DESIGN AND DEVELOPMENT OF FAST DISSOLVING TABLETS OF FELODIPINE USING DIFFERENT METHODS

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Submitted by

Reg. No. 26103002

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND DEVELOPMENT OF FAST DISSOLVING TABLETS OF FELODIPINE USING DIFFERENT METHODS",** submitted by the student bearing **Reg.No. 26103002** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

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DECLARATION

The work presented in this dissertation entitled "**DESIGN AND DEVELOPMENT OF FAST DISSOLVING TABLETS OF FELODIPINE USING DIFFERENT METHODS"** was carried out by me under the direct supervision of **Dr. V. VENU, M.Pharm., Ph.D.,** Asst. Professor, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Komarapalayam, in the partial fulfillment for the award of the degree of Master of Pharmacy in Pharmaceutics.

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Dedicated to

My Beloved Parents

& friends

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CONTENTS

INTRODUCTION

The Oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. Therefore, oral solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. Among the pharmaceutical dosage forms, the conventional tablets seem to be most popular, because of its ease of transportability and comparatively lower manufacturing cost.

There are several factors other than physicochemical properties of the drug that may influence the dissolution rate and hence, bioavailability of the drugs forms the solid dosage forms. It has shown that, the dissolution rate of pure drugs can be altered significantly by the proper selection of formulation components as well as processing methods.

Of the solid oral dosage forms tablets and capsules are more commonly employed. The tablets have advantages than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed. The adulteration can be easily found if it is done in either liquid form or solid form since deformation takes place if it is done in liquid form and powders cannot be added to the tablet if once they are formed. The major disadvantage of capsules over tablets is their higher cost. The capsules either hard capsule or soft capsule are susceptible to breakage if they are not stored properly.

Topical route is recently developed and is employed for only few drugs like nitroglycerine, scopolamine for systemic effect. Topical route has limitations in its ability to allow effective drug absorption for systemic drug action. Nevertheless it is possible that at least 90 % of all drugs used to produce systemic effect are administered by oral route.[1]

During the past four decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. The expenditure is quite reasonable when one considers how valuable tablets, as a dosage form, are to the industry. Because oral dosage forms can be self-administered by the patient, they

are obviously more profitable to manufacture than parenteral dosage forms that must be administered, in most cases, by trained personnel.[2]

Tablets are popular for several reasons: [3]

- The oral route represents a convenient and safe way of drug administration.
- The preparation procedure enables accurate dosing of the drug
- Tablets are convenient to handle and can be prepared in a versatile way with respect to their use and to the delivery of the drug.
- Tablets can be mass produced with robust and quality-controlled production Procedures giving an elegant preparation of consistent quality and, in relative terms, low price.

Tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package and shipment, increased stability and virtual tamper resistance.[2]

The disadvantage of tablet includes dysphasia or difficulty in swallowing is seen to affect nearly 35 % of population. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy. Many elder persons will have difficulty in taking conventional dosage forms because of hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular and nervous tissue. Others who may experience problems in swallowing are the mentally ill, developmentally disabled uncooperative patients and reduced liquid intake plan and nausea. In some cases such as motion sickness, sudden episode of allergic attack or coughing and unavailability of water swallowing tablets may become difficult.[4]

To fulfill the above needs pharmaceutical technologists have developed a novel type of dosage form for oral administration, fast dissolving tablets. Fast dissolving tablets are also called rapimelts, quick disintegrating tablets, oral disintegrating tablets etc.

Fast dissolving tablets are defined as the tablets, which are meant to disintegrate immediately upon contact with the saliva leading to faster release of the drugs in the oral cavity and disintegrate rapidly within 15 seconds to 3 minutes. The

faster the drug goes into solution, faster is the absorption and onset of clinical effect. For the drug attaining the therapeutic level by the gastric wall and elicit therapeutic effect, both rate and extent of absorption is important. The conventional tablet shows the delay in absorption and fast dissolving tablets disintegrate and dissolve rapidly and absorption takes place quickly, thus bioavailability increases.[5]

Some factors like GI disturbances and blood supply to GI differs with age as the elderly are considered as separate unique medicare population.[5]

Ideal characteristics of fast dissolving tablets[4, 6]

- They should not require water or other liquid at the time of administration.
- Should easily disintegrate and dissolve.
- Mask or overcome unacceptable taste of drug.
- They should have high drug loading.
- They should have pleasant feel in the mouth.
- They should have negligible or no residue in oral cavity after administration
- They should have low sensitivity against environmental conditions like moisture, temperature etc.
- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Should be portable without fragility concern.
- They should be manufactured using conventional tablet processing and packing equipment at low cost.

Advantages of fast dissolving tablets[6, 7]

- Ease of administration to patients who refuses to swallow a tablet such as pediatrics, geriatric patients and psychiatric patients.
- No need or little water is required to swallow the dosage form which is highly convenient feature for patients who are traveling and do not have access to water.
- Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

- Rapid disintegration and absorption of drug, which will produce quick onset of action.
- Quick absorption from the gastro intestinal tract improves bioavailability and reduces unwanted effects caused by the drugs and also improves patient compliance.
- Drug and dosage form stability.
- New business opportunities like product differentiation, line extension and life cycle management. Exclusivity of product promotion.
- Although chewable tablets have been on the market for some time, they are not the same as the new fast dissolving tablets. Patients for whom chewing is difficult or painful can use these new tablets easily. Fast dissolving tablets can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.

Disadvantages of FDT[8]

- Most fast dissolving tablets lack the mechanical strength common to traditional tablets. Many products are very lightweight and fragile requiring them to be individually packaged. Patients should be advised not to push these tablets through the foil film, but instead, peel the film back to release the fast-dissolving tablet.
- Due to the formulation of fast dissolving tablets which are also more susceptible to degradation via temperature and humidity, some of the newest fast dissolving tablet formulations are dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulations to ensure they are not exposed to high levels of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix.

Developmental challenges in fast dissolving drug delivery

The fast dissolving tablet formulation is defined by the food and drug administration (FDA) as, “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within matter of seconds, when placed upon

the tongue."[7] It is difficult for many patient to swallow tablets and hard gelatin capsule hence they do not comply with prescription, which results in high incidence of non compliance and ineffective therapy. Such problem can be resolved by mean of fast dissolving tablet. These FDT are designed to dissolve or disintegrates rapidly in saliva generally within <60 second.

1. Taste of the active ingredient[9]:

Some drugs have relatively no taste, and simply adding a suitable flavor can hide any slight unpleasant sensation. However, most drugs do require taste masking if they are to be incorporated into fast dissolving formulations. Numerous methods exist to achieve this, including simple wet granulation or roller compression with other excipients to minimize the presented surface area of the drug. Spray drying can also be employed to shroud the drug.

If further taste masking is needed, the resultant particle can be sealed with a suitable coating material (like hydroxy propyl methyl cellulose, ethyl cellulose, methacrylate and polyvinylpyrollidone). The choice of coating material will determine the mechanism of taste masking. In addition, the quantity of coat applied, how it is applied, and where other excipients are included in the coating will all affect the quality of taste masking.

Cyclodextrins (cyclic linked oligosaccharides) have been shown to prove some measure of taste masking by trapping the drug within the cyclic structure long enough to render initial dissolution. Other taste masking methods are namely coating methods including electrochemical, hot melt and super critical fluids. Encapsulation using coacervation has also been employed to encapsulate certain drugs.

2. Dose:

Molecules requiring high doses present three challenges to development of fast dissolving dosage forms: 1) Taste masking of active substance, 2) mouth-feel or grittiness and 3) tablet size. These challenges are not unrelated because most drugs will require taste masking depending on the degree of bitterness relative to the dose of the drug, which will in turn affect the final tablet size. As mentioned previously, drug may require coating, which will result in an increase in the particle size. The

extent to which this increase will affect the mouth feel and tablet size will depend on the dose of the drug and the amount of coating material required masking its taste.

3. Hygroscopy[10]:

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity that calls for specialized product package.

4. Friability[6]:

In order to allow fast dissolving tablets to disintegrating rapidly in the mouth, they are made of either very porous or soft moulded matrices or compressed into tablets with low compression force, which makes the tablet friable and/or brittle which are difficult to handle, often require specialized peel-off blister packing.

Techniques used in FDT[6]:

The performance of fast dissolving tablets depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.

Following technologies have been used by various researchers to prepare fast dissolving tablets: -

- Freeze-Drying or Lyophilization
- Tablet Molding
- Spray Drying
- Sublimation
- Direct Compression
- Cotton Candy Process
- Mass-Extrusion

Freeze-Drying or Lyophilization[11-14]:

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. Commonly used excipients with their uses and examples employed in manufacturing of fast dissolving tablets using Freeze-drying are listed on next page.

A typical procedure involved in the manufacturing of fast dissolving tablets using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped.

EXCIPIENTS	USE	EXAMPLE
Polymer	Strength and rigidity	Gelatin, alginate and dextrin
Polysaccharides	Crystallinity, hardness and palatability	Mannitol and sorbitol
Collapse protectants	Prevents shrinking	Glycerin
Flocculating agents	Uniform dispersion	Xanthan gum and acacia
Preservatives	Prevent microbial and fungal growth	Parabens
Permeation enhancer	Transmucosal permeability Enhancer	Sodium lauryl sulphate
pH adjusters	Chemical stability	Citric acid and sodium hydroxide
Flavors and sweeteners	Patient compliance	------
Water	Porous unit formation	-------

The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The Zydis formulations consist of a drug physically trapped in a water-soluble matrix (saccharine mixture and polymer), which is freeze dried to produce a product that dissolves rapidly when placed in mouth. The ideal candidate for Zydis technology should be chemically stable and water insoluble and particle size preferably less than 50 micron. Water soluble drugs might form eutectic mixtures and not freeze adequately, so dose is limited to 60 mg and the maximum drug limit is 400 mg for water insoluble drug as large particle sizes might present sedimentation problems during manufacture.

The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Moulding[15,16]:

The preparation of fast dissolving tablets using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. Mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30˚C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

Spray Drying[5]:

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing fast dissolving tablets.

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose sodium or crospovidone are used as superdisintegrants.

Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium.

Sublimation[17, 18, 64]:

The key to rapid disintegration of fast dissolving tablets is preparation of a porous structure in the tablet matrix. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and pthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

Vacuum drying technique has been very often used by researchers to sublime the volatile ingredients and thus maximize the porous structure in the tablet matrix. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of fast dissolving tablets because of the availability of improved excipients especially superdisintegrants and sugar based excipients. Direct compression, using directly compressible excipients is the most commonly used method of preparing fast dissolving tablets. Directly compressible excipients are very coarse and granular in

nature and give a coarse dispersion in the mouth with decreased mouth feel and compliance. It is very difficult to prepare fast dissolving tablets with drugs having very low bulk density, higher dose and poor flow property using this technique.

(a) Superdisintegrants[19-23]:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. This technique contains coated crystals and micro granules along with the disintegrants. In this technology, two types of granules are used; a disintegrating agent (e.g. modified cellulose- croscarmellose sodium), which has a high swelling force, and a swelling agent (e.g. starch), which has a low swelling force.

Other techniques like effervescent tablets in which disintegration is aided by evolution of carbon dioxide. Saliva activates the effervescent agent, causing the tablet to disintegrate. Care should be observed because effervescent excipients and final product require higher protection against humidity conditions.

(b) Sugar Based Excipients[24]:

This is another approach to manufacture fast dissolving tablets by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, lactose, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.

These excipients under defined manufacturing conditions gives a highly porous structure and friable exterior structure which helps in faster disintegration of fast dissolving tablets, they also provide a satisfactory mouth feel and so suitable for use in preparation of harder fast dissolving tablets by direct compression at low pressure.

There was no much attention to the direct compression of pharmaceuticals in the previous days (late 1950s). Now a day's great deal of attention has been given to both product and process development. The availability of new materials, new forms

of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable methods. In early 1960's, the introduction of spray dried lactose (1960) and avicel (1964) had changed the tablet manufacturing process and opened avenues of direct compression tableting.

Previously, the word direct compression was used to identify the compression of a single crystalline compound (i.e. sodium chloride, potassium chloride, potassium bromide, etc.) into a compact form without the addition of other substances. Current usage of the term direct compression is used to define the process by which tablets are compressed directly from the powder blends of active ingredient/s and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved.[25]

In the flow chart the benefits of the direct compression over other methods is described in the form of least steps involved.

Step	Direct compression	Dry granulation	Wet granulation
1	Mixed / blending of active drug and adjuvants	Mixing/blending of Active drug and adjuvants	Mixing/blending Active drug and adjuvants
	↓	↓	↓
2	**Compression**	Compression to slugs	Preparation if binder solution
		↓	↓
3		Size reduction of slugs and sieving ↓	Massing of binder solution of step 2 with powder mixture of step 1. ↓
4		Mixing of granules with pharmaceutical additives. ↓	Wet screening of damp mass ↓
5		**Compression**	Drying of wet granules ↓
6			Resifiting of dried granules and blending with pharmaceutical additives. ↓
7			**Compression**

Excipients used in direct compression:

The advent of direct compression is made possible by the commercial availability of directly compressible tablet vehicles which possess both fluidity and compressibility. These include wide range of fillers and disintegrants that are excessively manufactured to suit the condition of direct compression method.

Diluents:[25]

The directly compressible adjuvant should be free flowing. Flow ability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. Compressibility is required for satisfactory tableting, i.e., the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery.

Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed in to tablets with the given directly compressible excipient. A directly compressible adjuvant should have high dilution potential so that the final dosage form has a minimum possible weight.

A directly compressible adjuvant should be capable of being reworked without loss of flow or compressibility. On recompression, the adjuvant should exhibit satisfactory tableting characteristics.

The adjuvant should remain unchanged chemically and physically. The directly compressible adjuvant should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat.

A directly compressible adjuvant should have a particle size equivalent to the active ingredients present in the formulation. The particle size distribution should be consistent from batch to batch.

It should be colorless and tasteless.

It should be relatively cost effective and available in desired time. It should accept colorants uniformly.

Dry granulation technique:

The fast dissolving tablets has been prepared by means of dry granulation technology, which has the following advantages over other techniques of preparation:

1. It can be used for all types of drugs including moisture sensitive and heat sensitive.
2. It can be used for drugs having very low bulk density
3. It can be used for poorly compressible drugs and drugs having poor flow property.
4. The tablets can be packed into regular bottles, blister, strip pack or sachets.
5. The tablets can be stored in bulk in drums to be packaged subsequently. Moreover conventional tablet packaging feeders can be used for packing purpose. The process of dry granulation is cost effective as it avoids solvents, and the processes of drying like freeze drying, spray drying etc.
6. This reduces overall reduction in capital expenditure (conventional processing, packaging, and storage facilities). These dosage forms may be in the form of tablets, wafers, granules, or granules packed as such along with other pharmaceutically acceptable additives in a suitable package which upon contact with water, saliva or aqueous solution disintegrates within a few seconds.

Cotton Candy Process:

The cotton candy process is also known as the “candy floss” process and forms the basis of the technologies such as Flash Dose (Fuisz Technology). A fast dissolving tablets is formed using a candyfloss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into fast dissolving tablets. However the high processing temperature limits the use of this technology to thermo stable compounds only.

Mass Extrusion: [26]

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

New Orally Disintegrating Dosage Forms

Oral films and wafers

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion; solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low drug loading capacity and limited taste masking option.

ZYDIS (R.P. Scherer, Inc.)[14, 16, 27.]

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. The Zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form.

In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The

combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience.

There are some disadvantages to the Zydis technology. The process of freeze-drying is a relatively expensive manufacturing process. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%. If there is any pinhole or minor damage to the package, the patient may find the lyophilized product has collapsed due to absorption of moisture. As with most other drugs, patients should be advised to avoid storing the Zydis technology in the medicine cabinet in the bathroom. Patients should use their Zydis formulation within six months of opening the laminated foil pouch and immediately after opening its individual blister packaging.

ORASOLV (Cima Labs, Inc.)[4, 6, 7]

Orasolv was Cima's first fast-dissolving/disintegrating dosage form. The Orasolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The Orasolv technology is best described as a fast-dissolving tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the Orasolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste masking in Orasolv. This technology is frequently used to develop over-the-counter

formulations. The major disadvantage of the Orasolv formulations is its mechanical strength. The Orasolv tablet has the appearance of a traditional compressed tablet. However, the Orasolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for Orasolv. An advantage that goes along with the low degree of compaction of Orasolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilization and high degrees of compression, as utilized in Orasolv primary competitors, may disrupt such a taste masking approach.

DURASOLV (Cima Labs, Inc.)[6,7]

Durasolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to Orasolv, Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The Durasolv product is thus produced in a faster and more cost-effective manner. Durasolv is so durable that it can be packaged in either traditional blister packaging or vials. The newest Durasolv formulation, NuLev, is actually dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such Durasolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix. One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the Durasolv technology is best suited for formulations including relatively small doses of active compound.

WOWTAB (Yamanouchi Pharma Technologies, Inc.) [16]

The WOWTAB fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. It has just recently been introduced into the U.S. The WOWTAB technology utilizes sugar and sugar-like (e.g., mannitol)

excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the WOWTAB formulation is a bit more stable to the environment than the Zydis or Orasolv. It is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the WOWTAB is proprietary, but claims to offer superior mouth feel due to the patented SMOOTHMELT action. The WOWTAB product dissolves quickly in 15 seconds or less. The WOW in WOWTAB signifies the tablet is to be given Without Water. Two WOWTAB formulations currently on the U.S. markets are Benadryl Allergy and Sinus FASTMELT and Children's Benadryl Allergy and Cold FASTMELT.

