DEVELOPMENT OF FAST DISSOLVING TABLETS OF BISOPROLOL FUMARATE AND STATISTICAL OPTIMIZATION BY USING 3^2 FACTORIAL DESIGN

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI.

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MASTER OF PHARMACY
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Submitted By
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<u>CERTIFICATE</u>

This is to certify that the investigation in this thesis entitled **"Development of fast dissolving tablets of Bisoprolol Fumarate and statistical optimization by using 3^2 factorial design"** submitted to the TamilNadu Dr. M.G.R Medical University, Chennai, for the partial fulfillment of the award of Degree of **Master of pharmacy in Pharmaceutics,** was carried out by **Reg. No. 26105103** in the **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode-638112,** under my guidance and supervision.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation in this thesis entitled **"Development of fast dissolving tablets of Bisoprolol Fumarate and statistical optimization by using 3^2 factorial design",** submitted in partial fulfillment for the award of degree of **Master of Pharmacy in Pharmaceutics,** was carried out in the laboratories of The Erode College of Pharmacy & Research Institute, Erode, by **Reg. No. 26105103** under the guidance of **Mrs. T. Sudhamani, M. Pharm.,** Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode- 638112.

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DECLARATION

The research work embodied in this dissertation work entitled **"Development of fast dissolving tablets of Bisoprolol Fumarate and statistical optimization by using 3^2 factorial design"** was carried out by me in **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode-638112,** under the direct supervision of **Mrs. T. Sudhamani, M. Pharm.,** Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode – 638112.

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The work is original and has not been submitted in part or full for the award for any other Degree or Diploma of this or any other University.

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Abbreviations	Abbreviation Terminology
FDT	Fast dissolving/dispersible tablets
ODT	Orodispersible tablet
MDT	Mouth dissolving tablet
BP	British Pharmacopoeia
FDA	Food and drug administration
API	Active pharmaceutical ingredient
AC-Di-Sol	Croscarmalose Sodium
MMC	Micro crystalline cellulose
SSG	Sodium starch glycolate
PVP	Polyvinyl pyrolidin
Mg	Magnesium
C	Celsius
M	Molarity
cm	Centimeter
Conc.	Concentration
Fig	Figure
FT-IR	Fourier transform infra red
G	Gram
Kg	Kilogram
Kg/cm^2	Kilogram per square centimeter
w/w	Weight/weight
hrs	Hours
HCL	Hydrochloric acid
KCl	Potassium Chloride
pH	Hydrogen ion concentration
IP	Indian Pharmacopoeia
LBD	Loose bulk density
Rpm	Rotation per minute
Sec	Seconds
No.	Number

S. no.	Serial number
#	Mesh size
µg	Microgram
Mg	Milligram
Mm	Millimeter
Ml	Milliliter
Min	Minutes
nm	Nanometer
%	Percentage
θ	Angle of repose
RS	Reference standard
±	Standard Deviation
TBD	Tapped bulk density
T	Time
USP	United State Pharmacopoeia

1. INTRODUCTION [1, 2]

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving tablets (FDT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

FDT are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. FDT are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. 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 significantly greater than those observed from conventional tablets dosage form. The advantage of fast dissolving dosage forms are increasingly being recognized in both, industry and academics.

According to **European pharmacopoeia,** the FDT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva.

The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing FDTs are freeze-drying, spray-drying, tablet moulding, sublimation, sugar-

based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

Recent developments in technology have presented viable alternatives for the patients who may have difficulty in swallowing tablets or liquids.

To overcome these drawbacks, FDT or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types, of tablets that disintegrate/dissolve/disperse in saliva within few seconds.

1.1 TABLETS [3]:

Tablets may be defined as solid pharmaceutical dosage forms containing medicament or medicaments with or without suitable recipients & prepared either by compression or molding.

1.1.1 Advantages of tablets:

Some of the potential advantages of tablets are as follows.

➤ They are the unit dosage form having greatest capabilities amongst all the oral dosage form for the dose precision and least content variability.

➤ Their cost is lowest amongst all the oral dosage forms.

➤ They are easiest and cheapest for packaging and transportation.

➤ Tablets are better suited to large-scale production than other unit oral dosage forms.

➤ They lend themselves to certain special release profile products such as enteric or delayed release products.

➤ They have the best-combined properties of chemical, mechanical, microbiological stability amongst all the oral dosage forms.

1.1.2 Classification of tablets:

Based on the route of administration or the function, the tablets are classified as follows.

i) Tablets ingested orally:

➤ Compressed tablet

➤ Multiple compressed tablet

a) Layered Tablet

b) Compression coated Tablet

➢ Repeat action Tablet

➢ Delayed action and enteric-coated Tablet

➢ Sugar and chocolate-coated tablet

a) Film coated tablet

b) Chewable Tablet

ii) Tablets used in the oral cavity:

➢ Buccal Tablet

➢ Sublingual Tablet

➢ Troches and Lozenges

➢ Dental cones

iii) Tablets administered by other routes:

➢ Implantation Tablet

➢ Vaginal Tablets

vi) Tablets used to prepare solution:

➢ Effervescent Tablet

➢ Dispensing Tablet

➢ Hypodermic Tablet

➢ Tablets Triturates

1.1.3 Manufacturing Methods[3]:

Tablets are manufactured by Wet granulation, Dry granulation or direct compression method.

i) Wet Granulation:

Wet granulation is the process in which a wet mass of powder is formed by addition of liquid in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets.

ii) Dry Granulation:

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

iii) Direct Compression:

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity & forms a firm compact.

Table No.1.1 Processing steps commonly required in the various tablet granulation preparation techniques

Processing steps	Wet Granulation	Dry Granulation	Direct Compression
Raw materials	✓	✓	✓
Weight	✓	✓	✓

Screen	✓	✓	✓
Mix	✓	✓	-
Compress (slug)	-	✓	-
Wet mass	✓	-	-
Mill	✓	-	-
Dry	✓	-	-
Mill	✓	✓	-
Mix	✓	✓	-
Compress	✓	✓	✓

1.1.4 Advantages of Dry Method:

➢ This process is more economical. It requires fewer manufacturing steps, less processing time & thus reduces labour cost & less process validation.

➢ The processing steps required no need of moisture, heat, and high compaction pressure.

➢ There is an optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass & is available for dissolution.

➢ Disintegrating agents like starch are more effective when processed by dry granulation compression than wet granulation technique

In the present aging society, easy-to-use dosage forms for elderly patient, whose swallowing function is often decreased, are in great demand. The use of conventional tablets, capsules, and liquid or syrup preparations were not always easy-to-use dosage forms for elderly patients because of their decrease motor function. Similarly the use of conventional tablets is challenging to paediatric, geriatric, and uncooperative patients who may have difficulty to swallow tablets and is also problematic when water is unavailable or when patients have a persistent cough or gag-reflux.

These problems have been addressed by the recent introduction of FDT which also known as quick-dissolving tablet (also known as fast-dissolving multiparticulate, rapid-dissolving, mouth-dissolving, fast-melting, orodispersing tablets) is an oral dosage form that does not require water for swallowing. The tablets dissolve within 60 seconds when placed in mouth or in oral cavity.

1.2 FAST DISSOLVING TABLETS (FDT) [4]:

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the dosage form developed to facilitate ease of medication, the rapid disintegrating tablet is one of the most widely employed commercial products.

1.2.1 Definition:

A fast-dissolving drug delivery system in most cases is a tablet that dissolving or disintegrates in the oral cavity without the need of water or chewing. Most fast-dissolving drug delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patients saliva along with the soluble and insoluble excipients.

These are also called melt-in-mouth, repimelt, porous tablet, oro-dipersible, quick dissolving or rapid disintegrating tablets. FDTs are also called as Oro-dispersible tablets, Quick disintegrating tablets, Oral Disintegrating tablets, rapid dissolving tablets, Porous tablets and Rapimelts.

Recently, **European Pharmacopoeia** has used the term FDT that disperses readily and within 3 min in mouth before swallowing.

United State Food and Drug Administration (FDA) defined FDT as, "A solid dosage form containing medicinal substance of active ingredient which disintegrates usually within a matter of seconds."

"FDT are solid dosage form that contains medicinal substances and that disintegrate and dissolve rapidly without water (within seconds)."

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving dosage form or oral dissolving tablets. When this type of tablet is gone into the stomach, the 0.1N HCL will serve to rapidly dissolve the tablet.

Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. Target populations for these new fast dissolving/disintegrating dosage forms have generally been paediatric, geriatric, bedridden or developmentally disabled patients., who are travelling or who have little or no access of

water are also good candidates for fast dissolving / disintegrating tablets. Other groups that may experience problems using conventional oral dosage form include the mentally ill, developmentally disable and patients who are uncooperative. A difficulty in swallowing (dysphasia) tablets or capsules is common problem among all age groups, especially in elderly and paediatrics. For this reasons, tablets that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention.

Indeed, the FDT is an important and attractive alternative to liquid dosage form. Syrups are best for paediatrics but they are bulky and drugs are not as stable in liquid form as in solid form like tablets.

FDT are characterized by high porosity and low hardness, when administered an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true FDT. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The disintegration time of these tablets depend largely on size and hardness parameters.
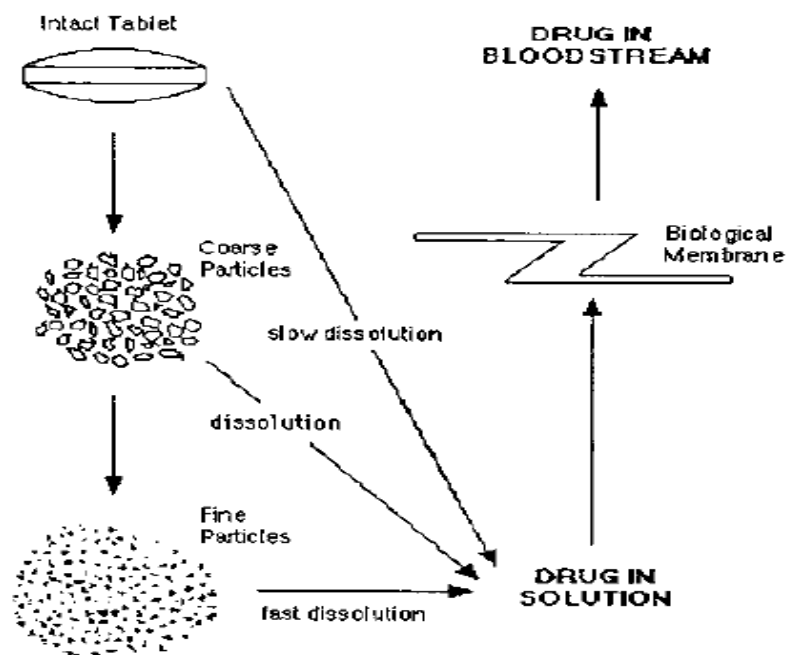
Fig. No. 1.1 Absorption of drug from intact tablet

1.2.2 Criteria for Fast Dissolving Drug Delivery System:[2]

➢ The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.

➢ Be compatible with taste masking.

➢ 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.

1.2.3 Requirements of FDT:

An ideal FDT should

➢ Require no water for oral administration, yet dissolving/disperse/disintegrate in a matter of seconds.

➢ Leave minimal or on residue in mouth after administration.

➢ Be harder and less friable.

➢ Exhibit low sensitivity to environment condition (temperature and humidity).

➢ Allow the manufacture of tablet by using conventional processing and packing equipment.

1.2.4 Advantages of FDT:

➢ Ease of administration to patient who refuses to swallow a tablet, such as paediatric, geriatric, and psychiatric patient.

➢ No need of water to swallow the dosage form, which is highly convenient feature for patient who are travelling and do not have immediate access to water.

➢ Convenience of administration and accurate dosing as compared to liquid.

➢ Rapid dissolution of drug and absorption, which may produce rapid, onset of action.

➢ Ability to provide advantage of liquid medication in the form of solid preparation.

➢ Some drugs are absorbed from the mouth and oesophagus 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, improved bioavailability and as a result of reduced dosage improved clinical performance through a reduction of unwanted effect.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drug from mouth, pharynx and oesophagus as saliva passes down.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

1.2.5 Disadvantages of FDT:
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated Properly
- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- Tablets are very fragile and lack physical resistance. Because the tablets are very porous and low compression forces are used to prepare them. They cannot be packed in conventional strips or in bottles and special packaging is required.
- Bitter drugs have to be taste masked by various techniques which in turn increases the time and cost of production

1.2.6 Silent feature of Fast Dissolving Drug Delivery System:
- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Quick disintegration and dissolution of the dosage form.
- Overcomes unacceptable taste of the drugs.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.

1.2.7 Mechanism of tablet disintegrates [5]:

Capillary action

⇓

Swelling

⇓

Because of heat of wetting

Disintegrating particle/particle repulsive forces

⇓

Deformation

⇓

Release of gases

⇓

Enzymatic action

i) Capillary action:

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 disintegrates 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.

ii) 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.
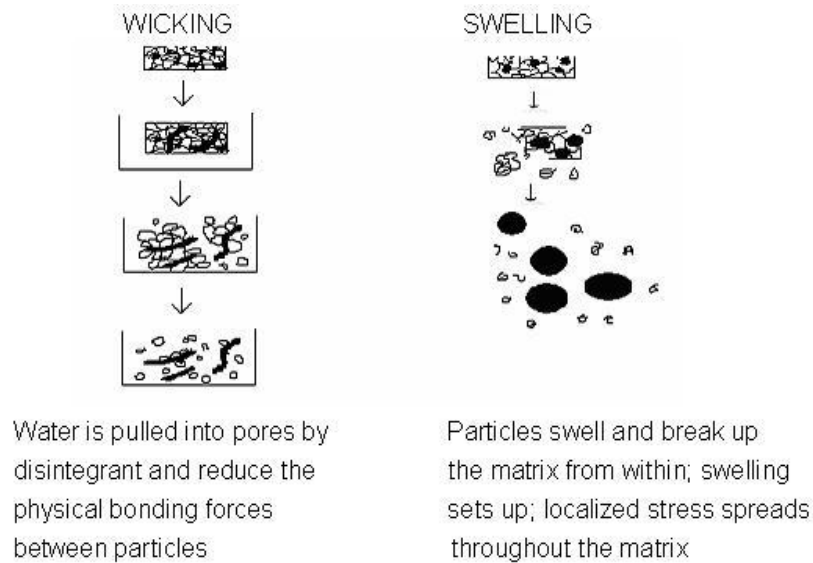
Fig. No. 1.2 Disintegration of tablet by wicking and swelling
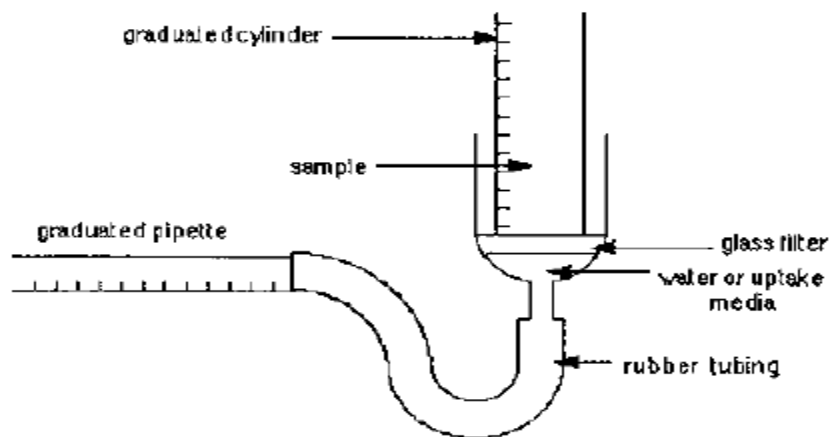
Fig. No. 1.3 Bulk swelling and water uptake apparatus

The apparatus is useful for the quantification of swelling and hydration rates for many excipients and polymers. Swelling tests depends on number of variables including water transport and rate of hydration through membrane. This metho is used to evaluate intrinsic swelling through the use of high speed cinemicroscopy in conjuction with computerized image analysis.

iii) Heat of wetting (air expansion):

When disintegrates with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrates and cannot describe the action of most modern disintegrating agents.

iv) Disintegrating particle / particle repulsive forces:

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

v) Deformation:

Hess had proved that 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 breakup of the tablet.
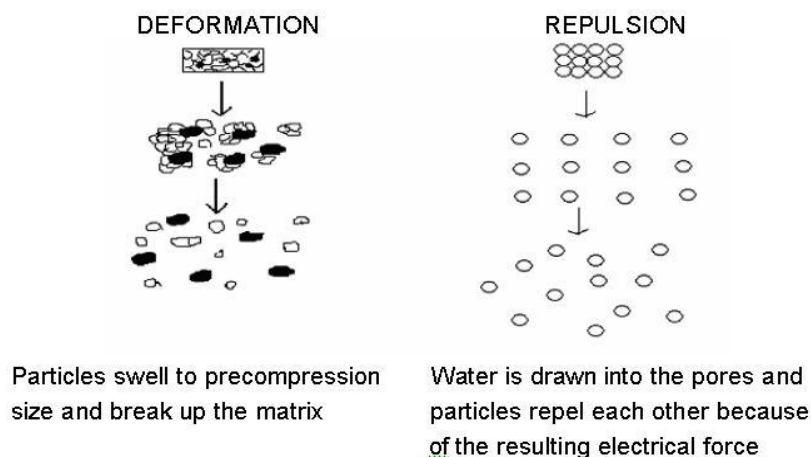
Fig. No. 1.4 Disintegration by deformation and repulsion

vi) Release of gases:

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrates are highly sensitive to small changes in humidity level and temperature ,strict control of environment is required during manufacturing of the tablets .The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

vii) Enzymatic reaction:

Here, enzymes presents in the body act as disintegrates. These enzymes destroy the binding action of binder and helps in disintegration.

viii) Fundamentals of fast dissolving /disintegrating tablets:

For rapid dissolution or disintegration of dosage form, water must rapidly penetrate into the tablet matrix to cause quick disintegration & instantaneous dissolution of the tablet. Several techniques are used to achieve these fundamentals, to formulate mouth-dissolving tablet. Some of the techniques are described below.

1.3 FORMULATION PROCESSES FOR MAKING FDT [6]:

There are several technologies that produce commercially available FDTs. Zydis (Cardinal Health, Dublin, Ohio), OraSolv/DuraSolv (Cima Labs, Eden Prairie, Minnesota), and WOWTAB (Yamanouchi Pharma Technologies, Norman, Oklahoma) are widely known technologies (Table 1). Some of the FDT products on the market are listed in Table 2. Although these technologies meet the special requirements for FDTs to some extent, none has all the desired properties. The currently available technologies have been reviewed in the literature. The technologies are usually grouped according to the method used in making FDTs, such as freeze drying, molding and compression; compression is the most widely used method for making FDTs. Some methods are focused on unique granulation methods, such as spray-drying and flash-heating, to make shear form formulations; some are focused on selecting specific excipients such as water-insoluble calcium salt, specific disintegrants combination, and specific sugar combination; and

some are focused on special treatment after compression, such as sublimation, sintering, and humidity treatments. Each method is examined in more detail below.

1.3.1 Freeze Drying:

Freeze drying (lyophilization) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. The resulting tablets are usually very light and have highly porous structures that allow rapid dissolution or disintegration. When placed on the tongue, the freeze dried unit dissolves almost instantly to release the incorporated drug. The entire freeze drying process is done at non elevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing. When stored in a dried state, the freeze-dried dosage form has relatively few stability problems during its shelf life. The freeze-drying process may result in a glassy amorphous structure of excipients as well as the drug substance, leading to the enhanced dissolution rate. Freeze drying, however, is a relatively expensive manufacturing process, and the formulation has poor stability at higher temperature and humidity.

The Zydis technology is the most well known example of the freeze drying method. In the Zydis formulations, the drug is physically trapped in a matrix composed of two components, a saccharide (e.g., mannitol) and a polymer. The carrier polymers commonly used in the Zydis system include (par tially hydrolyzed) gelatin, hydrolyzed dextran, dextrin, alginates, poly (vinyl alcohol), polyvinylpyrrolidone, acacia, and the mixtures. After the solution or dispersion is filled into blister cavities, it is then frozen in a liquid nitrogen freezing tunnel. The solvent in the frozen state is removed to produce porous wafers. Because the units are fragile and light-weight, they cannot withstand the pressure of being pushed through the foil of a conventional blister. A special peelable backing foil is used to package the Zydis units. Because the water content in the final freeze-dried product is too low for microbes to grow, the Zydis formulation is also self-preserving.

However, the Zydis formulation is so sensitive to moisture that the tablet may melt between sweaty fingers when it is taken out of the package. This dosage form may degrade at humidity greater than 65%, so a pinhole or minor damage to the package will lead to collapse of the tablet. There are some requirements for the Zydis technology. The drug should be chemically stable and water insoluble, with a particle size smaller than 50 μm. Precipitation may occur during manufacturing if large drug particles are used. The water soluble drugs may form eutectic mixtures that cannot be frozen adequately to form

the rigid structure necessary to support itself after solvent is removed, which may cause collapse of the freeze dried cake. For this reason, the dose for water-soluble drugs is usually limited to 60 mg. Higher drug dosing can be accommodated without losing the rapid disintegration property, however, if a thickened (i.e., paste-like) form of an oil-in-water emulsion is directly placed in the blister cell. There are 13 products currently available based on the Zydis technology.
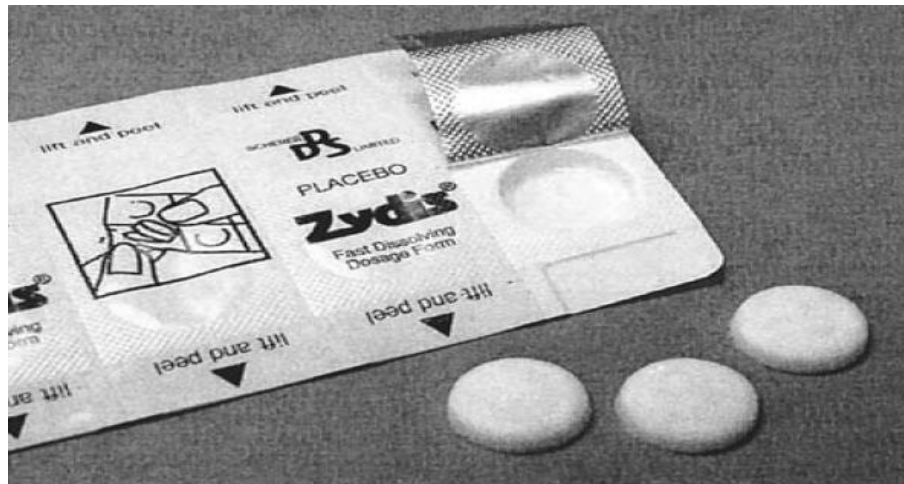
Fig. No. 1.5 Zydis dosage form and blister pack

The products on the US market include Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODTR, and Zyprexa ZydisR. In the worldwide market, oxazepam, lorazepam, loperamide, and enalapril are available in the Zydis formulations (Table 1).

