FORMULATION AND *INVITRO* EVALUATION OF PROMETHAZINE HCL RAPID DISSOLVING TABLETS.

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: CHAITHRA.S.S

REG.No.261710251

Under the Guidance of

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ASSOCIATE PROFESSOR

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J.K.K. NATTARAJA COLLEGE OF PHARMACY

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *INVITRO* EVALUATION OF PROMETHAZINE HCL RAPID DISSOLVING TABLETS ",** submitted by the student bearing **EG.No.261710251** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

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DECLARATON

I do hereby declared that the dissertation **"FORMULATION AND *INVITRO* EVALUATION OF PROMETHAZINE HCL RAPID DISSOLVING TABLETS ",** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2018-2019, under the guidance and supervision of **Mr. K. Jaganathan, M.Pharm.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **CHAITHRA.S.S**

Date: **REG.No.261710251**

Dedicated to Parents,

Teachers&

My Family

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“FORMULATION AND *INVITRO* EVALUATION OF PROMETHAZINE HCL RAPID DISSOLVING TABLETS ”

LIST OF ABBREVIATIONS

ODTs	: Orodispersible tablets
RDTs	: Rapid dissolving tablets
Polyplasdone XL	: Crospovidone
Ac-Di-Sol	: Crosscarmellose sodium
SSG	: Sodium starch glycolate
BP	: British Pharmacopoeia
IP	: Indian Pharmacopoeia
USP	: United States Pharmacopeia
FTIR	: Fourier Transform Infrared
IR	: Infrared
SD	: Standard Deviation
Rpm	: Revolutions per minute
UV	: Ultraviolet
g	: Gram
mg	: Milligram
mm	: milli meter
µg	: Microgram
pH	: Negative logarithm of hydrogen ion concentration
min	: Minutes
Conc.	: Concentration
sec	: Seconds
cc	: Cubic centimeter
kg	: Kilogram

MCC	: Microcrystalline cellulose
%	: Percentage
^{o}C	: Degree Celsius
nm	: Nanometer
FDA	: Food and drug administration of USA
FDTs	: Fast dissolving tablets
q. s	: Quantity sufficient
PF1	: Promethazine HCl rapid dissolving tablets prepared by using 2% SSG
PF2	: Promethazine HCl rapid dissolving tablets prepared by using 3.5% SSG
PF3	: Promethazine HCl rapid dissolving tablets prepared by using 5% SSG
PF4	: Promethazine HCl rapid dissolving tablets prepared by using 2 % Crosscarmellose sodium
PF5	: Promethazine HCl rapid dissolving tablets prepared by using 3.5 % Crosscarmellose sodium
PF6	: Promethazine HCl rapid dissolving tablets prepared by using 5 % Crosscarmellose sodium
PF7	: Promethazine HCl rapid dissolving tablets prepared by using 2 % Crospovidone
PF8	: Promethazine HCl rapid dissolving tablets prepared by using 3.5 % Crospovidone
PF9	: Promethazine HCl rapid dissolving tablets prepared by using 5 % Crospovidone

ABSTRACT

Aim: The aim of the work is an attempt to made formulation of rapid dissolving tablets of Promethazine HCl by direct compression method with the aid of superdisintegrant addition.

Method: Rapid dissolving tablets of Promethazine HCl were prepared by direct compression. Nine formulations were developed using three different superdisintegrants in varying concentrations in such a way that total weight of the tablet remains the same. The drug-polymer incompatibility was ruled out by FTIR studies. All the formulated tablets were subjected for pre and post-compression evaluation parameters. A comparison of *in vitro* drug release of optimized formulation (PF9) was compared with marketed product (Phenargan).

Results: From the FTIR studies, the drug-polymers computability was confirmed. All the formulated tablets were shown satisfactory results which complies with official limits.

Conclusion: Among the nine formulations, the formulation containing 5% crospovidone (PF9) showed highest drug release of 98.43% than other formulations. A comparison of *in vitro* drug release was made with marketed product of Promethazine HCl (Phenargan) which shows 93% drug release in 1 hour. From this study we can made the conclusion that formulated tablets of Promethazine HCl containing crospovidone are better and effective than conventional tablets to meet patient compliance and give fast relief from vomiting and emesis.

Keywords: Formulation; FTIR studies; *In vitro* drug release; Promethazine HCl; Rapid dissolving tablets; Superdisintegrant; etc.

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1. INTRODUCTION

1.1 INTRODUCTION TO RAPID DISSOLVING TABLETS

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance[1].

The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamic characteristics of drugs[2, 3].

These tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However, of all the above terms, United States of pharmacopoeia (USP) approved these dosage forms as ODTs (orally

disintegrating tablets). Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing. United States of Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute[4, 5.]

❖ **Characteristics of rapid dissolving tablets[6,7]**

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.
- Be compatible with other excipients used.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.
- Ease of administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.

- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

❖ **Benefits of rapid dissolving tablets[8,9]**

- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient especially for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of these tablets helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Rapid dissolution and absorption of drug, which may produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid form.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of tablets.

- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

❖ **Limitations of rapid dissolving dissolving tablets[9]**

- The tablets may leave unpleasant taste or grittiness in mouth if not formulated properly.
- The tablets usually have low hardness. So, they are friable and/or brittle and are difficult to handle. They often require specialized peel-off blister packaging and careful handling required.
- Delivery of drug from the fast dissolving formulation would not expected to avoid first pass metabolism since the unit disintegration rapidly and the drug would be swallowed.

1.2 CHALLENGES IN FORMULATING RAPID DISSOLVING TABLETS

- **Palatability[10,11]**

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient"s oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

- **Mechanical strength[12]**

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow

them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee and DuraSolv® by CIMA labs.

- **Hygroscopicity[10,13]**

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

- **Amount of drug[13]**

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

- **Aqueous solubility[14]**

Soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

- **Size of tablet[12]**

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size is both easy to take and easy to handle.

1.3 METHODS FOR PREPARING RAPID DISSOLVING TABLETS[15,16,17]

(a) Tablet Molding

Tablet produced by moulding are solid dispersion. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Moulding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compressing moulding). The solvent is then removed by air drying. Such tablets are less compact than compressed tablets and posses a porous structure that hastens dissolution.

The heat-moulding process involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mould to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) pouring the suspension into the blister packaging; well solidifying the agar solution at room temperature to form a jelly and drying at 30ºC under vacuum. Moulded tablets typically do not posses great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

(b) Spray drying

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and fine powders can be produced. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate, crosscarmellose, crospovidone are used as a

superdisintegrants. Disintegration and dissolution was further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g. sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder have been reported to disintegrate in less than 20 seconds in an aqueous medium.

(c) Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

(d) Freeze-Drying or Lyophillization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

(e) Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexamethelene tetramine, camphor, etc.) are added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials are then removed via sublimation, which generates porous structures. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

(f) Direct Compression

From the pharmaceutical manufacturer‟s point of view, direct compression is the simplest most cost-effective tablet manufacturing procedure. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations.

(g) Superdisintegrants addition

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are crosscarmelose, crospovidone and sodium starch glycolate,

which are a cross linked cellulose, cross-linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets.

Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch gycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants. The list of commonly used superdisintegrants with their description is shown in Table 1.1

Mechanism of Superdisintegrants:

There are four major mechanisms for tablet disintegration as follows:

1. Swelling

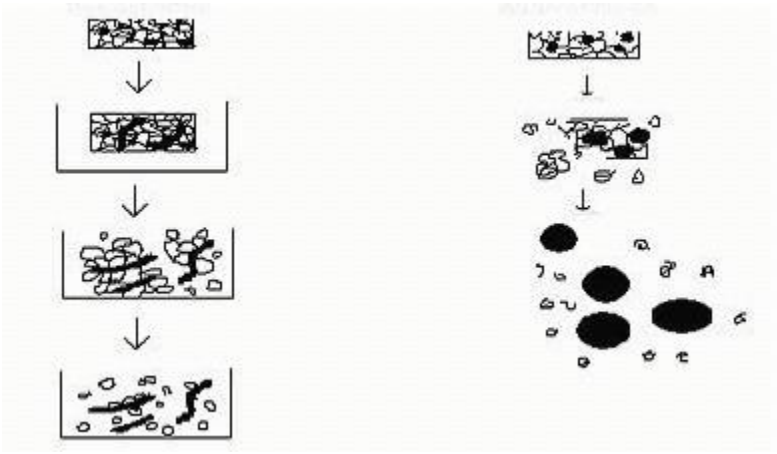
Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

2. Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards

aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. The wicking and swelling process of disintegration is shown in Fig. 1.1.

WICKING **SWELLING**



. **Fig. 1.1** Disintegration by wicking and swelling process

3. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrants attempts to explain the swelling of tablet made with „nonswellable" disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size

of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied. Disintegration of tablets by deformation and repulsion is shown in Fig. 1.2.

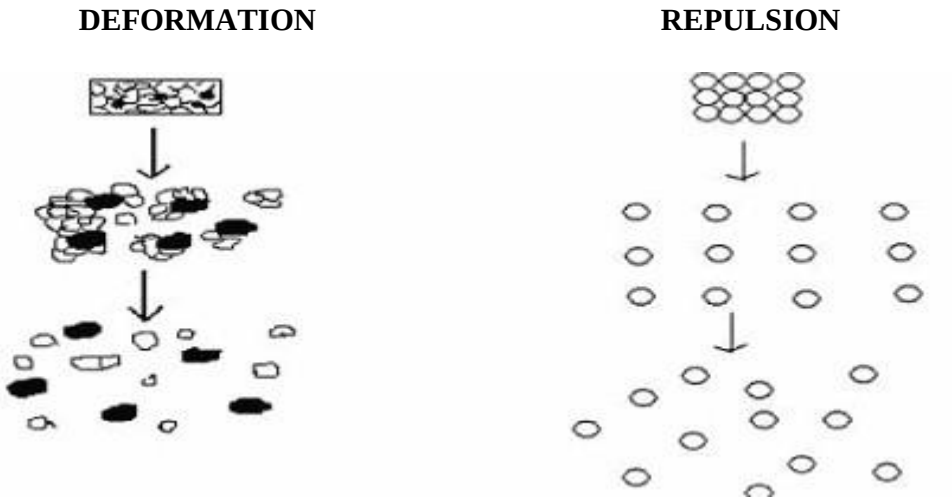


Fig. 1.2 Disintegration by deformation and repulsion process

(h) Sugar-based Excipients

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose, isomalt and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar based materials.

Table 1.1 List of super disintegrants

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked Cellulose	Swells 4-8 folds in < 10 seconds, acts by swelling and wicking both	Swells in two dimensions, used for direct compression or granulation
Crospovidone Crospovidone M® Kollidon® Polyplasdone	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel	Crosslinked Starch	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural superdisintegrant		Does not contain any starch or sugar, used in nutritional products
Calcium silicate		Wicking action	Highly porous, 20-40%

(i) Using acid treated yeast cell wall

Natural materials should be useful as pharmaceutical additives from the perspective of resource utilization and safety. Acidified brewers‟ yeast cell wall (AYC) has been examined with respect to novel applications as it can be used as an aqueous coating material for tablets and granules. In accordance with these properties of AYC, AYC maintains the baggy structure of the original yeast. In water, AYC is dispersed as independent particles with a surface hydrogel layer. Water is included within the structure unlike other polymers.

(j) Using hydroxyl waxy binders

This work describes a new approach to prepare fast dissolving tablets with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

(k) Melt granulation technique

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, apparatus of choice are the high shear mixers, where the product temperature is raised above the melting point of the binder either by a heating jacket or when the impeller speed is high enough, by the heat of friction generated by the impeller blades.

(l) Cotton candy process

The cotton candy process is also known as the candy floss process and forms the basis of the technologies such as Flash dose (Fuisz technology). An ODT is formed using a candy floss or shear form matrix and the matrix is formed from

saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then partially recrystallised to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently

(m) Suspension spray coating method

To obtain rapid disintegration granules (RDGs), a saccharide, such as trehalose, mannitol, or lactose, was spray coated with a suspension of corn starch using a fluidized-bed granulator (suspension method). As an additional disintegrant, crospovidone, light anhydrous silicic acid or hydroxy propyl starch was also included in the suspension.

1.4 PATENTED TECHNOLOGIES FOR RAPID DISSOLVING TABLETS[18-21]

❖ **Zydis technology**

Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Thirteen products are currently available using Zydis technology. In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. On the worldwide market, other Zydis formulations are available for oxazepam, lorazepam, loperamide and enalapril.

A Zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds.3 The Zydis formulation is

also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. The Zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form. In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch.

- **DuraSolv technology**

DuraSolv is Cima's second-generation fast dissolving tablet formulation. DuraSolv product is thus produced in a fashion similar to OraSolv; DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials.

The newest DuraSolv formulation, NuLev, is actually dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such DuraSolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity.

- **OraSolv technology**

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste-masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or

flavors; both coating the drug powder and effervescence are means of taste-masking in OraSolv. This technology is frequently used to develop over-the-counter formulations. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. The major disadvantage of the OraSolv formulations, its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets.

❖ **Flashdose technology**

Flash dose tablets consist of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing and are of two types:

- Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.
- Dual floss consists of a first shear form carrier material (termed "base floss", contains a carrier and at least one sugar alcohol generally sorbitol) and a second shear form binder matrix ("binder floss", contains a carrier and xylitol).

