Sustained Release Ambroxol Hydrochloride Matrix Tablets using the combination Guar gum and Karaya gum, in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Ambroxol hydrochloride is a potent mucolytic agent capable of inducing bronchial secretions used in the treatment of respiratory disorders. The Sustained release matrix tablets containing 75g Ambroxol hydrochloride were developed using different drug: polymer ratios.
- **Laksmi A P et al.** formulate Levofloxacin hemihydrate immediate release and Ambroxol HCl sustain release bilayer tablets in order to improve patient compliance. All the formulations were prepared by wet granulation method because of poor flow property exhibited by pure drugs. HPMC K4M and HPMC K100M were used for sustaining the release rate of Ambroxol from Ambroxol layer and superdisintegrants like sodium starch glycolate was used for immediate release of levofloxacin from immediate release layer. All the prepared formulations were evaluated for weight variation, hardness, thickness, friability, disintegration and dissolution tests. The

release pattern of Ambroxol was fitted to different kinetic models and among all the formulations; F11 of Ambroxol has shown a release rate up to 12 hours. All the formulations could be good expressed by Higuchi equation as the plots shows good linearity, and the correlation coefficient (r2) for the best formulation F11 was 0.9991 with slope n=0.530, which appears to show a coupling of diffusion and erosion mechanism-so called anomalous diffusion . F2 of levofloxacin disintegrated less than 12min. So, F11 of Ambroxol and F2 of levofloxacin were selected as best formulations. Stability studies were conducted at250 c for long term studies and 450 c for accelerated studies for the best formulations.

2.7. Literature review of optimized Levocetrizine hydrochloride tablets

- **Devireddy S et al.** studied orally disintegrating tablets of Levocetrizine dihydrochloride were formulated with different superdisintegrants (sodium starch glycollate, croscarmellose sodium, and crospovidone) using mannitol as a diluents. Tulsion-335_, Indion-204_, and poly kyron T-134_ cation exchange resins were used as taste-masking agents.
- **Mathure D M et.al.** formulated controlled release pellets of cetirizine dihydrochloride and optimize the effect of formulation variables i.e. concentration of Eudragit RLPO and ethyl cellulose. The experimental design selected was 32 full factorial designs using these two variables.
- **Gohel M C et al.** formulated, developed and Optimize Orodispersible Tablets (ODTs) of Cetirizine Hydrochloride. By direct compression method using different superdisintegrants i.e.Croscarmellose, Crosspovidone and Sodium Starch Glycolate. A 3design was applied to systematically optimize the drug disintegration concentration of Crospovidone (X1) and concentration of Croscarmellose(X2) was selected as independent variables. The Disintegration time (Y1) and Wetting time (Y2) were selected as dependent variable

2.8. Literature review of optimized Ambroxol hydrochloride tablets

- **Jain BV et al** made to prepare taste masked suspension of Ambroxol Hydrochloride by abating the intensely bitter taste of Ambroxol Hydrochloride. Taste abatement was done by complexing of Ambroxol hydrochloride with different Ion Exchange Resins

(IER) like Tulsion 335 and Indion 214 in different ratios. The prepared suspensions were evaluated for taste, drug content, particle size, viscosity, and sedimentation volume and drug release. The resonates prepared with drug- T335 ratio (1:2) at pH 8, gave maximum drug loading. Suspension containing above resonates showed more than 80% *In vitro* drug release within 30 min. Prepared formulation also showed good stability and can retain its palatable taste. The developed formulation was an additional advantage like simplification of manufacturing procedure and is economical. Thus, the "patient friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, can be successfully formulated using this technology.

- **Kuraku S et al.** discussed Ambroxol hydrochloride sustained release matrix tablets for treating bronchial asthma and chronic bronchitis. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in and cost-effective manufacturing process. Ambroxol hydrochloride tablets were prepared by direct compression method by using hydrophilic polymer like HPMC K4M, HPMC K15M and HPMC K100M. The prepared matrix tablets were tested for evaluation parameters such as drug content, hardness, friability, weight variation, in-vitro drug release and release kinetics. The formulation FS12 showed better sustained release of about 99.81% and follows Higuchi order with high regression value of 0.993 with complete drug release in 12 hrs made it to select as an optimized formulation compared with other formulations. Thus it was selected for *in vivo* investigation.
- **Bankar A B et al**. discussed the sustained release matrix formulation for Ambroxol hydrochloride was designed and developed to achieve a 12 h release profile. Using HPMC K15M and Eudragit RSPO as an inert matrix forming agent to control the release of Ambroxol hydrochloride. The matrix tablets for these formulations were prepared by direct compression and their in-vitro release tests were carried out for a period of 12 hours using USP dissolution test apparatus (type I- Basket) at 37±0.5°C and 100 rpm speed.A 32 full factorial design was used for optimization by taking the concentration of HPMC K15M (X1) and Eudragit RSPO (X2) were selected as independent variables, where as initial release at the 2hrs (Y1, % drug release), release rate at the 8 hrs (Y2, % drug release) and the concentration of Ambroxol

hydrochloride released in 12 hrs (Y3, % drug release) were chosen as dependent variables. The optimized formulation F4 follows Hixon Croswell order release kinetics with non-Fickian diffusion mechanism. From the study, it was concluded that the release of Ambroxol hydrochloride can be effectively sustained using combination of HPMC K15M and Eudragit RSPO.

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AIM &OBJECTIVES

3. AIM AND OBJECTIVES

3.1. AIM

To formulate sublingual tablets of Levocetrizine Hydrochloride and evaluate of formulated sublingual tablets of Levocetrizine Hydrochloride. To perform Statistical optimization of sublingual tablets of Levocetrizine Hydrochloride using different super distegrantants. Also formulation of sublingual bilayer tablets of Levocetrizine Hydrochloride and Ambroxol Hydrochloride were done along with evaluation of formulated sublingual bilayer tablets of Levocetrizine Hydrochloride and Ambroxol Hydrochloride and Statistical optimization of bilayer sublingual tablets of Levocetrizine Hydrochloride and Ambroxol Hydrochloride

3.2. OBJECTIVES

3.2.1. To formulate sublingual tablets of Levocetrizine Hydrochloride for treatment of allergic reaction.

3.2.2. To perform preformulation study, drug and excipients characterization.

3.2.3. To optimize Levocetrizine Hydrochloride tablets.

3.2.4. To evaluate the prepared Levocetrizine Hydrochloride tablets for post compression parameter.

3.2.5. To formulate sublingual bilayer tablets of Levocetrizine Hydrochloride and Ambroxol hydrochloride.

3.2.6. Evaluation of prepared bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol Hydrochloride.

3.2.7. To optimize bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride.

3.2. To study statistical optimization of formulated bilayer tablets of Levocetrizine Hydrochloride and Ambroxol Hydrochloride

3.3. RATIONALE

Levocetrizine, the active isomer of its parent compound, cetrizine, is one of the newest second-generation antihistamines. After only 1 dose, it has been found to suppress the cutaneous allergic response to a significantly greater extent than similar drugs in its class. In addition, Levocetrizine is effective in the treatment of nasal congestion. Levocetrizine hydrochloride, have low oral bioavailability due to high first pass metabolism (1)

While Ambroxol Hydrochloride is a potent mucolytic &mucokinetic, capable of inducing bronchial secretion. It depolymerizes mucopolysaccharides directly as well as by liberating lysosomal enzymes network of fibres in tenacious sputum is broken. It is used as expectorant and variety of respiratory disorders including asthma, bronchitis and used in the treatment of cough. It is particularly useful if mucus plugs are present (2).

In research work study, a 32 full factorial experimental design was employed to optimize the formulation of pellets. In order to optimize formulations, the amounts of Eudragit RLPO (X1) and the amount of the ethyl cellulose (X2), were chosen as independent variables. Eudragit RLPO, being hydrophilic is more permeable to water so it promotes release of drug. Ethyl cellulose is hydrophobic and retards drug release being less permeable to water. Hence the combination of a release promoting and retarding polymers was used to obtain controlled drug release. Selection of response variables was crucial. The target was to maintain the drug release throughout 24 hr but simultaneously to achieve maximum release at the end of this time period. Therefore the response variables selected for evaluation of controlled release were percent of drug release in 24hr and time required for release of 50% of the drug (t50%). The t50% should be as close to 12 hr as possible as it would be the more realistic measure of maintenance of controlled release (3).

Though the previous report study as given above the parameters used was wetting time and disintegration time but in present thesis, two responses were taken,1)Disintegration time(R1) and 2) Water absorption Ratio(R2).The computer software have been used almost at every step during the entire optimization cycle ranging from selection of design, screening of factors, use of response surface designs, generation of the design matrix, plotting of 3-D response surfaces and 2-D contour plots, application of optimum search methods, interpretation of the results, and finally the validation of the methodology (Potter, 1994).Using Design Expert 9.06 the statiscal optimization of sublingual Bilayer tablets of Levocetrizine hydrochloride and Ambroxol Hydrochloride was done.

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MATERIALS
& METHODOLOGY

4. MATERIALS AND METHODOLOGY

4.1. Preformulation studies

The various preformulation studies were performed in this section.

4.1.1Materials used for Preformulation studies

Table-4.1 Materials used for preformulation studies

Sl no	Materials	Suppliers
1.	Levocetrizine hydrochloride	Balaji Drugs,Mumbai-8
2.	Ambroxol hydrochloride	Balaji Drugs,Mumbai-8
3.	Crosscarmellose sodium	Himedia,Mumbai-8
4.	Sodium Starch glycolate	Merk specialist pvt limtd,Mumbai-18
5.	Camphor	Merk specialist pvt limtd,Mumbai-18

4.1.2. Methods used for Preformulation studies

1. Organoleptic properties

The bulk characterization parameters were studied by taking a small amount of sample in naked eye; color, texture etc were noticed.

2. Solubility Studies

A small quantity of the drug sample was taken in a test tube and solubility was determined by dissolving the drug in 1mlof various solvent like water methanol, ethanol, and phosphate buffer etc.

3. **Melting point Determination**

Small quantity of the drug was taken in a capillary tube (fused at one end) and placed in a melting point apparatus and temperature was noted at melting of drug.