Quicksolv (Janssen Pharmaceutica, Beese, Belgium) and Lyoc (Farmalyoc Laboratorie L., Lefon, Maisons-Alfort, France) are also prepared by the freeze drying method. In the Quicksolv formulation, the matrix compositions are dissolved in the first solvent (usually water), and then the solution is frozen. At the temperature at which the first solvent will remain in the solid form, the frozen solution contacts the second solvent, which is substantially miscible with the first solvent. For example, ethanol, menthol, or acetone is used as the second solvent with water as the first solvent. The matrix composition should be immiscible to the second solvent. Thus, the first solvent is substantially removed after a few hours of contacting the second solvent to result in a usable matrix. The final product disintegrates almost instantly. This method is claimed to prevent or reduce the incidence of cracking during the final preparation, having uniform porosity and adequate strength for handling. In the Lyoc formulation, the porous solid form is obtained by freeze drying an oil-in-water emulsion placed directly in the blister pockets. In order to prevent in-homogeneity by sedimentation during freeze drying, this

formulation requires a large proportion of undissolved inert filler to increase the viscosity of the suspension. The high proportion of filler reduces the porosity of the tablet, and as a result, the disintegration is slower. It is also noted that the tablet still has poor mechanical resistance.

NanoCrystal technology (Elan, King of Prussia, Pennsylvania) uses orally administered nanoparticles (<2 μm) in the form of rapidly disintegrating tablet matrix. The NanoCrystal orally disintegrating tablet dosage form was developed to facilitate the preparation of small-scale clinical supplies. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations such as granulation, blending, and tableting, which generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDTs because manufacturing losses are negligible. The final tablet is durable enough for conventional blister or bottle packaging and accepts as much as 200 mg of drug per unit. Other features include conventional, compendial inactive components and non-moisture sensitive inactive ingredients.

1.3.2 Molding:

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression molding.) Then the solvent can be removed by air-drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Recently, the molded forms have also been pre pared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure (novacuum lyophilization). Solid dispersion also can be used to make the tablets. The drug can remain discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to produce a solid solution or dissolve partially in the molten carrier while the remaining undissolved particles disperse in the matrix. The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth

feel) vary based on the type of the dispersion or dissolution. Because of their water-soluble sugar components, molded tablets disintegrate more rapidly and offer improved taste. However, molded tablets typically do not have great mechanical strength. The chance of erosion and breakage of the molded tablets during tablet handling and opening blister pockets is high. If hardness enhancing agents are added to the formulation, the rate of tablet disintegration usually decreases. Mechanical strength and good disintegration of the tablets can be improved by using nonconventional equipment and/or multistep processes. Using a nonconventional approach, however, requires substantially larger investment in machinery. Compared with freeze-drying, molded tablets can be produced more simply and efficiently at an industrial scale, although disintegration times may not be com parable to those of lyophilized forms. Takeda Chemical Industries (Osaka, Japan) and Nippon Shinyaku (Kyoto, Japan) have disclosed in compression-molding. The wetted mass was compressed at low pressure and subsequently dried to produce porous tablets with sufficient mechanical strength. The disintegration time was about 30–50 seconds in the mouth. In a patent by Novartis Consumer Health (Basel, Switzerland), the drug solution or suspension was dispersed into molds. The solvent was removed from the units usually by heating, pressure reduction, or microwave radiation. In a patent by Okada, the molded tablets contained a drug, a saccharide having a solubility of 30 (w/w) % or less at room temperature (e.g., lactose and mannitol), and a saccharide having a solubility of 30 (w/w) % or more at room temperature (e.g., glucose, fructose, sucrose, xylose, trehalose, xylitol, sorbitol, erythritol, dextrin, and pullulan). The amount of this saccharide was slightly above its solubility. The mixture was a creamy aqueous suspension having both low solubility and high solubility saccharides in water. The moisture was then removed from the suspension to obtain molded tablets.

1.3.3 Compaction:

Using a conventional tablet press to make fast-dissolving tablets is a very attractive method because of the low manufacturing cost and ease in technology transfer. However, the tablet press has been designed to make conventional tablets. When making conventional tablets, maintaining high tablet porosity is not a primary concern, and high compression force is used to ensure the tablet strength. Many strategies have been tried to achieve high porosity and adequate tablet strength using a tablet press. First several granulation methods have been tried to obtain granules suitable for making FDTs. Wet granulation, dry granulation, spray drying, and flash heating methods have been tried. The second approach is to select special types of excipients as the main component for FDTs.

The third approach is to compress tablets at low pressure and apply various after-treatments to the soft tablets. The three most widely used approaches are described in detail below.

i) Granulation methods:

a. Wet granulation:

It was found that even with effervescent agents presented in the tablet with lower than 5%, quick disintegration times could be achieved. Furthermore, it was also found that fast disintegration time could be achieved using only the acid component of the effervescent couple. In the patent, the formulation includes polyalcohols (e.g., mannitol, xylitol, sorbitol, maltitol, erythritol, and lactitol), 1–30% of an edible acid, and an active ingredient as the dry mixture. This mixture was wet granulated with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., poly(ethylene glycols), carrageenan, and ethylcellulose), which consisted of 1–10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained, and the tablets made by such granules had rapid disintegration times ranging from 3 to 30 seconds in the saliva.

b. Dry granulation:

Higher density alkali earth metal salts and water-soluble carbohydrates usually do not provide quick disintegration and a smooth mouth feel. Low-density alkali earth metal salts and water soluble carbohydrates are also difficult to compress and caused inadequate content uniformity. For these reasons, low-density alkali earth metal salts or water-soluble carbohydrates were precompacted, and the resulting granules were compressed into tablets that could dissolve fast. In this process, a powdered material with a density of 0.2–0.55 g/mL was precompacted to increase the density to 0.4–0.75 g/ml by applying a force ranging from 1 to 9 kN/cm. The resulting granules were compressed into tablets.

c. Melt granulation:

A new approach of preparing FDTs with sufficient mechanical strength, involving the use of a hydrophilic waxy binder (SuperpolystateR, PEG-6-stearate) by melt granulation or wet granulation. Because SuperpolystateR is a waxy material with a melting point of 33–37 °C and a hydrophilic to lipid balance (HLB) value of 9, it will not only act as a binder and increase the physical strength of tablets but also help the disintegration of the tablets. In case of melt granulation, granules were prepared in a high-speed blade mixer at 40–44 °C, according to the conventional hot-melt procedure. For wet granulation, an oil-in-water emulsion of SuperpolystateR was used as the granulating

agent. Then, granules were blended with crosscarmellose, aspartame, and magnesium stearate and compressed into tablets. The melt granulation FDTs had better hardness results than the wet granulation FDTs. The disintegration times of melt granulation tablets, however, was more than 1 minute.

d. Spray drying:

Spray drying methods are widely used in pharmaceutical and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous, fine powders. Allen and Wang produced a particulate support matrix for use in making FDTs by a spray-drying technique. The components included supporting agents composed of two polypeptide components of the same net charge (preferably nonhydrolyzed and hydrolyzed gelatin), a bulking agent (mannitol), and a volatilizing agent. To maintain the net charges of the polypeptide components, an acidifying or alkalinizing agent was included. The mixtures of the above components were spray dried to obtain porous granules. The reason to use polypeptide components of the same charge was that molecules would repel each other even after spray drying, so porous and low-bulk-density particles could be formed. By incorporating a volatilizing agent (ethanol in most cases), the surfacetension of the droplets was further reduced during spray drying, and more pores and channels were created. The dissolution rate of the matrix was further increased when combined with a bulking agent. A minimal amount of an effervescent agent was optionally included to further accelerate the dissolution rate. To aid in keeping the tablets intact during handling, a thin coating of polymeric material could be applied externally. This coating should not inhibit the capillary uptake of water during dissolution. Active ingredients can be microencapsulated or nanoencapsulated to further achieve taste masking.

e. Flash heat process:

Fuisz Technologies (Chantilly, Virginia) has introduced the Shearform Technology to make Flashdose. The Shearform Technology uses a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. In this process, the feedstock is subjected to centrifugal force and to a temperature gradient simultaneously. An internal flow is created by this condition to force the fl owing mass out of the opening provided in the perimeter of a spinning head. The mass is cooled down as it comes out of the opening to form a discrete fiber structure, as seen in cotton candy. The speed of spinning is about 3,000–4000 rpm, and the temperature gradient is about 180–250°C. The carrier materials include saccharides, polysaccharides, and mixtures

thereof. There were two systems used to create the Shearform floss having self-binding properties. The first system was named a single floss or unifloss. Typical flosses of this kind, made of sucrose, sorbitol, and xylitol, yielded effective selfbinding properties. The second system used two separate flosses. One was xylitolcontaining binder flosses and the other was base flosses that contain different sugar alcohols or saccharide. When the two flosses were combined, it was termed a dual floss system. The produced floss needed to be recrystallized to form freely flowing granules with self-binding properties. Two techniques were used in recrystallization. One was using crystallization enhancers including ethanol, polyvinylpyrrolidone, water (e.g., moisture), glycerin, and radiant energy (e.g., microwaves). The other was using crystallization modifiers, which were included in floss ingredients at 0.01–20.0% the weight of the floss. Typical crystallization modifiers were surfactants having an HLB of about 6 or more. A hygroscopic material such as xylitol must be present in the system to provide good self-binding characteristics to the final matrices. In order to produce and control the self-binding properties, this hygroscopic material must have a substantially higher hygroscopicity than that of the carrier carbohydrate (e.g., sucrose). The initial floss coming out of the spinning machine is in its amorphous state. However, because of its tendency to pick up moisture in the floss and induce crystallization by crystallization enhancers or modifiers, the floss recrystallizes into a more crystalline structure. Because of intimate contacts among all components in the matrix, recrystallization of one component can have significant impact on the characteristics of surrounding components and further change the properties of the matrix as a whole. The floss gradually loses its amorphous character as the recrystallization continues. The flowability of the floss is enhanced to make it suitable for the conventional tableting process.

ii) Direct compression:

From the pharmaceutical manufacturer's point of view, direct compression is the simplest and 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 and sweetness, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations.

a. Disintegrants used in FDT:

Some patents use effervescent couples as their disintegrant, while others use a combination of disintegrants.

Dobetti summarized different types of non-effervescent disintegrants used in the pharmaceutical area.

• **Starch and modified starches.** This group includes natural starches (such as maize starch and potato starch), directly compressible starches (such as starch 1500), modified starches (such as carboxymethylstarches and sodium starch glycolate), and starch derivatives (such as amylose).

• **Cross-linked polyvinylpyrrolidone**

• **Modifi ed celluloses** such as cross-linked sodium carboxymethylcellulose

• **Alginic acid and sodium alginate**

• **Microcrystalline cellulose**

• **Methacrylic acid-divinylbenzene copolymer salts**

In addition, poly (acrylic acid) superporous hydrogel (SPH) microparticles were recently reported as superdisintegrants possessing a unique porous structure.31 They were used as a wicking agent to decrease the disintegration time of FDTs. The poly(acrylic acid) SPH microparticles can swell approximately 80 times in distilled water and 50 times in pH 6.8 which contains 0.2 M phosphate buffer. The SPH microparticle size had a significant effect on the disintegration time and tensile strength of ketoprofen FDTs. The minimum disintegration time was observed when the microparticle size was in the range of 75-106 μm. Tensile strength of the tablets decreased as the SPH microparticle sizes decreased from 180-250 μm to 25-44 μm. However, when the microparticle sizes were smaller than 25 μm, the tensile strength of the resultant tablets increased as the size decreased. The optimal microparticle size should be in the range of 75-106 μm. The FDTs made of SPH microparticles in the range of 75-106 μm showed the fastest disintegration time (15.0 ± 2.0 s) and higher tensile strength (84.4 ± 4.1 N/cm2).

b. Inorganic excipients used in FDT:

Dobetti has developed a formulation using insoluble inorganic excipients as the main component for FDTs. According to the patent, disintegration of a tablet depends on the quantity of the disintegrant and insoluble inorganic excipient used. The disintegration also depends on the relative weight ratio between the water insoluble and soluble excipients, if the water-soluble excipients are used. It was also found that in their formulations, sufficient compression could be applied to form tablets with strong tensile

strength and low friability. The disintegration rates were not significantly affected by the high compression force. In the formulation, three major components were used:

• **Substantially water insoluble components:** This group includes water-insoluble excipients, water-insoluble drugs (either coated or uncoated), and water- insoluble lubricant and glidant. The water-insoluble excipients include insoluble inorganic salt (e.g., di- or tri-basic calcium phosphate) or organic filler (e.g., microcrystalline cellulose).

• **Substantially soluble components:** This group includes compressible sugars, flavouring agents, sweeteners, binders, and surfactants.

• **Disintegrants:** Examples are maize starch or modified starch, cross-linked polyvinylpyrrolidone, or sodium carboxymethylcellulose.

The disintegration time increased as the amount of insoluble component decreased. If the active ingredient was only a small portion of the whole formulation, the disintegration time could be optimized by including insoluble fillers (e.g., microcrystalline cellulose and silicon dioxide) or by increasing the amount of insoluble inorganic excipients (e.g., calcium salt such as dibasic calcium phosphate).

iii) Compaction and subsequent treatments:

a. Sublimation:

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When volatile materials are compressed into tablets using the conventional method, they can be removed via sublimation, resulting in highly porous structures. The volatile materials include urea, ammonium carbonate, ammonium bicarbonate, hexa methylene tetramine, and camphor. Heinemann disclosed a process to prepare porous tablets by sublimation. The mixtures of volatile adjuvants were made into tablets, which were subsequently heated to remove them. Roser and Blair used vacuum to remove the volatile materials. The full dissolution time was reduced from 10–15 minutes for the tablets formed from trehalose alone to less than 1 minute. In some cases, menthol, camphor, thymol, an organic acid such as adipic acid, and a lower fatty acid such as arachidic acid, capric acid, myristic acid, and palmitic acid were used as the volatile materials, and the sublimation temperature ranged from 40 to 60 °C. The disintegration time in the human mouth was claimed to be about 25 seconds.

Lo disclosed an efficient method for preparing high-strength, highly porous, fast-dissolving delivery devices. In this method menthol, a water-soluble, mentholsoluble polymer, and an active ingredient are mixed at a temperature that insures that the menthol

is substantially molten. The formulation is disposed in a mold and solidified, and the menthol is sublimed from the solidified molded formulation. Preferably, the solidification occurs at a temperature sufficient to provide a substantially amorphous menthol structure.

b. Humidity Treatment:

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase is known to be due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. As shown in Fig. No.1.6, when solid particles start to pick up moisture from the atmosphere, the water is adsorbed onto the surface (A), and then water molecules form a film on it with the vapor pressure over the adsorbed moisture layer equal to P_b (B). The solid starts to dissolve into the adsorbed moisture layer and the dissolution of solid in the adsorbed moisture will lead to a decrease in the vapor pressure P_b (C). The decrease in P_b is effectively off set by the increase in temperature of the film (and the solid) caused by the heat released on condensation of the water vapor. The moisture sorption occurs spontaneously, and the thickness of the condensate film grows as long as $P_a > P_b$. The solid continues to dissolve and saturate the fi lm, maintaining the vapor pressure over the adsorbed moisture layer (P_b). After drying, a solid bridge is believed to occur and increase bonding between the particles (D). It is also known that certain types of sugar change from the amorphous to the crystalline state when their solution is spray dried or used as a binder solution. Further investigations have shown that when an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially. The conceptual process of structural changes of amorphous sucrose to crystalline sucrose is shown in Fig. No.1.7.
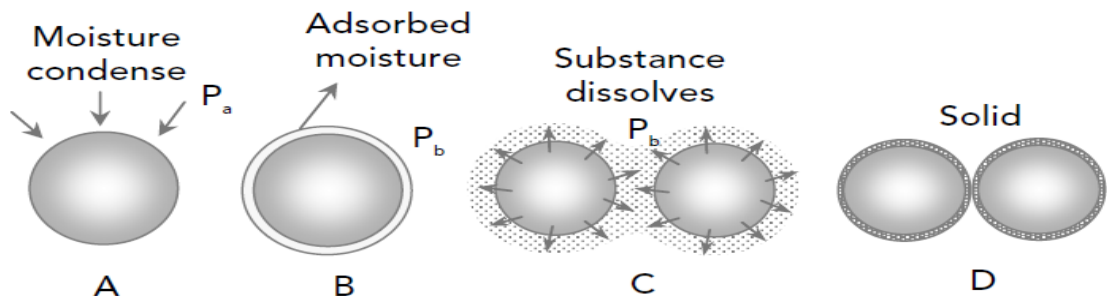
Fig.No.1.6 moisture sorption model explaining the increase mechanical strength of FDT
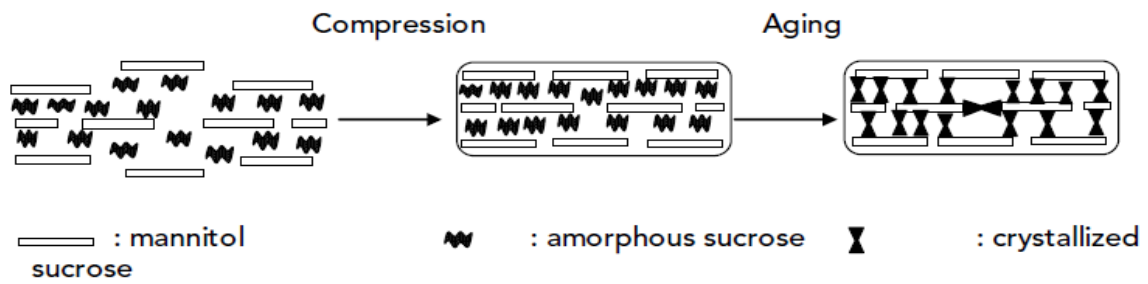
Fig.No.1.7 model describing the increase in tablet strength by transformation of amorphous sucrose to crystalline sucrose upon storing under a certain relative humidity

In a patent by Mizumoto et al., a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. After the tablets were formed, they were humidified and dried. The amount of the sugar in the formulation can be adjusted according to the drug content and tablet size. The "amorphous sugars" are those that can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactitol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity greater than or equal to the critical relative humidity of this mixture is chosen for the humidity condition. The advantage of using amorphous sugars is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. The crystalline form of the sugars has difficulty in controlling moisture absorption. Moisture absorption of the crystalline form is not sufficient to strengthen the tablets at a low humidity condition. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems. Another advantage of using amorphous sugars is that transformation of the amorphous state to the crystalline state is irreversible. The sugars in crystalline state have a high critical moisture point, so the strengthened tablets are less susceptible to moisture. System for making FDTs by humidity treatment consist following steps: (1) a water-soluble polymer was used as a binder solution to granulate active ingredients and other excipients, such as low modability sugars; (2) the granules were then compressed into tablets; (3) the tablets were humidified at relative humidity of about 50–100%; and (4) the tablets were dried. The hardness of the tablet was about 0.5–12.0 kilopounds, and the in vivo disintegration time was claimed to be about 1–40 seconds.
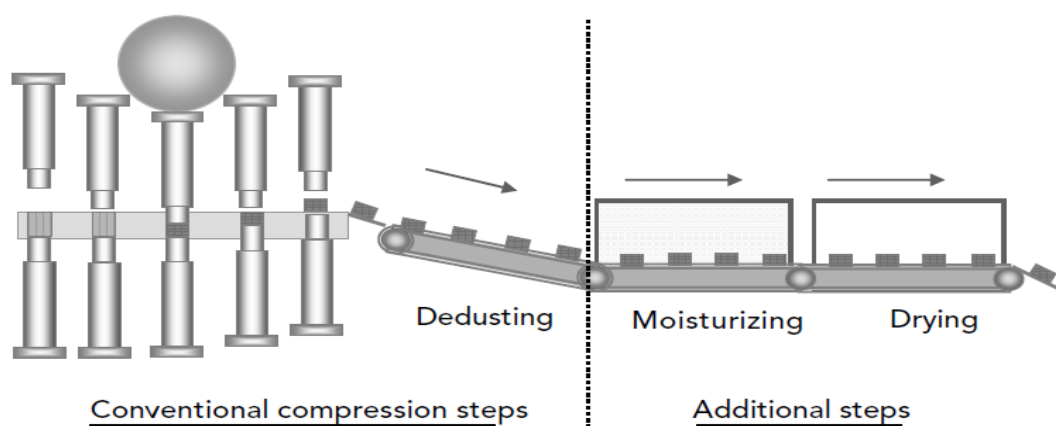
Fig.No.1.8 Schematic view of the manufacturing apparatus using moisture treatment

The left side of a dotted line shows the conventional compression and dedusting steps, while the right side shows the additional step requiring special chambers for moisture treatment and drying.

