DESIGN, DEVELOPMENT AND OPTIMIZATION OF CHITOSAN-SODIUM ALGINATE BASED MUCOADHESIVE DRUG DELIVERY SYSTEM

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IN
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Submitted by

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CERTIFICATE

This is to certify that the thesis entitled ***"Design, Development and Optimization of Chitosan- Sodium Alginate Based Mucoadhesive Drug Delivery System"*** *submitted to Gauhati University for the partial fulfilment of the award of degree of* ***Master of Pharmacy (M.Pharm) in Pharmaceutics*** *is a bonafide and original research work carried out by* ***Sheikh Sofiur Rahman*** *with* ***registration no 048364 of 2007-08*** *&* ***Roll no - MP/11/10*** *during the academic session 2011-2013 at Pharmaceutics laboratory, Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS) under my direct supervisions and guidance.*

He has carried out the research work independently with proper guidance and suggestions.

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DECLARATION BY THE CANDIDATE

I hereby declare that this thesis entitled ***"Design, Development and Optimization of Chitosan- Sodium alginate based Mucoadhesive drug delivery System"*** *is a bonafide and genuine research work carried out by me under the guidance of* ***Dr. Suvakanta Dash****, Principal GIPS, and* ***Dr. Bipul Nath****, Assistant Professor, Department of Pharmaceutics, GIPS.*

I also declare that the matter embodied in it is original and the same has not previously submitted for the award of any degree, diploma, associateship or fellowship of any other university or institution.

Date: *Signature of candidate*

Place**:** *SHEIKH SOFIUR RAHMAN*

DEDICATED TO MY BELOVED PARENTS

SHEIKH SOFIUR RAHMAN

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Thanks to one and all…..

Date:

Place

Signature:

SHEIKH SOFIUR RAHMAN

CONTENTS

LIST OF ABBREVIATIONS

Sl. No.	*Abbreviations*	*Full form*
1	µg	Microgram
2	µm	Micrometer
3	%	Percentage
4	pH	Hydrogen ion concentration
5	GIT	Gastrointestinal tract
6	CH	Chitosan
7	PE	Pectin
8	HPMC	Hydroxy Propyl Methyl Cellulose
9	gm	Gram
10	ATP	Adenosine Triphosphate
11	C_{max}	Peak serum concentration
12	AUC	Area under curve
13	CYP	cytochrome P450
14	USP	United States Pharmacopoeia
15	PhEur	European Pharmacopoeia
16	RH	Relative Humidity
17	UV	Ultraviolet
18	BP	British Pharmacopoeia
19	FT-IR	Fourier Transform Infrared
20	DSC	Differential Scanning Calorimetry
21	°C	Degree Celsius
22	mm	Millimetre
23	cm	Centimetre
24	FS	Formulation with Sodium alginate
25	FSC	Formulation with Sodium alginate and Chitosan

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ABSTRACT

In this research work poly-electrolyte complex (PEC) were developed in the form of tablet interaction of positively charged chitosan (cationic) with negatively charged polymers sodium alginate (anionic). The polyelectrolyte complex formation was confirmed by Fourier transform spectroscopy (FTIR), Differential scanning calorimetry (DSC), X-ray diffraction (XRD) study. Pantoprazole sodium sesquihydrate tablets containing sodium alginate and PEC prepared by direct compression method. The preformulation studies of the tablets were evaluated and found within the acceptable limits. The mucoadhesive strength, swelling index and in-vitro drug release of the prepared tablets were carried out. The swelling behaviour of the tablet shows that polymer with higher concentration had higher swelling index. The mucoadhesive strength of the tablet is also increases with the increasing adhesion time. Formulation containing single polymer concentration (15% w/w) shows release property both in pH 6.8& 7.4.; releasing about 43.16& 45.23 within a period of 6 hour. Formulation at the polymer concentration of (35% w/w) shows suitable sustain release property both in pH 6.8 & pH 7.4., releasing about 79.60% & 72.60 % of drug release within a period of 6 hour. From the in-Vitro release study it is evident that formulation containing 1:1 ratio of polyelectrolyte complex has the property of sustaining the drug release compared to the single polymer alone. From the release study, It is also evident that the formulation satisfy the drug release closer to the marketed enteric coated tablet with profound ability to sustain the drug release for sufficiently long period of time in phosphate buffer media (pH 6.8), thereby maximizing the therapeutic effect of the drug in condition of hyperacidity.

CHAPTER-1

1. INTRODUCTION ABOUT MUCOADHESIVE DRUG DELVERY SYSTEM

1.1. MUCOADHESION

1.2. ANATOMY OF MUCOUS MEMRANE

1. INTRODCUTION ABOUT MUCOAHESIVE DRUG DELIVERY SYSTEM [1-15]:

1.1. Mucoadhesion [1-6]:

The term bio adhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bio adhesive drug delivery, the term bio adhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bio adhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces.

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the oral route, using mucoadhesive dosage forms offers such a novel route of drug administration. Oral delivery system involves administration of drug through the oral mucosal membrane of oral cavity.

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self–administration of medication. It is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the alimentary tract, the more rapid

will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by paediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

1.2. Anatomy of mucous membrane [1, 2, 3, 6, 12-15]:

Mucous membranes are the moist linings of the orifices and internal parts of the body that are in continuity with the external surface. They cover, protect, and provide secretory and absorptive functions Sin the channels and extended pockets of the outside world that are incorporated in the body. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. They secrete a viscous fluid known as mucus, which acts as a protective barrier and also lubricates the mucosal membrane. Mucosal membranes of human organism are relatively permeable and allow fast drug absorption they are characterized by an epithelial layer whose surface is covered by mucus. The primary constituent of mucus

is a glycoprotein known as mucin as well as water and inorganic salts. However, it has general composition.

Table: 1. Composition of mucin:

Sl no	Composition	% Amount
1	Water	95
2	Glycoprotein's and lipid	0.5-5.0
3	Mineral salts	1
4	Free proteins	0.5-1

1.2.1. Examples of mucosa [1, 14, 15]:

- Buccal mucosa.
- Oesophageal mucosa.
- Gastric mucosa.
- Intestinal mucosa.
- Nasal mucosa.
- Olfactory mucosa.
- Oral mucosa.
- Bronchial mucosa.
- Uterine mucosa.
- Endometrium (mucosa of the uterus).
- Penile mucosa.

1.2.2. Functions of mucous layer [2, 5, 14, 15]:

The mucous layer, which covers the epithelial surface, has various roles.

- Protective role.
- Barrier role.
- Adhesion role.
- Lubrication role.

- Mucoadhesion role.
- **Protective role:** The Protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface.
- **Barrier role:** The role of mucus layer as barrier in tissue absorption of drugs and other substances is well known as its influence the bioavailibity of the drugs. The mucus constitutes diffusion barrier for molecules, and especially against drug absorption diffusion through mucus layer depends on molecule charge, hydration radius, ability to form hydrogen bonds and molecular weight.
- **Adhesion role:** Mucus has strong cohesive properties and firmly binds the epithelial cells surface as a continuous gel layer.
- **Lubrication role:** An important role of the mucus layer is to keep the membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules.
- **Mucoadhesion role:** One of the most important factors for bio adhesion is tissue surface roughness. Adhesive joints may fail at relatively low applied stresses if cracks, air bubbles, voids, inclusions or other surface defects are present. Viscosity and wetting power are the most important factors for satisfactory bio adhesion. At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bio adhesion.

1.2.3. Need of mucoadhesive [8]:

- Controlled release.
- Target &localised drug delivery.
- By pass first pass metabolism.
- Avoidance of drug degradation.
- Prolonged effect.
- High drug flux through the absorbing tissue.
- Reduction in fluctuation of steady state plasma level.

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a conventional dosage form are as follows:

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

1.2.4. Advantages of mucoadhesives [2, 5, 6, 9, 12,14]:

- A prolonged residence time at the site of drug action or absorption.
- A localization of drug action of the delivery system at a given target site.
- An increase in the drug concentration gradient due to the intense contact of particles with the mucosal.
- A direct contact with intestinal cells that is the first step before particle absorption.
- Ease of administration.
- Termination of therapy is easy.(except gastrointestinal)
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients. except gastrointestinal}
- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment
- Of intestine can be administered by this route. E.g. Buccal sublingual, vaginal.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Systemic absorption is rapid.

- This route provides an alternative for the administration of various hormones, narcotic analgesic.
- The oral mucosa is highly per fused with blood vessels and offers a greater permeability than the skin.
- Less dosing frequency.
- Shorter treatment period.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of drug administered.
- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages, which are as follows:

- Basic assumption is drug should absorbed throughout GIT.
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level.

1.2.5. Stages of mucoadhesion:

There are two stages of mucoadhession:

- Contact stage.
- Consolidation stage.

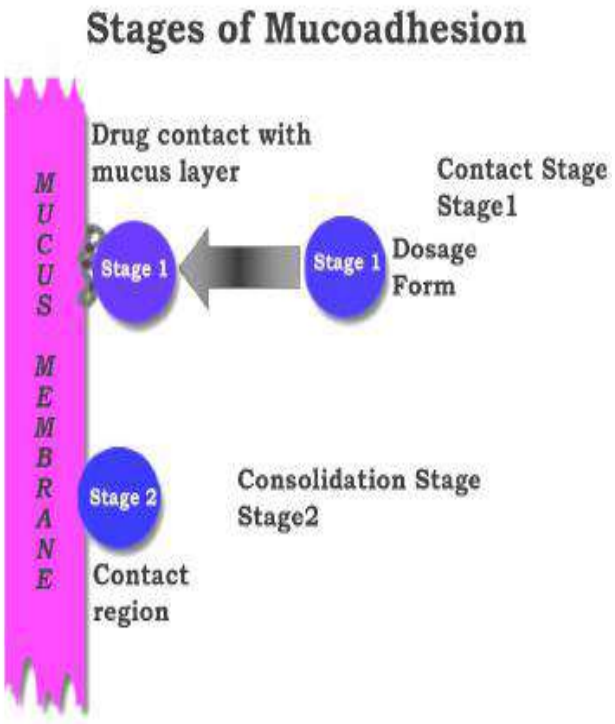

Fig: 1. The two steps of mucoadhesion

1.2.6. Mechanism of mucoadhesion[2, 3, 5, 8, 9, 14, 15]:

The concept of mucoadhesion is one that has the potential efficiency to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. Intimate contact of the drug with the mucosa should enhance absorption. The mechanisms responsible in the formation of bio adhesive bonds are not fully known, however most research has described bio adhesive bond formation as a three step process:-

- **Step1**: Wetting and swelling of polymer
- **Step2:** Interpenetration between the polymer chains and the mucosal membrane.

- **Step3:** Formation of Chemical bonds between the entangled chains**.**
- **Step 1:-**The wetting and swelling step of the dosage forms occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. This can be readily achieved by placing a bio adhesive formulation such as a tablet or paste within the oral cavity .Bio adhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occurs because the components within the polymers have an affinity for water.

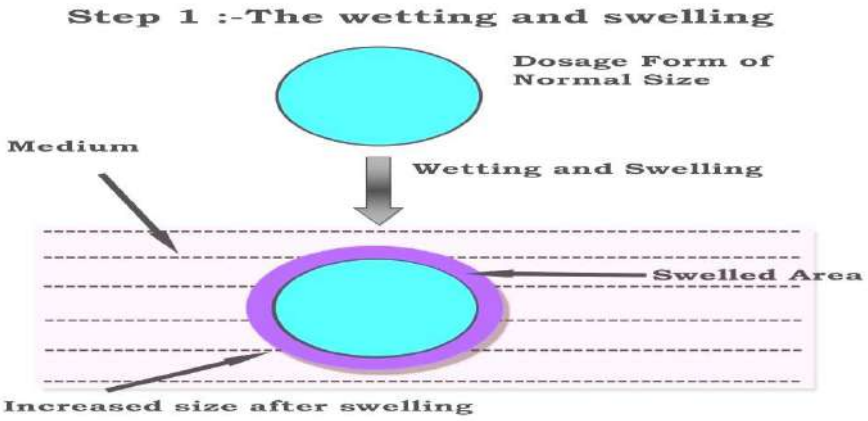

Fig.2. Wetting and Swelling of Polymer

- **Step 2:** The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In this step interdiffusion and interpenetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact. The strength of this bond depends on the degree of penetration between the two polymer groups.

In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

- **Step 3:-** In this step entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule. Hence the types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as Vander Waals Interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bio adhesive formulations in which strong adhesions between polymers are formed.

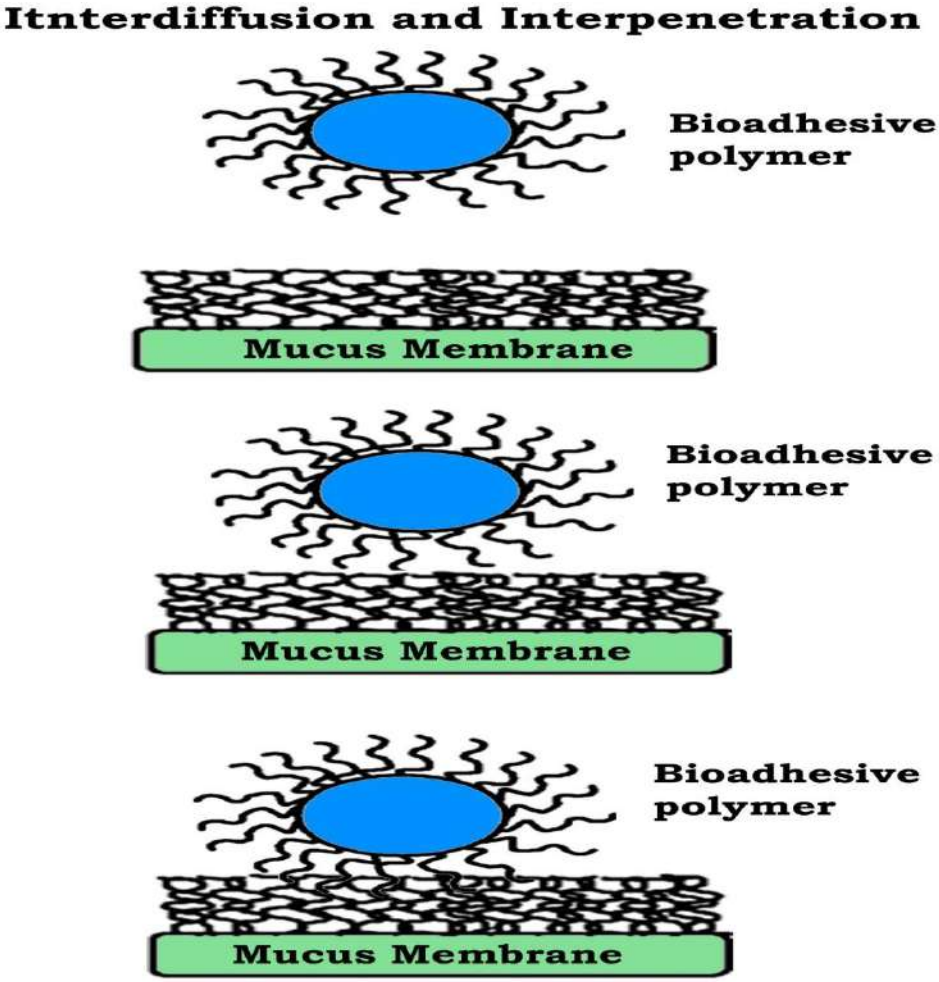

Fig.3. Interdiffusion and interpenetration of polymer and mucus

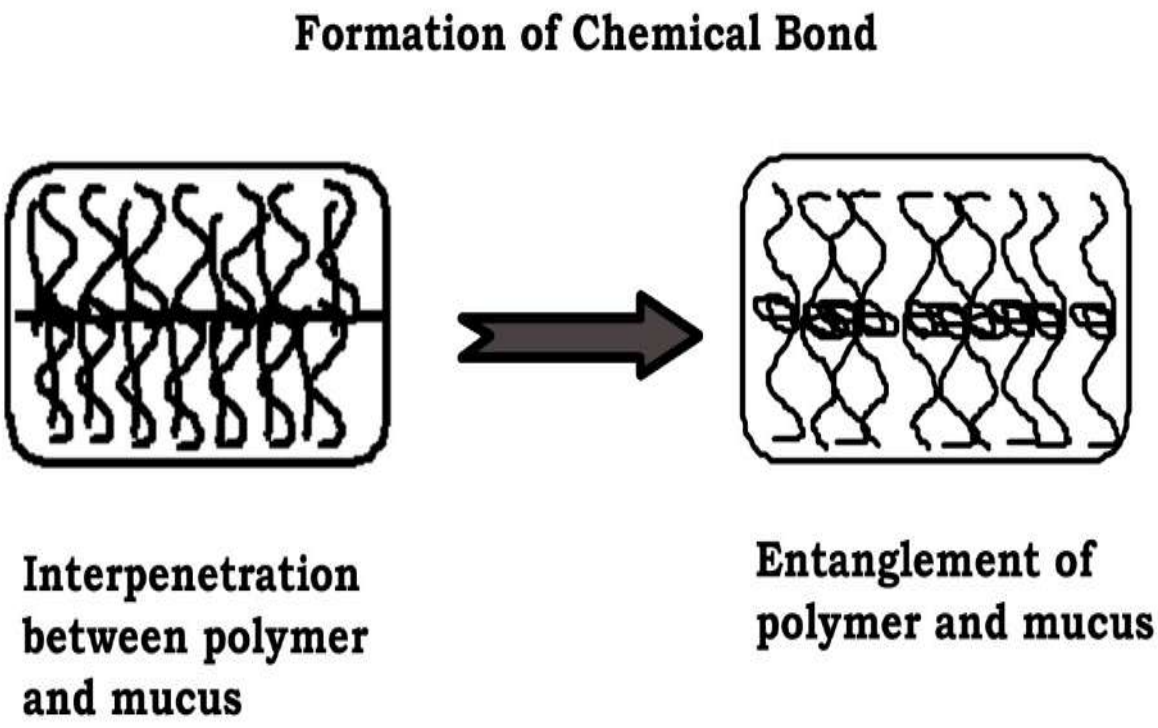

Fig.4. Entanglement of polymer and mucus by chemical bonds

CHAPTER-2

2. REVIEW OF LITERATURE

2. REVIEW OF LITERATURE:

- **Sing Kumar Pranjal, Shukla V.K, *et al*[16]**, have developed a mucoadhesive oral dosage form containing clarithromycin by using different mucoadhesive polymer like sodium carboxymethyl cellulose, carbopol 974P and sodium alginate to impart mucoadhesion. They have evaluated the tablet by different parameter such as weight variation, content uniformity, thikness, hardness, swelling index, ex vivo mucoadhesive strength, in vitro drug release. At last they have concluded that mucoadhesive tablets of clarithromycin can be good way to swelling and bioadhesion properties to improve the bioavailability.

- **Kaur Gurpreet, Kaur Amanpreet**[17], have been developed mucoadhesive buccal patches based on interpolymer complexes of chitosan-pectin for delivery of carvedilol and stated that the physicochemical interaction between CH and PE The patches were evaluated for their physical characteristics like mass variation, content uniformity, folding endurance, ex vivo mucoadhesion strength, ex vivo mucoadhesion time, surface pH, in vitro drug release, in situ release study, and in vivo bioavailability study. The swelling index of the patches was found to be proportional to the PE concentration. The surface pH of all the formulated bio adhesive patches was found to lie between 6.2 and 7.2. The optimized bio adhesive patch (C1, CH:PE 20:80) showed bio adhesive strength of 22.10± 0.20 g, in vitro release of 98.73% and ex vivo mucoadhesion time of 451 min with in a period of 8 h. The optimized patch demonstrated good in vitro and in vivo results.

- **Ambrogi. V,Perioli Luana, *et al*[18]**, have developed a metronidazole mucoadhesive tablet for vaginal administration by using FG 90C as new polymer. They assessed that FG90C is a suitable polymer to mucoadhesive sustained drug delivery. In order to prepare good tablets, chitosan must be blended with other polymer (PVP90 or PCPAA1) because it directs compression is not achievable. All polymer mixtures employed were useful to prepare tablets; polymer-polymer and drug-polymer negative interactions were not observed. Only in the case of PCPAA1, polymer-drug interactions are observed.

- **Rossato M.S,Burgalassi S, *et al*[19]**, have developed poloxamer 407 microsphere for protranmucosal drug delivery and they have evaluated novel microspheres based on poloxamer 407,alone or in mixture with gelucire 50/13, as possible buccal delivery system for atenolol (AT).The atenolol release from microspheres through the synthetic membrane was delayed with respect to drug solution, more markedly when micro particle contained as unique adjuvant, this formulation enhanced atenolol transmucosal permeation. The enhancement effect of poloxamer was confirmed by the permeation experiments.

- **Kim Kwono, Ved M. Prag[20]** , have developed intranasal zidovudine delivery to the brain by using poly(ethylene oxide/propylene oxide) copolymer thermo-reversible gelling agent and they have stated that a polar antiviral agent, zidovudine could preferentially transfer into the cerebrospinal fluid and brain tissues from the nasal cavity possibly via olfactory pathway. Intranasal

administration of zidovudine solution formulated with a thermo-reversible gelling system prepared with poloxamer 407 in aqueous buffer solution containing n-tridecyl-B-D- maltoside as permeation enhancer may provide a promising and durable therapeutic option for the treatment of CNS disorders and caused by HIV.

- **Mastrobattisa Enrico, Amidi Maryam**[21], have developed chitosan based delivery systems for protein therapeutics and antigen and they also stated that chitosan polymer have adjuvant properties, in particulate form. After parentral or mucosal administration of protein loaded chitosan particles they can be taken up and subsequently processed by antigen presenting cell, which may initiate an immune responses against the therapeutic action

- **Agu U, Remigius, Ugwoke. I. Michal, *et al*[22],** has developed a nasal mucoadhesive drug delivery system. They have been demonstrated that low absorption of drugs can be countered by using absorption enhancers or increasing the drug residence time in the nasal cavity, and that some mucoadhesive polymers can serve both functions.

- **Subharti Karvedil, K.R.Arya, *et al*[23],** have developed and evaluated mucoadhesive buccal tablets of sulbutamol sulphate by using polymer like HPMC K-4M and chitosan. They have evaluated the tablet for weight variation, hardness, thikness,drug content uniformity,swlling index and mucoadhesive strength.swlling index of batches containing more HPMC K-4M was greater than that containing less HPMC K-4M were excellent in bio adhesive nature.

- **Abraham Emilia T, George Meera**[24], have developed polyionic hydrocolloids for the intestinal delivery of protein drugs by using alginate and chitosan they stated that alginate being an anionic polymer, The pore size of alginate gel micro beads has been shown to be between 5 and 200 nm and coated beads and microspheres are found to be better oral delivery vehicles. Cross-linked alginate has more capacity to retain the entrapped drugs and mixing of alginate with other polymers such as neutral gums, pectin, chitosan, and eudragit have been found to solve the problem of drug leaching. Chitosan has only limited ability for controlling the release of encapsulated compound due to its hydrophilic nature and easy solubility in acidic medium. By simple covalent modifications of the polymer, its physicochemical properties can be changed and can be made suitable for the per oral drug delivery purpose. Ionic interactions between positively charged amino groups in chitosan and the negatively charged mucus gel layer make it mucoadhesive. The favourable properties like biocompatibility, biodegradability, pH sensitiveness, mucoadhesiveness, etc. has enabled these polymers to become the choice of the pharmacologists as oral delivery matrices for proteins.

- **Pillay.V, Munasur A.P, *et al***[25], have developed mucoadhesive propranolol matrices for buccal therapy and they have characterised the formulation in terms of mucoadhesivity,release kinetics, swelling/erosion, hydration dynamics and surface P^H. From the model fitting analysis they have found that the drug release was diffusion, polymeric relaxation and erosion based with the former two being more dominant over erosion. Textural profiling

showed initial rapid hydration, which could be beneficial for enhanced mucoadhesivity.

- **Han Fei, Xu Lu, *et al*[26]**, have developed a riboflavin gastromucoadhesive formulation and evaluated the pharmacokinetic profile and parameters of riboflavin via urinary excretion method were measured. They also studied on rat and man provide evidence for the validity of the hypothesis that the drug fibre provided good mucoadhesive properties invivo and should therefore be of considerable interest for the development of future mucoadhesive oral drug delivery dosage form.

- **Takeuchi Hirofumi,Yamamoto Hermit, *et al*[27],** have developed mucoadhesive nanoparticles system for peptide drug delivery by using polymer by using polymers chitosan and carbopol.The mucoadhesive properties of the polymer coated liposomes and polymeric nanoparticle were confirmed by means of different mucoadhesion tests. In applying these mucoadhesive nanoparticles to the oral and pulmonary administration of peptide drugs, more effective and prolonged action was observed in comparision with non-coated systems, thereby confirming the usefulness of mucoadhesive nanoparticulate systems for the delivery of peptide drugs.

- **Takeuchi Hirofumi,Thongborisute Jringjai[28],** have evaluated the mucoadhesiveness of polymers by biacore and mucin- particle method. In this study, the adhesivities of different molecular weight and hydrophobicity modified chitosans to mucins were determined. The biacore method showed

that citosan,and dodecylated chitosan could interact with mucin based on the increased resonance unit response after mucin was passed over the chitosans – immobilized sensor chip surface. The rate and strength were higher for unmodified chitosans than hydrophobic ally modified chitosans. The simple *in vitro* mucoadhesive test or mucin-particle method revealed that the turbidity of unmodified chitosan/mucin mixtures was higher than that of dodecylated chitosans for all concentration of chitosans and mucin. The results from both BIACORE and the mucin-particle method implied that hydrophobic modification of chitosan reduced its adhesivity to mucin. The results from these two methods corresponded well. Therefore, the BIACORE method has promised as an alternative method for evaluating the adhesivity of adhesive polymers to mucin.

- **Srivalli Raghava Mohan.K,Laksmi P.K, et al**[29]; have designed bilayer gastric mucoadhesive tablets of lamotrigine by using the HPMC K 15M or polyox and have found that combined use of polyox and have found that combined use of polyox and carbopol 974P demonstrated maximum mucoadhesive strength, the addition of eudragit L 100 ensured unidirectional drug release profile. The newly designed modified basket dissolution method in combination with model independent methods proved successful in characterizing the unidirectional drug release profile from the formulation. Therefore, for a drug like lamotrigine, a BCS class II drug with pH dependent solubility and incompatibility with the most promising mucoadhesive polymer, carbopol, a novel bilayered gastric mucoadhesive tablet may serve as the best possible rationale, potential, economic and industrially applicable

formulation for the delivery of lamotrigine for an extended period of time from 6 to12 h.

- **Cao Ri Qing, Liu Yan, et al**[30], have developed Valsartan mucooadhesive tablet. First they have developed two types of Valsartan loaded core pellets by an extrusion/spherinization method, and further dry coated with a mixture of HPMC and Carbomer at different ratios. The effect of the The effects of the pellet core composition, HPMC: CB ratioand coating level on the drug release from the coated pellets were investigated. The physicochemical properties of the core and coated pellets were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). In addition, the in vitro and in vivo mucoadhesion properties as well as the bioavailability of the coated pellets in rats were evaluated by using VAL suspension and core pellets as control preparations. The results of the release study demonstrated that the two types of core pellets, especially the pellets formulated with a solubilises and a pH modulator gave considerably faster drug release than the VAL powder. However, the core and coated pellets exhibited similar release profiles indicating that the dry powder-coating did not retard the drug release. Strong molecular interactions were observed between the drug and the carriers in FT-IR analysis. The coated pellets displayed distinct mucoadhesive property in vitro and delayed gastrointestinal (GI) transit in vivo. Furthermore, the coated pellets exhibit significantly higher $AUC_{0-12\ h}$ and C_{max}, as compared to the core pellets and drug suspension. It was concluded that the mucoadhesive pellets could render

poorly water soluble drugs like VAL with a rapid drug release, delayed GI transit and enhanced oral bioavailability.

- **Dharmala Kiran, Yoo Wook Jin, et al**[31], have developed sodium dodecyl sulphate mucoadhesive polymeric films as female controlled delivery (FCDDS) system against sexually transmitted diseases (STDs) by using different polymer carbopol 934 P , HPMC and PEG. They have evaluated the physicochemical properties of mucoadhesive polymeric films, such as tensile strength, contact angle, swelling ratio and erosion rate in a vaginal fluid stimulant. In addition, the drug release profile of SDS from the films and mucosal residence time were evaluated using a simulated dynamic vaginal system. It was demonstrated that the films made of Carbopol, HPMC and PEG were colorless, thin and soft and had proper physicodynamic properties for FcDDS. An increase in Carbopol content elevated tensile strength and swelling ratio but decreased the contact angle, erosion rate and the SDS release rate from the films. The films containing 0.25% (w/v) PEG as well as 0.75% (w/v) of combining Carbopol and HPMC remained on the vaginal tissue for up to 6 h. The films containing the ratio of Carbopol:HPMC:PEG = 1.5:1.5:1 and 1:2:1 seem to be optimal compositions for FcDDS, as they showed good peelability, relatively high swelling index and moderate tensile strength, and achieved the target release rate of SDS for 6 h.

- **Amiji Mansoor, Hejazi Radi**[32,] have reviewed Chitosan based gastrointestinal delivery system and found that chitosan is nontoxic, biocompatible, and biodegradable. He also postulated that chitosan have a

wide application in oral and/or buccal delivery, stomach- specific drug delivery, intestinal delivery,and colon- specific drug delivery. Chitosan appears to be a promising material for GI drug and gene delivery applications as many derivatives and for mutations are being examined.

- **Agnely F, Koffi. A.A; et al[33];** have developed quinine thermo sensitive poloxamer- based hydrogels by using HPMC intended for rectal administration and they have evaluated that rheological properties of the gels as a function of temperature . They found that HPMC in the presence of propandiol 1, 2 had a synergistic effect on the gelation of poloxamer 407.

- **Stokke B.T, Smidsrod O, et al[34]**, have stated that Polyelectrolyte complexes (PECs) of alginate and chitosan were formed by addition of 0.1% alginate solution to 0.1% chitosan solution and by adding the chitosan solution to the alginate solution under high shearing conditions. Variations in the properties of the polymers and the preparation procedure were studied, and the resultant PEC size, zeta potential (Zp), and pH were determined using dynamic light scattering (DLS), electrophoresis and by measuring turbidity and pH. Tapping mode atomic force microscopy (AFM) was used to examine some of the complexes. The particle size was decreased as the speed and diameter of the dispersing element of the homogenizer was increased. The net charge ratio between chitosan and alginate, and the molecular weights (MW) of both the alginate and chitosan samples were the most significant parameters that influenced the particle size, Zp, and pH. The mixing order also influenced the size of the PECs; however, the Zp and pH were not affected by the mixing

order. The stability of the complexes was investigated by incubation at an elevated temperature (37^0C), storage for one month at 4^0C, alteration of the pH of the PEC mixture, and addition of salt to physiological ionic strength (0.15 M NaCl). The properties of the PEC could be affected according to the molecular properties of the polyelectrolytes selected and the preparation procedures used. The resultant PEC sizes and properties of the complex were rationalised using a core-shell model for the structure of the complexes.

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CHAPTER-3

3.1. AIM AND OBJECTIVE

3.2. NEED OF THE STUDY

3.1. AIM AND OBJECTIVES:

- To prepare and evaluate chitosan, Sodium alginate mucoadhesive drug delivery system to prolong the drug release using the mechanism of polyelectrolyte complexes of both the oppositely charged natural polymer.
- To determine the percent mucoadheson in comparison with synthetic mucoadhesive polymer.
- To study the in-vitro drug release behaviour of all the developed formulation.
- To compare the drug release pattern of the developed formulation with marketed tablet.
- To propose the release mechanism of developed formulations.

3.2. NEED OF THE STUDY:

- The proposed mucoadhesive drug delivery system will be designed using positively charged natural polymer and negatively charged polymer, as they could form polyelectrolyte complexes and the formation of polyelectrolyte complexes are useful in sustaining the drug action as compared to single polymer alone which is useful to increase the absorption of drug specifically from the upper intestinal pH where maximum effectiveness of the model drug Pantoprazole could be attained. This is because Pantoprazole is slowly degraded in highly acidic medium of the stomach, showing maximum efficacy at higher pH regions (6.8-7.4).

CHAPTER-4

4. DRUG AND POLYMER PROFILE

4.1. PANTOPRAZOLE SODIUM SESQUIHYDRATE

4.2. SODIUM ALGINATE

4.3. CHITOSAN

4.4. CARBOPOL 934

4.5. MAGNESIUM STEARATE

4.6. LACTOSE

4. DRUG AND POLYMER PROFILE:

4.1 Pantoprazole Sodium Sesquihydrate [35-37]:

4.1.1. Chemistry:

- Chemically, Pantoprazole sodium sesquihydrate, is a sodium 5-(difluromethoxy)- 2-[[3,4,dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H benzimidazole sesquihydrate. (Fig: 5). Molecular formula is $C_{16}H_{15}F_2N_3O_4$ X 1.5 H_2O and molecular weight is 432.4 gm/mol. Because of gradual degradation of pantopzole sodium during heating, the melting point cannot be determined. It is a white to off- white powder.

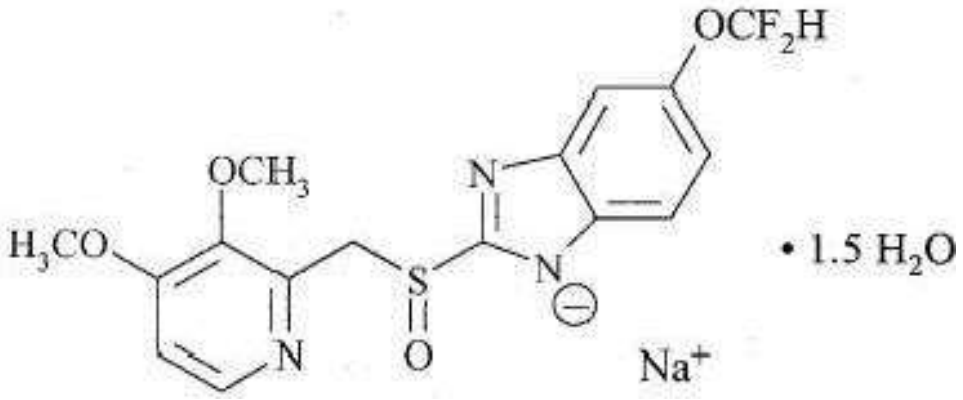


Fig: 5. Structure of Pantoprazole sodium sesquihydrate

4.1.2. Mechanism of action:

- Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+ K^+) - ATP ase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+ K^+) - ATP ase results in a duration of antisecretory effect that persists longer than 24 hr for all doses tested.

4.1.3. Pharmacokinetics:

- Pantoprazole sodium is prepared as an enteric coated tablet so that absorption of Pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple dosing. When Pantoprazole is given with food, its T_{max} is highly variable and may increase significantly.

4.1.3.1..Absorption:

- The absorption of Pantoprazole is rapid, with C_{max} 2.5 µg/ml that occurs approximately 2.5 hr after administration of a single or multiple oral 40 mg doses of Pantoprazole sodium delayed release tablet. Pantoprazole is well absorbed; it undergoes little first pass metabolism resulting in an absolutely bioavailability of approximately 77%. Administration of Pantoprazole with Food may delay its absorption up to 2 hr or long; however, the C_{max} and the extent of Pantoprazole absorption (AUC) are not altered.