Other Technologies

Flash Dose (Fuisz Technologies), Flashtab (Prographarm Group), and OraQuick (KV Pharmaceutical Co., Inc.) are three formulations on the worldwide market. Biovail Corp. recently announced the filing of an NDA for a FlashDose version of zolpidem tartrate. These technologies are similar to Zydis, WOWTAB, Orasolv and Durasolv in that they dissolve or disperse on the tongue within a minute. However, each also has unique characteristics to differentiate itself from the competition.

FLASHDOSE (Fuisz Technologies, Ltd.) [16]

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, FlashDose. The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres

has been patented by Fuisz, and is known as CEFORM1 and serves as an alternative method of taste masking.

FLASHTAB (Prographarm Group)[16]

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

ORAQUICK (KV Pharmaceutical Co., Inc.) [28]

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as Micro Mask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste masking.

A list of Patented Technologies using manufacturing techniques and description:[4,6,7.]

Technology	**Basis for technology**	**Company**
Zydis	Lyophilization	R. P. Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutical
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate Compressed Tablets	Ethypharm
Orasolv, Durasolv	Compressed Tablets	Cima Labs Inc.
Rapitab	Compressed Tablets	Schwarz Pharma
Wowtab	Compressed Molded Tablets	Yamanouchi PharmaTechnologies, Inc.
Fastmelt	Molding	Élan Corp.
Ziplets	Molding	Eurand
Flashdose	Cotton-candy process	Fuisz Technology Ltd.

SOLID DISPERSION:

Definition: [29] Solid dispersion in the pharmaceutical field are dispersion of one or more active ingredients, generally poorly water soluble drugs, in an inert carrier or matrix at solid state which are prepared by either melting the two (fusion) or dissolving them in a solvent or a combination of approaches followed by removal of the solvent.

METHODS FOR PREPARING SOLID DISPERSION**:**

(A) Hot melt method

Sekiguchi and Obi[30] used a hot melt method to prepare simple eutectic mixtures. In this method the drug and carrier were melted together at a temperature above the eutectic point (melting point). The molten mixture is then cooled rapidly. The resultant solid eutectic was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. Whether or not a molecular dispersion can be achieved

depends on the degree of supersaturation and rate of cooling attained in the process. In other words, the process has an effect on the resultant dispersion and can be varied to optimize the product.

(B) Solvent Method

Tachibani and Nakumara[31] were the first to use the solvent method. This process uses organic solvents to dissolve and intimately disperse the drug and carrier molecule. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range of 23-65 ºC. The solvent can also be removed by freeze-drying or by spray-drying.

(C) Melting solvent method: [29]

In the case where there is difficulty with thermal instability and immiscibility between the drug and the carrier, the hybrid melting solvent method can be employed.

The drug is first dissolved in a small quantity of organic solvent and added to the molten carrier. The solvent is then evaporated to generate a product that is subsequently milled to produce a powder.

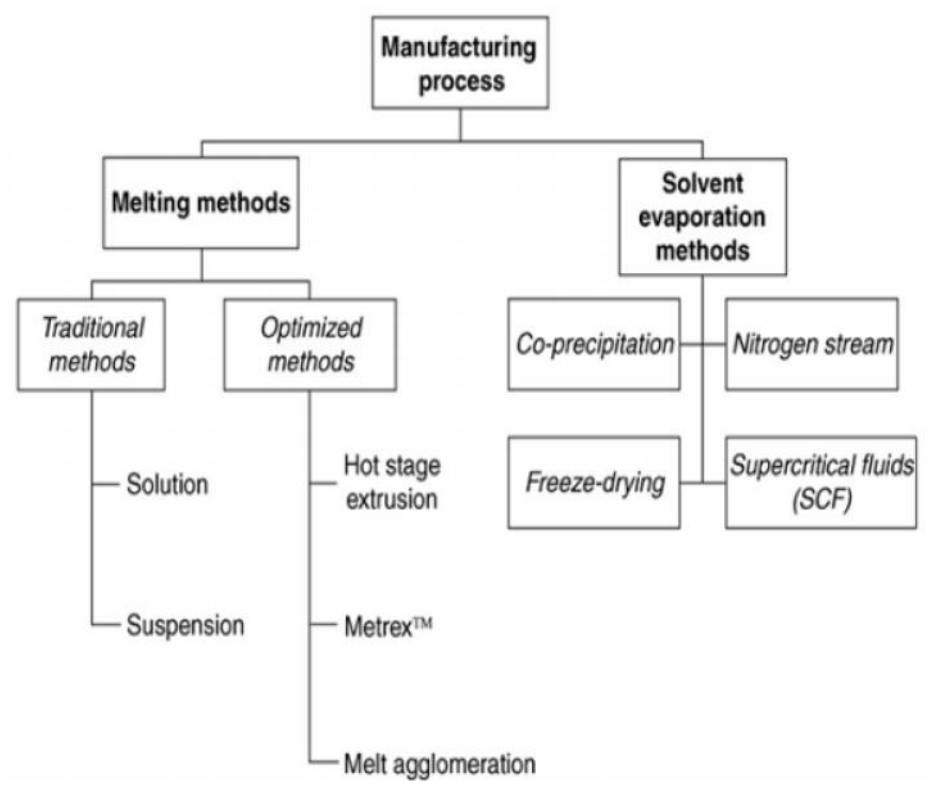
Dosage form development:

Solid dispersion must be developed into convenient dosage forms, such as tablets or capsules, for their clinical use and successful commercialization. Solid dispersions produced my melt method are usually hardened at very low temperatures and then pulverized with mortar and pestles. Similarly, solid dispersions produced by the solvent method are also pulverized after solvent removal and hardening. Some of the challenges in the dosage form development of such materials are difficulty of pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug-carrier incompatibility, and poor stability of dosage forms.[3]

A COMPARISION BETWEEN CONVENTIONAL SOLID DOSAGE FORMS AND ODIS

CONVENTIONAL SOLID DOSAGE FORMS	ORALLY DISINTEGRATING TABLETS
Swallowing problem interferes with patient compliance	Disintegrates in oral cavity, improving patient compliance
Reaches stomach in solid form, where it disintegrates and is absorbed	Reaches stomach in liquid form, which has several advantages: 1. Improved patient compliance 2. Faster onset of remedial action 3. Patient convenience

MANUFACTURING PROCESSES USED TO PRODUCE SOLID DISPERSION



Hypertension

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure and represents about 90-95% of hypertension cases. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumors (adrenal adenoma or pheochromocytoma)

Causes of Hypertension

1. Essential hypertension:

Essential hypertension is the most prevalent hypertension type, affecting 90-95% of hypertensive patients Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, stress, visceral obesity, potassium deficiency (hypokalemia) obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency. Risk also increases with aging, some inherited genetic mutations and family history. An elevation of renin, an enzyme secreted by the kidney, is another risk factor, as is sympathetic nervous system overactivity. Insulin resistance which is a component of syndrome X, or the metabolic syndrome is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

2. Secondary hypertension

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently than essential type by treating the underlying cause. Many secondary causes can cause hypertension; some are common and well recognized secondary causes such as Cushing's syndrome, which is a condition where both adrenal glands can overproduce the hormone cortisol. Hypertension results from the interplay of several pathophysiological

mechanisms regulating plasma volume, peripheral vascular resistance and cardiac output, all of which may be increased. More than 80% of patients with Cushing's syndrome have hypertension.[1] Another important cause is the congenital abnormality coarctation of the aorta

Mechanism of hypertension:

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased.

Three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Recently, work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated BP.

Symptoms of hypertension:

Mild to moderate essential hypertension is usually asymptomatic. Accelerated hypertension is associated with headache, somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy). Some signs and symptoms are especially important in infants and neonates such as failure to thrive, seizure, irritability or lethargy, and respiratory distress In children, hypertension may cause headache, fatigue, blurred vision, epistaxis, and bell palsy.

Some signs and symptoms are especially important in suggesting a secondary medical cause of chronic hypertension, such as centripetal obesity, "buffalo hump," and/or wide purple abdominal striae and maybe a recent onset of diabetes suggest glucocorticoid excess either due to Cushing's syndrome or other causes..

Mechanism of action Calcium channel blockers:

Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. This decreases intracellular calcium leading to a reduction in muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter (CCB's do not work on venous smooth muscle), a phenomenon called vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops.

With a relatively low blood pressure, the after load on the heart decreases; this decreases the amount of oxygen required by the heart. This can help ameliorate symptoms of ischemic heart disease such as angina pectoris.

Unlike β-blockers, calcium channel blockers do not decrease the responsiveness of the heart to input from the sympathetic nervous system. Since moment-to-moment blood pressure regulation is carried out by the sympathetic nervous system (via the baroreceptor reflex), calcium channel blockers allow blood pressure to be maintained more effectively than do β-blockers.

However, because calcium channel blockers result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. A β-blocker may be combined with a dihydropyridine calcium channel blocker to minimize these effects.

Ionic calcium is antagonized by magnesium ions in the nervous system. Because of this, dietary supplements of magnesium oxide and other magnesium preparations may increase or enhance the effects of calcium channel blockade.

Antihypertensive Drugs

Most antihypertensive drugs can effectively reduce mildly elevated blood pressure, but their use is associated with many side effects. Thus the decision whether to use a drug to control borderline or mild hypertension is made on the basis of the benefit: risk ratio.

Antihypertensive Drugs Classification

Drugs influence arterial blood pressure at four effector sites- arterioles (resistance vessels); veins (capacitance vessels); heart; and the kidneys—by several different mechanisms. They can be classified according to their site or mode of action as follows:

Diuretics

(i)Thiazides and related agents (hydrochlorothiazide, chlorthalidone etc.)

(ii) Loop diuretics (frusemide, bumetanide, ethacrynic acid)

(iii) Potassium-sparing diuretics (spironolactone, triamterene, amiloride)

II **Sympatholytic Drugs**

(i) Centrally acting agents (methyldopa, clonidine).

(ii) Ganglion blocking agents (trimethaphan).

(iii) Adrenergic neuron blocking agents (guanethidine, guanadrel, reserpine).

(iv) Beta-adrenoceptor blockers (metoprolol, atenolol etc.)

(v) Alpha-adrenoceptor blockers (prazosin, terazosin, doxazosin, phenoxybenzamine).

(vi) Alpha+beta blockers (labetalol, carvediol).

III. **Vasodilators**

(i) Arterial (hydralazine, minoxidil, diazoxide)

(ii) Arterial and venous (nitroprusside)

IV. **Calcium Channel Blockers**

Felodipine, Verapamil, nifedipine, nicardipine, nitrendipine.

Angiotensin Converting Enzyme Inhibitors

Captopril, enalparil.

VI. **Angiotensin II Receptor Blockers**

Losartan, valsartan

REVIEW OF LITERATURE

1. Vasillios et al.[43] have studied the effect of hydrogen bonding in solid dispersions of antihypertensive and antianginal drug Felodipine with the poly vinyl pyrrolidone (POVIDONE) or polyvinyl alcohol (PVA) water soluble polymers. Interaction energies, electron density, laplacian and vibrational data showed a stronger hydrogen bond of Felodipine with POVIDONE polymer in comparison to that with PVA.
2. Sreenivas et al[44] formulated ondansetron mouth disintegrating tablets by directly compression method by taking various disintegrants like crospovidone, croscarmellose sodium, pregelatinised starch, sodium starch glycolate and L-hydroxypropyl cellulose. They found the increasing order of various polymers in decreasing the wetting time is the following order crospovidone, croscarmellose sodium, pregelatinised starch, L-hydroxypropyl cellulose and sodium starch glycolate. They showed decreased wetting time with increased concentration of superdisintegrants. Rapid disintegrating is observed in crospovidone, croscarmellose sodium due to the rapid uptake of water and swelling effect respectively. They concluded that 10% disintegrant concentration is suitable for the preparation of ondansetron hydrochloride with croscarmellose sodium and crospovidone are the best.
3. Karavas et al.[45] have prepared pulsatile release formulations consisting of two layered tablets appropriate for preventing ischemic heart disease. For this reason the active core was constituted by a Felodipine/POVIDONE 10/90 w/w solid dispersion. Upon exposure of the prepared tablets to the release medium it was found that the drug release rate is directly attributed to the size of these nano dispersions while POVIDONE/Felodipine 90/10 w/w corresponds to an immediate release at an interval less than 30 minutes.
4. Gohel et al.[18] prepared mouth dissolving tablets of nimesulide by preparing granules containing nimesulide, camphor, crospovidone and lactose and then camphor was sublimed from granules, alternatively, first tablets were

prepared and then camphor was sublimed by vacuum. Sublimation of camphor from tablets resulted in superior tablets as compared with tablets prepared from granules that were exposed to vacuum.

5. Mahaparale et al.[47] prepared solid dispersions of meloxicam by solvent evaporation method with polyvinyl pyrrolidone (POVIDONE), (PVA 6000) and (PVA 4000). The dissolution study was carried out for all solid dispersions. All solid dispersions of Meloxicam showed higher solubility and faster dissolution then pure drug alone. Meloxicam: POVIDONE (1:9) ratio showed highest solubility and faster dissolution than any other solid dispersion.
6. Desai et al.[48] prepared orodissolving tablets of promethazine hydrochloride using super disintegrants, sodium starch glycolate and croscarmellose sodium by direct compression method. The formulations containing 4% of sodium starch glycolate and 1-3% of croscarmellose sodium were found to give the best results. Thus, the tablets apart from fulfilling all official and other specifications, exhibited higher rate of release.
7. Babu et al.[49] prepared solid dispersions of piroxicam in five super disintegrants namely primogel, microcrystalline cellulose, crospovidone, pregelatinized starch, croscarmellose sodium and with water soluble carriers polyvinyl pyrrolidone and polyethylene glycol. Solid dispersions of piroxicam in super disintegrants gave a marked enhancement in its dissolution rate and dissolution efficiency. Solid dispersion in super disintegrants could be used as an effective and efficient technique for enhancing the dissolution rate of piroxicam a poorly soluble drug.
8. Patel et al[50] formulated tablets of Piroxicam with POVIDONE K30 and sodium lauryl sulphate with a view to increase its water solubility. Sodium lauryl sulphate is used in solid dispersion with POVIDONE K30 by solvent evaporation method. This solid dispersion is made to tablets by using different disintegrating agents like sodium starch glycolate and crospovidone. 3^2 factorial designs were applied for the study and they found increase in dissolution with the superdisintegrant concentration. They found no significant change after four weeks kept at 45^0C.

9. Bolhuis et al[51] prepared the solid dispersion by surface depositions of the poorly soluble and hydrophobic drug on the surface of the hydrophilic and highly swelling superdisintegrants. They found that the wet granulation of drug with sodium starch glycolate show a large increase in the solubility of the drug. The granules containing too high concentration of superdisintegrant showed low drug release from the tablets. Thus viscous layer of superdisintegrants in the granules describes effect during the dissolution process.
10. Shu et al[53] formulated rapid oral disintegration tablets by direct compression using co-ground mixture of D-mannitol and crospovidone. The tablets manufactured from a physical mixture of 30%(w/w) co-ground mixture of D-mannitol and crospovidone (mixed ratio 9: 1) with 65.5%(w/w) of non-ground mannitol, 4%(w/w) of crospovidone, and 0.5%(w/w) of magnesium stearate had good properties for rapidly disintegrating tablets in the oral cavity. They presumed that crospovidone acted as a grinding assistant for D-mannitol in the co-grinding process, enhancing the hardness of tablets by increasing the contact area among powder particles.
11. Patel et al[54] selected crospovidone from three superdisintegrants as the prime study by considering wetting time and disintegrating time. In this work rofecoxib tablets were prepared by wet granulation method. Then they conducted study on optimizing the concentration of crospovidone and they concluded 10 % concentration as the best concentration for preparing fast disintegrating tablets. To these results 3^2 factorial design was employed taking concentration of crospovidone and mannitol as independent variable and wetting time and disintegration time as the dependent variables. The best formulae were compared with two marketed formulations and the obtained formulae showed better dissolution than marketed products.

12. Mahajan et al[55] prepared mouth dissolving tablets of sumatropan sulphate by using disintegrants sodium starch glycolate, carboxymethyl cellulose, Treated agar by direct compression. The tablets disintegrate by invitro and

in vivo methods in 10 minutes. The formulation containing combination of sodium starch glycolate and carboxymethyl cellulose was found to give the best results when compared to carboxymethyl cellulose and agar.