In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

❖ **WOW tab technology**

WOW tab technology is patented by Yamanouchi Pharmaceutical WOW means "without water". This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, mannitol) and granulated with a high mouldability saccharide (e.g. maltose, sorbitol) and compressed into tablets. The WOWTAB product dissolves quickly in 15 seconds or less. The WOW in WOWTAB signifies the tablet is to be given with out Water. Two WOWTAB formulations currently on the U.S. market are Benadryl Allergy & Sinus FASTMELT and Children's Benadryl Allergy & Cold FASTMELT.

❖ **Flashtab technology**

The Flashtab technology is yet another fast dissolving/disintegrating oral tablet formulation. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute.

❖ **Frosta technology**

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

❖ **LYOC technology**

It is patented by PHARMALYOC. Oil in water emulsion is prepared and placed directly in to blister cavities followed by freeze drying. Non- homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

❖ **QUICKSOLV technology**

This technology is patented by Janssen Pharmaceutical. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

❖ **AdvaTab technology**

AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be combined with Eurand‟s complimentary particle technologies like its world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

❖ **OraQuick technology**

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology known as Micro Mask, has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and

therefore leads to faster and more efficient production. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics and anti-infectives.

❖ **Advantol™ 200**

Advantol™ 200 is a directly compressible excipients system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma‟s Advantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust “soft-melt” tablet. The list of commercially available fast dissolving tablets is shown in Table 1.2

Table 1.2 List of commercially available Orodispersible/FDT tablets

Trade Name	Active Drug	Manufacturer
Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca,Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA

2. AIMS AND OBJECTIVES

Antiemetic drugs like Domperidone, Ondensetron hydrochloride, Granisetron hydrochloride, Promethazine hydrochloride have the oral problems like difficulty in swallowing, less oral bioavailability, first pass metabolism in conventional tablet dosage forms. To overcome such problems the antiemetic drugs can be formulated in the form of fast dissolving tablets where the drug is rapidly disintegrated in mouth within fraction of seconds and improves the oral drug bioavailability. Rapid dissolving tablets can be prepared by methods like direct compression, wet granulation, sublimation, effervescent methods along with superdisintegrants to increase *in vitro* dispersion time. Some of the newer methods to formulate quick release dosage forms include Zydis, Orasolv, Flashtab, Wowtab, oraquick, Ziplet, etc.

Promethazine HCl is a first generation H1 receptor antagonist used medically as an antihistamine and antiemetic. It is chemically (RS)-dimethyl [1-methyl-2-(phenothiazone-10-yl) ethyl] amine hydrochloride is an effective and well tolerated antiemetic that has been associated with a wide variety of chemotherapy and radiotherapy regimens, but in conventional dosage forms it undergoes first pass metabolism where the oral bioavailability (88%) was reduced to 27%.

Hence, in the present study an attempt has been made to formulate rapid dissolving tablets of Promethazine HCl by direct compression method using three superdisintegrants sodium starch glycolate, (SSG) crosscarmellose sodium and crospovidone, microcrystalline cellulose (MCC) as diluent with other excipients like sweetener and flavour with a view to develop a convenient means of administration to those patients suffering from difficulties in swallowing, nausea and motion sickness.

❖ **Objectives of the present work**

- To study the preformulation factors of Promethazine HCl such as, solubility, melting point, pH, pKa, λ_{max} and standard calibration curve of drug in phosphate buffer pH 6.8.
- To study the drug-polymers compatability by FT-IR spectroscopy.
- To formulate fast dissolving tablets of Promethazine HCl using superdisintegrants in different ratios by direct compression technique.
- To study the pre-compression parameters like bulk density, tapped density, angle of repose, carr's index and haunser ratio for prepared tablet formulations
- To evaluate prepared tablets by different post-compression parameters such as thickness, hardness, friability, *in vitro* dispersion time, content uniformity, weight uniformity, wetting time, water absorption ratio and *in vitro* dissolution study.
- To study *in vitro* dissolution of rapid dissolving tablets of Promethazine HCl in phosphate buffer pH 6.8 solution.

2.1 PLAN OF WORK

1. Literature survey
2. Selection of drug and polymers
3. Preformulation studies
   - Solubility
   - Melting point
   - Determination of λ_{max}
4. Preparation of standard calibration curve of Promethazine HCl
5. Formulation design of rapid dissolving tablets of Promethazine HCl by direct compression method using different superdisintegrants in different concentrations.
6. Drug- Polymer Compatability by FT-IR studies.

7. Evaluation of rapid dissolving tablets of Promethazine HCl

❖ Pre-compression parameters

- Angle of repose
- Bulk density
- Carr's index
- Haunser ratio

❖ Post-compression parameters

- Thickness
- Hardness
- Friability
- Weight variation
- *In vitro* dispersion time
- Wetting time
- Water absorption ratio
- % Drug content
- *In vitro* dissolution study

3. REVIEW OF LITERATURE

Dina NM *et al.*, [22] formulated orally disintegrating tablets by using spray dried excipients base. The purpose of this study is to assess the suitability of spray dried excipient base in the formulation of orally disintegrating tablets (ODT) of Valdecoxib (low aqueous solubility) and Metoclopramide (high aqueous solubility) spray dried excipients base was prepared using Scientech spray drier. Super disintegrants (such as Ac-Di-Sol, kollidon CL, sodium starch glycolate), diluent (mannitol) along with sweetening agent (aspartame) were used in the formulation of the tablets.

Mishra DN *et al.*, [23] formulated rapidly disintegrating oral tablets of Valdecoxib. For formulation, they used sodium starch glycolate, croscarmellose sodium and crospovidone as superdisintegrants and mannitol as diluent. The formulated tablets were evaluated for hardness, friability, weight variation, disintegration time and *in-vitro* dissolution studies. Finally it was concluded that the fast dissolving tablets of the poorly soluble drug can be made by direct compression technique using selective superdisintegrants.

Shishu R *et al.*, [24] prepared rapidly disintegrating tablets of Chlorpheniramine maleate using taste masked granules. The taste masked granules were prepared using amino alkyl methacrylate copolymers (Eudragit E-100) by the extrusion method. *In vitro* release profile obtained at pH 6.8 indicate that perceivable amount of drug will not be released in saliva while high percent release (more than 80% in 30 min) would be obtained at acidic pH 1.2 of the stomach. These taste masked granules were directly compressed into tablets using sodium starch glycolate as a superdisintegrant.

Malke S *et al.*, [25] prepared fast dissolving tablets of Oxcarbazepine containing Avicel

PH 102 as a diluent and Ac-Di-Sol as a superdisintegrants by wet granulation process. A modified disintegration method was used for studying disintegration. Since the drug is poorly water soluble, drug release was tested in various media and the effect of surfactant on drug release was studied.

Swamy PV *et al*., [26] designed Orodispersible tablets of Meloxicam with a view to enhance patient compliance. A combination of superdisintegrants i.e., sodium starch glycolate-crospovidone and sodium starch glycolate-croscarmellose sodium were used with directly compressible mannitol to enhance mouth feel. Based on *in vitro* dispersion time (approximately 10 sec), two formulations (one from each batch) were tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short term stability (at 45°C for 3 weeks) and drug-excipients interaction (IR spectroscopy). Among the two formulations, the formulation containing 2% sodium starch glycolate and 1.5% crosscarmellose sodium was found to be better formulation.

Setty CM *et al*., [27] prepared Aceclofenac fast dispersible tablets by direct compression method using different superdisintegrants, crosscarmellose, sodium starch glycolate and crospovidone and their effect on wetting time, disintegration time, drug content, *in vitro* drugs release and stability parameters had been studied. Disintegration time and dissolution parameters decreased with increase in the level of croscarmellose sodium, where as, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycolate in tablets. However the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on the aggregate size in the dissolution medium.

Jain CP *et al*., [28] prepared fast dissolving tablets of Valsartan using different superdisintegrants by direct compression method, evaluated for physicochemical

properties and *in vitro* dissolution. Effect of disintegrant on disintegration behavior of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing crospovidone.

Gohel MC *et al.*, [29] prepared mouth dissolving tablets of Nimesulide by preparing granules containing Nimesulide, camphor, crospovidone and lactose and then camphor was sublimed from granules, alternatively, first tablets were prepared and then camphor was sublimed by vacuum. Sublimation of camphor from tablets resulted in superior tablets as compared with tablets prepared from granules that were exposed to vacuum.

Patel DM *et al.*, [30] developed fast dissolving tablets of Etoricoxib; a 3^2 full factorial design was applied to investigate the combined effect of two formulation variables: amount of menthol and crospovidone. Granules containing Etoricoxib, menthol, crospovidone, aspartame and mannitol were prepared by wet granulation technique. Menthol was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed in to tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The result of multiple regression analysis indicated that for obtaining FDTs optimum amount of menthol and higher percentage of crospovidone should be used.

Rangasamy M *et al.*, [31] prepared fast dissolving tablets of Terbutaline sulfate were by the direct compression method after incorporating superdisintegrants such as Explotab, Ac Di-Sol and Polyplasdone XL in different concentrations. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, wetting time, drug content, water absorption ratio, *in vitro* dispersion time, *in vitro*

disintegration time and *in vitro* drug release. Among all, the formulation (containing 5% w/w concentration of Polyplasdone XL) was the best formulation, which releases up to 99.33% of the drug in 10 min.

Pandey S *et al*., [32] formulated and optimized fast dissolving tablets of Diclofenac sodium by direct compression method, using super disintegrants such as cross linked carboxy methyl cellulose (Ac-Di-Sol), sodium starch glycolate (Explotab) and crospovidone (Polyplasdone XL) in different concentrations. They reported that tablets containing Ac-Di-Sol showed better disintegrating character along with rapid release.

Furtado S *et al*., [33] prepared Orodispersible tablets of Famotidine using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, *in vitro* and *in vivo* dispersion, mouth feel and *in vitro* dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile.

Bi. Y *et al*., [34] carried out preparation and evaluation of a compressed tablet, rapidly disintegrating in the oral cavity. They had chosen microcrystalline cellulose and L-HPC as disintegrants and Ethenzamide and Ascorbic acid as poorly and easily soluble model drugs. The properties of these tablets, such as hardness, porosity, wetting time, water uptake and disintegration time were determined. When the MCC/L-HPC ratio was in the range of 8:2 to 9:1, the shortest disintegration time was observed.

Bhalero AV *et al.,* [35] carried out development and evaluation of Clonazepam fast dissolving tablets using superdisintegrants and solid dispersion technique by using PVP K-30 and combination of 5% w/w crosscarmellose sodium and 5% w/w sodium starch glycolate and they reported that so formulated tablets showed least dispersion

time of 8seconds and faster dissolution rate.

Sharma S *et al*., [36] carried out formulation and characterization of fast dissolving tablets of Promethazine thecolate by direct compression with Ac-Di-Sol, sodium starch glycolate and crospovidone in different concentrations and it has been found that tablets containing Ac-Di-Sol showed superior organoleptic properties, along with excellent *in vitro* and *in vivo* dispersion time and drug release, as compared to conventional tablets.

Gattani SG *et al.*, [37] developed formulation and evaluation of mouth dissolving tablets of Ondensetron hydrochloride using natural superdisintegrants along with Ac-Di-Sol, primogel, polyplasdone XL and they reported that Ac-Di-Sol was found to be more effective than others due its high swelling capacity.

Gnanaprakash K *et al*.,[38] carried out formulation and evaluation of fast dissolving tablets of Valdecoxib with β-cyclodextrin using superdisintegrants polyvinyl pyrrolidine, sodium carboxy methyl cellulose and crospovidone by direct compression and they reported that increased proportion of polymers, superdisintegrants and solubilizing agents have shown enhanced cumulative drug release rate 99.88% within 10 minutes.

Parmar RB *et al*., [39] worked on formulation and evaluation of Domperidone fast dissolving tablets by using superdisintegrants Avicel PH 102 and sodium starch glycolate by direct compression and they found a good hardness of 3kg/cm2, disintegration time of 27 seconds and *in vitro* drug release is 95% within 30 minutes as compared to the marketed product, which gives quick release from emesis.

Nagendra kumar D *et al*., [40] studied formulation design of novel fast dissolving tablets of Granisetron hydrochloride using low and high compressible saccharides such as mannitol and sorbitol by direct compression. In this study the conclusion was

made that the formulated tablets have showed good *in vitro* drug release studies.

Na zhao *et al*., [41] made comparison of three different classes of superdisintegrants primogel, polyplasdone XL, Ac-Di-Sol in promoting aspirin tablets disintegration and dissolution and they reported that Ac-Di-Sol was found to disintegrate tablets rapidly into small particles.

Singh J *et al*., [42] developed optimization and formulation of orodispersible tablets of Meloxicam by non-aqueous wet granulation using crospovidone and mannitol and they showed disintegration time of 32 seconds, drug content 98.5% and fast drug release rate of 99.5% within 30 minutes as compared with conventional tablet.

Singh SK *et al*., [43] made fast disintegrating combination tablets of Omeprazole and Domperidone in nine formulations with three different levels of superdisintegrants, Kollidon CL, Ac-Di-Sol and sodium starch glycolate. The tablets were prepared using mannitol as diluent and sodium saccharin as sweetening agent and the were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. Drug content was estimated by using HPLC method and assay of sample was compared with standard drugs. From the results obtained, they concluded that formulation prepared with 4.76% of Ac-Di-Sol showed disintegration time of 15 seconds which is faster than other formulations.