4.1.3.2. Distribution:

- The apparent volume of distribution of Pantoprazole is approximately 11.0 to23.6 L, distributing mainly in extracellular fluid. The serum protein binding of Pantoprazole is about 98%, primarily to albumin.

4.1.3.3. Metabolism:

- Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic

pathways include oxidation by CYP3A4. Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 h, they still have minimal accumulation (≤ 23%) with once daily dosing.

4.1.3.4. Elimination

- After a single oral or intravenous dose of Pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with18% excreted in the faeces through biliary excretion. There was no renal excretion of unchanged Pantoprazole.

4.3.5. Drug-Drug Interactions:

- Pantoprazole given with atazanavir, indinavir, nelfinavir may be reduce the plasma concentrations. Co administration with atazanavir is not recommended. Plasma levels of certain azole antifungal (e.g. itraconazole, ketoconazole) may be reduced, avoid this combination if possible. Proton pump inhibitors may increase serum digoxin levels. midazolam, zinc is incompatible with Pantoprazole.

4.3.6. Contraindications:

- Pantoprazole sodium delayed-release tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

4.3.7. Precautions:

- Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

4.3.8. Side Effects

- The common side effects are abdominal pain, blurred vision, dry mouth, fatigue, flushed, dry skin, increased hunger, increased thirst, increased urination, nausea, sweating, troubled breathing, unexplained weight loss and vomiting. The other side effects are belching, bloated, full feeling, excess air or gas in the stomach or intestines, passing gas, sleeplessness, trouble sleeping and unable to sleep.

4.3.9. Uses:

- Pantoprazole is used to treat erosive esophagitis or "heartburn" caused by gastroesophageal reflux disease (GERD), a condition where the acid in the stomach washes back up into the esophagus. Pantoprazole may also be used to treat Zollinger-Ellison syndrome, a condition where the stomach produces too much acid.

4.3.10. Dose:

- It is administered orally dose of 40 mg once daily for up to 8 h.

4.3.11. Storage:

- Store the medicine in a closed container at room temperature, away from heat, Moisture and direct light.

4.2 .Sodium Alginate [38-40]:

4.2.1. Chemistry:

- It is chemically sodium alginate. It occurs as an odourless and tasteless, white to pale yellowish- brown colour powder**.**

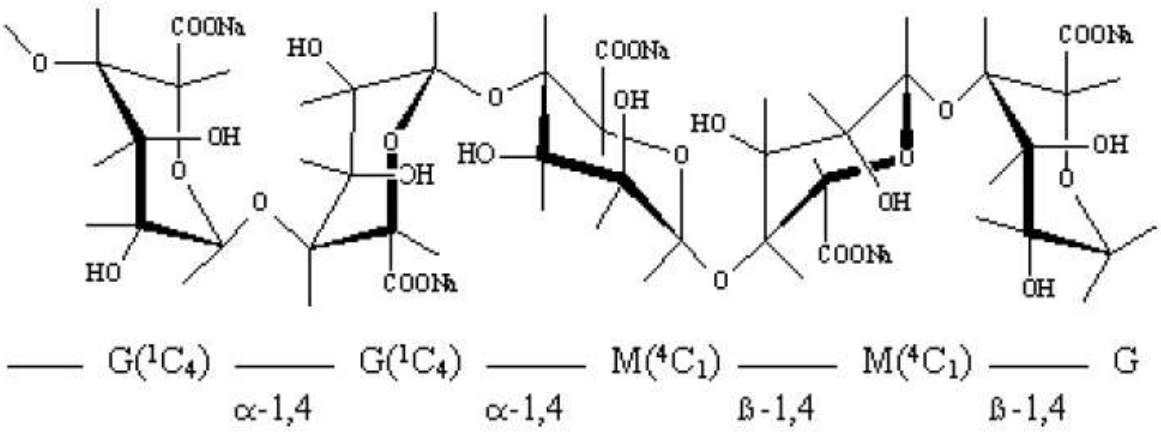


Fig: 6. Structural Formula of Sodium Alginate.

4.2.2. Typical properties:

4.2.2.1. Acidity/alkalinity:

- PH ≈7.2 for a 1% w/v aqueous solution.

4.2.2.2. Solubility:

- It is practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

4.2.2.3. Viscosity (dynamic):

- Various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity.

- Typically, a 1% w/v aqueous solution, at 208c, will have a viscosity of 20–400 m pas (20–400 cp).viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. Above pH10, viscosity decreases.

4.2.2.4. Safety:

- It is generally regarded as a nontoxic and non-irritant material, although excessive oral consumption may be harmful.

4.2.2.5. Functional Category:

- It is generally used as Stabilizing agent; suspending agent; tablet and capsule disintegrate; tablet binder; viscosity-increasing agent.

4.2.3. Applications in pharmaceutical formulation or technology:

- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.
- In tablet formulations, sodium alginate may be used as both a binder and disintegrate; it has been used as a diluents in capsule formulations.
- Sodium alginate has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.
- Therapeutically, sodium alginate has been used in combination with an H2-receptor antagonist in the management of gastroesophageal reflux, and as a hemostatic agent in surgical dressings.
- Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties.
- Sponges composed of sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressings or as tissue engineering matrices.

4.2.4. Incompatibilities:

- Sodium alginate is incompatible with acridine derivatives, crystal violet, phenyl mercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%.

4.2.5. Stability and Storage Conditions:

- Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humilities and a cool temperature.
- Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years.(Solutions should not be stored in metal containers.
- Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration using a 0.45 mm filter also has only a slight adverse effect on solution viscosity.
- Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used.
- The bulk material should be stored in an airtight container in a cool, dry place.

4.3. Chitosan[38-40]:

4.3.1. Nonproprietary Names:

- BP: Chitosan hydrochloride
- PhEur: Chitosani hydrochloridum.

4.3.2. Synonyms:

- 2-Amino-2-deoxy-(1,4)-b-D-glucopyranan; deacetylated chitin; deacetylchitin; b-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-b-D-glucopyranosamine.

4.3.3. Chemical Name:

- Poly-b-(1, 4)-2-Amino-2-deoxy-D-glucose

4.3.4. Chemistry:

- Chitosan occurs as odourless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cottonlike'.

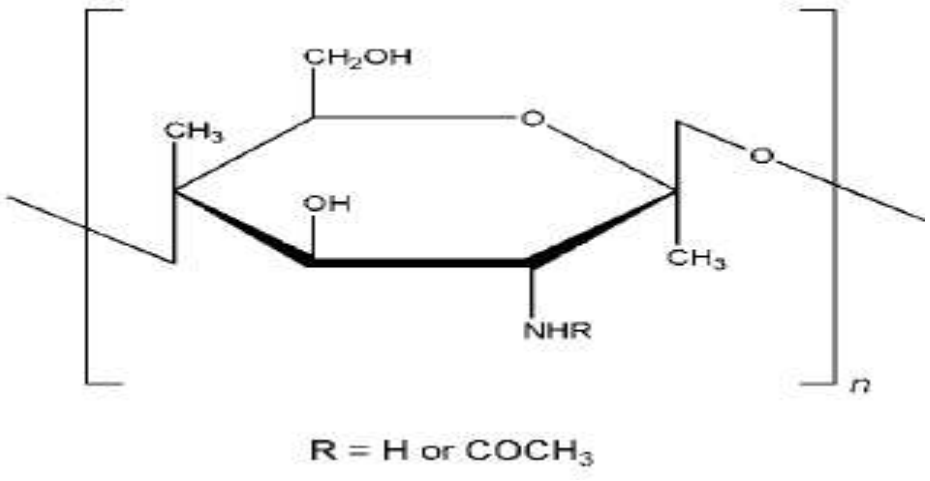


Fig: 7.Structural Formula of Chitosan

4.3.5. Typical Properties:

- Chitosan is a cationic polyamine with a high charge density at pH <6.5; and so adheres to negatively charged surfaces and chelates metal ions.
- It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation).
- The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character.

4.3.5.1. Acidity/alkalinity:

- pH = 4.0–6.0 (1% w/v aqueous solution

4.3.5.2. Density:

- The density of chitosan is 1.35–1.40 g/cm3.

4.3.5.3. Glass transition temperature:

- The glass transition temperature of chitosan is 203^0 C

4.3.5.4. Moisture content:

- Chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

4.3.5.5. Particle size distribution:

- The particle size is <30 mm.

4.3.5.6. Solubility:

- It is sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5.
- Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids.

4.3.5.7. Viscosity (dynamic):

- It has a wide range of viscosity types is commercially available. Owing to its high molecular weight and linear, unbranched structure, chitosan is an excellent viscosity-enhancing agent in an acidic environment.
- It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear.
- The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation.

4.3.5.8. Safety

- Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations.
- It is also used in cosmetics. Chitosan is generally regarded as a nontoxic and non-irritant material.

4.3.5.9. Functional Category:

- Chitosan is used as coating agent; disintegrate; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent.

4.3.6. Applications in Pharmaceutical Formulation or Technology:

- Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations.
- The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and use for gene delivery.

4.3.7. Incompatibilities:

- Chitosan is incompatible with strong oxidizing agents.

4.3.8. Stability and Storage Conditions:

- Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying.
- Chitosan should be stored in a tightly closed container in a cool, dry place.

4.4. Carbopol 934 [38-40]:

4.4.1. Nonproprietary Names

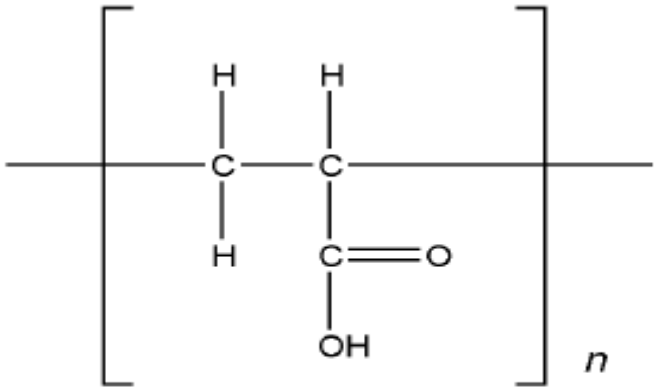
- BP: Carbomers
- PhEur: Carbomera
- USPNF: Carbomer

4.4.2. Synonyms

- Acritamer; acrylic acid polymer; Carbopol; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

4.4.3. Empirical Formula and Molecular Weight

- Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are cross linked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis.



Acrylic acid monomer unit in carbomer resins.

Fig: 8. Structural Formula of Carbopol 934

4.4.5. Functional Category

- Bio adhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

4.4.6. **Applications in Pharmaceutical Formulation or Technology:**

- Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic, rectal and topical preparations.
- Carbomer grades, even with low residual benzene content, such as carbomer 934P, are no longer included in the PhEur2005. However, carbomer having low residuals only of other solvents than the ICH-defined 'Class I OVI solvents' may be used in Europe.
- In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipient.
- Carbomer resins have also been investigated in the preparation of sustained-release matrix beads,(23) as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms,(24,25) as a bio adhesive for a cervical patch(26) and for intranasally administered microspheres,(27) in magnetic granules for site-specific drug delivery to the oesophagus(28) and in oral mucoadhesive controlled drug delivery systems.(29,30)
- Carbomers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use.

4.4.7. Description

- Carbomers are white-colour, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor.

Typical Properties:

- **Acidity/alkalinity:**
  - pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion;
  - pH = 2.5–3.0 for a 1% w/v aqueous dispersion.
- **Density (bulk):** 1.76–2.08 g/cm3
- **Density (tapped):** 1.4 g/cm3
- **Glass transition temperature:** 100–1058C
- **Melting point**: decomposition occurs within 30 minutes at 2608C.
- **Moisture content**: normal water content is up to 2% w/w.However, carbomers are hygroscopic and typical equilibrium moisture content at 258C and 50% relative humidity is 8–10% w/w. The moisture content of a carbomer does not affect its thickening efficiency, but an increase in the moisture content makes the carbomer more difficult to handle because it is less readily dispersed.
- **Particle size distribution**: primary particles average about 0.2 mm in diameter. The flocculated powder particles average 2–7 mm in diameter and cannot be broken down into the primary particles. Recently, a granular carbomer having a particle size in the range 180–425 mm has been introduced. Its bulk and tap densities are also higher than those of other carbomers.
- **Solubility:** soluble in water and, after neutralization, in ethanol (95%) and glycerine.
- **Specific gravity:** 1.41
- **Viscosity (dynamic):** carbomers disperse in water to form acidic colloidal dispersions of low viscosity that, when neutralized, produce highly viscous gels.

4.4.8. Stability and Storage Conditions:

- Carbomers are stable, hygroscopic materials that may be heated at temperatures below 1048C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 2608C.
- Carbomer powder should be stored in an airtight, corrosion- resistant container in a cool, dry place.

4.5. Magnesium Stearate[38-40]:

4.5.1. Nonproprietary Names:

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate.

4.5.2. Synonyms:

- Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

4.5.3. Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.34

- The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and acid and in minor proportions other fatty acids.

4.5.4. Structural Formula:

$[CH_3 (CH2)_{16}COO]_2Mg$

4.5.6. Functional Category:

- Tablet and capsule lubricant

4.5.7. Applications in Pharmaceutical Formulation or Technology:

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.

- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

4.5.8. Description:

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

4.5.9. Stability and Storage Conditions:

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

4.5.10. Incompatibilities:

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

4.6. Lactose [38-40]:

4.6.1. Nonproprietary Names:

- BP: Anhydrous lactose
- JP: Anhydrous lactose
- PhEur: Lactosum anhydricum
- USPNF: Anhydrous lactose.

4.6.2. Synonyms:

- Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tableting; Lactopress Anhydrous; lactosum; lattioso; milk sugar; Pharmatose DCL 21; Pharmatose DCL 22; saccharum lactis; Super-Tab Anhydrous.

4.6.3. Empirical Formula and Molecular Weight:

$C_{12}H_{22}O_{11}$ 342.30

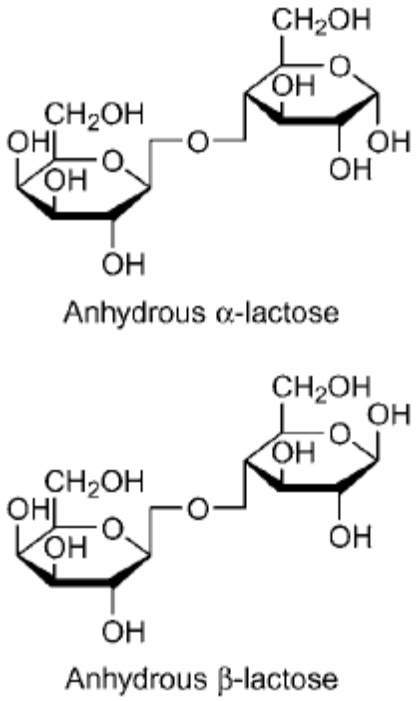


Fig: 9. Structural formula of Lactose:

4.6.4. Functional Category:

- Binding agent; directly compressible tableting excipient; lyophilisation aid; tablet and capsule filler.

4.6.5. Applications in Pharmaceutical Formulation or Technology:

- Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder.
- Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

4.6.6. Description:

- Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose.
- Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous lactose.

4.6.7. Typical Properties:

- **Angle of repose**: 398 for Pharmatose DCL 21 and 388 for Super-Tab Anhydrous.
- **Brittle fracture index**: 0.0362
- **Bonding index**: 0.0049 (at compression pressure 177.8 MPa)(a)
- **Density (true)**: 1.589 g/cm3 for anhydrous b-lactose; 1.567 g/cm3 for Super-Tab Anhydrous.
- **Density (bulk)**: 0.68 g/cm3 for Pharmatose DCL 21; 0.67 g/cm3 for Pharmatose DCL 22; 0.65 g/cm3 for Super-Tab Anhydrous.
- **Density (tapped):** 0.88 g/cm3 for Pharmatose DCL 21; 0.79 g/cm3 for Pharmatose DCL 22; 0.87 g/cm3 for Super- Tab Anhydrous.

- **Melting point:**
- 223.08C for anhydrous a-lactose;
- 252.28C for anhydrous b-lactose;
- 232.08C (typical) for commercial anhydrous lactose.
- **Solubility**: soluble in water; sparingly soluble in ethanol (95%) and ether.

4.6.8. Stability and Storage Conditions:

- Mold growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; at 808C and 80% RH, tablets containing anhydrous lactose have been shown to expand 1.2 times after one day. Lactose anhydrous should be stored in a well-closed Container in a cool, dry place

4.6.9. Incompatibilities:

- Lactose anhydrous is incompatible with strong oxidizers.
- When mixtures containing a hydrophobic leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 408C and 75% RH, the mixture containing anhydrous lactose showed greater moisture uptake and drug degradation

CHAPTER-5

5. MATERIALS AND METHOD

5.1. METHODS (PREFORMULATION STUDIES OF DRUG AND EXCIPIENTS)

5.2. PROTOTYPE FORMULATION DEVELOPMENT

5.3. SWELLING STUDIES

5.4. MEASUREMENT OF MUCOADHESIVE STRENGTH

5.5. DISSOLUTION STUDIES OF VARIOUS PROTOTYPE TABLET FORMULATIONS

5.6. KINETIC EVALUATION OF DISSOLUTION DATA

5. MATERIALS AND METHODS

Table: 2. Materials (Chemicals and reagents):

SL NO	Material	Source
1	Pantoprazole sodium sesquihydrate	Yerrow chem., Mumbai-37
2	Sodium alginate	Himedia,Mumbai-86
3	chitosan	Balaji,Drugs, Mumbai-37
4	Sodium CMC	Balaji,Drugs, Mumbai-37
5	Carbopol 934	Balaji,Drugs, Mumbai-37
6	Sodium hydroxide	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
7	Hydrochloric acid	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
8	Potassium dihydrogen phosphate	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
9	Sodium dihydrogen phosphate	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
10	Magnesium stearate	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
11	Lactose	Merck specialist pvt ltd,shiv sagar estate, Mumbai-400018
12	Ethanol	Changshu Yangyuan chemical, china
13	Acetone	Changshu Yangyuan chemical, china
14	Methanol	Changshu Yangyuan chemical, china

Table: 3. Instruments and equipments

Sl no	Instrument	Company name
1	Digital weighing balance	Denver Instrument
2	UV Visible spectrophotometer	Shimadju,Model no:UV 1800 240V
3	Tablet compression machine (I.P/B.P/U.S.P. standard)	Shakti,9001:2000 Company
4	Hardness tester	Rolex Tablet hardness tester
5	Friability tester	Rochi friabiliter
6	Dissolution test apparatus	Libinda,DS 8000
7	FT-IR	Bruker Model no:10059736
8	Melting point determination	Macroscientific works10A/UA,Janwahar Nagar, Delhi-11007
9	Hot air oven	International commercial Traders,18,Kolkata-700001
10	Bulk density apparatus	Rolex
11	Viscometer	Brookfield viscometer DV-E viscometer
12	Texture Analyzer	Stable Microsystem, Model:TA-XT Express
13	DSC instrument	Parkin Elmer

5.1. Methods (Preformulation studies of drug and excipients):

5.1.1. Solubility determination [41]:

A minute quantity of the drug sample was taken in a test tube and solubility of the drug was determined by dissolving the drug in 1 ml of various solvent like water, 0.1 M HCl, methanol, ethanol, phosphate buffer, Acetone etc.

5.1.2. Melting point determination [41]:

It was placed a little of drug sample in a dry capillary tube of 1-mm internal diameter forming a column about 3 mm high. Heat the melting-point apparatus to a temperature 5-10 °C below the expected temperature of melting and adjust the heating so that the temperature in the chamber rises about 1 °C per minute. Introduce the capillary tube into the melting point apparatus, and noted the temperature when the drug substance becomes completely melted to liquid state; this is considered to be the melting point.

5.1.3. FT-IR spectroscopy study [42-44]:

This was carried out to find out the compatibility between the drugs Pantoprazole sodium sesquihydrate and the polymer sodium alginate, chitosan, carbopol, sodium CMC. 10 mg of the sample were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at10 kg/cm^2 using a hydraulic press. The pellet was kept into the sample holder and scanned from 400 cm-1 to 4000 cm-1 in Bruker FT-IR spectrophotometer. Samples were prepared for drug Pantoprazole sodium sesquihydrate, polymer sodium alginate, chitosan, sodium CMC, carbopol 934 and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group peaks.

5.1.4. Differential scanning calorimetry (DSC) studies [44-47]:

Differential scanning calorimetry (DSC) of the bulk drug Pantoprazole sodium sesquihydrate and the excipient were performed using (Parkin Elmer) for measurement of the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. About 6-7 mg of the individual components or drug-excipients combinations were weighed in aluminium DSC pans and hermetically sealed capsules were prepared with aluminium lids. An initial ramp was used to jump the temperature to 40ºC and then a constant heating rate of 10 ºC/min was used up to 300 ºC under nitrogen atmosphere.

5.1.5. Powder X-ray diffraction study [46-47]:

Powder X-ray diffraction patterns of pure drugs, and drug–polymer physical mixtures were measured using powder X-ray diffract meter (model JDX-3530, Jeol, Japan) with Ni-filtered Cu radiation generated at 30 kV and 30 mA as an X-ray source

5.1.6. Viscosity determination [48-49]:

The viscosity of the polymer were determined by preparing carbopol 0.5% w/v in 50 ml water, sodium CMC 0.5%w/v in 50 water, sodium alginate 0.5% w/v in 50 ml water, chitosan 0.5%w/v in 50 ml glacial acetic acid . The viscosities of prepared polymeric solution were determined by using Brookfield viscometer. At 25 spindle and 1, 5, 10, 50 rpm were selected and for determining the viscosity.

5.1.7. UV analysis of the drug:

5.1.7.1. Determination of absorption maxima (λmax) in water:

10 mg of Pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 10 ml water in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with water. The resulting solution was labelled as standard working Solution. 0 .4 ml of the working solution was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in UV-visible spectrophotometer. The λ max of the Pantoprazole sodium sesquihydrate was found to be 289 nm.

5.1.7.2. Preparation of standard calibration curve in water:

From above standard working solution, 0.2 ml, 0.4 ml, 0.6 ml and 0.8 ml, 1ml, 1.2 was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using water as blank.

5.1.7.3. Preparation of standard calibration in 0.1 M HCl:

10 mg of Pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 10 ml of 0.1M HCL buffer (p^H 1.2) in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with pH 1.2 0.1 M HCL buffer. The resulting solution was labelled as standard working Solution. From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with pH 1.2 0.1M HCL buffer in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using the pH 1.2 0.1M HCL buffer as blank.

5.1.7.4. Preparation of standard calibration curve in phosphate buffer pH 6.8:

10 mg of Pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 10 ml of distilled water in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with water. The resulting solution was labelled as standard working Solution. From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with water in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using water as blank

5.1.7.5. Preparation of standard calibration in phosphate buffer pH 6.8:

10 mg of Pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 10 ml of pH 6.8 phosphate buffer in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted

up to 10 ml with pH 6.8 phosphate buffer. The resulting solution was labelled as standard working Solution. From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffers in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using the pH 6.8 phosphate buffers as blank.

5.1.7.6. Preparation of standard calibration in phosphate buffer pH 7.4:

10 mg of Pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 10 ml of pH 7.4 phosphate buffer in 10 ml volumetric flask (stock solution). 1 ml was taken from the stock solution and transferred into 10 ml volumetric flask and diluted up to 10 ml with pH 6.8 phosphate buffer. The resulting solution was labelled as standard working Solution From standard working solution, 0.2 ml, 0.4ml, 0.6 ml, 0.6 ml, 0.8 ml, 1 ml, and 1.2 ml was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffer in 10 ml volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 289 nm using the pH 6.8 phosphate buffers as blank.

5.1.7.7. Saturation Solubility determination [50]:

The Solubility of the selected drug was determined in distilled water, 0.1M HCl,phosphate buffer pH 6.8 by the following procedure: Excess amount of drug was taken and dissolved in a measured amount of solution of each Solvent in a volumetric flask to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. After 24 hour the solution was sonicated for 30 min & the resultant solution was centrifuged to separate supernatant then withdrawn the supernatant and successively diluted and

analyzed concentration of Pantoprazole by UV (Ultraviolet) Spectrophotometer at 289 nm.

5.2. Prototype formulation development:

Prototype tablet were prepared using various tablet excipients selected from compatibility studies. The concentrations of polymer used for prototype formulation development were (15-35%). For tablet preparation following excipients were selected sodium alginate, chitosan, lactose, magnesium stearate were weighed according to the formula and transferred in a mortar and pestle and mixed thoroughly. The above excipients were dried and mixed with the 40 mg drug and passed through sieve no 120 were directly compressed in tablet machine using 6mm round punch. The different batches of Pantoprazole tablets were collected and stored in air tight containers .The tablets were prepared each weighing 150 mg as per shown in table and its drug release studies were performed in USP dissolution type II apparatus.

5.2.1. Pre compression parameters: **[16, 50]**

5.2.1.1. Bulk density (Db):

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

$$Db = M/\mathbf{V_b}$$

Where, M - Mass of the powder

V_b - Bulk volume of the powder

5.2.1.2. Tapped density (Dt):

It is the ratio of total mass of powder to the tapped volume of powder. The graduated measuring cylinder containing accurately weighed powder was manually tapped for 50 times. Volume occupied by the powder was noted. It is expressed in gram/ml and is calculated by following formula.

$$D_t = M/V_t$$

Where, M - Mass of the powder

V_t - Tapped volume of the powder

5.2.1.3. Compressibility index (I) and Hausner's ratio:

Carr's index and Hausner's ratio measure the property of powder to be compressed and the flow ability of powder. Carr's index and Hausner's ratio were calculated using following formula.

$$I = D_t - D_b/D_t \times 100$$

Where, D_t – Tapped density of the powder

D_b – Bulk density of the powder

Hausner's ratio= $Dt/D_b = V_b/V_t$

5.2.1.4. Angle of repose (θ):

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Pantoprazole powder were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula.

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where, h – Height of the pile in cm

r – Radius of the pile.

Table: 4.Prototype formula for the preparation of Pantoprazole sodium sesquihydrate tablets:

Batch Code	Conc. of Cationic polymer %(w/v)	Conc. of anionic Polymer %(w/v)	Pantoprazole sodium sesquihydrate (mg)	Sodium alginate (mg)	Chitosan (mg)	Lactose (mg)	Magnesium stearate (mg)	Total weight Mg
FS1	---	15	40	22.5	---	84.5	3	150
FS2	---	35	40	52.5	---	54.5	3	150
FC1	15	---	40	---	22.5	84.5	3	150
FC2	35	---	40	---	52.5	54.5	3	150
FSC1	7.5	7.5	40	11.25	11.25	84.5	3	150
FSC2	17.5	17.5	40	26.5	26.5	54.5	3	150

FS1: Formulation with 15% sodium alginate, **FS2**: Formulation with 35% sodium alginate, **FC1**: Formulation with 15% chitosan, **FC2**: Formulation with 35% chitosan,

FSC1: Formulation with 15% sodium alginate and chitosan,

FSC2: Formulation with 35% sodium alginate and chitosan

5.2.2. Physical evaluation of prototype Pantoprazole sodium sesquihydrate tablets

5.2.2. Post compression parameters [51-53]:

5.2.2.1. Hardness test:

The prepared tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in kg/cm^2.

5.2.2.2. Friability test:

The friability was determined using Roche friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability (F) was calculated for each batch by using the following formula

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

5.2.2.3. Weight variation test:

20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%. IP limit for weight variation in case of tablets weighing more than 80 mg but less than 250 mg is ± 7.5 %.

5.2.2.4. Uniformity of drug content:

The prepared Pantoprazole sodium sesquihydrate tablets were tested for their drug content. Three tablets of each formulation were weighed and finely powdered. About 40 mg equivalent of Pantoprazole sodium sesquihydrate was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. 1 ml of the filtrate was further diluted to 100 ml with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured by UV-Visible spectrophotometer at 288.5 nm.

5.2.2.5. Thickness:

Collect 2 tablets from each batch of formulation and the thickness of the tablets were measured with the help of vernier calliper. The average thickness is calculated.

5.3. Swelling Studies [54-55]:

The tablets of each formulation were kept in a basket and weighed individually (W1) and placed separately in dissolution medium containing 900 ml of phosphate buffer (pH 7.4). At regular time of intervals (1, 2, 4, and 5 hours) the tablets were removed from the medium and dried by tissue paper. The basket with tablet were re-weighed (W2); the swelling index of each formulation calculated by using this formula.

Swelling Index (S.I.) = W1-W2 / W1×100

W1 = Initial Weight, W2 = Final Weight

5.4. Measurement of mucoadhesive strength[56-57]:

The mucoadhesion was determined by measuring the maximal force required to separate the test material from the mucosal surface. The mucosal surface of goat intestine was used in the test. The goat intestine is relatively free of intestinal content, and provided a macroscopically flat and uniform surface. The middle section, discarding the first 40-50 mm at either ends of fresh intestine from goat was used. This was cut into 2 cm lengths, opened longitudinally to expose the inner mucosal surface, and fixed at the upper plate of instrument with a two-sided adhesive tape. The intestine was kept in phosphate buffer solution of pH 7.4 during the preparation time the texture analyzer (Stable Microsystem) and associated software was introduced for the measurement of mucoadhesion. The tablet was attached to the upper probe of the instrument and the intestine was placed to the upper stamp plate(diameter 10 mm).The pH 7.4 phosphate buffer solution was spread on the intestinal mucosa to standardize hydration prior to testing, and the mucosa was brought into contact with the test

material. After a preload of 500 gm for 15 sec of contact time, the mucosa was raised at a constant speed of 10 mm/min and the detachment force was recorded since this value is for the contact area 1.13 cm^2 between the upper stamp plate and test material, the mucoadhesive force per area was calculated and expressed as ‘‘mucoadhesion’’ gm/cm3.

5.5. Dissolution studies of various prototype tablet formulations:

Drug release studies of prototype tablets and marketed tablets were conducted in different dissolution medium at pH 6.8 and 7.4. The drug release rate from prototype mucoadhesive tablets and marketed tablets were studied using the USP (II) dissolution test apparatus (Libinda, DS8000). The assembly is kept in a jacketed vessel of water maintained at 37 ± 2^0C. The dissolution vessel were filled with 900 ml of phosphate buffer pH 6.8and 7.4. The vessel maintained at 50 rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through what man filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 289 nm up to 6 hours.

5.6. Kinetic evaluation of dissolution data [58-59]:

To examine the release mechanism of Pantoprazole from the prepared mucoadhesive tablets, the results were analyzed according to the following equation

$$\frac{M_t}{M_\infty} = k.t^n$$

Where Mt / M∞ is the fractional drug released at time *t*, *k* is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system [device], and *n* is the diffusion exponent that characterizes the mechanism of drug

release. It is known that for non-swelling tablets, drug release can generally be expressed by the Fickian diffusion mechanism, for which $n = 0.5$, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which $n = 1$. For non-Fickian release, the n value falls between 0.5 and 1.0 [$0.5 < n < 1.0$]; whereas in the case of super case II transport, $n > 1$.

Data of the *invitro* release was fit into different equations and kinetic models to explain the release kinetics of Pantoprazole from mucoadhesive tablets. The kinetic models used were zero-order equation (eq. 1), first-order equation (eq. 2), Higuchi equation (eq. 3) , Krosmeyer-Peppas equation (eq. 4)

$$Q_t = K_0 t \text{ ---------- (1)}$$

$$Q_t = Q_0 (1- e^{-k1}t) \text{ ---------- (2)}$$

$$Q_t = K_H.t^{1/2} \text{ ---------- (3)}$$

$$Q_0 1/3 - Q_t 1/3 = K_{HC}\, t \text{ ---------- (4)}$$

Where,

Q_t ------- Is the amount of drug release in time t

Q_0 ------- Is the initial amount of the drug

F ------- Is the fraction of drug release in time t

n ------- Exponent value

And K_0, K_1, K_H, and K_{HC} are release rate constants for Zero-order, First-order, Higuchi and Koresmeyer-Peppas model respectively.

Selection of final batches:

Among the different batches, the best two were identified and selected based on their physicochemical and release characteristics, for further studies.

Table: 5.Final batch formula for the preparation of Pantoprazole sodium sesquihydrate tablets:

Batch Code	Pantoprazole sodium sesquihydrate (mg)	Sodium alginate (mg)	Chitosan (mg)	Lactose (mg)	Magnesium stearate (mg)	Total weight Mg
FS2 (35%)	40	52.5	___	54.5	3	150
FSC2 (35%)	40	26.5	26.5	54.5	3	150

5.7. Coating of Pantoprazole sodium sesquihydrate tablets [59]:

5.6.1. Preparation of enteric coating solution

The enteric coating solution was prepared by simple solution method. It was prepared by 10% w/w of Eudragit L100 an enteric polymer, triethyl citrate 2.4 % w/w as plasticizer and acetone and isopropyl alcohol mixture was used as solvent. Eudragit L 100 was triturated with already prepared one half of solvent mixture. Triethyl citrate was added and made up the volume with rest of the solvent mixture; this mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a coating solution was obtained.

Table: 6.Composition of coating solution:

Ingredients	Quantity
Eudragit L 100	10%(w/v)
Triethyl citrate	25% (w/w)
Acetone	Vol. in ml
Isopropyl alcohol	Vol.in ml

5.6.2. Enteric coating of Pantoprazole sodium sesquihydrate tablets by dipping method

The Pantoprazole tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate or Drug coat L100) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for its in *vitro* dissolution study.

CHAPTER-6

6. RESULT AND DISSCUSSION

6.1. PREFORMULATION STUDIES OF PANTOPRAZOLE SODIUM SESQUIHYDRATE

6.2. CHARACTERIZATION OF PANTOPRAZOLE SODIUM SESQUIHYDRATE

6.3. IN-VITRO DRUG RELEASE STUDY OF FINAL BATCH COATED FORMULATION

6. RESULT AND DISSCUSSION:

6.1. Preformulation study pantoprazole sodium sesquihydrate

6.1.1. Organoleptic properties:

1. Nature	A white or almost white powder
2. Color	pale powder
3. Odor	characteristic.
4. Taste	Slightly Bitter taste

5. Solubility-

In water	Soluble.
In acetone	freely Soluble.
In methanol	Soluble.
In ethanol	Soluble.
In phosphate buffer P^H 6.8	Sparingly soluble.

From the solubility study of the drug it has been seen that the drug is soluble in polar solvent so it can be concluded that the drug is polar.

6.1.2. Melting point determination:

The melting point of the drug sample was found to be 196^0C, which matched the melting point as reported in official pharmacopoeia (B.P). This reveals that drug sample is retaining the desired property of purity.

6.1.3. Drug Polymer Interaction Study by FT-IR spectrophotometer:

FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug Pantoprazole and the polymers Sodium alginate, chitosan, used for the preparation of tablets. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies at wavelength between 400 cm-1 to 4000cm-1 is shown Table. From the FT-

IR study it is clearly understood the identical FT-IR bands were also present in the drug-polymer physical mixture as like that of the drug. This confirms that there are no drug-excipient interactions present.