13. Shimizu et al[56] prepared fast-disintegrating tablet of lansoprazole. Since lansoprazole is an antiulcer agent and is unstable under acidic conditions, they developed lansoprazole as an orally disintegrating tablet containing enteric-coated microgranules. The effect of compression on dissolution behavior was investigated, as compression affected cleavage and crushing of the enteric layer. To decrease cleavage and crushing of the enteric layer, the effects of the combined ratio of methacrylic acid copolymer dispersion to ethyl acrylate-methyl methacrylate copolymer dispersion and the concentration of triethyl citrate on the dissolution in the acid stage and the dissolution in the buffer stage were evaluated.
14. Kuchekar et al[57] attempted to make mouth-dissolving tablets of salbutamol sulphate and they employed 2^n factorial design to select the superdisintegrant from croscarmellose sodium, treated agar and sodium starch glycolate for the formulations preparations. They employed direct compression method for the preparations of tablets. They concluded formulations containing sodium starch glycolate showed excellent release compared to other formulations. They showed better release even at the lower concentrations of sodium starch glycolate.
15. Mishra et al[57] attempted to make fast disintegrating tablets of valdecoxib usingdifferent superdisintegrants like sodium starch glycolate, croscarmellose sodium, crospovidone and L-HPC. They used direct compression method for the preparation of tablets. They did co-grinding of all the ingredients prior to the tableting. The order of enhancement of various disintegrants is in the following order L-hydroxypropyl cellulose> Ac-Di-Sol> sodium starch glycolate > crospovidone and dissolution obeyed Hixon Crowell cube root dissolution model.
16. Fukami et al[60] formulated fast disintegrating tablets using amino acids such as L-lysine HCl, L-alanine, glycine and L-tyrosine as disintegration accelerator. Based on surface free energy of amino acids wetting time and disintegration time of the tablets was examined. The wetting time of the

tablets increased in the order of L-lysine HCl, L-alanine, glycine and L-tyrosine, whereas the disintegration time in the oral cavity of the tablets increased in the order of L-alanine, glycine, L-lysine HCl and L-tyrosine. The fast disintegration of tablets was explained by the theory presented by Matsumaru.

17. Avinash et al[61] formulated highly porous mouth dissolving tablets of domperidone by using meltable binder polyethylinglycol 4000 a diluent mannitol and Camphor, ammonium bicarbonate that sublimes rapidly. The later is removed from the tablets by sublimation process after compressing. Two of the formulations having 40% w/w of ammonium bi carbonate and 20% of camphor respectively emerged to be the most satisfactory exhibiting the disintegrating time of 19.66±1.53 seconds and 21.33± 1.16 seconds and other parameters were found to be satisfactory.
18. Shenoy et al[62] prepared fast dissolving tablets of diclofenac sodium using direct compression by incorporating superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone in different concentrations. They found that croscarmellose sodium is best superdisintegrant compared to others and crospovidone and sodium starch glycolate do not show much effect may be due to secondary burst effect and the pore size increase with increase in superdisintegrant and matrix will have enough pressure to with stand. Another reason could be that in the presence of disintegrant the matrix might distort and allow the superdisintegrants to be absorbed faster.
19. Fukami et al[65] prepared rapidly disintegrating tablets using glycine as a disintegrant. They evaluated the disintegration behavior of tablets in oral cavity. The tablets containing carboxymethyl cellulose showed the least wetting time 3 seconds with 4 kg hardness and showed the fastest disintegration due to excellent wetting property. They also studied the effect of ethanzamide and ascorbic acid on disintegration time. They observed that ethanzamide has no effect on disintegration property. However, the disintegration time increases with ascorbic acid.
20. Chaudhari et al[67] masked the bitter taste of the drug by complexing with eudragid E100 at different concentrations of 1:1 to 1:10. Moth dissolving

tablets were prepared by using Ac-Di-Sol and polyplastadone as superdisintegants. They used direct compression as the method of preparation of tablets. They found that all the formulations showed faster release compared to marketed products that show 20 min for the 100% all formulations showed 81% to 87% release of the drug in first 2 minutes. Stability studies showed that there is a slight increase in disintegration time and decreased in dissolution may be due to formation of lumps of eudragid.

21. Ahmed et al[69] developed ketoprofen tablets which dissolve rapidly in the mouth, therefore needing not to be swallowed. The solubility and dissolution rate of poorly water soluble ketoprofen was improved by preparing lyophilized tablets (LT) of ketoprofen using freeze drying technique. Results obtained from dissolution tablets showed that lyophilized tablets of ketoprofen significantly improved the dissolution rate of the drug compared with the physical mixture and the plain drug.

22. Pawar et al[70] prepared solid dispersions of trimethoprim by fusion method using polyethylene glycol 4000, polyethylene glycol 6000 and mannitol as carriers. Two carriers proportions were used in each case. All solid dispersions showed increased dissolution rate as compared to pure trimethoprim. Mannitol dispersion showed higher dissolution rate then polyethylene glycol 4000 and polyethylene glycol 6000 dispersions.

AIM AND OBJECTIVES

AIM

To design and develop fast dissolving tablets of felodipine using solid dispersion and sublimation method**.**

OBJECTIVE

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson's disease, schizophrenia . These conditions are those which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets because of ease of administration, swallowing, pleasant taste and the availability in several flavors.

Felodipine which is used in the present study is a dihydropyridine derivative, widely accepted for its excellent antihypertensive and antianginal properties since it is calcium antagonist compound (calcium channel blocker). Felodipine is practically insoluble in water and its dissolution rate is limited by its physicochemical properties[36]. For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets. Because, faster disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug[40].

Though, fast disintegrating tablets are prepared by many processes direct compression using superdisintegrants is more preferred method since it is economical and includes less procedure steps.

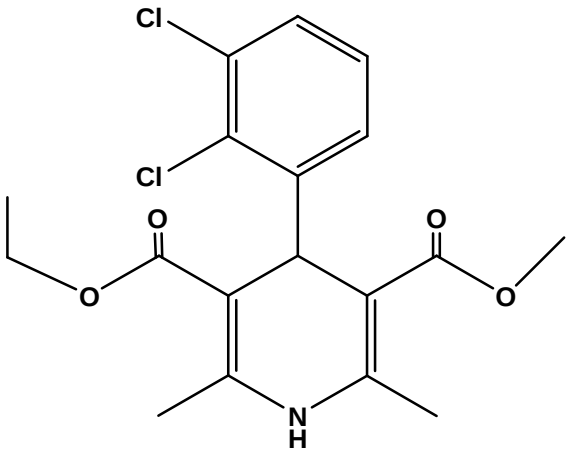
Effect of method of preparation (i.e. solid dispersion and sublimation) on dissolution rate, disintegration time and wetting time was studied.

PLAN OF WORK

- Selection of drug.
- Preformulation studies.
- FT-IR study
- Construction of standard curve
- Preparation of solid dispersion
- Characterization of solid dispersion by XRD.
- Formulation by using sublimation method.
- Selection of method for Fast dissolving tablet. (Direct compression).
- Evaluation of FDT tablet by,
    - Tablet Physical Appearance
    - Weight variation
    - Friability
    - Thickness
    - Hardness
    - Disintegration time
    - Wetting time
    - In-vitro dissolution study
- Accelerated stability study of Fast Dissolving tablet.

DRUG PROFILE[33-36]

Felodipine which is used in the present study as a model drug, is a dihydropyridine derivative, that is chemically described as ethyl methyl-4-(2,3, dichlorphenyl) -1- 4- dihydro-2, 6- dimethyl pyridine -3,5-dicarboxylate.



It is white or light yellow, crystalline powder.

It is practically insoluble in water, freely soluble in dehydrated alcohol, in acetone, in dichloro methane and in methyl alcohol.

Protein binding: 99% bound to albumin fraction.

Bioavailability: Approximately 20%.

Half life(t1/2): 8 to 18 hrs.

Mechanism of Action:

Felodipine blocks the calcium inflow into cells. It is 100 times, more active against calcium channels in blood vessels then in the heart. It causes peripheral vasodilation, reduction of resistance and fall of blood pressure. No action in the heart and on the venous channels. Renal blood flow increases. In patients with congestive failure causes reduction in pulmonary wedge pressure with improvement in symptoms. In angina, increase in excersice tolerance and reduction in frequency and intensity of angina attacks.

Pharmacokinetics:

Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first pass metabolism, with a bioavailability of about 15%. It is extensively metabolized in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and the remainder in faeces. The terminal elimination half life is reported to be 11 to 16 hours after oral administration of an immediate release preparation. Felodipine is about 99% bound to plasma proteins.

Uses and administration:

Felodipine is a dihydropyridine calcium-channel blocker. It is used in the management of hypertension and angina pectoris.

Contraindication:

Unstable angina, uncontrolled heart failure

Adverse effects:

Flushing, headache, palpitation, dizziness, fatigue, gravitational oedema, rarely rash, pruritus, cutaneous vasculities, gum hyperplasia, urinary frequency, impotency and fever.

Dosage:

In hypertension the usual initial dose is 5mg daily; the usual maintenance dose is 2.5-10 mg daily and doses above 20 mg daily are not usually needed. In angina the usual initial dose is 5mg daily increases if necessary to 10 mg daily.

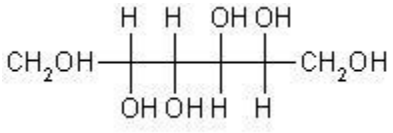
EXCIPIENT PROFILE

MANNITOL[37]

Synonyms : Cordyceptic acid, manita, manna sugar, Pearlitol.

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

Structural formula :



Functional category : Tablet and capsule diluent, sweetening agent, tonicity agent, vehicle (bulking agent) for lyophilized preparations.

Applications : As a diluent in tablets (10-90% w/w). It is not hygroscopic and can be used in moisture sensitive active ingredients. In the manufacture of chewable tablet formulations because of negative heat of solution.

Description : White, Odorless, crystalline powder or free flowing granules, it has a sweet taste.

Solubility : freely soluble in water practically insoluble in ether.

Storage conditions : Bulk materials should be stored in a well closed container, in a cool, dry place.

Incompatibilities : Mannitol solution, 20% w/v or stronger, may be salted out by sodium or potassium chlorides. It has incompatibility with xylitol infusion and may form complexes with metals like Fe, Al and Cu.

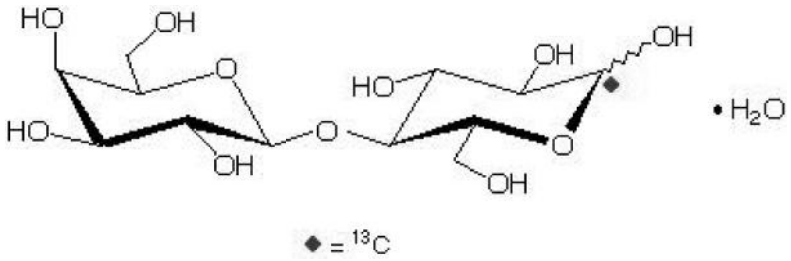
Safety : When consumed orally in large amount laxative effect may occur.

LACTOSE[37]:

Synonyms : Lactose monohydrate, Lactosum monohydricum

Chemical name : O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous

Structural formula :



Functional category: Diluent for dry-powder inhalers; tablet and capsule diluent.

Description : Lactose occurs as white to off-white crystalline Particles or powder. Lactose is odorless and slightly Sweet tasting; α-lactose is approximately 15% as sweet as sucrose, while β-lactose is sweeter than the α-form.

Solubility : Practically insoluble in chloroform,ethanol and ether; soluble in water in 1: 4.63 at 20˚C, 1: 3.14 at 40˚C, 2.04 at 50˚C, 1:1.07 at 80˚C.

Storage conditions : Mold growth may occur under humid condition (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp condition. Saturated solution of β-lactose may precipitate crystals of α-lactose on standing. Solution also shows mutarotation. Lactose should be stored in well-closed container in a cool, dry place.

Applications in pharmaceutical formulation and technology:

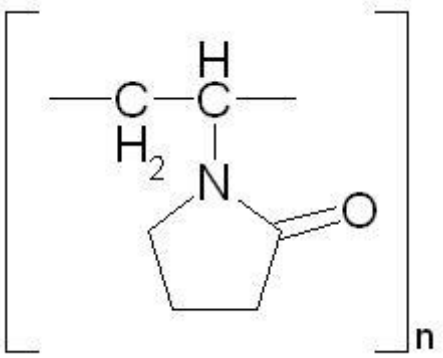
Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant feed formulae. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent upon the type of encapsulating machines used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine permits better mixing with other formulation ingredients and utilizes the binder more efficiently. In lyophilized products lactose is added to freeze-dried solution to increase plug size and aid caking. Lactose is also used in combination with sucrose (appx.1:3) to prepare sugar-coating solutions.

CROSPOVIDONE[37]

Synonym : Crosslinked povidone, polyvinylpolypyrrolidone; 1-vinyl-2-pyrrolidinone homopolymer, Kollidon CL, Polyplasdone XL, Polyplasdone XL-10.

Chemical name : 1-Ethenyl-2-pyrrolidinone homopolymer

Chemical structure :



Functional category : Disintegrant

Description : It is a white to creamy white, finely divided Free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Applications in pharmaceutical formulation:

Crospovidone is a water insoluble disintegrant. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to gel formation. Crospovidone superdisintegrant is effective in wet granulation, dry granulation and direct compression in tablet processing. They are manufactured using a unique process. Unlike most polymeric disintegrants, which consist of a natural or semi-natural water-soluble polymer, which is then cross-linked chemically, the polymerization and cross-linking occurs simultaneously to yield a controlled insoluble mass. This results in amorphous, spherical particles that are then spray dried to produce a free flowing compressible powder to enable even distribution and excellent powder flow.

The spherical particles unique to crospovidone superdisintegrant distribute evenly throughout the tablet and have a greater surface area/volume ratio than other disintegrants. This feature, coupled with the amorphous open structure of the particles, results in rapid swelling in all directions in the presence of any physiological fluid. This leads to the rapid development of high internal stresses, which cause the tablet to disintegrate. The fully cross-linked nature of crospovidone means that it is completely insoluble and will not develop any viscosity. Feature and benefits of crospovidone superdisintegrant:

Unique Chemistry:

High swell pressure	Highly effective at low concentration Cost-effective
Completely insoluble	Will not gel during tablet dissolution ensuring smooth processing and disintegration performance Excellent reproducibility.
Synthetic	Consistent quality and no danger of microbial contamination.
Not a sodium salt	Low sodium level is important for compatibility issues and for low sodium diet.
Compatible with all drugs	Give product confidence
Official in all major pharmacopoeias	Accepted globally by licensing authorities

Unique Morphology

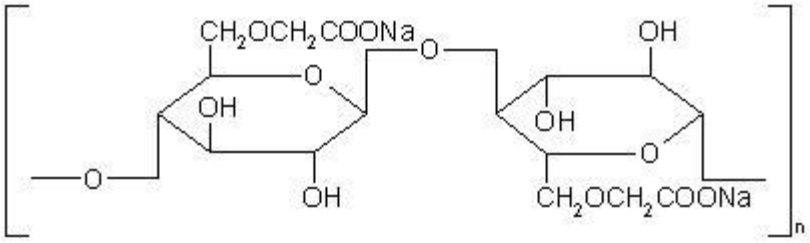
Rapid swelling in all directions	High performance Cost-effective
Excellent flowability	Provides process flexibility and uniform production possible by wet granulation or by direct compression.
Excellent compressibility	Does not interfere with tablet compression or cause instability on storage Improves hardness and reduces friability

CROSCARMELLOSE SODIUM[37]

Synonyms : Ac-Di-Sol, Crosslinkedcarboxymethylcellulose sodium, modified cellulose gum, Nymcell ZSX, Primellose, Solutab.

Chemical name : Cellulose sodium salt of carboxymethyl ether.

Structural formula :



Functional category : Tablet capsule disintegrant.

Description : Croscarmellose sodium occurs as an odorless, white coloured powder.

Applications in pharmaceutical formulation or technology:

It swells 4-8 folds in 10 seconds. The cellulose derivative swells in two dimensions radially. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulation croscarmellose sodium is added to in both the wet and dry stages of the process so that wicking and swelling ability can both be utilized.

MAGNESIUM STEARATE[37]

Synonyms : Magnesium Octadecanoate, stearic acid magnesium Salt.

Chemical name : Octadecanoic acid magnesium salt.

Structural formula : $[CH_3(CH_2)_{16}COO]_2Mg$.

Description : It is a fine, white, precipitated or milled, impalatable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and adhere to skin.

Functional categories: Tablet and capsule lubricant.

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

Stability and storage : It is stable and should be stored in well- closed container in a cool, dry place.

Incompatibilities : Incompatible with strong acids, alkali and iron salts. most alkaloidal salts.

Application : It is widely used in pharmaceutical formulations. It is used as lubricant in capsule and tablet manufacture at concentration between 0.25- 5.0 %. It is also used in barrier cream.

COLLOIDAL SILICON DIOXIDE[37]

Synonyms **:** Aerosil, colloidal anhydrous silica, anhydrous silicic acid, silicic anhydride, silicon dioxide fumed.

Structural formula **:** SiO_2

Description **:** Light, loose, bluish-white coloured, odorless, tasteless, nongritty amorphous powder.

Functional category **:** Adsorbent, anticacking agent, emulsion stabilizer, glidant, Suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.

Solubility **:** Practically insoluble in organic solvents, water and acids. Soluble in hot solutions of alkali hydroxide.

Stability and storage **:** It should be stored in a well-closed container.

Safety **:** It should not be administered parenterally.

Applications in pharmaceutical formulation and technology:

It is used as glidant in tabletting, to stabilize emulsions and as a thixotropic thickening agent, suspending agent in gels and semisolid preparations, to promote particulate suspension in aerosols. It is also used tablet disintegrant and adsorbent dispersing agent for liquids in powders. It is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.

CAMPHOR[38]

Synonyms	**:**	Cinnamomum Camphora
Systemic name	**:**	1,7,7-Trimethyl bicycle [2.2.1] heptane-2-one
Molecular Formula	**:**	$C_{10}H_{16}O$
Molar Mass	**:**	152.23 gms/mole
Description	**:**	It is a waxy, white or transparent solid with a strong aromatic odour.
Functional Categories	**:**	Sublime agent and plasticizer.
Solubility	**:**	Solubililty in water 0.12 gms in 100 ml Solubililty in acetic acid ~ 200gm in 100 ml Solubililty in ethanol ~ 100 gm in 100 ml Solubililty in acetone ~ 250 gm in 100 ml Solubililty in ether ~ 100 gm in 100 ml Solubililty in chloroform ~ 200 gm in 100 ml
Storage	**:**	It should be stored in well closed container and in a cool and dry place.
Application	**:**	It is used as sublime agent in tablet manufacturing. A modern use includes plasticizers for cellulose nitrate, as an antimicrobial agents.