4.2 DRUG EXCIPIENTS COMPATIBILITY STUDY

4.2.1. Materials and Instruments used for Drug Excipients Compatibility Study

Table-4.2 Materials used for drug excipients compatibility studies

Sl no	Materials	Suppliers
1.	Levocetrizine hydrochloride	Balaji Drugs,Mumbai-8
2.	Ambroxol hydrochloride	Balaji Drugs,Mumbai-8
3.	Crosscarmellose sodium	Himedia,Mumbai-8
4.	Sodium Starch glycolate	Merk specialist pvt limtd,Mumbai-18
5.	Camphor	Merk specialist pvt limtd,Mumbai-18

4.2.2. INSTRUMENTS USED IN THE STUDY

Table-4.3 Instruments used for drug compatibility studies

INSTRUMENTS	COMPANY NAME
1.FTIR	Bruker Model no-10059736
2.DSC	Parkine almer 2000

4.2.3. DRUG EXCIPIENTS COMPATIBILITY STUDIES USING FTIR

The FTIR studies were performed to study drug-excipients interaction in the range 4000-400/cm using an FTIR spectrometer (IR AFFINITY-1 CE, Shimadzu, Japan) equipped with a pyroelectric detector. Data were acquired using IR solution software (1**).**

4.2.4. DRUG EXCIPIENTS COMPATIBILITY STUDIES USING DIFFENTIAL SCANNING CALORIMETRY (DSC)

In drug formulation it is essential to evaluate the possible interactions between the active principle and the superdisintegrants. Levocetrizine hydrochloride and Ambroxol hydrochloride powder were mixed with various superdisintegrants in the ratio of 1:1 and the resulting physical mixture was examined on differential scanning calorimeter. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 100C/minute). Thermo gram of pure drug was used as a reference (2).

4.3. Estimation of Levocetrizine hydrochloride in analytical sample

4.3.1. Materials and instruments used for estimation of Levocetrizine hydrochloride in analytical sample

Table-4.4 Materials used estimation of Levocetrizine hydrochloride in analytical sample

Sl no	Materials	Supplier name
1	Levocetrizine Hydrochloride	Balaji Drugs,Mumbai-8
2	Disodium hydrogen phosphate	Merk specialist pvt limtd,Mumbai-18
3	Potassium dihydrogen phosphate	Merk specialist pvt limtd,Mumbai-18

Table-4.5 Instruments used for estimation of Levocetrizine hydrochloride in analytical sample

INSTRUMENTS	COMPANY NAME
1.Weighing balance	Denver instruments
2.UV visible spectrophotometer	Shimadju,Model no:UV 1800240V

4.3.1. DETERMINATION OF ABSORTION MAXIMA (λ max) OF LEVOCETRIZINE HYDROCHLORIDE IN PHOSPHATE BUFFER

100mg of drug was weighed and dissolved in 100ml of phosphate buffer 6.8 in volumetric flask.10ml was transferred in another 100ml of volumetric flask and diluted up to 100ml(standard working solution).The spectra of the solution was run in 200-400nm UV-visible spectrophotometer.

4.3.1.1. PREPARATION OF STANDARD CURVE OF LEVOCETRIZINE HYDROCHLORIDE IN PHOSPHATE BUFFER 6.8

Standard calibration curve of Levocetrizine hydrochloride in acetate buffer pH 6.87: Solution ranging from 2 to 10 mg/ml were prepared using buffer (pH 6.8); separately, absorbance was measured for each solution at wavelength of 231nm using Shimadzu UV/visible 1800 spectrophotometer, graph was plotted for absorbance versus concentration of Levocetrizine hydrochloride(3).

4.3.1.2. SIMULTANEOUS ESTIMATION OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE BY USING UV-VISIBLE SPECTROSCOPY

Preparation of standard stock solution:

Accurately weighed 25 mg of each Levocetrizine hydrochloride and Ambroxol hydrochloride API were transferred to separate amber colored volumetric flask of 100 ml capacity, and dissolved in 50 ml distilled water and then diluted up to the mark with the same

to get 250 µg/ml LCT & AMB.

Preparation of standard working solution:

Standard working solution of 100 µg/ml concentrations of both drugs in separate amber colored volumetric flask from standard stock solution was freshly prepared before the use.

Preparation of calibration curve of LVT &AMB

Calibration curve of both drugs were prepared using standard solution. Also overlapping of spectra was determined (4).

4.4. OPTIMISATION OF FAST DISSOLVING TABLETS OF LEVOCETRIZINE HYDROCHLORIDE

4.4.1. Materials required for preparation of Fast dissolving tablets of Levocetrizine Hydrochloride

Table-4.6 Materials used for preparation of fast dissolving tablets of Levocetrizine Hydrochloride

MATERIALS	MANUFACTURERS/SUPPLIERS
1.LEVOCETRIZINE HYDROCHLORIDE	Balaji Drugs,Mumbai-8
2.CROSSCARMELLOSE SODIUM	Himedia,Mumbai-8
3.SODIUM STARCH GLYCOLATE	Merk specialist pvt limtd,Mumbai-18
4.MICROCRYSTALLINE CELLULOSE	Merk specialist pvt limtd,Mumbai-18
5.SODIUM SACHARINE	Balaji Drugs,Mumbai-8
6.TALC	Balaji Drugs,Mumbai-8
7.MAGNESSIUM STEARATE	Balaji Drugs,Mumbai-8
8.MANNITOL	Merk specialist pvt limtd,Mumbai-18
9.VANELLIN	Merk specialist pvt limtd,Mumbai-18
10.DISODIUM HYDROGEN PHOSPHATE	Merk specialist pvt limtd,Mumbai-18
11.POTASSIUM DIHYDROGEN PHOSPHATE	Merk specialist pvt limtd,Mumbai-18

4.4.2. INSTRUMENTS USED IN THE STUDY

Table-4.7 Instrument used in the study

INSTRUMENTS	COMPANY NAME
1.DIGITAL WEIGHING BALANCE	Denver instruments
2.UV-VISIBLE SPECTROPHOTOMETER	Shimadju,Model no:UV 1800240V
3.TABLETS COMPRESSION MACHINE	Shakti Pharmatech,Ahmedabad,India
4.HARDNESS TESTER	Rolex India
5.FRIABILITY TESTER	Rochi Friabilator
6.DISINTEGRATION TESTER	Rolex India
7.FTIR	Bruker Model no-10059736
8.DSC	Parkine almer 2000

4.4.3. SOFTWARE USED IN THE STUDY

Table-4.8 Software used in the study

NAME OF THE SOFTWARE	VERSION	COMPANY NAME
Design expert	9.0.6.2	Stat-Ease,Inc.2021 East Hennepin Ave,Suite480,Minneapolis,MN55413

4.4.4. FORMULATION OF LEVOCETRIZINE HYDROCHLORIDE SUBLINGUAL TABLETS

Levocetrizine hydrochloride fast dissolving tablets were formulated by using the ingredients SSG and CCS. All the ingredients with drug except Magnesium stearate were taken in the mortar. The powder blend was mixed well by using mortar and pestle for 15 to 30 minutes, and then mixture was passed through # 80 sieves. Finally Magnesium stearate was added as lubricant and mixed thoroughly. The powder blend was compressed using 16 stations tablet compression machine (Shakti Pharmatech,Ahmedabad,India) to produce tablets of Levocetrizine hydrochloride weighing 120mg having diameter of 6mm(5).

4.4.5. OPTIMISED LEVOCETRIZINE HYDROCHLORIDE SUBLINGUAL TABLETS

Using Design Expert 9.06, the formulation for Levocetrizine Hydrochloride sublingual tablets were prepared with incorporation of 2 super disintegrants-Crosscarmellose sodium and Sodium starch glycolate**.** The selection of these superdisintegrants was done on the basis of effectiveness and cost. Crosscarmellose sodium having concentration up to 5% & same of Sodium starch glycolate is 4-8%.

Table-4.9 Ingredients for optimized Levocetrizine hydrochloride sublingual tablets

Formulation no	Run	Levocetrizine hydrochloride	Crosscarmellose sodium	Sodium starch glycolate	Microcrystalline cellulose	Sodium saccharine	Talc	Magnesium stearate	Mannitol
1	1	5	16	10	63	4	1	1	20
2	2	5	10	6	73	4	1	1	20
3	3	5	4	6	79	4	1	1	20
4	4	5	4	2	83	4	1	1	20
5	5	5	4	10	75	4	1	1	20
6	6	5	10	6	73	4	1	1	20
7	7	5	16	6	67	4	1	1	20
8	8	5	10	2	77	4	1	1	20
9	9	5	10	10	69	4	1	1	20
10	10	5	16	2	71	4	1	1	20

Each tablets contains 120mg

For optimization study, following parameters were incorporated-

Table-4.10 Levels and responses of optimization

LEVELS	**RESPONSES**
-1	Disintegration time(R1)
0	Water absorption ratio(R2)
+1	

4.4.6. PRE-COMPRESSION PARAMETER

Prior to compression, powder was evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose method. Compressibility index of powder was determined by Carr's index and Hausner's ratio.

4.4.6.1. BULK DENSITY

Accurately weighed powder was transferred into graduated measuring cylinder. The powder bed was then made uniform and the volume occupied by the powder was noted as per graduation marks on the cylinder as ml. It is expressed in g/ml and calculated as below

$$D=M/Vb$$

Where M-mass of the powder

Vb-bulk volume of the powder

4.4.6.2. TAPPED DENSITY

It is the total mass of the powder to the tapped volume of the powder. It is expressed in g/ml.

Calculated by formula

$$Dt=M/Vt$$

Where M-mass of the powder

Vt-tapped volume of the powder (6).

4.4.6.3. Compressibility index (I)

Carr's index and Hausner's ratio measure the propensity of the powder to be compressed and the flow of granules, given by formula-

Carr's index, $I= (Dt-Db/Dt) X100$

Hausner's ratio=tapped density/bulk density

4.4.6.4. Angle of repose (ɵ)

This is the maximum angle between the surface of the pile of a powder and the horizontal plane. Sufficient quantities of granules were passed through a funnel from a particular height onto a flat surface until it formed a heap, which touched the tipped of the funnel. The height of the radius of the heap was measured. The angle of repose was calculated as

$$\text{Angle of repose, } \tan\theta=h/r$$

Where h-height of the pile

r-radius of the pile (7).

4.4.7. POST-COMPRESSION PARAMETER

4.4.7.1. Hardness

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in kg/cm2(8).

4.4.7.2. Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier calliper (Pico India). The average values were calculated.

4.4.7.3. Uniformity of weight

Weight variation test was done as per standard procedure. 20 tablets from each formulation was weighed using an electronic balance, and the average weight was calculated.

4.4.7.4. Friability

The friability of tablets was measured using six tablets using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted, and reweighed. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

Friability (%) = ([Initial weight − Final weight]/initial weight) × 100(9).

4.4.7.4. Drug content

10 tablets were powdered and the powder equivalent to 15 mg was dispersed in phosphate buffer pH 6.8. Volume of the solution made up to 10 mL by media. The mixture was filtered and 1 ml of the filtrate was diluted to 10 mL using phosphate buffer pH 6.8. The absorbance of the sample preparations was measured at 231.0 nm for Levocetrizine hydrochloride.