Table:7.IR interpretation of drug, chitosan and physical mixture of drug-chitosan:

Sl No	Interpretatation	IR absorption bands (cm-1)		
		Drug	Chitosan	Drug+Chitosan
1	C-H(Aromatic)	2977.33	----	2946.17
2	C-H	2943.16	2868.90	2917.72
3	S=O	1070.98	----	1070
4	C-O	1380.77	1318	1391
5	C=N	1586.05	----	1586
6	C-N	1455.97	1419	1452
7	C-C	1357.97	1576&1644	1359
8	N-H	----	3350.79	____
9	O-H	----	3254.70	____

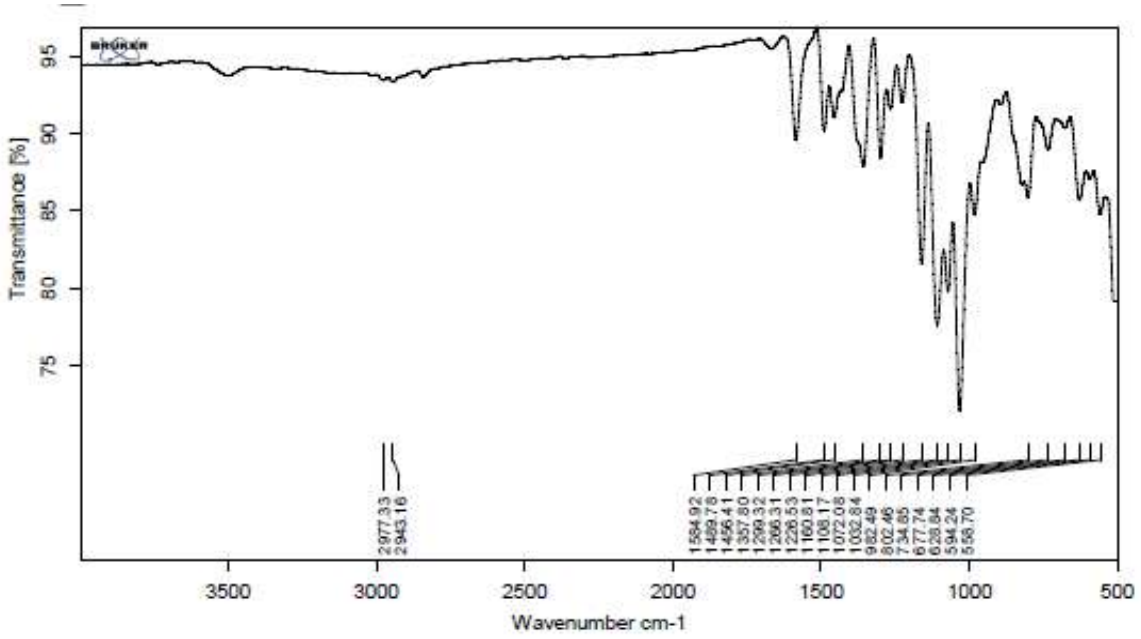


Fig: 10. IR spectrum of Pantoprazole

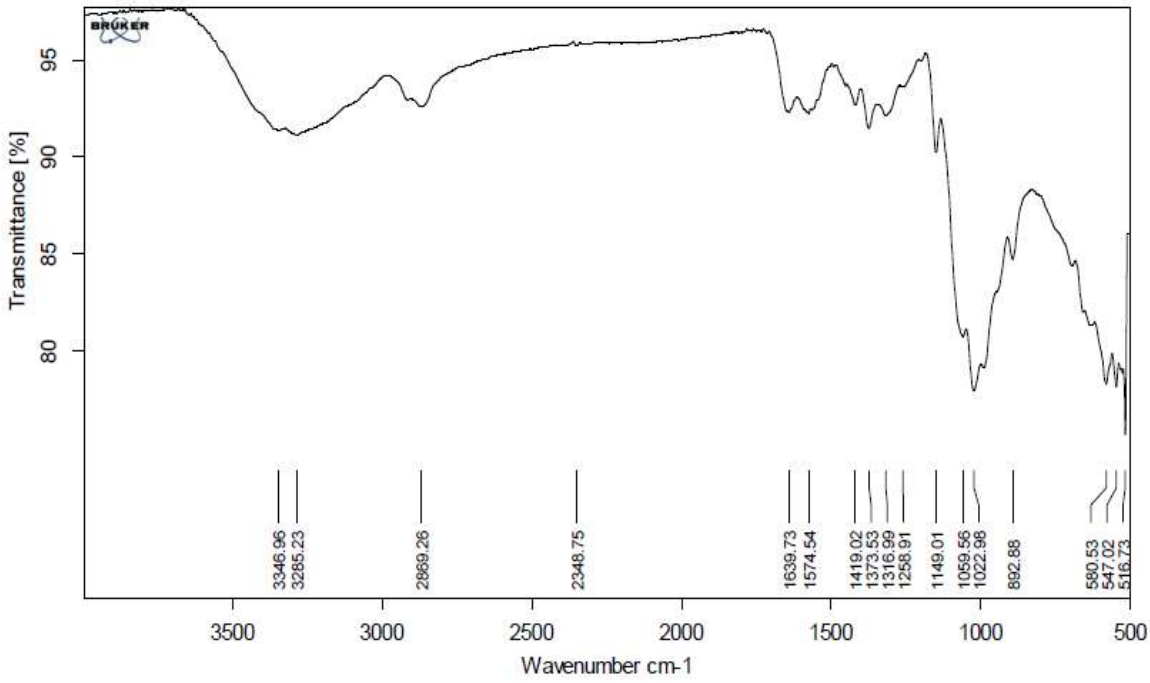


Fig: 11. IR spectrum of chitosan.

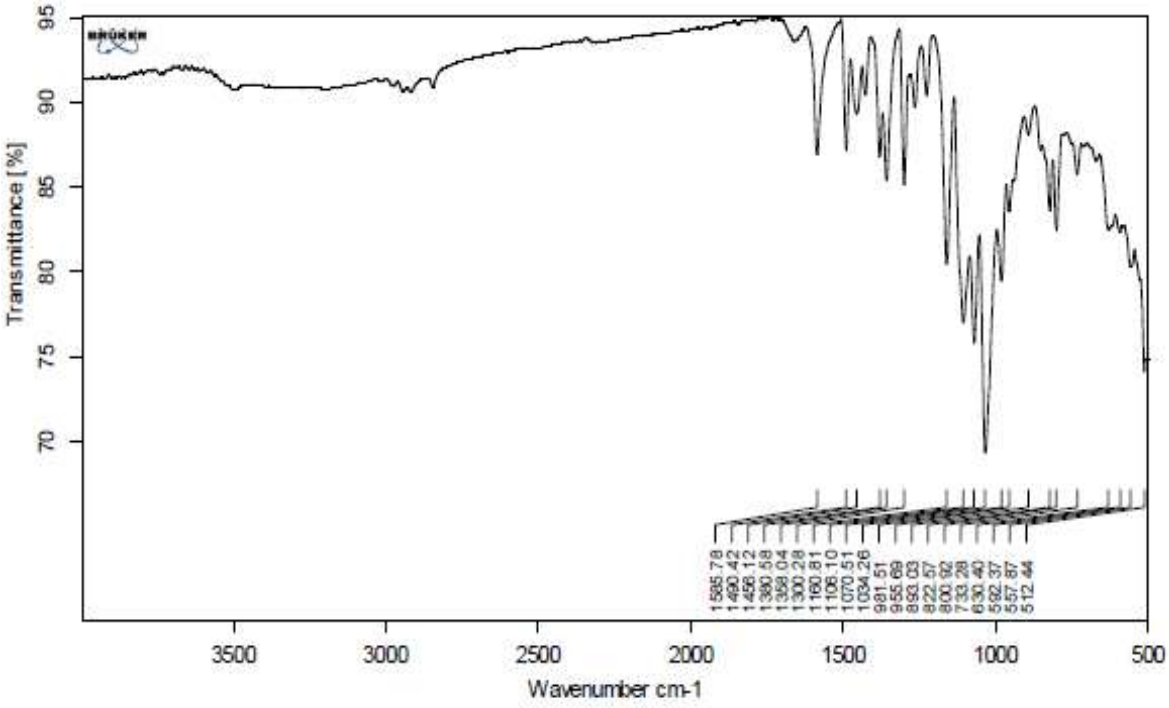


Fig: 12. IR spectrum of the mixture of Pantoprazole and chitosan.

Table: 8. IR interpretation of drug, sodium alginate and physical mixture of drug sodium alginate.

Sl No	Interpretation	IR absorption bands (cm-1)		
		Drug	Sodium alginate	Drug+Sodium alginate
1	O-H	-----	3252.55	-----
2	C-H	2943.16	2923.47	----
3	C-O	1380.77	1730.55	----
4	C=N	1586.05	1593.48	1586.54
5	C-C	1357.97	1354.91	1360.01
6	C-N	1455.97	1402.05	1427.88
7	C-H(Aromatic)	2977.33	------	-----
8	S=O	1070.98	------	-----

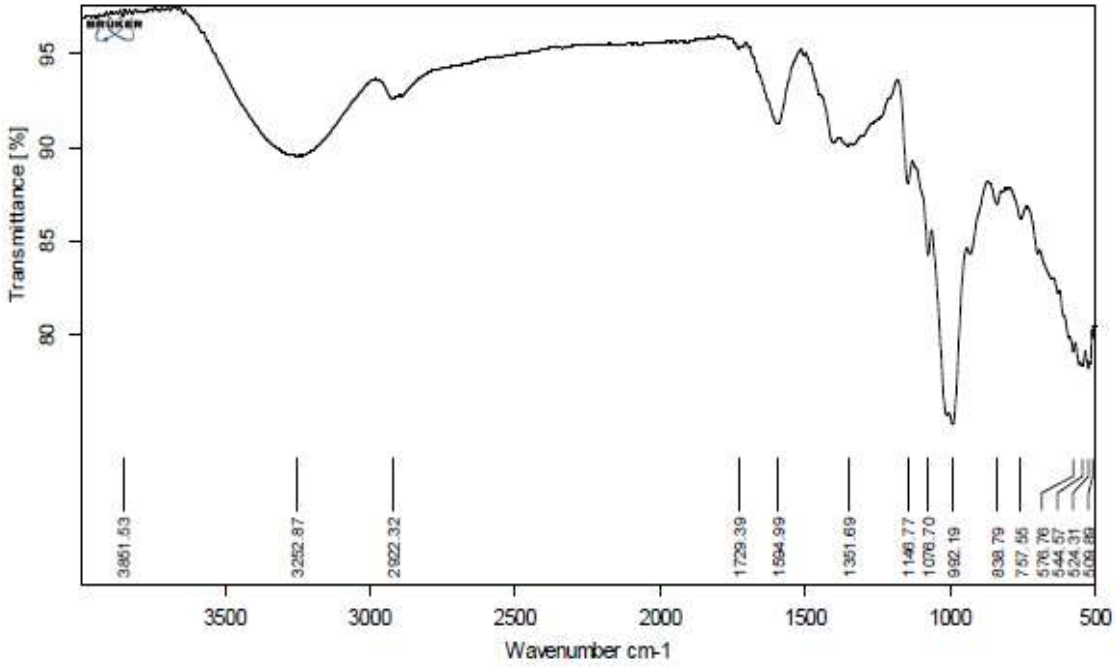


Fig: 13. IR Spectrum of Sodium Alginate

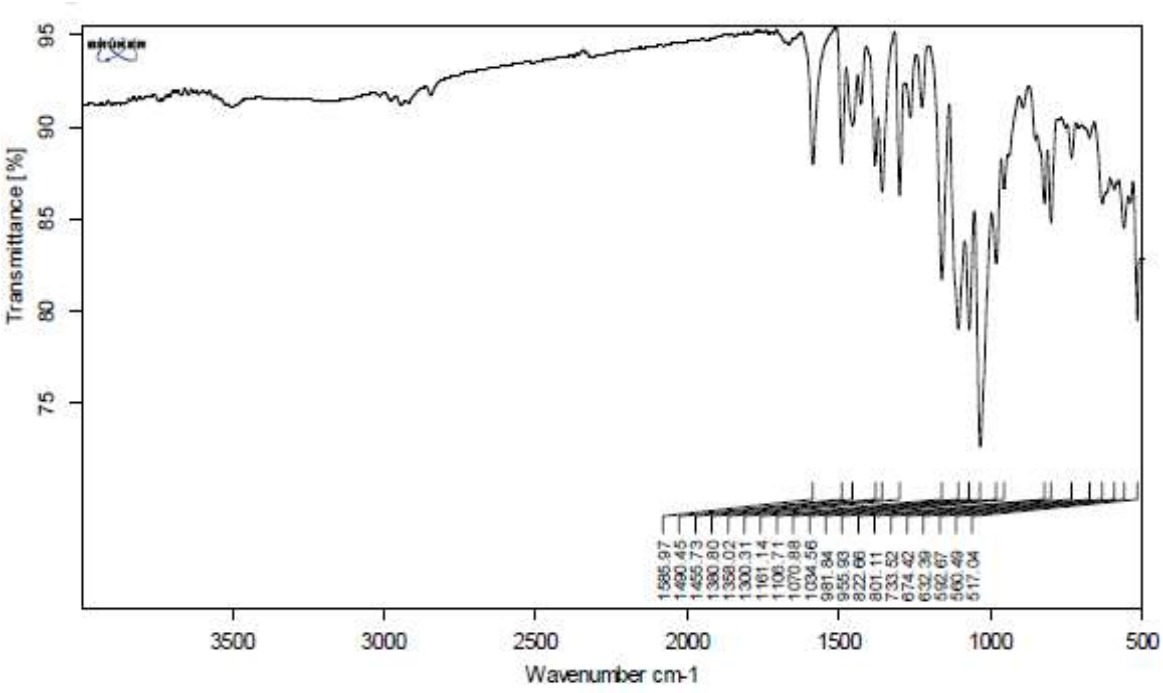


Fig: 14. IR Spectrum of the mixture of Pantoprazole and Sodium Alginate

Table: 9.IR interpretation of drug, carbopol 934 and physical mixture of drug-carbopol 934.

Sl No	Interpretation	IR absorption bands (cm-1)		
		Drug	Carbopol 934	Drug+Carbopol 934
1	C-H(Aromatic)	2977.33	----	2820
2	C-H	2943.16	3010	3130
3	S=O	1070.98	----	1037
4	C-O	1380.77	1703	1704
5	C=N	1586.05	----	1520
6	C-N	1455.97	----	1428
7	C-C	1357.97	1413.04	1300
8	N-H	----	-----	----
9	O-H	----	2938.13	3302

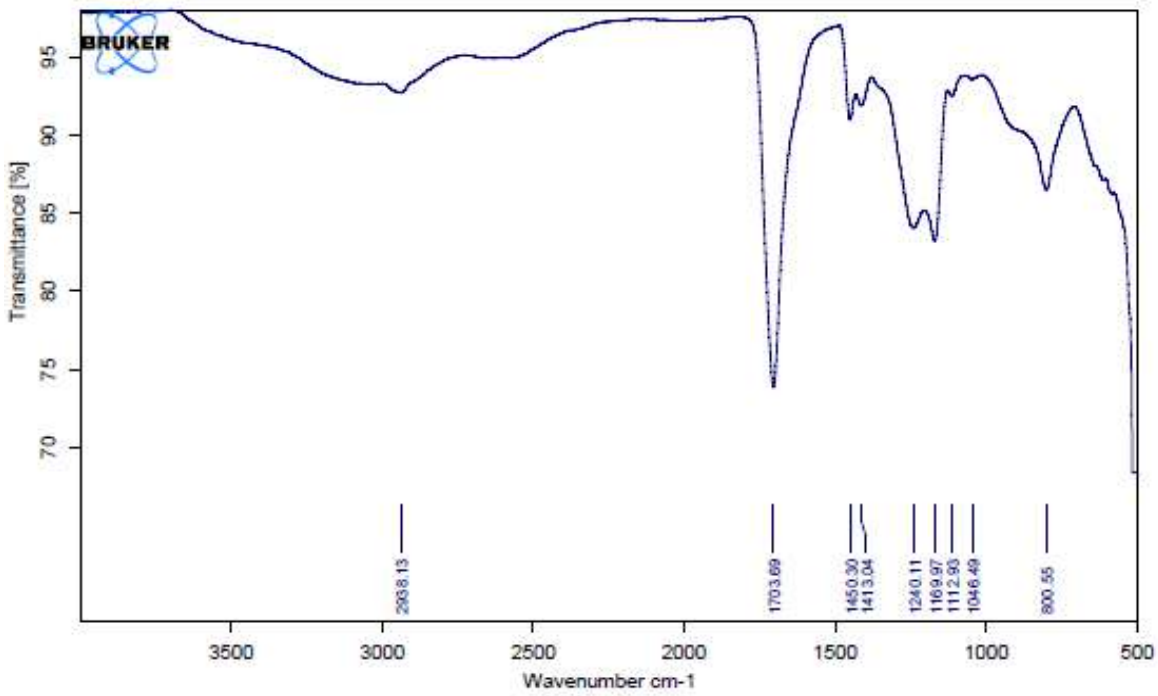


Fig: 15. IR Spectrum of Carbopol 934.

Table: 10. IR interpretation of drug, Sodium CMC and physical mixture of drug-sodium CMC.

Sl No	Interpretation	IR absorption bands (cm-1)		
		Drug	**Sodium CMC**	**Drug+Sodium CMC**
1	C-H(Aromatic)	2977.33		----
2	C-H	2943.16	2934	2930
3	S=O	1070.98		1070.43
4	C-O	1380.77	1319	1301
5	C=N	1586.05	-----	1586.32
6	C-N	1455.97	-----	-----
7	C-C	1357.97	1409	------
8	N-H	-----		-----
9	O-H	-----	3380	-----
10	C=O	-----	1627	-----

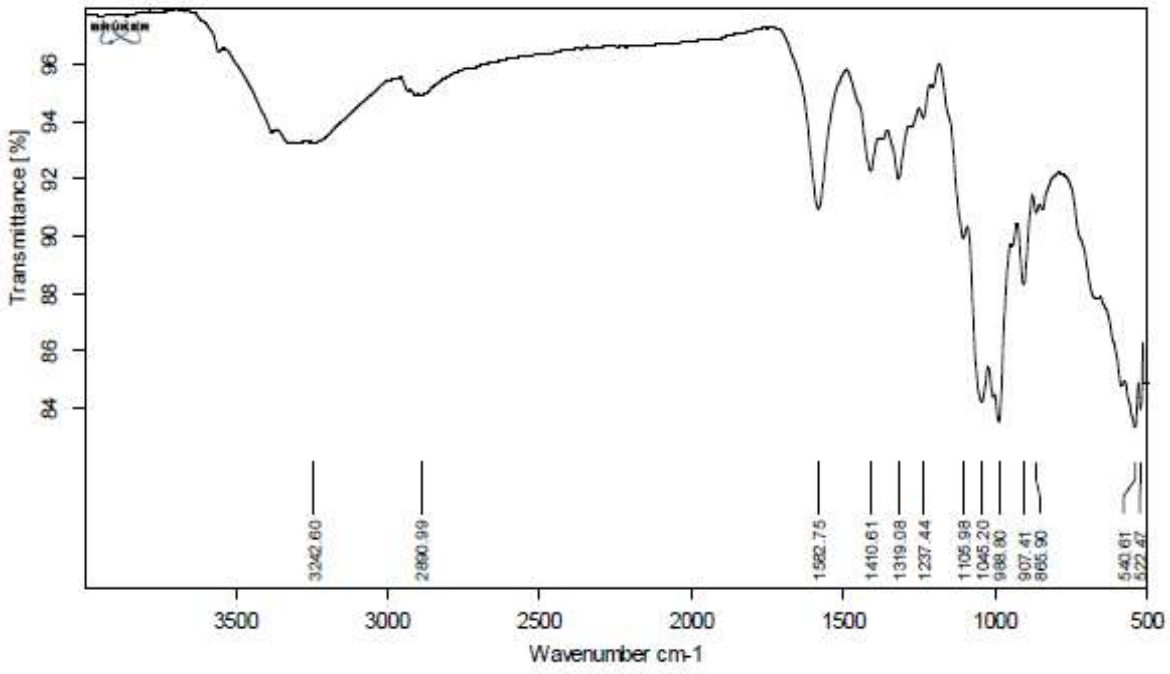


Fig: 16. IR spectrum of sodium CMC.

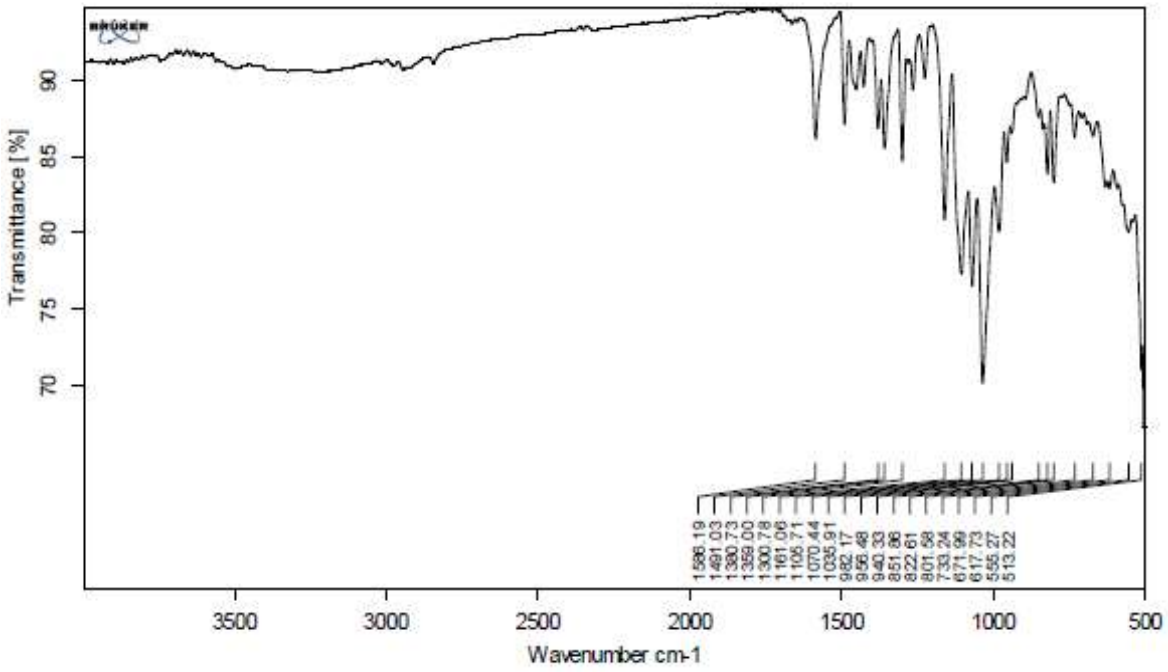


Fig: 17. IR spectrum of the mixture of Pantoprazole and sodium CMC.

6.1.4. DSC study:

DSC studies of the pure drug and excipient were carried out to determine if there was any interaction between the drug and the excipient. The thermo gram of pure Pantoprazole shows a sharp endothermic peak at 158 °C. Which corresponds to its melting point? The thermo gram of Pantoprazole with excipient like chitosan, lactose, magnesium stearate,sodium alginate, show sharp endothermic peak at 156.18^0C,161.61^0C,156.52^0C,122.19^0C respectively **(Shown from fig:18 to fig:23)** due to the presence of Pantoprazole. Results shows that the endothermic peak of the pure drug was also retained into the drug-physical mixture. Thus, the thermal data did not reveal any interaction between the drug and the excipients used for the prototype formulation development.

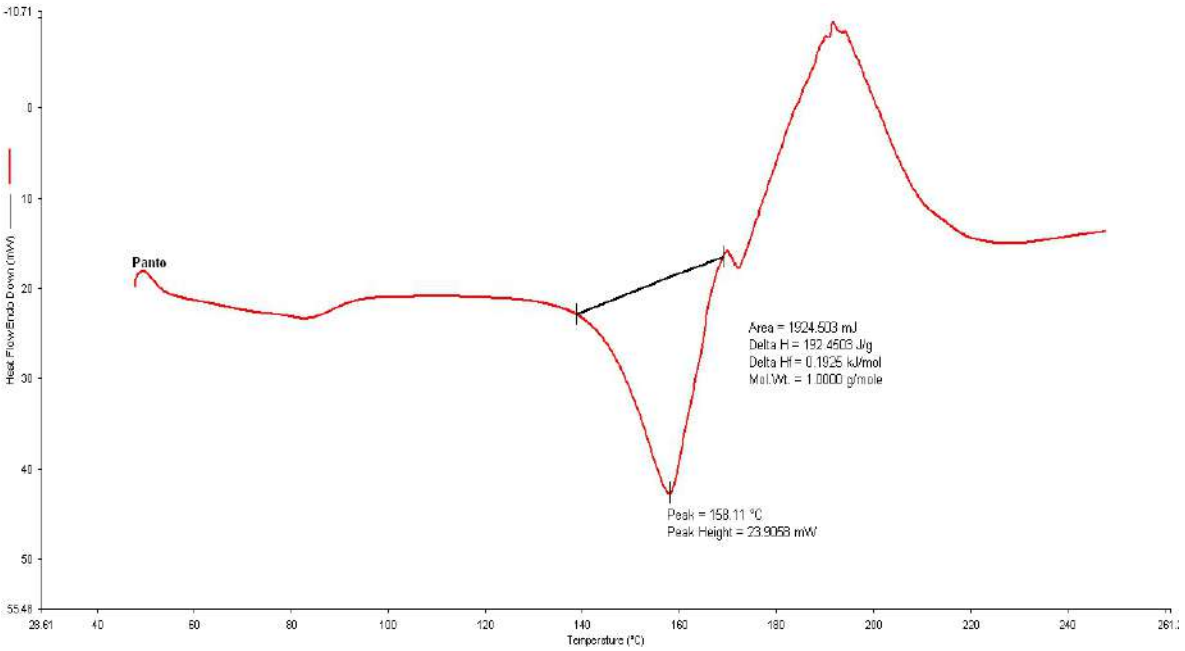


Fig: 18. DSC thermogram of Pantoprazole

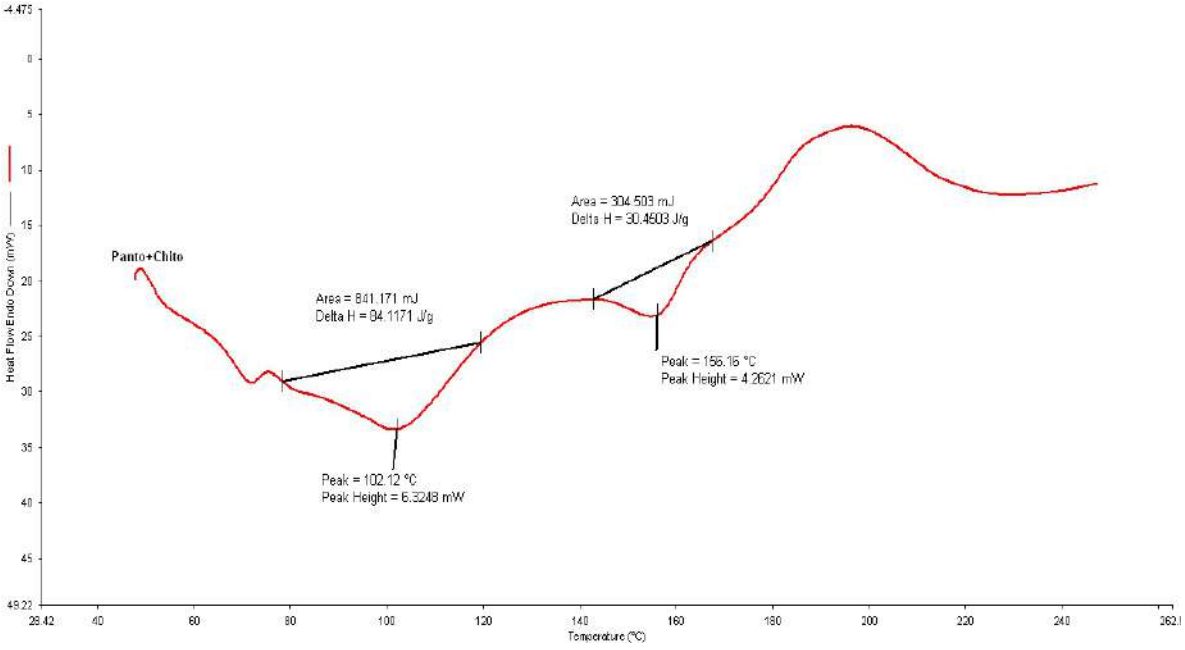


Fig: 19. DSC thermo gram of the mixture of Pantoprazole and chitosan

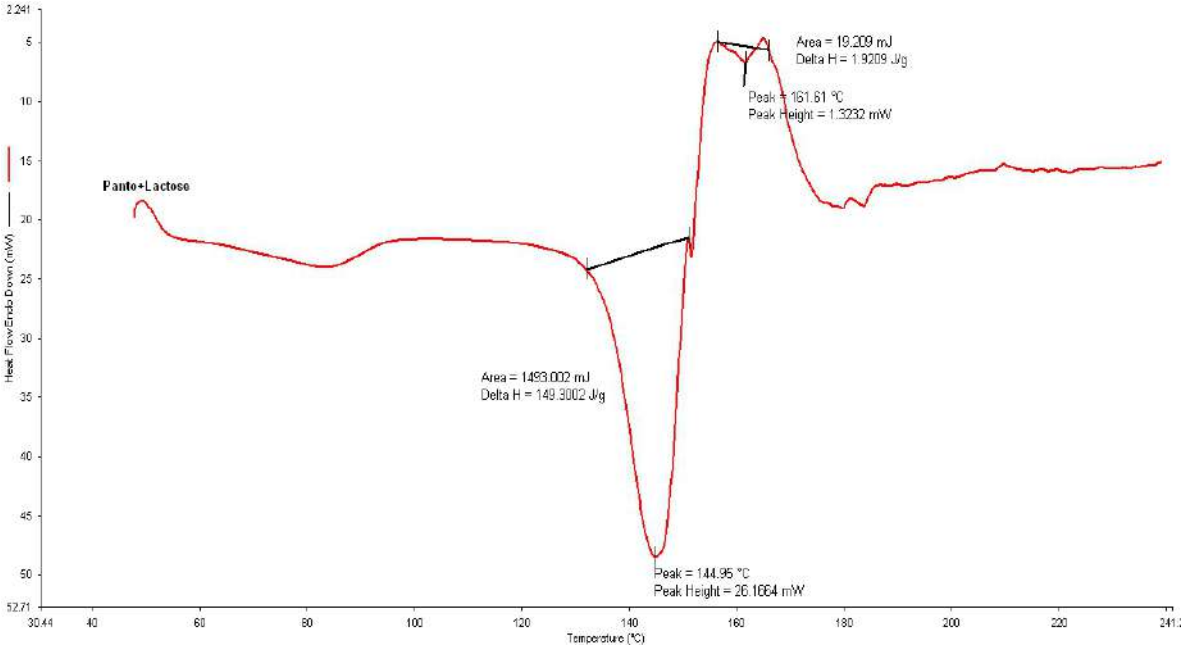


Fig: 20. DSC thermo gram of the mixture of Pantoprazole and lactose.

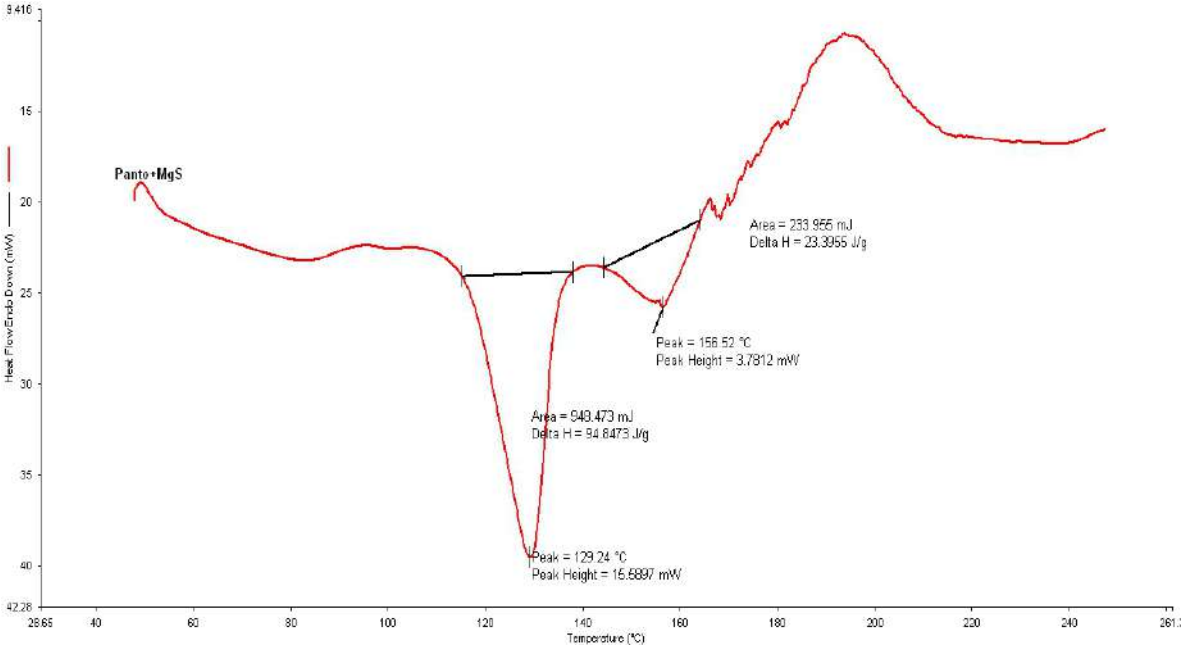


Fig: 21. DSC thermo gram of the mixture of Pantoprazole and magnesium stearate.