Madan J *et al*., [44] formulated fast dissolving tablets of freeze dried Aloe Vera Gel by dry granulation method with three superdisintegrants. The tablets were evaluated for crushing strength, disintegration time, wetting time, friability, drug content and drug release. A 3^2 full factorial design was applied to investigate the combined effect of two formulation variables-amounts of microcrystalline cellulose and mannitol. from this investigation they reported that satisfactory fast dissolving Aloe Vera tablets can be formulated by the factorial design.

Aithal K *et al*., [45] designed Granisetron hydrochloride fast dissolving tablets using superdisintegrants by direct compression. Evaluation is done for both powder blend of tablet in respect to bulk density, tapped density angle of repose, carr's index, hardness, friability, weight variation, thickness, wetting time, disintegration time, drug content and *in vitro* dissolution studies.

Chaudhari RD *et al*., [46] formulated and evaluated the taste masked orodispersible dosage form of Levocetrazine dihydrocholride. In the work an attempt was made to mask the taste, by complexation technique using ion exchange resin, tulsion 335 to formulat an orodispersible dosage form. The tablet were evaluated for the drug content, content uniformity, weight variation, hardness, friability, water absorption ratio, *in vitro* and *in vivo* disintegration time and *in vitro* drug release. The tablet disintegrated *in vitro* and *in vivo* within 18 and 22 seconds respectively. The result showed that Levocetrazine dihyrocholride was successfully taste masked and formulated into orodispersible dosage form as an alternative to conventional tablets.

Raghavendra NG *et al*., [47] prepared fast dissolving tablets of some ayurvedic churnas by vacuum drying method using ammonium bicarbonate as subliming agent in varying concentrations. The blends were evaluated for pre-compression parameters and formulations were evaluated for post-compression parameters and stability studies were conducted for three months. In all the six formulations, friability is less than 1%, hardness was found to be 4-4.50kg/cm^2. The formulation BLC3 shows less *in vitro* dispersion time 18 sec and formulation SC3 shows *in vitro* dispersion time of 20 sec. The stability studies results revealed that disintegration and wetting time of all the tablets decreased significantly.

Devi VK *et al*., [48] prepared orodispersible tablets of Fluconazole by sublimation method using ammonium carbonate, mannitol as diluent and polyethylene glycol as

binder, sodium saccharine as sweetener and magnesium stearate as a flow promoter. Prepared tablets were evaluated for their hardness, friability, weight variation, wetting time, disintegration time, content uniformity and dissolution studies.

Amin P *et al*., [49] formulated mouth dissolving tablets of Roxithromycin: indion 214 complex, Dicyclomine hydrochloride: indion 204 (0) complex and Montelukast sodium. Dose is 330, 80 and 5.19 mg respectively. They were prepared by direct compression using croscarmellose sodium, sodium starch glycolate, crospovidone and indion 414 were used as superdisintegrants. Complete taste masking of bitter drugs like Roxithromycin and dicyclomine hydrochloride was achieved using 1:5 and 1:3 ratio of indion 204 respectively. Prepared tablets were evaluated for quality control parameters like appearance, taste, mouth feel, hardness, weight variation, *in vitro* dispersion time, *in vivo* dispersion time, drug content and drug release. They concluded that indion 414 exhibited very good superdisintegrants action resulting in a cost effective formulation.

Babu *et al*., [50] prepared solid dispersions of Piroxicam in five superdisintegrants namely microcrystalline cellulose, crospovidone, pregelatinized starch, crosscarmellose sodium and with water soluble carriers polyvinyl pyrolidone and polyethylene glycol. Solid dispersions of Piroxicam in superdisintegrants gave a marked enhancement in its dissolution rate and dissolution efficiency. Solid dispersion in super disintegrants could be used as an effective and efficient technique for enhancing the dissolution rate of Piroxicam a poorly soluble drug.

Wen X *et al*., [51] prepared the formulation of an inclusion complex of β-cyclodextrin with Carvedilol. It was prepared by using convenient new method of microwave irradiation. Phase-solubility studies demonstrated the ability of β- cyclodextrin to complex with Carvedilol and increase drug solubility. The structure of inclusion

complex was determined by fluorescence spectroscopy and 1H NMR, 13C NMR measurements in solution. The solid inclusion was characterized by infrared spectroscopy, Differential scanning calorimetry (DSC) and element analysis. These experimental results confirmed the existence of 1:2 inclusion complex of Carvedilol with β-cyclodextrin, the formation constant of complex was determined by the fluorescence method.

Perissutti B *et al*., [52] developed fast release dosage form of Carbamazepine by melt granulation process using high shear mixture. The tablets were prepared by PEG-400 as binder, lactose monohydrate as hydrophilic filler and crospovidone as disintegrating agent. Analysis of physical mixture of powder was carried out by means of X-ray diffraction and DSC. The effect of intragrannular and extragrannular addition of crospovidone was also evaluated. The result showed that crospovidone enhance the remarkable dissolution rate of granulates in comparison of physical mixture and pure drug.

Madhusudan *et al*., [53] prepared solid dispersions of various compositions of Sulphamethoxazole using mannitol as carrier. Solid dispersion of Sulphamethoxazole – mannitol in the proportion of 1:2 prepared by melting and melt solvent were developed into tablet dosage forms by both wet granulation and direct compression methods. Solid dispersion tablets of melt solvent method prepared by direct compression method showed highest dissolution rate.

Sugimoto *et al*., [54] prepared tablets having both high porosity and practical strength, amorphous sucrose, which has good compatibility. Mannitol powder with freeze-dried amorphous sucrose was tableted at low compression and stored under certain conditions. The increase in the tensile strength of the tablet was due to crystallization of the amorphous sucrose and formation of new internal contact points in the tablet.

They concluded that this crystalline transition method is a very useful method to prepare a rapidly disintegrating tablet.

Chowdary *et al*., [55] prepared Ibuprofen dispersible tablets by employing potato starch, primogel, microcrystalline cellulose and pregelatinised starch, the tablets were evaluated for drug content of active ingredient, hardness, friability, disintegration time, uniformity of dispersion and dissolution rate. Tablets formulated employing primogel disintegrant and tablets formulated employing potato starch as internal disintegrant and primogel and pregelatinised starch as external disintegrants fulfilled the entire official and other requirements of dispersible tablets.

Sumiya K *et al*., [56] prepared orally-disintegrating tablets of Clonidine hydrochloride by the method of drying an aqueous suspension. The suspension was prepared using powdered lactose and the composition ratio was 2:1. The suspension was dried under 4oC (72 ± 15% RH). They observed that the orally disintegrating tablet of Clonidine hydrochloride was useful in a clinical situation for the preanesthetic medication of pediatric patients aged 1-2 yr.

Bolhuis GK *et al*., [57] prepared the solid dispersion by surface depositions of the poorly soluble and hydrophobic drug on the surface of the hydrophilic and highly swelling superdisintegrants. They found that the wet granulation of drug with sodium starch glycolate show a large increase in the solubility of the drug. The granules containing too high concentration of superdisintegrant showed low drug release from the tablets.

Abdelbary G *et al*., [58] prepared orally disintegrating tablets using a hydrophilic waxy binder. The problem of certain RDT is their low physical resistance and high friability. This work describes a new approach to prepare RDT with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder

(Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37 ºC and an HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used.

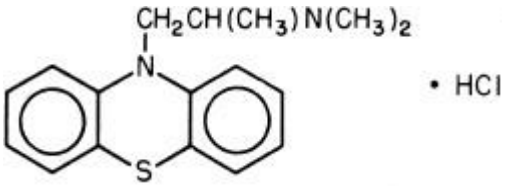
Takao M *et al*., [59] designed a novel fast-disintegrating tablet. Advantages of this formulation have sufficient hardness and can be manufactured by commonly used equipment. Saccharides can be divided into high- and low compressibility categories, and an appropriate material for fast-disintegrating tablets was created by taking advantage of this fact. To improve the compressibility of low-compressibility saccharides, particle modification was conducted by coating and granulating a low compressibility saccharide with a high one to enable the production of a fast disintegrating tablet.

Okuda Y *et al*., [60] Prepared new formulation for orally disintegrating tablets using a suspension spray coating method. The aim of this study was to design a new orally disintegrating tablet (ODT) that has high tablet hardness and a fast oral disintegration rate using a new preparation method. To obtain rapid disintegration granules (RDGs), a saccharide, such as trehalose, mannitol or lactose was spray-coated with a suspension of corn starch using a fluidized-bed granulator (suspension method).

3.1 DRUG PROFILE[61-64]

3.1.1 PROMETHAZINE HYDROCHLORIDE

Chemical structure :



Molecular formula : $C_{17}H_{20}N_2S$•HCl

Molecular weight : 320.88.

Chemical name : (RS)-N, N-dimethyl-1-(10H-phenothiazin-10-yl) propan-2-amine hydrochloride.

Solubility : Promethazine HCl as the hydrochloride salt is freely soluble in water and somewhat soluble in alcohol.

Melting point : 220-222ºC.

p^{Ka} and pH : 9.1 and 5.8.

Log P : 4.7

Dose : 10 mg to 25 mg and maximum dose per day is 25 mg.

Storage : Store in a cool dry place, away from direct heat and light.

Beer's Range : 2-12µg/ml.

- **Properties:** Promethazine HCl appears as a white to faint yellow crystalline powder that is practically odourless. Slow oxidation may occur upon prolonged exposure to air usually causing blue discoloration.
- **Mechanism of action:** Promethazine HCl is a phenothiazine, is an H_1-antagonist with anticholinergic, sedative, antiemetic effects and some local anaesthetic properties. It is used as an antiemetic to prevent motion sickness. Like other H_1-

antagonists, promethazine competes with free histamine for binding at H_1-receptor sites in the GI tract, uterus, large blood vessels and bronchial muscle. The relief of nausea appears to be related to central anticholinergic actions and may implicate activity on the medullary chemoreceptor trigger zone.

- **Pharmacokinetics:** Following oral administration, Promethazine HCl is completely absorbed, with absolute bioavailability of 25% due to first-pass metabolism. The apparent mean elimination half-life of Promethazine HCl generally ranges from 16 to 20 hours. It is metabolized by the cytochrome P450 2D6 (CYP2D6). Following oral dosing of Promethazine an average of 60% and 20% of total metabolites are recovered in the urine and feces, respectively. Promethazine HCl was 30% bound to plasma proteins, primarily with albumin. It is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg.
- **Contraindications:** Promethazine HCl is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, sedative hypnotics, including barbiturates, general anaesthetics, narcotics, narcotic analgesics, tranquilizers, etc.), and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine. Phenergan tablets and suppositories are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.
- **Adverse effects:** Adverse effects include restlessness, drowsiness and diarrhoea, hypotension. Hypertension, dizziness, headache and depression may occur and there are isolated reports of blood disorders, hypersensitivity reactions (rash, bronchospasm) and neuroleptic malignant syndrome. Promethazine stimulates

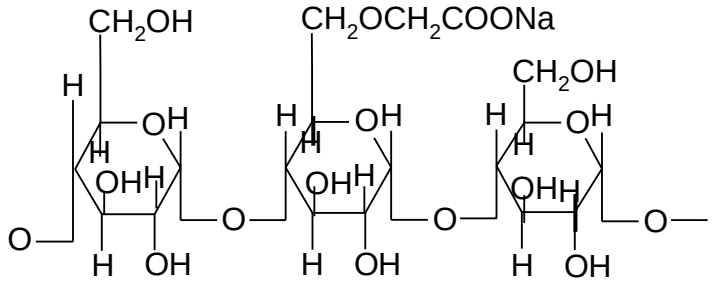
prolactin secretion and may cause galactorrhoea or related disorders. Transient increase in plasma aldosterone concentrations has been reported.

- **Drug interactions**: *In vitro* studies of cytochrome P450 isoenzymes using human liver microsoms indicate that neither Promethazine nor its metabolites are likely to affect metabolism of other drugs metabolized by cytochrome P450 isoenzymes. The interaction with ciprofloxacin on the pharmacokinetics of a single dose of Promethazine was studied. The C_{max} and AUC Promethazine of increased by 7-fold and 10-fold, respectively. These changes leads to decrease in blood pressure, increased drowsiness and increased in psychomotor impairment. Promethazine delayed the T_{max} of acetaminophen by 16 minutes. Consumption of alcohol with Promethazine HCl increases side effects.
- **Indications:** Promethazine HCl is used
    - In disorders of decreased gastrointestinal motility such as gastorparesis.
    - In gastro esophageal reflux disease.
    - In dyspepsia.
    - To stimulate gastric emptying during radiographic examinations.

3.2 EXCIPIENT PROFILES[65- 68]

3.2.1 SODIUM STARCH GLYCOLATE

Structural formula:



Synonyms **:** Explotab, Primogel.

Non-proprietary Name : BP-Sodium starch glycolate, USPNF-Sodium starch glycolate.

Functional category **:** Tablet and capsule disintegrant.

Chemical names **:** Sodium carboxymethyl starch.

Solubility **:** Practically insoluble in water, sparingly soluble in ethanol

Incompatibilities **:** Incompatible with ascorbic acid.