Tatara et al. also used moisture treatment and devised an apparatus to handle the fragile tablets before moisture treatment. An active ingredient and other excipients were compressed in low pressure, and then the resultant tablets were moisturized and dried to produce porosity between 20 and 40%. the manufacturing apparatus includes a rotary punch-press, a relay conveyor for transferring tablets, a moisturizing section, a drying section, and a delivery conveyor. In the moisturizing section, the condition was set to allow tablets moisturized at 45 °C, 95% relative humidity for 60 seconds. In the drying section, the temperature was set to 50 °C for 60 seconds. With this apparatus the fragile tablets before moisture treatment were gently transferred throughout the process.

c. Sintering:

Lagoviyer et al. disclosed a process that increased tablet strength by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. The components in this formulation include bulk agents, structure agents, solvent, and binding agents. A bulk agent in this formulation is used to provide bulk volume to the overall tablet, and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. The suitable structure agents should provide dedusting, moisturizing, drying and conventional compression steps. The left side of a dotted line shows the conventional compression and dedusting steps, while the right side shows the additional step requiring special chambers for moisture treatment and drying. A porous support structure to allow quick dissolution of the tablets in the mouth. The structural agents include agar, gelatin, albumin, and chondroitin. Bulking and structural agents were

dissolved in a suitable solvent, and the dissolved mixture was spray dried or dispersed to obtain a bead or granulated product with a low density. Choice of the solvent is based on its ability to provide a desired porosity to the bead or granulated product upon drying. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol, or a mixture thereof. The binders need to melt at the sintering stage, form bonding among granules, and resolidify as the temperature of the final sintering or heating step decreases. Binders are water soluble polymers such as poly (ethylene glycol) (PEG), with a molecular weight of approximately 1000 to 1,000,000. PEG melts at 50–90 °C. PEG has the advantage of functioning both as a binder and as a capillary attractant. The amount of binding polymer ranged from 0.5% to 25% of the weight of the final product. The binding agents and active ingredients can be introduced to the formulation in several ways. A binding agent and active ingredient can also be dry blended to the spray-dried or dispersed granulated product. They can alternatively be dissolved into solvent with bulking agent and spray dried into granules. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra-tablet bonds and help weld the product shape together. Typically, a laboratory oven is set at around 50–100 °C. The heating time ranges from 3 to 45 minutes. The binding agents are resolidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3–60 seconds. The heat treatment or sintering step in the patent improved the product's strength and durability. Because the active ingredient can be introduced into the formulation in several ways, taste-masking technologies can be easily incorporated into the process. The dosage form allows the incorporation of a wide range of dosage levels. Because of the high temperature treatment, when heat-labile drugs are incorporated in the formulation, careful attention should be given in this process. These technologies are commonly applied for the production and development of FDTs.

1.4 FDT FORMULATION TECHNOLOGY:

Because the direct compression is most desirable in terms of producing FDTs with high mechanical strength, ease of manufacturing, and low cost, currently available FDT formulations using direct compression are described in detail.

1.4.1. OraSolv and DuraSolv Technology [7]:

OraSolv technology (Cima Labs) produces tablets by low compression pressure. It uses an effervescent disintegration pair that releases gas upon contact with water. The widely used effervescent disintegration pairs usually include an acid source and a

carbonate source. The acid sources include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids. The carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. The carbon dioxide evolved from the reaction may provide some "fizzing" sensation, which is a positive organoleptic sensation. The amount of effervescent agent is in general about 20–25% of the total weight of the tablet. Because of the soft and fragile nature of OraSolv tablets, a special packaging system, known as PakSolv, was developed to protect the tablets from breaking during transport and storage. PakSolv is a "dome-shaped" blister package that prevents the vertical movement of the tablet within the depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolv also offers light, moisture, and child resistance. As a second-generation technology, the DuraSolv technology was developed by Ciba to provide stronger tablets for packaging in blisters or bottles. The key ingredients in this formulation are nondirect compression filler and lubricant. The particle size of the nondirect compression filler is preferably between about 20 and 65 μm, while for direct compressible fillers at least 85% of the particles are over 100 μm in size. These nondirect compression fillers, such as dextrose, mannitol, sorbitol, lactose, and sucrose, have the advantage of quick dissolution and avoid some of the gritty or sandy texture usually present in direct compressible versions of the sugar. The amount of a nondirect compression filler is usually about 60–95% of the total tablet weight. The tablets have low friability, which is about 2% or less when tested according to the USP, and the hardness of the tablets is at least about 15–20 N. The disintegration time is less than 60 seconds. About 1–2.5% of lubricant can be added to the formulation, compared with 0.2–1% of lubricant in conventional tablets. The lubricant blending times can also be increased to 10–25 minutes or longer. Relatively modest compressive force is needed to compress the formulation. This method can produce tablets by the direct compression method and use conventional tableting methodologies and conventional package equipment. Thus, the production cost is significantly decreased.

Fig. No. 1.9 Typical PakSolv package

1.4.2. Wowtab Technology:

WOWTAB technology employs a combination of low- and high-moldability saccharides to produce fast-dissolving tablets using conventional granulation and tableting techniques. According to the patent, saccharides were divided into two groups: those with high moldability and those with low moldability. Lowmoldability saccharides produce tablets with hardness between 0 and 2 kg, when 150 mg of such a saccharide is compressed under pressure of 10–50 kg/cm2 using a die 8 mm in diameter. The typical low-moldability saccharides include lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides produce tablets with hardness above 2 kg when prepared under the identical conditions. The typical high- moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When tablets are made by compressing a saccharide having low moldability or high moldability alone, the desired properties of adequate hardness and quick disintegration in the mouth cannot be achieved simultaneously.

Moreover, if saccharides having low moldability and high moldability are mixed (physical mixture) before tableting, quick disintegration and dissolution in the mouth cannot be obtained. As clearly indicated in the patents, there is no single saccharide that can make tablets having both high strength and fast disintegration properties. For this reason, a saccharide having low moldability was granulated with a saccharide having high moldability as a binder. The low-moldability saccharides were used as the main component. The tablets show an adequate hardness and fast disintegration and dissolution when put in the mouth.

1.4.3. Flashtab Technology:

Flashtab technology (Ethypharm, France) produces tablets by compression of granular excipients. This technology uses almost the same excipients as do conventional

compressed tablets. Excipients used in this technology comprise two groups of components: disintegrating agents, such as carboxymethylcellulose or insoluble reticulated polyvinylpyrrolidone; and swelling agents, such as carboxymethylcellulose, starch, modified starch, carboxymethylated starch, microcrystalline cellulose, and possibly directly compressible sugars. The mixture of excipients is prepared by either dry or wet granulation methods. The produced tablets are known to have satisfactory physical resistance and disintegrate in the mouth within 1 minute.

1.4.4. AdvaTab Technology:

AdvaTab technology (Eurand) produces FDT tablets based on a proprietary tablet composition that was designed and patented by Kyowa Hakko Kogyo (Tokyo, Japan), in which the lubrication is dispensed onto each tablet by using a spray during the production process. Traditional tablets are produced using an internal lubrication system, which disperses lubricant on the inside and the surface of the tablets. This method can decrease tablet mechanical strength. AdvaTab is produce d using 10–30 times less hydrophobic lubricant and can be 30–40% stronger than conventional tablets. As a result, the tablets are hard and durable yet do not impede liquid entry upon contact with saliva. AdvaTab can handle high drug loading and coated drug particles. Importantly, the technology does not require specialty packaging and, as a result, can be packaged in both standard bottles and push-through blisters.

1.4.5. Dispersible Tablet Technology:

Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8–10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

1.4.6. Pharmaburst Technology:

Pharmaburst technology (SPI Pharma, New Castle, Delaware) uses off -the-shelf coprocessed excipients to create an FDT that, depending on the type of active and loading

(up to 700 mg), dissolves within 30–40 seconds. The quantity of Pharmaburst required in a formulation depends on the active in the tablet. It is necessary to carry out initial studies on a formulation by varying the amount of Pharmaburst from 50 to 80%, depending on the desired mouth feel and disintegration time. The process involves a dry blend of a drug, flavor, and lubricant that are compressed into tablets on a standard tablet press with stock tooling. The manufacture process can be carried out under normal temperature and humanity conditions. The tablets can be packaged in blister packs or bottle.

1.4.7. Frosta Technology:

The core concept of Frosta technology is compressing highly plastic granules at low pressure to produce strong tablets with high porosity. The highly plastic granules comprise three classes of components: a porous and plastic material, a water penetration enhancer, and a binder. The highly plastic granules can then be compressed at low pressure to form a fast-melting pharmaceutical tablet. A porous, plastic material is water soluble or water dispersible, sometimes almost instantaneously upon contact with water. Plastic deformation of powders dramatically increases the chance of the interparticle contacts necessary to form bonds between particles. If a porous and plastic material is polymeric, it is essential to prevent formation of a viscous layer of the material at the tablet surface when it dissolves in aqueous medium. One way of making such tablets is to mix porous, plastic material with a water penetration enhancer at certain ratios. In this process, the porous and plastic particles are separated by water-penetration-enhancing particles, which prevent formation of a viscous layer on the tablet surface. The binder here can also secure the porous material and water penetration enhancer during granulation. These two components can be easily segregated during mixing without the binder. If the binder is in the liquid or semi-solid state, it should not significantly destroy the porous structure of the porous materials. One way of achieving this is to use aqueous binder solutions with very low water activity. The highly plastic granule approach produces FDTs with excellent hardness and fast disintegration time ranging from several seconds to about 30 seconds, depending on the size of the tablets.

Table No. l.2 Examples of commercially available, preapproval, or submitted orally disintegrating tablet products

Technology	Brand name	Active ingredient	Company	Application
Zydis®	Claritin® RediTabs®	Loratadine	Schering Corporation Zydis®	Antihistamine
	Feldene Melt®	Piroxicam	Pfi zer	NSAID
	Maxalt®-MLT®	Rizatritpan benzoate	Merck	Migrane
	Zyprexa®	Olanzapine	Eli Lilly	Psychotic disorders
	Zofran® ODT®	Ondansetron	Glaxo Smith Kline	Anti-emetic
Quicksolv®	Propulsid® Quicksolv®	Cisapride monohydrate	Janssen	Gastrointestinal prokinetic agent
OraSolv	Tempra Quicklets Tempra FirsTabs	Acetaminophen	Bristol-Myers Squibb	Analgesic
DuraSolv®	Alavert®	Loratadine	Wyeth Consumer Healthcare	Allergy
	NuLev®	Hyoscyamine sulfate	Schwarz Pharma	Anti-ulcer
WOWTAB®	Benadryl® Fastmelt®	Diphenhydramine citrate	Pfi zer	Allergy ,sinus pressure relief
	Nasea OD	Ramosetoron HCl	Yamanouchi	Anti-emetic
QuickTabs™	Excedrin® QuickTabs	Acetaminophen	Bristol-Myers Squibb	Pain reliever
FlashDose®	Ralivia FlashDose®	Tramadol HCl	Biovail	Analgesics
	Zolpidem ODT	Zolpidem tartrate	Biovail	Sleep disorders
Flashtab®	Nurofen® Flashtab®	Ibuprofen	Boots Healthcare	NSAID
OraQuick	Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	ETHEX Corporation	Anti-ulcer
Ziplets™	Cibalginadue FAST	Ibuprofen	Novartis Consumer Health	NSAID

1.5. DETERMINATION OF DISINTEGRATION TIME OF FDT

FDTs should be strong enough to survive rough handling during manufacturing and shipping processes, and yet friable enough to instantly dissolve or disintegrate into small particles for easy swallowing by the patient. Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of FDTs because of their fast disintegration. It is also hard to distinguish among FDTs, which release their ingredients very quickly. In vitro testing may not always reflect the real in vivo disintegration of tablets. In general, the method described in the US Pharmacopoeia can produce data for evaluation of the disintegration time; however, no additional information might be extracted. It is also possible to evaluate the tendency of the disintegration kinetics by visual examination. However, these evaluations are not sufficiently objective. When developing FDT formulations, it is important to evaluate the effect of different excipients on the disintegration time. In order to predict the disintegration time of FDTs and the effects of different formulation parameters, a few methods have been proposed. It is important to define a suitable method to better distinguish between the disintegration times of different FDTs and to find better correlation between in vitro and in vivo data. To achieve this goal, a modified dissolution apparatus was applied to FDTs with disintegration times too fast to distinguish the differences between the tablets when the conventional methods were used.

1.5.1. *In-Vivo* determination of disintegration time:

In-vivo disintegration tests of FDTs can be conducted on volunteers who are usually randomized to receive the treatments and then directed to clean their mouths with water. Tablets are placed on their tongues, and the time for disintegration is measured by immediately starting a stopwatch. The volunteers are allowed to move FDTs against the upper roof of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side.

Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.

1.5.1. *In-Vitro* determination of disintegration time:
i) Modified US pharmacopoeia method:

Instead of using the disintegration apparatus described in the US Pharmacopoeia, a modified method has been proposed. The disintegration apparatus was the same as the USP dissolution test Apparatus 2, which uses a paddle stirring element and 1000-mL

cylindrical vessel at 37 °C. Distilled water was chosen for the disintegration medium instead of a buffer solution. A tablet to be tested was put on the bottom of a sinker, which was placed in the middle of the vessel and hung by a hook to the lid of the vessel with a distance of 6–8.5 cm. Disintegration time was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely. The opening of mesh of the sinker was 3–3.5 mm in height and 3.5–4 mm in width.

ii) Texture analyzer method:

The Texture Analyzer (Stable Micro Systems, U.K.) was applied to measure the beginning and ending time of disintegration. A tablet was adhered to the bottom of a probe, which was attached to the load cell with a very thin layer of glue or double-sided tape. A small amount of water, usually 0.4 ml, in a beaker or petri dish was used as a disintegration medium at room temperature. The tablet was submerged in water and compressed against the bottom of the beaker or petri dish with a constant pressure. The beaker size could be varied, and the beaker could even be a water bath to keep the temperature constant. The instrument was programmed to apply a moderate force for up to 60 seconds so that the penetration distance could be measured as the tablet was compressed while submerged in the water. The probe distance would be steady as the tablet remained cohesive. However, as the tablet disintegrated, the compression distances increased, because the probe had to keep the pressure constant. The time for the tablet to disintegrate was determined by measuring the distance the probe travelled into the tablet. Typical time-distance profiles generated by the Texture Analyzer software enabled the calculation of beginning and ending of disintegration time.

El-Arini and Clas performed the in vitro disintegration test of commercially available FDTs by the Texture Analyzer instrument. The differences in the disintegration mechanisms of the FDTs, which derived from the formulation and/or manufacturing process, were reflected in the shape of their disintegration profiles. Moreover, the in vitro disintegration times obtained by the simulated in vivo conditions were correlated with the reported in vivo disintegration times.

3. CCD camera method:

The CCD camera apparatus comprises two distinct sections—a disintegration component and a measurement device. The mode of measurement involves the continuous acquisition of pictures by the CCD camera to record the time course of disintegration. The acquired pictures are simultaneously transferred to the computer and stored. The key point of this apparatus is to combine the detailed pictures obtained by the CCD camera.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises an inner tank containing a stirring bar, a grid fabricated from stainless-steel, and a disintegration medium (distilled water, 200 ml, 37 ± 2 °C); the second component is an outer tank of thermostated water. The grid is constructed of three hollow areas equidistant from the centre. These hollow points represent the position of the tablets, and a support is added for each tablet to avoid movement during the disintegration test.

The CCD camera method permits documentation of the disintegration time course with sequentially obtained pictures. The computer enables calculation of the surface area of each tablet at any time point, as well as the design of graphs that show decrease in the tablet surface area as a function of time. The disintegration time and the area under the curve can be calculated from these graphs as qualitative parameters that can be correlated to the oral disintegration time. Consequently, results depend on the direction and focal length of the camera relative to the tablet. The disadvantage of the method involves difficulty associated with the application of mechanical stress to test tablets. Thus, the time required for a single test is several minutes, which is greater than that for the in vivo disintegration time.

4. Rotary-shaft method:

FDTs generally receive some mechanical stress produced by the tongue in the human mouth. Narazaki et al. developed a suitable disintegration method for FDTs. In this method, the FDT is placed on stainless steel wire gauze, which is slightly immersed in test medium, and a rotary shaft is employed to provide mechanical stress to the tablet by means of its rotation and weight. The critical parameters of this method are the rotation speed and the mechanical stress. To assess our method, several placebo FDTs were prepared and exposed to severe storage conditions (60 °C/75% RH for 1 week) in order to obtain FDTs with a wide range of disintegration times. These placebo FDTs were used to compare the disintegration times obtained by several methods. The disintegration time of the placebo FDTs in human sensory test varied widely after storage. The disintegration times determined by the conventional disintegration test were in good correlation to those in the human sensory test, but the slope was 0.241, far from 1. There was no correlation between the disintegration time of FDTs in the human sensory test and those determined by the conventional dissolution test. In contrast, a good correlation between the disintegration times was obtained and the slope was 0.858, very close to 1. It was concluded that this method was suitable for the measurement of the disintegration time of

FDTs. This new method might provide a valuable approach for establishing the official disintegration test for FDTs in the future.

5. Sieve method:

A simple device based on a shaking water bath was designed to measure the disintegration time of FDTs. The device is composed of a 10-mesh sieve and a glass cylinder. The sieve is placed into the cylinder at a certain position so that 2 ml of disintegration medium fills the space below the sieve of the cylinder. Then, 1 ml of the medium is added into the device, so that it is available for an FDT to be tested. The device is in a reciprocal shaking water bath keeping the temperature at 37 °C. While the shaker is running in horizontal back-and-forth motions with 150 rpm, an FDT is placed onto the top of the sieve immersed in the disintegration medium. The FDT starts disintegration into small particles and/or dissolves. The time at which the particles of the tablet go through the sieve completely is determined as the disintegration time. The disintegration time is measured using a stopwatch, and this quick method gives reproducible data that are highly useful in screening various formulations and testing many formulation variables.

2. LITERATURE REVIEW

2.1 REVIEW OF FDT

Lokesha Puttalingaiah *et al.,* **(2011)**[8] reviewed that oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Fast disintegrating tablets are solid dosage forms which dissolve rapidly in saliva without chewing and additional water, overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in paediatric and geriatric patients. FDT have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several fast disintegrating tablets technologies.

Rakesh Pahwa *et al.,* **(2010)** [9] studied the importance of Orally Disintegrating Tablets which is an alternative to conventional tablet and capsule formulations to obviate the problem of dysphagia and to improve patient compliance. In pediatrics and geriatrics ODTs have gained considerable attention as preferred, these techniques render the disintegration of tablet rapidly and dissolve in mouth without chewing or additional water intake.

Tejvir Kaur *et al.,* **(2010)** [10] aimed to design dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. Though oral drug delivery systems, preferably, tablets are the most widely accepted dosage forms, for being compact, offering uniform dose and painless delivery. Yet, dysphagia is the most common disadvantage of conventional tablets. This is seen to afflict nearly 35% of the general population and associated with a number of conditions, like parkinsonism, mental disability, motion sickness, unconsciousness, unavailability of water etc. To overcome such problems, certain innovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) have been developed. These are novel dosage forms which dissolve in saliva within a few seconds, when put on tongue. Such MDTs can be administered anywhere and

anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients.

Sharma Shailesh *et al.,* **(2010)** [11] studied Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. The FDT has remarkable disintegration properties; without water, it is rapidly disintegrated in the mouth within only a few seconds. When the FDT is placed in the oral cavity, saliva quickly penetrates into the tablet causing rapid disintegration. One of the most important characteristics of the FDT is its disintegration time in the oral cavity; however, a suitable method to access the disintegration properties described in the official books has not been developed. It is difficult to assess the disintegration rate for the FDT with these tests due to its rapid disintegration rate even in a small amount of water. To overcome this problem, several new methods have been proposed.

Debjit Bhowmik *et al.,* **(2009)** [12] reviewed that Fast dissolving Tablets are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, and an unavailability of water, swallowing conventional tablets may be difficult.

Bhupendra G. Prajapati *et al.,* **(2009)** [13] reviewed recent patents on Fast Dissolving Drug Delivery System. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Fast-dissolving/disintegrating tablets

(FDDTs) are a perfect fit for all of these patients. FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate.

Simone Schiermeier *et al.,* **(2002)** [14] formulated fast dispersible tablets which disintegrated either rapidly in water to form a stabilized suspension or disperse instantaneously in the mouth to be swallowed without the aid of water. They employed a rotatable central composite design to predict the effects of the quantitative factors, mannitol and crosspovidone as well as compression force on the characteristics of the tablet.

2.2 REVIEW OF DRUG AND SUPER DISINTEGRANTS

Panati Dinakar *et al.,* **(2010)** [15] aimed to investigate the formulation of bisoprolol fumarate transdermal patches by using Poly vinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) using glycerin as plasticizer for controlled release medication in order to treat the blood pressure and cardiac diseases. Studies disclosed that Bisoprolol is more effective than Propanolol, Atenolol and Metoprolol. After optimizing the polymer ratio the best patches were selected based on the physical evaluation. Then physical evaluation and *in vitro* studies were performed by using Franz diffusion cell employing porcine ear skin as the membrane. From the above results F2 formulation was found to have good controlled release over the formulation F1. Further in order to find the effect of plasticizer in the drug release for the F2 formulation, glycerin was replaced with Tri ethyl citrate (TEC). Thus the prepared film shows good release of about 98.3% with TEC as plasticizer.

Sudhir Bhardwaj *et al.,* **(2010)** [16] formulated and evaluated the fast dissolving tablet of aceclofenac (anti-inflammatory and analgesic) which was selected as the model drug. The poor aqueous solubility of the drug results in variable dissolution rate and hence poor bioavailability. It was concluded that the fast dissolving tablets of the poor soluble drug can be made by direct compression technique using selective super disintegrates

showing enhanced dissolution, taste masking and hence better patient compliance and effective therapy.

R. Margret Chandira *et al.,* (2010) [17] formulated and evaluated mouth dissolving tablets of the etoricoxib which is a new non-steroidal anti-inflammatory drug (NSAID). In the present investigation variety of super disintegrants like primogel, kollidone, ac-di-sol, l-HPMC and l-HPC were selected and tablets were prepared by direct compression method in different concentration like 4% and 8%. The main criteria for mouth dissolving tablets are to disintegrate or dissolve rapidly in oral cavity with saliva in 15sec to 60sec with need of water. The disintegrants used in study fulfills the criteria by disintegrating the tablets in specified time limit.