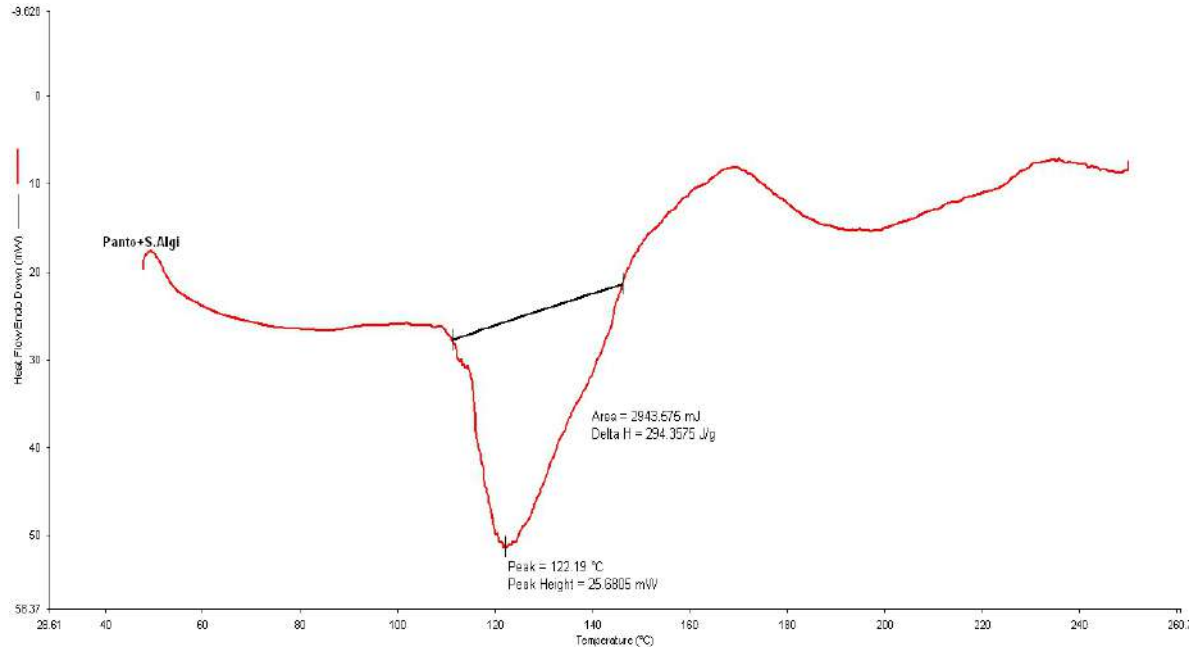


Fig: 22. DSC thermo gram of the mixture of Pantoprazole sodium alginate

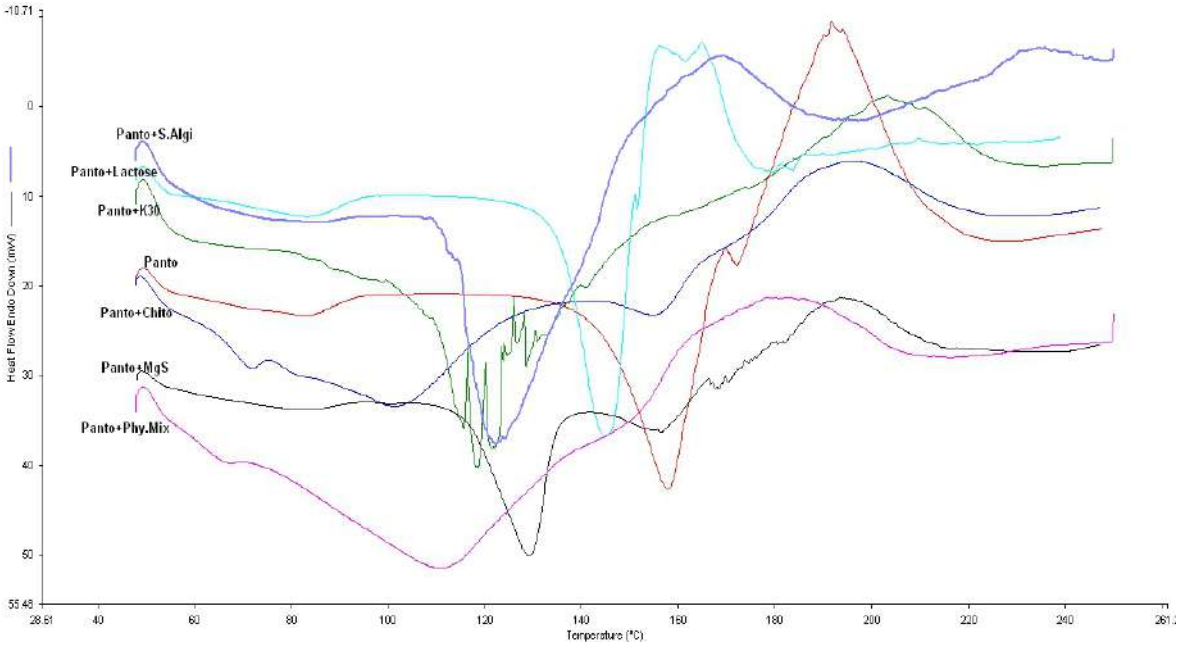


Fig 23: Comparative DSC thermogram of the drug, excipient physical mixture

6.1.5.Powder X-ray diffraction study: The XRD pattern of Pantoprazole initially displays crystalline at lower 2Ɵ angle as 2Ɵ angle increases it shows its amorphous nature similar result shows in case of physical mixture of Pantoprazole**(shown in fig:24 and fig:25),** hence it reveals that the drug is compatible with the excipient.

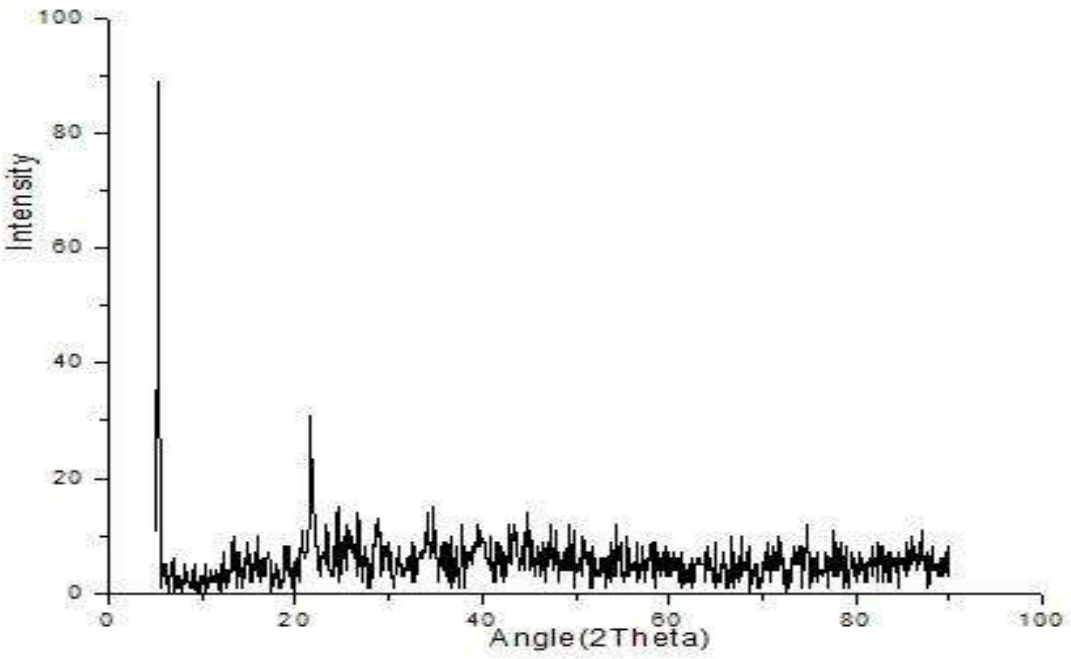


Fig: 24. XRD of pure drug

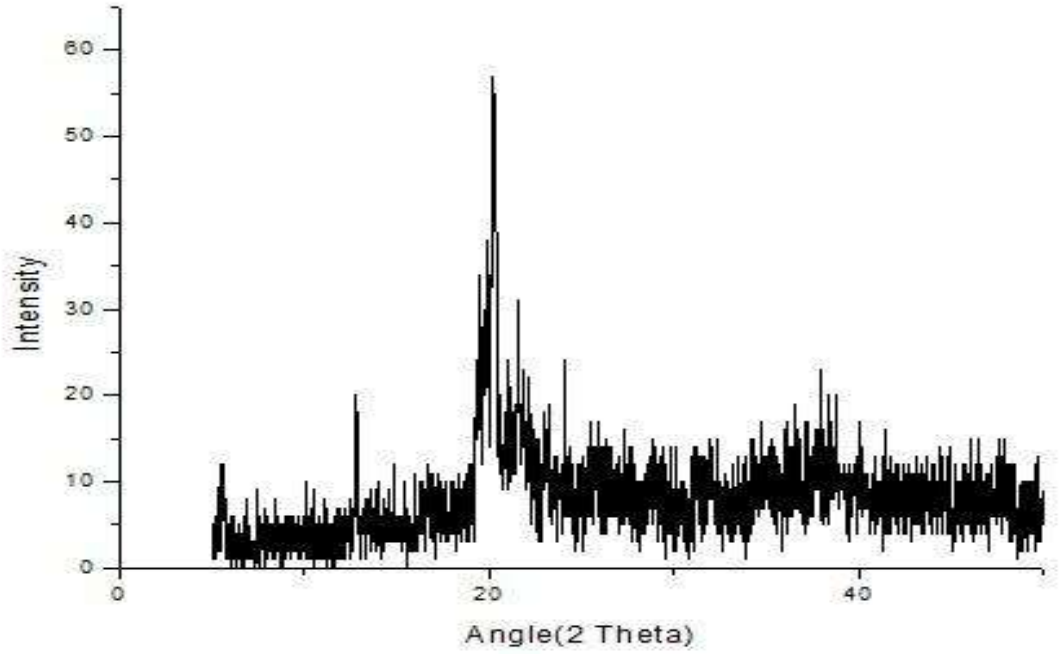


Fig: 25. XRD of physical mixture of Pantoprazole

6.1.6. Viscosity determination:

From the viscosity study, the viscosity of different mucoadhesive polymers at spindle speed of 50 rpm was found to be 240, 557, 461 and 470 cps for Carbopol, Sodium CMC, and Sodium. Alginate and Chitosan respectively. From the results it is evident that the viscosity of Sodium. CMC is higher followed by sodium alginate, chitosan and coarbopol polymers.

Table: 11. Viscosity data for polymer

RPM	0.5% Concentration (Viscosity in cps)			
	Carbopol 934	**Sodium CMC**	**Sodium alginate**	**Chitosan**
1	3800	10100	2506	203500
5	860	2340	25060	26020
10	430	770	3790	2260
50	240	557	461	470

6.1.7. UV analysis of drug

6.1.7. 1.Preparation of standard calibration curve:

Standard calibration curve for the drug Pantoprazole sodium sesquihydrate were done separately in water, HCl pH 1.2 acidic buffers and pH (6.8, 7.4) phosphate buffer. **(Shown in tables 12 to 15)** show the concentrations of Pantoprazole sodium sesquihydrate in HCl pH 1.2 acidic and pH (6.8, 7.4) phosphate buffers and the respective absorbance. The (**Figures 26 to 29**) shows the calibration curves of Pantoprazole sodium sesquihydrate in pH 1.2 acidic buffers and pH (6.8, 7.4) phosphate buffer respectively.

Table: 12. Preparation standard calibration curve in water:

Sl no	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.0665
3	4	0.1449
4	6	0.2163
5	8	0.2775
6	10	0.3738
7	12	0.5041

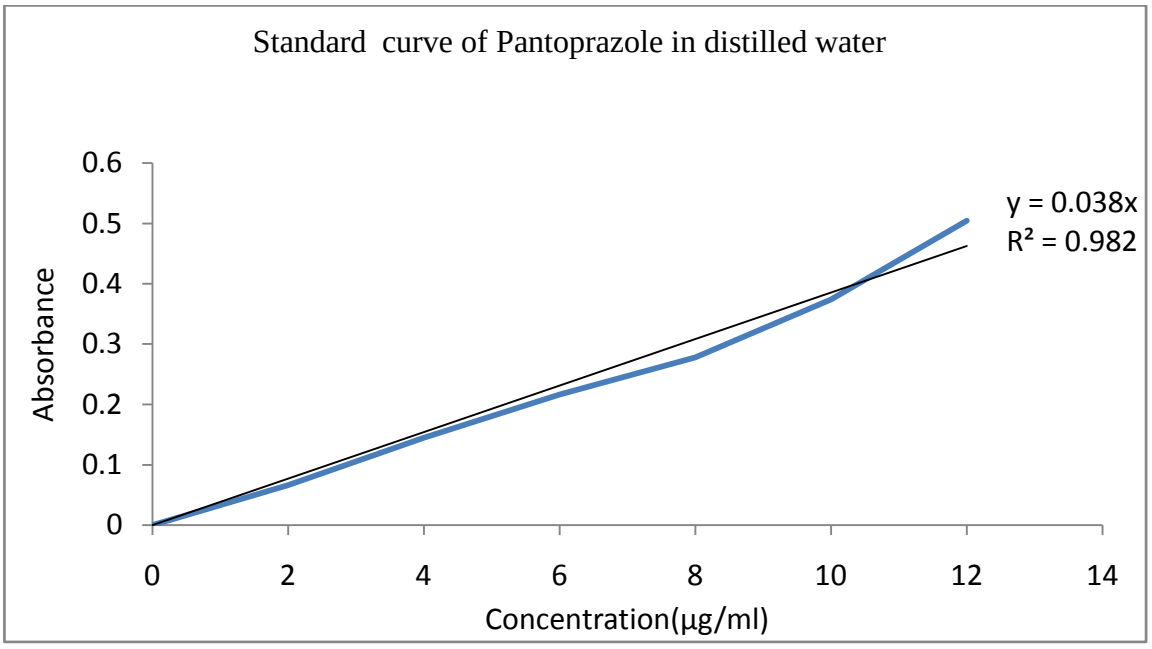


Fig: 26. Standard curve of Pantoprazole in water.

Table: 13. Preparation of standard calibration curve in 0.1M HCl (pH 1.2)

Sl No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.0892
3	4	0.1517
4	6	0.2241
5	8	0.2773
6	10	0.3765

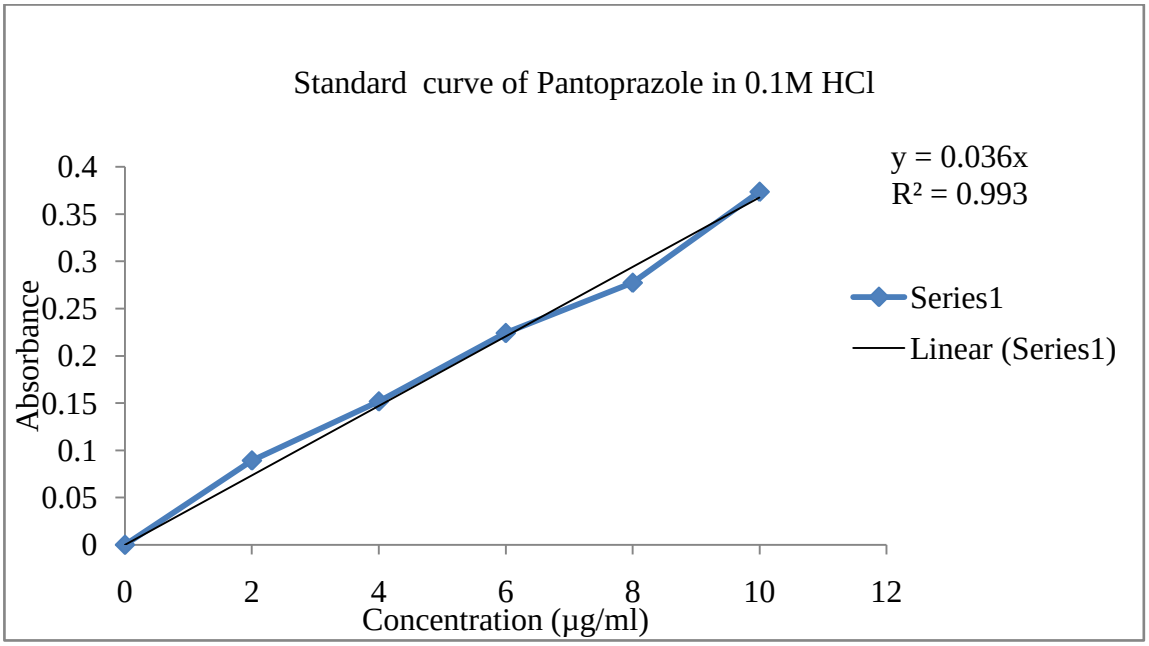


Fig: 27. Standard curve of Pantoprazole in 0.1 M HCl.

Table: 14. Preparation of standard calibration curve in phosphate buffer pH= 6.8

Sl no	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.1402
3	4	0.1970
4	6	0.2446
5	8	0.2780
6	10	0.3447

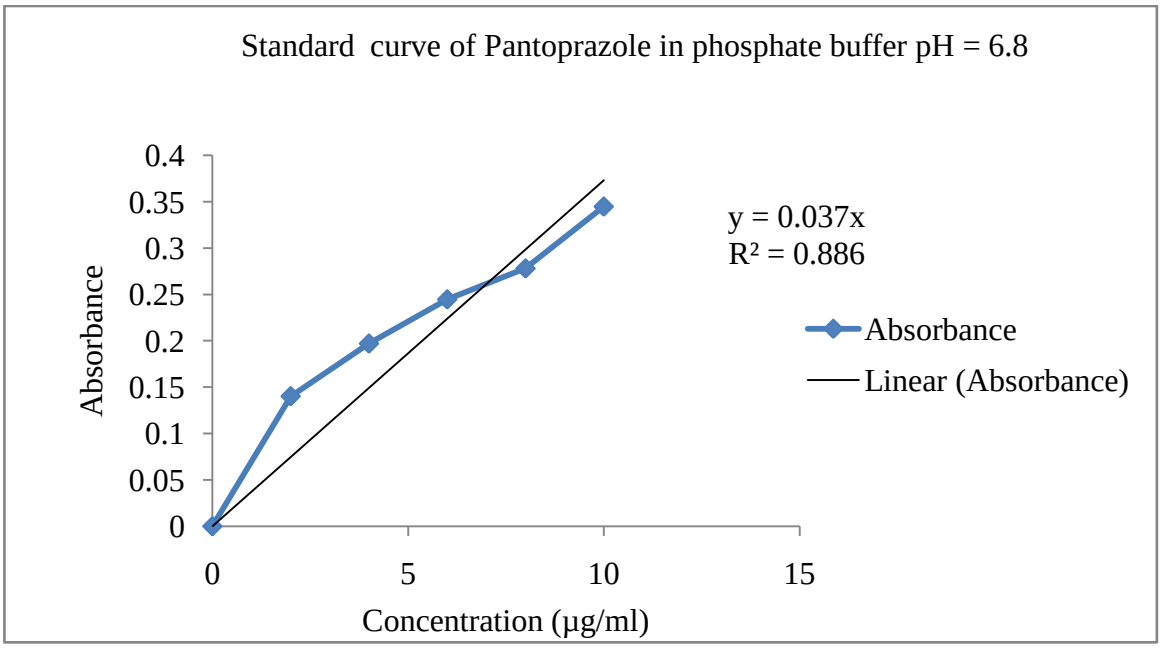


Fig: 28.Standard curve of Pantoprazole in phosphate buffer pH 6.8

Table: 15. Preparation of standard calibration curve in phosphate buffer pH =7.4

Sl No	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.0927
3	4	0.1703
4	6	0.2722
5	8	0.2781
6	10	0.4179

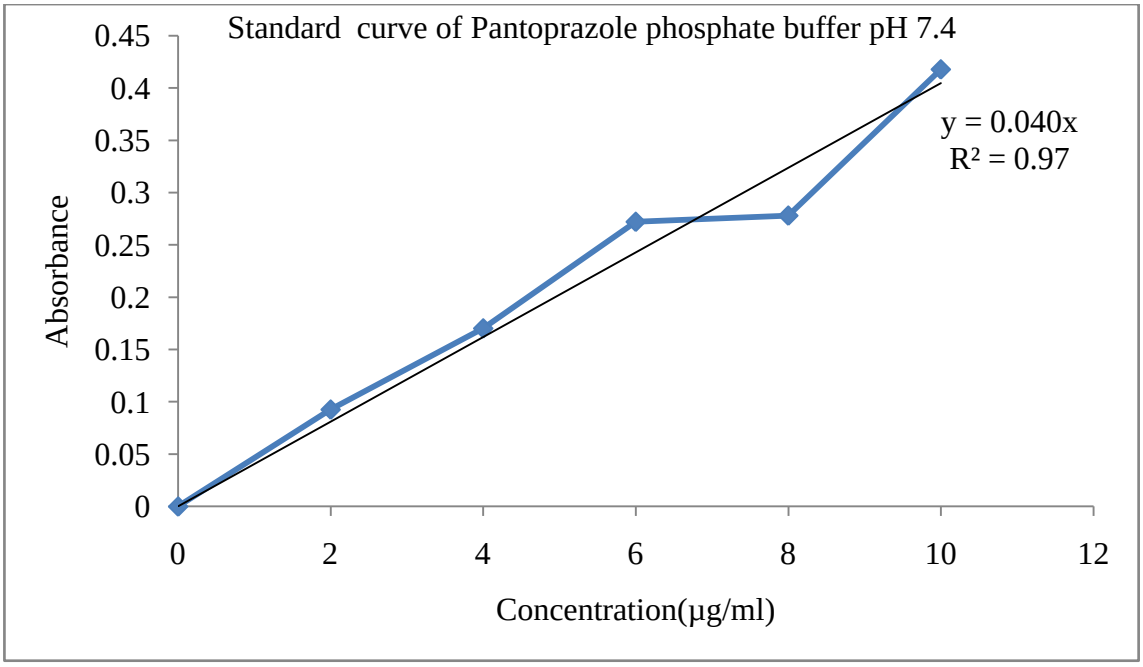


Fig: 29. Standard curve of Pantoprazole phosphate buffer pH 7.4

6.1.7. 2.Saturation solubility:

The saturation solubility of the drug sample was determined in various solvent like water, 0.1M HCL, phosphate buffer pH6.8 and found to be 976 mg/ml, 104.7 mg/ml, and 1.774 mg/ml.

Table: 16.Saturation solubility data:

Sl no	Solvent used	Absorbance	Saturation solubility(mg/ml)
1	Water	0.3754	976
2	0.1M HCl pH 1.2	0.0495	104.7
3	Phosphate buffer pH 6.8	0.3736	1.774

6.2. Characterization of Pantoprazole sodium sesquihydrate tablets:

6.2.1. Pre-compression parameters:

The prepared Pantoprazole powder for tablet ting was prepared by direct compression method. The prepared Pantoprazole powder were evaluated for, angle of repose, bulk density, tapped density and compressibility index, Hausner's ratio. The bulk densities and tapped densities of the powder were found to be in the range of 0.4217 to 0.4618 gm/ml and 0.4632 to 0.5302 gm/ml. The angle of repose varied from 23.62 to 25.32 which good flow properties of the powder. Hausner's ratio was ranged between 1.09 to 1.16, while the compressibility index was in the range of 7.94 to 14.40 these values indicates that the powder mixture of all batches of formulation exhibited good flow properties.

Table: 17. Physical properties of drug-excipient physical mixture:

Batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (Ɵ)
FS1	0.4717	0.5123	7.94	1.09	23.50
FS2	0.4218	0..4632	8.96	1.09	23.62
FC1	0.4314	0.4991	13.64	1.15	25.32
FC2	0.4614	0.5147	10.29	1.12	25.02
FSC1	0.4252	0.4956	14.20	1.17	24.07
FSC2	0.4538	0.5302	14.40	1.16	25.30

6.2.2. Post compression parameters

The Pantoprazole sodium sesquihydrate tablets were prepared by direct compression method. The results of physicochemical evaluation of prepared tablets are shown in Table 5.5 and Figures 5.11 to 5.13. The tablets were evaluated for Average weight, hardness, friability The hardness , friability, thickness, weight variation, drug content were found to be from 3.5 to 4.5 kg/cm^2, less than 1%(in case of all formulation),4.2-4.5 mm,93.67% to 99.24 respectively ,all these studied compiled the official requirement as per IP.

Table: 18.Physical evaluations of prototype mucoahdesive tablets:

Batch code	Parameter				
	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	% Weight variation	Drug content %
FS1	3.5	0.52	4.2	149.1±0.6	99.24
FS2	4.2	0.68	4.5	149±0.7	98.16
FC1	4.2	0.64	4.3	149.2±0.7	96.87
FC2	4.5	0.68	4.5	149±0.6	93.67
FSC1	4.3	0.85	4.5	149.1±0.8	98.13
FSC2	4.3	0.76	4.5	149.2 ±0.8	99.12

6.2.3. *In vitro* drug release characteristics:

The *in vitro* dissolution studies for the marketed tablet and all the trial batches formulation were carried out in USP apparatus type II using dissolution medium of phosphate buffer pH 6.8 and 7.4 respectively**,(shown in tables 19 to 21 and figures 30 to 32).** The percentage of release of Pantoprazole sodium sesquihydrate tablets made of sodium alginate alone (Batch) varied from 72.15 to 85.66 %. Tablet prepared from chitosan alone released 61.74 to 75.54 %. But, the tablet prepared from the combination of both the polymers at 1:1 ratio at two concentrations was found to be 58.60 to 63.44.The release rate of marketed tablet was found to be 70.98 to 96 % for 6 hr. From the in-vitro drug release study it is concluded that sodium alginate and combination of sodium alginate (35% concentration) have desirable *in vitro* release profile for sustainably the drug release.

Table: 19.*In vitro* drug release profile of Pantoprazole sodium sesquihydrate marketed tablet formulations in phosphate buffer pH 6.8.

Time(Min)	percentage of drug released		Mean
	MF1	MF2	MKT
0	0	0	0
30	52.12	69.23	60.68
60	60.58	69.08	64.83
90	49.48	54	51.74
120	66.82	79.6	73.21
150	70.83	62.45	66.64
180	70.98	65.2	68.09
240	63.025	67.3	65.16

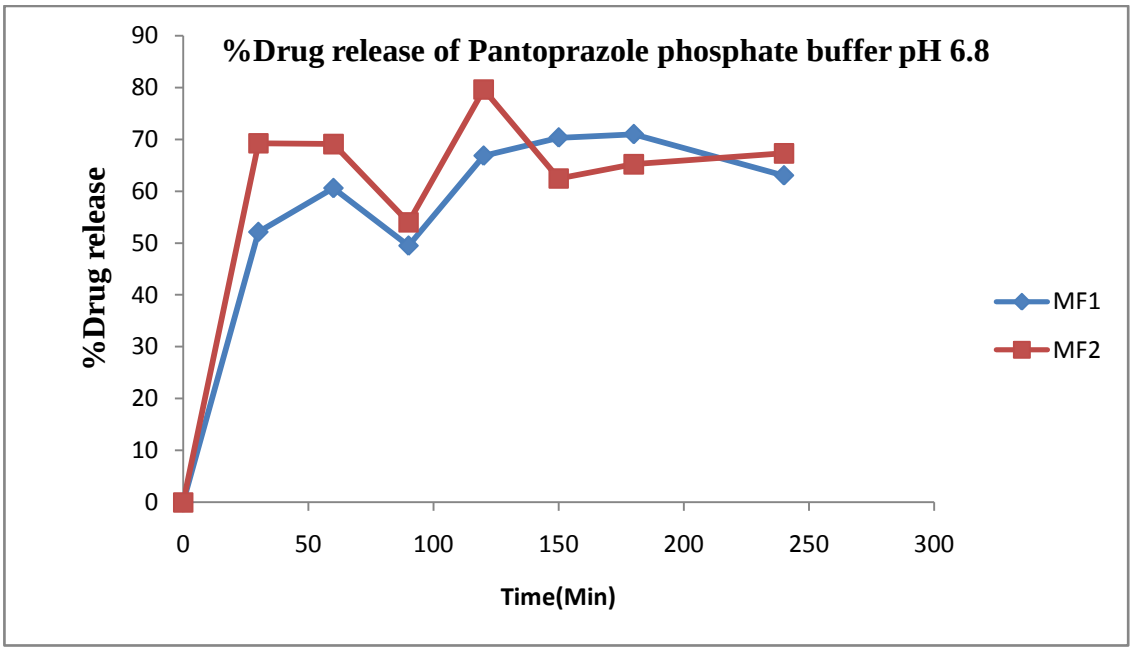


Fig: 30. Percentage drug release of Pantoprazole marketed tablet

MF1=Marketed formulation-1, MF2= Marketed formulatin-2

Table: 20.*In vitro* drug release profile of Pantoprazole sodium sesquihydrate marketed tablet formulations in phosphate buffer pH 7.4.

Time(Min)	percentage of drug released		Mean
	MF1	MF2	MKT
0	0	0	0
20	18.49	58.73	38.61
40	52.8	70.28	61.54
60	73.66	71.1	72.38
120	76.49	77.53	77.01
180	73.9	77.08	75.49
240	75.25	96.05	85.65
300	76.37	75.55	75.96

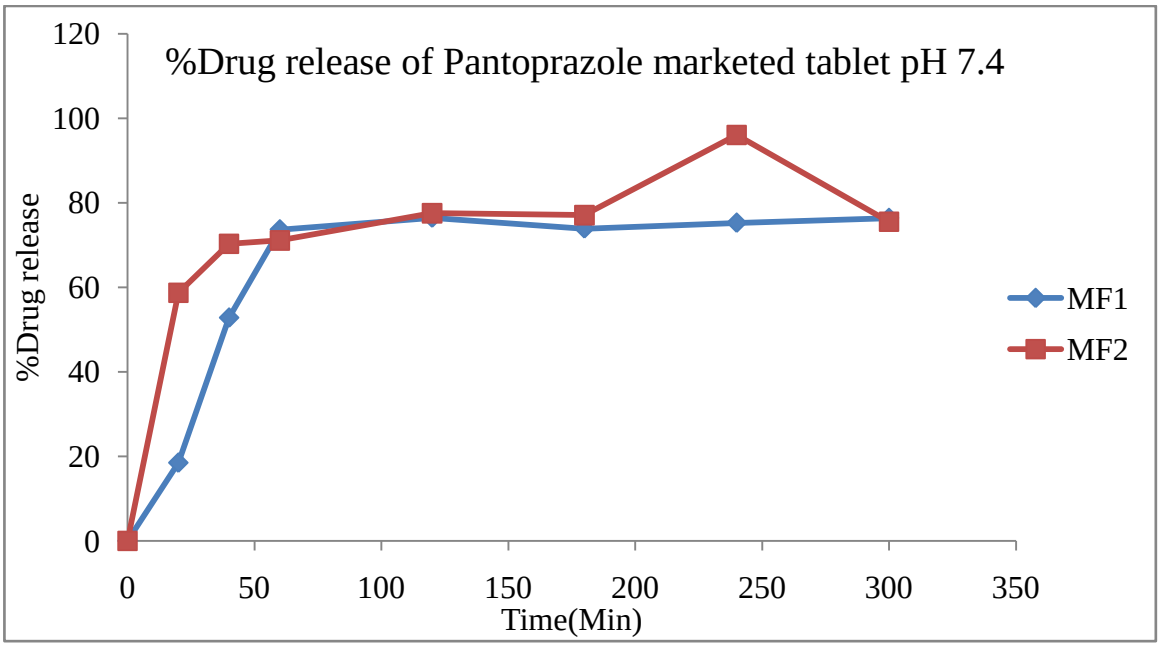


Fig: 31. Percentage drug release of marketed Pantoprazole tablet pH 7.4

MF1: Marketed formulation 1, MF2: Marketed formulation 2.

Table: 21.*In vitro* drug release profile of Pantoprazole sodium sesquihydrate for various tablet formulations:

Time (Min)	%Drug release of coded Formulations						
	FS1	**FS2**	**FC1**	**FC2**	**FSC1**	**FSC2**	**MKT**
0	0	0	0	0	0	0	0
20	20.28	1.94	37.56	50.79	17.23	1.88	38.61
40	30.33	7.35	58.29	52.99	29.12	9.46	61.54
60	58.60	17.63	94.23	67.03	28.85	16.83	72.38
120	51.96	39.35	51.74	60.94	55.37	53.30	77.01
180	62.73	45.50	63.49	75.74	63.44	58.60	75.49
240	81.26	68.70	61.21	42.27	47.98	50.57	85.65
300	85.66	72.15	61.74	33.56	35.25	45.68	75.96

FS1: Formulation with 15% sodium alginate, **FS2**: Formulation with 35% sodium alginate,

FC1: Formulation with 15% chitosan, FC2: Formulation with 35% Chitosan,

FSC1: Formulation with 15% sodium alginate and chitosan,

FSC2: Formulation with 35% Sodium alginate, chitosan

MKT: Marketed tablet.

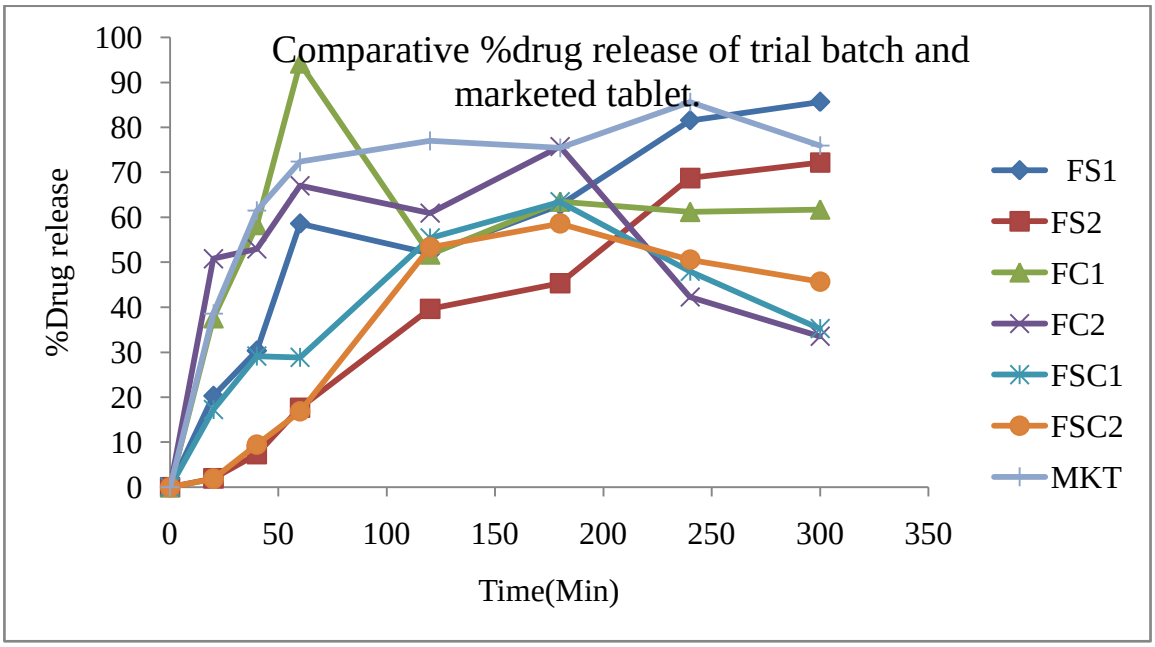


Fig: 32. Comparative in-vitro drug release profile of various trial batch formulations with marketed tablet in phosphate buffer pH 7.4

6.2.4. Swelling index of prototype mucoadhesive Pantoprazole tablet:

From the % swelling index study it is seen that the polymers with higher concentration had higher swelling index this was due to the fact that when the polymers concentration is increases the movement of the polymers also increases.