LACTOSE SPRAY DRIED

Synonyms: FlowLac 100; Lactopress Spray-Dried; NF Lactose–316 Fast Flo; NF Lactose–315; Pharmatose DCL 11; Pharmatose DCL 14; Super-Tab Spray-Dried.

Chemical name: Spray-dried lactose is a mixture of amorphous lactose, which Is a 1:1 mixture of a-and-b-lactose, and O-b-galactopyranosyl-(1!4)-a-D- glucopyranose monohydrate.

Empirical Formula and Molecular Weight:

C12H22O11 342.30 (for amorphous)

C12H22O11_H2O 360.31 (for monohydrate)

Functional Category: Binding agent; directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler.

Applications in Pharmaceutical Formulation or Technology:

Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

Description:

Lactose occurs as white to off-white crystalline particles or powder. It is odourless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80–90% specially prepared pure a-lactose monohydrate along with 10–20% of amorphous lactose.

Method of manufacture:

A suspension of a-lactose monohydrate crystals in a lactose solution is atomized and dried in a spray drier(2,3) Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles. The compactibility of the material and its flow characteristics are a

function of the primary particle size of the lactose monohydrate and the amount of amorphous lactose.

Safety:

Lactose is widely used in pharmaceutical formulations as a diluent in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose in tolerance, which occurs in individuals with a deficiency of the enzyme lactase.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material being handled. Excessive generation of dust, or inhalation of dust, should be avoided.

Stability and Storage Conditions

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

TALC

Synonyms: Altalc, hydrous magnesium calcium silicate; hydrous magnesium silicate, purified French chalk, soapstone, steatite, Magsil Star, superior.

Chemical name : Talc

empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Description:

Talc is a very fine, white to greyish-white, odourless, 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.

Stability and Storage conditions:

Talc is a stable material and may be sterilized by heating at 160^0C 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.

Functional Category :

Anti caking agent; glidant; tablet and capsule diluents; tablet and capsule lubricant.

Applications :

- Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

MATERIALS AND METHODOLOGY

INSTRUMENTATION

Sl. no	Instruments /Equipments	Model and Manufacturer/ supplier
1	Digital balance	Shimadzu AX-200 corporation, Japan
2.	Electronic balance	Oriental
3	UV-Visible spectrophotometer	UV-1700 Shimadzu corporation, Japan
4	Hot air oven	Servewell instruments and equipments pvt. ltd., Banglore.
5	Tap density apparatus (USP)	Electro lab, Mumbai.
6	Rotary compression machine	Rimek mini press 1, Karnavathi engineering ltd, Gujarat
7	Friabilator	EF-2 Friabilator, Electrolab, Mumbai
8	Hardness tester	Pfizer hardness tester, Servewell instruments and equipments pvt. ltd., Banglore
9	Disintegration apparatus	Electrolab ED2L Disintegration tester (USP).
10	Dissolution apparatus	Electrolab TDT - 08 L Dissolution tester (USP).
11	Digital pH meter	7007, Digisun electronics, Hyderabad
12	Desiccator	Tarson, Kolkata.
13	Vernier calipers	RK industries, India
14	Glass ware	Borosil
15	Sieves	Filterwel test sieves
16	Water bath shaker	Remi motors
17	FTIR	Shimadzu corporation 8600, Japan
18	Stability Chamber	Labcare, Mumbai
19	Vacuum Oven	Labcare instrument, Bangalore.

MATERIALS

Sl.No	Material	Source
1	Felodipine	Gift sample, Cipla Ltd, B'lore.
2	Croscarmellose sodium	Gift sample, Maple biotech pvt. Ltd, Pune.
3	Sodium starch glycolate	Gift sample, Maple biotech pvt. Ltd, Pune.
4	Crospovidone	Gift sample, Concertina Pharm (p) Ltd, Hyd.
5	Microcrystalline cellulose	S.D. Fine chemicals Pvt limited, Mumbai
6	Mannitol	N. R. Chem. Mumbai
7	Aspartame	Ranbaxy, Mumbai
8	Magnesium Stearate	S.D. Fine chemicals Pvt limited, Mumbai
9	Talc	S.D. Fine chemicals Pvt limited, Mumbai
10	Sodium hydroxide	S.D. Fine chemicals Pvt limited, Mumbai
11	Potassium dihydrogen ortho phosphate.	S.D. Fine chemicals Pvt limited, Mumbai
12	Potassium Permanganate	S.D. Fine chemicals Pvt limited, Mumbai
13	Hydrochloric Acid	S.D. Fine chemicals Pvt limited, Mumbai
14	Camphor	Suresh chemicals,Chennai.
15	Sodium lauryl Sulphate	S.D. Fine chemicals Pvt limited, Mumbai
16	Methanol	S.D. Fine chemicals Pvt limited, Mumbai

METHODS

Analytical methods for the estimation of Felodipine:

Preparation of phosphate buffer pH 6.5[84]

Place 41.2 ml of 1M sodium dihydrogen phosphate, 39.2 ml of 0.5 M disodium hydrogen phosphate and 1 gm of sodium lauryl sulphate were mixed and filled up with purified water upto 1000 ml.

Determination of λ max for Felodipine:

A 5 mcg/ml solution of Felodipine in phosphate buffer pH 6.5 containing 0.1 % sodium lauryl sulphate was scanned in UV range between 200-400 nm. Felodipine showed maximum absorbance at 362.0 nm (fig 1) in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate. Thus 362.0 nm was used as wavelength (max) for further analysis.

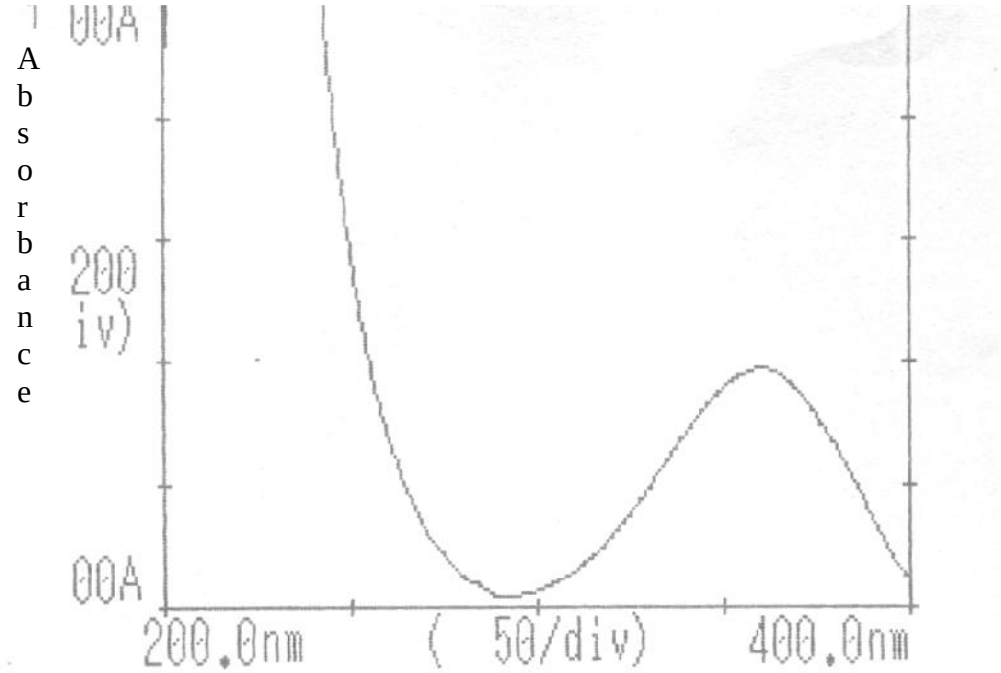
Preparation of calibration curve:

Weighed quantity of Felodipine (5mg) was dissolved in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate in 100 ml volumetric flask and the volume was made up with the same. The stock solution obtained was 50 mcg/ml solution. Aliquots of 0.5,1,1.5,2 and 2.5 ml if stock solution were pipetted into 25 ml standard volumetric flasks and volume was made upto 25 ml with phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate to give the concentration of 1, 2, 3, 4 and 5 mcg/ml. The absorbance was measured at 362.0 nm against reagent blank phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate (Table 1, fig 2).

Solubility studies:

The solubility of felodipine was determined in water and buffers (acid buffer pH 1.2 and phosphate buffer pH 6.5) containing different amount of solublizer. The solubility study was conducted by taking excess amount of the drug in the 10 ml of the solution and the solutions were kept in the water bath shaker for 48 hours. Then the solutions were filtered and diluted with sufficient amount of the same solvent. The absorbances of the solutions were determined at 362 nm. The solubility data for the drug in various buffers and water is shown in table 6.

Figure 1: UV absorption spectra of Felodipine in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate.

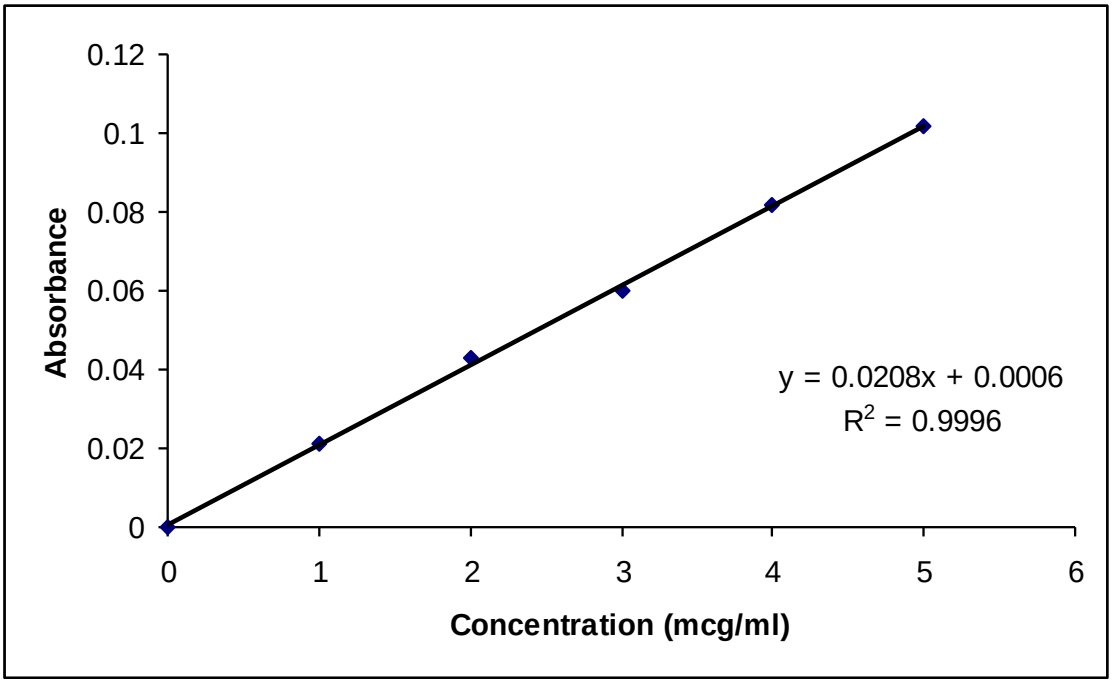


Wavelength (nm)

Table 1: Analysis of Calibartion curve data for Felodipine in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate at 362.0 nm.

Sl.No	Cons(µg/ml)	Abs(nm)
1	**0**	**0.00**
2	**1**	**0.021**
3	**2**	**0.043**
4	**3**	**0.060**
5	**4**	**0.082**
6	**5**	**0.102**

Figure 2: Calibration curve for Felodipine in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate at 362.0 nm



PREFORMULATION STUDIES[45]

The following preformulation studies were performed for felodipine formulations: -

Angle of Repose:

A funnel was fixed at a particular height on a burette stand. A graph paper was placed below the funnel on the table. The powdered drug passed through the funnel until it forms a pile. The radius of the pile was noted down. Angle of repose of the powder material was calculated using the formula. Results are shown in Table 5.

Angle of repose $\theta = \tan^{-1} H/r$

Where, H is height of the pile, and r is radius of the pile.

Determination of Densities:

Apparent Bulk Density:

The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Tapped Density:

Weighed powder sample was transferred to a graduated cylinder and was placed on the tapped density test apparatus, was operated for a fixed number of taps (100). The tapped density was determined as the ratio of weight of sample to tapped volume.

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$

Carr's Index (% Compressibility):

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\%\ \text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio:

The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio. Results are shown in Table 5.

Preparation of solid dispersions of Felodipine:

Solid dispersions of Felodipine were prepared by solvent evaporation and melt method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier was added (POVIDONE, PVA and Mannitol in ratio of 1:1, 1:2, 1:4 and 1:9) . The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Drug content of solid dispersions:

10 mg of 1:1 solid dispersions, 15 mg of 1:2 solid dispersions, 20 mg of 1:4 solid dispersions and 50 mg of 1:9 solid dispersions were weighed and transferred to 250 ml of volumetric flask. Dissolved in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700, Shimadzu Corporation, Japan) at 362 nm.

Preparation of tablets containing solid dispersions of Felodipine:

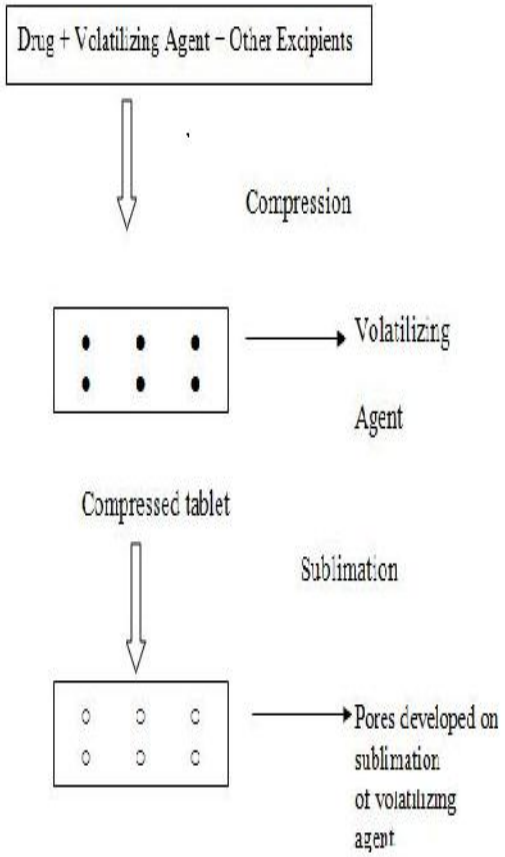
The solid dispersions equivalent to 5 mg of drug were taken. Then mixed with directly compressible diluent and superdisintegrants in a plastic container. Magnesium stearate and aerosil were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Preparation of tablets by direct compression method:

Tablets containing 5 mg of Felodipine were prepared by direct compression method and the various formulae used in the study are shown in Table 2. The drug, diluent and superdisintegrants were properly mixed together (in a plastic container). Aerosil and magnesium stearate were passed through mesh number 60, mixed, and blended with initial mixture in a plastic container. The tablets were prepared by direct compression method by manual feeding using 7 mm bi concave punches on a ‘Rimek mini press 1’ a 10 station rotary compression machine.

Preparation of tablets by sublimation technique:

The tablets containing 5 mg of Felodipine were prepared by sublimation method and formulae used are shown in table 3. The drug, directly compressible diluent, super disintegrants and camphor were properly mixed together (in a plastic container). Aerosil, magnesium stearate and talc were passed through mesh no. 60, mixed and blended with initial mixture in a plastic container. The tablets were prepared by direct compression method by manual feeding using 7 mm bi concave punches on a 'Rimek mini press 1' a 10 station rotary compression machine. After compression the tablets were heated by vacuum drying technique at 50^{o} C until a constant weight was obtained to ensure the complete removal of sublimable component. The sublimable component was removed to make the tablet porous.



Steps involved in sublimation method

Preparation of tablets containing Camphor:

Felodipine 5 mg was taken and then it was mixed with sprayed dried lactose, directly compressible microcrystalline cellulose, superdisintegrants and different concentrations of camphor (3%, 5%, 10%, 20% and 40%) in a plastic container. Magnesium stearate, aerosil and talc were passed through sieve no. 60 mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Table 2: Formulae used in the preparation of tablets using POVIDONES solid dispersion

Ingredients (mg)	P1	P2	P3	P4	P
Amount of solid Dispersion equi-valent to 5 mg Of drug	10.16	15.24	26.31	52.63	26.31
Lactose	109.34	104.26	93.19	66.87	93.19
MCC	20	20	20	20	20
Croscarmilose Sodium	6	6	6	6	-
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5
Tablet Weight	150	150	150	150	150

Table 3: Formulae used in the preparation of tablets using PVA solid dispersion

Ingredients (mg)	E1	E2	E3	E4	E
Amount of solid Dispersion equi-valent to 5 mg Of drug	10.16	14.88	24.80	50.81	24.80
Lactose	109.34	104.26	94.70	68.69	94.70
MCC	20	20	20	20	20
Croscarmilose Sodium	6	6	6	6	-
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5
Tablet Weight	150	150	150	150	150

Table 4: Formulae used in the preparation of tablets using Mannitol solid dispersion

Ingredients (mg)	**M1**	**M2**	**M3**	**M4**	**M**
Amount of solid Dispersion equi-valent to 5 mg of drug	9.92	15.62	26	52	52
Lactose	109.58	103.88	93.5	67.5	73.5
MCC	20	20	20	20	20
Croscarmilose Sodium	6	6	6	6	-
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5
Tablet Weight	150	150	150	150	150

Table 5: Formulae used in the preparation of tablets using Sublimation method

Ingredients (mg)	C	C1	C2	C3	C4	C5
Felodipine	5	5	5	5	5	5
Spray dried Lactose	107.5	97	94	86.5	71.5	41.5
Directly com Pressed MCC	30	30	30	30	30	30
Camphor	-	4.5	7.5	15	30	60
Crospovidone	-	6	6	6	6	6
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3
Tablet Weight	150	150	150	150	150	150

EVALUATION OF TABLETS

Hardness:

Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. Results are shown in Table 8.