Description: Sodium starch glycolate is a white to off-white, odourless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 μm in diameter with some less spherical granules ranging from 10-35 μm in diameter.

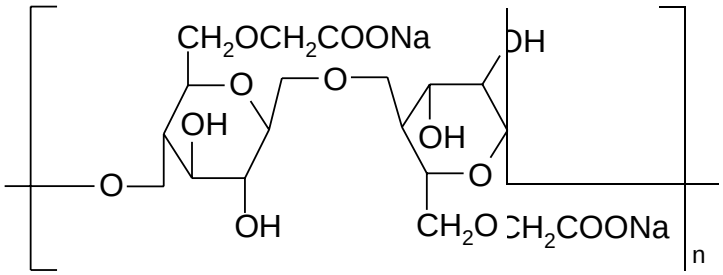
Stability and storage conditions: It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Safety: It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications: As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

3.2.2 CROSSCARMELLOSE SODIUM

Structural formula:



Synonyms : Ac-Di-Sol, Cross-linked carboxymethylcellulose sodium.

Non-proprietary name : USPNF: Crosscarmellose sodium.

Functional category : Tablet and capsule disintegrant.

Chemical names : Cellulose, carboxymethyl ether, sodium salt, cross-linked.

Molecular weight : 90000-700000.

pH (1% w/v dispersion) : 5.0-7.0.

Description: Crosscarmellose sodium occurs as an odourless, white coloured powder.

Solubility: Insoluble in water. Although crosscarmelose sodium rapidly swells to 4-8 times of its original volume on contact with water.

Storage condition: Crosscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with Crosscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 300ºC for 14 months.

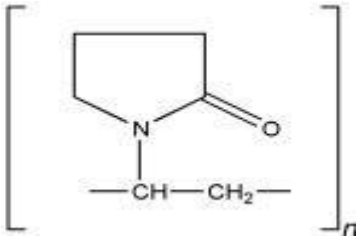
Incompatibilities: The efficacy of disintegrants, such as Crosscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain which contain hygroscopic material such as sorbitol.

Safety: Crosscarmellose is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially non toxic and non irritant material.

Applications: As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

3.2.3 CROSPOVIDONE

Structural formula:



Synonyms **:** Crosslinked povidone, E1202, Kollidon CL, Polyplasdone XL, Polyplasdone XL-10, PVPP and 1- vinyl-2-pyrrolidinone homopolymer.

Non-proprietary Names : BP-Crospovidone, PhEur-Crospovidonum, USPNF: Crospovidone.

Chemical name **:** 1-Ethenyl-2-pyrrolidinone homopolymer.

Molecular weight **:** $(C_6H_9NO)n$ >1 000 000.

Functional category **:** Tablet disintegrant.

Description: Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odourless and hygroscopic powder.

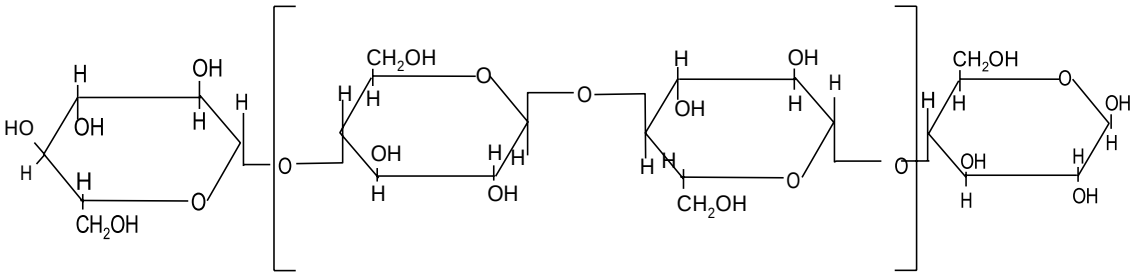
Stability and storage conditions: Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Applications in pharmaceutical formulation or technology: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration

in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.

3.2.4 MICROCRYSTALLINE CELLULOSE

Structural formula:



Microcrystalline Cellulose

Synonyms : Cellulose gel: Crystalline cellulose: Avicel PH101, 102.

Non-proprietary name: NF-Microcrystalline cellulose, USP- Microcrystalline cellulose.

Chemical names : Cellulose.

Empirical formula : $(C_6H_{10}O_5)n = 220$.

Molecular weight : 36,000(approx).

Density : Apparent density - 0.28g/cm^3; Tap density - 0.43g/cm^3.

Functional category : Tablet and capsule diluent, tablet disintegrant, suspending and viscosity increasing agent.

Description: Purified, partially depolymerised cellulose occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.

Solubility: Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.

Storage conditions: Stable, hygroscopic. Store in a well closed container.

Applications: Tablet binder/diluent, tablet disintegrant, tablet glidant.

3.2.5 ASPARTAME

Synonyms **:** APM, Sanecta, Aspartyl phenylamine methyl ester, Nutrasweet, Tri-sweet.

Non proprietary name : USP – Aspartame**,** IP – Aspartame**,** BP – Aspartame.

Chemical name **:** L-aspartic acid, L-phenylalanine.

Functional category **:** Sweetening agent.

Description: It occurs as white and almost odourless crystalline powder.

Solubility: Slightly soluble in ethanol (95%), sparingly soluble in water, solubility increases at higher temperature and at more acidic pH.

Stability and Storage Conditions: It is stable in dry conditions. In presence of moisture, hydrolysis occurs. Degradation also occurs during prolonged heat treatment. Bulk material should be stored in a well-closed container, in a cool, dry place.

Safety: The WHO has set an acceptable daily intake of 40 mg/kg body weight. Reported adverse effects are headache, grandmal seizures, memory loss, gastrointestinal and dermatological symptoms.

Applications: It is used as an intense sweetening agent in tablets, powder mixes and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste and has sweetening powder of 180-200 times that of sucrose.

3.2.6 TALC

Synonyms **:** Magsil Osmanthus, Magsil Star, Purtalc, Steatite.

Functional category : Glidant, tablet and capsule lubricant, anti- cackling agent.

Applications **:** It is used as a lubricant in solid dosage forms (1-10%), in topical preparations as dusting powder (90-99 %).

Stability : Talc is a stable material.

Solubility : Practically insoluble in dilute acids and alkalies, organic solvents and water.

Incompatibilities : Incompatible with quaternary ammonium compounds.

Description: It is a very fine, white to greyish-white coloured, odourless, impalpable, unctuous powder. It adheres to the skin, is soft to touch and free from grittiness.

.**Storage conditions:** It should be stored in a well-closed container in a cool, dry, place.

3.2.7 MAGNESIUM STERATE

Synonyms : Metallic stearic; magnesium salt.

Non-proprietary name: NF- Magnesium stearate; BP/EP- Magnesium stearate.

Empirical formula : $C_{36}H_{70}MgO_4$.

Chemical names : Octadecanoic acid; magnesium salt; magnesium stearate

Molecular weight : 591.3.

Density (He) : 1.03-1.08 g/cm^3

Bulk volume : 3.0-8.4 ml/g

Tapped volume : 2.5-6.2 ml/g

Functional category : Tablet and capsule lubricant.

Description: It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint characteristic odour and taste. The powder is greasy to touch and readily adheres to the skin.

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

Stability and storage conditions: Stable, non-self polymerizable. Store in a cool, dry place in a well closed container.

Incompatibilities: Incompatible with strong acids, alkalies, iron salts and with strong oxidising materials.

Safety: Described as inert or nuisance dust. OSHA has adopted limits of 15mg/m3 for the total dust and 5mg/m3 for the respirable fraction. Dust clouds of magnesium stearate may be explosive. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

Applications: Tablet and capsule lubricant, glidant and antiadherent in the concentration range of 0.25 to 2.0%.

4. MATERIALS AND METHODS

4.1 MATERIALS

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The double distilled water was used in all experiments.

Table 4.1 List of chemicals used with grade and supplier

SR. No.	Materials used	Grade	Manufacturer
1.	Promethazine HCl	API	Mayer healthcare Pharmaceuticals, Bangalore
2.	Microcrystalline cellulose	LR	S D fine chemical Ltd, Mumbai
3.	Sodium starch glycolate	LR	Shreeji chemicals, Mumbai
4.	Crosscarmellose sodium	LR	Shreeji chemicals, Mumbai
5.	Crospovidone	LR	Shreeji chemicals, Mumbai
6.	Talc	LR	S D fine chemical Ltd, Mumbai
7.	Magnesium sterarte	LR	S D fine chemical Ltd, Mumbai
8.	Aspartame	LR	Shreeji Chemicals, Mumbai
9.	Raspberry flavor	Pharma Grade	Micro labs, Bangalore
10.	Potassium dihydrogen orthophosphate	LR	S D fine chemical Ltd, Mumbai
11.	Sodium hydroxide	LR	S D fine chemical Ltd, Mumbai

Table 4.2 List of instruments used

SR. No.	Instrument	Manufacturer
1.	UV visible spectrophotometer	Shimadzu Corporation, Japan.
2.	FTIR spectrophotometer	IR-Affinity-1, Shimadzu, Japan.
3.	Electronic balance	Citizen scales Pvt. Ltd
4.	Digital pH meter	Digisun Electronics, Hyderabad
5.	Bulk density apparatus	Biological museum, Agra
6.	Tablet punching machine	Shakti, Ahmadabad
7.	Roche friabilator	Biological museum, Agra
8.	Tablet hardness tester	Pfizer
9.	Digital caliper	Aerospace
10.	USP dissolution XXIII apparatus	Electrolab TDL-08L
11.	Disintegration apparatus	Electrolab
12.	Hot air oven	Universal

4.2 METHODS

4.2.1 Preformulation studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Preformulation studies were performed on the drug (API), which included melting point determination, solubility and compatibility studies.

The following preformulation studies were performed for Promethazine HCl and polymers;

1. Determination of solubility

Solubility of Promethazine HCl was performed in solvents water and alcohol

2. Determination of melting point

Melting point of pure Promethazine HCl was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Promethazine hydrochloride by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100ºC min rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded. This was performed thrice and the average value was calculated.

3. Determination of λ_{max}

A solution of Promethazine HCl containing conc. 10µg/ml was prepared in phosphate buffer pH 6.8 and UV spectrum was taken using Shimadzu (UV-1800) spectrophotometer. The solution was scanned in the range of 200-400nm.

4.2.2 Formulation development[72, 73,74]

In this work, direct compression method with the aid of superdisintegrants was attempted for the formulation development of rapid dissolving tablets of Promethazine HCl. The Promethazine HCl tablets are available in 12.5mg, 25mg and 50mg doses in the market. Dose of 25 mg is selected for the present study.

Development of the formulation in the present study was mainly based on the type and concentration of polymers and the properties of the drug. Various polymers in different concentrations (2%, 3.5% and 5%) were used so as to get tablets with good physical properties. The formulation design of rapid dissolving tablets of Promethazine HCl is shown in Table 4.3

Table 4.3 Formulation design of Promethazine HCl rapid dissolving tablets

Ingredients(mg)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
Promethazine HCl	25	25	25	25	25	25	25	25	25
SSG	2.5	5	7.5	-	-	-	-	-	-
Crosscarmellose	-	-	-	2.5	5	7.5	-	-	-
Crospovidone	-	-	-	-	-	-	2.5	5	7.5
Aspartame	5	5	5	5	5	5	5	5	5
Raspberry flavour	3	3	3	3	3	3	3	3	3
Talc	10	10	10	10	10	10	10	10	10
Magnesium state	3	3	3	3	3	3	3	3	3
MCC(q.s)	150	150	150	150	150	150	150	150	150

❖ **Manufacture of Promethazine HCl rapid dissolving Tablets[75]**

Promethazine HCl rapid dissolving tablets were manufactured in nine formulations PF1 to PF9 using the ingredients mentioned in the Table 4.3 keeping the total weight (150 mg) of the tablet constant in all the formulations. The drug and the excipients were passed through #60-sieve. Weighed amount of drug and excipients

except magnesium stearate were mixed in a polybag by geometric addition method for 20 minutes manually. The blend was then lubricated by further mixing with magnesium sterate (#60-sieve). The mixture blend was subjected for drying to remove the moisture content at 40 to 45ºC, the mixture was blended with flavor and the powder blend was then compressed on 10-station rotary punching machine using flat faced punches. Round punches measuring 8 mm diameter were used for compression of tablets.

4.2.3 Evaluation of Promethazine HCl tablets.

1. Drug–polymer compatibility studies

In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Promethazine hydrochloride and the selected polymers. Potassium bromide, pure drug and the polymers were heated to 105ºC for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Promethazine HCl was compared with FT-IR spectra of polymers. The spectras were shown in Figures5.2, 5.3, 5.4, 5.5 and the IR spectrum data was shown in Table 5.2.

2. Pre-compression parameters [69, 70, 71]

- **Angle of Repose (θ)**

The frictional force in a loose powder or granules can be measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

Different ranges of flowability in terms of angle of repose are given in below table.