H. A. Patel *et al.,* (2010) [18] studied the *in-vitro* evaluation of fast dissolving tablets of domperidone, the formulations containing croscarmellose sodium, cross povidone, and sodium starch glycolate as superdisintegrants, disintegrated faster as compared to the formulation containing microcrystalline cellulose and *In-vitro* drug release showed that almost drug was released in the range of 94-97% in 10 minutes. It also concludes that direct compression method is better than wet granulation method

Indhumathi D. *et al.,* (2010) [19] studied the design and optimization of orodissolving tablet of antidepressant drug by superdisintegrants addition method. Mouth dissolving tablet offers a solution for pediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. *In-vitro* dissolution studies showed the release is in the following order of superdisintegrants: crospovidone > pregelatinized starch > croscarmellose > sodium starch glycolate. Maximum *in-vitro* dissolution was found to be with formulation f-7 and crospovidone (4%) conformed to be best by *in-vivo* pharmacokinetic studies

A. Prameela Rani *et al.,* (2010) [20] formulated and evaluated orodispersible metformin tablets and carried out comparative study on isphagula husk and crosspovidone as superdisintegrants. In the present study an attempt has been made to prepare fast disintegrating tablets of Met.Hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with Isphagula husk, natural superdisintegrant and Crosspovidone, synthetic superdisintegrant. The pure drug and formulation blend was examined for angle

of repose, bulk density, tapped density, Compressibility index and Haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 10sec. Based on dissolution rate the disintegrants can be rated as Isphagula husk > Crosspovidone. Hence Ishagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Met.Hcl. All the dissolution parameters were calculated and compared with market tablet. A 3.78 fold increase in the dissolution rate was observed with F4 formulation when compared to market tablet (Glucophage). It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants (natural and synthetic).

Mahaveer P. Khinchi et al., (2010) [21] formulated orally disintegrating tablets of salbutamol sulphate by employing direct compression technique using directly compressible mannitol (pearlitol SD 200), micro crystalline cellulose (MCC), various concentration of super disintegrating agents like Ac-di-sol, Primojel, and Polyplasdone R-XL as 2%, 3%, 4%, and 5%. These formulations were evaluated for thickness, friability, weight uniformity, disintegration time, wetting time, and *in-vitro* dissolution study. All the Formulations has showed satisfactory the result i.e. disintegration was less than one minute and *in-vitro* release was within three minute thus ensure the immediate effect. The formulation A-4 and A-8 prepared by Ac-di-sol 5% and Polyplasdone R- XL 5% showed 100% drug release within two minute and three minute respectively while 100% drug release of marketed conventional tablet was found to be within twenty five minute which was much higher as compared to mouth dissolving tablet.

Suhas M. Kakade et al., (2010) [22] designed mouth dissolving tablets of losartan potassium with a view to enhance the patient compliance and provide a quick onset of action. The main objective of the study was to formulate mouth dissolving tablets of losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug and were prepared by direct compression and using super disintegrants like Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug con-tent, disintegration time and in-vitro

dissolution profile and found satisfactory. Among all, the formulation F3 containing 5%w/w superdisintegrant Polyplasdone XL 10 was considered to be best formulation, which release up to 99.26% in 12 min.

Yamsani Madhusudan Rao *et al*.**, (2010)** [23] reported that formulated Bilayer tablets provided immediate release of glimepiride and metformin HCl as sustained release over a period of 8 hours.The immediate release layer was prepared using sodium starch glycolate as super disintegrant and sustained release using HPMC K4M and sodium carboxy methyl cellulose as polymers and PVP K30 as binder. Formulations containing higher concentration of sodium starch glycolate and SCMC in IR and SR layer respectively were optimised for bilayer tablets.

Raghavendra *et al.,* **(2009)** [24] formulated fast dissolving tablet of poorly soluble drug carbamazepine by direct compression technique with β cyclodextrin complexes using various superdisintegrants such as crosscarmellose sodium, crospovidone, sodium starch glycholate, Indion 414. Carbamazepine is used to control different types of seizers in treatment of epilepsy. Poor solubility in biological fluids and poor bioavailability after oral administration is major problem with this drug. Hence to enhance solubility of drug complex with β cyclodextrin is prepared and compressed in to tablets. Different formulations showed disintegration time between 26.86 to58.54 sec. all formulations showed release of 99.89% within 4 min.

Venkatesh *et al.,* **(2009)** [25] formulated Oro-dispersible tablets of anti emetic drug Ondansetron hydrochloride, it is a very bitter drug and slightly soluble in water. An attempt was made to mask the taste and to formulate into a dispersible tablet by complexation with ion exchange resins, Cationic exchange resins like Indion-204, Indion-234 and Tulsion-335 were utilized for the sorption of drug. Drug- resinates were prepared in drug to resin ratio of 1:5 and 1:6.The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, wetting time, *in-vitro* and *in-vivo* disintegration time, and *in-vitro* dissolution studies. Dispersion not showing any bitter taste, indicate the capability of ion exchange resins used, both as taste masking and super disintegrating agents. Almost more than 90% of drug was released from the formulations within 1 hour.

B. Jayakar *et al.,* (2009) [26] performed design and characterization of fast dissolving tablet of telmisartan by using Superdisintegrants–Crospovidone, Ac-de-sol, and sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate by adding surfactant SLS and hence its bioavailability. The Disintegration time of Fast Dissolving tablets were increased by the addition of concentration of Superdisintegrants.

Raguia Ali Shoukri *et al.,* (2009) [27] studied *in-vitro* and *in-vivo* evaluation of nimesulide lyophilized orally disintegrating tablets development of a lyophilized orally disintegrating tablet that enhanced the in vitro dissolution and in vivo absorption of nimesulide, a drug with poor solubility and poor bioavailability is presented.

C. P. Jain *et al.,* (2009) [28] investigated fast dissolving tablets of Valsartan were prepared using different superdisintegrants by direct compression method. 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. The release of Valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

Narmada G. Y. et al., (2009) [29] formulated fast dissolving tablet of amlodipine besylate for rapid action. Sublimation method was adapted to prepare the tablets by using a 2^3 full factorial design. FT-IR and D.T.A studies revealed that there was no physico-chemical interaction between amlodipine besylate and other excipients. All formulations are evaluated for pre-compression and post-compression parameters, wetting time, water absorption ratio. The results obtained showed that the quantity of starch potato, sodium starch glycolate, camphor significantly affect response variables. The results indicate that the optimized tablet formulation provides a short DT of 8 sec with sufficient crushing strength and acceptable friability. Stability studies of optimized formulation revealed that formulation is stable.

P.S. Zade *et al.,* (2009) [30] designed to prepare bitterless fast dissolving tablet of Tizanidine Hydrochloride using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with

three super disintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. The blend was examined for angle of repose, bulk density, tapped density and hausner's ratio. The tablets were evaluated for hardness, drug content and friability and disintegration time. The disintegration in oral cavity was also tested and was found to be 22 sec. Other tablets were prepared by using camphor as sublimating agent. It was concluded that tablets prepared by addition of superdisintegrant has less disintegration time than those prepared by sublimation method.

3. AIM AND OBJECTIVE

3.1 AIM:

Bisoprolol Fumarate is a cardioselective β-blocker which is used for the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, diuretics, and optionally cardiac glycosides.

The presently preferred route of administration for Bisoprolol fumarate is oral. The oral dosage form is of compressed tablet prepared by direct compression method.

The rapid onset of action is not achieved through conventional dosage form. To overcome this problem fast dissolving drug delivery system was choosen.

The main aim of the present work is to formulate 'Fast Dissolving Tablet' of Bisoprolol Fumarate by using various super disintegrants like Croscarmellose sodium, SSG, Crosspovidone, PVP K-30.

3.2 OBJECTIVES

- To provide a drug delivery system which provides rapid onset of action.
- To provide a drug delivery system which increases the patient compliance, effectiveness of therapy and reduces the chance of adverse effects.
- To develop a physicochemical stable drug delivery system of Bisoprolol fumarate
- To evaluate all the parameters of formulation in detail.
- To optimize the parameters using factorial design.

4. PLAN OF WORK

The present work was carried out to prepare and evaluate Fast Dissolving drug delivery system of Bisoprolol Fumarate with different superdisintegrants in various concentrations. The following experimental protocol was therefore designed to allow a systemic approach to the study.

1. Preformulation studies
    a) Identification and Characterization of Bisoprolol Fumarate
        - Melting point determination
        - FTIR spectroscopy
    b) Preparation of standard calibration curve in pH 1.2
    c) Compatibility studies of drug & excipients by FTIR
2. Evaluation of Pre Compression parameters
    a) Angle of repose
    b) Bulk density
    c) Tapped density
    d) Carr's index
    e) Hausner's ratio
3. Formulation of Fast dissolving tablets of Bisoprolol Fumarate
4. Evaluation of Post Compression parameters
    a) Thickness
    b) Hardness
    c) Weight variation
    d) Friability
    e) Wetting time
    f) Disintegration time
    g) Drug content
    h) *In- vitro* drug release study
    i) Stability studies
5. Statistical optimization of parameters by 3^2 full factorial design

5. DRUG PROFILE

5.1 BISOPROLOL FUMARATE [31]:

Chemical Formula: $C_{18}H_{31}NO_4 \cdot \frac{1}{2} C_4H_4O_4$

Chemical Structure:
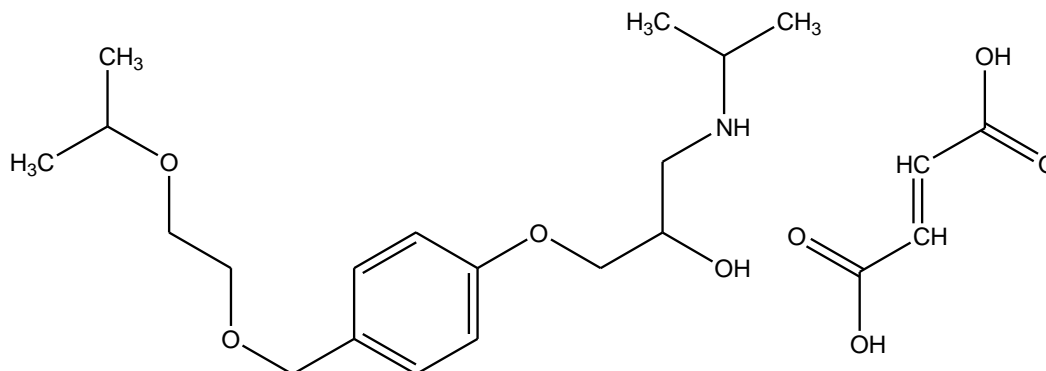
IUPAC Name: (±) -1- [[a- (2-isopropoxyethoxy)-p-tolyl]oxy]-3- (isopropylamino)-2-propanol fumarate

Brand Names: Concor, Zebeta, Concore, Monocor

Drug Category: Selective β1 adrenergic receptor blocker

Molecular Weight: 766.97

CAS number: 66722-44-9

State: Solid

Taste: bitter less

Appearance: It is a white crystalline powder

Melting Point: $101^{o}C$

Solubility: readily soluble in water, methanol, ethanol, and chloroform.

Indication: For the treatment of hypertension

Dose: Minimum 1.25mg to Maximum 10mg/day

Bioavailability: >90%

Pharmacology:

Bisoprolol has both lipid and water soluble properties making it a prime candidate over other β-blockers and even over other β1-blockers, being water soluble it will have decreased incidence of central nervous system side effects (inability to diffuse into brain) compared to purely lipophilic compounds. Bisoprolol has an approximate half-life of 10-12 hours and when ingested has nearly complete absorption into the blood stream. The high absorption is indicative of high bioavailability (approx. 90%). When being eliminated, the body evenly distributes it (50-50) between kidney excretion and liver biotransformation (then excreted). These factors make it a convenient once/day dosage when it's being administered.

Bisoprolol beta 1-selectivity is especially important in comparison to other non-selective beta blockers. The effects of the drug are limited to areas containing β1 adrenoreceptors which is mainly the heart and a little bit of the kidney. Bisoprolol minimizes the side effects that might occur from administration of a non-specific beta blocker where blockage of the other adrenoreceptors (β2, β3, α1, α2) occurs. The other receptors elicit a variety of responses in the body and blockage of them could cause a wide range of reactions; but β1 adrenoreceptors are cardio specific for the most part, making Bisoprolol ideal for treatment of cardiac events. Bisoprolol has a higher degree of β1-selectivity compared to other β1-selective β-blockers such as atenolol, metoprolol and betaxolol.

Mechanism of Action:

Bisoprolol is cardioprotective because it selectively and competitively blocks catecholamine (adrenalin) stimulation of beta-1 adrenergic receptors (β1 adrenoreceptor) mainly found in the heart muscle cells and heart conduction tissue (cardio specific) but also found in juxtaglomerular cells in the kidney. Normally adrenalin and noradrenalin stimulation of the β1 adrenoreceptor activates a signalling cascade (Gs protein and cAMP) which ultimately lead to increased contractility and increased heart rate of the heart muscle and heart pacemaker respectively. Bisoprolol competitively blocks the activation of this cascade and therefore decreases the adrenergic tone/stimulation of the heart muscle and pacemaker cells. Decreased adrenergic tone shows less contractility of heart muscle and lowered heart rate of heart pacemaker.

These are the favourable factors that are decreased and treat hypertension, heart attacks and ischemia. The decreases in contractility and heart rate are beneficial for hypertension because they reduce blood pressure but for preventive measures for heart attacks and cardiac ischemia these decreases in heart rate and contraction decrease the hearts demand for oxygen and nutrients; primary treatment post heart attacks is to prevent recurrence of the infarction.

Absorption:

Bisoprolol fumarate is almost totally (> 90%) absorbed after oral administration. On its first passage through the liver (first-pass effect) a maximum of 10% of the dose is inactivated by metabolisation.

The high absorption rate and small first-pass effect result in an absolute bioavailability of 88%. Bisoprolol fumarate can be taken on an empty stomach or with breakfast

Protein Binding:

Plasma protein binding is about ~30%

Biotransformation:

Minimally metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Half Life: Elimination half-life: 10 −12 h

6. EXCIPIENTS PROFILE

6.1 CROSCARMELLOSE SODIUM [32]:

Chemical Formula: $[(C_6H_{10}O_5) Na^+] n$ $n \sim 220$

Chemical Structure:
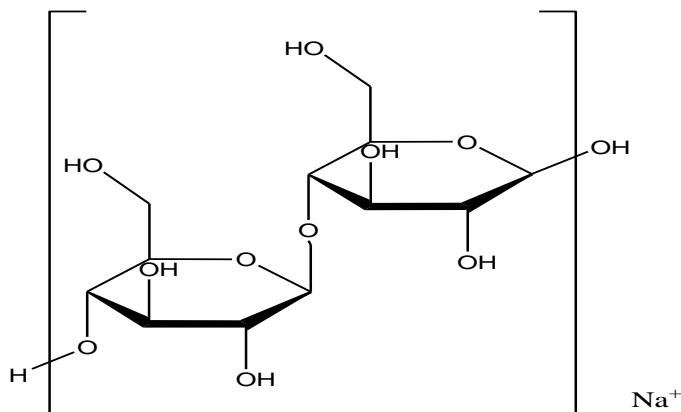
CAS number   : 74811-65-7

Synonyms   : Ac-Di-Sol; Cross linked carboxymethylcellulose sodium;

                   explocel; modified cellulose gum; primellose; solutab.

Chemical name   : Cellulose, carboxymethyl ether, sodium salt, cross linked.

Nonproprietary name: BP: Croscarmellose sodium.

                   PhEur: Carmellosumnatricumconexum.

                   USPNF: Croscarmellose sodium.

Functional category   : Tablet and capsule disintegrant.

Molecular weight   : 90000 – 700000

Melting point   : brown at 227^0C, chars at 252^oC

Description   : as an odorless, white or grayish White Powder.

Solubility   : Insoluble in water, but rapidly swells 4 to 8 times it's

                   Original volume on contact with water.

Application: Croscarmellose sodium is used in oral pharmaceutical formulation as a disintegrant for capsules, tablets, and granules.

In tablet formulations, Croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 15% w/w may be used as a tablet disintegrants.

Stability and storage conditions:

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

6.2 SODIUM STARCH GLYCOLATE [33]:

Chemical Formula: $(C_{26}H_{44}O_{17}Na)n$

Chemical Structure:
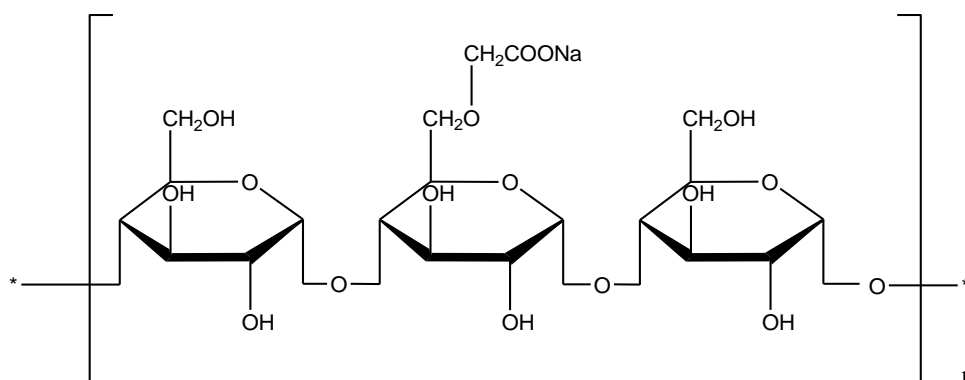
CAS number : 9063-38-1

Synonyms : Carboxymethyl starch, sodium salt, explotab, primojel,

vivastar p.

Chemical name:	Sodium carboxymethyl starch.
Nonproprietary names:	BP: Sodium starch glycolate.
	PhEur: Carboxymethylamylumnatricum.
	USPNF: Sodium starch glycolate.
Functional category:	Tablet and capsule disintegrant.
Molecular weight:	500000-1000000
Melting point:	Does not melt, but chars at approximately $200^{o}C$
Description:	Sodium starch glycolate is a white to off-white, odour, tasteless, free flowing powder. It consist of oval or spherical granules 30-100µm in diameter.
Swelling capacity:	In water, sodium starch glycolate swell up to 300 times in volume.

Solubility:

Sparingly soluble in ethanol (95%), practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer. It swells up to 300 times of its volume in water.

Applications:

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either by direct compression or wet granulation processes. The usual concentration employed in the formulation is between 2 % and 8 %, with the optimum concentration about 4 % ,although in cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Storage and stability:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Its physical properties remain unchanged up to four years if it stored in moderate temperature and humidity.

Regulatory status:

Included in the FDA inactive ingredients guide (oral capsule and tablets) included in nonparental medication licensed in the UK

6.3 CROSSPOVIDONE [34]:

Chemical Formula: $(C_6H_9NO)_n$

Chemical Structure:
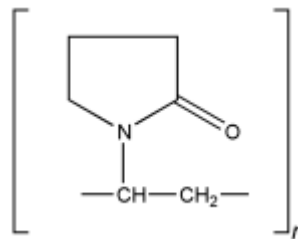
Synonym: PVP, Povidone, PolyvidonePoly [1-(2-oxo-1-pyrrolidinyl) ethylene] 1-

Ethenyl-2-pyrrolidon homopolymer 1-Vinyl-2-pyrrolidinon-Polymere

Copovidone PNVP

CAS number: 9003-39-8

Molecular formula: $(C_6H_9NO)_n$

Molar mass: 2.500 - 2.5000.000

Appearance: white to light yellow, hygroscopic, amorphous powder

Density: 1, 2 g/cm³

Melting point: 110 - 180 °C (glass temperature)

Solubility: Completely insoluble in water, acids, alkalis, and all organic

solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses

in water, but Does not gel even after prolonged exposure

Physical Characteristics: pH (10% slurry): 5.0 – 8.0 Moisture (Karl-Fisher): £ 5.0%

Uses:

1. Medical

The polymer PVP was used as a blood plasma expander for trauma victims after the first half of the 20th century. It is used as a binder in many pharmaceutical tablets; it simply passes through the body when taken orally. However, autopsies have found that crospovidone does contribute to pulmonary vascular injury in substance abusers who have injected pharmaceutical tablets intended for oral consumption. The long-term effects of crospovidone within the lung are unknown. PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known for instance under the trade name Betadine.

2. Technical

PVP is also used in many technical applications:

➤ As adhesive in glue stick and hot melts
➤ As special additive for batteries, ceramics, fibreglass, inks, inkjet paper and in the chemical-mechanical planarization process
➤ As emulsifier and disintegrant for solution polymerization
➤ As photoresist for cathode ray tubes (CRT)
➤ use in aqueous metal quenching
➤ for production of membranes, such as dialysis and water purification filters
➤ As a binder and complexation agent in agro applications such as crop protection, seed treatment and coating
➤ As a thickening agent in tooth whitening gels
➤ As an aid for increasing the solubility of drugs in liquid and semi-liquid dosage forms (syrups, soft gelatine capsules) and as an inhibitor of recrystallisation
➤ As an additive to Doro's RNA extraction buffer

3. Other uses

PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives that must be moistened, such as old-style postage stamps and envelopes. It has also been used in contact lens solutions and in steel-quenching solutions.

PVP is the basis of the early formulas for hair sprays and hair gels, and still continues to be a component of some. As a food additive, PVP is a stabilizer and has E number E1201. PVPP is E1202. It is also used in the wine industry as a fining agent for white wine. Other references state that polyvinyl pyrrolidone and its derivatives are fully from mineral synthetic origin. Therefore, its use in the production should not be a problem for vegans.

In molecular biology, PVP can be used as a blocking agent during Southern blot analysis as a component of Denhardt's buffer. It is also exceptionally good at absorbing polyphenols during DNA purification. Polyphenols are common in many plant tissues and can deactivate proteins if not removed and therefore inhibit many downstream reactions like PCR.

Safety:

The USFDA has approved this chemical for many uses and it is generally considered safe. However, there have been documented cases of allergic reactions to PVP/povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the PVP has come in contact with autologous serum (internal blood fluids) and mucous membranes. For example, a boy having an anaphylactic response after application of PVP-I (PVP-Iodine) for treatment of impetigo was found to be allergic to the PVP component of the solution. A woman, who had previously experienced urticaria (hives) from various hair products, later found to contain PVP, had an anaphylactic response after povidone-iodine solution was applied internally. She was found to be allergic to PVP. In another case, a man experiencing anaphylaxis after taking acetaminophen tablets orally was found to be allergic to PVP.

Povidone is commonly used in conjunction with other chemicals. Some of these, such as iodine, are blamed for allergic responses, although testing results in some patients show no signs of allergy to the suspect chemical. Allergies attributed to these other chemicals may possibly be caused by the PVP instead.