Table: 22. Swelling index of prototype formulation:

Time(hour)	%Swelling index					
	FS1	**FS2**	**FC1**	**FC2**	**FSC1**	**FSC2**
0	0	0	0	0	0	0
1	28.57	93.33	120	206.67	131.25	226.67
2	-7.14	40	46.67	246.67	150	140
3	-42.85	0	153.33	273.33	106.25	140
4	35.71	-20	66.67	326.67	112.5	100

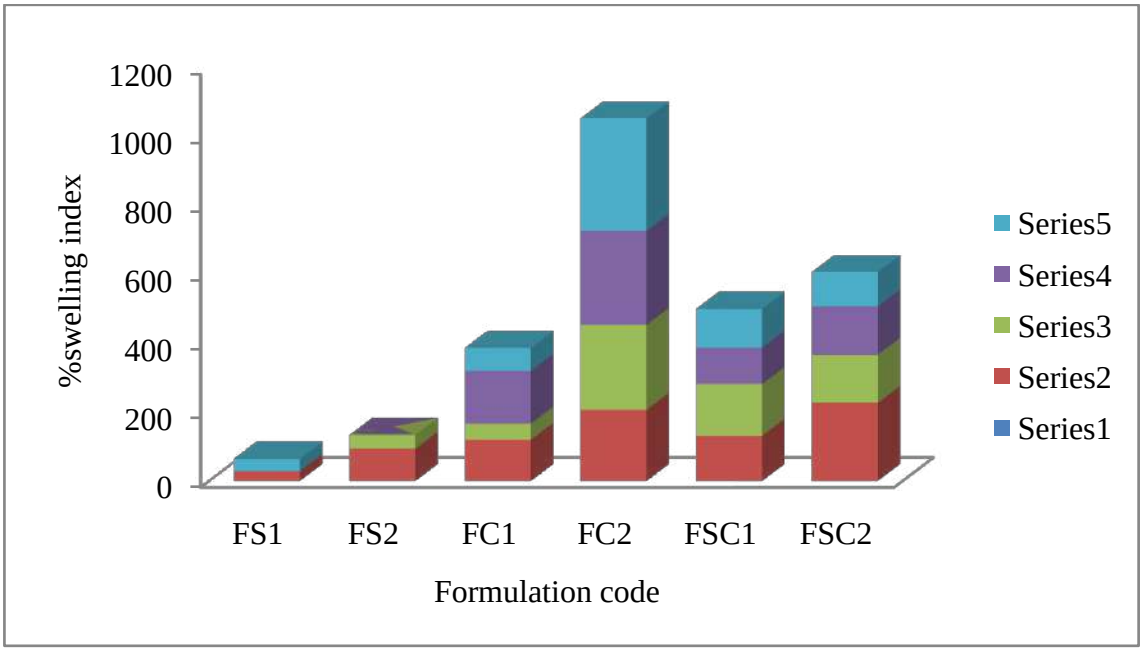


Fig: 33. Percentage swelling index of prototype formulation

6.2.5. Mucoadhesive strength of prototype formulation:

The mucoadhesive strength increases from 58.1 to 234.4 gm with the increase in polymer concentration from 15 to 35 % **(shown in Fig.34)** The raise in mucoadhesive strength may be due to increase in availability of adhesive sites of natural polymer with mucin tends to increase in bond strength. Polymer swelling permits a mechanical entanglement by exposing the bio adhesive sites for hydrogen bonding and or electrostatic interaction between the polymer and the mucous network. Swelling of natural polymer based initiation of deep contact with the mucous layer permits a mechanical entanglement by exposing the bio adhesive sites for hydrogen bonding and or electrostatic interaction and the building of secondary bonds favouring both chemical and mechanical interactions.

Table: 23.Mucoadhesive strength of prototype formulation

Formulation code	FS1	FS2	FC1	FC2	FSC1	FSC2
Mucoadhesive strength (gm)	208	213.5	195	58.1	117.6	234.4

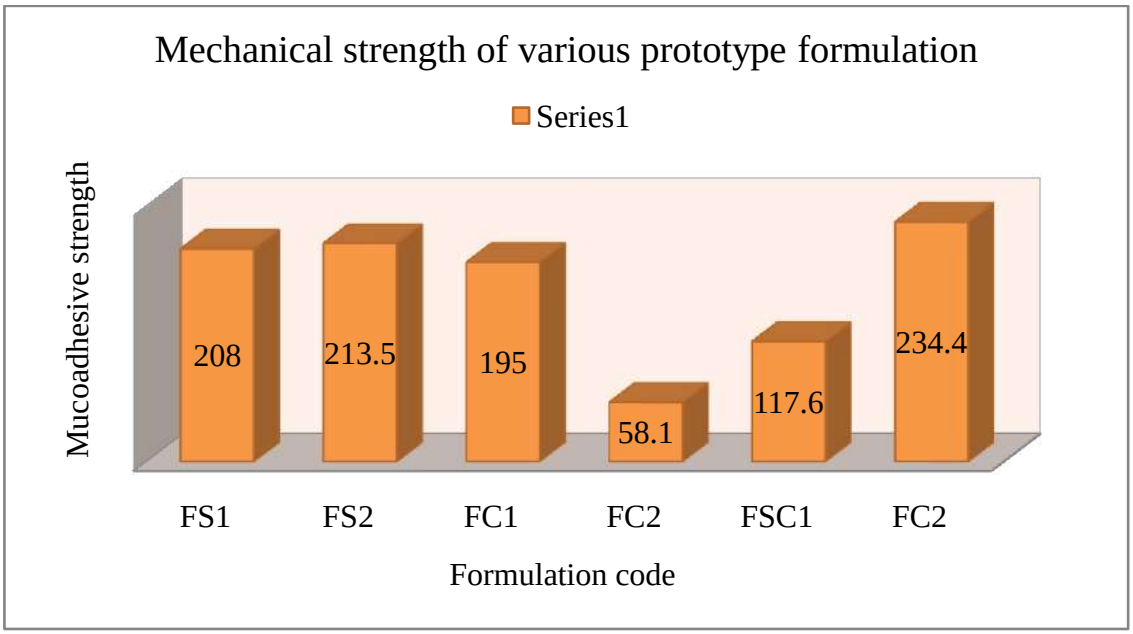


Fig: 34. Mucoadhesive strength of prototype formulation

6.2.6. *In-Vitro* drug release study of final batch formulation:

Table: 24. % Drug release of optimized Pantoprazole in phosphate buffer pH 6.8 (FS2 35%):

Time (Min)	Absorbance	Conc.(µg/ml)	% Drug Release
0	0	0	0
30	0.0498	0.187	3.27
60	0.0514	0.239	4.18
90	0.0586	0.471	8.24
120	0.0622	0.587	10.27
150	0.0678	0.768	13.44
180	0.0848	1.316	23.03
240	0.1193	2.429	42.51
300	0.185	4.548	79.60

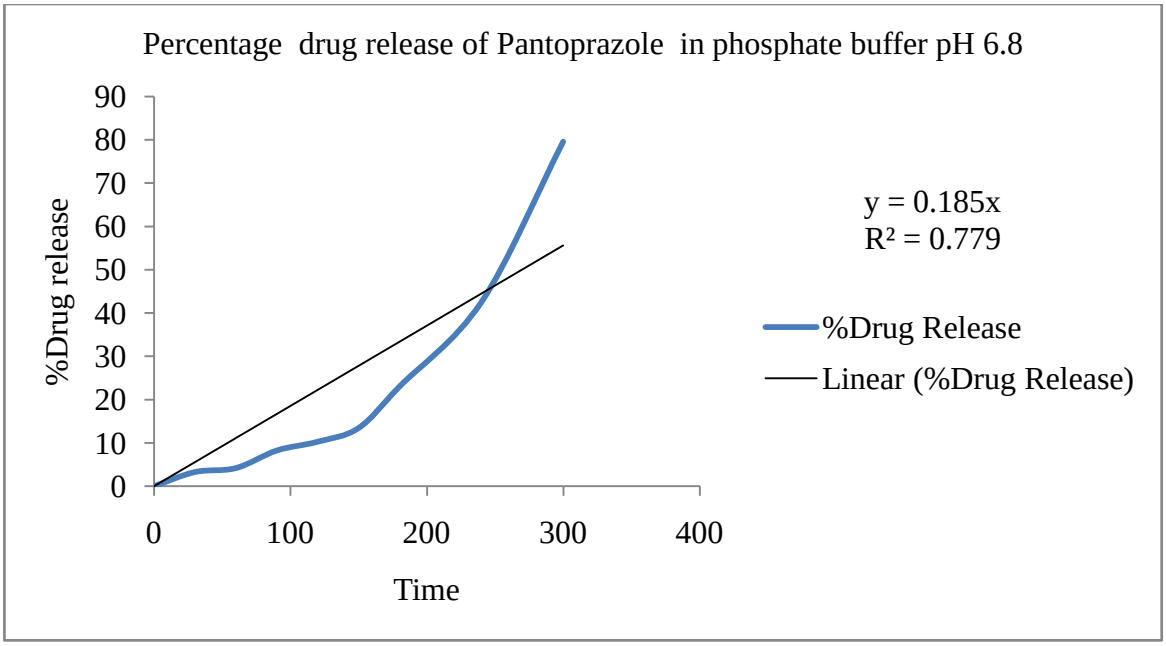


Fig: 35. % Drug release of optimized Pantoprazole in phosphate buffer pH 6.8 (FS2 35%):

6.2.6.1. Kinetic study of optimised Pantoprazole in phosphate buffer pH 6.8

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 - K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($In\ Q = InQ_0 - K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2\ t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K\ t_n$) the graph was plotted in log percent of drug released Vs log time (**Figures 36 to 39).** The release of Pantoprazole sodium sesquihydrate from the tablets was Zero order diffusion controlled as indicated by higher r^2 values in zero order and first order kinetic model **(Tables 25 to 28)**. The n values obtained from the Higuchi kinetic model showed that the release mechanism was super case-II transport.

Table: 25. Zero order drug release in phosphate buffer pH 6.8 (FS2)

Time(Min)	%Drug Release
0	0
30	3.27
60	4.18
90	8.24
120	10.27
150	13.44
180	23.03
240	42.51
300	79.6

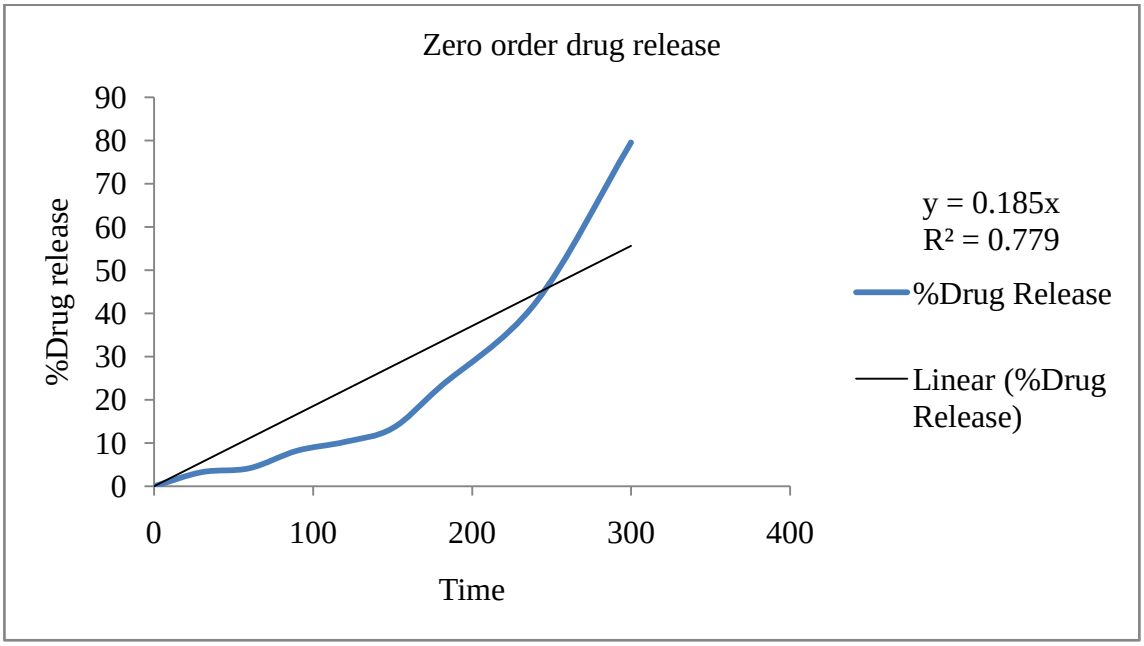


Fig: 36.Time Vs % drug release in phosphate buffer pH 6.8 (FS2)

Table: 26. First order drug release kinetic in phosphate buffer pH 6.8 (FS2 35%)

Time(Min)	Log %drug release remaining
0	2
30	1.99
60	1.98
90	1.96
120	1.95
150	1.94
180	1.88
240	1.76
300	1.31

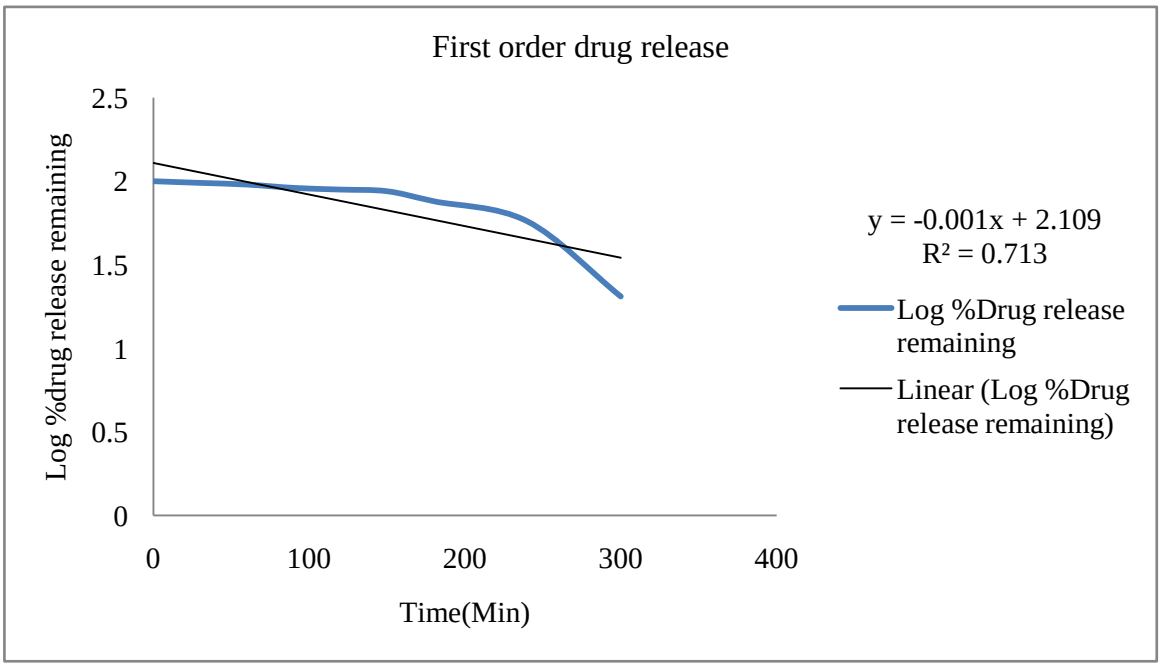


Fig: 37. Time Vs log %drug release remaining in phosphate buffer pH 6.8(FS2)

Table: 27. Higuchi kinetic model in phosphate buffer pH 6.8 (FS2 35%)

Square root of time(Min)	%Drug Release
0	0
5.48	3.27
7.75	4.18
9.49	8.24
10.95	10.27
12.25	13.44
13.42	23.03
15.49	42.51
17.32	79.6

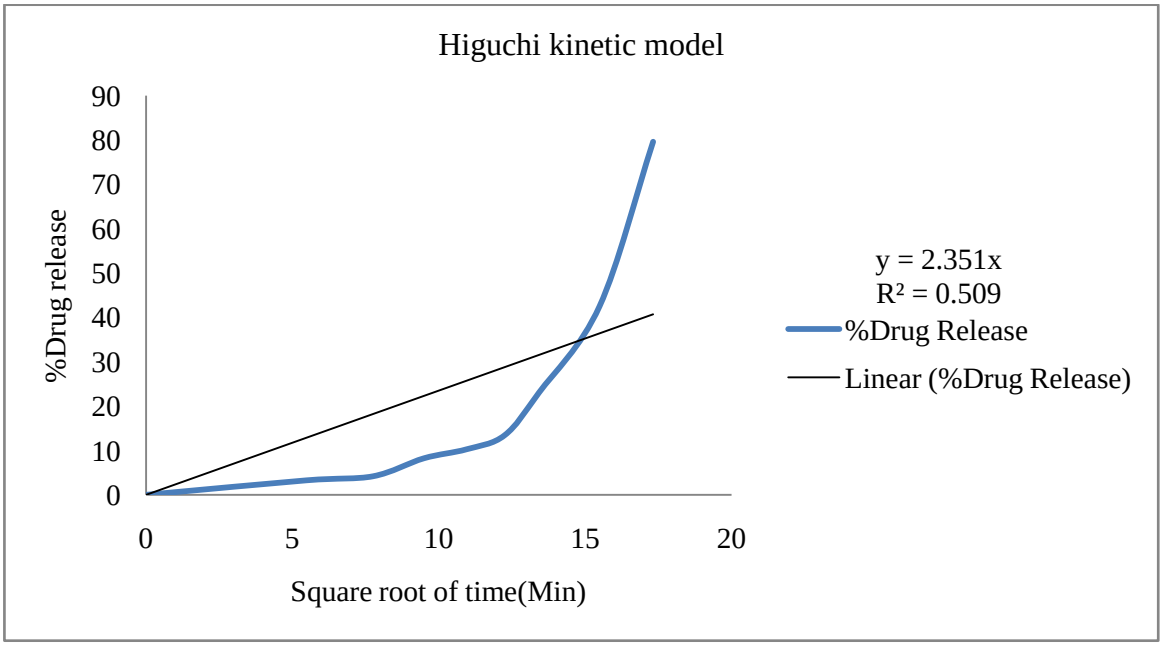


Fig: 38. Square root of time Vs % Drug release in phosphate buffer pH 6.8(FS2)

Table: 28. Korse-meyer Peppas model phosphate buffer pH 6.8 (FS2 35%)

Log time(Min)	Log %Drug Release
1.48	0.5145
1.78	0.2504
1.95	0.29
2.08	0.318
2.17	0.3365
2.26	0.3541
2.38	0.3766
2.48	0.3945

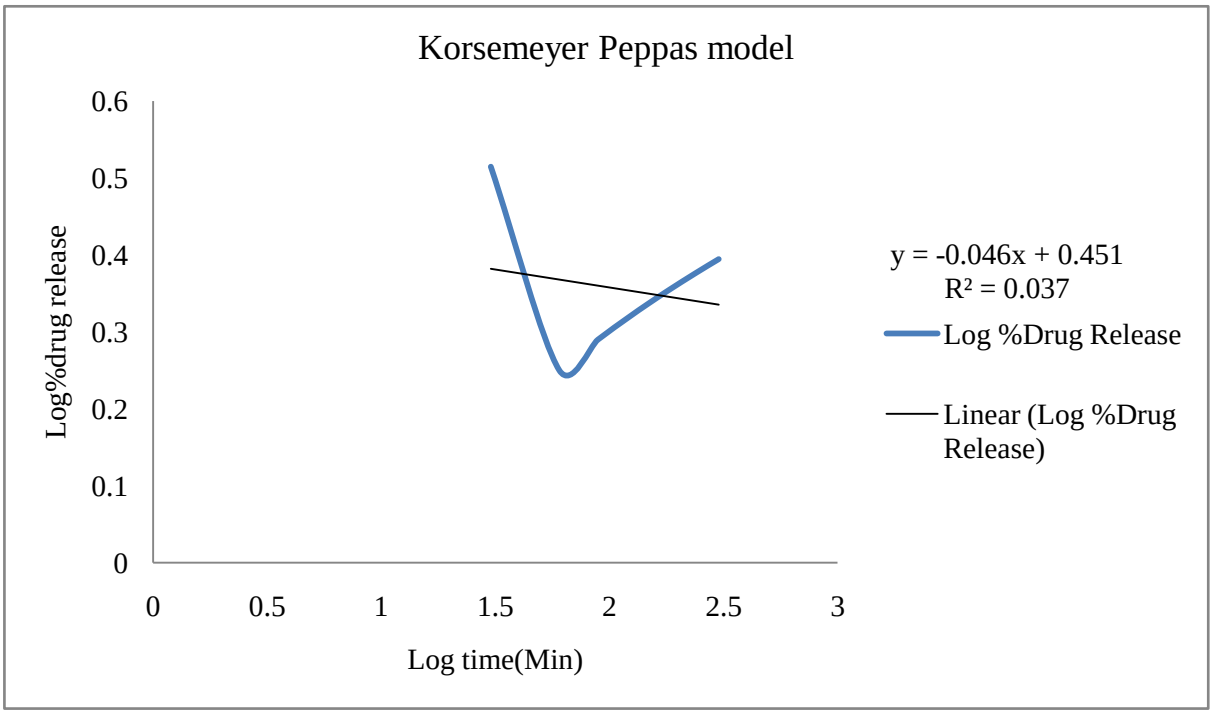


Fig: 39.Log time Vs Log % drug release in phosphate buffer pH 6.8(FS2)

Table: 29. Kinetic data of Pantoprazole in phosphate buffer

Zero order		First order		Higuchi model		Korsemeyer Peppas model	
K_0	r^2	K_0	r^2	K_0	r^2	K_0	r^2
0.185	0.78	0.001	0.71	2.35	0.509	0.046	0.037

Table: 30. % Drug release of optimized Pantoprazole tablet in phosphate buffer in pH 6.8 (FSC-2 35%):

Time (Min)	Absorbance	Conc.(µg/ml)	% Drug Release
0	0	0	0
30	0.047	0.097	1.69
60	0.0489	0.158	2.77
90	0.0528	0.284	4.97
120	0.058	0.452	7.90
150	0.05989	0.513	8.97
180	0.0966	1.697	29.69
240	0.1291	2.745	48.04
300	0.1307	2.797	48.94

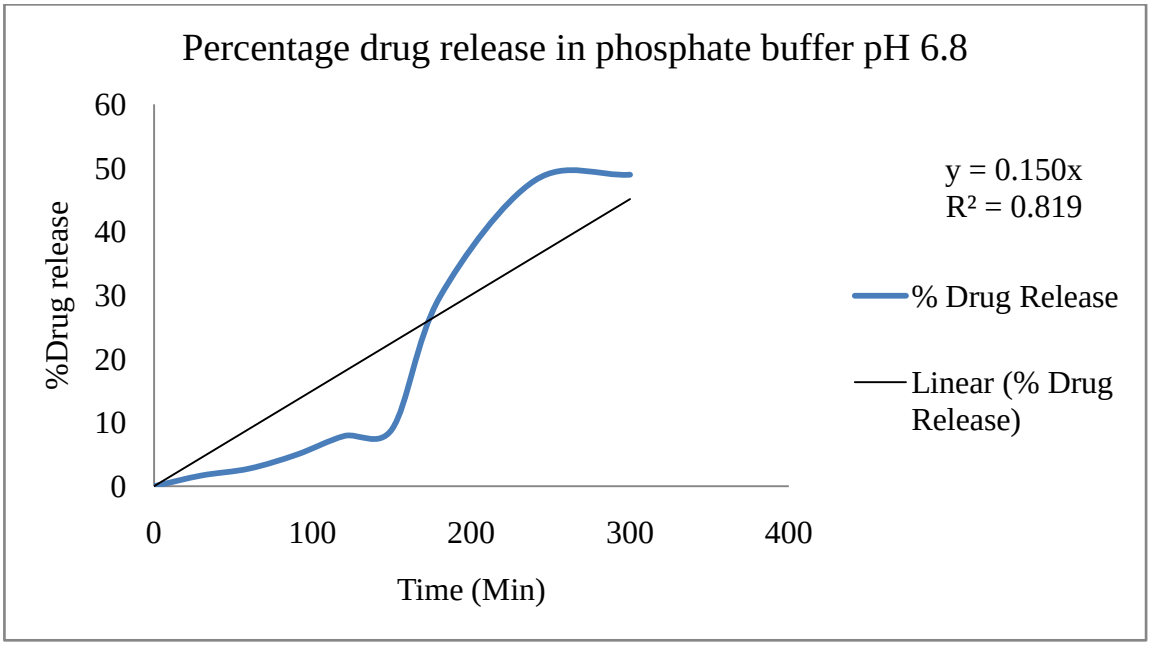


Fig: 40. % Drug release of optimized Pantoprazole tablet in phosphate buffer pH 6.8 (FSC-2 35%):

6.2.6.2. Kinetic study of optimised Pantoprazole in phosphate buffer pH 6.8:

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 - K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($In\ Q = InQ_0 - K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2\ t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K\ t_n$) the graph was plotted in log percent of drug released Vs log time **(Figures 41 to 44)** The release of Pantoprazole sodium sesquihydrate from the tablets was Korsemeyer Peppas diffusion controlled as indicated by higher r^2 values in Korsemeyer Peppas and Higuchi model **(Shown in table 35).** The n values obtained from the Higuchi kinetic model showed that the release mechanism was super case-II transport.

Table: 31.Zero order drug release in phosphate buffer pH 6.8 (FSC2 35%)

Time (Min)	% Drug Release
0	0
30	1.69
60	2.77
90	4.97
120	7.90
150	8.97
180	29.69
240	48.04
300	48.94

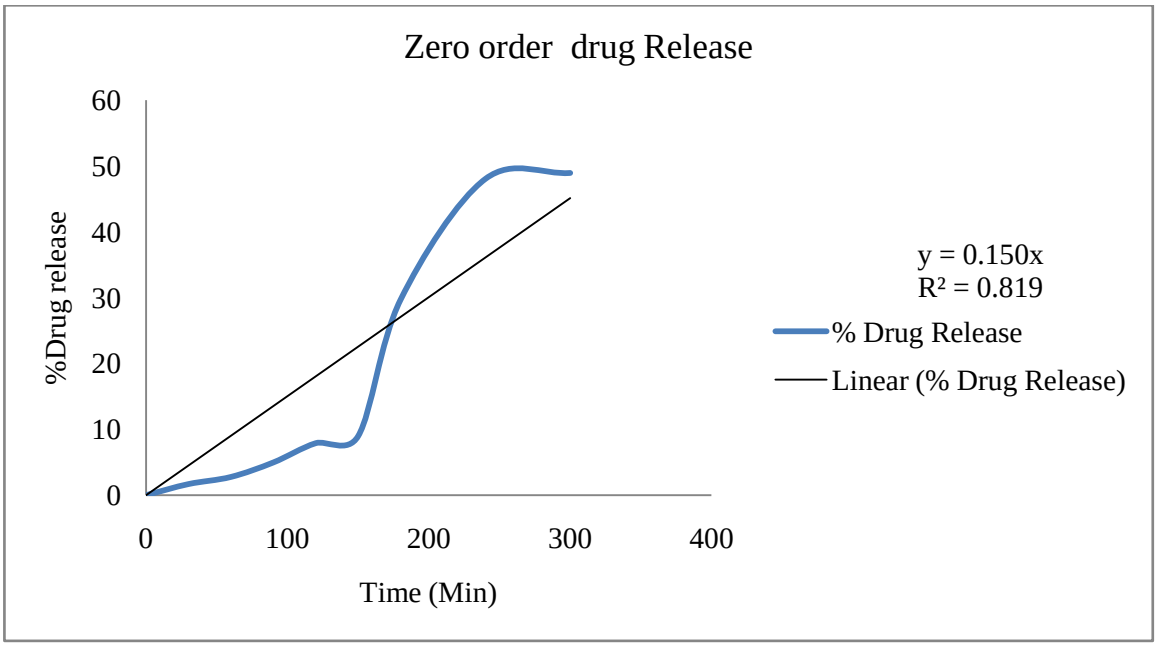


Fig: 41. Time Vs %Drug release in phosphate buffer pH 6.8(FSC2)

Table: 32.First order drug release in phosphate buffer pH 6.8 (FSC2 35%)

Time (Min)	Log %drug remaining
0	2
30	1.99
60	1.99
90	1.98
120	1.96
150	1.95
180	1.85
240	1.72
300	1.71

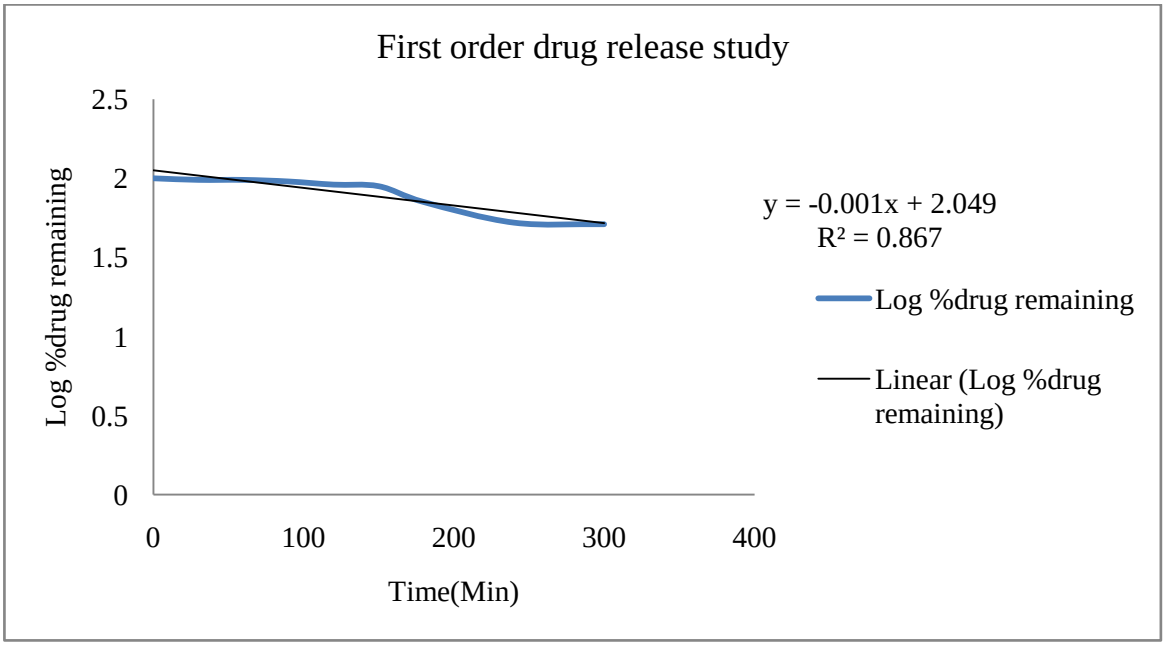


Fig: 42.Time Vs Log % drug remaining in phosphate buffer pH 6.8(FSC2)

Table: 33. Higuchi Kinetic model in phosphate buffer pH 6.8 (FSC2 35%)

Square root of time(Min)	%Drug release
0	0
5.48	1.69
7.75	2.77
9.49	4.97
10.95	7.9
12.25	8.97
13.42	29.69
15.49	48.04
17.32	48.94

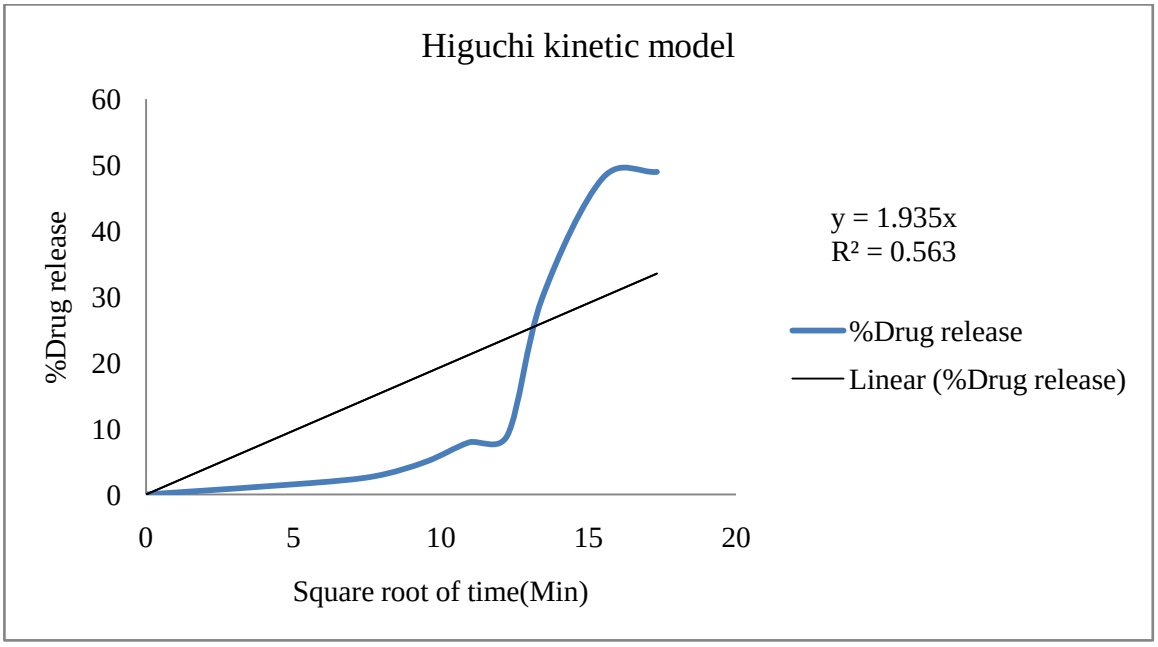


Fig: 43.Square root of time Vs % Drug release in phosphate buffer pH 6.8(FSC2)

Table: 34. Korsemeyer Peppas model in phosphate buffer pH 6.8 (FSC2 35%)

Log time(Min)	Log % drug release
1.48	0.2279
1.78	0.4425
1.95	0.6964
2.08	0.8976
2.18	0.9528
2.26	1.473
2.38	1.682
2.48	1.689

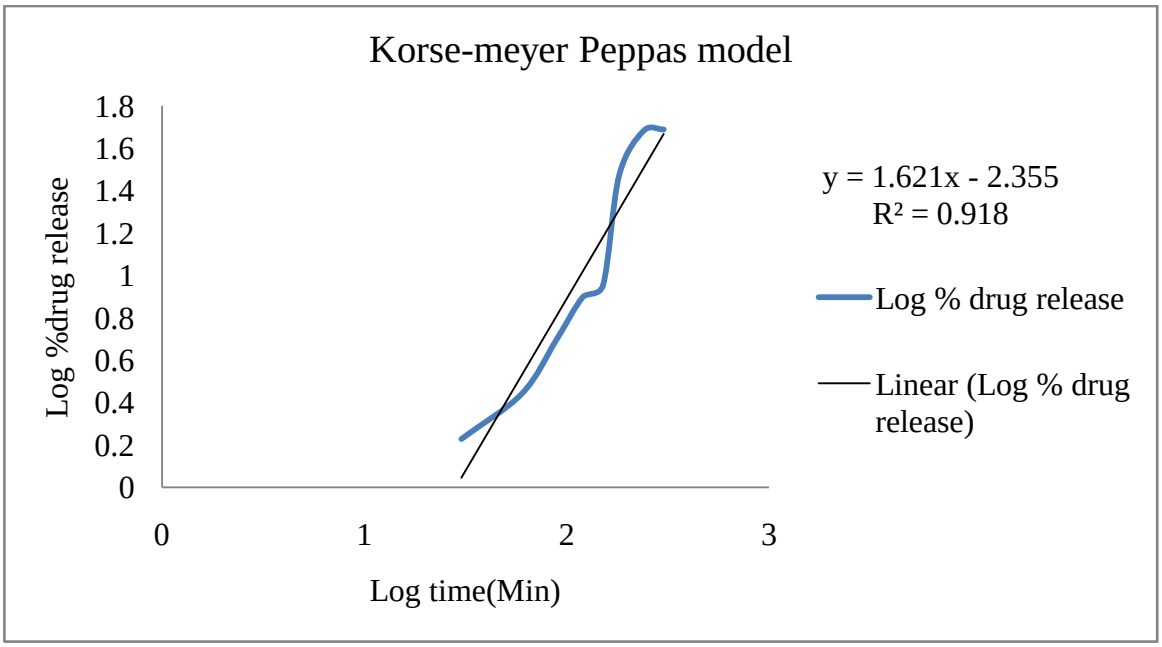


Fig: 44.Log time Vs Log % drug release in phosphate buffer pH 6.8(FSC2)

Table: 35.Kinetic data of Pantoprazole in phosphate buffer pH 6.8(FSC2)

Zero order		First order		Higuchi model		Korsemeyer pappas model	
K_0	r^2	K_1	r^2	K_n	r^2	n	r^2
0.150	0.82	0.001	0.87	1.94	0.563	1.62	0.92

Table: 36. %Drug Release of optimized Pantoprazole tablet in phosphate buffer pH 7.4 (FS2 35%):

Time(Min)	Absorbance	Concentration(µg/ml)	%Drug release
0	0	0	0
20	0.0126	0.1179	2.06
40	0.0249	0.4333	7.58
60	0.0483	1.0333	18.08
120	0.0968	2.2769	39.85
180	0.1097	2.6077	45.63
240	0.1632	3.9795	69.64
300	0.1698	4.1487	72.60

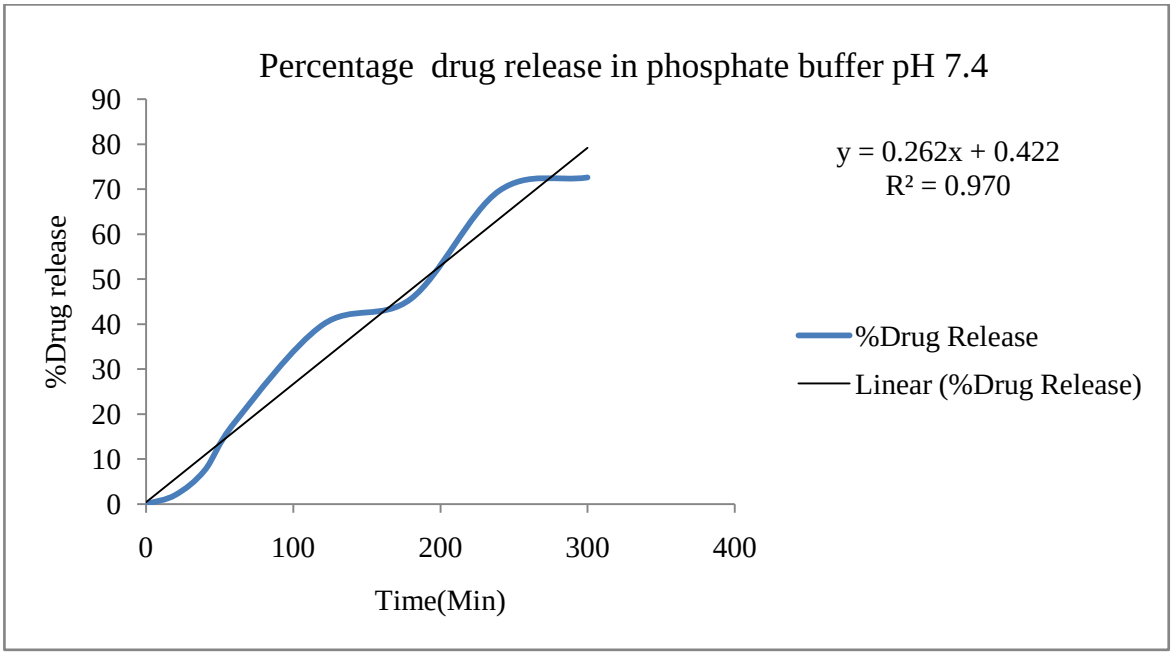


Fig: 45. %Drug release of optimized Pantoprazole tablet in phosphate buffer pH 7.4 (FS2 35%):

6.2.6.3. Kinetic study of optimised Pantoprazole in phosphate buffer pH 7.4(FS2)

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 - K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($In\ Q = InQ_0 - K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2\ t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K\ t_n$) the graph was plotted in log percent of drug released Vs log time **(Figures 46 to 49)** The release of Pantoprazole sodium sesquihydrate from the tablets was Zero order diffusion controlled as indicated by higher r^2 values in Zero order kinetics and Korsemeyer Peppas **(Shown in table 41)**. The n values obtained from the Korsemeyer Peppas kinetic model showed that the release mechanism was super case-II transport.