Thickness and Diameter:

The thickness and diameter of 4 tablets (2 tablets from each batch) were recorded during the process of compression using calipers (Mitotoyo; Japan).

Friability:

Two tablets were accurately weighed and placed in the friabilator (Electrolab. EF-2 Friabilator) and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula.

$F = (1- W_0 / W) \times 100$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

The tablets that loose less than 1% weight were considered to be compliant. Results are shown in Table 8.

Disintegration test:[83]

Tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker containing 900 ml of distilled water and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

Wetting time:[19]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured.

Drug Content of tablets:

Tablets were weighed individually, pulverized, and diluted to 250ml with sufficient amount of phosphate buffer pH 6.5 containing 0.1% SLS. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700 Shimadzu Corporation, Japan) at 362 nm.

Dissolution studies of tablets:

The in vitro dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (phosphate buffer pH 6.5 containing 0.1% SLS) was taken in vessel and the temperature was maintained at 37 ± 0.5^{o}C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with phosphate buffer pH 6.5 containing 0.1% SLS prior to analysis in the UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 362 nm.

Stability studies of the tablet formulations:

The stability study of the tablets was carried out according to ICH guidelines at 40±2^{o}C/75±5%RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai).

FTIR Studies:

IR spectra for drug, excipients and formulations P3, E3 and M4 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

XRD Studies:

X-ray diffraction analysis of pure drug Felodipine, POVIDONE, PVA, Mannitol and formulations P3, E3 and M4 were performed. This was done by measuring the 2θ ranges from 10-50 on a PW 3710 X ray generator diffractometer. The X-ray diffraction patterns were recorded automatically using rate meter with time per step is 0.500 sec. and scanning speed of 2θ/ minute.

RESULTS AND DISCUSSION

Solubility studies:

The solubility studies of felodipine in water / buffer solutions were carried out to know the solubility and decide the appropriate dissolution medium. Table 6 shows the solubility data of felodipine in water/ buffer solutions. In this study phosphate buffer pH 6.5 containing 0.1% SLS was used as dissolution media as it can maintain perfect sink conditions.

Table 6: Solubility study data of Felodipine

Sl.No	Name of the solvent/buffer	Concentration (mg/ml) (± SD), n=3
1	Water	0.0012 ±0.002
2	Hydrochloric acid buffer pH 1.2	0.016 ±0.092
3	Hydrochloric acid buffer pH 1.2 + 0.1%SLS	0.021 ±0.107
4	Hydrochloric acid buffer pH 1.2 + 0.3% SLS	0.027 ±0.074
5	Hydrochloric acid buffer pH 1.2 + 0.5% SLS	0.163 ±0.014
6	Phosphate buffer pH 6.5	0.004 ±0.040
7	Phosphate buffer pH 6.5+ 0.1% SLS	0.054 ±0.012
8	Phosphate buffer pH 6.5+ 0.3% SLS	0.222 ±0.010
9	Phosphate buffer pH 6.5+ 0.5% SLS	0.340 ±0.029

Precompressional Parameters:

Table 7 shows the Precompressional parameters of powder blend. There was a change in the angle of repose of formulations as the method of preparations changed from solid dispersion to sublimation.

Table 7: Precompressional Parameters:

Formulation (±SD), n=3	Angle of Repose (θ) (±SD), n=3	Compressibility (±SD), n=3	(%) Hausner's Ratio
P	23.65 ± 2.22	16.66 ± 4.22	1.37 ± 0.06
P1	24.21 ± 3.52	29.57 ± 0.060	1.32 ± 0.05
P2	23.70 ± 0.28	23.80 ± 1.34	1.31 ± 0.02
P3	22.49 ± 1.12	23.60 ± 2.60	1.35 ± 0.04
P4	34.06 ± 0.95	27.22 ± 1.67	1.32 ± 0.03
E	23.38 ± 0.25	23.00 ± 2.30	1.24 ± 0.02
E1	32.90 ± 1.30	20.00 ± 2.50	1.25 ± 0.07
E2	22.18 ± 1.45	27.41 ± 2.10	1.37 ± 0.02
E3	30.10 ± 1.91	23.85 ± 0.60	1.30 ± 0.00
E4	28.72 ± 0.50	18.62 ± 0.32	1.22 ± 0.09
M	24.68 ± 1.80	27.41 ± 0.75	1.37 ± 0.02
M1	22.76 ± 0.35	23.80 ± 4.60	1.31 ± 0.06
M2	24.58 ± 0.90	27.41 ± 0.60	1.37 ± 0.01
M3	23.70 ± 3.00	23.80 ± 0.50	1.28 ± 0.02
M4	25.60 ± 2.80	22.80 ± 0.64	1.30 ± 0.01
C	33.80 ± 0.51	16.66 ± 5.00	1.20 ± 0.03
C1	22.99 ± 0.72	22.61 ± 3.42	1.57 ± 0.05
C2	22.12 ± 1.52	25.80 ± 2.26	1.34 ± 0.04
C3	22.49 ± 2.20	20.00 ± 1.20	1.25 ± 0.05
C4	23.90 ± 4.20	22.80 ± 0.60	1.20 ± 0.02
C5	22.59 ± 0.89	25.45 ± 1.22	1.34 ± 0.03

Angle of Repose ranged between 22.42 to 34.06, 22.18 to 32.90, 22.76 to 25.60, 22.12 to 33.80 in POVIDONE, PVA and mannitol solid dispersions formulations and camphor sublimation respectively.

% compressibility ranged from 16.66 to 29.59, 18.62 to 27.41, 22.80 to 27.41 and 16.66 to 25.80 in POVIDONE, PVA and mannitol solid dispersions formulations and Camphor sublimation respectively.

Hausners ratio increased from 1.31 to 1.37, 1.22 to 1.37, 1.28 to 1.37 and 1.20 to 1.57 in POVIDONE, PVA and mannitol solid dispersions formulations and camphor sublimation respectively. Although, flow parameters showed varying results, most of the formulation showed good flow property.

Postcompressional parameters:

Hardness:

Table 8 shows that, hardness of the tablet increased when mannitol was used as a carrier, where as the hardness of the tablets prepared by sublimation method has been decrease .[64]

% Friability:

Table 8 shows the friability values of all the tablet formulations. The results indicated that the % friability of formulations was between 0.21% and 0.64%. The low values of friability indicate that tablets were mechanically hard enough.

Thickness:

As shown in the table 8, thickness of the tablets range from 3.28 to 3.95 mm. Tablets prepared with mannitol showed highest thickness because of their least density.

Table 8: Post compressional parameters of Tablets

Formulation	Hardness test (kg/cm^2) (±SD), n=6	Friability (%) (±SD), n=10	Thickness (mm) (±SD), n=4
P	4.50 ± 0.28	0.26 ± 0.04	3.50 ± 0.00
P1	3.55 ± 0.10	0.30 ± 0.04	3.65 ± 0.050
P2	3.55 ± 0.15	0.32 ± 0.02	3.48 ± 0.058
P3	3.50 ± 0.20	0.33 ± 0.04	3.50 ± 0.060
P4	6.05 ± 0.31	0.33 ± 0.02	3.42 ± 0.055
E	3.08 ± 0.20	0.26 ± 0.02	3.75 ± 0.050
E1	4.50 ± 0.25	0.32 ± 0.05	3.80 ± 0.100
E2	5.09 ± 0.40	0.26 ± 0.06	3.84 ± 0.060
E3	4.50 ± 0.35	0.24 ± 0.00	3.82 ± 0.072
E4	3.57 ± 0.32	0.46 ± 0.01	3.68 ± 0.075
M	4.00 ± 0.45	0.42 ± 0.04	3.95 ± 0.050
M1	3.55 ± 0.10	0.30 ± 0.04	3.88 ± 0.058
M2	4.50 ± 0.15	0.50 ± 0.02	3.93 ± 0.090
M3	4.08 ± 0.40	0.33 ± 0.03	3.70 ± 0.060
M4	4.50 ± 0.35	0.26 ± 0.06	3.75 ± 0.072
C	4.50 ± 0.12	0.40 ± 0.02	3.28 ± 0.050
C1	3.09 ± 0.20	0.21 ± 0.01	3.75 ± 0.075
C2	3.00 ± 0.25	0.33 ± 0.03	3.68 ± 0.078
C3	2.50 ± 0.30	0.28 ± 0.00	3.53 ± 0.058
C4	2.08 ± 0.35	0.30 ± 0.01	3.48 ± 0.055
C5	2.00 ± 0.20	0.64 ± 0.02	3.52 ± 0.055

Note : Values in parenthesis are standard deviation (±SD)

Figure 3: Hardness and Disintegration time of tablets prepared with POVIDONE solid dispersion.

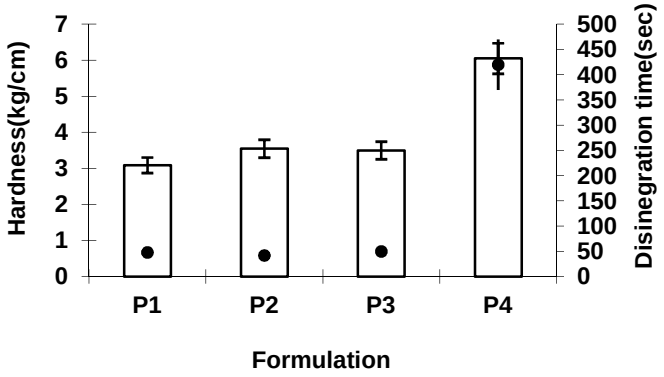


Figure 4: Hardness and Disintegration time of tablets prepared with PVA solid dispersion.

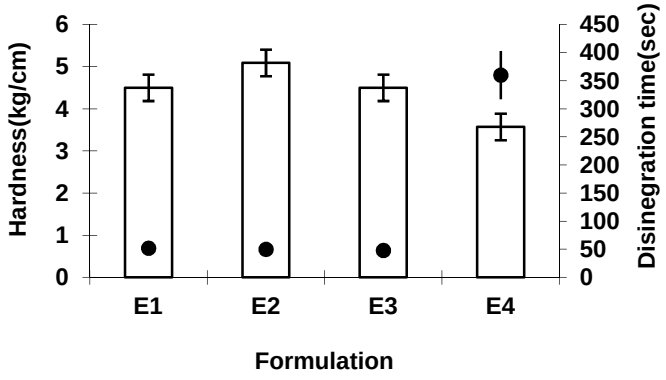


Figure 5: Hardness and Disintegration time of tablets prepared with Mannitol solid dispersion.

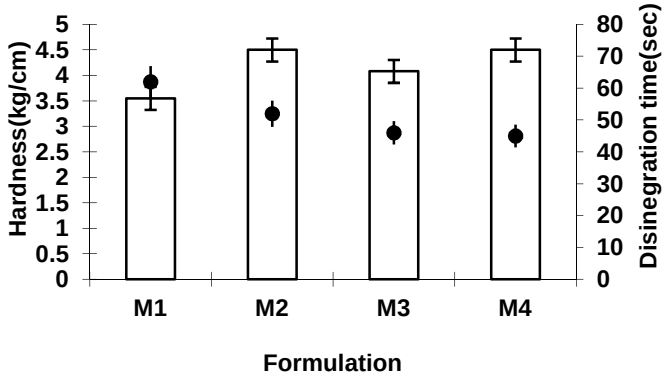
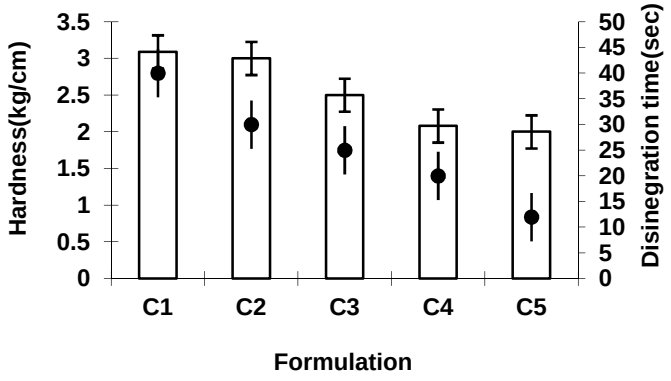


Figure 6 Hardness and Disintegration time of tablets prepared with Camphor sublimation method.



Disintegration time:

Table 9 shows the disintegration time of the formulations. Tablets prepared with POVIDONE (P1,P2,P3) , PVA (E1,E2,E3) and mannitol (M1, M2,M3,M4) disintegrated rapidly while tablets prepared with POVIDONE (P and P4), with PVA (E and E4) and with mannitol (M) did not disintegrate in specified limit of time for fast dissolving tablet. This may be due to more hardness of the tablets as these carriers act as strong binders at higher level within the tablets. During compression, the carrier could plasticize, soften or melt, filling the pores within tablets and thus making them non-disintegrating. It is also possible that the soften and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating along with the reduction of porosity of tablets makes disintegration difficult. As the method of preparation of tablets changed to sublimation, the disintegration time decreased significantly regardless of the diluent used. It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrate the tablet rapidly. Above results shows that tablets prepared with 4 % superdisintegrants and 40 % camphor (sublimation method) showed least disintegration time in comparison with the all other formulations because of their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of crospovidone in bringing about faster disintegration[18].

Wetting time:

Results of wetting time studies are shown in table 9. Wetting time of formulations P, P4, E, E4, M and C were significantly higher than other formulations. Wetting times of the formulations C1 to C5 were significantly lower than all remaining formulations. It is because of highest porosity of the tablets[18].

Drug content of tablets:

Drug content of tablets ranged between 95.91 to 102.00 %. Results are shown in table 10.

Table 9: Disintegration time and wetting times of tablet formulations

Note: Values in parenthesis are standard deviation (±SD)

Formulation	Disintegration time (sec)(±SD), n=6	Wetting time(sec) (±SD), n=6
P	120 ± 6.50	80 ± 5.70
P1	48 ± 2.00	35 ± 3.75
P2	42 ± 3.44	40 ± 2.20
P3	50 ± 2.90	48 ± 2.50
P4	220 ± 5.5	145 ± 8.50
E	110 ± 1.70	81 ± 4.40
E1	52 ± 2.45	42 ± 3.27
E2	50 ± 2.00	40 ± 3.16
E3	48 ± 3.50	45 ± 3.11
E4	215 ± 4.12	142 ± 5.12
M	120 ± 2.75	75 ± 4.42
M1	62 ± 1.60	40 ± 3.30
M2	52 ± 2.22	30 ± 2.20
M3	46 ± 2.45	35 ± 2.00
M4	45 ± 2.00	30 ± 1.50
C	250 ± 9.00	250 ± 5.50
C1	40 ±7.00	25 ± 6.00
C2	30 ± 1.00	22 ± 2.20
C3	25 ± 2.00	20 ± 2.00
C4	20 ± 2.10	18 ± 1.50
C5	12 ± 2.00	08 ± 2.00

Table10 : Dissolution parameters ($t_{50\%}$ and $t_{90\%}$) and drug content of tablets.

Formulation	$t_{50\%}$ (min) (±SD), n=4	$t_{90\%}$ (min) (±SD), n=4	Drug content (%) (±SD), n=6
P	7.42 ± 0.12	28.33 ± 0.30	99.00 ± 1.97
P1	1.34 ± 0.25	10.07 ± 0.25	96.15 ± 2.20
P2	1.32 ± 0.14	8.52 ± 0.19	96.15 ± 1.50
P3	1.17 ± 0.40	6.12 ± 0.26	96.00 ± 1.55
P4	12.34 ± 0.32	15.15 ± 0.22	98.00 ± 3.00
E	9.53 ± 0.05	41.34 ± 0.25	95.10 ± 0.50
E1	4.54 ± 0.95	20.48 ± 0.35	96.50 ± 2.15
E2	1.30 ± 0.80	12.05 ± 0.19	97.00 ± 2.14
E3	1.37 ± 0.05	8.20 ± 0.15	98.55 ± 2.50
E4	1.37 ± 0.11	17.28 ± 0.10	95.91 ± 3.00
M	3.50 ± 0.22	25.00 ± 0.25	98.55 ± 2.20
M1	1.44 ± 0.04	10.19 ± 0.09	98.55 ± 0.60
M2	1.19± 0.22	8.23 ± 0.42	96.00 ±1.20
M3	1.09 ± 0.06	4.40 ± 1.02	100.96 ± 0.75
M4	1.13 ± 0.20	3.60 ±1.00	96.15 ± 1.20
C	19.14 ± 0.15	59.00 ± 0.45	102.00 ± 2.27
C1	5.02 ± 0.14	7.06 ± 0.45	97.35 ± 1.50
C2	3.05 ± 1.00	5.19 ± 0.30	98.00 ± 3.30
C3	1.46 ± 1.00	3.32 ± 0.30	98.07 ± 0.90
C4	1.40 ± 0.60	2.18 ± 0.06	99.00 ± 2.20
C5	0.36 ± 0.20	0.58 ± 0.07	98.55 ± 1.50

Note: Values in parenthesis are standard deviation (±SD)

In vitro release studies of tablets

The dissolution of Felodipine from tablets is shown in Figures 7 to 11. Table 10 shows the $t_{50\%}$ and $t_{90\%}$ values of release profiles of tablets. These values changed with change of carriers and method of preparation of tablets.. The dissolution of the drug from the tablets prepared by camphor sublimation method was quicker than those prepared by solid dispersion methods using POVIDONE, PVA and mannitol as carriers. This may be due to their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of crospovidone in bringing about faster disintegration[18].crospovidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation [89] and disintegrates tablets rapidly (fig.10)

The dissolution rate of tablets prepared with solid dispersions of felodipine in the ratio 1:1, 1:2, 1:4 (P1,P2,P3) with POVIDONE, in the ratio 1:1, 1:2, 1:4 (E1,E2,E3) with PVA and in the ratio 1:1, 1:2, 1:4, 1:9 (M1,M2,M3,M4) with mannitol increased significantly ($P<0.05$) than P, E and M respectively. This may be due to the use of croscarmilose sodium, which causes swelling to 4-8 folds in 10 seconds[37] and due to particle size reduction and improved wettability.