Angle of Repose (ɵ)	Flow
>25	Excellent
25-30	Good
30-40	Passable
<40	Very poor

Method: A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

- **Bulk Density**

Loose bulk density (LBD) and tapped bulk density (TBD) of Promethazine HCl and the tablet blends were determined using bulk density apparatus. The pure drug was passed through #18 sieve to break the clumps, if any. Accurately weighed 5 g of the drug or 25 g of polymers was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14 ± 2 mm. The tapped volume was measured to the nearest graduated unit. The tapping was repeated additional 200 times. Again the tapped volume was measured to the nearest graduated unit. The same thing was done for powder blends of the tablets. The LBD and TBD were calculated in g per ml using following formula.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

- **Compressibility Index (Carr's Index)**

The compressibility index of the granules was determined by carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is shown in below table

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

- **Hausner ratio**

The hausner ratio of the powder was determined by the following equation.

Hausner ratio = TBD / LBD

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

3. Post-compression parameters[76, 77,78]

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content, *in vitro* dispersion time, water absorption ratio, wetting time and *in vitro* drug release studies.

❖ **Thickness**

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper.

❖ **Hardness Test**

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. "Hardness factor", the average of the six determinations, was determined and reported. The force was measured in kilograms per centimeter square.

❖ **Friability Test**

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator (Electrolab, Mumbai) was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

❖ **Weight Uniformity Test**

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The total weight of tablets formulated was 150

mg. The percentage deviation for weight uniformity of tablets as per IP limits is shown in below table.

Average weight of tablet	Percentage deviation
80 mg or less	±10
More than 80 mg and less than 250 mg	±7.5
250 mg or more	±5

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limit of 7.5% is allowed as the tablet weighs 150 mg

❖ ***In vitro*** **dispersion Time**

In vitro dispersion time was measured by dropping a tablet into a petridish containing 10 ml of phosphate buffer pH 6.8 solution (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested. *In vitro* dispersion time was found and expressed in seconds.

❖ **Wetting time and Water absorption ratio**

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure. Two circular tissue papers of 10 cm diameter are placed in a petridish having the same inner diameter. Ten ml of phosphate buffer solution, 6.8 pH containing Eosin, a water soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper so that

complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time.

❖ **Drug content determination**

➢ *Calibration of Promethazine HCl in phosphate buffer (pH6.8) solution at λ_{max} 249.60*

- *Preparation of Buffers and Reagents*

  Sodium hydroxide solution (0.2 M): Eight grams of sodium hydroxide was taken in 1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water.

  Potassium dihydrogen phosphate solution (0.2 M): 27.218 g of Potassium dihydrogen phosphate was added in 1000 ml volumetric flask containing about700 ml distilled water and volume was made up to the mark with distilled water.

- *Procedure for Calibration of Promethazine HCl in phosphate buffer (pH6.8) solution:* From stock solution, appropriate aliquots were pippetted into different volumetric flasks and volumes were made up to 10 ml with phosphate buffer (pH 6.8) solution, so as to get drug concentrations of 2, 4, 6, 8, 10 and 12 µg/ml. The data are given in the Table 5.7 and calibration curve constructed is shown in the Fig.5.8.

➢ *Procedure of determining drug content*

Three uncoated tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark with phosphate buffer (pH 6.8) solution. The contents were shaken periodically and kept for 24 hours for solvation of drug completely. The mixtures were filtered, appropriately diluted, and

absorbences were measured at λmax 249.60 nm against blank reference. The drug content in each tablet was calculated using the standard calibration curve of Promethazine HCl in phosphate buffer pH 6.8 solution.

❖ ***In vitro* drug release**

➢ *Calibration of Promethazine HCl in phosphate buffer (pH6.8) solution at* λ_{max} *249.60*

The procedure for the calibration curve of Promethazine HCl is same as mentioned under Drug content determination section.

➢ *Procedure for determining In vitro drug release studies*

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 50. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 5 ml were withdrawn after every 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min. Samples were filtered through 10 µm filter. The fresh dissolution medium was replaced every time to maintain sink condition. The collected samples were analyzed at 249.60 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

5. RESULTS

5.1 PREFORMULATION STUDIES

1. Determination of solubility

Promethazine HCl was found to be freely soluble in water and alcohol.

2. Determination of melting point

The melting point of Promethazine HCl was found to be in the range of 220ºC.

3. Determination of λ_{max}

Table 5.1 Wavelength of maximum absorption of Promethazine HCl in phosphate buffer pH6.8

SR. No.	Solvent	λ_{max}
1	Phosphate buffer pH 6.8	249.60

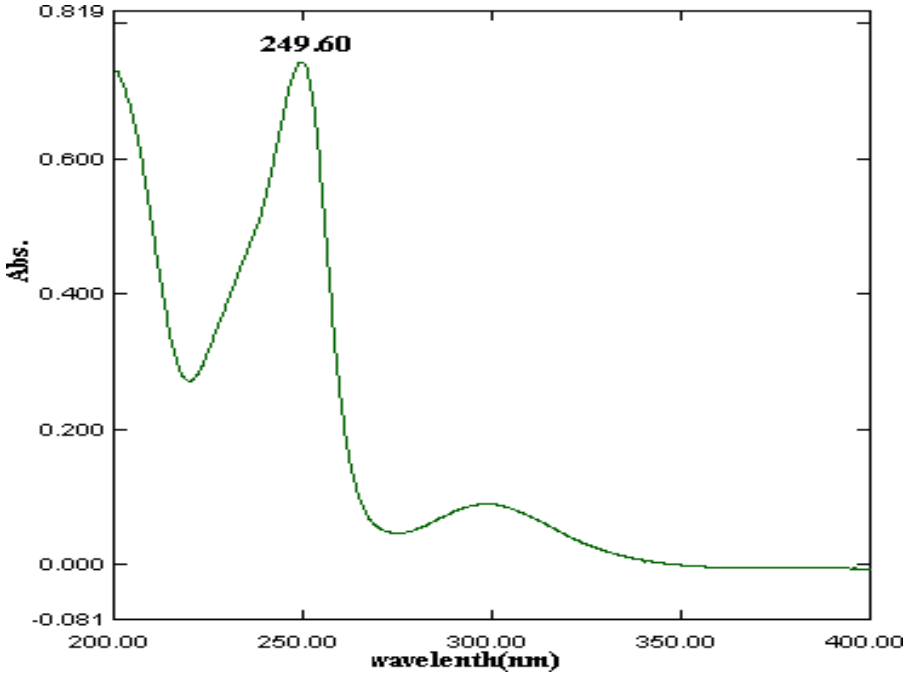


Fig. 5.1 UV spectra of Promethazine HCl in phosphate buffer pH 6.8

5.2 EVALUATION PARAMETERS OF PROMETHAZINE HCl TABLETS

❖ **Drug–polymer compatibility by FTIR studies**

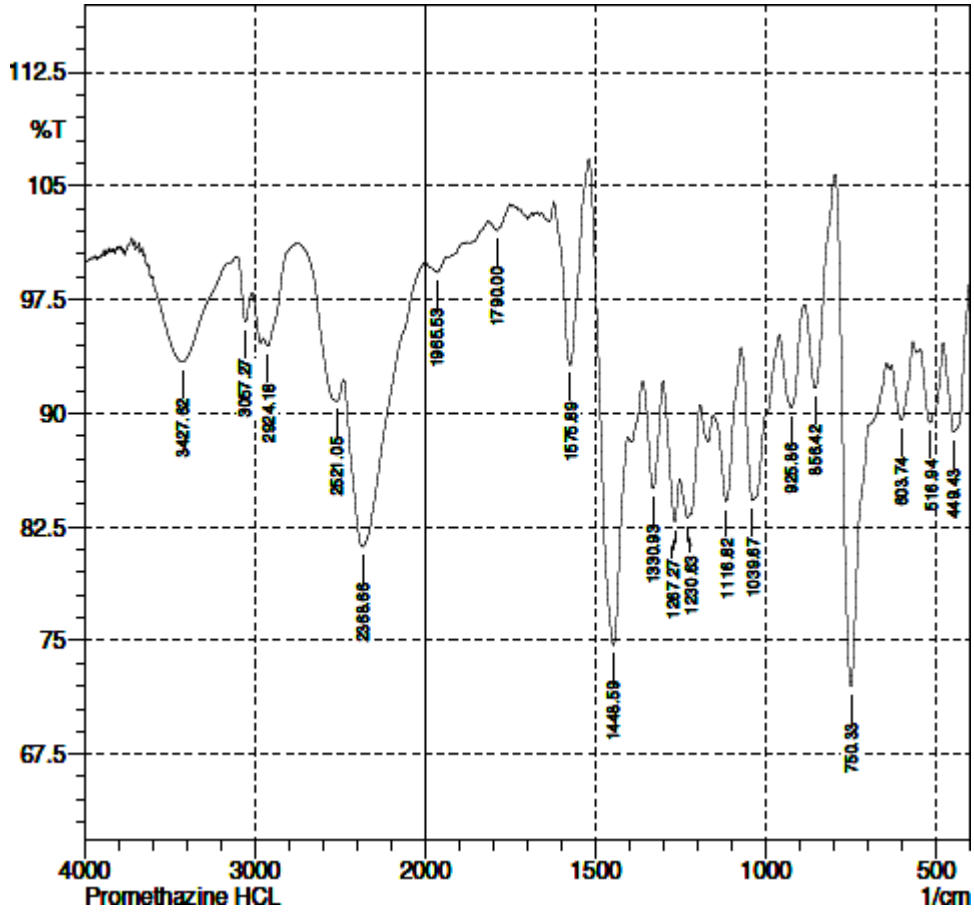


Fig. 5.2 IR spectra of Promethazine HCl

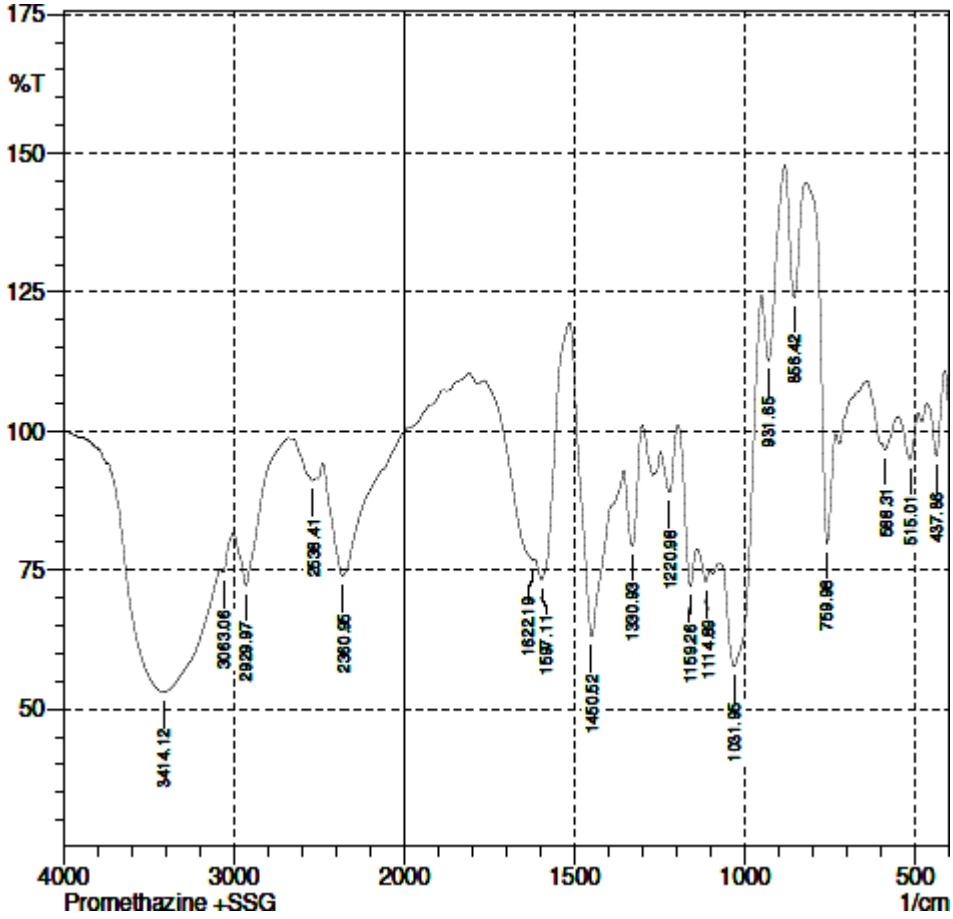


Fig 5.3 IR spectra of physical mixture of Promethazine HCl and SSG

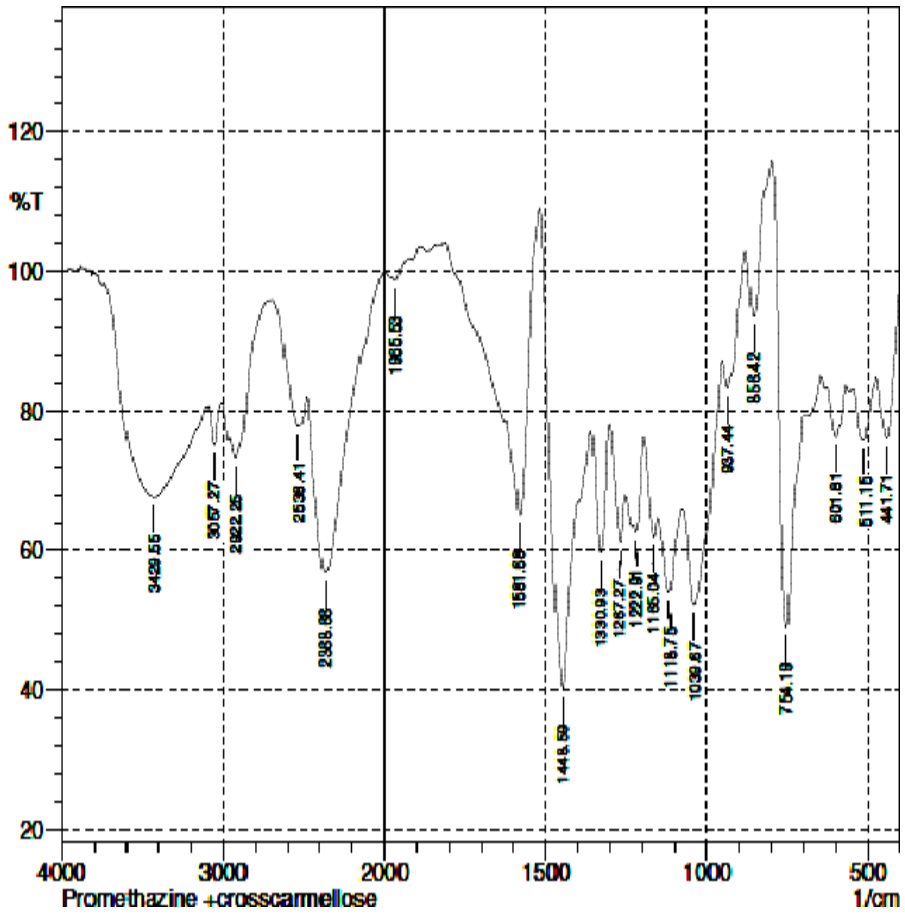


Fig. 5.4 IR spectra of physical mixture of Promethazine HCl and Crosscarmellose sodium