Table: 37. Zero Order release in phosphate buffer pH 7.4 (FS2):

Time	%Drug Release
0	0
20	2.06
40	7.58
60	18.08
120	39.85
180	45.63
240	69.64
300	72.6

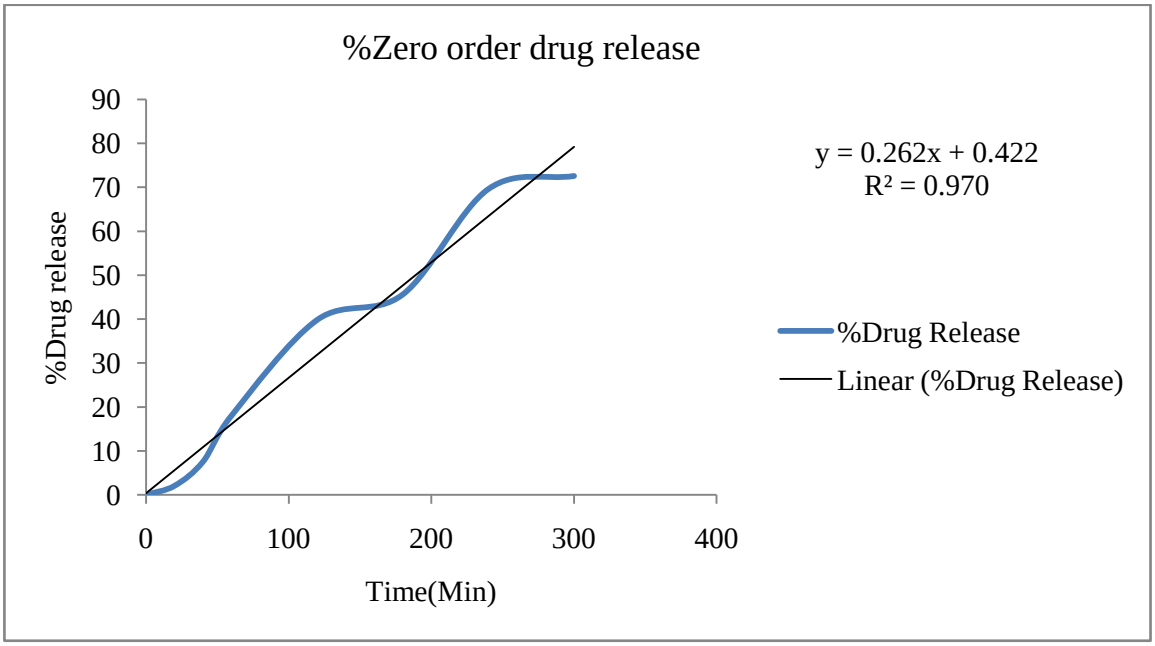


Fig: 46.Time Vs %Drug release in phosphate buffer pH 7.4 (FS2)

Table: 38. First order release kinetics in phosphate buffer pH 7.4 (FS2):

Time(Min)	Log %drug remaining
0	2
20	1.99
40	1.97
60	1.91
120	1.77
180	1.74
240	1.48
300	1.43

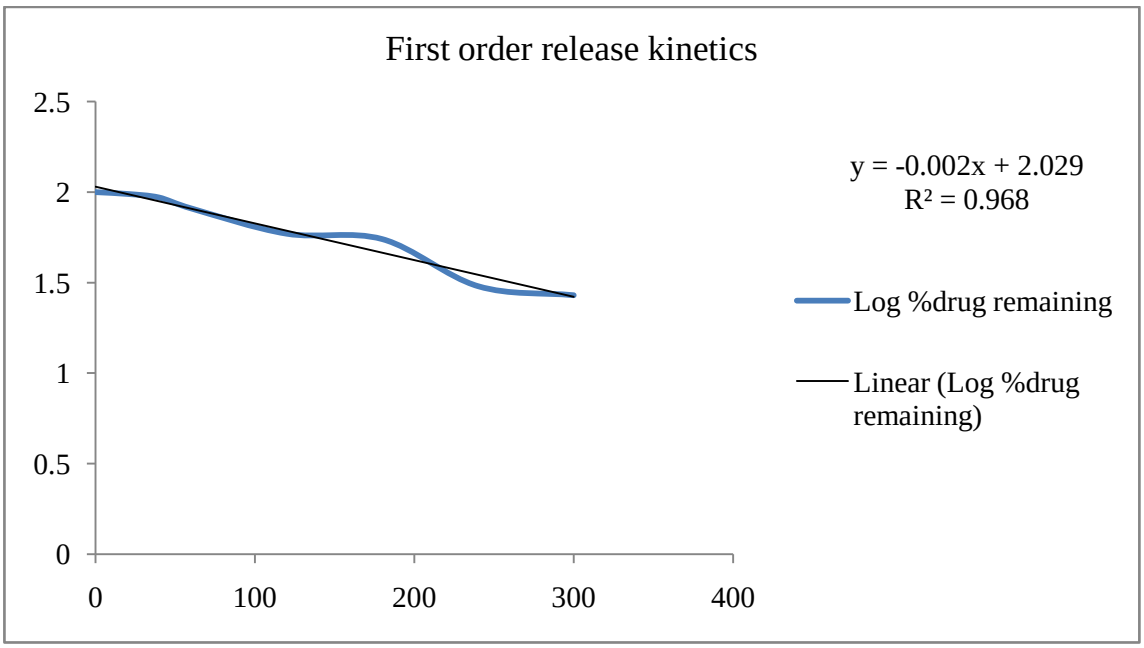


Fig: 47.Time Vs Log % drug remaining in phosphate buffer pH 7.4(FS2)

Table: 39. Higuchi kinetic model in phosphate buffer pH 7.4(FS2)

Square root of Time(Min)	%Drug Release
0	0
4.47	2.06
6.32	7.58
7.74	18.08
10.95	39.85
13.41	45.63
15.49	69.64
17.32	72.6

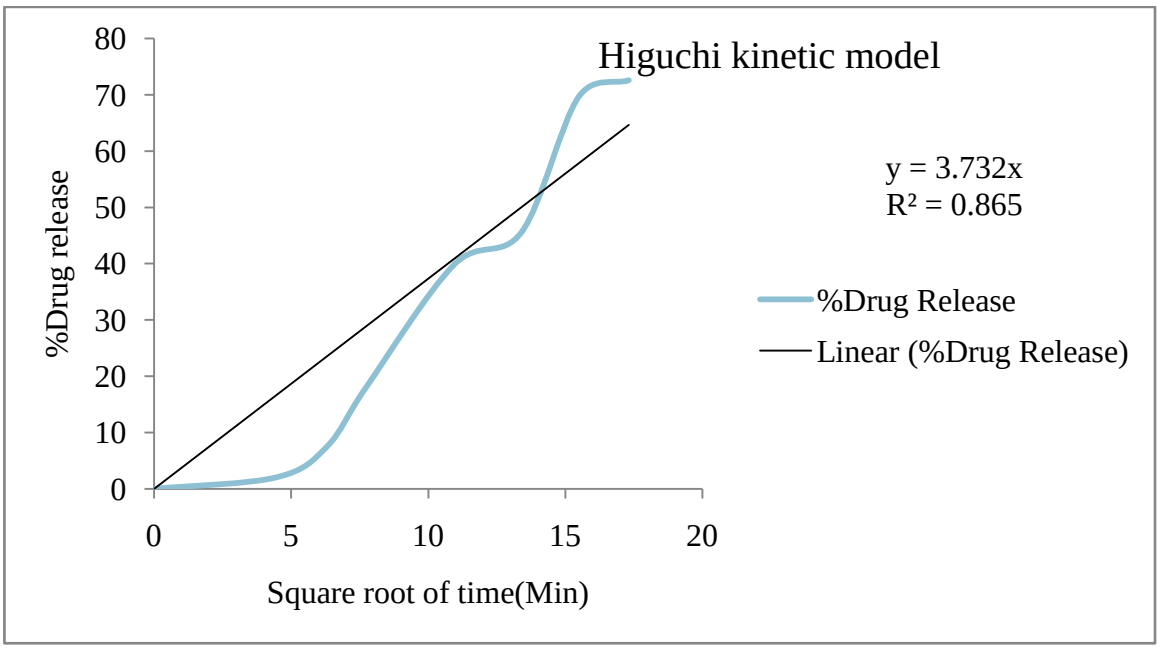


Fig: 48.Square root of time Vs % Drug release in phosphate buffer pH 7.4(FS2)

Table: 40. Korse-Meyer Peppas model in phosphate buffer pH 7.4:

Log time(Min)	Log %Drug release
1.3	0.3138
1.6	0.8796
1.79	1.26
2.08	1.6
2.26	1.66
2.38	1.84
2.48	1.86

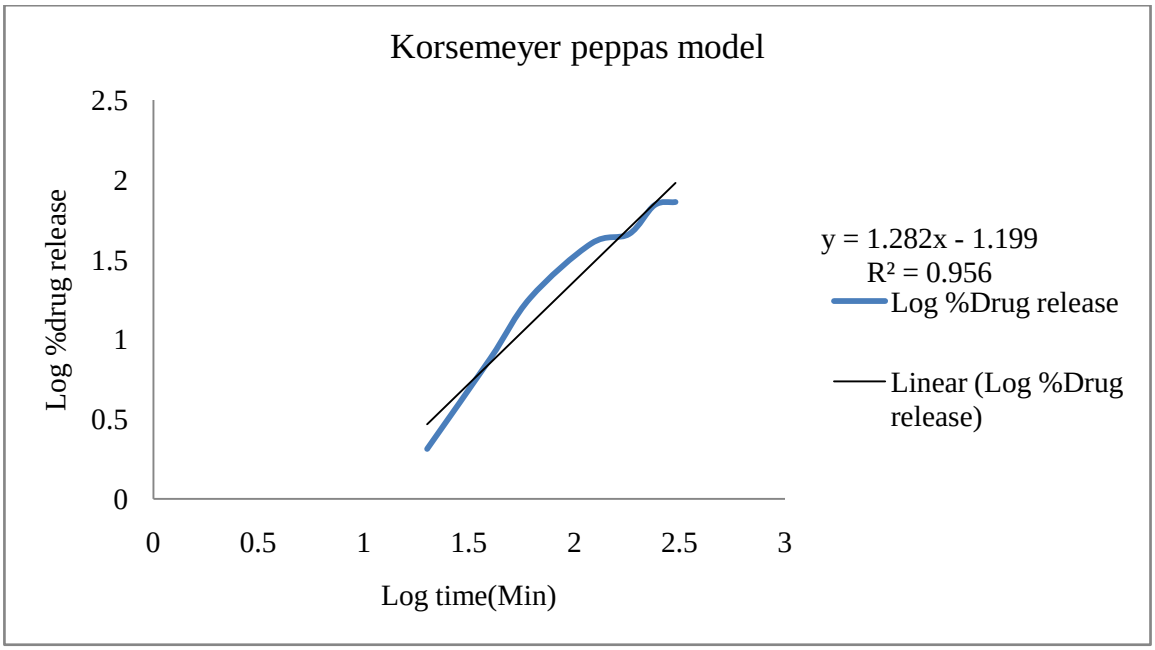


Fig: 49. Log time Vs Log % drug release in phosphate buffer pH 7.4(FS2)

Table: 41. Kinetic data of Pantoprazole in phosphate buffer pH 7.4(FS2)

Zero order		**First order**		**Higuchi model**		**Korse-meyer Peppas model**	
K_0	r^2	K_1	r^2	K_n	r^2	n	r^2
0.262	0.97	0.002	0.968	0.373	0.865	1.28	0.956

Table: 42. %Drug release of optimized Pantoprazole tablet in phosphate buffer pH 7.4 (FSC2 35%)

Time(Min)	Absorbance	Concentration(µg/ml)	%Drug Release
0	0	0	0
20	0.0123	0.1103	1.93
40	0.0291	0.5410	9.47
60	0.0451	0.9513	16.65
120	0.1163	2.7769	48.60
180	0.1358	3.2769	57.35
240	0.1493	3.6231	63.40
300	0.1573	3.8282	66.99

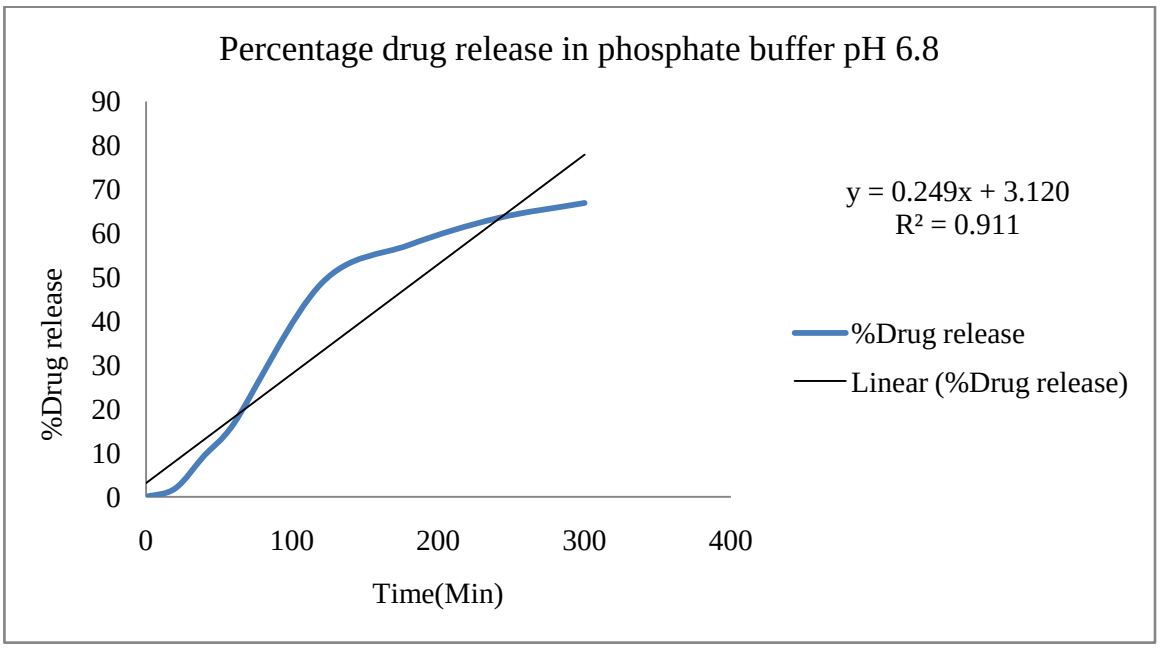


Fig: 50. %Drug release of optimized Pantoprazole tablet in phosphate buffer pH 7.4 (FSC2 35%)

6.2.6.4. Kinetic study of optimised Pantoprazole in phosphate buffer pH 7.4(FSC2):

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 – K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($In\ Q = InQ_0 – K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2\ t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K\ t_n$) the graph was plotted in log percent of drug released Vs log time (**Figures 51 to 54)** The release of Pantoprazole sodium sesquihydrate from the tablets was First order diffusion controlled as indicated by higher r^2 values in First order kinetics and korsemeyer Peppas (**Shown in table 46)**. The n values obtained from the korsemeyer Peppas kinetic model showed that the release mechanism was super case-II transport.

Table: 43.Zero order drug release in phosphate buffer pH 7.4 (FSC2).

Time(Min)	%Drug release
0	0
20	1.93
40	9.47
60	16.65
120	48.6
180	57.35
240	63.4
300	66.9

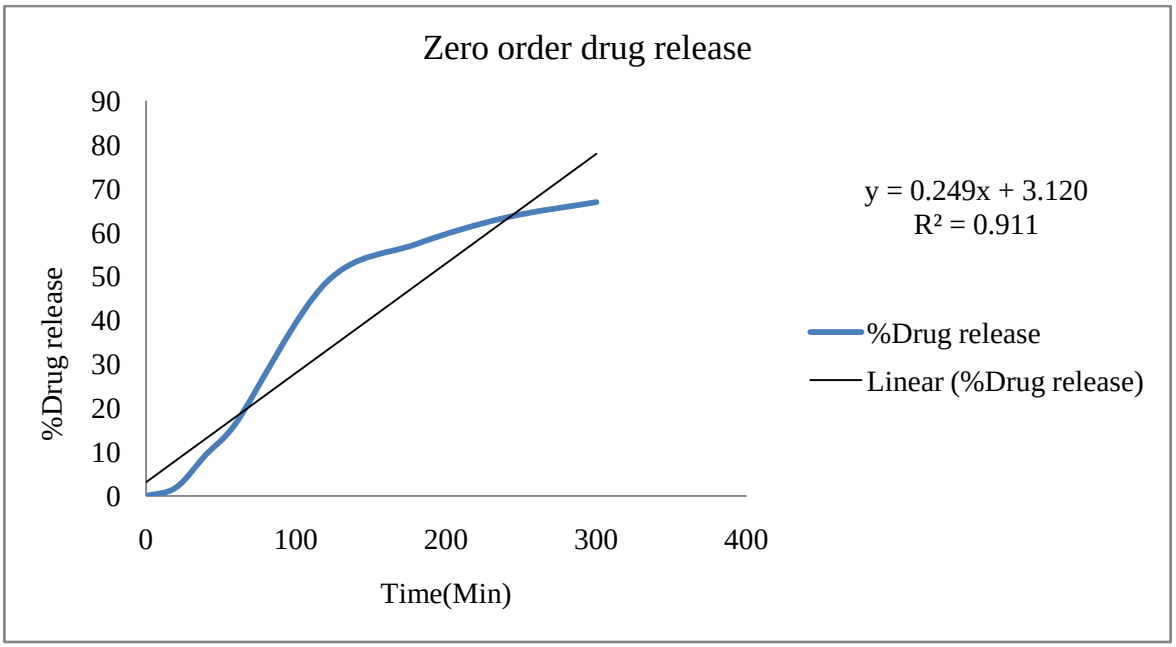


Fig: 51. Time (Min) Vs % Drug release in phosphate buffer pH 7.4 (FSC2)

Table: 44.First order drug release in phosphate buffer pH 7.4(FSC2):

Time(Min)	Log %drug remaining
0	2
20	1.99
40	1.95
60	1.92
120	1.71
180	1.62
240	1.56
300	1.51

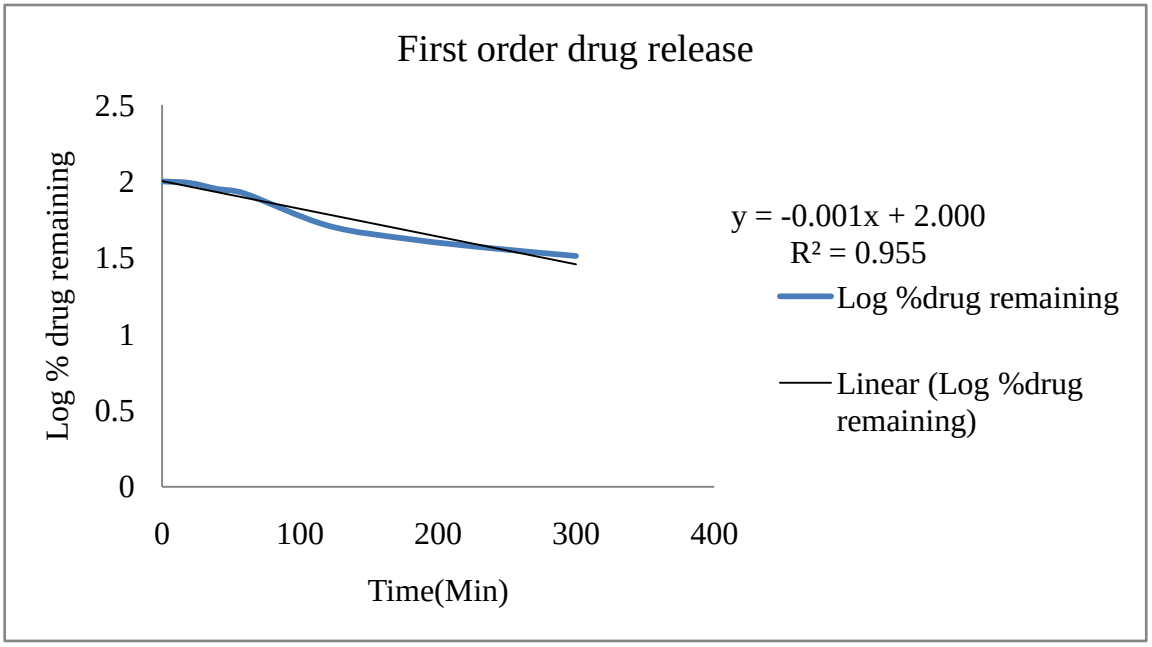


Fig: 52.Time Vs Log % drug remaining in phosphate buffer pH 7.4 (FSC2)

Table: 45. Higuchi kinetic model in phosphate buffer pH 7.4(FSC2):

Square root of time(Min)	%Drug release
0	0
4.47	1.93
6.32	9.47
7.74	16.65
10.95	48.6
13.41	57.35
15.49	63.4
17.32	66.9

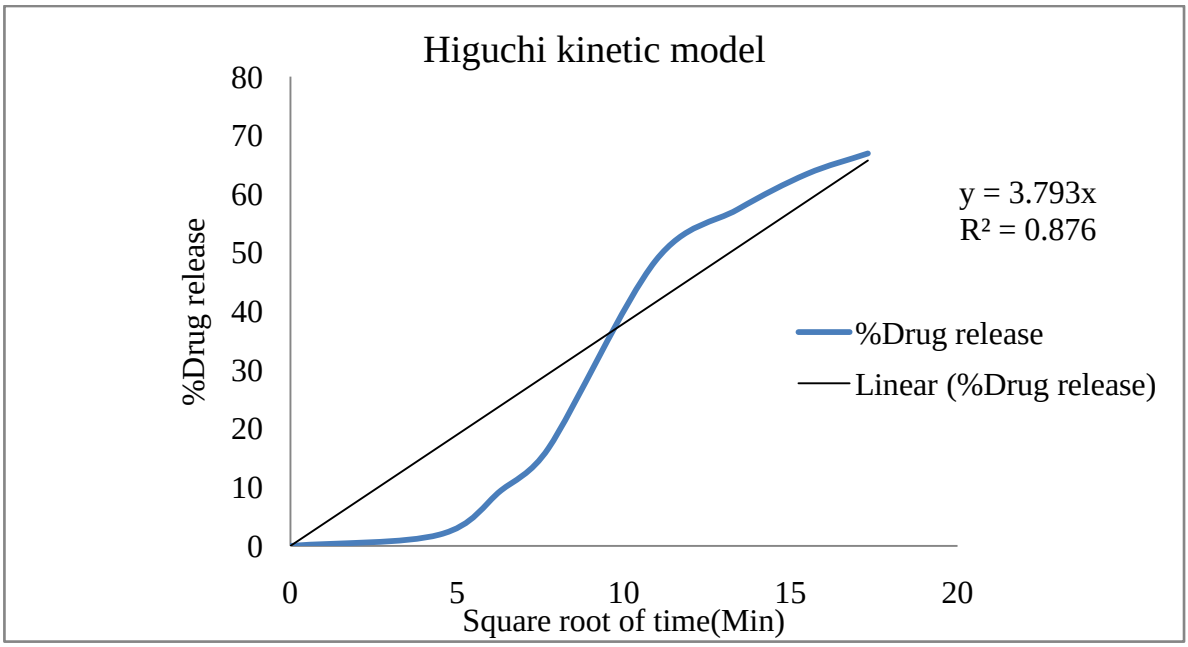


Fig: 53. Square root of time Vs % Drug release in phosphate buffer pH 7.4

(FSC2)

Table: 46. Korse-meyer Peppas model in phosphate buffer pH 7.4(FSC2)

Log time(Min)	Log % drug release
1.3	0.2856
1.6	0.9763
1.79	1.22
2.08	1.68
2.26	1.75
2.38	1.8
2.48	1.82

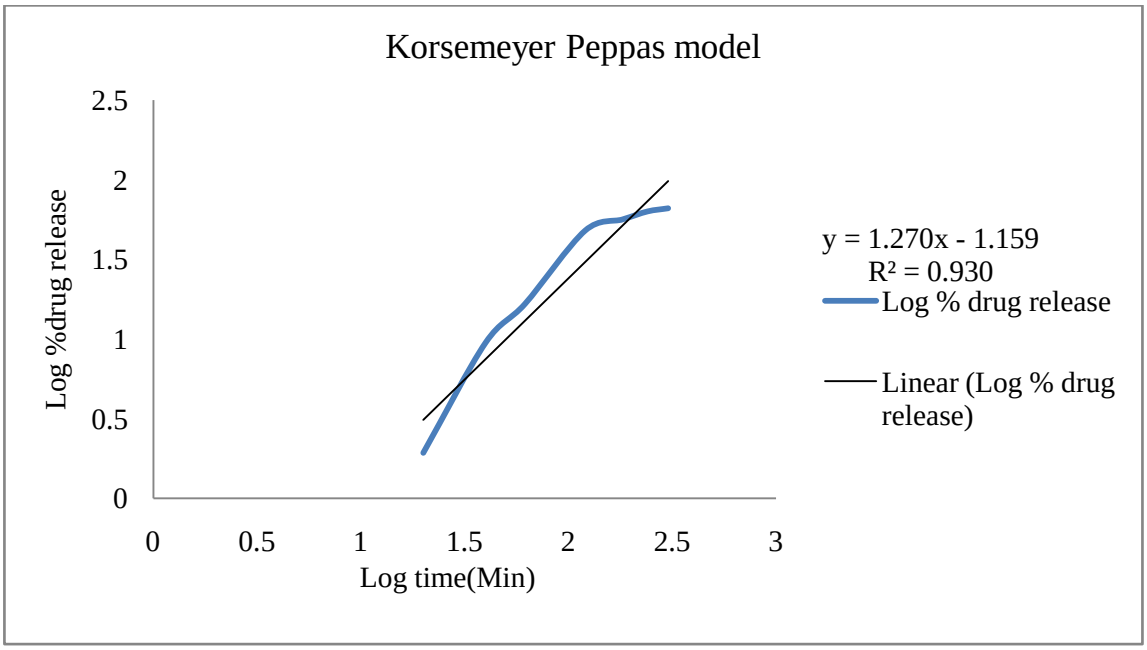


Fig: 54. Log time (Min) Vs Log % drug release in phosphate buffer pH 7.4 (FSC2)

Table: 47.Kinetic data of Pantoprazole in phosphate buffer pH 7.4(FSC2)

Zero order		First order		Higuchi model		Korsemeyer Peppas model	
K_0	r^2	K_1	r^2	K_H	r^2	K_n	r^2
0.249	0.911	0.001	0.955	3.73	0.876	1.270	0.930

6.2.7. Swelling index study of final batch formulation:

From the % swelling index study it is evident that the polymers with higher concentration had higher swelling index this was due to the fact that when the polymers concentration is increases the movement of the polymers also increases.

Table: 48. Swelling index data of Pantoprazole (FS2 (35%)

Time(Min)	Swelling index
0	0
1	79.46
2	75
3	70.83
4	4.16

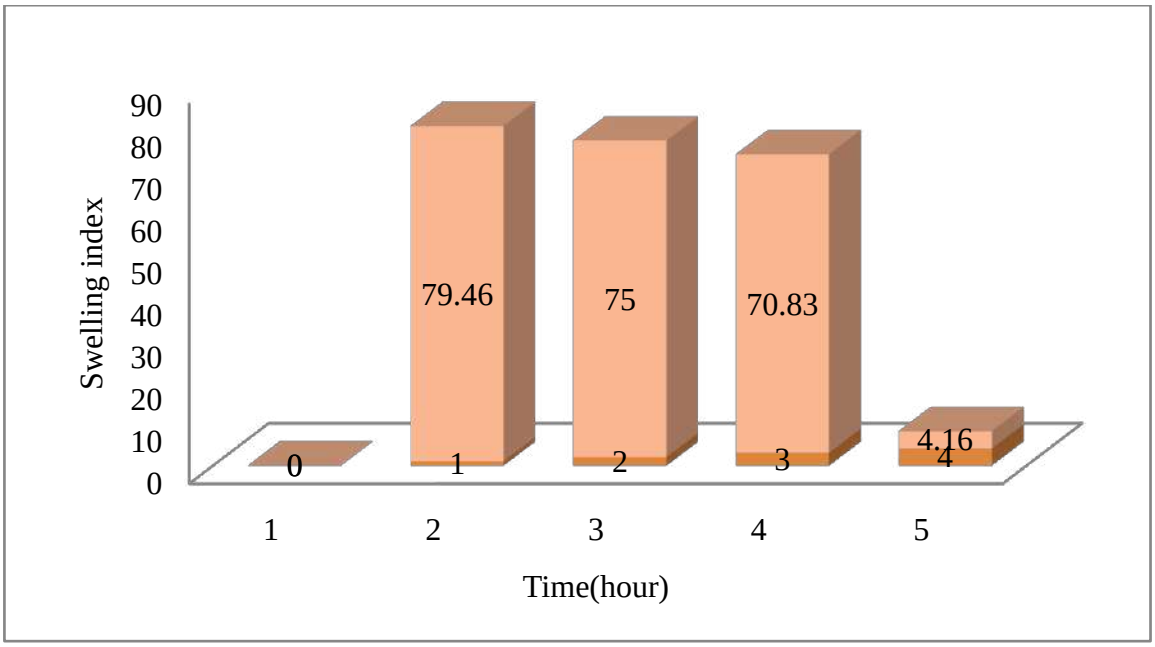


Fig: 55. Swelling index of FS2 (35%)

FS2 (35%): Formulation with sodium alginate 35%

Table: 49.Swelling index data of Pantoprazole (FSC2 35%):

Time(hour)	Swelling index(SI)
0	0
1	173.33
2	233.33
3	213.33
4	193.33

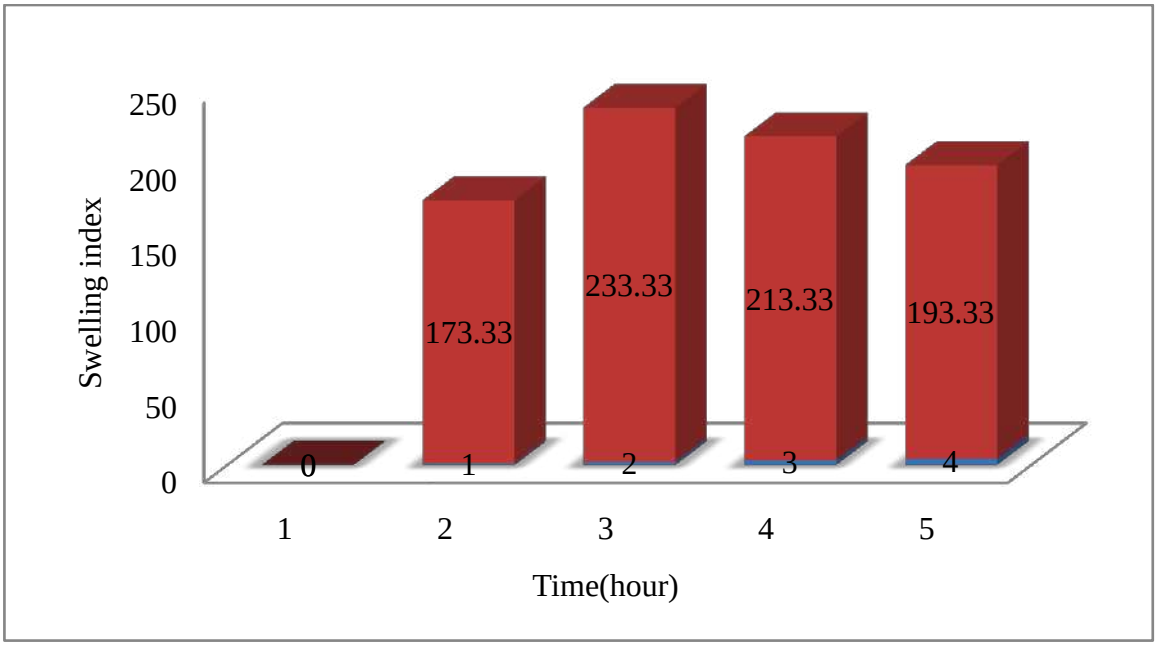


Fig: 56. Swelling index of FSC2 (35%).