In addition to micronization, conversion of drug to amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions[52].

However, tablets prepared with POVIDONE solid dispersions in the ratio 1:9(P4) and with PVA solid dispersion in the ratio 1:9(E4) did not further enhance the dissolution rate unlike solid dispersions. In practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tabletted .

This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which effect results in a decreased effective surface area for dissolution[51]. Fig 7, 8,9 shows the dissolution profiles of tablets prepared from solid dispersions of Felodipine with POVIDONE,PVA and MANNITOL.The dissolution rate of tablets (P1, P2, P3, E1, E2, E3, M1, M2, M3, M4) increased significantly ($p<0.05$) than dissolution rate of tablets P, E and M respectively

INVITRO DISSOLUTION

Table 11: Dissolution profile of solid dispersion with POVIDONE

Time(min)	P1	P2	P3	P4
0	0	0	0	0
2.5	75.25	77.86	78.59	20.17
5	78.74	81.54	84.25	22.02
7.5	81.56	83.12	87.99	32.35
10	83.46	86.57	99	43.38
12.5	86.95	98.89	-	46.48
15	98.02	-	-	53.26
17.5	-	-	-	62.67
20	-	-	-	72.8
25	-	-	-	81.27
30	-	-	-	96.23

Figure 7: Dissolution profiles of formulations containing POVIDONE solid dispersions

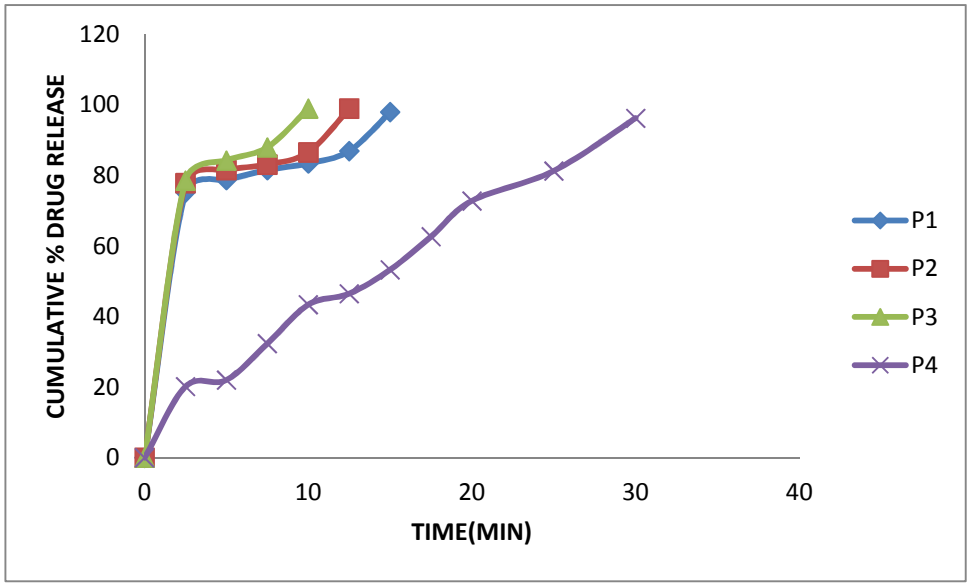


Table 12: Dissolution profile of solid dispersion of PVA

Time(min)	E1	E2	E3	E4
0	0	0	0	0
2.5	37.58	69.23	70.12	69.25
5	43.94	76.24	78.25	72.58
7.5	58.37	79.57	86.27	78.41
10	65.84	83.14	99.68	82.35
12.5	71.54	90.27	-	86.41
15	80.64	98.67	-	89.48
17.5	82.74	-	-	90.26
20	85.25	-	-	91.87
22.5	89.86	-	-	94.74
25	97.54	-	-	98.24

Figure 8: Dissolution profiles of formulations containing PVA solid dispersions

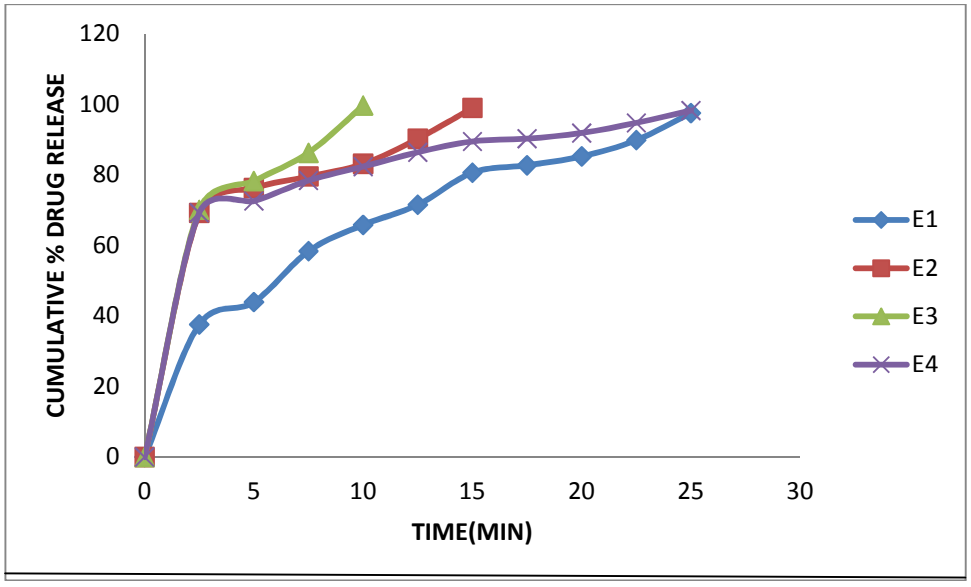


Table no 13: Dissolution profile of solid dispersion of MANNITOL

Time(min)	M1	M2	M3	M4
0	0	0	0	0
2.5	64.25	77.58	74.25	85.97
5	75.28	79.98	88.97	97.67
7.5	81.57	86.67	97.24	-
10	86.97	98.24	-	-
12.5	91.45	-	-	-
15	97.66	-	-	-
17.5	-	-	-	-

Figure 9: Dissolution profiles of formulations containing Mannitol solid Dispersions

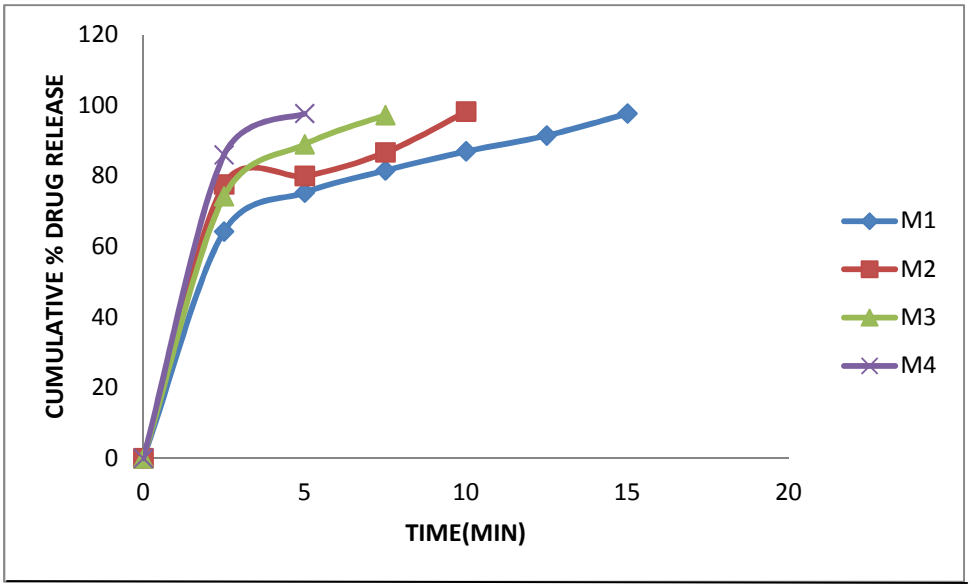


Table 14 : Dissolution profile of sublimation method

TIME(MIN)	C1	C2	C3	C4	C5
0	0	0	0	0	0
1	36.47	39.25	40.87	47.58	91.28
2	38.14	43.84	50.99	86.24	98.54
3	40.02	50.75	80.77	97.64	-
4	46.62	60.47	97.54	-	-
5	69.22	84.99	-	-	-
6	78.68	98.54	-	-	-
7	85.47	-	-	-	-
8	97.28	-	-	-	-

Figure10: Dissolution profiles of formulations prepared by sublimation method

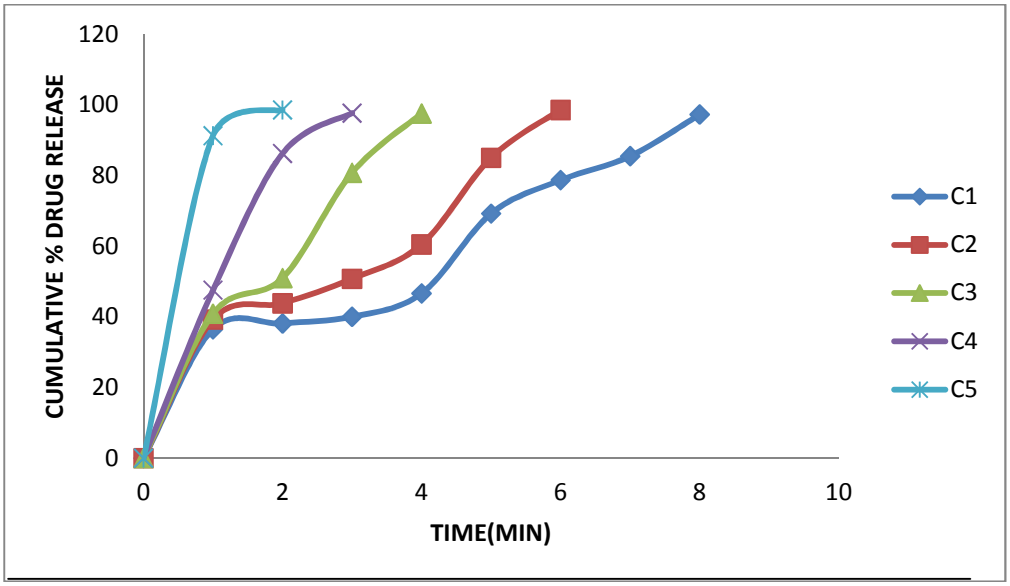


Table 15: Dissolution profile of P, E, M, C (NO SUPERDISINTEGRANT)

TIME(MIN)	P	E	M	C
0	0	0	0	0
2.5	31.28	23.04	32.54	19
5	38.32	28.32	37.96	36.1
10	55.82	48.25	50.68	38.45
15	61.23	60.78	72.36	40.01
20	72.8	63.89	79.14	41.25
25	83.74	70.58	85.01	42.01
30	89.37	74.64	97.37	43.25
35	91.47	78.69	-	44.25
40	98.87	82.47	-	45.21
45	-	85.96	-	-
50	-	97.68	-	-

Fig.11 Dissolution profile of P,E,M,C.(NO SUPERDISINTEGRATION ADDED)

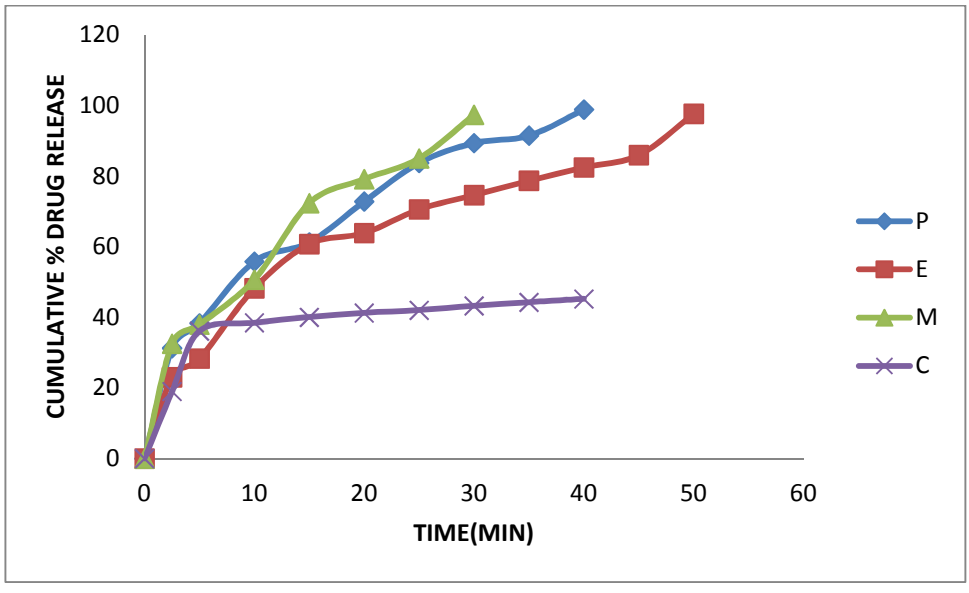
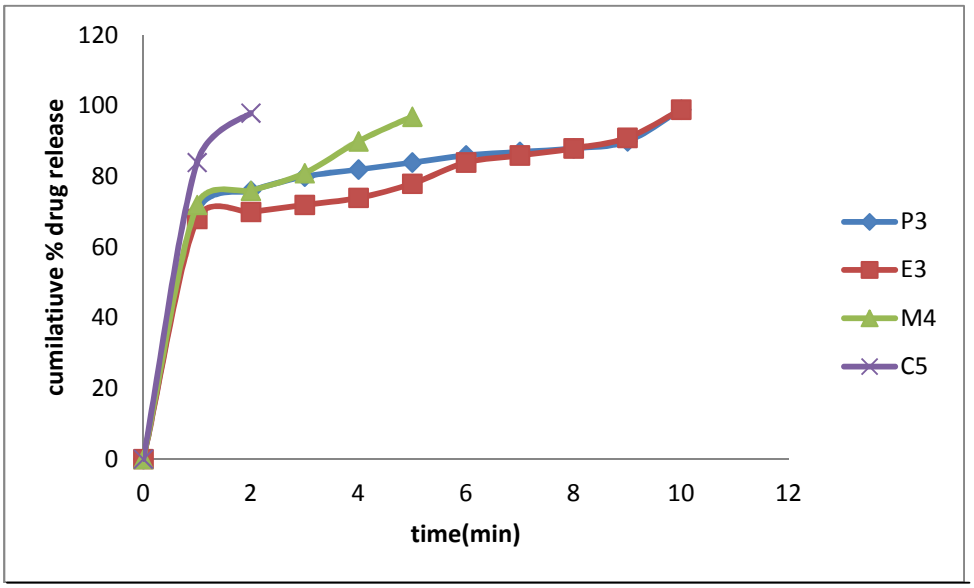


Figure 12: Dissolution profiles of best formulations



Drug excipients compatibility studies:

FT-IR analysis:

The IR spectrum of the pure drug felodipine used in the present study shows characteristic absorption bands in the following IR region (Fig 12).

IR (KBR) cm^{-1}

3370(NH Stretching)

3069(Aromatic CH stretching)

2840, 2948(Ch stretching of CH_2 and CH_3 Groups)

1700, 1688 (C=O stretching)

1644 (NH Bending)

1621, 1495, 1460 (C = C ring stretching)

1099 (C O C stretching)

727, 801 (Substituted benzene ring)

564 (Cl stretching)

The polymer POVIDONE (Fig 13) used in present study shows the characteristic absorption bands in the following IR region

Broad peak at 3424 to 3481 may be due to the hydrogen bonded OH groups. 2895 to 2955 CH stretching.1290 CH bending.

The polymer PVA (Fig 14) used in the present study shows the characteristic absorption bands in the following IR region.

The broad peak at 3447(OH Hydrogen bonded), the peaks at 2694, 2740, 2884, 2948(CH stretching), 1342(CH bending) and 963(C-O).

The polymer Mannitol (Fig 15) used in the present study shows the characteristic absorption bands in the following IR region.

The broad peaks at 3220 to 3405(OH hydrogen bonded), the peaks at 2719, 2902, 2948 and 2970(CH stretching), the peak at 1281(CH bending) and peak at 929(C-O).

The IR spectrum of the formulation P3 (Fig 16) shows the characteristic absorption bands in the following IR region.