4.4.7.5. Wetting time

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined (8, 9).

4.4.7.6. Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wet tablet was then weighed. Water absorption ratio,**R = 100 (Wa - Wb)/Wb**

Where Wb and Wa are the weights of tablet before and after water absorption, respectively

4.4.7.7. In-vitro disintegration time

Disintegration time for sublingual tablets was determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temperature was 37±0.5°C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured (7, 8).

4.5. OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE

4.5.1 .Materials required for Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

Table-4.11 Materials used for bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

MATERIALS	MANUFACTURERS/SUPPLIERS
1.LEVOCETRIZINE HYDROCHLORIDE	Balaji Drugs,Mumbai-8
2.AMBROXOL HYDROCHLORIDE	Balaji Drugs,Mumbai-8
3.CROSSCARMELLOSE SODIUM	Himedia,Mumbai-8
4.SODIUM STARCH GLYCOLATE	Merk specialist pvt limtd,Mumbai-18
5.MICROCRYSTALLINE CELLULOSE	Merk specialist pvt limtd,Mumbai-18
6.SODIUM SACHARINE	Balaji Drugs,Mumbai-8
7.TALC	Balaji Drugs,Mumbai-8
8.MAGNESSIUM STEARATE	Balaji Drugs,Mumbai-8
9.MANNITOL	Merk specialist pvt limtd,Mumbai-18
10.CAMPHOR	Merk specialist pvt limtd,Mumbai-18
11.DISODIUM HYDROGEN PHOSPHATE	Merk specialist pvt limtd,Mumbai-18
12.POTASSIUM DIHYDROGEN PHOSPHATE	Merk specialist pvt limtd,Mumbai-18

4.5.2. INSTRUMENTS USED IN THE STUDY

Table-4.12. Instruments used in the study

INSTRUMENTS	COMPANY NAME
1.DIGITAL WEIGHING BALANCE	Denver instruments
2.UV-VISIBLE SPECTROPHOTOMETER	Shimadju,Model no:UV 1800240V
3.TABLETS COMPRESSION MACHINE	Shakti Pharmatech,Ahmedabad,India
4.HARDNESS TESTER	Rolex India
5.FRIABILITY TESTER	Rochi Friabilator
6.DISINTEGRATION TESTER	Rolex India
7.FTIR	Bruker Model no-10059736
8.DSC	Parkine almer 2000

4.5.3 SOFTWARE USED IN THE STUDY

Table-4.13.Materials used for preformulation studies

NAME OF THE SOFTWARE	VERSION	COMPANY NAME
Design expert	10.0	Stat-Ease,Inc.2021 East Hennepin Ave,Suite480,Minneapolis,MN55413

4.5.4. Formulation of Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

4.5.4.1. Preparation of optimized Levocetrizine hydrochloride layer

Levocetrizine hydrochloride fast dissolving tablets were formulated by using the ingredients SSG and CCS. All the ingredients with drug except Magnesium stearate were taken in the mortar. The powder blend was mixed well by using mortar and pestle for 15 to 30 minutes, and then mixture was passed through # 80 sieves. Finally Magnesium stearate was added as lubricant and mixed thoroughly. The powder blend was compressed using 16 stations tablet compression machine (Shakti Pharmatech,Ahmedabad,India) to produce tablets of Levocetrizine hydrochloride weighing 120mg having diameter of 6mm(5).

Table-4.14 Materials used for preparation of optimized Levocetrizine hydrochloride layer

Sl no	Ingredients	Amounts(mg)
1	Levocetrizine hydrochloride	5
2	Crosscarmellose sodium	16
3	Sodium starch glycolate	10
4	Microcrystalline cellulose	63
5	Sodium saccharine	4
6	Talc	1
7	Magnesium stearate	1
8	Mannitol	20

4.5.4.2. Preparation of optimized Ambroxol hydrochloride layer

Ambroxol hydrochloride fast dissolving tablets were formulated by using the ingredients Sodium starch glycolate and Camphor. All the ingredients with drug except Magnesium stearate were taken in the V-blender. The powder blend was mixed well at 20 rpm for 15 minutes, and then mixture was passed through # 40 sieves. Finally Magnesium stearate was added as lubricant and mixed thoroughly. The powder blend was compressed using 8 stations tablet compression machine (Shakti Pharmatech, Ahmadabad, India) to produce tablets of Ambroxol hydrochloride weighing 60mg having diameter of 6mm (10).

Table-4.15 Materials used for Ambroxol hydrochloride layer

Formulation no	Run	Ambroxol hydrochloride(mg)	Sodium starch glycolate(mg)	Camphor(mg)	Microcrystalline cellulose(mg)	Sodium saccharine(mg)	Talc(mg)	Magnesium stearate(mg)	Mannitol(mg)
1	1	7.5	2	5	2	3	3	5	32.5
2	2	7.5	10	5	2	3	3	5	24.5
3	3	7.5	2	15	2	3	3	5	22.5
4	4	7.5	10	15	2	3	3	5	14.5
5	5	7.5	2	7	2	3	3	5	30.5
6	6	7.5	10	7	2	3	3	5	22.5
7	7	7.5	3	5	2	3	3	5	31.5
8	8	7.5	3	15	2	3	3	5	21.5
9	9	7.5	3	7	2	3	3	5	29.5

4.5.4.3Formulation of Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

The Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride were prepared by using two layers as discussed above. The optimized Levocetrizine hydrochloride layer and Ambroxol hydrochloride were compressed using double sided tablet press (11).

4.5.5 Evaluation of Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

4.5.5.1. Pre-Compression Parameter

Prior to compression, powder was evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose method. Compressibility index of powder was determined by Carr's index and Hausner's ratio (12).

Bulk density and Tapped density

Tapped density is the total mass of the powder to the tapped volume of the powder. It is expressed in g/ml.It is expressed in g/ml.

Bulk density, $D=M/V_{b,}$ Where M-mass of the powder

V_b-bulk volume of the powder

Tapped Density, Dt=M/Vt, Where M-mass of the powder

Vt-tapped volume of the powder.

Compressibility index (I) and Hausner ratio

Carr's index and Hausner's ratio measure the propensity of the powder to be compressed and the flow of granules (6).It is given by formula-

Carr's index, I= (Dt-Db/Dt) X100

Hausner's ratio=tapped density/bulk density

Angle of repose (ɵ)

This is the maximum angle between the surface of the pile of a powder and the horizontal plane. Sufficient quantities of granules were passed through a funnel from a particular height onto a flat surface until it formed a heap, which touched the tipped of the funnel. The height of the radius of the heap was measured (13).The angle of repose was calculated as

Angle of repose, tanɵ=h/r

Where h-height of the pile

r-radius of the pile.

4.5.5.2. POST-COMPRESSION PARAMETER

Hardness

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in kg/cm2(14).

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated (7)

Uniformity of weight

Weight variation test was done as per standard procedure. 20 tablets from each formulation were weighed using an electronic balance, and the average weight was calculated (8).

Friability

The friability of tablets was measured using six tablets using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted, and reweighed. The percentage friability was calculated from the loss in weight as given in equation below (8). The weight loss should not more than 1%.

Friability (%) = ([Initial weight − Final weight]/initial weight) × 100.

Drug content

10 tablets were powdered and the powder equivalent to 15 mg was dispersed in phosphate buffer pH 6.8. Volume of the solution made up to 10 mL by media. The mixture was filtered and 1 ml of the filtrate was diluted to 10 mL using phosphate buffer pH 6.8. The absorbance of the sample preparations was measured at 243.0 nm for Ambroxol hydrochloride (8)

Wetting time

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined (7, 8)

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wet tablet was then weighed (7, 8)

Water absorption ratio (**R) = 100 (Wa - Wb)/Wb**

Where Wb and Wa are the weights of tablet before and after water absorption, respectively

In-vitro disintegration time

Disintegration time for sublingual tablets was determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temperature was 37±0.5℃. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured (15)

4.5.6. Optimization Data Analysis and Numerical Optimization

Various Response surface methodological techniques in computations for the current optimization study were performed employing Design Expert Software (Version 10.0, Stat-Ease Inc, Minneapolis, MN) (10). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented below:

$Y = \beta o + \beta 1\ X_1 + \beta 2\ X_2 + \beta 3\ X_1 X_2 + \beta 4\ X^2_1 + \beta 5\ X^2_2 + \beta 6\ X_1 X^2_2 + \beta 7\ X^2_1 X_2$

Where, βo is the intercept representing the arithmetic average of all quantitative outcomes of 10 runs; β1 to β7 are the coefficients computed from the observed experimental values of Y; and X1 and X2 are the coded levels of the independent variable(s).

The terms X1X2 and Xi2 (i = 1 to 2) represent the interaction and quadratic terms, respectively (10). Statistical validation of the polynomial equation was established on the basis of ANOVA provision in the Design Expert Software. Various feasibility and grid searches were conducted to find the composition of optimum formulations. Also, the 3-D

response surface graphs and 2-D contour plots were constructed using the output files generated (7).

RESULT AND DISCUSSION

Table-4.16 Preformulation study

Sl no	Parameters	Result
1	**Bulk characterization**	• Levocetrizine hydrochloride is crystalline powder • Ambroxol hydrochloride is crystalline powder
2	**Color**	• Levocetrizine hydrochloride is white powder • Ambroxol hydrochloride is off white
3	**Odour**	Both are odorless
4	**Solubility**	Soluble in • water, • ethanol, • phosphate buffer 6.8
5	**Melting point**	• Levocetrizine hydrochloride has melting point 215˚c.

		• Ambroxol hydrochloride has melting point 240˚c.

From the result it was clearly seen about various preformulation parameters of both the drugs Levocetrizine hydrochloride and Ambroxol hydrochloride had its own level of preformulation parameters-solubility both soluble in water, melting point 215˚c for Levocetrizine hydrochloride and240˚c for Ambroxol hydrochloride.

4.2.1.1. FTIR STUDIES

The FTIR study showed following interpretation-.