FSC2 (35%): Formulation with the combination of sodium alginate and chitosan

6.2.8. Mucoadhesive strength of final batch formulation:

From the mucoadhesive strength study it is evident that at higher polymer concentration 35 % **(formulation with sodium alginate and combination of sodium alginate & chitosan**) the mucoadhesive strength is increases with the increase in adhesion time **(Shown in fig: 57&58)** The raise in mucoadhesive strength may be due to increase in availability of adhesive sites of natural polymer with mucin tends to increase in bond strength. Polymer swelling permits a mechanical entanglement by exposing the bio adhesive sites for hydrogen bonding and or electrostatic interaction between the polymer and the mucous network. Swelling of natural polymer based initiation of deep contact with the mucous layer permits a mechanical entanglement by exposing the bio adhesive sites for hydrogen bonding and or electrostatic interaction and the building of secondary bonds favouring both chemical and mechanical interactions

Table: 50.Mucoadhesive strength data of Pantoprazole FS2 (35%)

Sl No	Adhesion time(Sec)	Mucoadhesive strength(gm)
1	10	67.7
2	20	101.2
3	60	163
4	90	188.8
5	150	218.8

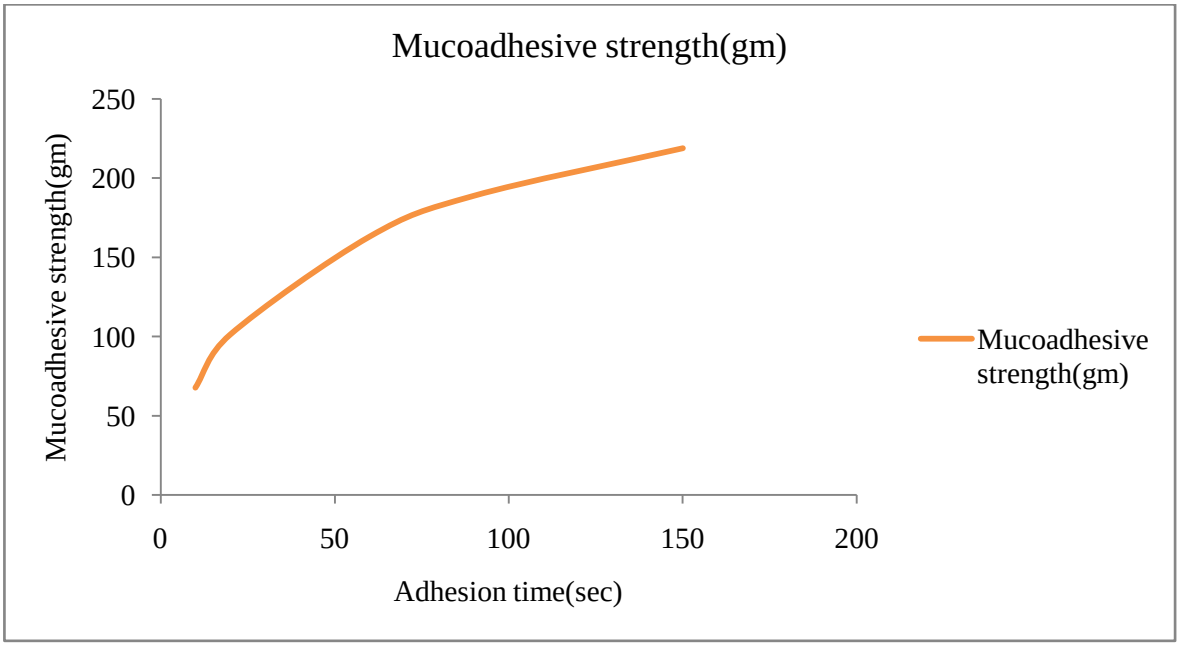


Fig: 57. Adhesion time Vs Mucoadhesive strength (FS2)

Table: 51. Mucoadhesive strength data of Pantoprazole (FSC2 35%)

Sl No	Adhesion time(sec)	Mucoadhesive strength(gm)
1	60	160.6
2	120	199.6
3	150	214.1

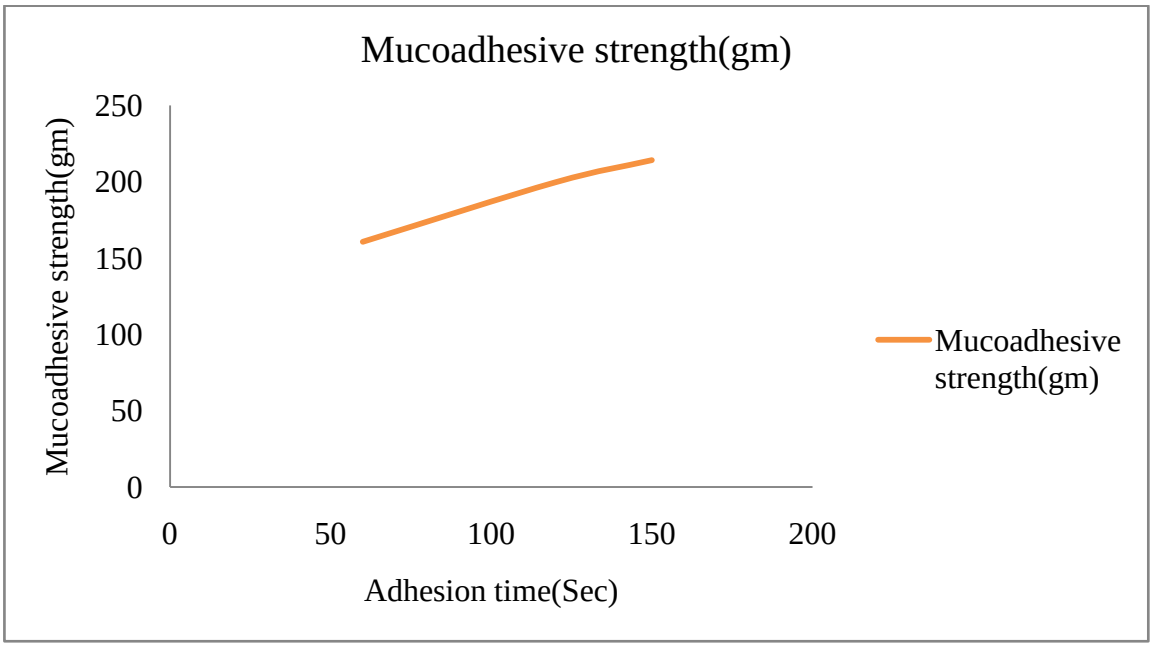


Fig: 58.Adhesion time Vs Mucoadhesive strength

6.3. *In-Vitro* drug release study of final batch coated formulation:

The final batch tablets were coated by dipping coating method and drug release studies were carried out in phosphate buffer pH 6.8.

Table: 52. % Drug release of final batch Pantoprazole in phosphate buffer pH 6.8 (FS2 35% thickness 6%):

Time(Min)	Absorbance	% Drug release
0	0	0
30	0	0
60	0	0
90	0	0
120	0	0
180	0.0107	1.21
240	0.0514	19.47
300	0.0586	22.71
360	0.0622	24.32
420	0.0678	26.83

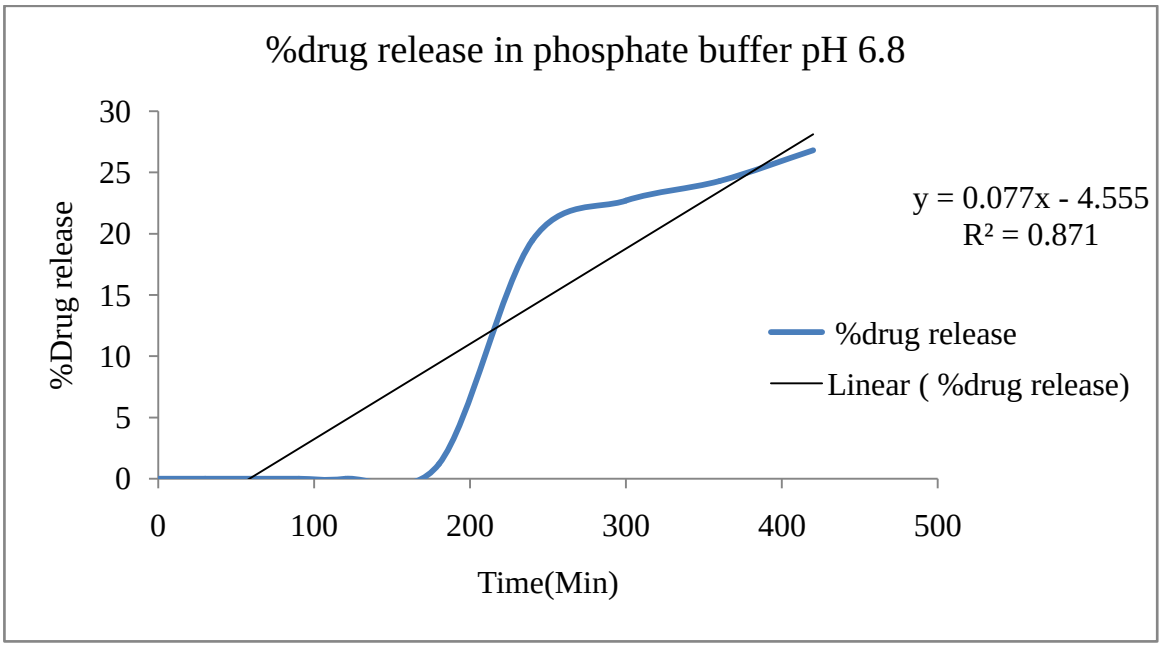


Fig: 59. %Drug release of coated formulation (FS2 35% thickness 6%)

6.3.1. Kinetic study of final batch Pantoprazole in phosphate buffer pH 6.8(FS2 35% thickness 6%):

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 – K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($\ln Q = \ln Q_0 – K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2 t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K t_n$) the graph was plotted in log percent of drug released Vs log time (**Figures 60 to 63).** The release of Pantoprazole sodium sesquihydrate from the tablets was first order diffusion controlled as indicated by higher r^2 values in zero order and first order kinetics (**Shown in table to 28)**. The n values obtained from the Higuchi kinetic model and Korse-meyer Peppas model showed that the release mechanism was super case-II transport and non-Fickian transport.

Table: 53. Zero order drug release in phosphate buffer pH 6.8 (FS2 35% thickness 6%)

Time(Min)	%Drug release
0	0
30	0
60	0
90	0
120	0
180	1.21
240	19.47
300	22.71
360	24.32
420	26.83

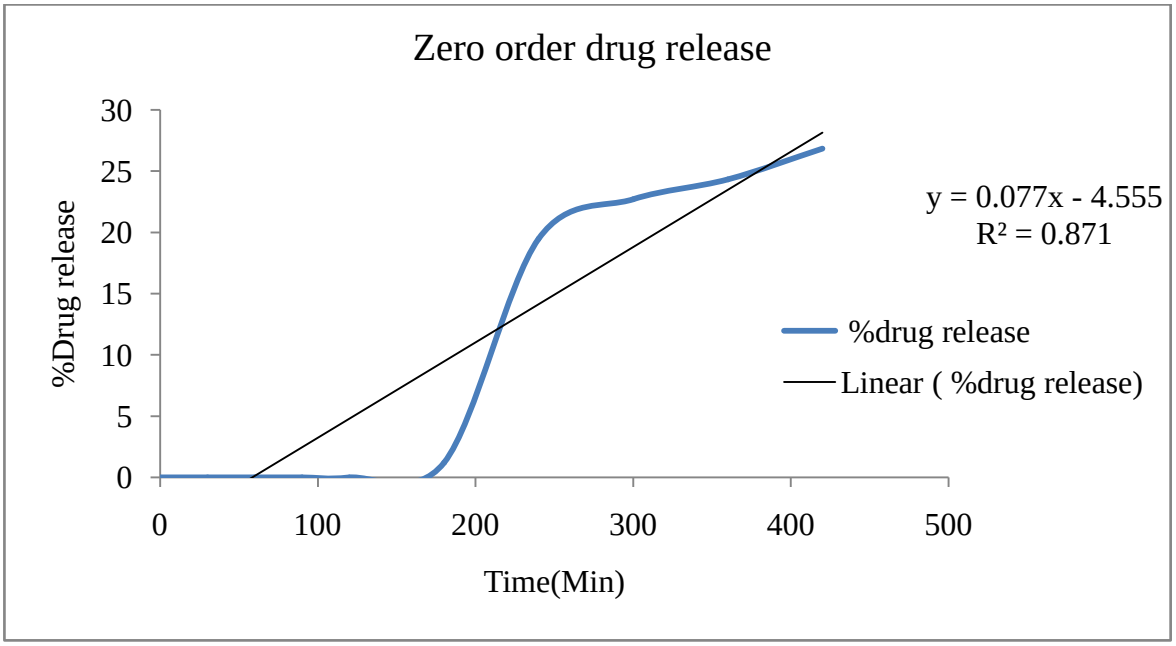


Fig: 60.Time Vs % drug release

Table: 54.First order drug release in phosphate buffer pH 6.8 (FS2 35% thickness 6%)

Time(Min)	Log % drug remaining
0	2
30	2
60	2
90	2
120	2
180	1.99
240	1.91
300	1.89
360	1.88
420	1.86

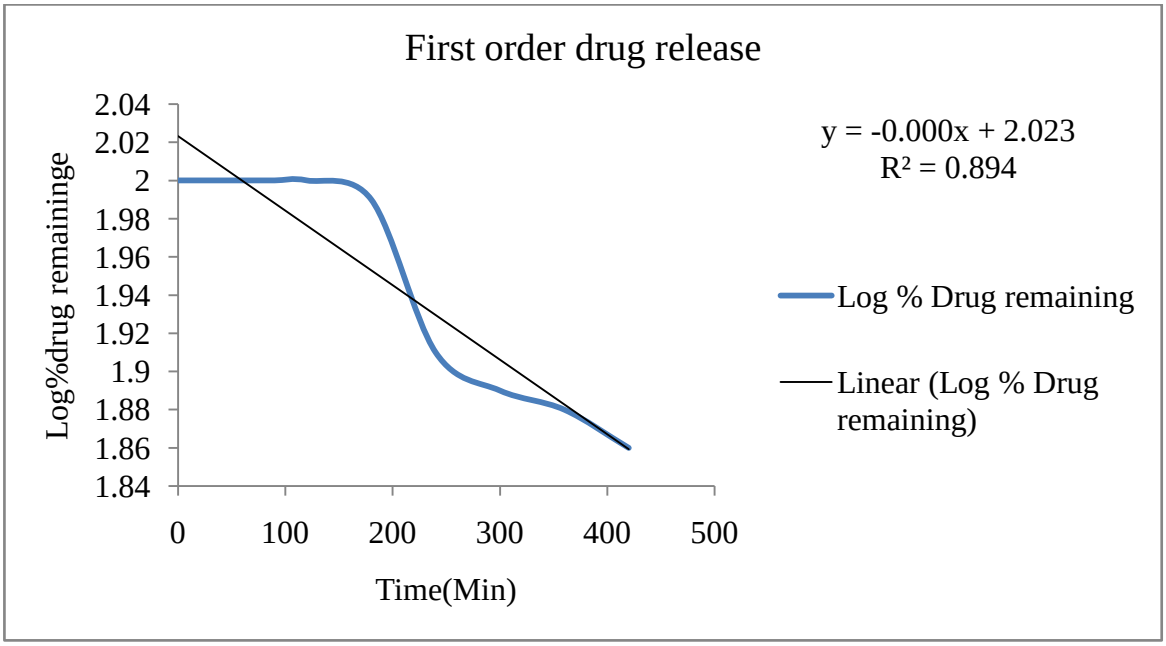


Fig: 61. Time Vs Log %drug release remaining

Table: 55.Higuchi kinetic model in phosphate buffer pH 6.8 (FS2 35% thickness 6%)

Square root of time(Min)	%Drug release
0	0
5.47	0
7.75	0
9.49	0
10.45	0
13.42	1.21
15.49	19.47
17.32	22.71
18.97	24.32
20.49	26.83

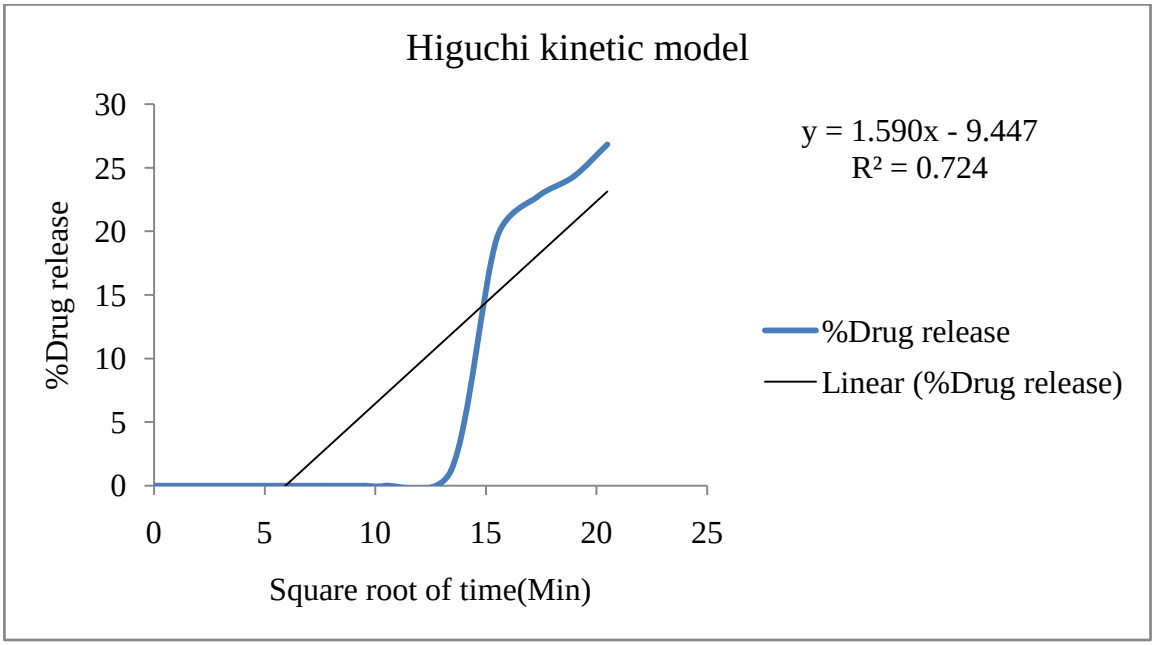


Fig: 62. Square root of time Vs %Drug release

Table: 56.Korsemeyer Peppas model in phosphate buffer pH 6.8 (FS2 35% thickness 6%):

Log time(Min)	Log% drug release
0	0
1.48	0
1.78	0
1.95	0
2.08	0
2.26	0.082
2.38	1.28
2.48	1.35
2.56	1.38
2.62	1.42

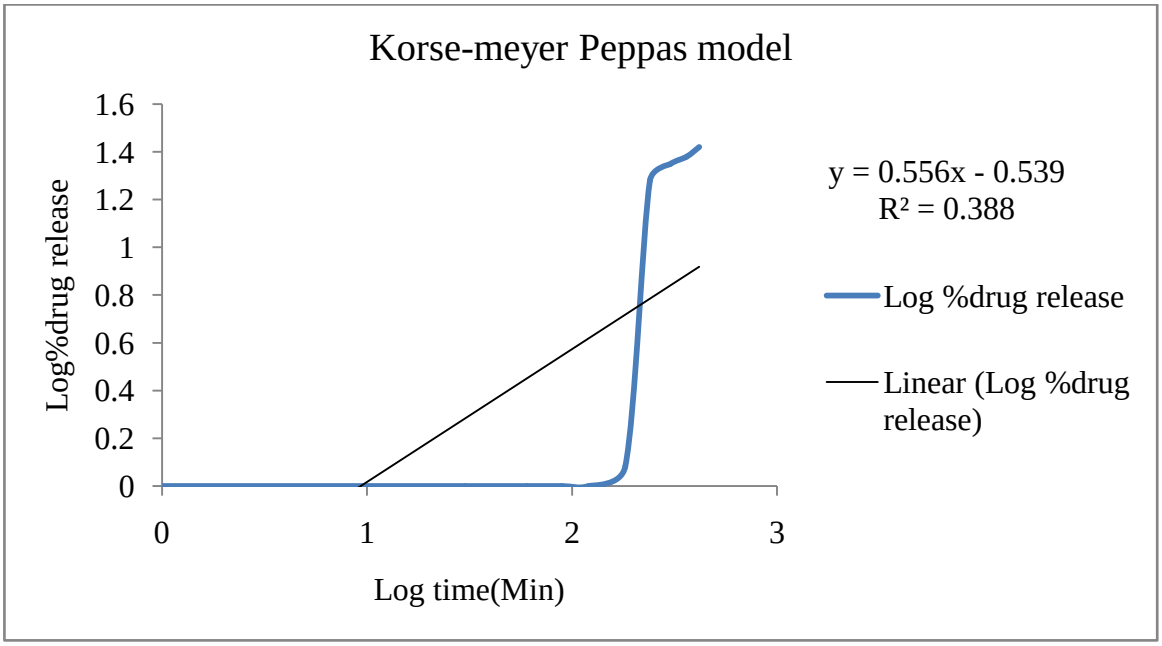


Fig: 63. Log time Vs Log% drug release

Table: 57.Kinetic data in phosphate buffer pH 6.8 (FS2 35% thickness 6%):

Zero order		First order		Higuchi model		Korse-meyer Peppas model	
r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
0.87	0.077	0.89	0	0.724	1.59	0.38	0.55

Table: 58. % Drug release of final batch Pantoprazole in phosphate buffer pH 6.8 (FS2 35% thickness 8%):

Time(Min)	Absorbance	% Drug release
0	0	0
30	0	0
60	0	0
90	0	0
120	0	0
180	0.0165	3.81
240	0.0261	8.12
300	0.0292	9.51
360	0.0294	9.60
420	0.0301	9.92

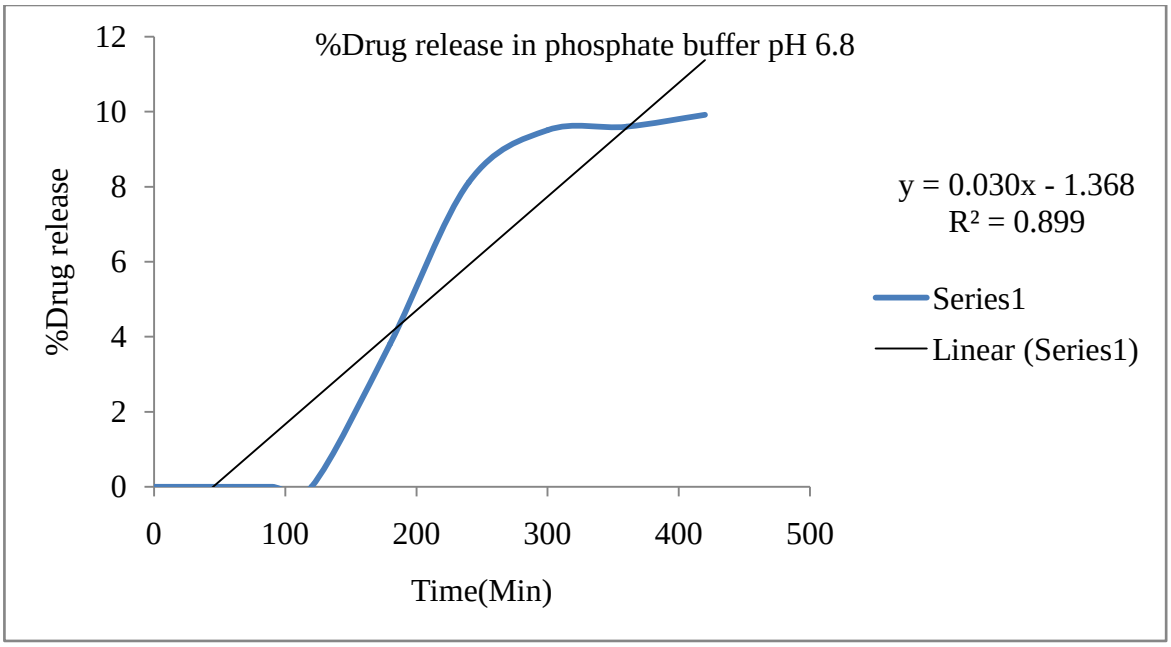


Fig: 64. %Drug release of coated formulation (FS2 35% thickness 8%)

6.3.2. Kinetic study of optimised Pantoprazole in phosphate buffer pH 6.8(FS2 35% thickness 8%):

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 – K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($\ln Q = \ln Q_0 – K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2 t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K t_n$) the graph was plotted in log percent of drug released Vs log time (**Shown figures 65 to 68).** The release of Pantoprazole sodium sesquihydrate from the tablets was zero order diffusion controlled as indicated by higher r^2 values in zero order kinetics and first order kinetic model **(Shown in tables 58 to 61)**. The n values obtained from the Higuchi kinetic model showed that the release mechanism was non-Fickian transport.

Table: 59.Zero order drug release in phosphate buffer pH 6.8 (FS2 35% thickness 8%)

Time(Min)	%Drug release
0	0
30	0
60	0
90	0
120	0
180	3.81
240	8.12
300	9.51
360	9.60
420	9.92

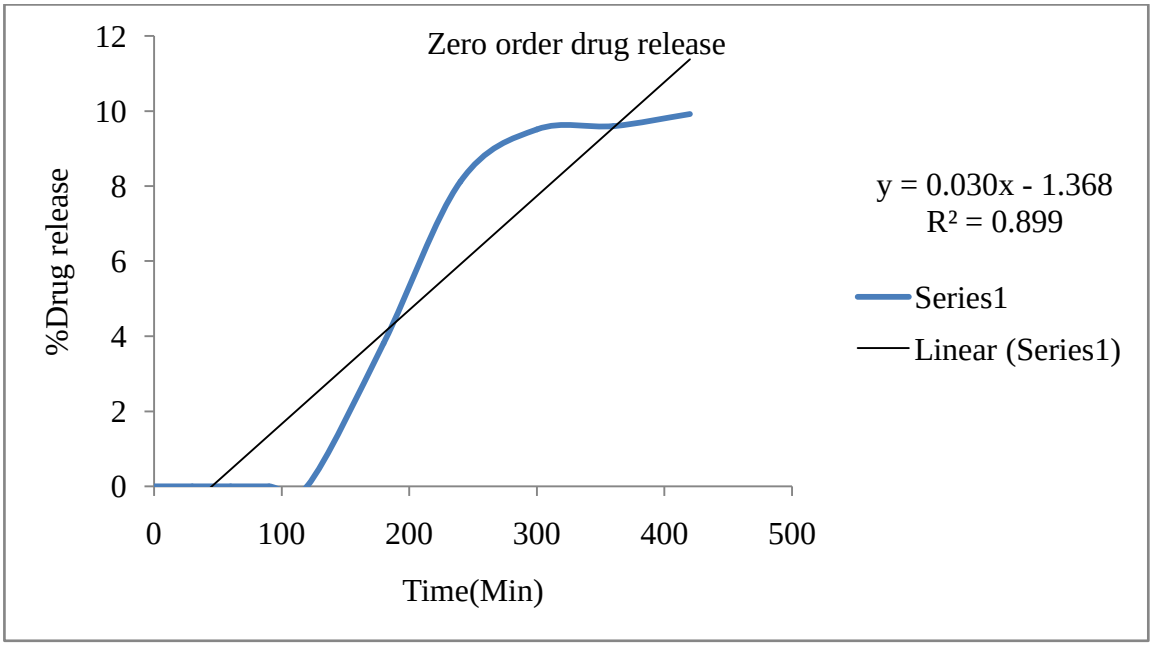


Fig: 65. TimeVs %Drug release

Table: 60.First order drug release in phosphate buffer pH 6.8 (FS2 35% thickness 8%)

Time(Min)	Log % drug remaining
0	2
30	2
60	2
90	2
120	2
180	1.99
240	1.96
300	1.95
360	1.95
420	1.95

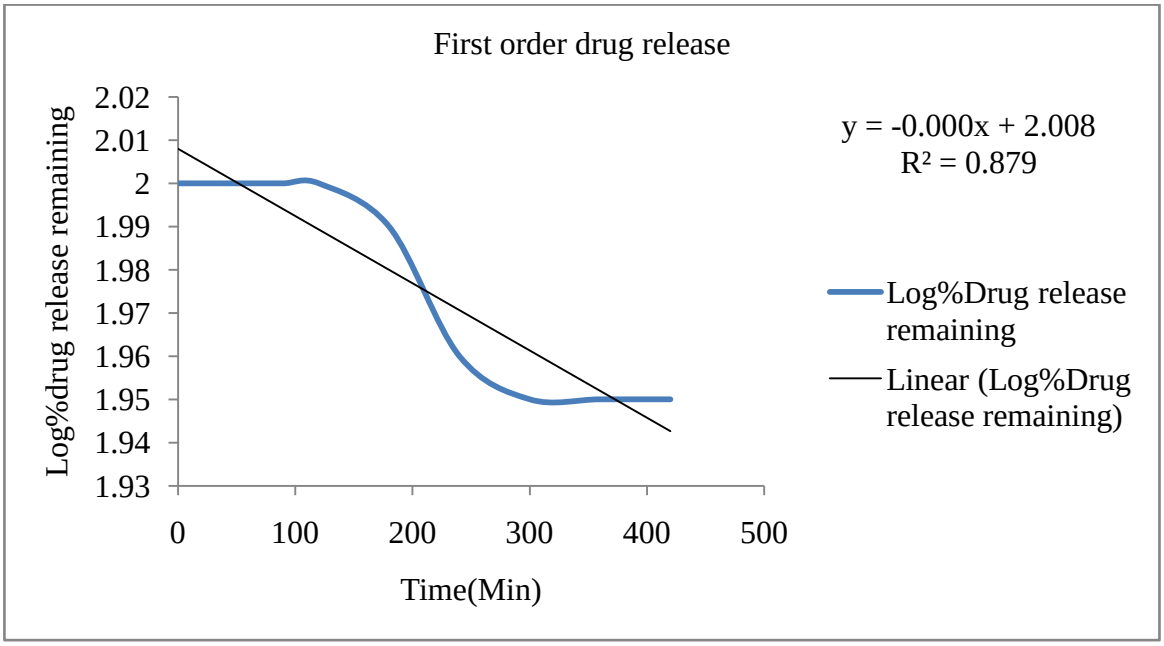


Fig: 66. Time (Min) Log %drug release remaining

Table: 61.Higuchi kinetic model in phosphate buffer pH 6.8 (FS2 35% thickness 8%)

Square root of time(Min)	%Drug release
0	0
5.47	0
7.75	0
9.49	0
10.95	0
13.41	3.81
15.49	8.12
17.32	9.51
18.97	9.60
20.49	9.92

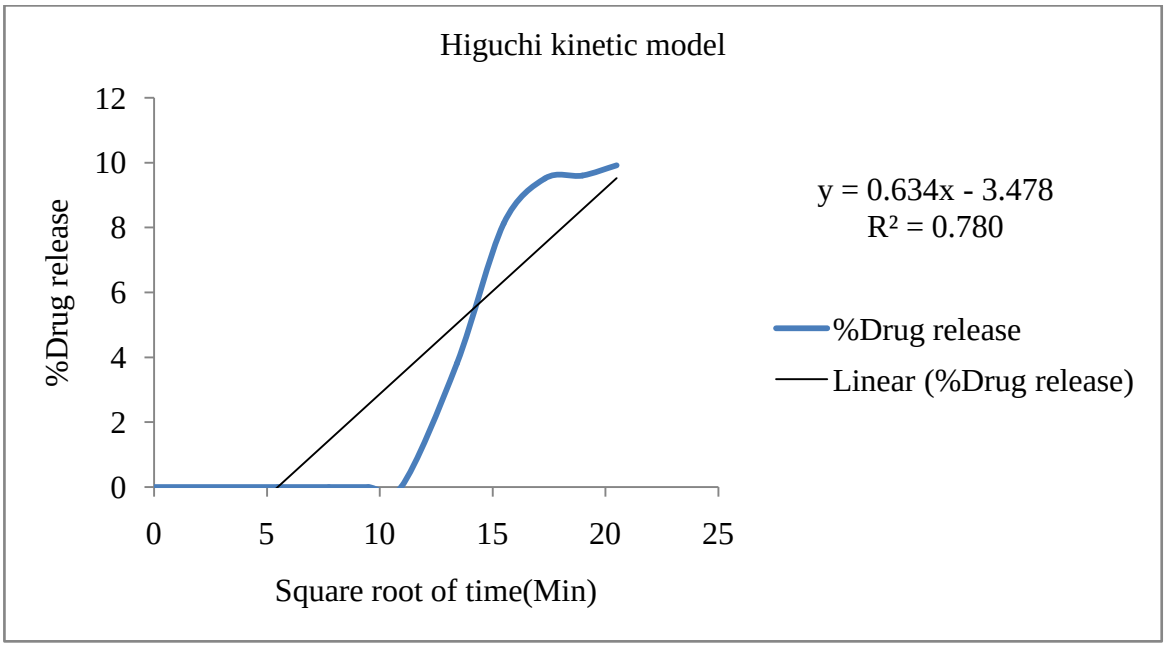


Fig: 67. Square root of time (Min) Vs %drug release

Table: 62.Korse-meyer Peppas model in phosphate buffer pH 6.8 (FS2 35% thickness 8%)

Log time(Min)	Log % drug release
0	0
1.48	0
1.78	0
1.95	0
2.08	0
2.26	0.580
2.38	0.909
2.48	0.978
2.56	0.982
2.62	0.997