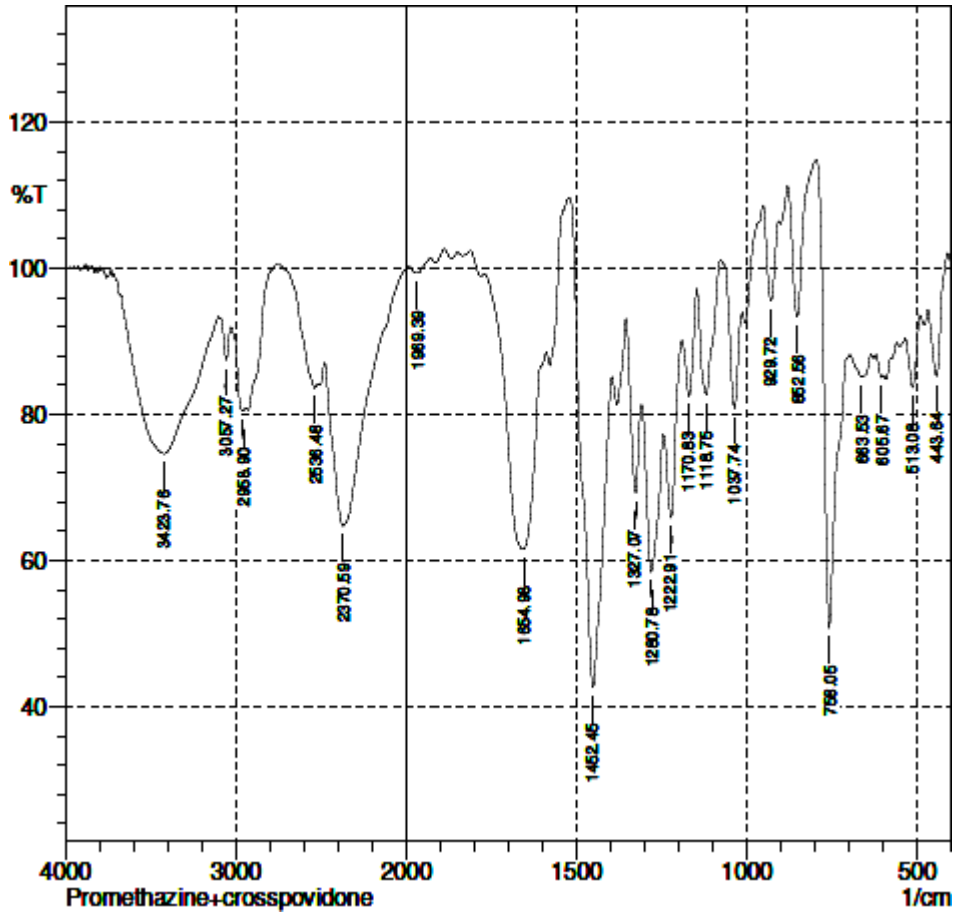


Fig. 5.5 IR spectra of physical mixture of Promethazine HCl and Crosspovidone

Table 5.2 FTIR Spectra data of drug and polymers

SR. No.	IR Spectrum	Peaks cm^{-1}	Groups	Stretching / Deformation
1	**Promethazine HCl**	3057.27	C-H Aromatic	Stretching
		2924.18	C-H Alkane	Stretching
		1575.89	C=C Aromatic	Stretching
		1330.93	$-CH_3$ Methyl group	Stretching
2	**Physical mixture of Promethazine HCl and SSG**	3063.06	C-H Aromatic	Stretching
		2922.97	C-H Alkane	Stretching
		1597.11	C=C Aromatic	Stretching
		1330.53	$-CH_3$ Methyl group	Stretching
3	**Physical mixture of Promethazine HCl and Crosscarmellose sodium**	3057.27	C-H Aromatic	Stretching
		2922.25	C-H Alkane	Stretching
		1581.68	C=C Aromatic	Stretching
		1330.53	$-CH_3$ Methyl group	Stretching
4	**Physical mixture of Promethazine HCl and Crospovidone**	3057.27	C-H Aromatic	Stretching
		2958.10	C-H Alkane	Stretching
		1654.98	C=C Aromatic	Stretching
		1327.07	$-CH_3$ methyl group	Stretching

❖ **Physical parameters of drug and superdisintegrants**

Table 5.3 Physical parameters of drug and polymers

Drug/Polymer	Bulk density(g/cc)	Tapped density(g/cc)	Angle of repose(ɵ)	Carr's index	Haunser ratio
Promethazine HCl	0.54	0.44	23º 70ı	19.54	1.27
SSG	0.53	0.42	24º 22ı	18.33	1.26
Croscarmellose	0.51	0.45	23º 65ı	16.66	1.18
Crospovidone	0.55	0.44	21º 58ı	19.22	1.25

5.3 EVALUATION OF PROMETHAZINE HCL TABLETS

Table 5.4 Precompression parameters of Promethazine HCl tablets

Formulation Code	*Angle of repose (ɵ)	*Bulk density (g/cc)	*Tapped density (g/cc)	*Carr's index	*Haunser ratio
PF1	22.02±1.64	0.56±0.001	0.67±0.015	15.75±1.50	1.19±0.01
PF2	22.08±2.73	0.54±0.002	0.65±0.008	17.96±1.71	1.19±0.04
PF3	24.77±1.04	0.54±0.004	0.65±0.022	14.46±1.43	1.14±0.04
PF4	25.03±0.35	0.51±0.004	0.66±0.010	20.81±0.63	1.20±0.04
PF5	23.88±0.76	0.52±0.004	0.65±0.008	21.87±1.11	1.23±0.03
PF6	23.54±0.70	0.53±0.002	0.61±0.007	21.91±1.05	1.22±0.03
PF7	24.39±0.64	0.57±0.009	0.69±0.007	18.81±0.93	1.21±0.02
PF8	22.62±0.69	0.56±0.026	0.66±0.013	16.65±0.59	1.23±0.03
PF9	21.57±1.89	0.54±0.017	0.67±0.017	18.76±0.80	1.21±0.04

*Value expressed as mean ±SD, n=3

Table 5.5 Results of thickness, hardness, friability and weight variation of Promethazine HCl tablets

Formulation code	*Thickness (mm)	*Hardness (kg/cm^2)	Friability (%)	Weight variation
PF1	2.62±0.01	3.7±0.38	0.51	149.10±0.20
PF2	2.63±0.07	3.4±0.33	0.48	151.09±0.33
PF3	2.86±0.02	3.4±0.65	0.45	150.19±0.21
PF4	2.63±0.05	4.2±0.25	0.72	150.33±1.76
PF5	2.52±0.01	3.8±0.31	0.70	148.80±1.03
PF6	2.53±0.05	3.8±0.72	0.67	150.33±2.12
PF7	2.51±0.05	3.2±0.22	0.64	149.60±1.28
PF8	2.50 ± 0.05	3.1±0.30	0.60	150.43±1.71
PF9	2.65 ±0.03	2.8±0.38	0.54	151.67±1.27

*Value expressed as mean ±SD, n=3

Table 5.6 Results of *In vitro* dispersion time, wetting time and water absorption ratio of Promethazine HCl tablets

Formulation code	**In vitro* dispersion time (sec)	*Wetting time (sec)	*Water absorption ratio
PF1	58.00±4.13	68.33±3.51	78.28 ±1.91
PF2	55.33±4.16	64.13±3.81	80.15± 1.10
PF3	40.33±3.18	48.12±3.21	87.34±1.52
PF4	54.21±3.10	60.65±3.00	75.32±1.98
PF5	48.11±4.10	54.00±4.00	84.11±1.23
PF6	45.33±3.11	50.33±3.11	92.82±2.00
PF7	38.00±1.98	50.21±3.05	82.20±3.21
PF8	27.66±2.51	44.00±2.31	90.66±3.05
PF9	18.34±1.15	39.30±1.54	96.54±3.00

***** Value expressed as mean ±SD, n=3

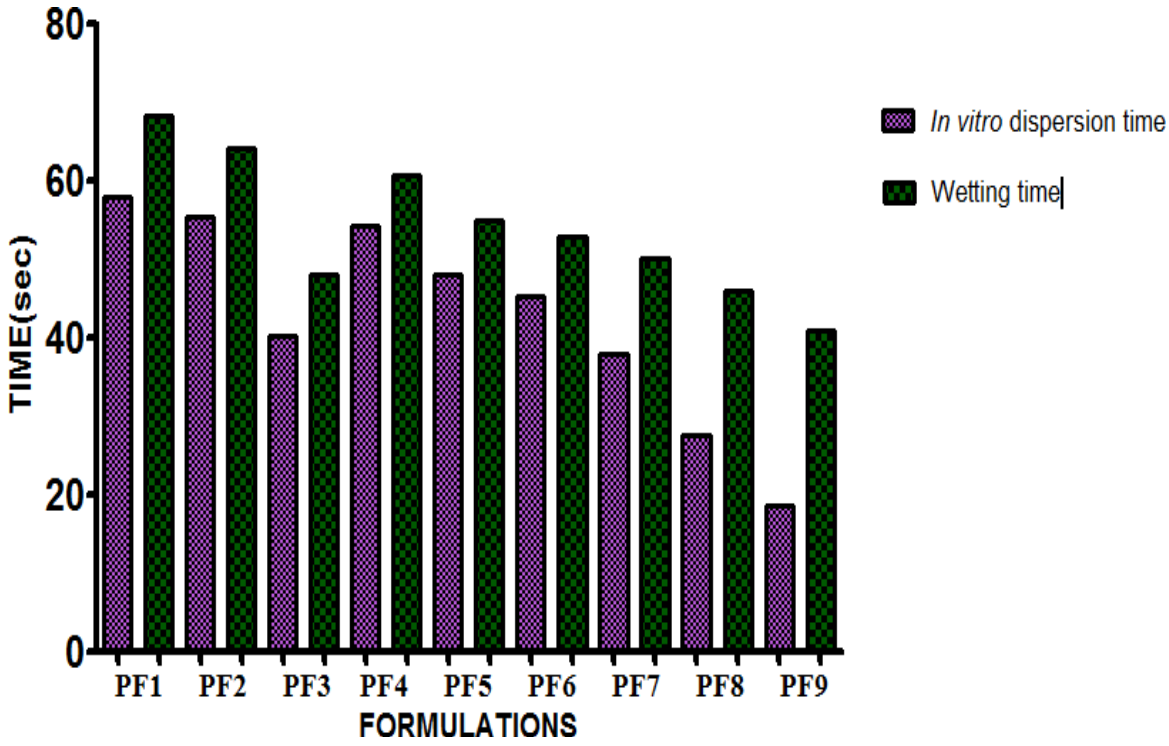


Fig. 5.6 Comparison between *in vitro* dispersion time and wetting time of Promethazine HCl tablets