Table-4.17. IR interpretation of the drug and excipients

Sl no	Functional Groups	Levocetrizine Hydrochloride()	Levocetrizine Hydrochloride+ Sodium starch glycolate	Ambroxol Hydrochloride	Ambroxol Hydrochloride+Crosscarmelosee sodium
1	N-H stretching	1135	3283	3098.45	-
2	C-H stretching	1433	995(vinyl)	3025.23(vinyl)	-
3	C=C stretching	-	1582(enolic)	1486	1486
4	Amides	1742	-	1688(1,4 quinones)	1688(1,4 quinones)
5.	C-N vibration	1317	-	-	-
6	C-Cl streching	756	756	731.05	701.99

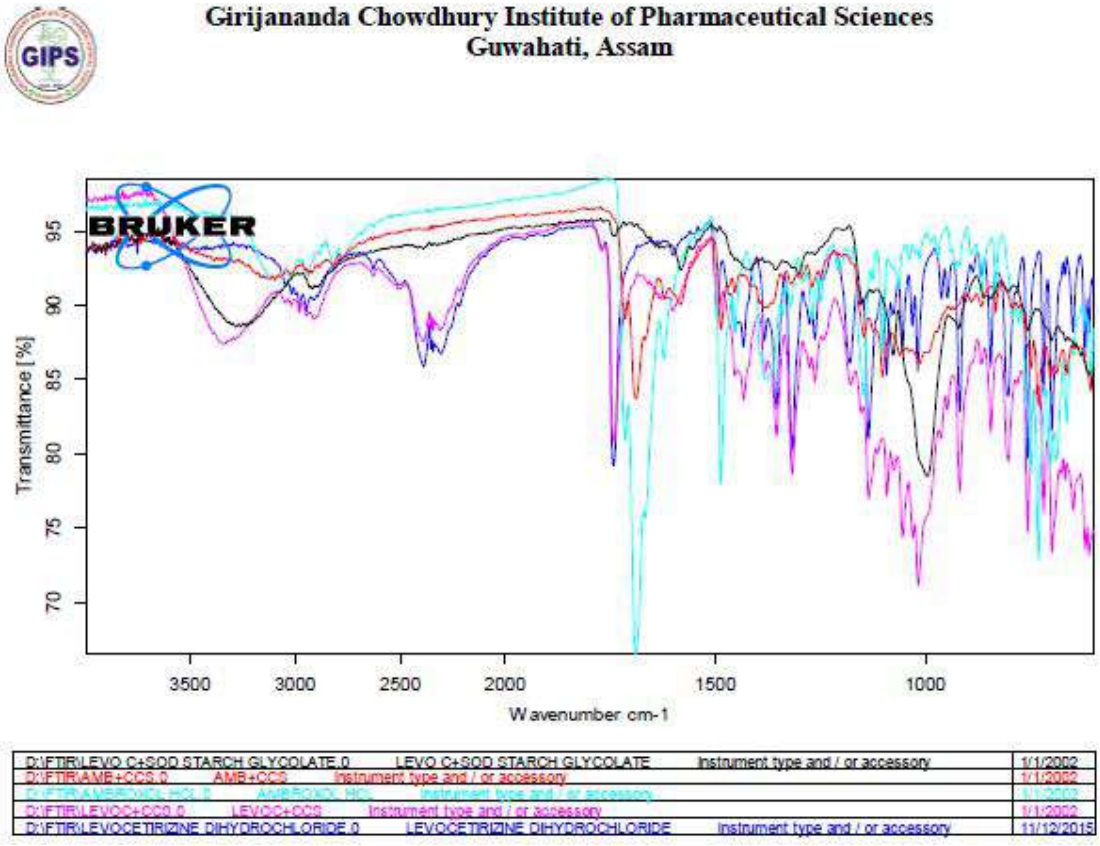

Fig no-4.1: FTIR study of all drug mixture

In the FTIR study, the various spectra were found as given table. The N-H stretching was found in 1135 cm-1 in Levocetrizine hydrochloride, 3283 cm-1 in Levocetrizine hydrochloride + Sodium starch glycolate,3098.45cm-1 in Ambroxol hydrochloride. Also C-H stretching was found in 1433 cm-1 in Levocetrizine hydrochloride,995 cm-1 in Levocetrizine hydrochloride +Sodium starch glycolate ,3025 cm-1 in Ambroxol hydrochloride and C-Cl stretching was found in 756 cm-1 in Levocetrizine hydrochloride,731 cm-1 in Ambroxol hydrochloride and 701.99 cm-1 in Ambroxol hydrochloride+Crosscarmellose sodium. As we study about the structural formula of the drugs, excipients, the following functional groups were seen. So we can conclude that there is no incompatibility found in drug and excipients in the given samples

4.2.1.2. DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

The final DSC report will give the overlapping of Levocetrizine Hydrochloride, Crosscarmellose sodium .It was seen that no such incompatibility between drug and excipients were found.

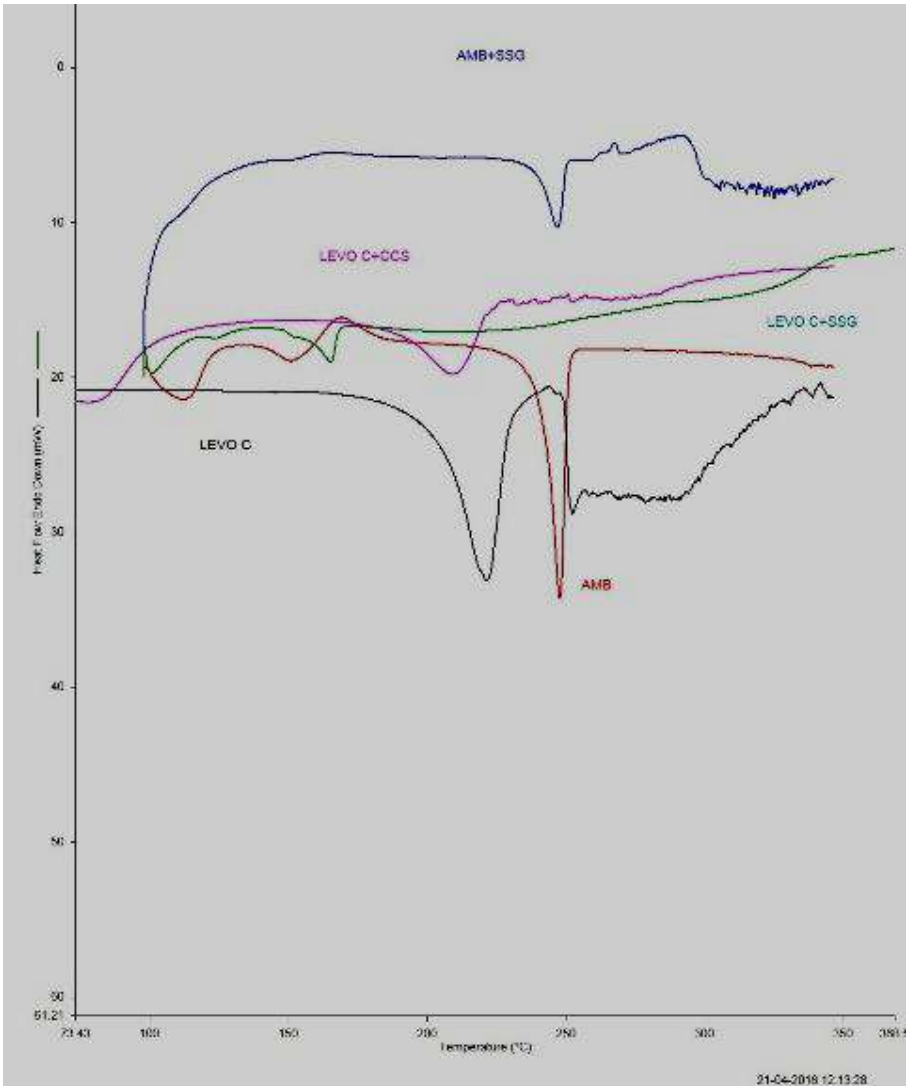

Fig no-4.2: DSC study of all drug mixture

From the DSC study, the results were founds as-

The melting point of Levocetrizine hydrochloride was found at 220˚c (215˚c), Ambroxol hydrochloride was found at 242˚c (240˚c) etc were in the range. Here we can conclude that there is no type of drug excipients compatibility study found.

4.2. Estimation of Levocetrizine hydrochloride and Ambroxol hydrochloride in analytical sample

4.2.1. Absorption spectra of the Levocetrizine hydrochloride

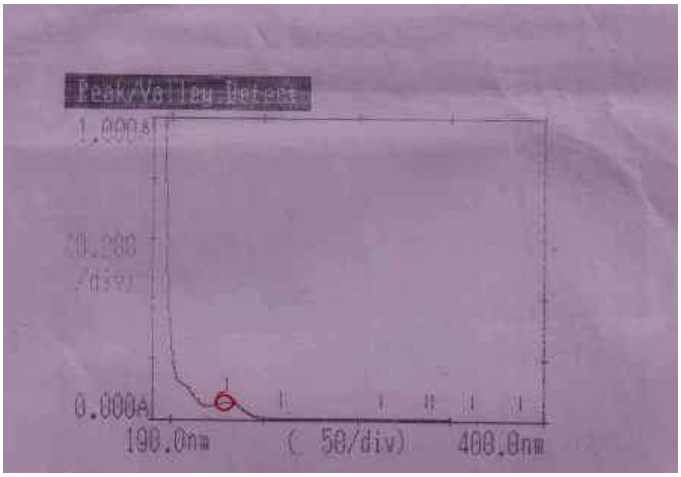

Fig no-4.3: Absorption spectra of Levocetrizine hydrochloride

In the above figure, the absorption spectra of the drug, Levocetrizine was given. The absorption spectra was prepared using phosphate buffer 6.8, in the range of 200-400nm.The peak was found to be in 230nm (U.S.P 231nm).

The standard curve of Levocetrizine hydrochloride was prepared as per procedure given in the methodology section. The following table shows the absorbance at various concentrations. Figure shows standard curve of Levocetrizine Hydrochloride.