6.4 PVP K-30 [35]:

Nonproprietary Names:	BP: Povidone
	JP: Povidone
	PhEur: Povidonum
	USP: Povidone
Synonyms:	E1201; <u>Kollidon</u>; <u>Plasdone</u>; poly[1-(2-oxo-1-yrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.
Chemical Name:	1-Ethenyl-2-pyrrolidinone homopolymer
Chemical Formula:	$(C_6H_9NO)_n$
Molecular Weight:	2500–3 000 000

Structural Formula:
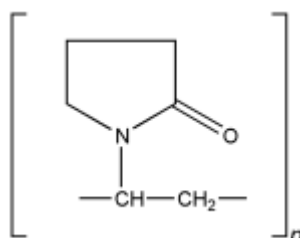
CAS number:	9003-39-8

Functional Category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology

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

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

Uses of PVP K-30:

Table No. 6.1 Uses of PVP K-30

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

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations

Description:

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

Typical Properties:

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).

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

Density (tapped): 0.39–0.54 g/cm^3

Density (true): 1.180 g/cm^3

Flowability: 16 g/s

Melting point: softens at 150°C.

Solubility:

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

Viscosity (dynamic):

the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

6.5 MICROCRYSTALLINE CELLULOSE (MCC) [36]:

Synonyms	:	Avicel, cellulose gel, emocel, fibrocel, tabulose, vivacel
Chemical name	:	Cellulose
CAS number	:	9000-11-7
Chemical formula	:	$(C_6H_{10}O_5)$
Molecular weight	:	36,000
Non proprietary name:		BP Microcrystalline cellulose

PhEur: Cellulosum microcrystalline cellulose

USPNF: microcrystalline cellulose

Melting point	:	Chars at 260-270°C
Nominal mean particle size:		100μm
Specific surface area	:	1.21-1.30m^2/g

Description:

Microcrystalline cellulose is purified partially depolymerized cellulose that occurs as a white colored, odourless crystalline powder composed of porous particles. It is commercially available at different size grades, which have different properties and applications.

Property of some commercially available grade of microcrystalline cellulose:

Table No. 6.2 Grade of microcrystalline cellulose

Grade	Nominal mean partical size (μm)	Moisture content (%)
Avicel PH 101	50	≤ 5.0
Avicel PH 102	100	≤ 5.0
Avicel PH 103	50	≤ 3.0
Avicel PH 105	20	≤ 5.0
Avicel PH 112	100	≤ 1.5
Avicel PH 113	50	≤ 1.5
Avicel PH 200	180	≤ 5.0
Avicel PH 301	50	≤ 5.0
Avicel PH 302	100	≤ 5.0

Pharmaceutical application of MCC:

Table No. 6.3 Pharmaceutical application of MCC

USE	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule diluents	20-90
Tablets disintegrant	5-15
Tablet binder/ Diluents	20-90

Application:

Microcrystalline cellulose is widely used in pharmaceuticals primarily as diluents in oral tablet and capsule formulations, where it is used in both wet granulation and direct compression processes..in addition to use as diluents, MCC also has some lubricant and disintegrant properties that make it useful in tableting. It is used as tablet disintegrant in 5-20% concentration, while as diluents 20-29% concentration is employed.

6.6 MANNITOL [37]:

Chemical name: hexanitro mannitol
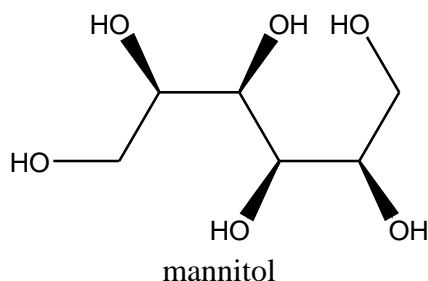
mannitol

Synonym: mannitol hexanitrate, nitromannite, nitromannitol, nitranitol, mannitrin

IUPAC: (2R,3R,4R,5R)-Hexane-1,2,3,4,5,6-hexol-1,2,3,4,5,6-hexanitrate

CAS number: 69-65-8

Molecular formula: $C_6H_8N_6O_{18}$

Molar mass: 452.15712

Density: 1.604 g/cc

Melting point: 112 °C = 234 °F

Mol. mass: 182.172

Bioavailability:

In pharmacology, **bioavailability** is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient (due to inter-individual variation).   Bioavailability is one of the essential tools in Pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

For dietary supplements, herbs and other nutrients in which the route of administration is nearly always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed. Bioavailability is defined slightly differently for drugs as opposed to dietary supplements primarily due to the method of administration and Food and Drug Administration regulations.

Use: This polyol is used as an osmotic diuretic agent and a weak renal vasodilator Mannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, thus, lowers the intraocular pressure. However, it requires an intact blood-ocular barrier to work. Mannitol can also be used to temporarily encapsulate a sharp object (such as a helix on a lead for an artificial pacemaker) while it is passed through the venous system. Because the mannitol dissolves readily in blood, the sharp point will become exposed at its destination.

Mannitol may be administered in cases of severe Ciguatera poisoning. Severe ciguatoxin, or "tropical fish poisoning" can produce stroke-like symptoms. Mannitol is the primary ingredient of Mannitol Salt Agar, a bacterial growth medium, and is used in others. In oral doses larger than 20 g, mannitol acts as an osmotic laxative, and is sometimes sold as a laxative for children

Toxicology: Mannitol is contraindicated in patients with anuria and Congestive Heart Failure

6.7 MAGNESIUM STEARATE [38]:

Non-proprietary name: BP: Magnesium stearate

PhEur: Magnesiistearas

USPNF: Magnesium stearate

Synonyms: E 572, Hyqual, Magnesium salt.

Chemical name: Octadecanoic acid Magnesium Salt.

CAS number: 557-04-0

Empirical Formula: $C_{36}H_{70}MgO_4$

Molecular Formula: 591.27

Functional category: Tablet and capsule lubricant

Flowability: Poorly flowing, cohesive powder

Melting point: 88.5^oC

Moisture content: 3.85%

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

Description:

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

Polymerisation:

A trihydrate, acicular from and a dehydrate lamellar form have been isolated with the latter processing the better lubricating properties.

Stability and storage condition:

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

Incompatibilities:

Incompatible with strong acid, alkalis and iron salts. Avoid mixing with strong oxidizing material.

Safety:

Magnesium stearate is used as a pharmaceutical excipients and is generally regarded as being nontoxic following oral administration. However oral consumption of

large quantities may result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities.

Handling precaution:

Observe normal precaution appropriate to the circumstances and quantity of material handled. Eye protection and glove are recommended

6.8 TALC [39]:

Synonyms –

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name:	Talc
CAS number:	14807-96-6
Empirical Formula:	$Mg_6(Si2O5)_4(OH)_4$
Functional Category:	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.

Use: Dusting powder (90.0–99.0%)

Glidant and tablet lubricant (1.0–10.0%)

Tablet and capsule diluent (5.0–30.0%)

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water

.

Specific gravity: 2.7–2.8.

Specific surface area: 2.41–2.42m^2/gm.

Stability and Storage Conditions - Talc is a stable material and may be sterilized by heating at 160^{0}C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

7. MATERIALS AND INSTRUMENTS

7.1 MATERIALS USED FOR THE RESEARCH WORK

Table No. 7.1 Materials used for the research work

Sr.No	Name	Grade	Company
1	Bisoprolol Fumarate	Pharma	Merck Ltd.,Aurangabad
2	Hydrochloric acid	AR	Loba Chem Pvt. Ltd., Mumbai.
3	Potassium hydroxide	AR	Loba Chem Pvt. Ltd., Mumbai.
4	Potassium di-hydrogen phosphate	AR	S.D.Fine Chem Ltd., Mumbai.
5	Sodium hydroxide	AR	Loba Chem Pvt. Ltd., Mumbai.
6	Di. Sodium hydrogen phosphate	AR	Loba Chem Pvt. Ltd., Mumbai.
7	Deionized water	AR	Leo Scientific, Erode.
8	Lactose	AR	Loba Chem Pvt. Ltd., Mumbai.
9	Microcrystalline cellulose	AR	Loba Chem Pvt. Ltd., Mumbai.
10	Sod. Starch Glycolete	AR	Loba Chem Pvt. Ltd., Mumbai.
11	Cross Povidone	AR	Loba Chem Pvt. Ltd., Mumbai.
12	PVP K-30	AR	Loba Chem Pvt. Ltd., Mumbai.
13	Crosscarmellose sodium	AR	Loba Chem Pvt. Ltd., Mumbai.
14	Mannitol	AR	Loba Chem Pvt. Ltd., Mumbai.

7.2 INSTRUMENTS USED FOR THE RESEARCH WORK

Table No.7.2 Instruments used for the research work

S. No.	Instruments	Manufacturer
1	Rotary Press Tablet Compression Machine	RIMEK Minipress-I, Karnavati Engineering Ltd., Mehsana, Gujarat.
2	Electronic Balance	Dhona Instruments Pvt. Ltd., Kolkata.

3	Digital pH meter	Model No. NIG 333, Naina Solaris Ltd. India.
4	Monsanto Hardness tester	Cadmach Machinery Pvt. Ltd., Ahmedabad.
5	Roche Friabilator USP XVIII	Model No. EF-1W, Electrolab Pvt. Ltd., Goregaon (E), Mumbai.
6	Sieves	Sethi Standard Test Sieves
7	Double Beam UV-Spectrophotometer	Techcomp UV 2300
8	Dissolution Apparatus USP XVIII	Model No. TDT – 06P, Electrolab Pvt. Ltd., Goregaon (E), Mumbai.
9	FTIR Spectrophotometer	Model No. 8400 S, Shimadzu Asia Pacific Pvt. Ltd., Singapore.
10	Digital Vernier Caliper	ASAHI, India.
11	Ultrasonicator	PCI, Mumbai.
12	Magnetic stirrer	Model No. 1MLH, Remi, Mumbai
13	Design expert 8.0.7.1	Stat-Ease, Inc. Minneapolis

8. METHODOLOGY

8.1 PREFORMULATION STUDIES:

8.1.1 Identification and Characterization of Bisoprolol Fumarate

i) Melting point:

The melting point of Bisoprolol Fumarate was determined by capillary method and checked, whether it complies with the reported ones or not.

ii) FT-IR spectroscopy [40, 41]:

Bisoprolol Fumarate was dried in hot air oven at 50^0C for 2 hours. The samples were mixed with potassium bromide (KBr) in ratio 1:100 by using mortar and pestle. This physical mixture was compressed under pressure of 10 Ton/nm^2 and converted in a circular disc. This disc was then placed in the scanning slot of Fourier Transform Infra-red (FT-IR) Spectrophotometer and scanned at range from 400 to 4000 cm^{-1} to obtain the FTIR of Bisoprolol Fumarate

8.1.2 Preparation of standard curve in pH 1.2 [42]:

Accurately weighed 100 mg of Bisoprolol Fumarate was dissolved in 100 ml of distilled water. The solution was suitably diluted to prepare solutions of strengths ranging from 1 to 10 μg / ml with 0.1 N HCl. These solutions were scanned by UV spectrophotometer at 220 nm and the calibration curve was plotted.

The reagents were prepared as per IP.

i. **Preparation of 0.1M hydrochloric acid (HCl) solution:** Conc. HCl diluted with distilled water so that final solution contains 3.646 g of hydrochloric acid in 1000.0 ml to obtain 0.1M hydrochloric acid solution.

ii. **Preparation of 0.2M hydrochloric acid (HCl) solution:** Conc. HCl diluted with distilled water so that final solution contains 7.292 g of hydrochloric acid in 1000.0 ml to obtain 0.2M hydrochloric acid solution.

iii. **Preparation of 0.2M potassium chloride (KCl) solution:** Dissolve approx. 14.911 g of potassium chloride in distilled water and diluted to 1000.0 ml with distilled water to obtain 0.2M potassium chloride solution.

iv. **Preparation of dilution media (pH 1.2 hydrochloric acid buffer):** About 250.0 ml of 0.2M potassium chloride solution was placed in a 1000.0 ml volumetric flask. To

this, about 425.0 ml of 0.2M hydrochloric acid was added and then volume was adjusted to 1000 ml with distilled water. Then prepared solution was tested using pH meter. The pH of solution was adjusted to pH 1.2 with the help of 0.2M hydrochloric acid.

8.1.3 Compatibility studies of drug & excipients by FT-IR:

IR spectra of drug and all super disintegrants long with drug in KBr pellets at moderate scanning speed between 4000-400cm^{-1} was carried out using FTIR. The peak values and the possibility of functional groups shown in spectra were compared with standard values.

8.2 EVALUATION OF PRE COMPRESSION PARAMETERS [43, 44]:

8.2.1 Angle of repose

Angle of repose was determined by using fixed funnel method. It is the maximum angle that can be obtained between the free flowing surface of lubricated blend of matrix tablets heap and the horizontal plane. Accurately weighed lubricated blends were allowed to fall freely through a funnel until apex of conical pile just touched the tip of the funnel. The angle of repose θ was determined according to the following formula:

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

Where,

h = height of the pile

r = radius of the pile

θ = angle of repose

8.2.2 Bulk density

Ten grams of drug and excipients mixture (powder) was placed into 100 ml measuring cylinder and volume was noted. The bulk density was calculated by the following equation

$$\rho o = M/Vb$$

Where,

ρo =bulk density,

M =mass of the powder and

Vb= Volume of powder

8.2.3 Tapped density

10 gm of drug and excipients mixture (powder) was taken in measuring cylinder. The cylinder was then subjected to a fixed number of taps (100). The final volume was recorded and the tap density was calculated by the following equation

$$\rho t = M/V$$

Where, ρt=tapped density,

M= mass of the powder and

Vt =Volume of powder on tapping.

8.2.4 Compressibility index

Compressibility of the drug was determined using the following equation

% compressibility= (ρt- ρo/ ρt) 100

Where,

ρt is the tapped density and

ρo is the bulk density.

8.2.5 Hausner's ratio

A similar index has been defined by Hausner

$$\text{Hauser's ratio} = \frac{\text{Tapped Density}}{\text{Bulk density}}$$

It indicates that the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Value less than 1.25 (= 25% Carr's index) indicates good flow while greater than 1.25 indicate poor flow (= 33% Carr's index). Between 1.25 and 1.5 added Glidants normally improves flow.

8.3 FORMULATION OF FAST DISSOLVING TABLETS:

Bisoprolol Fumarate fast dissolving tablets were prepared by direct compression method. A total number of twelve formulations were prepared. All the ingredients were passed through 60-mesh sieve separately and collected, finally compressed into tablets after lubrication with magnesium stearate (2%) and talc (2%) by using 9/32 mm concave punch using RIMEK 8 station tablet compression machine.

Table No. 8.1 Formulation of blend

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bisoprolol fumarate	5	5	5	5	5	5	5	5	5	5	5	5
Crosspovidone	2	4	6	-	-	-	-	-	-	-	-	-
Croscarmilose sodium	-	-	-	2	4	6	-	-	-	-	-	-

SSG	-	-	-	-	-	-	2	4	6	-	-	-
PVP K-30	-	-	-	-	-	-	-	-	-	2	4	6
Mannitol	55	55	55	55	55	55	55	55	55	55	55	55
MCC	26	24	22	26	24	22	26	24	22	26	24	22
Lactose	8	8	8	8	8	8	8	8	8	8	8	8
Mag. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2

*each tablet weight 100 mg

8.4 EVALUATION OF POST COMPRESSION PARAMETERS [45]:

8.4.1 Thickness

The thickness of the tablets was determined using a digital vernier calliper (ASAHI, India). Five tablets from each batch were used and average values were calculated.

8.4.2 Hardness

Hardness of the tablets has been defined as the force required for breaking a tablet in diametric compression. The resistance of the tablets to chipping, abrasion or breakage under the conditions of storage, transportation and handling before usage depends in its hardness. For each formulation, the hardness of 3 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

8.4.3 Weight variation

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Table No. 8.2 Weight variation limits

Average weight of Tablets (mg.)	Maximum percentage deviation
130 or less	10
130 – 324	7.5
324 mg or more	5

Not more than two of the individual weights deviate from the average weight by more than the percentage shown in above table and none deviates by more than twice of that percentage.

8.4.4 Friability

Friability was measured to find the strength of tablet by Roche Friabilator. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 10 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability was calculated as follows,

Percentage friability =   (Initial weight – Final weight / Initial weigh)   x 100

8.4.5 Wetting time

A piece of tissue paper folded double was placed in a Petri dish containing 6 ml of water .the tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0c.Wetting time corresponding to the time taken for the tablet to disintegrate when kept motionless on the Petri dish.

8.4.6 Disintegration time

Disintegration time was determined using USP tablet disintegration test apparatus using 900ml of distilled water without disk at room temperature (30^0C). If 1 or 2 tablets fail to disintegrate completely, repeat the test on additional 12 numbers. Not less than 16 of the total of 18 numbers tested disintegrate completely.

8.4.7 Drug content

The drug content was determined by eluting the crushed tablet with continuous stirring in 100 ml 1N HCl for 4 hour to ensure complete elution. The solution was filtered. After suitable dilution the drug content was determined at 220 nm by UV/VIS spectrophotometer. According to USP acceptable limit is ± 10%.

Calculation:

$$\text{Amount of BF} = \frac{\text{spl abs}}{\text{Std abs}} \times \frac{\text{std wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{spl wt}} \times \frac{100}{1} \times \frac{\text{avg wt}}{100} \times \text{potency}$$

8.4.8 *In-vitro* Dissolution Study

Dissolution profiles of Bisoprolol Fumarate fast dissolving tablets were determined using the USP 24 Method II with paddle speed 50 rpm. Dissolution was performed in 900 ml of 0.1N HCl maintained at 37 ± 0.5°C. 5 ml of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1N Hcl, pre-warmed at 37± 0.5°C. Samples withdrawn were filtered through whatmann filter paper, suitably diluted with 0.1N HCl and analyzed at 220 nm.

8.4.9 Stability studies [46]

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a pre-determined level of labelled potency and its physical characteristic have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environment factor such as temperature, humidity and light enabling recommended storage condition, re-test periods and shelf lives.

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principle of accelerated stability studies is adopted.

The international conference on harmonization (ICH) guideline titled "stability testing of new drug substance and product" (QIA) describes the stability test requirements for drug registrations application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

➢ Long term testing: 25^0c $\pm$ 2^0c/60% RH $\pm$ 5% for 12 months.

➢ Accelerated testing: 40^0c $\pm$ 2^0c/ 75 % RH $\pm$ 5% for 6 months.

Method:

The selected formulation were packed in tightly closed container were plugged with cotton and capped. they were then stored at 40^0c $\pm$ 2^0c/ 75 % RH $\pm$ 5% for 3 months in humidity chamber (Thermolab Mumbai) and valuate for their physical appearance and

drug solution were further scanned to observe any possible spectral changes T80% was calculated by using dissolution studies.

8.5 STATISTICAL OPTIMIZATION OF PARAMETERS BY FACTORIAL DESIGN [29, 47]:

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Yi) is measured for each trial.

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_1X_2+\beta_4X_1^2+\beta_5X_2^2+\beta_6X_1^2X_2+\beta_7X_1X_2^2+\beta_8X_1^2X_2^2$$

Where, Y is the dependent variable,

X_1, X_2 are independent variables,

b_0 is the arithmetic mean response of the nine runs and

bi is the estimated coefficient for the factor Xi.

The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The factors were selected based on preliminary study. The concentration of lactose (X1) and concentration of Magnesium stearate (X2) were selected as independent variables. % friability, wetting time, disintegration time and *in-vitro* drug release was respectively selected as dependent variables were tested for significance by using Design Expert 8.0.7.1

9. RESULTS AND DISCUSSION

The present work was aimed to find out the effects of various superdisintegrants on the dissolution profile, *In-vitro* release Kinetic studies and various properties of oral dispersible tablets of Bisoprolol Fumarate.

9.1 PREFORMULATION STUDIES:

9.1.1 Identification and Characterization of Bisoprolol Fumarate:

i) Melting point

The melting point of Bisoprolol Fumarate was determined by capillary method and was found to be 101 °C. It complies with the standards as given in USP.

### ii) Identification test for Bisoprolol Fumarate.

Infrared absorption spectrophotometry: All the prominent and primary peaks were observed in FTIR spectrum of Bisoprolol Fumarate. (Fig. 9.1) and match with the reference spectrum.