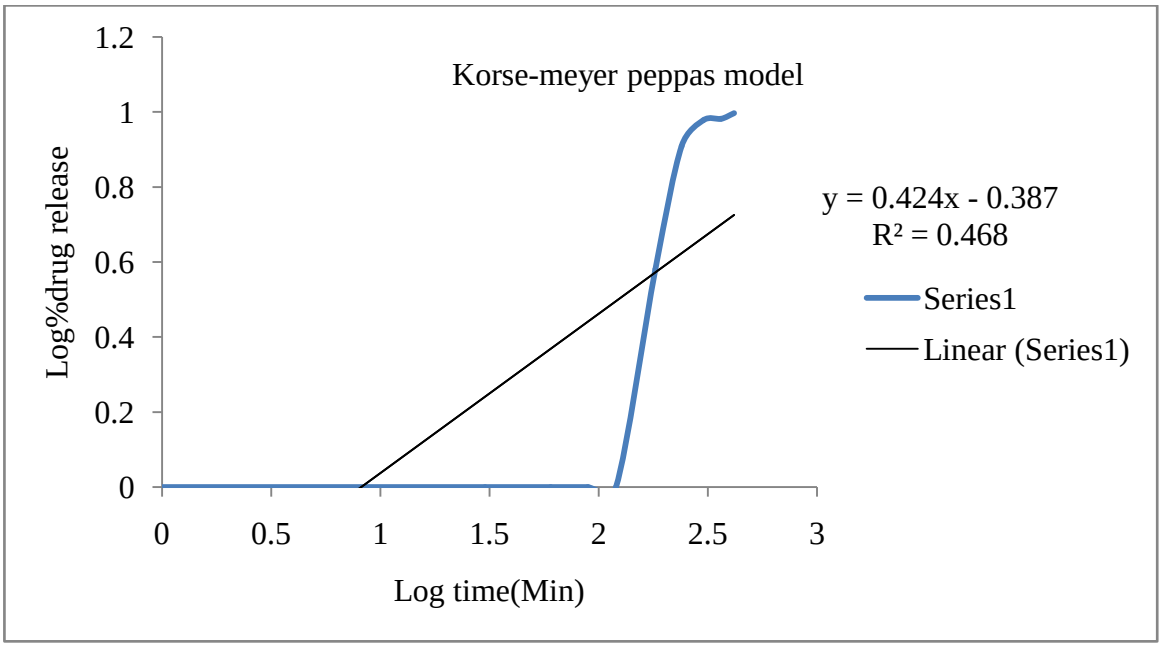


Fig: 68. Log time (Min) Vs Log %drug release

Table: 63.Kinetic data in phosphate buffer pH 6.8 (FS2 35% thickness 8%):

Zero order		First order		Higuchi model		Korse-meyer Peppas model	
r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
0.89	0.03	0.88	0	0.78	0.634	0.47	0.42

Table: 64. % Drug release of final batch Pantoprazole in phosphate buffer pH 6.8 (FSC2 35% thickness 6%):

Time(Min)	Absorbance	% Drug release
0	0	0
30	0	0
60	0	0
90	0	0
120	0	0
180	0.0191	4.98
240	0.0195	5.16
300	0.0196	5.21
360	0.0203	5.51
420	0.0232	6.82

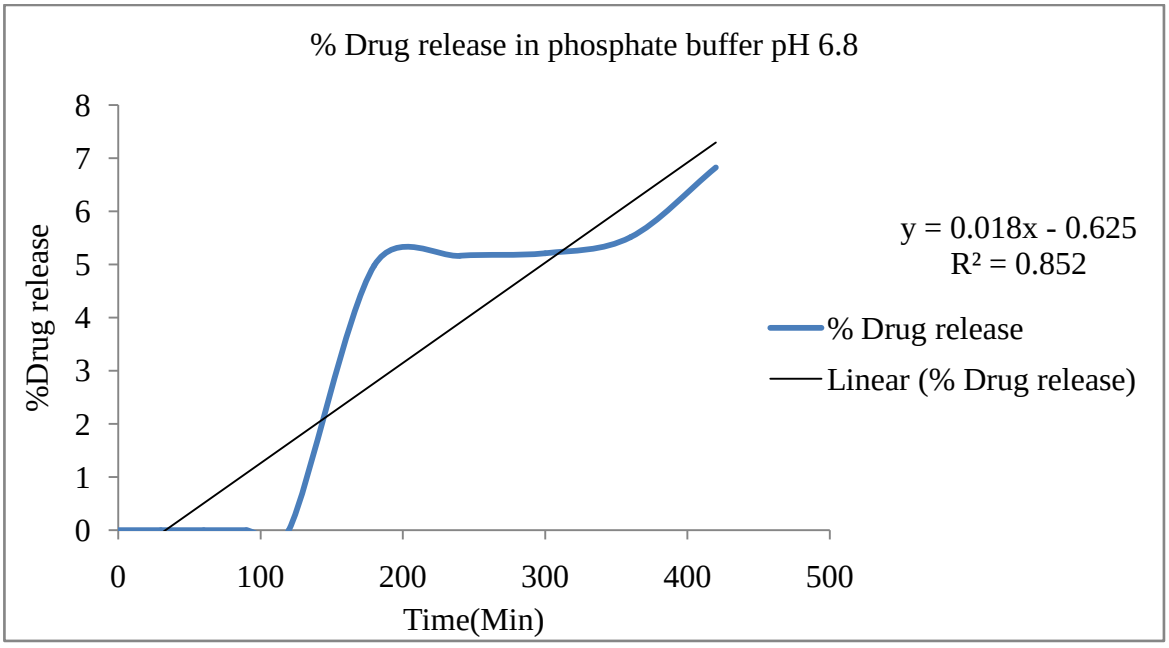


Fig: 69. %Drug release of coated formulation (FSC2 35% thickness 6%)

6.3.3. Kinetic study of optimised Pantoprazole in phosphate buffer pH 6.8(FSC2 35% thickness 6%):

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 – K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($In\ Q = InQ_0 – K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2\ t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K\ t_n$) the graph was plotted in log percent of drug released Vs log time (**Figures 70 to 73).** The release of Pantoprazole sodium sesquihydrate from the tablets was first order diffusion controlled as indicated by higher r^2 values in first order and zero order kinetics model **(Shown in tables 68)**. The n values obtained from the Higuchi kinetic model showed that the release mechanism was super case-II transport

Table: 65.Zero order drug release in phosphate buffer pH 6.8 (FSC2 35% thickness 6%)

Time(Min)	% Drug release
0	0
30	0
60	0
90	0
120	0
180	4.98
240	5.16
300	5.21
360	5.51
420	6.82

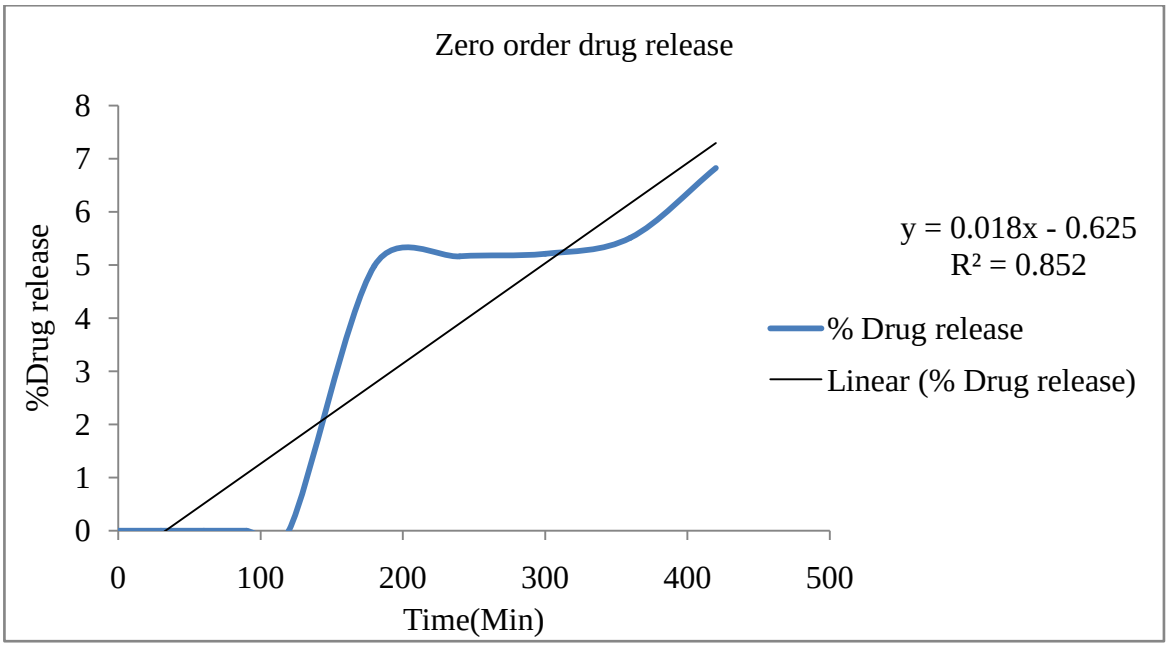


Fig: 70. Time Vs %Drug release

Table: 66.First order drug release in phosphate buffer pH 6.8 (FSC2 35% thickness 6%)

Time(Min)	Log % drug remaining
0	2
30	2
60	2
90	2
120	2
180	1.98
240	1.97
300	1.97
360	1.97
420	1.96

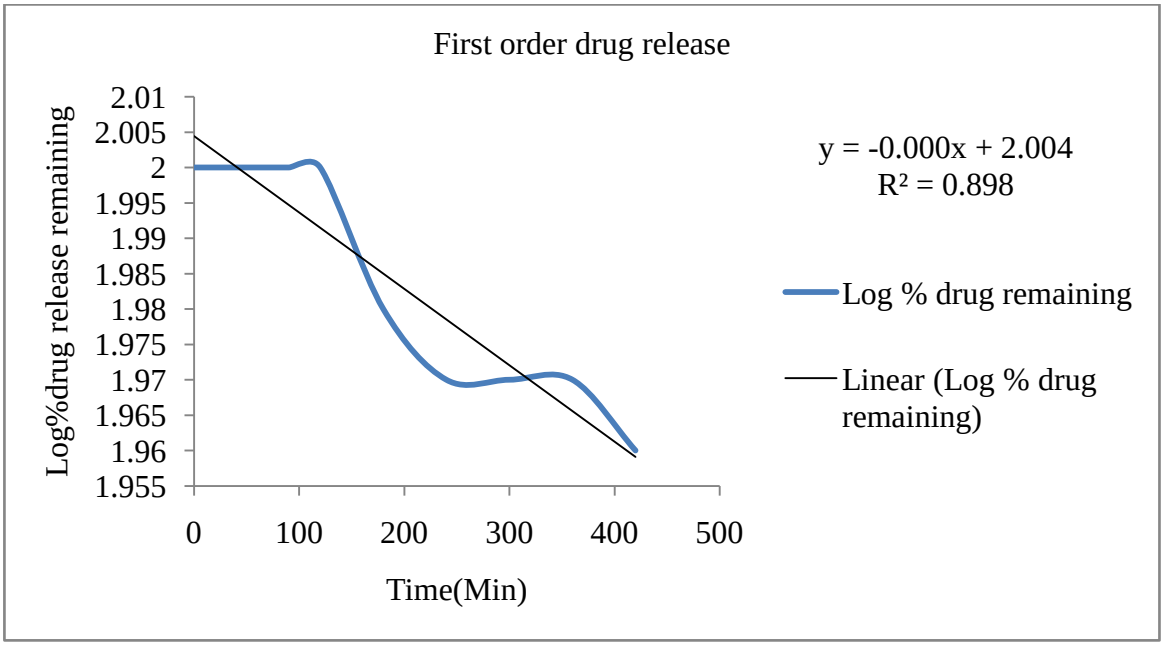


Fig: 71. Time (Min) Vs Log% drug release remaining

Table: 67.Higuchi kinetic model in phosphate buffer pH 6.8 (FSC2 35% thickness 6%)

Square root of time(Min)	% Drug release
0	0
5.47	0
7.75	0
9.49	0
10.95	0
13.41	4.98
15.49	5.16
17.32	5.21
18.97	5.51
20.49	6.82

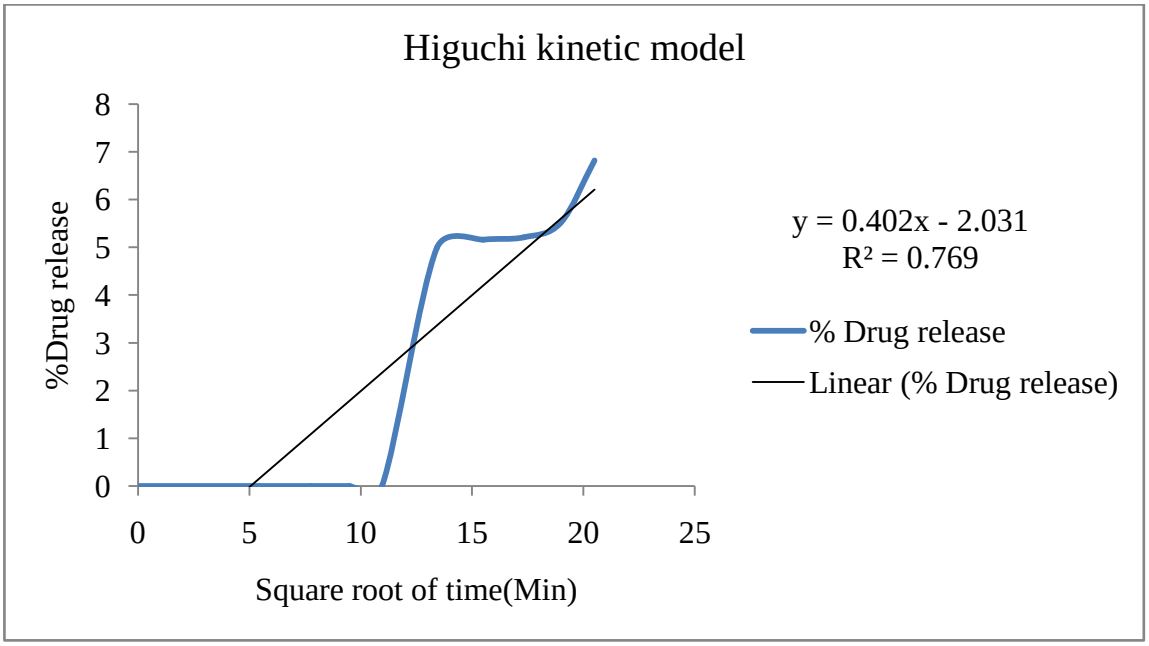


Fig: 72. Square root of time (Min) Vs% drug release

Table: 68.Korse-meyer Peppas model in phosphate buffer pH 6.8 (FSC2 35% thickness 6%)

Log time(Min)	Log% drug release
0	0
1.47	0
1.78	0
1.95	0
2.08	0
2.25	0.670
2.38	0.713
2.48	0.716
2.55	0.741
2.62	0.834

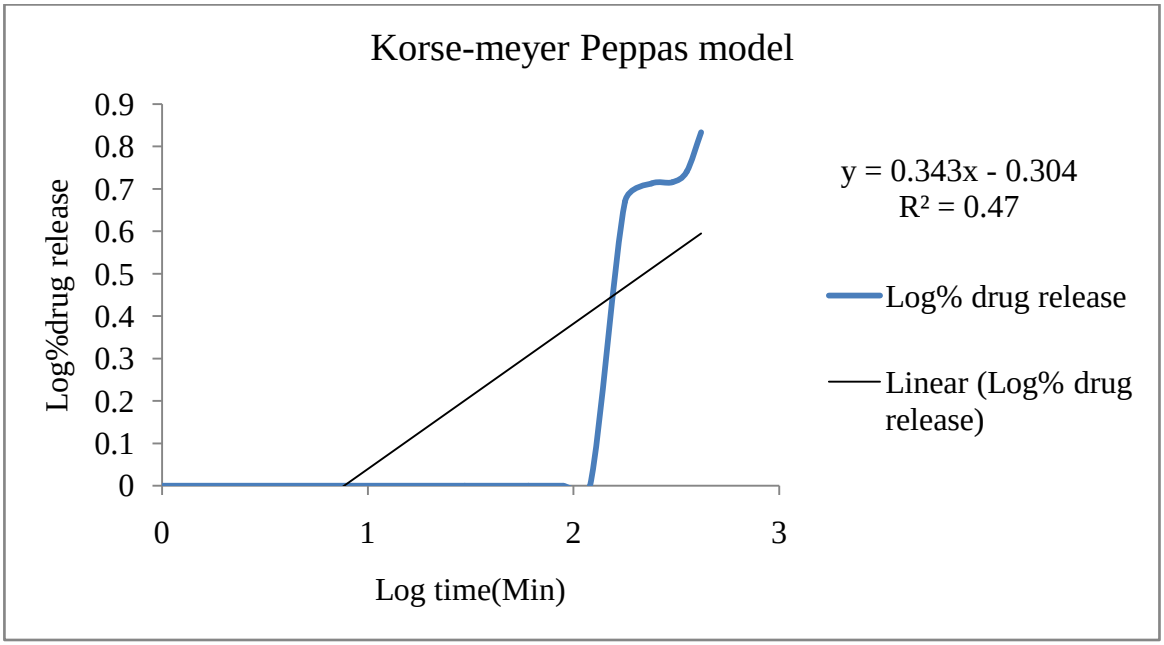


Fig: 73. Log time (Min) Vs Log% drug release

Table: 69.Kinetic data in phosphate buffer pH 6.8 (FSC2 35% thickness 6%):

Zero order		First order		Higuchi model		Korse-meyer Peppas model	
r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
0.85	0.018	0.90	0	0.77	0.40	0.47	0.34

Table: 70. % Drug release of final batch Pantoprazole in phosphate buffer pH 6.8 (FSC2 35% thickness 8%):

Time(Min)	Absorbance	% Drug release
0	0	0
30	0	0
60	0	0
90	0	0
120	0	0
180	0.0272	8.62
240	0.0283	9.10
300	0.0297	9.73
360	0.0493	18.53
420	0.0528	20.10

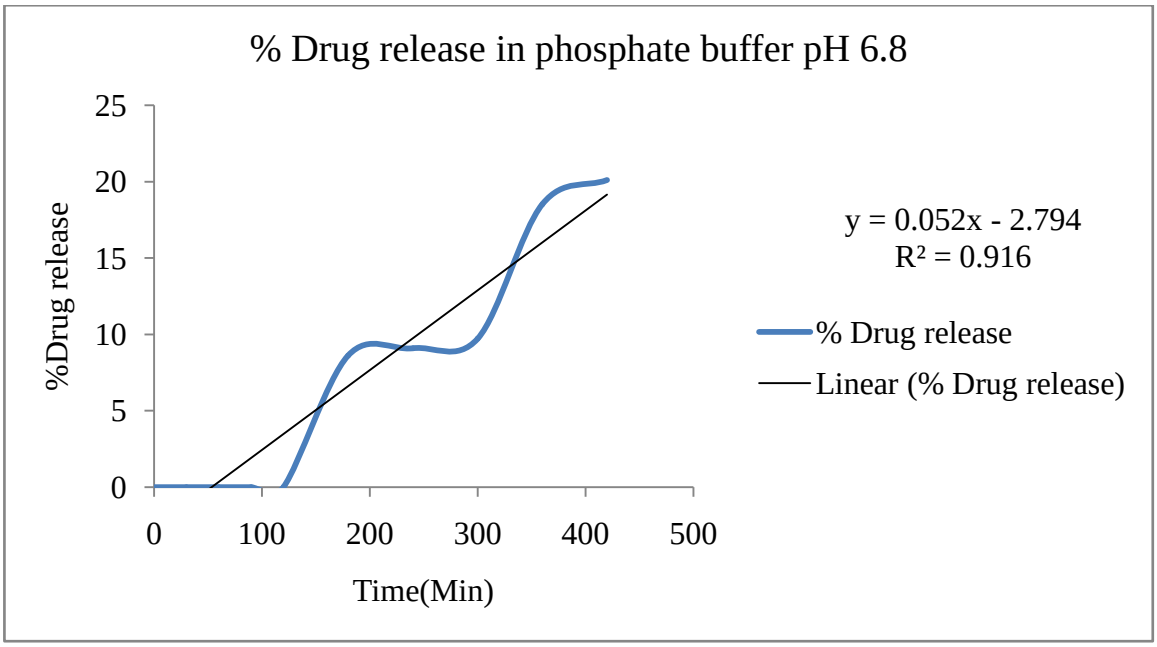


Fig: 74. %Drug release of coated formulation (FSC2 35% thickness 8%)

6.3.4. Kinetic study of optimised Pantoprazole in phosphate buffer pH 6.8(FSC2 35% thickness 6%):

The *in vitro* release data obtained from Pantoprazole sodium sesquihydrate in phosphate buffer pH 6.8 were fitted to various kinetic models such as Zero order, First order, Higuchi model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 – K_0t$) the graph was plotted in percent of drug released Vs time, and in first order release kinetics ($\ln Q = \ln Q_0 – K_1t$) the graph was plotted in log percent of drug remaining Vs time. For Higuchi model kinetics ($Q = K_2 t^{1/2}$) the graph was plotted in percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K t_n$) the graph was plotted in log percent of drug released Vs log time (**Figures 75 to 78).** The release of Pantoprazole sodium sesquihydrate from the tablets was zero order diffusion controlled as indicated by higher r^2 values in zero order kinetics and Higuchi model **(Shown in table 74)**. The n values obtained from the Higuchi kinetic model and Korse-meyer Peppas model showed that the release mechanism was super case-II transport and non-Fickian transport.

Table: 71.Zero order drug release in phosphate buffer pH 6.8 (FSC2 35% thickness 8%)

Time(Min)	% Drug release
0	0
30	0
60	0
90	0
120	0
180	8.62
240	9.10
300	9.73
360	18.53
420	20.10

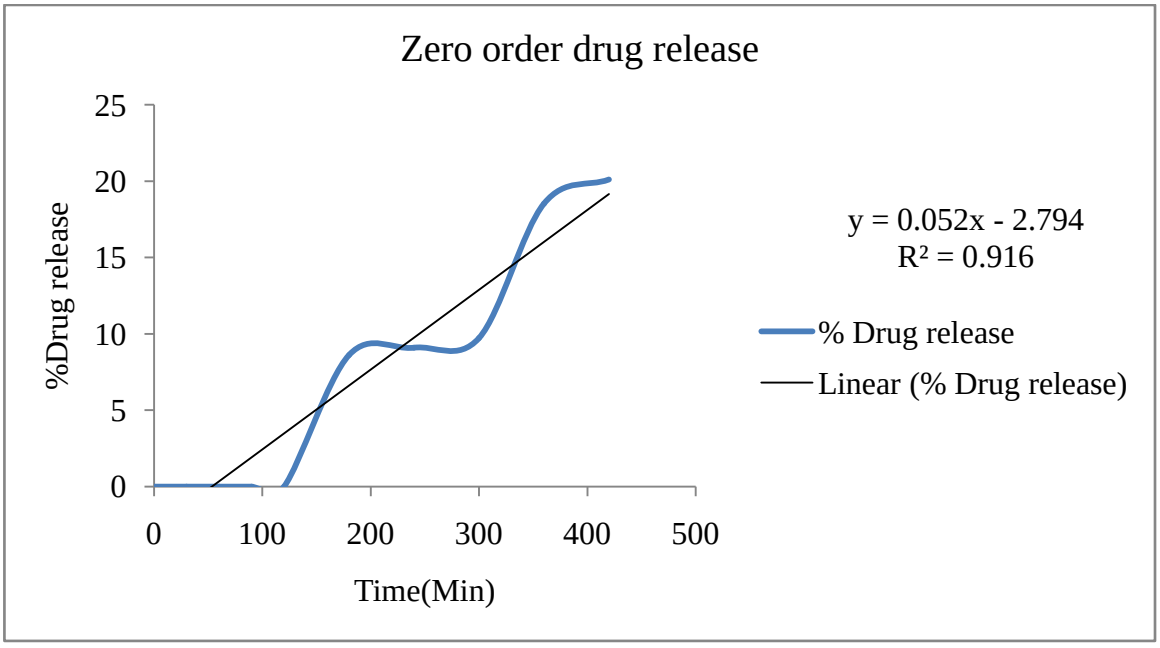


Fig: 75. Time (Min) Vs %drug release

Table: 72.First order drug release in phosphate buffer pH 6.8 (FSC2 35% thickness 8%)

Time(Min)	Log % drug release remaining
0	0
30	0
60	0
90	0
120	0
180	1.96
240	1.96
300	1.95
360	1.91
420	1.90

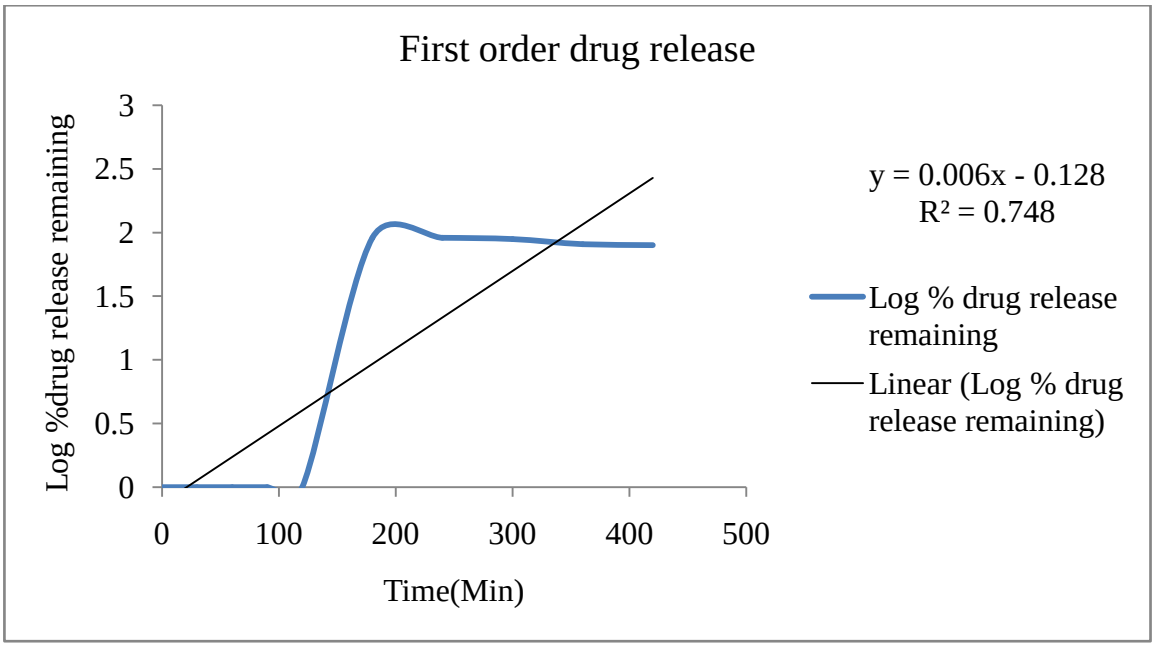


Fig: 76. Time (Min) Vs Log %drug release remaining

Table: 73.Higuchi kinetic model in phosphate buffer pH 6.8 (FSC2 35% thickness 8%)

Square root of time(Min)	% Drug release
0	0
5.47	0
7.75	0
9.49	0
10.95	0
13.41	8.62
15.49	9.10
17.32	9.73
18.97	18.53
20.49	20.10

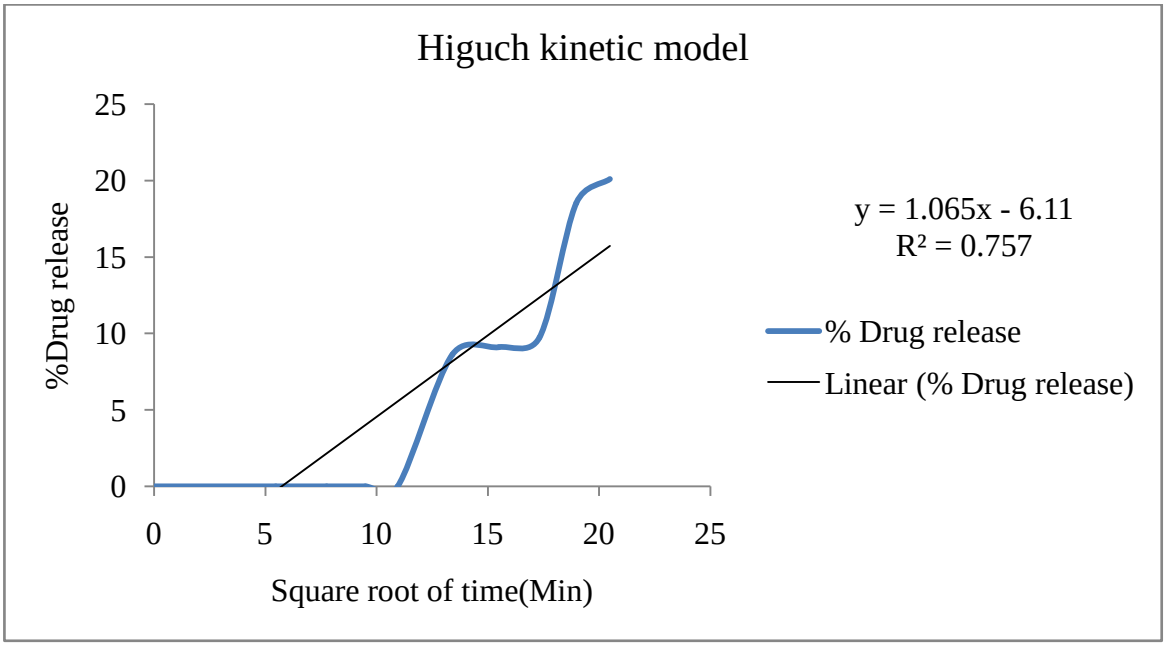


Fig: 77. Square root of time (Min) Vs %drug release

Table: 74.Korse-meyer Peppas model in phosphate buffer pH 6.8 (FSC2 35% thickness 6%)

Log time(Min)	Log% drug release
0	0
1.47	0
1.78	0
1.95	0
2.08	0
2.25	0.936
2.38	0.959
2.48	0.989
2.55	1.27
2.62	1.30

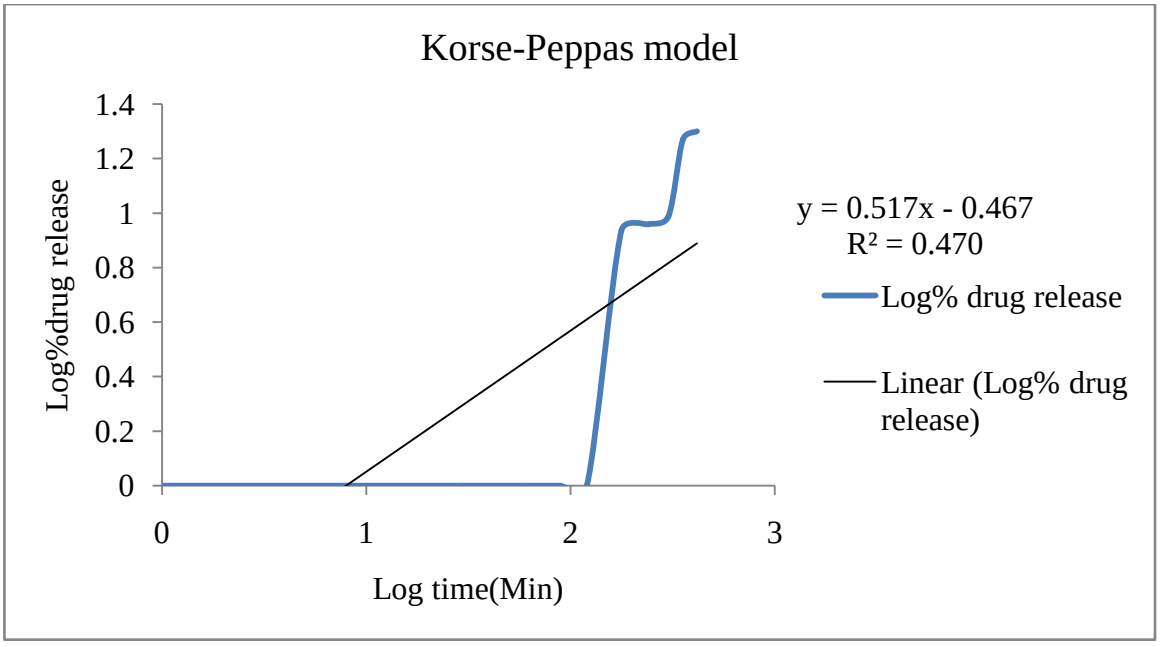


Fig: 78. Log time (Min) Vs Log% drug release

Table: 75.Kinetic data in phosphate buffer pH 6.8 (FS2 35% thickness 8%):

Zero order		First order		Higuchi model		Korse-meyer Peppas model	
r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
0.92	0.05	0.75	0.006	0.76	1.07	0.47	0.52

CHAPTER-7

7. CONCLUSION

7. CONCLUSION:

In the present investigation, combination of cationic and anionic polymer was used to sustain the drug release in the form of coated tablet with a view to maximize its therapeutic effect for prolonged period of time. From the preformulation study, the selected drug Pantoprazole was evaluated for its identity and purity and found to be pure, and drug melting point was found to be 196^0c which is closer to the value reported in literature .From the compatibility study there was no drug-polymer interaction found among the drug–polymer and excipient used .Viscosity study reveals that chitosan has the highest viscosity at 1 rpm as compared to sodium alginate, chitosan, carbopol and sodium CMC. From the UV analysis it is concluded that, UV spectroscopic method can be used for analyses the drug in formulating. From the result of physical properties of the drug excipients mixture, it is found that the mixture has good flow properties. The results of the physicochemical evaluation of the tablet like hardness, friability, thickness, weight variation and drug content were was found to be within the acceptable limit which is compiled the official requirement as per IP. The swelling behaviour of the tablet shows that polymer with higher concentration had higher swelling index. The mucoadhesive strength of the tablet is also increased with the increasing adhesion time. Formulation containing single polymer concentration (15% w/w) shows release property both in pH 6.8& 7.4.; releasing about 43.16& 45.23 within a period of 6 hour. Formulation at the polymer concentration of (35% w/w) shows suitable sustain release property both in pH 6.8 & pH 7.4., releasing about 79.60% & 72.60 % of drug release within a period of 6 hour. From the in-Vitro release study it is evident that formulation containing 1:1 ratio of polyelectrolyte complex has the property of sustaining the drug release compared to the single polymer alone. From the release study, It is also evident that

the formulation satisfy the drug release closer to the marketed enteric coated tablet with profound ability to sustain the drug release for sufficiently long period of time, in phosphate buffer media (pH 6.8), thereby maximizing the therapeutic effect of the drug in condition of hyperacidity .

Future prospects:

In-vivo pharmacokinetic study of the developed formulation was left out for future study which will be invaluable to predict the in-vivo performance of the dosage form using animal models. Also Gamma-scintigraphy study of the developed formulation was left out to exactly predict the site, movement and disintegration of the dosage form specifically in the upper intestinal pH conditions. The real time stability study of the developed formulation need to be performed to ascertain whether the stability of the drug remain unaffected throughout its storage period. Further SEM study left out to determine the surface topography of the final formulations after appropriate period of dissolution study.

CHAPTER-8

8. REFERENCES

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