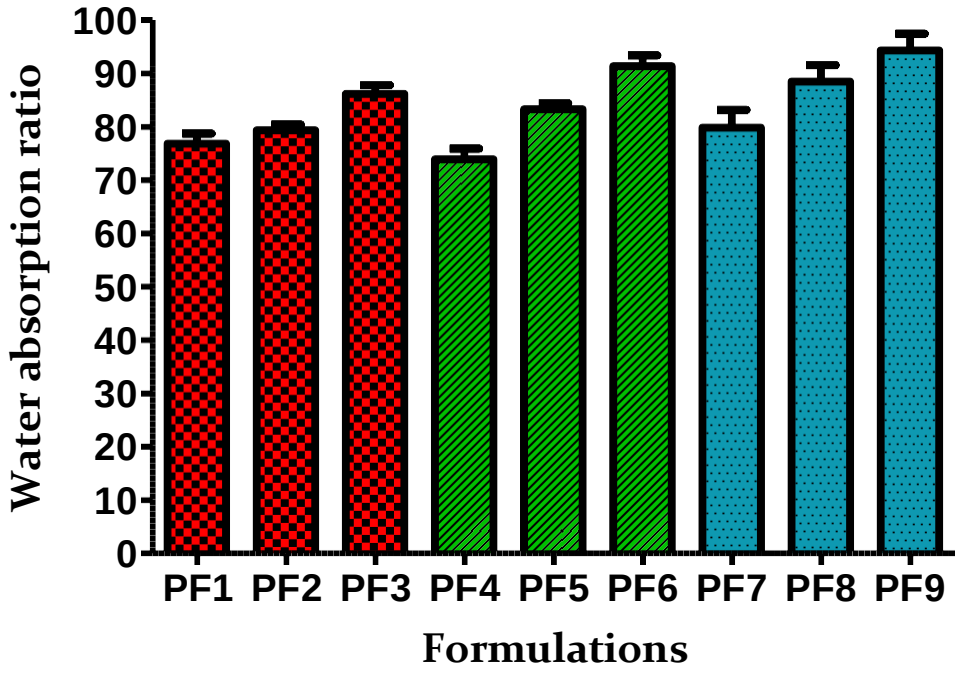


Fig. 5.7 Water absorption ratio of Promethazine HCl tablets

❖ **Determination of drug content of Promethazine HCl tablets**

Table 5.7 Data for calibration curve of Promethazine HCl at 249.60 nm

SR. No.	Concentration (µg/ml)	Absorbance at 249.60 nm
1	2	0.282
2	4	0.433
3	6	0.576
4	8	0.727
5	10	0.868

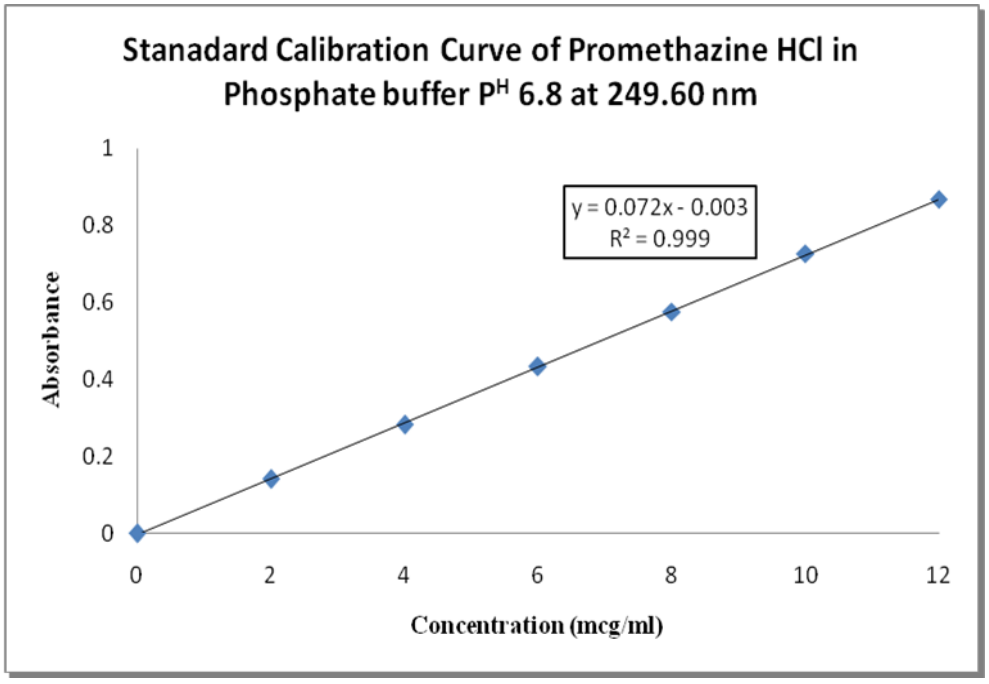


Fig. 5.8 Standard calibration curve of Promethazine HCl in phosphate buffer pH at 249.60nm

Table 5.8 Data for % drug content of Promethazine HCl tablets

Formulation code	%Drug content
PF1	98.21±0.66
PF2	98.21±0.66
PF3	96.78±0.86
PF4	98.55±0.76
PF5	98.73±1.10b
PF6	98.22±0.38
PF7	99.28±0.28
PF8	98.91±0.81
PF9	99.71±0.16

❖ ***In vitro*** **drug release profile of Promethazine HCl tablets**

Table 5.9 *In vitro* drug release data of Promethazine HCl tablets containing SSG

SR. No.	Time (min)	% Cumulative drug release		
		PF1	PF2	PF3
1	0	0	0	0
2	2	31.23±0.65	35.87±0.21	38.67±0.96
3	4	37.98±1.12	42.87±1.12	43.12±0.54
4	6	46.80±1.23	48.40±0.76	57.54±0.43
5	8	52.54±0.76	56.65±0.76	65.78±0.54
6	10	58.85±0.98	63.87±0.75	72.78±1.10

Table 5.10 *In vitro* drug release data of Promethazine HCl tablets containing Crosscarmellose sodium

SR. No.	Time (min)	% Cumulative drug release		
		PF4	PF5	PF6
1	0	0	0	0
2	2	32.67±0.23	36.19±0.34	35.28±0.87
3	4	43.12±0.67	44.78±1.45	47.32±1.15
4	6	57.54±0.65	59.63±1.00	60.22±0.37
5	8	65.78±0.78	68.20±1.32	73.73±0.62
6	10	72.78±1.15	74.87±0.78	82.65±0.47

Table 5.11 *In vitro* drug release data of Promethazine HCl tablets containing Crospovidone

SR. No.	Time (min)	% Cumulative drug release		
		PF7	PF8	PF9
1	0	0	0	0
2	2	42.76±0.76	45.72±0.73	47.98±1.00
3	4	55.87±0.43	59.98±0.54	62.12±0.62
4	6	72.50±1.32	75.65±0.32	79.43±0.91
5	8	84.92±1.12	89.64±0.65	88.90±0.47
6	10	91.43±0.63	94.34±1.34	98.43±1.27

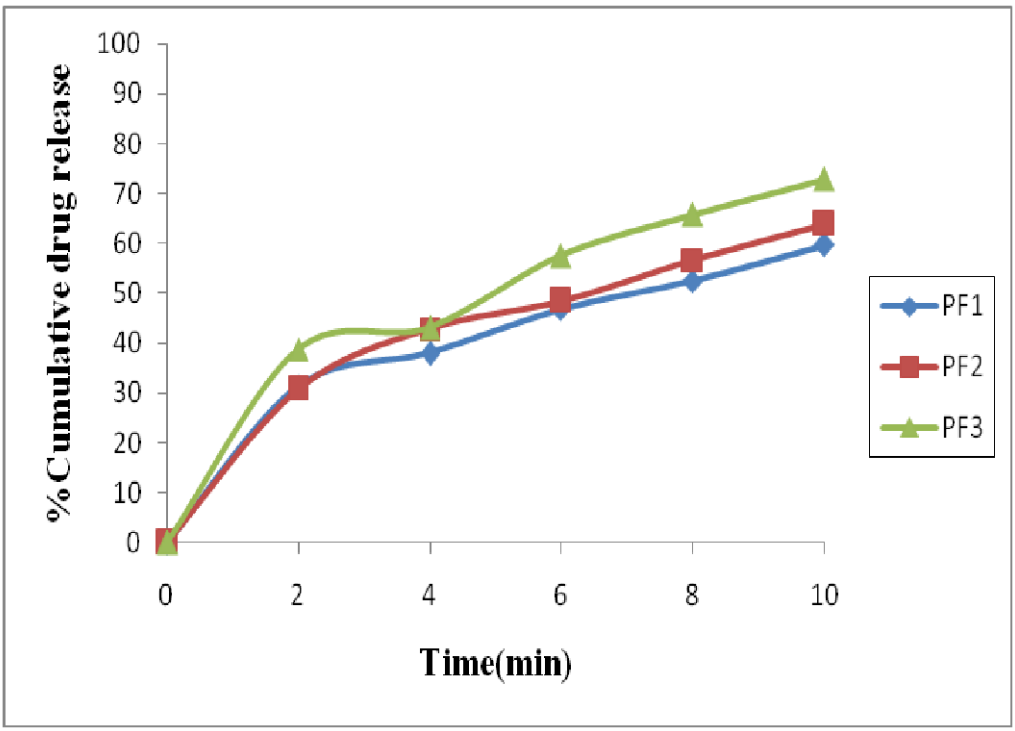


Fig. 5.9 *In vitro* drug release profile of Promethazine HCl tablets containing SSG

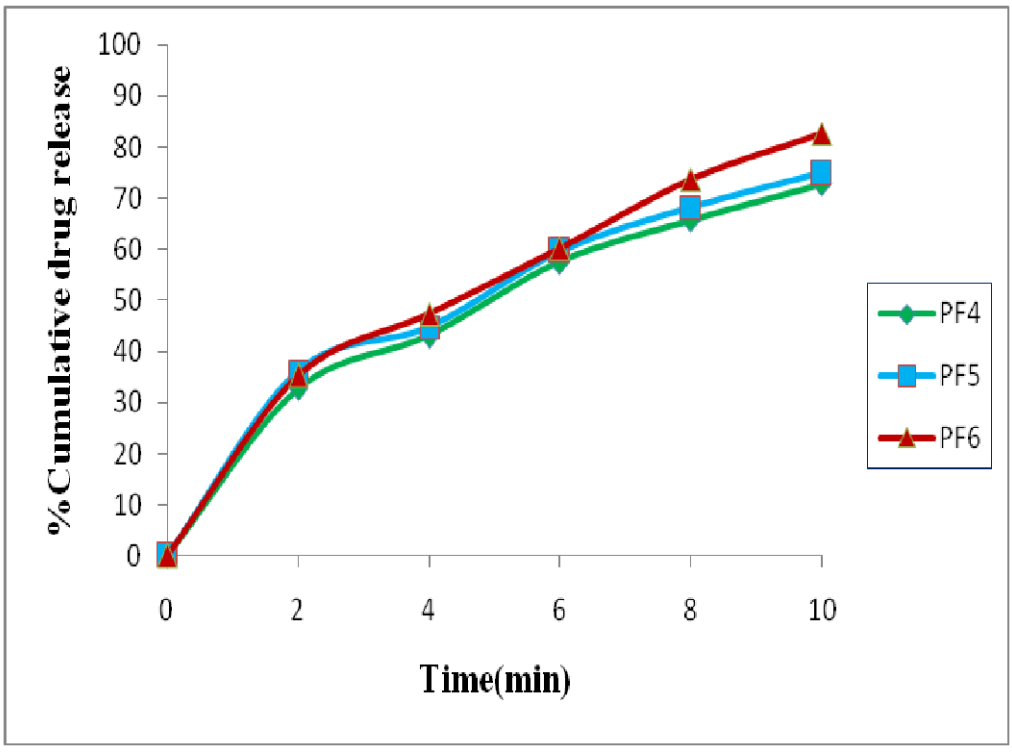


Fig. 5.10 *In vitro* drug release profile of Promethazine HCl tablets containing Crosscarmellose sodium

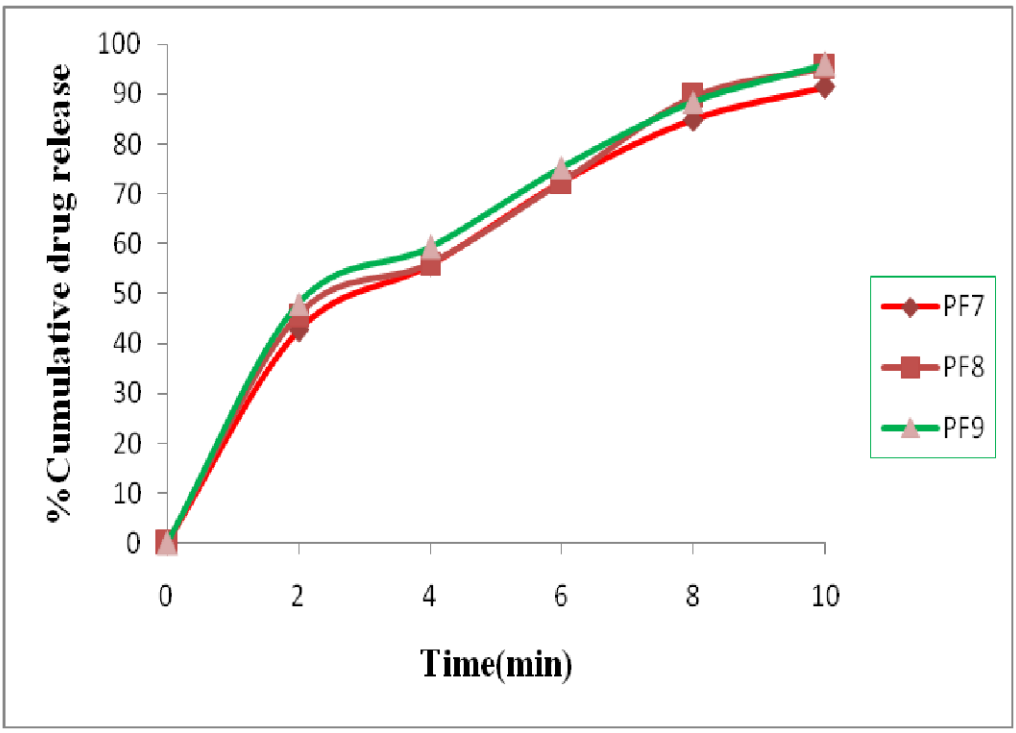


Fig.5.11 *In vitro* drug release profile of Promethazine HCl tablets containing Crospovidone

❖ **Comparison with Marketed Product**

Brand name: Phenargan

Company name: Novartis

Labelled claim: Promethazine HCl 25mg, total weight of tablets 150mg.