Table No. 9.1 FT-IR interpretation of bisoprolol fumarate

Group	Range	Std. peak
C-H bending (alkynes)	600-700	663.53
N-H Wagging, (Amines)	655-910	805.31
C-O stretching, (alcohol)	1045-1055	1049.75,
C-N stretching, (amine)	1030-1230	1091.75, 1123.57
C-O stretching, (carboxylic acid)	1000-1320	1236.41, 1235.45
C-H rocking, (alkynes)	1350-1370	1365.65
C=C stretching, (alkenes)	1606-1616	1615.44
-CH3 (alkanes)	2865-2875	2867.28
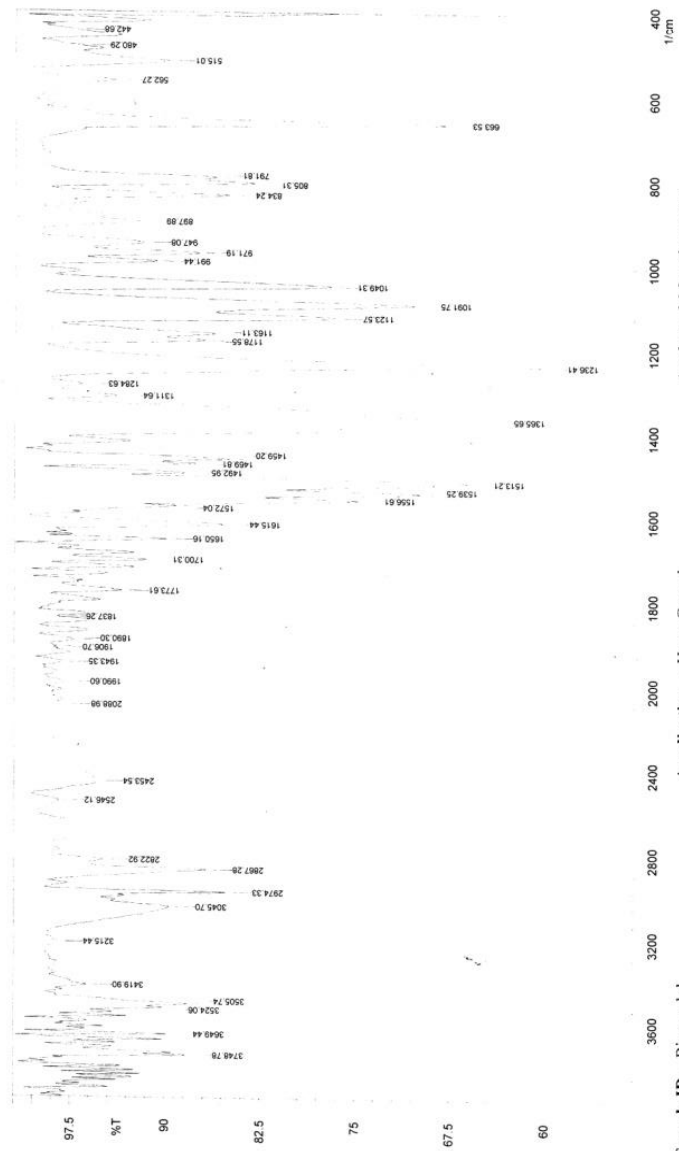
Fig No. 9.1 FTIR Spectrum of drug sample

9.1.2 Standard calibration curve of bisoprolol fumarate in buffer pH 1.2:

i) Preparation of standard calibration curve in HCl buffer pH 1.2:

Standard calibration curve was prepared for concentration of 1µg/ml to 10µg/ml at 220 nm. The graph of concentration v/s absorbance was plotted and data were subjected to linear regression analysis. The data of absorbance is as shown in Table No. 9.2. The data had correlation coefficient of 0.997 and equation of regressed line is, **y=0.101X-0.035**

Table No. 9.2 Absorbance values for standard calibration curve of Bisoprolol Fumarate in hydrochloric acid buffer pH 1.2

Sr. no.	Concentration (µg/ml)	Absorbance
1	1	0.069
2	2	0.166
3	3	0.241
4	4	0.349
5	5	0.457
6	6	0.583
7	7	0.697
8	8	0.785
9	9	0.881
10	10	0.992

The chart shows:
- y-axis: **Absorbance** (values 0, 0.2, 0.4, 0.6, 0.8, 1)
- x-axis: **Conc (µg/ml)** (values 0 to 10)
- y = 0.101x - 0.035
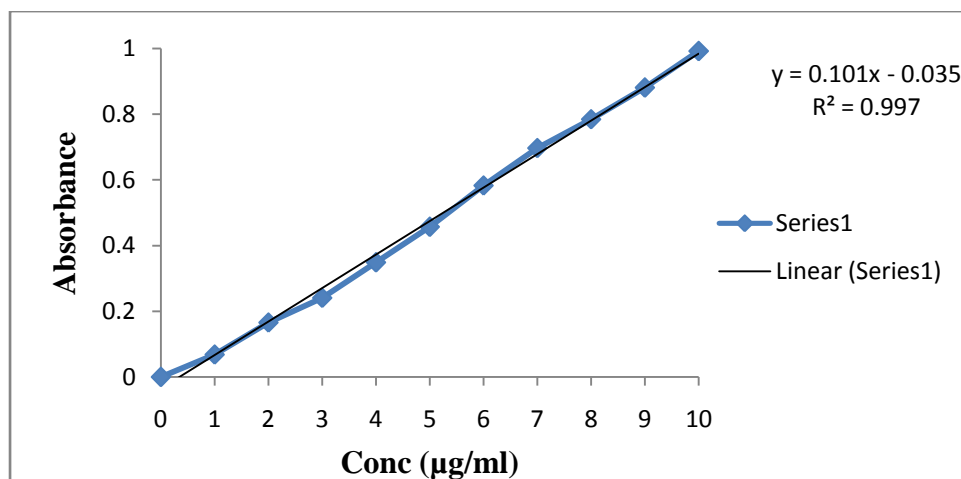- R² = 0.997
- Series1
- Linear (Series1)

Fig. No.9.2 Standard calibration curve of Bisoprolol Fumarate in pH 1.2 buffer

The calibration curve for Bisoprolol Fumarate in pH 1.2 buffers in the concentration range of 1µg/ml to 10µg/ml was a straight line. The absorbance increased with the increase in concentration. Thus the standard curve followed the Beer-Lambert's Law.

9.1.3 Organoleptic characteristics:

Table No.9.3 Organoleptic characteristics of Pure Drug

| Sr.no	Properties	Results
1	Colour	White
2	Odour	Odour less
3	Taste	Bitter less
4	Appearance	Amorphous powder

9.1.4 Drug and Excipients compatibility studies:

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and Excipients. About 1 mg of this mixture was mixed with 100 mg of potassium bromide (KBr) and compressed to from a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to400cm-1 in a **Perkin Elmer FT-IR Spectrophotometer.** The IR spectrum of the physical mixture was done to detect any appearance or disappearance of peaks. The compatibility between the drug and to selected super disintegrants was evaluated using FTIR matching method.

Table No. 9.4 Drug and excipients compatibility

Group	Range	FT-IR of pure drug	FT-IR of physical mixture
C-H bending (alkynes)	600-700	663.53	662.57
N-H Wagging, (Amines)	655-910	805.31	805.31, 835.31, 835.21
C-O stretching, (alcohol)	1045-1055	1049.75,	1050.28
C-N stretching, (amine)	1030-1230	1091.75, 1123.57	1091.75, 1123.57
C-O stretching, (carboxylic acid)	1000-1320	1236.41, 1235.45	1235.45, 1236.41
C-H rocking, (alkynes)	1350-1370	1365.65	1363.72, 1364.68
C=C stretching, (alkenes)	1606-1616	1615.44	1614.47, 1613.51
-CH3 (alkanes)	2865-2875	2867.28	2866, 2867.28

NANDHA COLLEGE OF PHARMACY, ERODE-52.
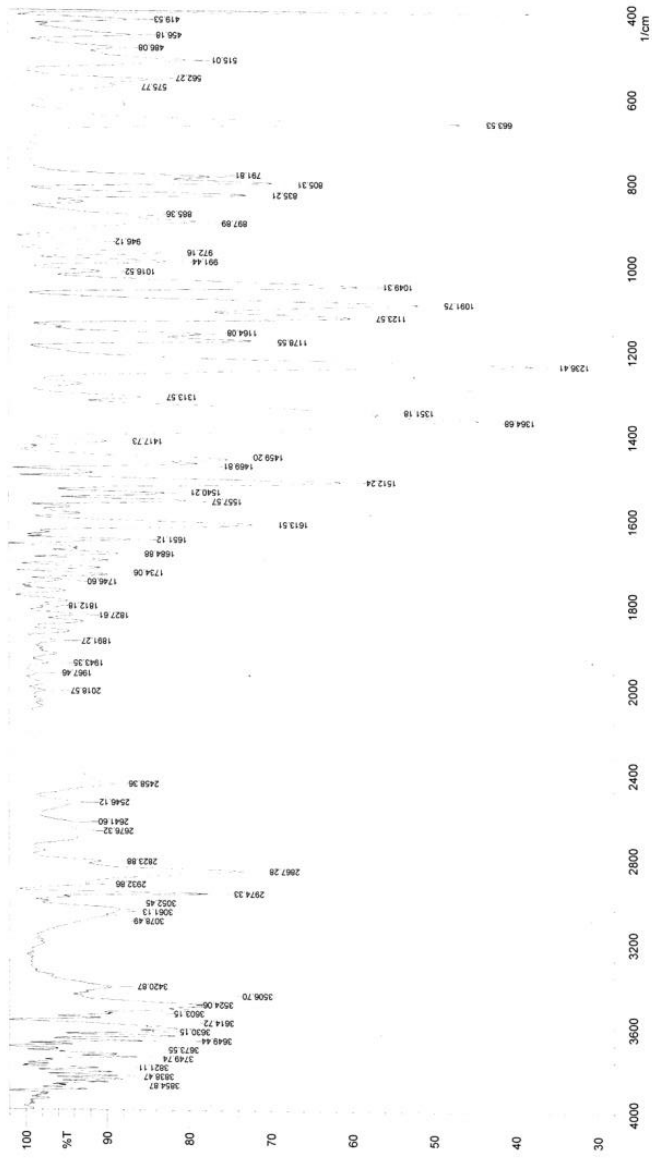
⊕ SHIMADZU

Sample ID : Bisoprolol+Ac Di Sol

Resolution : 4 cm⁻¹

Apodization : Happ-Genzel

No.of Scans : 20

Analyst : M.Jagadeswaran

Date : 22.02.2012
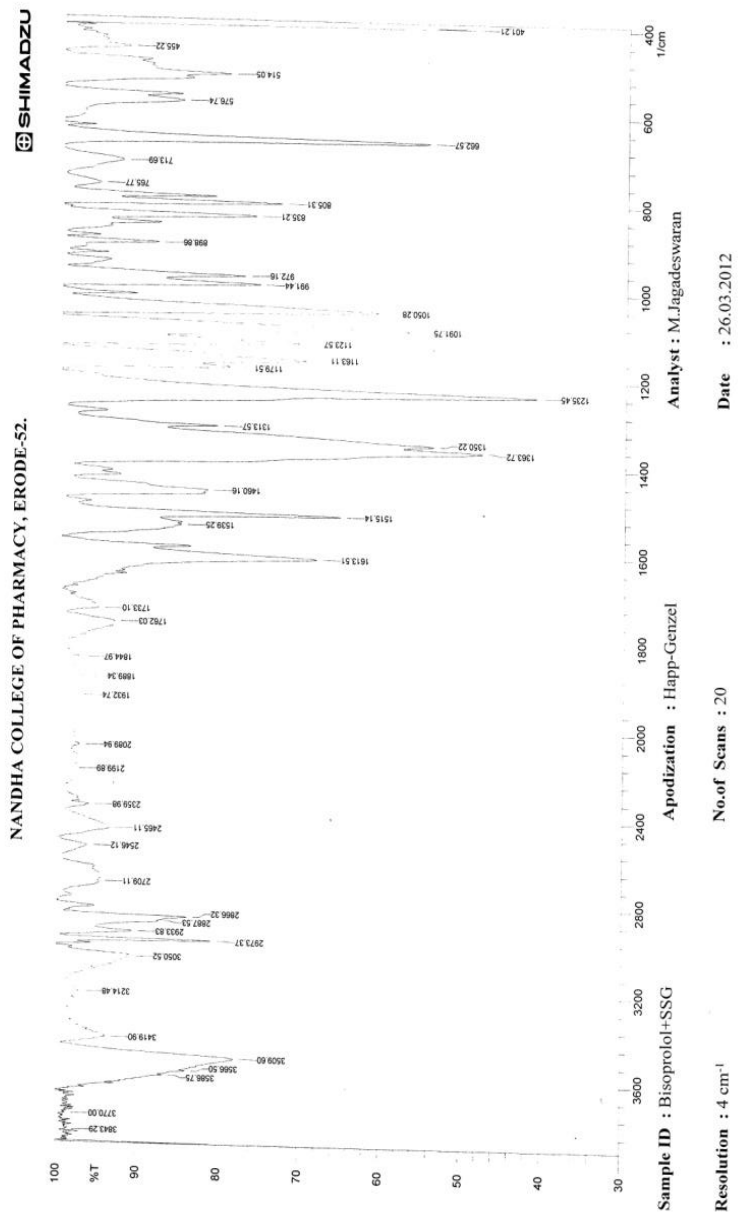
Fig. No. 9.3 FT-IR Spectrum of Drug with Ac-di-sol
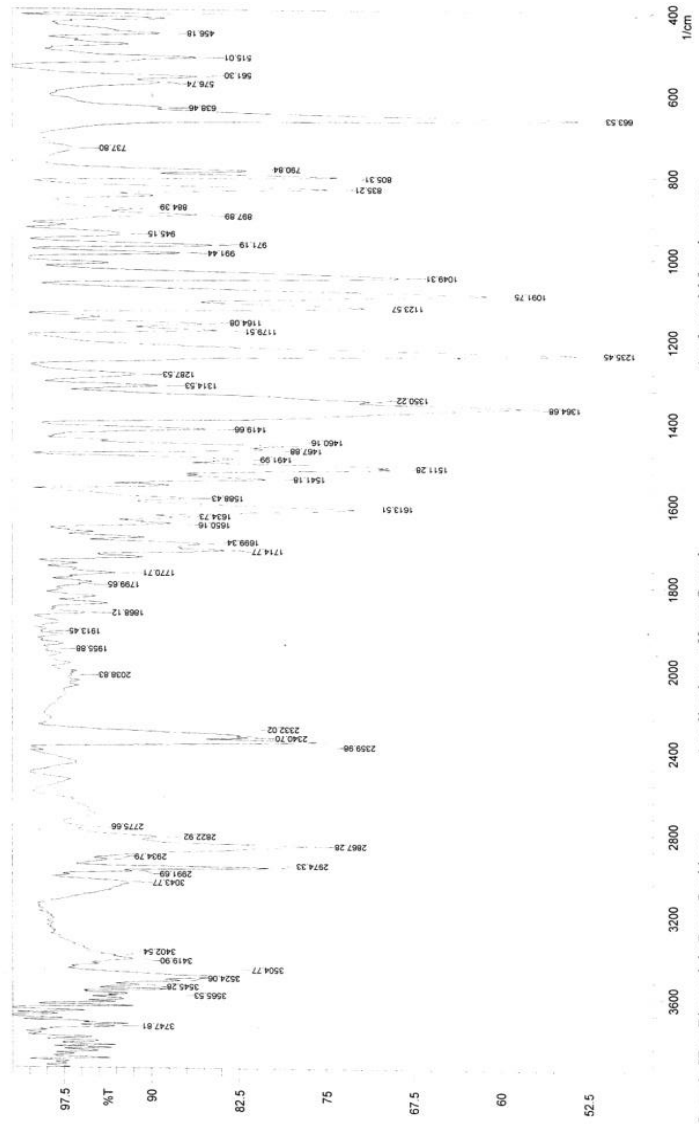

Fig. No. 9.4 FT-IR Spectrum of Drug with sodium starch glycolate

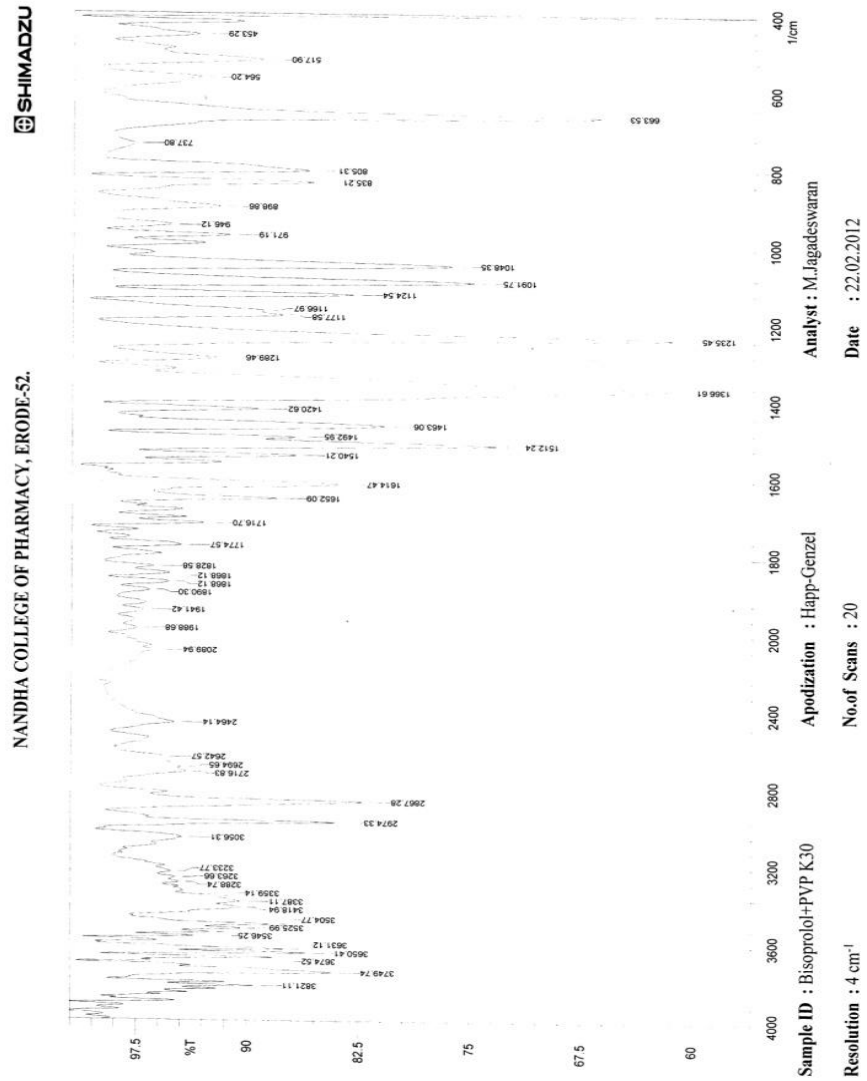**Fig. No. 9.5 FT-IR Spectrum of Drug with Crospovidone**

Fig. No. 9.6 FT-IR Spectrum of Drug with PVP K-30

9.2 PRECOMPRESSION STUDY OF TABLET BLEND:

Twelve formulations were prepared by using 2%, 4%, 6% concentration of superdisintegration like croscarmellose sodium (Ac-di-Sol), sodium starch glycolate,

Crospovidone and PVP K-30. For each designed formulation, powder mixed blend of drug and excipients was prepared and evaluated for various parameters as follows.

Table No. 9.5 Comparison of Pre compression parameters

Formulation Code	Formulation parameters				
	Angle of repose(º)	Bulk density(Kg/cm^2)	Tapped density(Kg/cm^2)	Carr's index (%)	Hausner's ratio
F1	24.91	0.31	0.36	13.888	1.161
F2	26.79	0.32	0.37	13.513	1.156
F3	23.45	0.3	0.34	11.764	1.133
F4	22 .86	0.33	0.36	8.333	1.090
F5	25.21	0.31	0.34	8.823	1.096
F6	22.17	0.33	0.38	13.157	1.151
F7	23.86	0.32	0.36	11.111	1.125
F8	26.54	0.3	0.35	14.285	1.166
F9	28.13	0.31	0.34	8.823	1.096
F10	25.37	0.33	0.39	15.384	1.181
F11	26.51	0.34	0.37	8.108	1.088
F12	29.10	0.32	0.35	8.571	1.093

9.2.1 Angle of Repose (θ):

The angle of repose of all formulated batches prepared with different superdisintegrants and various powder mixed blends, was measured by cylinder method. Angle of repose was found in the range from 22º70' to 29º10' this implies excellent free flowing nature of blends.

9.2.2 Bulk density:

The bulk density of all formulated batches prepared with different superdisintegrants and various powder mixed blends. The bulk density was found in the range from 0.53 to 0.54 g/cm^3

9.2.3 Tapped density:

The tapped density of all formulated batches prepared with different superdisintegrants and various powder mixed blends, was measured by cylinder method. The tapped density was found in the range from 0.602 to 0.627 g/cm^3

9.2.4 Compressibility Index:

The compressibility index of all formulated batches prepared with different superdisintegrants and various powder mixed blends by using bulk density and tapped density data, compressibility index was calculated. It was found in the range 11.48 % to 15.89 %

9.2.5 Hausner ratio:

The Hausner ratio of all formulated batches prepared with different superdisintegrants and various powder mixed blends was calculated by using bulk density and tapped density data. It was found in the range of 1.12 to 1.20.

9.3 FORMULATION OF FDT:

Fig. No. 9.7 Formulated tablet

9.4 COMPARITIVE STUDIES OF POST-COMPRESSION PARAMETERS:

The research works was carried out to analysis and study the impact of various superdisintegrants on enhancing the dissolution rate of Bisoprolol Fumarate. The experiment was design with twelve formulations which were categorize into three group based on the concentration of three different superdisintegrants.

Table No. 9.6 comparative study of post compression parameters

Code	Formulation parameters					
	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)

F1	101	2.5	3.2	0.43	32	57
F2	103.25	2.5	3.4	0.51	30	54
F3	99.56	2.6	3.1	0.49	28	56
F4	100.78	2.4	3.3	0.50	29	57
F5	101.24	2.7	3.3	0.56	27	55
F6	100.67	2.5	3.2	0.48	24	54
F7	104.53	2.3	3.4	0.57	36	59
F8	98.76	2.7	3.3	0.49	33	57
F9	99.89	2.6	3.1	0.60	32	56
F10	100.37	2.4	3.5	0.55	38	60
F11	102.65	2.5	3.4	0.44	37	58
F12	100.05	2.3	3.3	0.49	37	57

9.4.1 Weight variation:

Tablets were prepared using dry granulation technique. Since the material was free flowing, tablets were obtained of uniforms weight due to uniform die fill. The tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications less than 7.5%.

9.4.2 Thickness uniformity:

Tablets were evaluated by using vernier caliper. The thickness of tablets was found to be exact 2.5 mm uniform thickness was obtained due to uniform die fill.

9.4.3 Hardness:

Tablets were evaluated by using hardness tester. Hardness of the tablets was found in the range 3.1 to 3.5 Kg/cm^2

9.4.4 Friability:

Tablets were evaluated by using Roche Friabilator and Friability of tablets was observed in acceptable range 0.43 to 0.60 (Less than 1%).