It is quite interesting to note that, the spectrum contains very broad peaks in the range 3200 to 3500 and a very sharp peak almost merged with the broad peak at 3370 indicating the presence of OH of POVIDONE and NH of Felodipine. Further it has the aromatic CH peak from 3050 and CH stretching of POVIDONE in the range 2836 to 2978.The spectrum shows the presence of carbonyl group of drug at 1700 and 1688,NH bending 1643 and C=C ring stretching at 1617,1496 and 1443. Since all the major peaks of the pure drug and POVIDONE are present without any change in their positions in the spectrum of the formulation P3 .It may be concluded that the drug and polymer have retained their identity without loosing their properties and not going in to a chemical interaction with each other. Thus the conclusion from the IR spectra of the drug and formulation is that there is no interaction between drug and polymer.

Similarly the IR spectra of formulations E3 (Fig 17) and M4 (Fig 18) reveal that the pure drug Felodipine has not gone into the interaction with PVA in the formulation E3 and Mannitol in the formulation M4

Figure 12: FTIR spectrum of felodipine

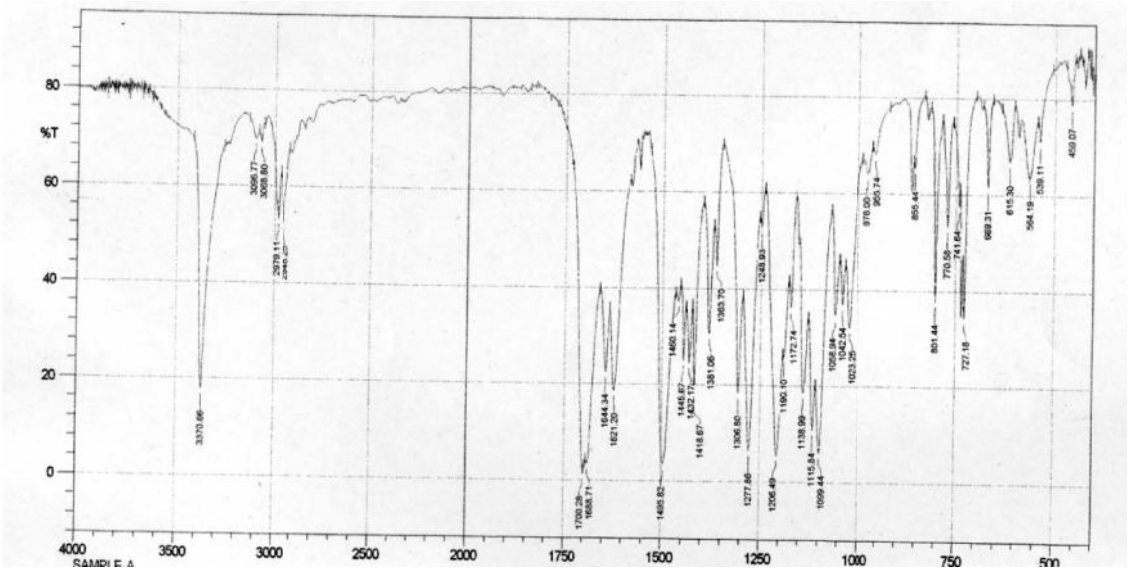


Figure 13: FTIR spectrum of POVIDONE

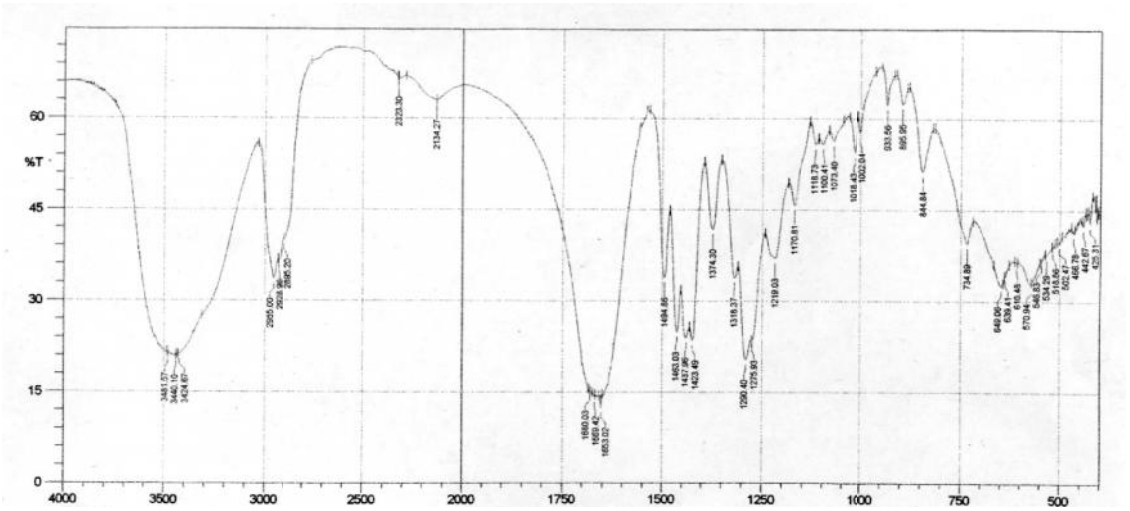


Figure 14: FTIR spectrum of PVA

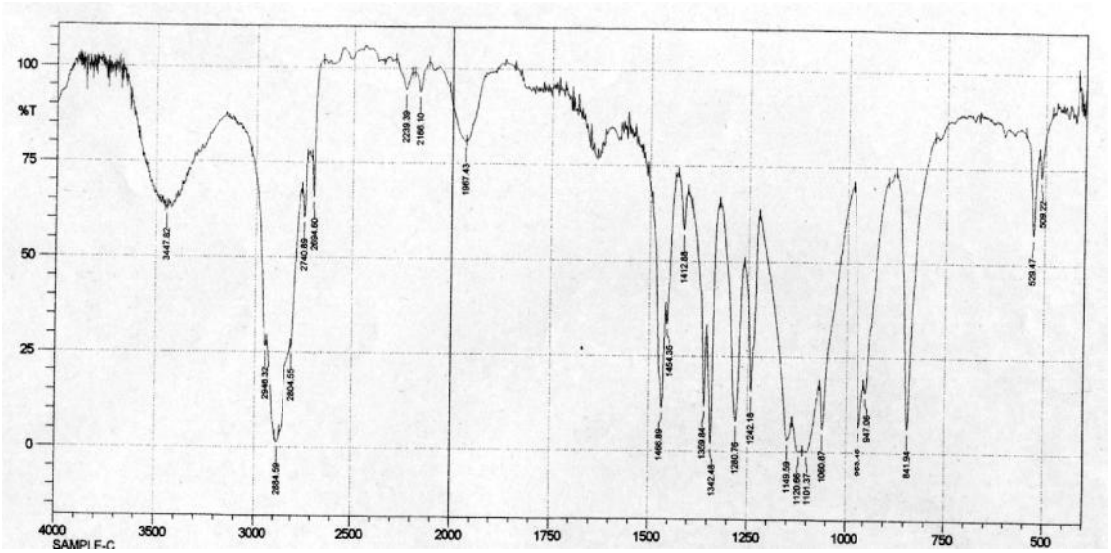


Figure 15: FTIR spectrum of Mannitol

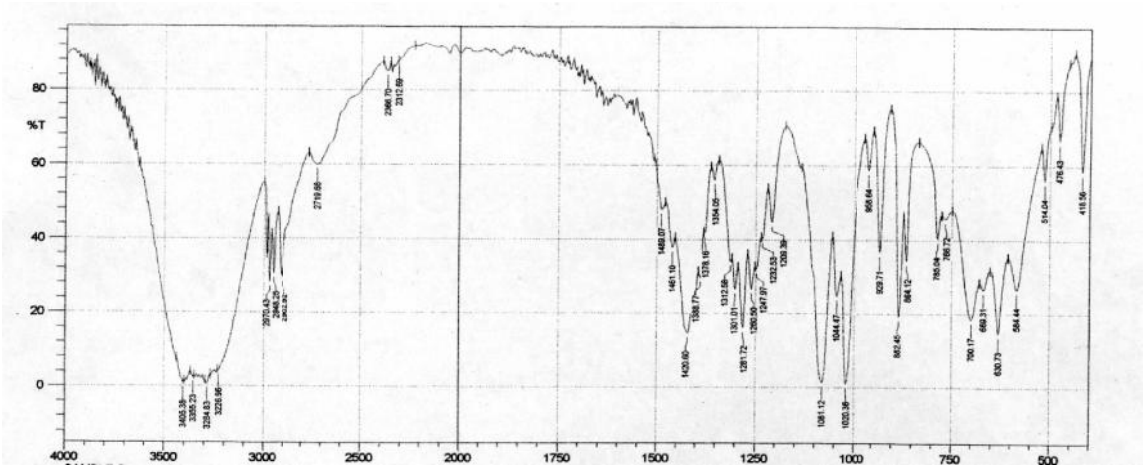


Figure 16: FTIR spectrum of formulation P3

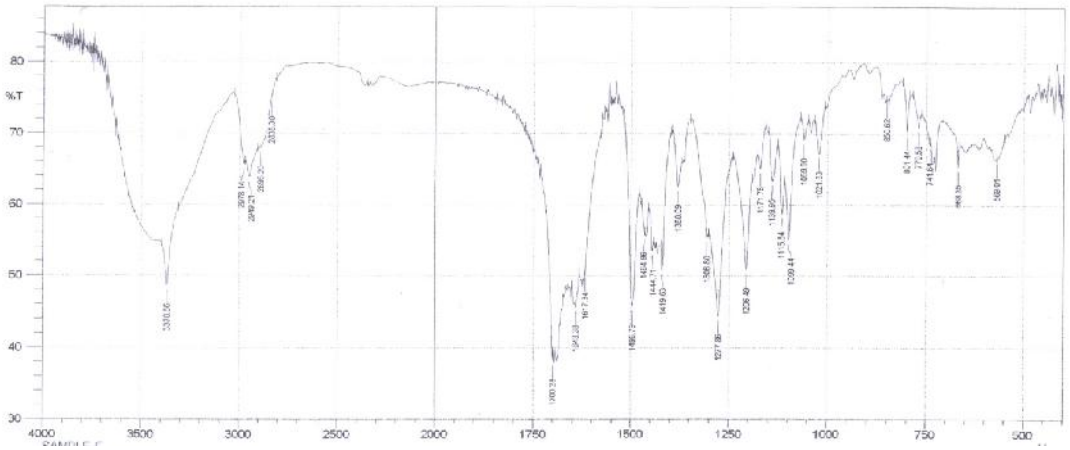


Figure 17: FTIR spectrum of formulation E3

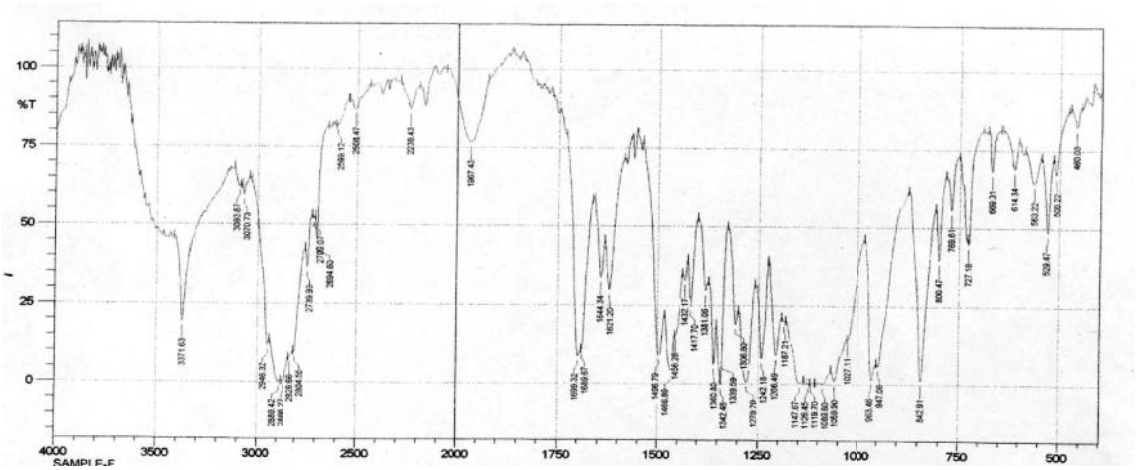
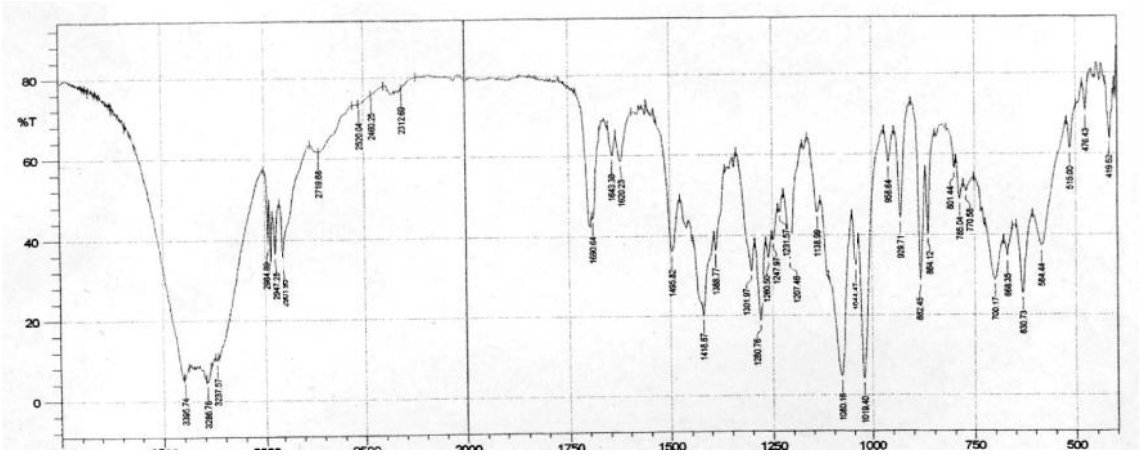


Figure 18: FTIR spectrum of formulation M4



X-Ray Diffraction pattern:

One of the common approaches to improve the bioavailability of poorly water soluble drugs is to enhance their dissolution rate by formation of amorphous dispersions and, preferably molecular dispersions[45].

X-ray diffraction patterns of formulation P3, E3 and M4 revealed that felodipine a crystalline material shows characteristic peaks at 2θ 10.20, 10.35, 10.77, 13.16, 14.64, 16.20, 17.71, 20.48, 23.34, 24.49, 25.40, 26.47, 27.55, 29.25, 31.99, 33.89, 36.87, 39.55, 43.11, 44.64 and 47.61.However the XRD patterns of its solid dispersion in POVIDONE, PVA and mannitol shows the typical profiles of amorphous material as observed from the values. A peak corresponding to felodipine crystals completely disappeared in solid dispersions prepared with POVIDONE, PVA and mannitol.. These results indicate that drug was dispersed in amorphous form in the solid dispersions of POVIDONE, PVA and mannitol (Fig 19-25)