Table-4.18.Absorbance of Levocetrizine hydrochloride in different concentration

Sl no	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.232
3	4	0.4374
4	6	0.6359
5	8	0.8333
6	10	0.9872

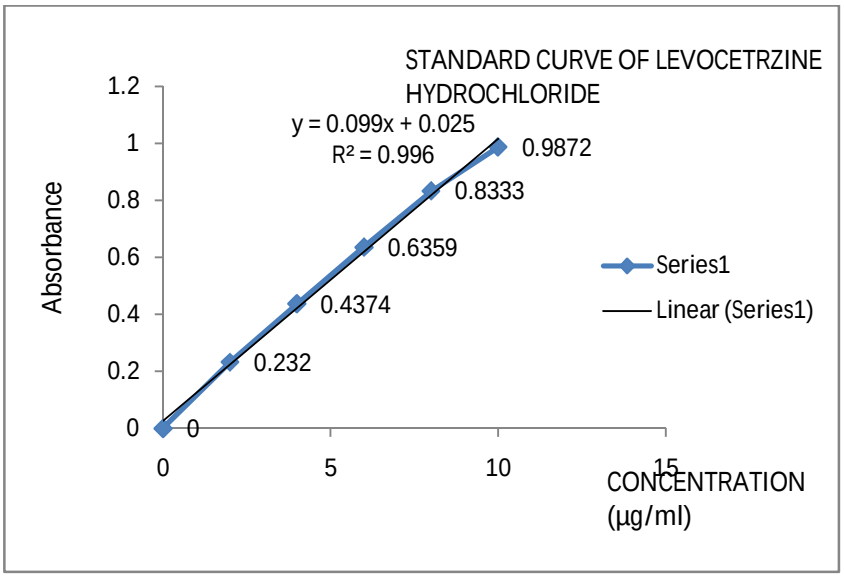

Fig no-4.4: Standard curve of Levocetrizine hydrochloride

4.2.2 Absorption spectra of Ambroxol hydrochloride

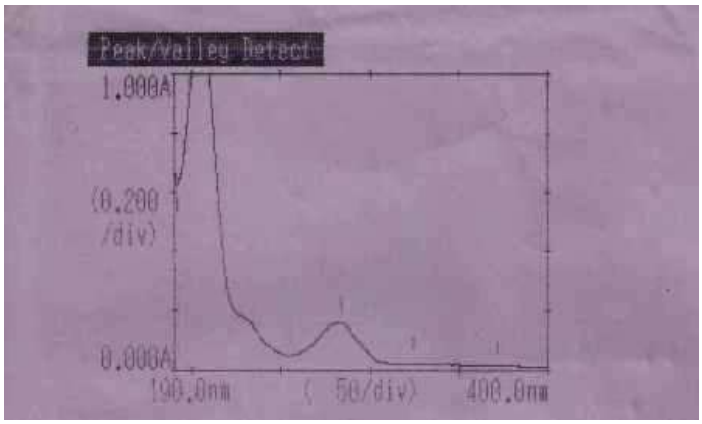

Fig no-4.5 Absorption spectra of Ambroxol Hydrochloride

As previously seen, the absorption spectra of Ambroxol Hydrochloride was prepared by using phosphate buffer 6.8,in the range of 200-400nm.The peak was found to be in 204nm(I.P 244nm)

The standard curve of Levocetrizine hydrochloride was prepared as per procedure given in the methodology section. The following table shows the absorbance at various concentrations. Figure shows standard curve of Ambroxol Hydrochloride.

Table-4.19.Absorbance of Ambroxol hydrochloride in different concentration

Sl no	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.0213
3	4	0.0448
4	6	0.0637
5	8	0.0831
6	10	0.1071

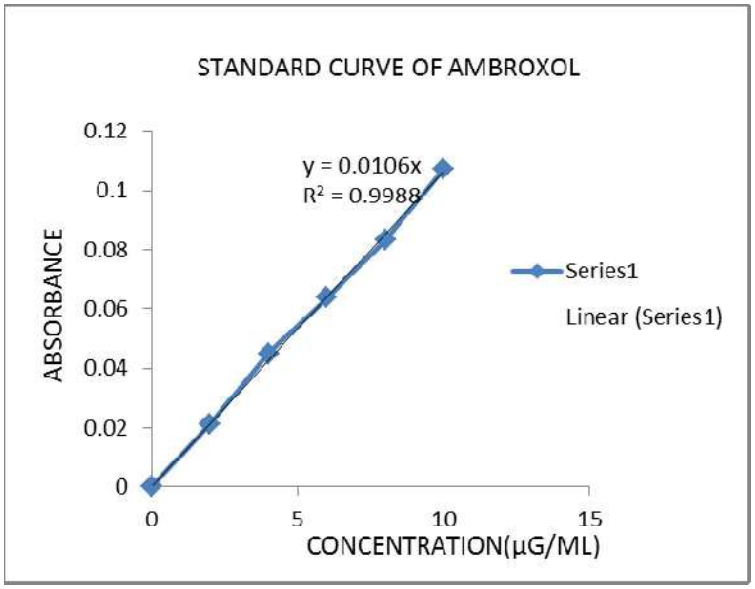

Fig no-4.6: Standard curve of Ambroxol hydrochloride

4.2.3. SIMULTANEOUS ESTIMATION OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE

In the present study, simultaneous estimation of Levocetrizine Hydrochloride and Ambroxol Hydrochloride was done using UV spectrophotometrically. The solvent used in the method is distilled water. Linearity range was 10-35µg/ml for Ambroxol hydrochloride. The wavelength for Ambroxol hydrochloride was 243 and LVC was 231nm.The overlapping was seen in 260nm.The calibration curves for both drugs and overlapping curve was given below.

4.2.3.1CALLIBARTION CURVE OF LEVOCETRIZINE HYDROCHLORIDE

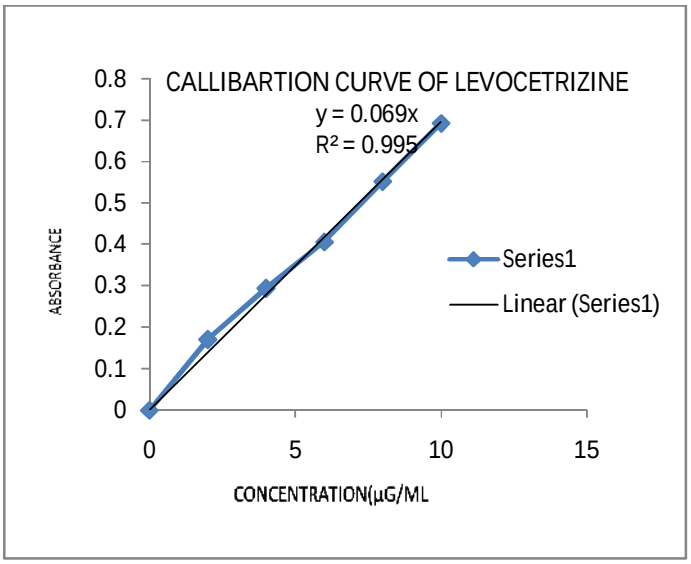

Fig no- 4.7: Calibration curve of Levocetrizine hydrochloride

The calibration curve of Levocetrizine hydrochloride was prepared by using distilled water, the curve was plotted in fig no-4.7.

4.2.3.2CALLIBARTION CURVE OF AMBROXOL HYDROCHLORIDE

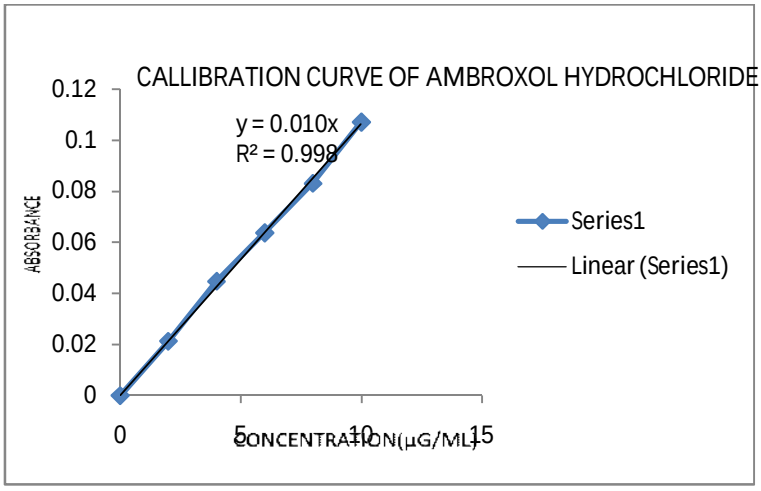

Fig no-4.8: Calibration curve of Ambroxol hydrochloride

By using same procedure the calibration curve of Ambroxol Hydrochloride was prepared using distilled water, the curve was plotted in fig no 4.8.

4.2.3.3 OVERLAPPING OF SPECTRA OF LEVOCETRIZINE AND AMBROXOL HYDROCHLORIDE

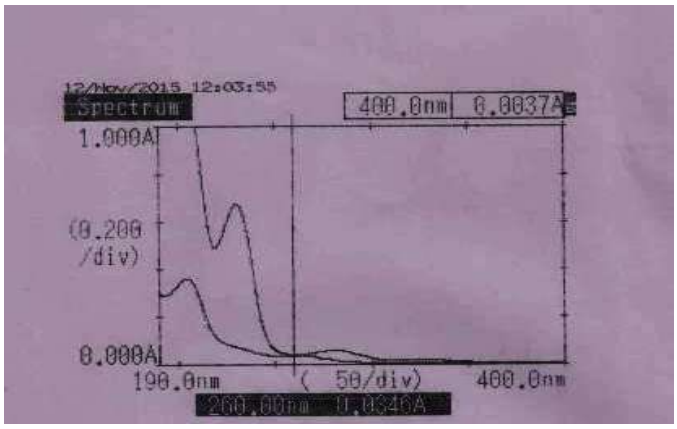

Fig no-4.9: OVERLAPPING OF SPECTRA OF LEVOCETRIZINE AND AMBROXOL HYDROCHLORIDE

Linearity- From the calibration curve of both Levocetrizine hydrochloride and Ambroxol hydrochloride, the linearity was observed in concentration 5-35µg/ml for Levocetrizine and 5-45µg/ml for Ambroxol hydrochloride. The co-efficient of co relation was found as 0.995 for Levocetrizine hydrochloride and 0.998 for Ambroxol hydrochloride. The high value of co-efficient of correlation indicates good linearity of calibration curve as given for both the drugs in fig and the overlapping spectrum of Levocetrizine Hydrochloride & Ambroxol Hydrochloride was seen, the point of intersection of 2 spectra was found to be 260 nm.

Here we can conclude that the proposed UV spectrophotometric method was simple, sensitive and accurate for determination of Levocetrizine hydrochloride and Ambroxol hydrochloride in analytical sample.

4.4. OPTIMISATION OF FAST DISSOLVING TABLETS OF LEVOCETRIZINE HYDROCHLORIDE

4.4.1. PRE-FORMULATION PARAMETERS

The pre-formulation parameters for tablet blend was given in following table-

Table-4.20 Pre-formulation parameters of the tablet blend

Formulation no	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose (θ)
F1	0.364	0.545	10.8	1.11	31.5
F2	0.362	0.485	10.2	1.21	30
F3	0.379	0.530	10.2	1.13	29.6
F4	0.375	0.493	10.5	1.57	30.2
F5	0.360	0.477	10.8	1.06	31.5
F6	0.419	0.471	10.9	1.20	28.6
F7	0.417	0.456	11.1	1.07	32.1
F8	0.416	0.458	10.0	1.09	25.6
F9	0.428	0.428	11.2	1.99	24.3
F10	0.442	0.433	10.9	1.50	30.2

The results of pre-compression studies reveal that the bulk density of powder blend was found between 0.362-0.442 g/cm^3 and tapped density was found between 0.428-0.530g/cm^3 which is in limit of both bulk density and tapped density. Also in case of Carr's index it was found in between 10-11.2 and Hausner's ratio in between 1.06-1.99 which holds the assumption of good compressibility. Lastly angle of repose of the powder blend was found in between 25.6-31.5 which was having property of good flow of the powder blend.