9.4.5 Wetting time:

A piece of tissue paper folded twice was placed in a small petri-dish (6.5cm) containing 6ml of water, a tablet was placed on the paper and the time for complete

wetting was measured the wetted tablet was then weighed and the water absorption ratio was calculated for each batch. The ratio was calculated for each batch.
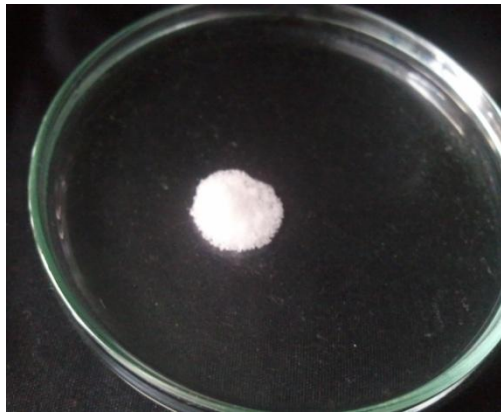
9.4.6 Disintegration time:

Tablets were evaluated for disintegration time in the disintegration test apparatus (I.P). The disintegration time was found in between 24 to 38 sec for all the batches. The batch **F6** showed the fastest disintegration (24 sec)
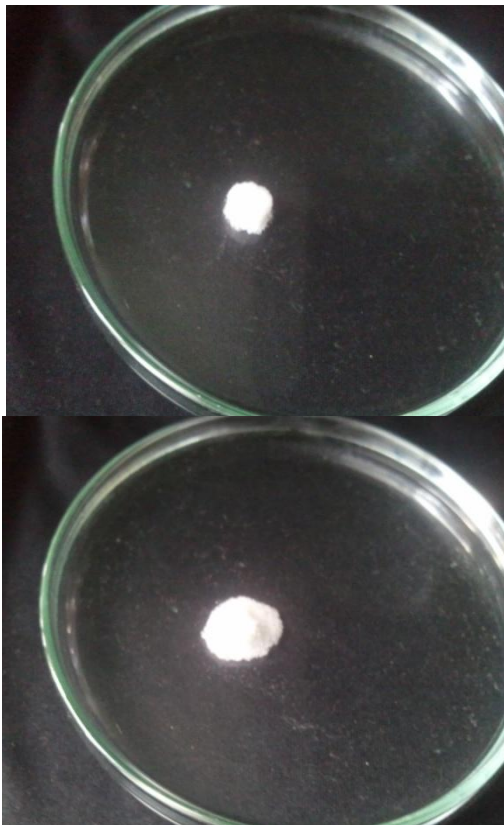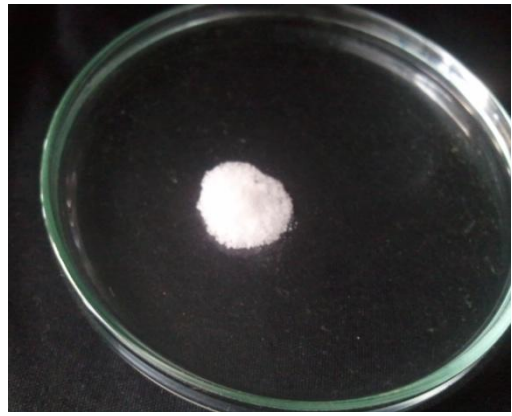

a) At 5 sec   b) At 10 sec

c) At 15 sec

d) At 20 sec

e) At 25 sec

f) At 25 sec (side view)

Fig. No. 9.8 Disintegration time of F6 at different time intervals

9.4.7 Drug content:

Table No. 9.7 Percentage drug content

S. No.	Formulation code	% Drug content
1	F1	98.96
2	F2	98.99
3	F3	99.20
4	F4	99.02
5	F5	99.37
6	F6	99.54
7	F7	98.60
8	F8	99.08
9	F9	99.26
10	F10	99.46
11	F11	98.92
12	F12	99.17

The results for content uniformity are presented in Table No 9.7. The results showed drug content were lying within the limits. The assay limit of bisoprolol fumarate

tablets as per USP is 90-110%. The assays of the tablets were carried out as a process given in USP

9.4.8 *In-vitro* release studies:

The Comparative analysis of each formulation was based on in vitro kinetic parameters, which elucidated the release profile. The time taken for 80% drug release was taken as a response for comparative interpretation of superdisintegrants. The in-vitro releases of fast dissolving tablets of Bisoprolol Fumarate for all formulation were given as follows.

***In vitro* drug release studies details:**

Apparatus used	: USP XXIII dissolution test apparatus
Dissolution medium	: 0.1N HCL
Dissolution medium volume	: 900 ml
Temperature	: 37±0.5ºC
Speed of basket paddle	: 50 rpm
Sampling intervals	: 1 min
Sample withdrawn	: 10 ml
Absorbance measured	: 220 nm

i) *In-vitro* release studies of batch F1-F3 in 0.1N HCL

Table No. 9.8 *In-vitro* release studies of batch F1-F3 in 0.1N HCL

S. No	Time (min)	Percentage drug Release		
		F1	F2	F3
1	1	6.06	6.24	6.77
2	2	12.33	12.87	13.23
3	3	18.64	19.53	20.07
4	4	26.76	27.48	30.16
5	5	32.61	33.51	40.31
6	6	38.85	40.29	50.69
7	7	45.83	47.29	60.06
8	8	52.86	56.28	70.19
9	9	59.20	64.96	78.95
10	10	66.12	71.55	83.30
11	11	73.61	78.53	91.41

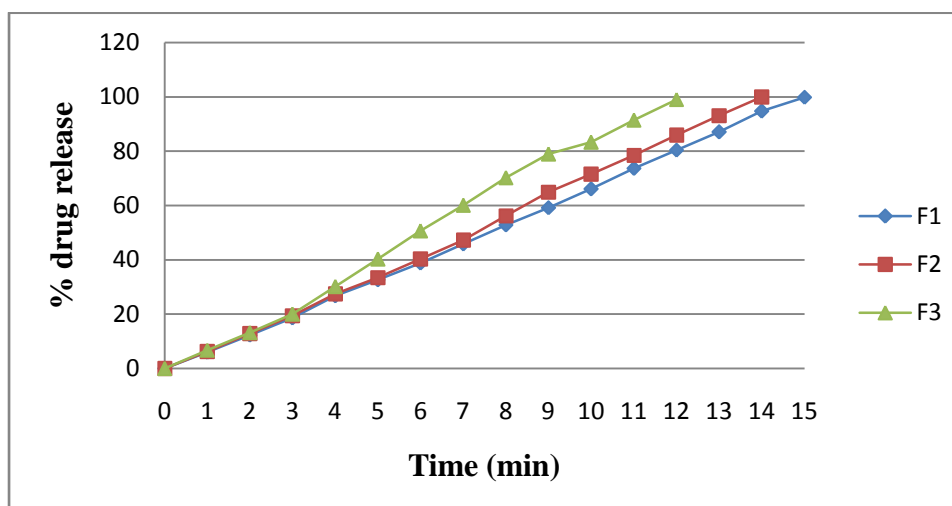| 12 | **12** | 80.42 | 85.91 | 99.03 |
13	**13**	87.09	93.14	-
14	**14**	94.69	99.88	-
15	**15**	99.83	-	-

Fig. No. 9.9 *In-vitro* **release studies of batch F1-F3 in 0.1N HCL**

ii) *In-vitro* **release studies of batch F4-F6 in 0.1N HCL**

Table No. 9.9 *In-vitro* **release studies of batch F4-F6 in 0.1N HCL**

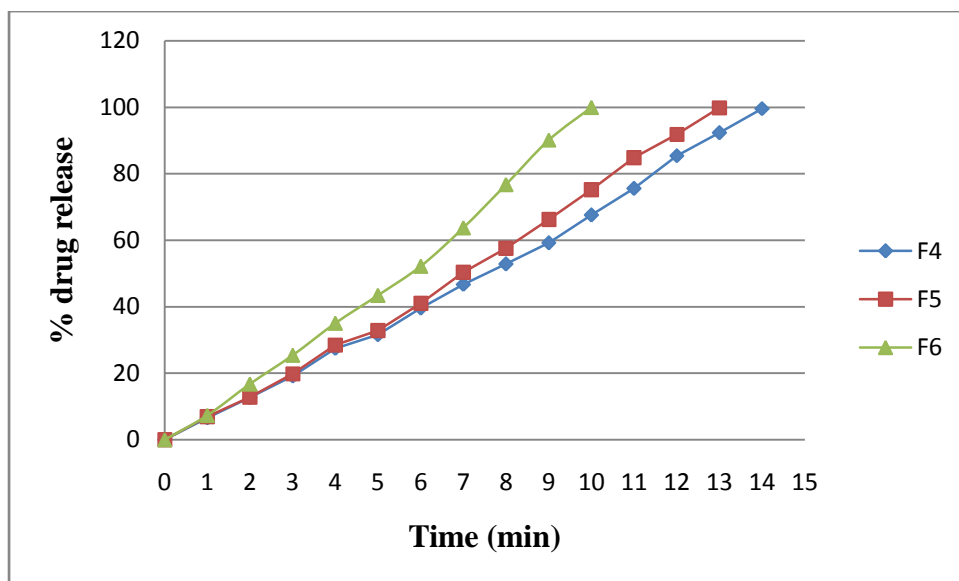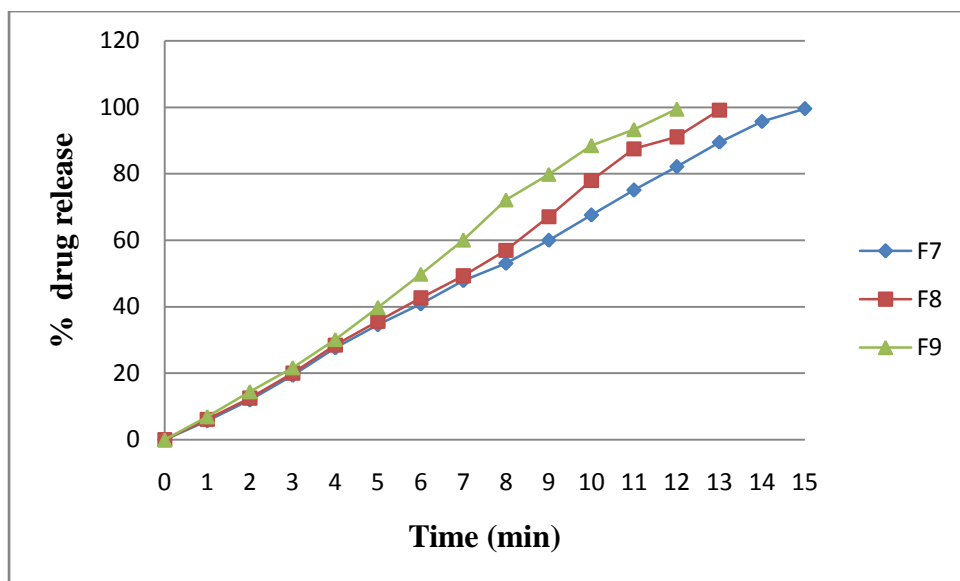| S. No	Time (min)	Percentage drug Release		
		F4	**F5**	**F6**
1	1	6.59	6.95	7.30
2	2	12.69	12.87	16.79
3	3	19.17	19.89	25.44
4	4	27.48	28.55	35.02
5	5	31.55	32.81	43.41
6	6	39.56	41.01	52.21
7	7	46.73	50.32	63.72
8	8	52.87	57.55	76.72
9	9	59.21	66.24	90.15
10	10	67.56	75.15	99.91
11	11	75.59	84.83	-
12	12	85.44	91.88	-
13	13	92.32	99.86	-
14	14	99.59	-	-

Fig. No. 9.10 *In-vitro* release studies of batch F4-F6 in 0.1N HCL

iii) *In-vitro* release studies of batch F7-F9 in 0.1N HCL

Table No. 9.10 *In-vitro* release studies of batch F7-F9 in 0.1N HCL

S. No	Time (min)	Percentage drug Release		
		F7	**F8**	**F9**
1	1	5.70	6.23	6.95
2	2	11.97	12.50	14.47
3	3	19.34	20.06	21.68
4	4	27.65	28.55	30.17
5	5	34.57	35.65	39.79
6	6	40.82	42.62	49.81
7	7	47.82	49.27	60.06
8	8	53.07	57.03	72.15
9	9	59.95	67.14	79.85
10	10	67.58	78.02	88.49
11	11	75.08	87.53	93.24
12	12	82.08	91.04	99.45
13	13	89.47	99.19	-
14	14	95.66	-	-
15	15	99.55	-	-

Fig. No. 9.11 *In-vitro* **release studies of batch F7-F9 in 0.1N HCL**

iv) *In-vitro* **release studies of batch F10-F12 in 0.1N HCL**

Table No. 9.11 *In-vitro* **release studies of batch F10-F12 in 0.1N HCL**

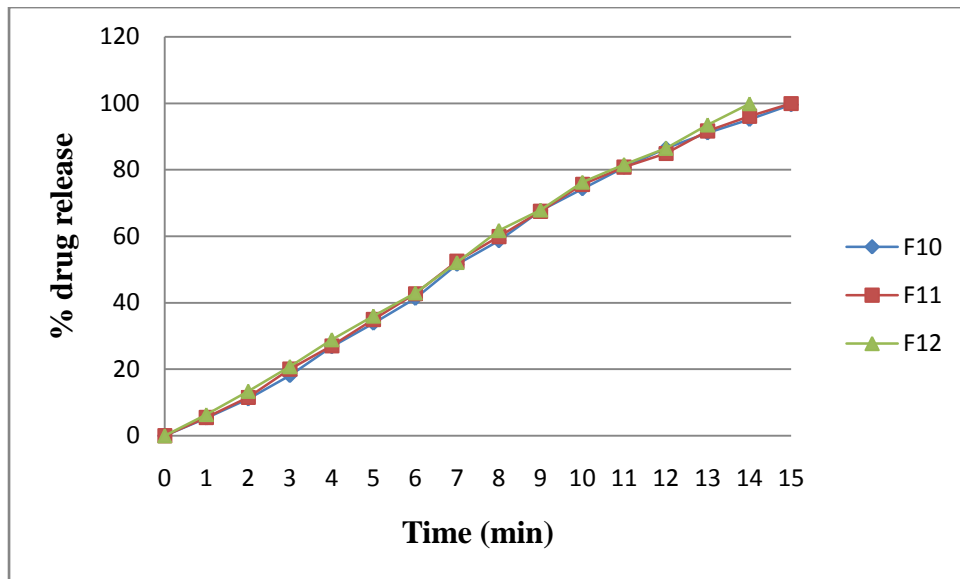| S. No	Time (min)	Percentage drug Release		
		F10	F11	F12
1	1	5.34	5.52	6.41
2	2	11.07	11.61	13.40
3	3	18.09	20.05	20.78
4	4	26.74	27.11	28.91
5	5	33.84	34.92	36.02
6	6	41.33	42.78	42.99
7	7	51.54	52.46	52.14
8	8	58.59	59.88	61.69
9	9	67.65	67.51	67.91
10	10	74.25	75.54	76.30
11	11	80.71	80.76	81.52
12	12	86.50	84.94	86.42
13	13	91.06	91.64	93.48
14	14	95.12	96.05	99.86
15	15	99.55	99.95	-

Fig. No. 9.12 *In-vitro* **release studies of batch F10-F12 in 0.1N HCL**

COMPARATIVE *IN-VITRO* DRUG RELEASE PROFILE OF FAST DISSOLVING TABLET OF BISOPROLOL FUMARATE IN 0.1N HCL

Table No. 9.12 Comparative *in-vitro* drug release profile

| Time	Percent drug release											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	6.06	6.24	6.77	6.59	6.95	**7.31**	5.70	6.24	6.95	5.35	5.52	6.42
2	12.33	12.87	13.23	12.69	12.87	**16.79**	11.97	12.51	14.47	11.08	11.61	13.40
3	18.64	19.53	20.07	19.18	19.89	**25.44**	19.35	20.06	21.68	18.09	20.06	20.78
4	26.76	27.48	30.16	27.48	28.56	**35.03**	27.65	28.55	30.18	26.75	27.12	28.92
5	32.61	33.51	40.31	31.55	32.81	**43.42**	34.58	35.66	39.79	33.84	34.93	36.03
6	38.85	40.29	50.69	39.57	41.01	**52.21**	40.82	42.63	49.81	41.34	42.79	43.00
7	45.83	47.29	60.06	46.73	50.33	**63.72**	47.82	49.28	60.07	51.54	52.47	52.14
8	52.86	56.28	70.19	52.87	57.55	**76.73**	53.07	57.03	72.16	58.60	59.88	61.70
9	59.20	64.96	78.95	59.22	66.24	**90.16**	59.96	67.14	79.86	67.65	67.51	67.91
10	66.12	71.55	83.30	67.56	75.16	**99.91**	67.59	78.02	88.49	74.26	75.55	76.30
11	73.61	78.53	91.41	75.59	84.83	-	75.08	87.54	93.25	80.72	80.77	81.53
12	80.42	85.91	99.03	85.44	91.89	-	82.08	91.04	99.45	86.50	84.95	86.43
13	87.09	93.14	-	92.32	99.87	-	89.48	99.20	-	91.07	91.64	93.49
14	94.69	99.88	-	99.59	-	-	95.66	-	-	95.12	96.05	99.87
15	99.83	-	-	-	-	-	99.56	-	-	99.55	99.95	-
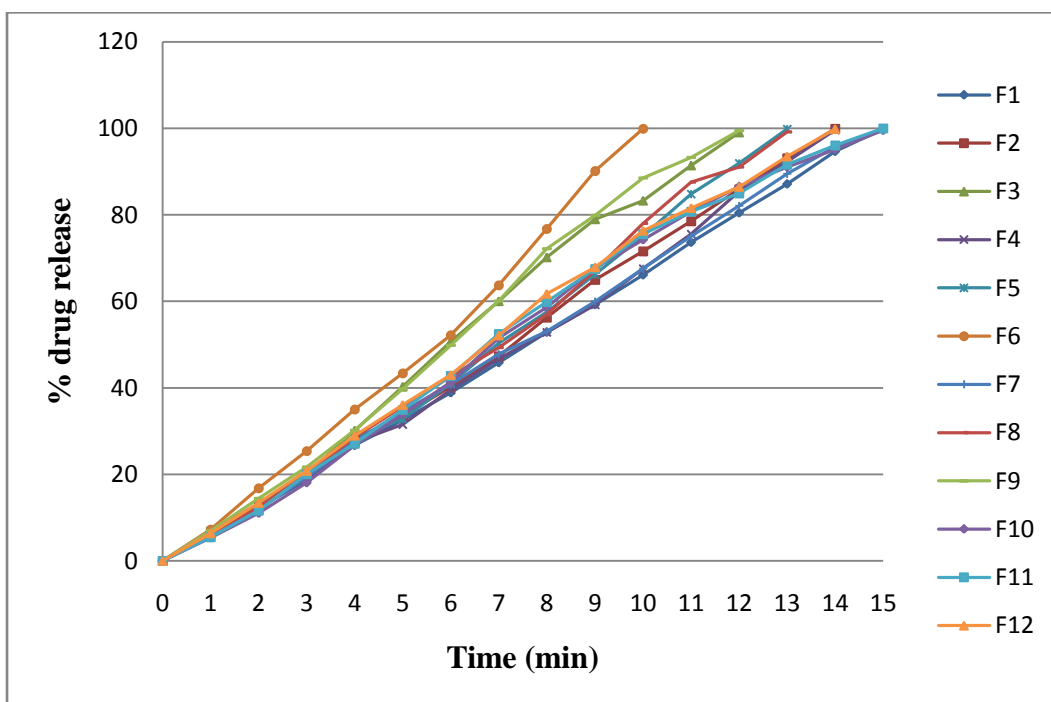
Fig. No. 9.13 Comparative *in-vitro* drug release profile of Bisoprolol Fumarate FDT in 0.1N HCL

9.4.9 Stability studies

The optimised FDT were subjected to stability studies and results were tabulated.

Table No. 9.13 Stability study at 40°C/75% RH

Parameters	1st month		2nd month		3rd month	
	RT	40°C	RT	40°C	RT	40°C
Uniformity of weight	passes	passes	passes	passes	passes	Passes
Thickness (mm)	2.5±0.091	2.5±0.094	2.5±0.073	0.950±0.098	0.955±0.095	0.951±0.089
Hardness (Kg/cm^2)	6.74±0.693	6.74±0.682	6.74±0.684	6.74±0.697	6.74±0.691	6.74±0.688
Disintegration time (sec)	2.77±0.261	2.76±0.285	2.77±0.229	2.77±0.249	2.77±0.237	2.77±0.289
Friability (%)	0.16±0.232	0.16±0.325	0.17±0.211	0.16±0.281	0.16±0.261	0.16±0.247

9.5 EXPERIMENTAL DESIGN FOR OPTIMIZATION

In the present study a 3^2 full factorial design was employed. The experimental trials were performed at 9 possible combinations and the two independent formulation variables evaluated included:

Table No. 9.14 Selected factor levels for the experimental design for optimization.

Factor Details			Factor Level		
Code	Actual	Units	-1	0	+1
X1	Lactose	mg	6	8	10
X2	Magnesium Stearate	mg	1	2	3

Table No. 9.15 Observations of FDT parameter evaluation for factorial design trials.

Code	Run	Independent Variables		Dependent Variables			
		X1	X2	% Friability	Wetting time (sec)	Disintegration Time (sec)	*In-vitro* Release* (min)
7	1	-1	-1	0.81	70	56	98.87
8	2	0	-1	0.38	58	29	99.91
9	3	+1	-1	0.59	67	41	99.06
5	4	-1	0	0.35	45	23	99.92
3	5	0	0	0.63	59	38	98.99
1	6	+1	0	0.86	63	59	98.24
2	7	-1	+1	0.34	54	43	99.26
4	8	0	+1	0.21	68	57	98.21
6	9	-1	+1	0.23	74	63	98.04

*At the end of 10th min

9.5.1 Effect of formulation variables on % Friability (R1):

Fig. No. 9.14 represents the observed response values compared to that of predicted values. The effect of factors A and B can be further elucidated with the help of response surface plot **Fig. No. 9.15**
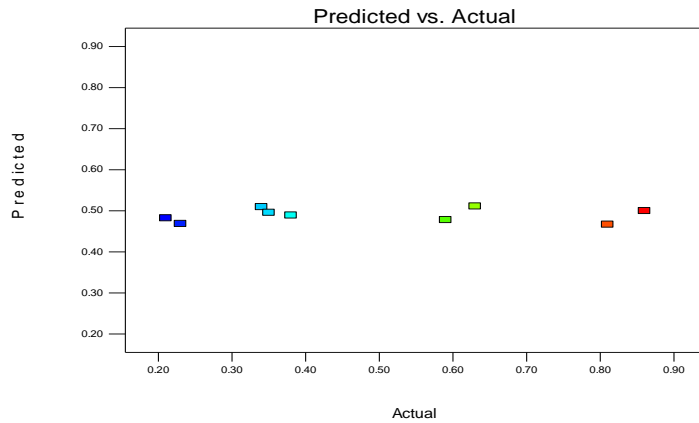
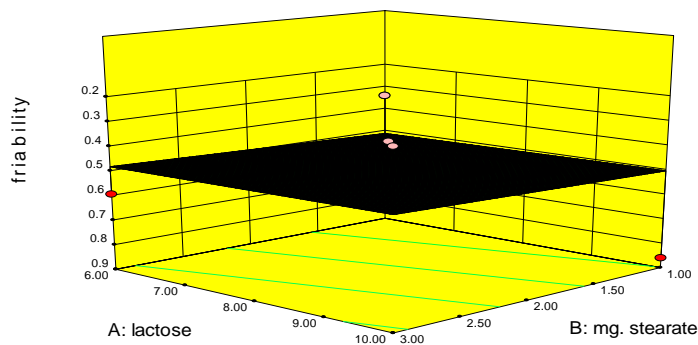**Fig. No. 9.14 Correlation between actual and predicted values for % Friability (R1).**

Fig. No. 9.15 Response surface plots showing the effect of Lactose and Mag.Stearate (R1).