Table 5.12 Characterization of the marketed tablets of Promethazine HCl (Phenargen)

SR. No.	Evaluation Parameter	Observations
1	Thickness*	2.70±0.05 mm
2	Hardness*	4.3±1.23 kg/cm^2
3	Friability*	0.35±0.03 %
4	Weight variation	151±2.49 mg
5	% Drug content*	98.20±1.79%
6	% Cumulative drug release	93.48 (1 hour)

*Each value is an average of three determinations

Table 5.13 *In vitro* dissolution profile of Promethazine HCl tablet formulation PF9 and marketed product (Phenargan)

Time (min)	% Cumulative drug release	
	PF9	Marketed product (Phenargan)
2	47.98±1.00	1.64±0.78
4	62.12±0.62	8.64±0.43
6	79.43±0.91	19.70±0.93
8	88.90±0.47	27.99±1.15
10	98.43±1.27	39.16±1.20
20	-	54.90±1.00
30	-	67.78±0.56
40	-	75.34±0.87
50	-	82.10±1.26
60	-	93.48±1.00

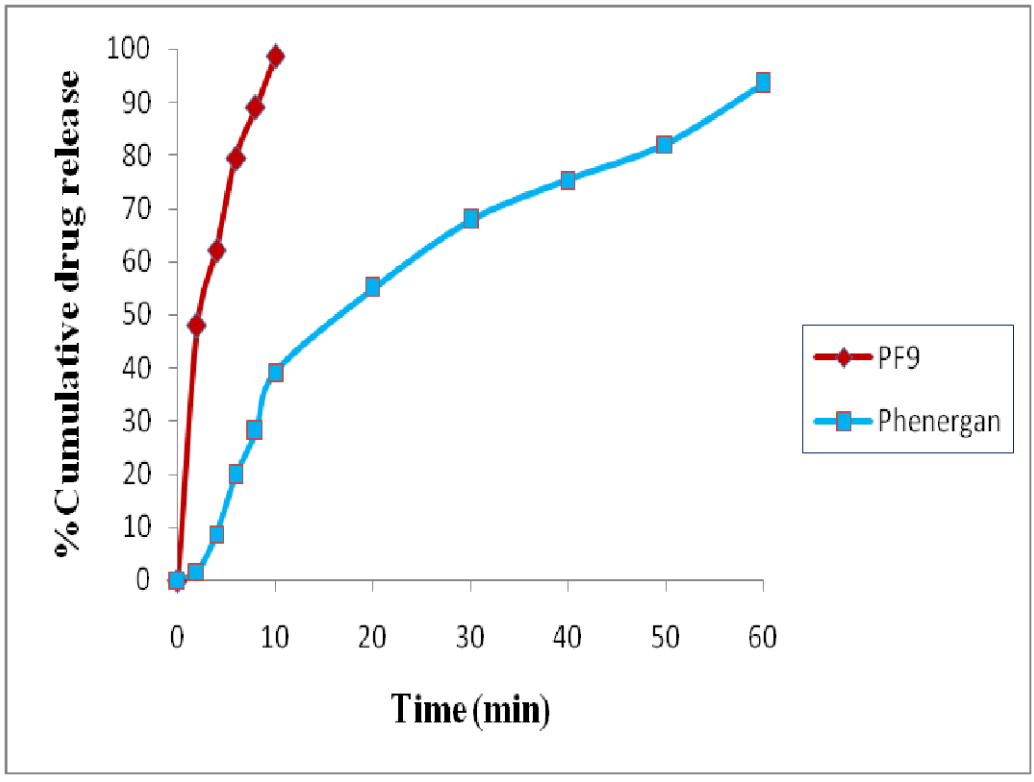


Fig.5.12 Comparison of *in vitro* drug release profile of Promethazine HCl tablet formulation PF9 with marketed product (Phenargan)

6. DISCUSSION

In the present study, an attempt was made to develop and evaluate rapid dissolving tablets of Promethazine HCl (25mg) for better treatment of vomiting especially for motion sickness condition. In general Promethazine HCl having only 26% oral bioavailability because of high first pass metabolism rate. Thus, formulated rapid dissolving tablets of Promethazine HCl prevents or avoids first pass metabolism and their absorption directly takes place into the saliva which results in better oral bioavailability compared to conventional Promethazine HCl tablets.

A. PREFORMULATION STUDIES

- The solubility of Promethazine HCl reveals that it was soluble in water and alcohol.
- The melting point of Promethazine HCl was found to be 222ºC, which complied with BP standards thus indicating purity of obtained drug sample.
- In Preformulation studies, it was found that, the λ_{max} of Promethazine HCl by UV spectroscopic method was found at 249.60 nm in pH6.8 buffer as shown in Fig. 5.1. A standard calibration curve of Promethazine HCl was made in phosphate buffer pH 6.8 by taking absorbance V/S concentration between 2-12µg/ml ranges, the data was given in Table 5.7 and calibration curve is shown in Fig.5.8. This complied with BP standards thus indicating purity of obtained drug.

B. Evaluation of Promethazine HCl rapid dissolving tablets

❖ Drug –polymer compatibility by FTIR studies

FTIR of drug-polymers interaction studies are shown in Fig 5.2 to 5.5 and the datas are reported in Table 5.2. It was found that Promethazine HCl was compatible

with superdisintegrants used in the formulation and there were no extra peaks observed.

❖ **Pre-compression parameters**

Precompression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density, carr's index and haunser ratio. Before formulation of tablets the drug and superdisintegrants were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP.

Angle of repose of all the formulations was found to be raging from 21.57-25.03, bulk density was found to be 0.51-0.57g/cc, tapped density was in between 0.61-0.69g/cc, Carr's index was found to be within 14.46-21.21 and haunser ratio was found to be within 1.19-1.23 indicating compressibility of the tablet granules is good as reported in Table 5.4.

❖ **Post-compression parameters**

- **Tablet thickness and hardness**

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (150 mg). The thickness of the batch from PF1-PF9 was found to be 2.50 - 2.86 mm and hardness was found to be 2.8 - 4.2 kg/cm^2 as reported in Table 5.5 and thus tablets were having good mechanical strength.

- **Friability**

Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets. The friability of all the formulated tablets of Promethazine HCl was found to be between 0.45 - 0.72 % are reported in Table 5.5 and all the

formulated tablets of Promethazine HCl were shown the % friability within the official limits.(i.e. not more than 1%).

- **Weight variation**

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight are reported in Table 5.5 and was found to be within (±7.5) the prescribed official limits.

- ***In vitro* dispersion time**

All the formulated tablets (PF1-PF9) have shown *in vitro* dispersion time of less than 60 seconds, showing that formulated Promethazine HCl tablets were better and effective for the treatment of vomiting than conventional tablets. Among all the formulations, tablets prepared with crospovidone were shown less than 40 sec. of dispersion time. The obtained results were showed in Table 5.6.

- **Wetting time**

The wetting time of all the formulations (PF1-PF9) were found to be within 39.30-68.33 seconds, which complies with the official specifications. The results were showed in Table 5.6. An comparison of *in vitro* dispersion time and wetting time was shown in Fig. 5.6

- **Water absorption ratio**

The water absorption ratio of all the formulated batches was found to be 75-96 % which was satisfactory in giving effective and better formulations of rapid dissolving tablets. The results were shown in Table 5.6. The water absorption ratio of all the formulations was represented in Fig. 5.7

- **Drug content**

The drug content of all the nine formulations of Promethazine HCl tablets were found to be within the range of 96.78-99.71% which were within the limits of BP

specifications. The drug content of all the formulations of Promethazine HCl tablets is shown in Table 5.8

- ***In vitro* dissolution study**

Total nine formulations were formulated PF1 to PF9 by using three different superdisinegrants in varying concentrations. The formulations PF1-PF3 were formulated with the help of sodium starch glycolate in concentration 2.5%, 5%,7. 5% respectively .The formulations PF4-PF6 were formulated with the help of crosscarmellose in concentration 2.5%, 5%, 7.5% respectively and the formulations PF7-PF9 were formulated with the help of crospovidone in concentrations 2.5%, 5%, 7.5% respectively. The formulations PF7-PF9 containing crospovidone showed more than 90% drug release. Among those three the formulation PF9 showed highest drug release of 98.43%. The data for *in vitro* drug release of formulations was shown in Tables 5.9, 5.10 and 5.11, the *in vitro* drug release profiles were shown in Fig.5.9, 5.10 and 5.11. The characterization of marketed tablets of Promethazine HCl (Phenargan) is displayed in Table 5.12. A comparision of optimized formulation (PF9) was made with marketed tablets (Phenargan) to show that formulated Promethazine HCl tablets were effective and suitable than conventional tablets. The comparison of *in vitro* drug release profile of optimized formulation (PF9) and marketed product (Phenargan) was shown in Fig. 5.12.

7. CONCLUSION

The conclusion drawn from the present investigation is given below;

- Preformulation studies of Promethazine HCl were performed. From the FT-IR, the interference was verified and found that Promethazine HCl did not interfere with the polymers used.
- Nine batches of rapid dissolving tablets of Promethazine HCl were successfully prepared using sodium starch glycolate, crosscarmellose and crospovidone by direct compression method.
- The tablets were evaluated for parameters like thickness, hardness, friability, *in-vitro* dispersion time, wetting time, water absorption ratio, % drug content and *in- vitro* drug release studies.
- Based on the results, formulation containing 7.5% crospovidone (PF-9) was identified as ideal and better formulation among all formulations developed for Promethazine HCL tablets.
- *In vitro* release of optimized formulation of Promethazine HCl rapid dissolving tablets of PF-9 was found to be 98.43% drug release within 10 min. with *in vitro* dispersion time being 18 sec.
- The final optimized formulation (PF9) was compared with marketed product of Promethazine HCl tablets (Phenargan) which shows 93.48% drug release in 1 hr. From this observation it was concluded that the formulated tablets of Promethazine HCl (PF9) were superior and effective in achieving patient compliance.

8. SUMMARY

Promethazine HCl is a first generation H1 receptor antagonist used medically as an antihistamine and antiemetic. It is an effective and well tolerated antiemetic, especially used in motion sickness condition. It has been associated with a wide variety of chemotherapy and radiotherapy regimens, but in conventional dosage forms it undergoes first pass metabolism where the oral bioavailability (88%) was reduced to 27%.

The present study is an attempt to develop and formulate rapid dissolving tablets of Promethazine HCl, with superdisintegrants which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action and to prevent the first pass metabolism of Promethazine HCl.

The identification characterstics of drug like solubility, melting point, λ_{max} were performed to findout the purity of drug. All the parameters observed were satisfactory and were within the prescribed official limits.

In this system direct compression method was used, microcrystalline cellulose (MCC) is used as a diluent, sodium starch glycolate (SSG), crosscarmellose and crospovidone were used as superdisintegrants, talc is used as flow promoter, magnesium sterate was used as lubricant, aspartame as sweetener and raspberry flavour is used to improve mouth feel.

The drug- polymer compatibility was confirmed by FTIR studies. The results obtained by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps.

The pre-compression parameters like bulk density, tapped density, Carr's 'index and angle of repose were determined. The final formulation showed acceptable flow properties. The post-compression parameters like the thickness, hardness, friability and *in vitro* dispersion time, wetting time, water absorption ratio and *in vitro* drug release were carried out and the values were found to be within IP, BP limits.

The final optimized formulation of Promethazine HCl tablets containing 5% crospovidone (PF9) was compared with marked conventional tablets of Promethazine HCl (Phenargan) and the results reveled that formulated rapid dissolving tablets of Promethazine HCl were effective and better to meet patient compliance.

Hence based on the formulation development and their results, direct compression method is more suitable for Promethazine HCl rapid dissolving tablets in terms of palatability, physical and chemical properties better with reference product.

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10. ANNEXURES

LIST OF PUBLICATIONS

❖ **Review article**

1. **Sandeep divate***, Kunchu Kavitha, Ganesh Nangan Sockan. Fast disintegrating tablets: An emerging trend. International journal of pharmaceutical sciences review and research **(Accepted).**

❖ **Research articles**

1. Kavitha K, **Sandeep D. S.***, Mehaboob Yadawad, More Mangesh. Formulation and evaluation of oral fast dissolving tablets of Promethazine HCl by sublimation method. International journal of Pharmtech Research **(Communicated).**
2. **D. S. Sandeep***, K. Kavitha, T. Tamizhmani. Formulation and *in vitro* evaluation of rapid dissolving tablets of Promethazine hydrochloride by superdisintegrant addition method. Asian journal of pharmaceutics **(Communicated).**