4.4.2. POST COMPRESSION PARAMETERS OF THE PREPARED LEVOCETRIZINE HYDROCHLORIDE FAST DISSOLVING TABLETS

Table-4.21.Post compression parameters of the prepared Levocetrizine Hydrochloride Fast dissolving tablets

Formulation no	Thickness(mm)	Hardness(kg/cm2)	Uniformity of weight	Friability (%)	Drug content (%)	Wetting time(sec)	Water Absorption ratio	In vitro disintegration time(sec)

F1	2.5	2.9	120±0.37	0.23	95.9	13.3	59.6	120
F2	2.4	2.5	120±0.89	0.32	88.0	21.5	90.9	60
F3	2.6	3	120±0.23	0.56	73.7	18.5	60.9	120
F4	2.5	3	120±0.99	0.87	77.0	18.6	91.9	50
F5	2.5	3	120±0.45	0.77	80.9	19.3	60.2	126
F6	2.4	2.3	120±0.89	0.65	90.0	13.6	89.7	58
F7	2.5	2.3	120±0.56	0.26	89.8	18.3	74.8	65
F8	2.5	2.5	120±0.88	0.58	87.8	12.3	70.9	60
F9	2.5	2.4	120±0.90	0.13	56.9	14	65.7	101
F10	2.5	2.5	120±0.55	0.19	77.7	11	71.6	97

The prepared tablets were evaluated for different post-compression parameters like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits which depicted in Table.4.21. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of various prepared fast dissolving tablets of Levocetrizine hydrochloride was found to be within the range of 50 to 120 seconds.

4.4.3 STASTICAL OPTIMISATION OF LEVOCETRIZINE HYDROCHLORIDE TABLETS

4.4.3.1 ANOVA- Analysis of variance

Analysis of variance of the responses indicated that response surface models developed for disintegration time and water absorption were significant and adequate, without significant lack of fit. Influences of formulation variables on the response factors are shown.

Table-4.22.ANOVA –Influence of formulation variables on the response factors

Response Factor	**Model F-value**	**Prob>F**	**Lack of fit F-value**	**Prob>F**
Disintegration	10.47	0.0205	21.96	0.1553

Time				
X_1.Crosscarmellose sodium	44.05	0.0027	do	do
X_2. Sodium Starch Glycolate	0.78	0.4273	do	do
Water Absorption Ratio	34.64	0.0022	0.32	0.8247
X_1.Crosscarmellose sodium	165.41	0.0002	do	do
X_2.Sodium Starch Glycolate	0.029	0.8739	do	do

Model summary statistics for the selected significant models are shown in Table 5. It can be observed that R2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R2 value is in good agreement with the adjusted R2 value, resulting in reliable models

Table 4.23 Model Summary Statistics- Influence of formulation variables on the response factors

Response Factor	**Std. Deviation**	**R^2**	**Adjusted R^2**	**Predicted R**
Disintegration Time	11.56	0.9290	0.8402	0.5116
Water absorption ratio	2.92	0.9774	0.9492	0.8685

4.4.3.2 Mathematical equations: Mathematical relationships generated using multiple regression analysis for the studied response variables are expressed as equations (I and II). The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

Disintegration time=132.22– 10.69 X_1 +13.69 X_2 +4.79 X_1 X_2 +0.27 X^2_1 – 1.227 X^2_2 -13.04 X_1 X^2_2 + 3.69 X^2_1 X_2- (I)

Water Absorption ratio= 61.17+ 0.17 X_1 -1.68 X_2– 7.187 X_1 X_2 +0.12 X^2_1 +0.141 X^2_2 -0.28 X_1 X^2_2 – 0.0169 X^2_1 X_2 – (II)

4.4.3.3 Response Surface Analysis

The 3-dimensional response surface plots are shown in Fig and the corresponding contour plots for the studied response properties viz., disintegration time and water absorption ratio are shown in respectively.

A. Effect of variable in Disintegration Time-

The variables on the present study i.e. the amount of Crosscarmellose sodium and Sodium starch glycolate had equal effects in both the responses. These variables effect equally on the disintegration time (sec) as can be seen in the contour (fig-4.4.3.3.1) as well as 3D-surface plot (fig-4.4.3.3.2).

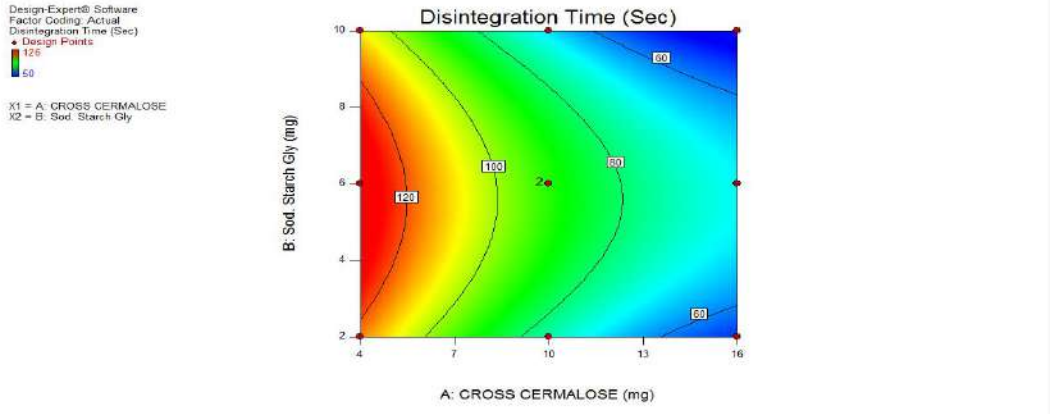

Fig no-4.10: Contour plot showing the relationship between various levels of two factors on disintegration time

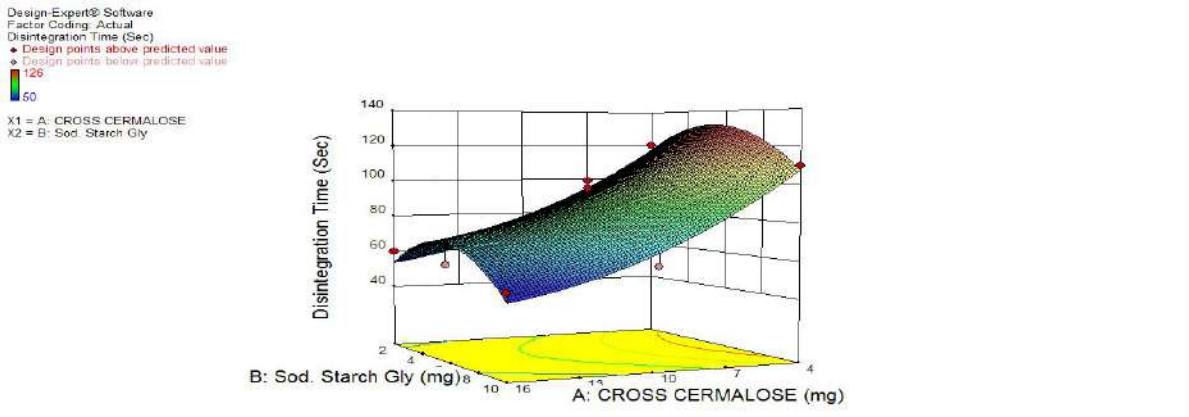

Fig no-4.11:3D-Response surface plot showing the influence of two different super disintegrants on disintegration time

B. Effect of Variables in Water absorption ratio

The variables on the present study i.e. the amount of Crosscarmellose sodium and Sodium starch glycolate had equal effects in both the responses. These variables effect equally on the water absorption ratio as can be seen in the contour (fig-4.10) as well as 3D- surface plot (fig-4.11).

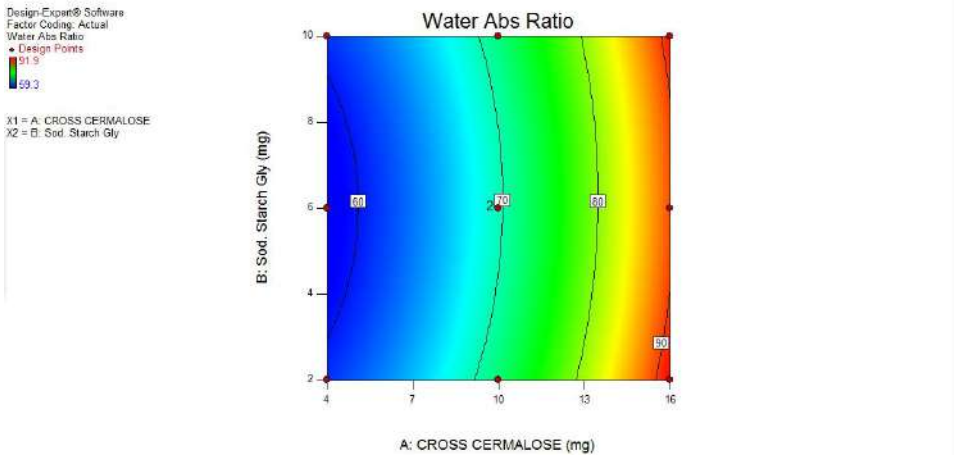

Fig no-4.12: Contour plot showing the relationship between various levels of two factors on Water absorption ratio

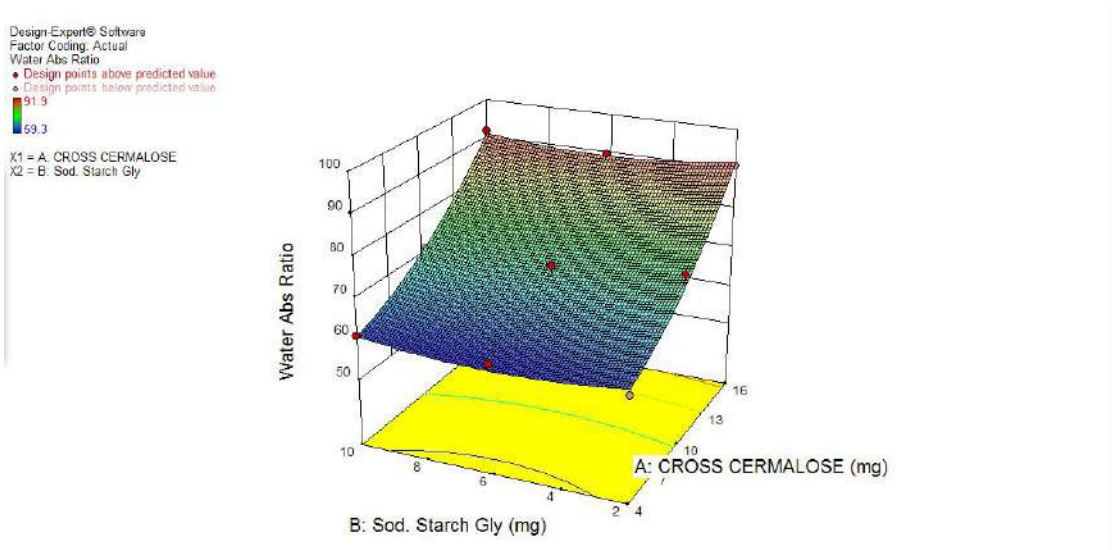

Fig no-4.13: 3D-Response surface plot showing the influence of two different superdisintegrants on water absorption ratio

Validation of Results

In order to evaluate the optimization capability of the models generated according to the results of the central composite design, tablets including the optimized formulation were prepared using the optimal process variable settings. All results of the physical evaluation were found to be within limits. Table 4.24 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error.