The models (R1) were found to be not significant with F value of 0.014 and P value of 0.9863. In this case A and B are not significant model terms. The model describing the % Friability (R1) can be written as: **R1 = +0.53954 -2.37437E-003*A- 0.015680*B.**

9.5.2 Effect of formulation variables on Wetting time (R2):

Fig. No. 9.16 represents the observed response values compared to that of predicted values. The effect of factors A and B can be further elucidated with the help of response surface plot **Fig. No. 9.17**
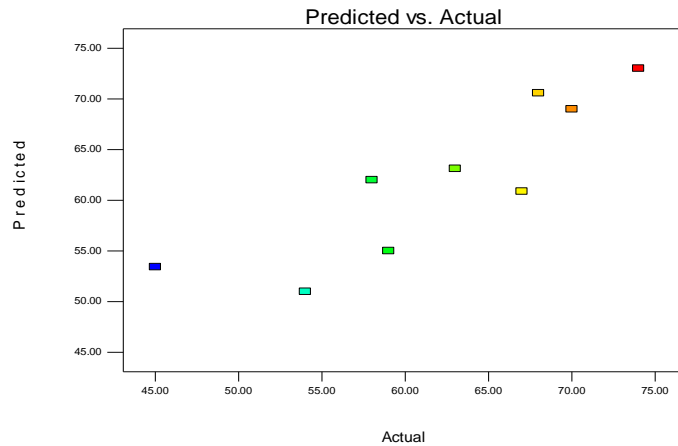
Fig. No. 9.16 Correlation between actual and predicted values for Wetting time (R2).
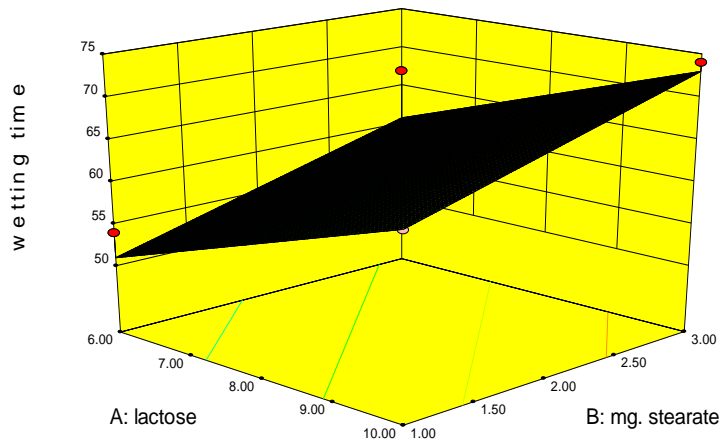

Fig. No. 9.17 Response surface plots showing the effect of Lactose and Mg. sterate on Wetting time (R2).

The terms R2 of the model were found to be significant with an F value of 9.30 and P value of 0.014. In this case A and B are significant model terms. The model describing the Witting time (R2) can be written a:

R2 = +27.84746+3.03293*A+4.94454*B.

9.5.3 Effect of formulation variables on Disintegration time (R3):

Fig. No. 9.18 represents the observed response values compared to that of predicted values. The effect of factors A and B can be further elucidated with the help of response surface plot **Fig. No. 9.19**
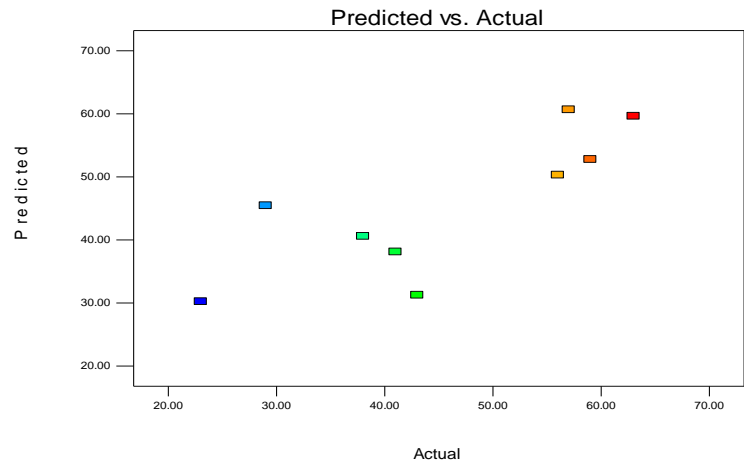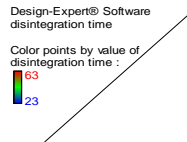
Fig. No. 9.18 Correlation between actual and predicted values for disintegration time (R3).
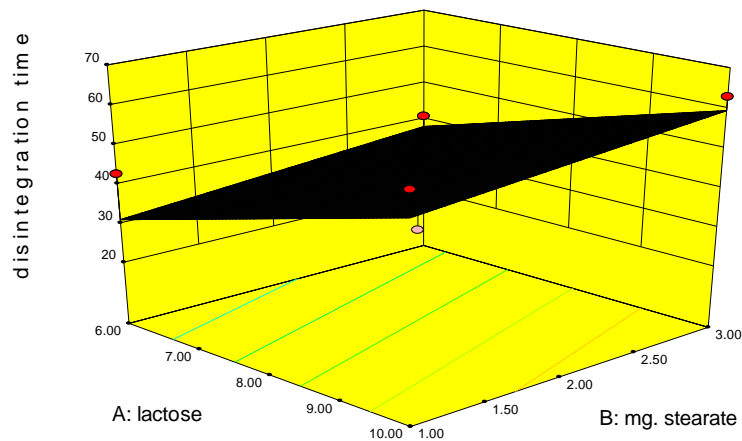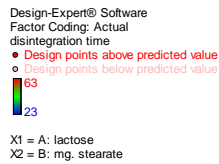

Fig. No. 9.19 Response surface plots showing the effect of Lactose and Mg. Sterate on disintegration time (R3).

The terms R3 of the model were found to be significant with an F value of 5.36 and P value of 0.0463. In this case A and B are significant model terms. The model describing the disintegration time (R3) can be written as:

R3 = -4.46115+5.38020*A+3.43198*B.

9.5.4 Effect of formulation variables on *In-vitro* Release (R4)

Fig. No. 9.20 represents the observed response values compared to that of predicted values. The effect of factors A, B and C can be further elucidated with the help of response surface plot **Fig. No. 9.21**
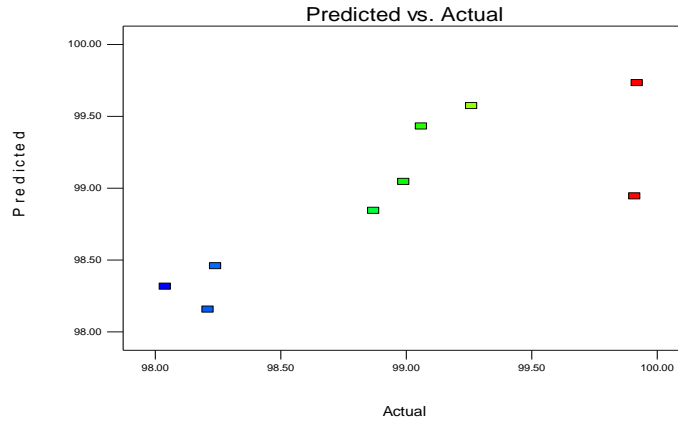
Fig. No. 9.20 Correlation between actual and predicted values for In-vitro Release (R4).
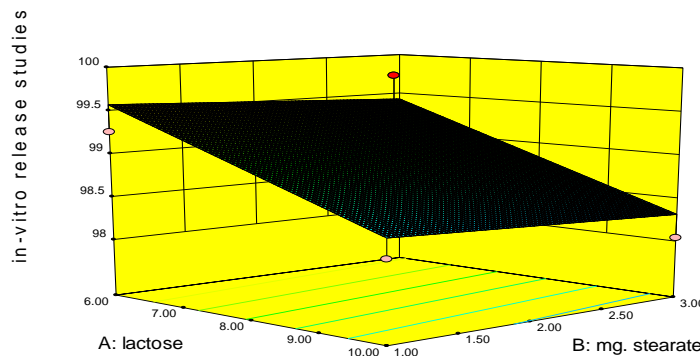

Fig. No. 9.21 Response surface plots showing the effect of Lactose and Mg. sterate on *In-vitro* Release (R4).

The terms R4 of the model were found to be significant with an F value of 5.68 and P value of 0.0412. In this case A and B are significant model terms. The model describing the In-vitro release (R4) can be written as: R**2 = +101.31602-0.27864 * A-0.071213 * B**.

9.5.5 Analysis of Variance for Dependent Variables from Factorial Design

Table No. 9.16 Analysis of Variance for Dependent Variables from Factorial Design

Source	Sum square	d.f	Mean	square F value	Probability
% Friability					
					R2=0.0046
Lactose	1.804E-004	1	1.804E-004	2.318E-003	0.9632
Mg. stearate	1.967E-003	1	1.967E-003	0.025	0.8789
Wetting time					
					R2=0.7561
Lactose	294.36	1	294.36	11.17	0.0156
Mg. stearate	195.59	1	195.59	7.42	0.0344

Disintegration time				
				R2=0.6409
Lactose	926.29	1	926.29	9.72	0.0206
Mg. stearate	94.23	1	94.23	0.99	0.3584
In-vitro release studies				
				R2=0.6545
Lactose	2.48	1	2.48	11.18	0.0155
Mg. stearate	0.041	1	0.041	0.18	0.6841

9.5.6 Optimized formula:

A numerical optimization technique, focused on the desirability approach, was used to generate the optimum settings for the most effective formulation. The objective in the design of the process was to optimize the dependent (response) variables R1, R2, R3 and R4. The optimized formulation was prepared, evaluated for the various responses and showed a good relationship between experimental and predicted values, which confirms the practicability and validity of the model.

Table No. 9.17 Comparison between the experimental (E) and predicted (P) values for the most probable optimal formulation

Optimized formulation	% Friability	Dependent variables		
		Wetting time (sec)	Disintegration time (sec)	In-vitro release studies (min)
Predicted (P)	0.59	58	41	98.99
Experimental (E)	0.48	62	38	99.04

10. CONCLUSION

From the present study which was carried out to formulate and optimize the parameter of Fast dissolving tablets contain Bisoprolol Fumarate by direct compression method; the following conclusion can be drawn.

The total weight of F6 batch was 100 mg contained Bisoprolol Fumarate -5%, croscarmilose sodium -6%, Mannitol-55%, microcrystalline cellulose 26%, Lactose-8%, magnesium stearate- 2%, talc-2%.

The Prefromulation study provided the following information of optimized batch as Angle of repose- 22°17' good to flow, Bulk density-0.33 g/cm^3, Tapped density-0.38 g/cm^3, Compressibility Index-11.11 % good to flow, Hausner's ratio-1.125.

Post parameter evaluation of tablets were found to be Weight variation-100.67± obeys the IP limits ± 7.5 % , Thickness uniformity-2.5 mm, Hardness-3.2 Kg/cm^2, Friability-0.48 %, Wetting time-54, Disintegration time-24 sec, *In-vitro* release studies- in 10 min.

From the above result it has been concluded that croscarmilose sodium at high concentration (6%) given quick disintegration (24 sec) and *in-vitro* drug release (99.91%) in 10 min. Based on disintegration and in-vitro drug release formulation (F6) containing croscarmilose sodium (6%) was the optimized batch.

The results of a 3^2 full factorial design revealed that the amount of lactose and magnesium stearate significantly affect the dependent variables such as % friability, wetting time, disintegration time and *In-vitro* drug release. Thus it is concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

11. BIBLIOGRAPHY

1. Shailesh Sharma, New Generation of Tablets: Fast Dissolving Tablets, Pharmaceutical reviews, 2008, Vol 6, Issue 1.

2. Debjit Bhowmik, Chiranjib. B, Krishnakanth, Pankaj and R. Margret Chandira Fast Dissolving Tablet: An Overview Journal of Chemical and Pharmaceutical Research, 2009, Vol 1, Issue 1, P 163-177

3. Leon Lachman, Herberman, Joseph L.Kanig, The theory and practice of industrial pharmacy third edition, 1991, P 293-336

4. Yourong Fu, Shicheng Yang, Seong Hoon Jeong, Susumu Kimura, and Kinam Park Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies Critical Review in Therapeutic Drug Carrier Systems, 2004, Vol 21, Issue 6, P 433–475

5. Mary Kathryn Kottke and Edward M. Rudnic,Tablet dosage forms, Modern Pharmaceutics, Fourth Edition, Edited by Gilbert S. Banker, P 291-303

6. Patrick Kearney.,The Zydis Oral Fast-Dissolving Dosage Form., Modified-Release Drug Delivery Technology,edited by Michael J. Rathbone, Marcel Dekker, Inc. 2002, P 191

7. S. Indiran Pather, Rajendra K. Khankari, and Derek V. Moe. OraSolv and DuraSolv: Efficient Technologies for the Production of Orally Disintegrating Tablets, Modified-Release Drug Delivery Technology, edited by Michael J. Rathbone, Marcel Dekker, Inc. 2002, P 203

8. Lokesha Puttalingaiah, Kunchu Kavitha, Tamizh Mani T., Fast disintegrating tablets: An overview of formulation, technology and evaluation, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011, Vol 2, Issue 2, P 589-601

9. Rakesh Pahwa, Mona Piplani, Prabodh C. Sharma, Dhirender Kaushik and Sanju Nanda, Orally Disintegrating Tablets - Friendly to Pediatrics and Geriatrics, Archives of Applied Science Research, 2010, Vol 2, Issue 2, P 35-48

10. Tejvir Kaur, Bhawandeep Gill, Sandeep Kumar and G. D. Gupta, Mouth dissolving tablets: a novel approach to drug delivery, Int. J. Curr. Pharm. Res., 2010, Vol -3, Issue-1, P 17

11. Sharma Shailesh, Hardenia Shiv Shankar and Gupta G. D., Novel *in-vitro* disintegration evaluation for fast dissolving tablets, Journal of Global Pharma Technology, 2009, Vol 1, Issue 1, P 113-120

12. Debjit Bhowmik, Chiranjib B., Krishnakanth, Pankaj and R. Margret Chandira, Fast Dissolving Tablet: An Overview Journal of Chemical and Pharmaceutical Research, 2009, Vol 1, Issue 1, P 163-177

13. Bhupendra G Prajapati and Nayan Ratnakar, A Review on Recent patents on Fast Dissolving Drug Delivery System, International Journal of Pharm Tech Research, 2009, Vol 1, No.3, P 790-798.

14. Simone Schiermeier and Peter Christian Schmidt, Fast dispersible ibuprofen tablets, European Journal of Pharmaceutical Sciences, April 2002, Vol 15, Issue 3, P 295–305

15. Panati Dinakar, C. Varalakshmi, P. K. Prakash Reddy, S. Mohanlakshmi, Formulation and evaluation of Bisoprolol fumarate transdermal patches, Journal of Pharmacy Research, 2010, Vol 3, Issue 8, P 1955-1957

16. Sudhir Bhardwaj, Vinay Jain, R.C. Jat, Ashish Mangal, Suman Jain, Formulation and evaluation of fast dissolving tablet of aceclofenac, International Journal of Drug Delivery, 2010, Vol 2, P 93-97.

17. R. Margret Chandira, BS Venkataeswarlu, MV Kumudhavalli, Debjit Bhowmik and B. Jayakar, Formulation and evaluation of mouth dissolving tablets of the etoricoxib, Pak. J. Pharm. Sci., April 2010, Vol 23, No 2, P 178-181

18. H.A.Patel, J.K.Patel, K.N.Patel,R.R.Patel, Studies on formulation and in vitro evaluation of fast dissolving tablets of domperidone, International Journal of Pharmaceutical Sciences, 2010, Vol 2, Issue 1, P 470-476.

19. Indhumathi D, Grace Rathnam, Design and optimization of orodissolving tablet of antidepressant drug by superdisintegrants addition method, International Journal of Pharmaceutical Sciences Review and Research, May – June 2010, Volume 2, Issue 2, Article 001

20. A. Prameela Rani1, N. Archana, P. Siva Teja, P. Mohan Vikas, M. Sudheer Kumar and C. Bala Sekaran, Formulation and evaluation of orodispersible metformin tablets: a comparative study on isphagula husk and crosspovidone assuperdisintegrants, International Journal of Applied Pharmaceutics, 2010, Vol 2, Issue 3

21. Mahaveer P. Khinchi, M. K. Gupta, Anil Bhandari, Dilip Agrawal, Natasha Sharma, Sandeep Kr.Gupta, Effect of various super disintegrants on drug release of orally disintegrating tablet, IJPRD, July 2010, Vol 2, Issue 5

22. Suhas M. Kakade, Vinodh S. Mannur, Ketan B. Ramani, Ayaz A. Dhada, Chirag V. Naval, Avinash Bhagwat, Formulation and evaluation of mouth dissolving tablets of losartan potassium by direct compression techniques, Int. J. Res. Pharm. Sci, 2010, Vol 1, Issue 3, P 290-295.

23. Reddy S, Panakanti P, Kandagatla R, Yamsani MR. Formulation and Release Characteristic of a Bilayer Matrix Tablet Containing Glimepride Immediate Release Component and Metformin Hydrochloride as Sustain Release Component. Int J of Pharma Sci and Nanotec, 2010, Vol 3, Issue 1, P 851-859.

24. N. G. Raghavendra Rao, T. Patel and S. Gandhi, Development and evaluation of carbamazepine fast dissolving tablets prepared with a complex by direct compression technique, Asian journal of pharmaceutics, 2009, Vol 3, Issue 2 , P 97-103

25. Venkatesh, Sajal Kumar Jha and Roopa Karki, Formulation Development and Evaluation of Taste MaskedORO-dispersible tablets of anti emetic drug, Journal of Pharmacy Research, 2009, Vol 2, Issue 4, P 606-609

26. B. Jayakar, K. Sampath Kumar and Debjit Bhowmik, Design And Characterisation of Fast Dissolving Tablet of Telmisartan, International Journal of Pharma Recent Research, 2009, Vol 1, Issue 1, P 31-40

27. Raguia Ali Shoukri, Iman Saad Ahmed, Rehab N. Shamma, In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets, European Journal of Pharmaceutics and Biopharmaceutics, 2009, Volu 73, Issue 1, P 162-171.

28. C.P. Jain and P.S. Naruka, Formulation and evaluation of fast dissolving tablets of valsartan, International Journal of Pharmacy and Pharmaceutical Sciences, 2009, Vol 1, Issue 1.

29. Narmada G. Y., Mohini K., Prakash Rao B., Gowrinath and Kumar K. S., Formulation, evaluation and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method, Ars Pharm, 2009, Vol 50, Issue 3, P 129-144

30. P.S. Zade, P.S. Kawtikwar, D.M. Sakarkar, Formulation, Evaluation and Optimization of Fast dissolving tablet containing Tizanidine Hydrochloride, International Journal of PharmTech Research, 2009 Vol 1,No 1, P 34-42

31. United State Pharmacopoeia 29-NF 24, Vol 30, Issue 5, P 1588

32. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 206-208

33. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 663-666

34. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 208-210

35. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 581-585

36. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 133-134

37. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 424-428

38. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 404-407

39. Raymond C R, Paul J S, Martan Equinn. Handbook of Pharmaceutical Excipients, 6th Edition, 2009, P 728-731

40. Robert M. Silverstein, Francis X. Webster. Infrared Spectrometry. In: Robert M. Silverstein. Editors. Spectrometric Identification of Organic Compounds. 6th Ed. John Wiley and Sons. Inc. New York, P. 71–143.

41. Y. R. Sharma. Elementary Organic Spectroscopy,Principles and chemical applications, P 69-339.

42. Akmar Sandip, Paramane Sonali, Kothapalli Lata, Thomas Asha, Jangam Sumitra, Mohite Mukesh and Deshpande Avinash, Spectrophotometric Estimation of Bisoprolol Fumarate in Bulk Drug and Tablets, Oct– Dec 2007, Vol 41, Issue 4, P 353-357

43. C. V. S. Subrahmanayam. Micromeritics. In: C. V. S. Subrahmanayam. Editors. Textbook of physical pharmaceutics. 2nd Ed. Vallabh Prakashan. Delhi, 2000, P 180-234.

44. Martin, P. Bustamante and A. Chun, Micromeritics, in Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore, 2002, P 446–448.

45. H. C. Ansel, L. V. Allen and N. G. Popovich, Capsules and Tablets, in Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippincott Williams &Wilkins, Philadelphia, 2002, P 204–209.

46. Alfred Martin. Diffusion and Dissolution. In: Alfred Martin, Pilar Bustamante and A. H. C. Chun. Editors. Physical Pharmaceutics. 4th edition, Lippincott Wi Jens T. Carstensen. Preformulation. In: Jens T. Carstensen. Editors. Drug Stability; Principles and practice. 3rd Ed. Revised and Expanded. Marcel Dekker Inc; New York. USA, 2008, P 237.

47. http://www.statease.com/dx8trial.html