Table-4.24.Composition of the Optimized Formulation, the Predicted and Experimental values of Response Variables, and Percentage Prediction Error

Composition **Crosscarmellose sodium :Sodium Starch glycolate**	**Responses** **variable**	**Experimental** **Value**	**Predicted Value**	**Percentage Error**
16 :10	Disintegration Time(sec)	61	45.28	3.47
	Water Absorption ratio	69.67	91.21	2.36

From the above table, it was cleared that the percentage errors for optimized batch with response variable disintegration time was found to be 3.47 and that of water absorption ratio was found to be 2.36.

4.5. OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE

4.5.1. PRE-FORMULATION PARAMETERS

The pre-formulation parameters for tablet blend was given in following table-

Table 4.25: Pre-formulation parameters of the tablet blend

Formulation no	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose (θ)
F1	0.364	0.545	10.8	1.11	31.5
F2	0.362	0.485	10.2	1.21	30
F3	0.379	0.530	10.2	1.13	29.6
F4	0.375	0.493	10.5	1.57	30.2
F5	0.360	0.477	10.8	1.06	31.5
F6	0.419	0.471	10.9	1.20	28.6
F7	0.417	0.456	11.1	1.07	32.1
F8	0.416	0.458	10.0	1.09	25.6
F9	0.428	0.428	11.2	1.99	24.3

The results of pre-compression studies reveal that the bulk density of powder blend was found between 0.362-0.442 g/cm^3 and tapped density was found between 0.428-0.530g/cm^3 which is in limit of both bulk density and tapped density. Also in case of Carr's index it was found in between 10-11.2 and Hausner's ratio in between 1.06-1.99 which holds the assumption of good compressibility. Lastly angle of repose of the powder blend was found in between 25.6-31.5 which was having property of good flow of the powder blend.

4.5.2POST COMPRESSION PARAMETERS OF THE PREPARED BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE TABLETS

Table-4.26.Post compression parameters of bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride

Formulation no	Thickness(mm)	Hardness(kg/cm2)	Uniformity of weight	Friability (%)	Drug content (%)	Wetting time(sec)	Water Absorption ratio	In vitro disintegration time(sec)
F1	3	3.5	180±0.37	0.72	95.9	25	44.4	34
F2	3	3.5	180±0.89	0.68	96.8	17	22.2	70
F3	3	3.5	180±0.23	0.70	93.7	20	58.9	110
F4	3	3.5	180±0.99	0.69	97.0	21	72.2	107
F5	3	3.5	180±0.45	0.81	90.9	26	64.7	57
F6	3	3.5	180±0.89	0.71	92.0	21	52.9	65
F7	3	3.5	180±0.56	0.78	99.8	17	50	120
F8	3	3.5	180±0.88	0.61	97.8	20	61.1	130
F9	3	3.5	180±0.90	0.88	96.9	27	56.2	110

The prepared tablets were evaluated for different post-compression parameters like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits which depicted in Table.4.26. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of various prepared bilayer tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride was found to be within the range of 34 to 130 seconds.

4.5.3. STASTICAL OPTIMISATION OF BILAYER SUBLINGUAL TABLETS OF LEVOCETRIZINE HYDROCHLORIDE AND AMBROXOL HYDROCHLORIDE TABLETS

4.5.3.1. ANOVA- Analysis of variance

Analysis of variance of the responses indicated that response surface models developed for disintegration time and water absorption were significant and adequate, without significant lack of fit. Influences of formulation variables on the response factors are shown.

Table-4.27.ANOVA –Influence of formulation variables on the response factors

Response Factor	Model F-value	Prob>F	Lack of fit F-value	Prob>F
Disintegration Time	10.80	0.0391	14.83	0.289
X_1.Sodium starch glycolate	10.56	0.0475	do	do
X_2. Camphor	10.11	0.0501	do	do
Water Absorption Ratio	34.64	0.0022	0.32	0.4866
X_1.Sodium starch	165.41	0.0002	do	do

glycolate				
X_2.Camphor	0.029	0.8739	do	do

Model summary statistics for the selected significant models are shown in Table 5. It can be observed that R2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R2 value is in good agreement with the adjusted R2 value, resulting in reliable models

Table 4.28: Model Summary Statistics- Influence of formulation variables on the response factors

Response Factor	**Std. Deviation**	**R^2**	**Adjusted R^2**	**Predicted R**
Disintegration Time	17.46	0.9474	0.8596	0.3668
Water absorption ratio	7.83	0.8157	0.7052	0.8685

4.5.3.2. Mathematical equations: Mathematical relationships generated using multiple regression analysis for the studied response variables are expressed as equations (I and II). The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

Disintegration time=$113.67 - 23.17\ X_1 + 22.67X_2 - 16.75\ X_1\ X_2 - 52.50.27\ X^2_1 + 42.00\ X^2_2 - 973.14X_1\ X^2_2 + 1190.17X^2_1\ X_2$- (I)

Water Absorption ratio= $53.67 - 3.35\ X_1 + 12.67\ X_2 - 42.44\ X_1\ X_2 + 11.22\ X^2_1 + 160.52\ X^2_2 - 537.74X_1\ X^2_2 + 142.157\ X^2_1\ X_2$ – (II)

4.5.3.3. Response Surface Analysis

The 3-dimensional response surface plots are shown in Fig and the corresponding contour plots for the studied response properties viz., disintegration time and water absorption ratio are shown in respectively.

A. Effect of variable in Disintegration Time-

The variables on the present study i.e. the amount of Sodium starch glycolate and Camphor had equal effects in both the responses. These variables effect equally on the disintegration time (sec) as can be seen in the contour (fig-4.14) as well as 3D- surface plot (fig-4.15).

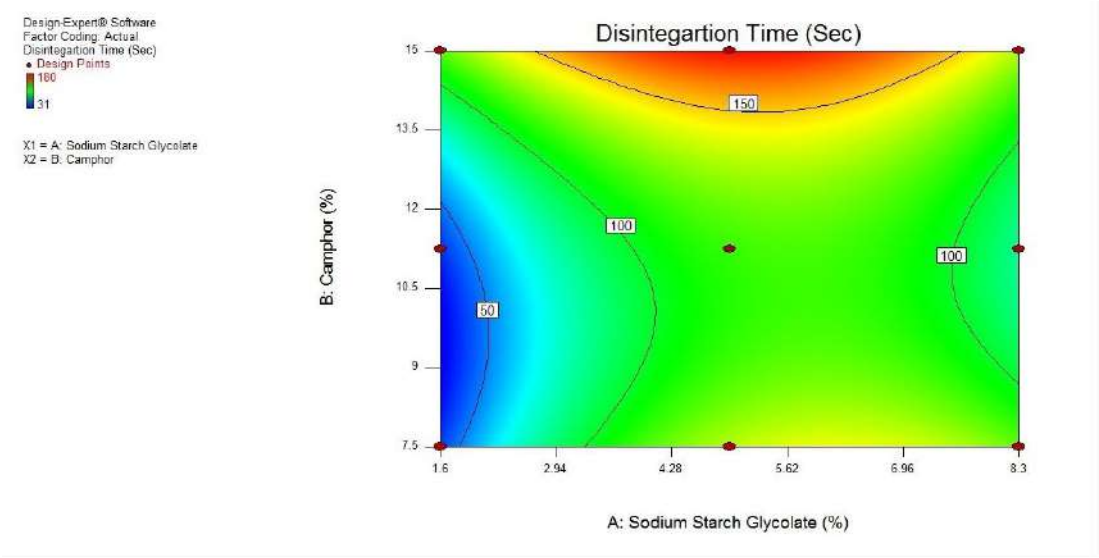

Fig no-4.14: Contour plot showing the relationship between various levels of two factors on disintegration time

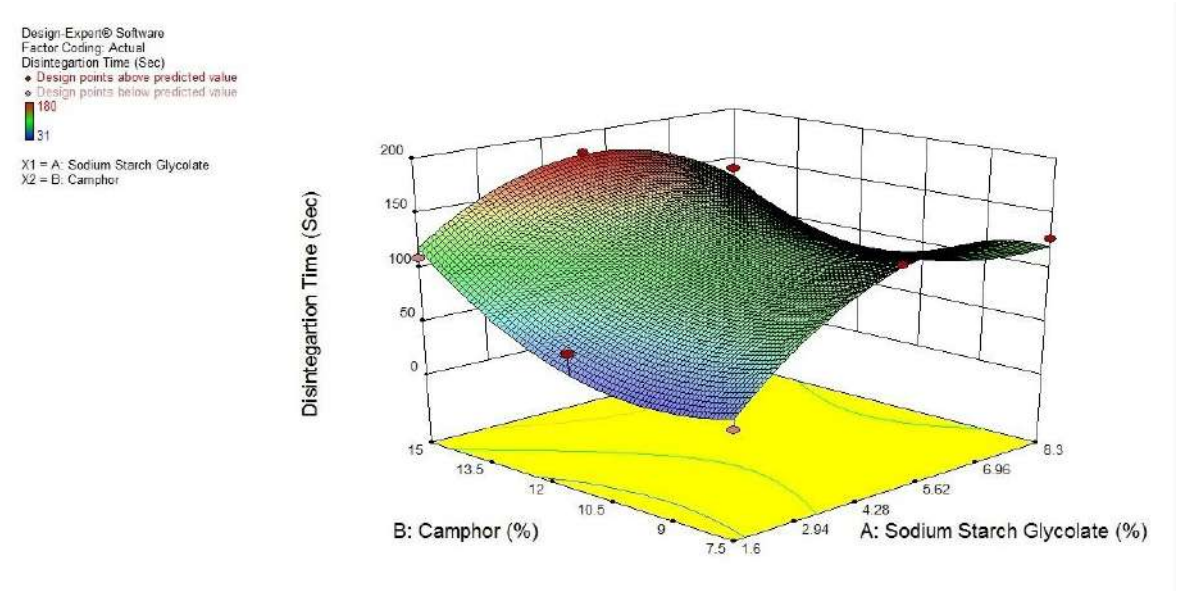

Fig no-4.15:.3 D-Response surface plots showing the influence of two different factors on disintegration time

B.Effect of Variables in Water absorption ratio

The variables on the present study i.e. the amount of Sodium starch glycolate and Camphor had equal effects in both the responses. These variables effect equally on the water absorption ratio as can be seen in the contour (fig-4.16) as well as 3D- surface plot (fig-4.17).

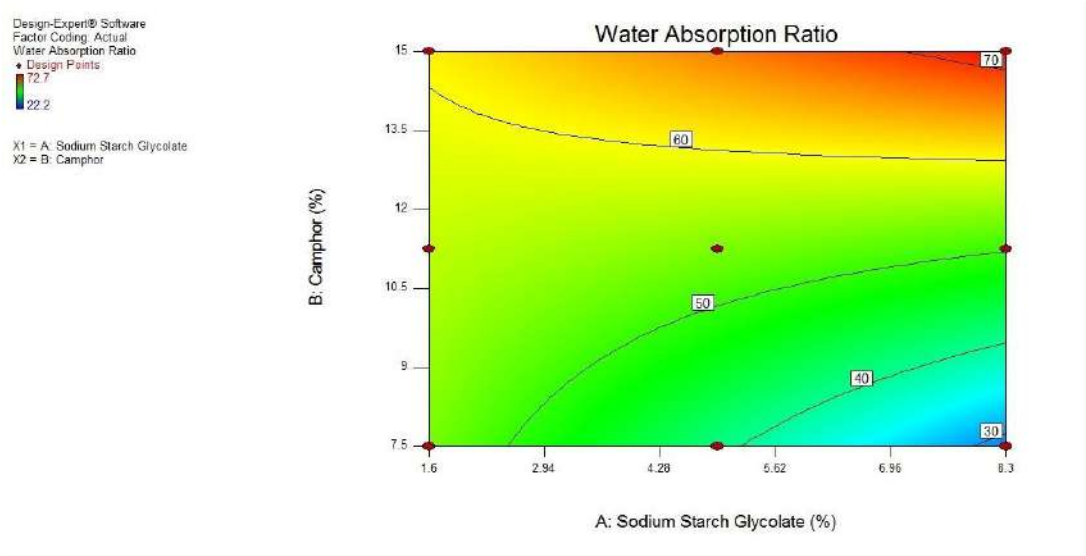

Fig no-4.16: Contour plot showing the relationship between various levels of two factors on Water absorption ratio

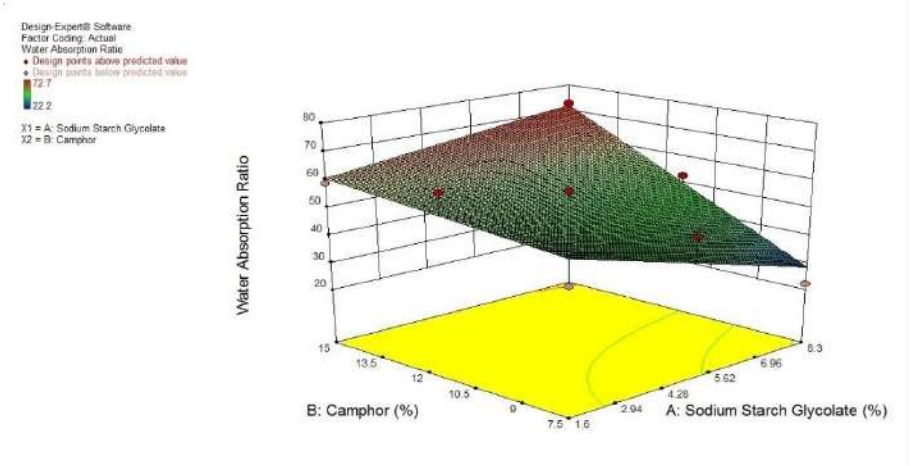

Fig no-4.17:3D-Response surface plot showing the influence of two factors on water absorption ratio

Validation of Results

In order to evaluate the optimization capability of the models generated according to the results of the central composite design, tablets including the optimized formulation were prepared using the optimal process variable settings. All results of the physical evaluation were found to be within limits. Table 4.29 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error.

Table-4.29.Composition of the Optimized Formulation, the Predicted and Experimental values of Response Variables, and Percentage Prediction Error

Composition Sodium Starch glycolate: Camphor	Responses variable	Experimental Value	Predicted Value	Percentage Error
4.95:15	Disintegration Time(sec)	61	45.28	3.47
	Water Absorption ratio	69.67	91.21	2.36

From the above table, it was cleared that the percentage errors for optimized batch with response variable disintegration time was found to be 3.47 and that of water absorption ratio was found to be 2.36.

4.6. MARKETED BRAND STUDY

Two brands have been selected for marketed study-

4.6.1. Abcet 5mg

The brand taken for Levocetrizine hydrochloride and Ambroxol hydrochloride tablets is Abcet 5 mg.

Trade name: Abcet (5mg), 75mg Ambroxol hydrochloride and 5mg Levocetrizine Hydrochloride

Manufacturer: Procure Medica

Unit: 75mg/5mg

Type: Tablets

Quantity: 10 tablets

Price: 49.5/-

Post compression parameters

Table-4.30: Evaluation parameters

Individual weights	Hardness	Thickness	Weight Variation	Friability	Water absorption ratio	Wetting time	Disintegration time	Drug content
180mg	2kg	3	180±0.76	0.67	87.8	23 sec	45 sec	98%

4.6.2. Levosix 5mg

The brand taken for Levocetrizine hydrochloride is Levosix 5 mg.

Trade name: Levosix (5mg), 75mg Ambroxol hydrochloride and 5mg Levocetrizine Hydrochloride

Manufacturer: Systolic Lab pvt Ltd

New Delhi-110008

Unit: 5mg

Type: Tablets

Quantity: 10 tablets

Price: 31/-

Post compression parameters

Table-4.31: Evaluation parameters

Individual weights	**Hardness**	**Thickness**	**Weight Variation**	**Friability**	**Water absorption ratio**	**Wetting time**	**Disintegration time**	**Drug content**
140mg	2kg	3	140±0.76	0.70	76.8	17 sec	26 sec	99.5%

4.7. Comparative study with marketed brands

The table signifies the comparative study of formulated products with marketed brands-

Table-4.32: Comparative study for marketed brands

Name	Water absorption ratio (%)	Disintegration time(sec)	Drug content (%)
1.Levocetrizine hydrochloride fast dissolving tablets	69.67	61	91.9

2.Bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride	22.2	125	92.7
3. Levosix 5mg	76.8	26	99.5
4.Abcet 5mg	87.8	45	98

As we can observe from the given table, the comparison with marketed brands, the data found was within limit. So we can expect that both the formulations were satisfied for comparative study with the marketed brands.

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SUMMARY

5. SUMMARY

Literature reveals that there are various types of bilayer sublingual tablets found in the market. As Levocetrizine hydrochloride well known 3rd generation antihistaminic, very useful for allergic reaction also Ambroxol hydrochloride for its mucolytic activity has their position in the drug therapy. So bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride seems to be useful for respiratory tract infections.

The present work involves formulation, evaluation and statistical optimization of bilayer tablets of above drug. Here optimization part was carried out using computer tool "Design expert-9.0& 10.0.

The preformulation study was carried out and drug compatibility study was done using both FTIR and DSC. There was no incompatibility found between drug and excipients.

The pre compression parameters for both layers were found within the acceptable limits of pharmacopoeial specification

The prepared tablets were evaluated for different post-compression parameters like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of various prepared fast dissolving tablets of Levocetrizine hydrochloride was found to be within the range of 50 to 120 seconds and disintegration time of various prepared bilayer tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride was found to be within the range of 34 to 130 seconds.

From these parameters water absorption ratio and disintegration time was taken for optimization responses, the result found was within limits; also optimized batch was prepared and evaluated. The evaluation parameters satisfy the data given by design expert software.

Lastly two marketed brands had been selected for the comparative study for the prepared batch and the results were found in the range.

CONCLUSION

6. CONCLUSION

The concept of bilayer has been introduced to attain sustain release of drug which refers to tablet containing subunits that either may be same (Homogeneous) or different (Heterogeneous). Bilayer tablet allows for designing and modulating the dissolution and release characteristics. Bilayer tablet are prepared for one layer for immediate release while second layer is designed to release drug, later as second dose or in an extended release pattern. Levocetrizine hydrochloride is a third generation non-sedative antihistamine, developed from the second-generation antihistamine, cetirizine. Levocetrizine works by blocking histamine receptors. Ambroxol Hydrochloride is a potent mucolytic &mucokinetic, capable of inducing bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes network of fibres in tenacious sputum is broken.

Literature reveals that there are various types of bilayer sublingual tablets found in the market. As given earlier, the drug have their own therapeutic activity so, bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride seems to be useful for respiratory tract infections.

The drug excipients compatibility studies confirmed that both the drugs were compatible for excipients like superdisintegrants Crosscarmellose sodium, Sodium starch glycolate etc.

The pre-compression parameters and post compression parameters were obtained from both layers and were within the acceptable limits of pharmacopoeial specification.

The drug release study from Levocetrizine hydrochloride layer showed that the increase in concentration of super disintegrants give increase in disintegration time and water absorption ratio. The drug release was found between 77.7-95.9 % in Levocetrizine hydrochloride layer. The drug release for bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride was found 93-99 %.

From the statiscal data analysis, performed by Design expert software (Version 10.0, 9.0.6.2)an optimized formulation was prepared using super disintegrants Crosscarmellose sodium and Sodium starch glycolate for Levocetrizine hydrochloride layer and Sodium starch glycolate and Camphor for bilayer sublingual tablets.

Responses taken for optimization were disintegration time and water absorption ratio and responses were found within limit. Also optimized batch were found within the limit.

Hence the formulated bilayer sublingual tablets of Levocetrizine hydrochloride and Ambroxol hydrochloride can be used for allergic reaction and respiratory infection.