Figure 19: XRD patterns of pure Felodipine

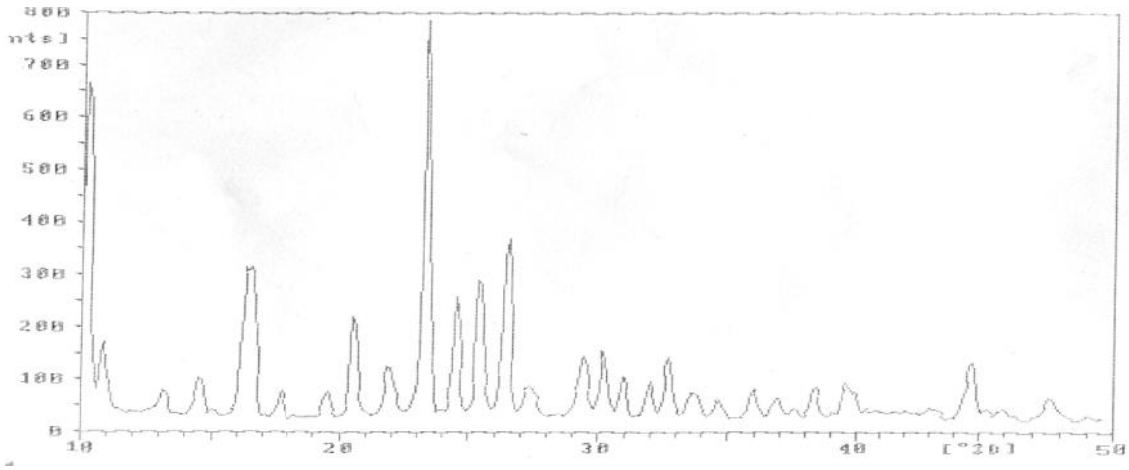


Figure 20: XRD patterns of pure POVIDONE

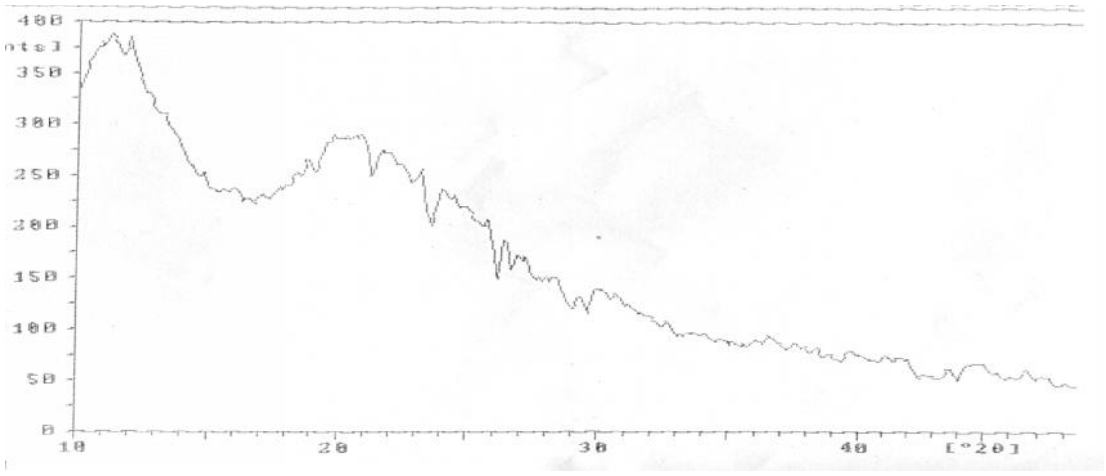


Figure 21: XRD patterns of Felodipine solid dispersion with POVIDONE

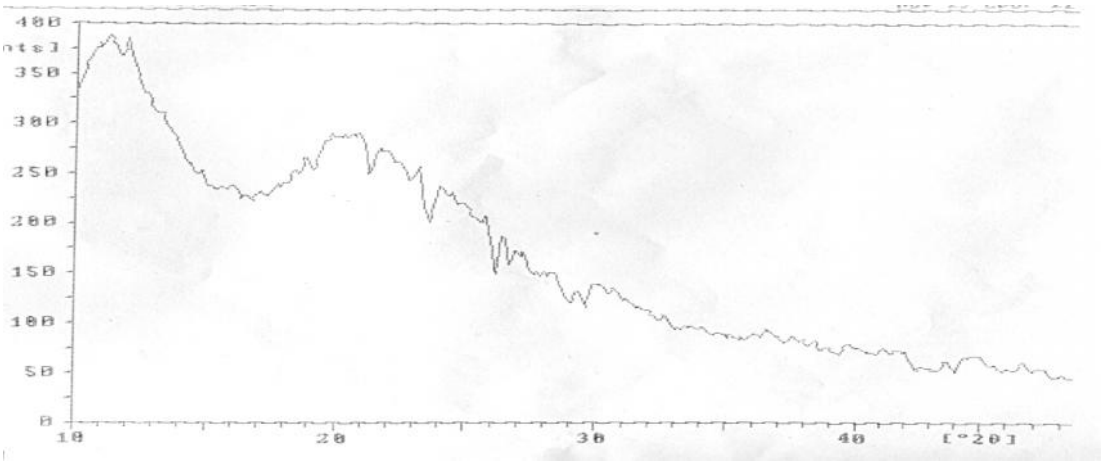


Figure 22: XRD patterns of pure PVA

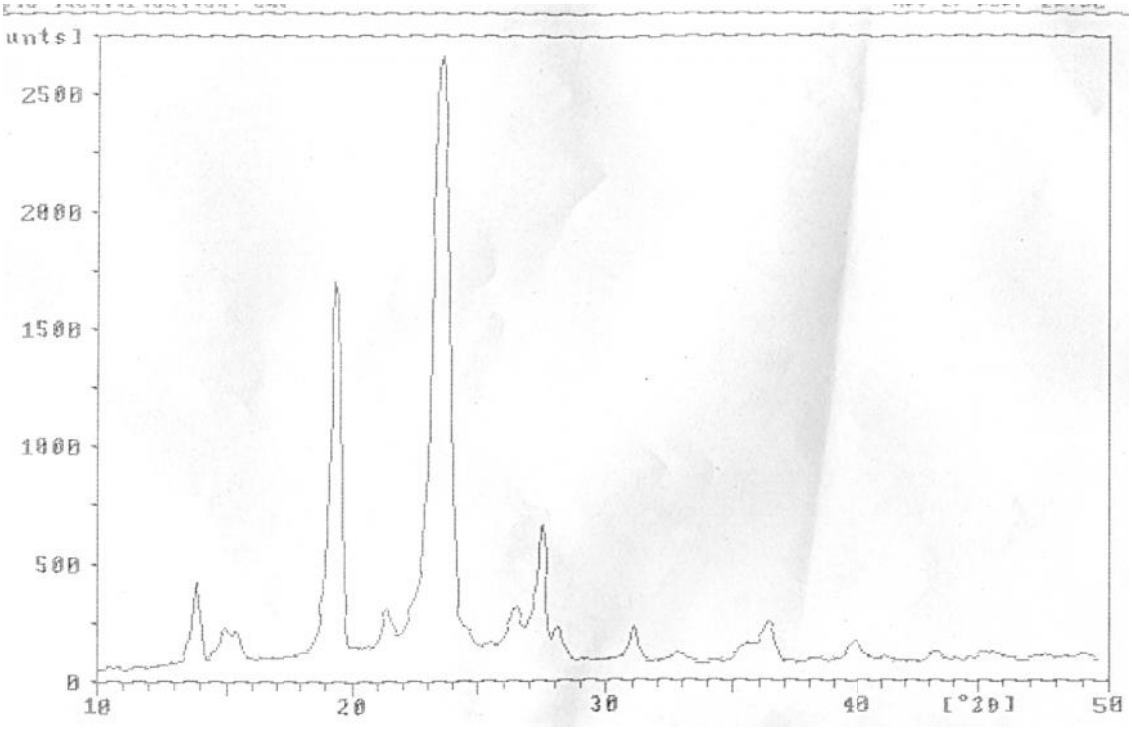


Figure 23: XRD patterns of Felodipine solid dispersion with PVA

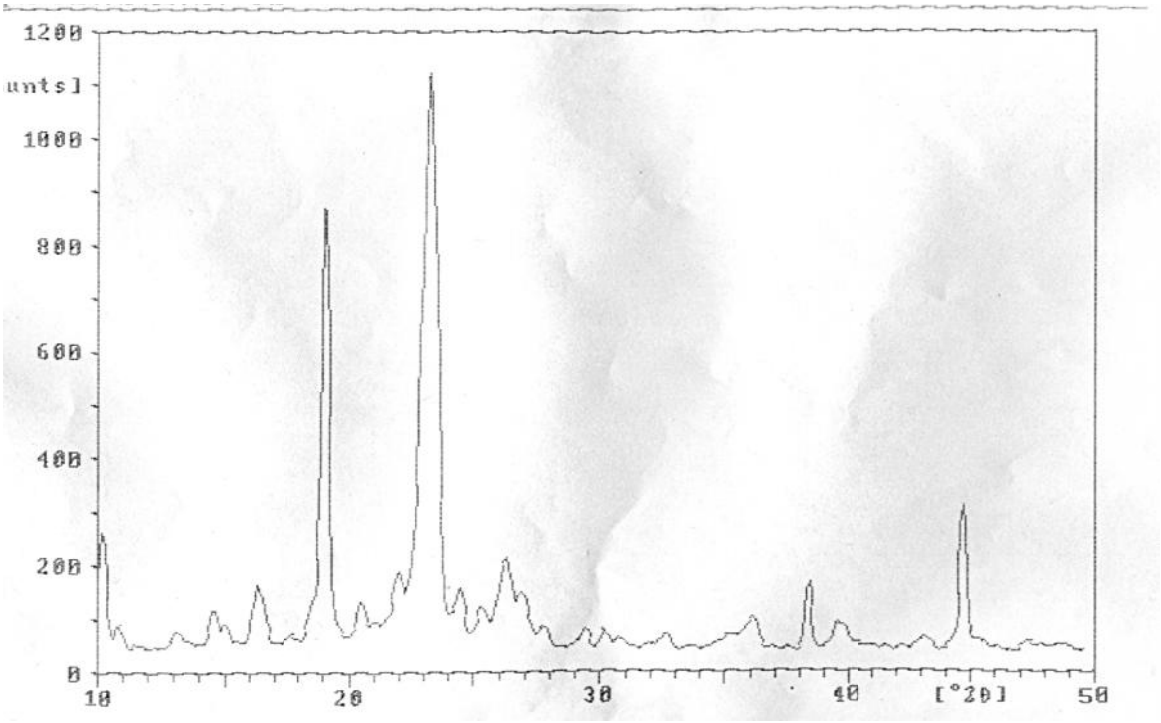


Figure 24: XRD patterns of pure Mannitol

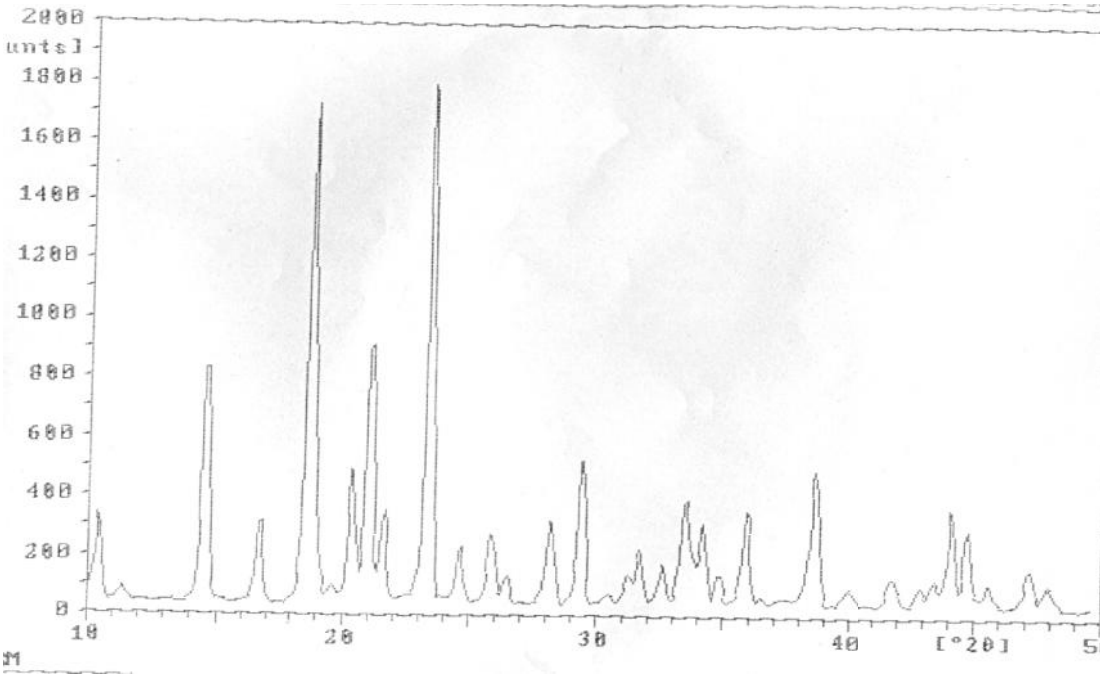
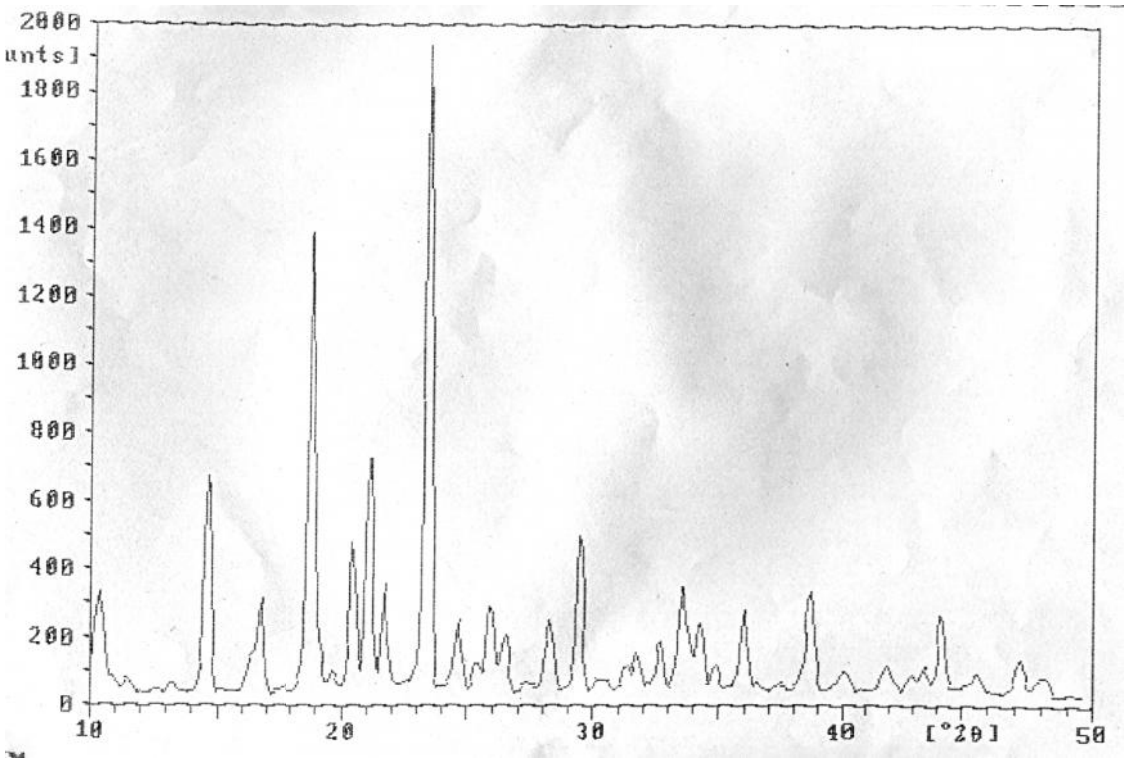


Figure 25: XRD patterns of Felodipine solid dispersion with Mannitol



Stability studies:

Table 11 shoes the parameters of tablets after stability studies. The increase ($P<0.05$) in the disintegration time was observed in case of tablets prepared with mannitol solid dispersion. This may be due to increase in the hardness of the tablets during storage[87]. Decrease ($P<0.05$) in the disintegration time was observed in tablets prepared by camphor sublimation method. Since during the preparation of tablets by camphor sublimation method, only 6 hours at 60^{o}C was used, where as 90 days and 45^{o}C were used during stability studies. The long storage of 90 days at 45 ^{o} C might have removed trace amount camphor that was not removed during the short period of preparation. No change was observed in the disintegration time of tablets prepared with POVIDONE and PVA solid dispersions. No significant change in the thickness was observed in all the tablets and drug content of all formulation was within the acceptable limits.

Table 16: Tablet parameters after stability studies.

Formulation	Disintegration Time (sec) (±SD), n=6	Thickness (mm) (±SD), n=4	% drug content (±SD), n=6
P	140 ±10.15	3.50 ± 0.052	99.00 ± 0.62
P1	50.00 ± 6.33	3.62 ± 0.050	96.00 ± 0.72
P2	44.00 ± 4.11	3.45 ± 0.051	95.36 ± 1.35
P3	48.00 ±3.92	3.48 ± 0.062	94.72 ± 0.72
P4	240.0 ± 4.56	3.38 ± 0.039	97.62 ±1.55
E	130 ± 3.78	3.68 ± 0.084	94.65 ± 0.58
E1	55.00 ± 2.35	3.78 ± 0.081	95.75 ± 0.42
E2	52.00 ± 4.15	3.80 ± 0.045	97.00 ± 0.62
E3	50.00 ± 5.95	3.78 ± 0.080	97.31 ± 0.75
E4	230.0 ± 4.72	3.65 ± 0.072	94.91 ± 1.31
M	141.0 ± 3.15	3.88 ± 0.059	97.92 ± 2.27
M1	108.0 ± 4.90	3.68 ± 0.048	97.52 ± 2.21
M2	95.00 ± 2.72	3.72 ± 0.052	95.57 ± 2.00
M3	85.00 ± 3.57	3.68 ± 0.055	99.65 ± 1.55
M4	75.00 ± 3.50	3.72 ± 0.065	95.15 ± 1.32
C	270.0 ± 8.00	3.18 ± 0.062	100.0 ± 0.05
C1	41.00 ± 3.45	3.68 ± 0.059	97.00 ± 0.48
C2	28.00 ± 3.11	3.58 ± 0.050	98.00 ± 0.58
C3	24.00 ± 2.92	3.55 ± 0.058	97.57 ± 0.48
C4	18.00 ± 2.56	3.42 ± 0.058	98.92 ±1.31
C5	14.00 ± 3.61	3.48 ± 0.050	98.00 ± 0.90

Note: Values in parenthesis are standard deviation (±SD)

SUMMARY

The demand for fast dissolving tablets has enormously increased during the last decade, particularly for geriatric and pediatric patients who have difficulty in swallowing conventional tablets and capsules. Oral administration of the drugs is difficult in patients having concomitant vomiting or diarrhea. Fast dissolving or fast disintegrating dosage form is advantageous for such patients. Fast dissolvable or fast disintegrating dosage forms are meant to disintegrate immediately upon contact with the saliva leading to faster release of the drugs in the oral cavity.

Felodipine is a dihydropyridine calcium channel blocker. It's widely used in the management of hypertension and angina pectoris. Felodipine is practically insoluble in water. Here felodipine is used as a model drug in formulating the fast dissolving tablets.

In the present work direct compression was employed to prepare tablets. Lactose and micro crystalline cellulose were selected as diluent. Croscarmilose sodium and crospovidone were selected as superdisintegrants. Magnesium stearate and aerosil were selected as lubricant and glident respectively. Tablets were compressed individually using biconcave 7mm punches in Rimek minipress 1, a 10 station rotary compression machine. Tablets were evaluated for change in parameters by change in the method of preparation (i.e. solid dispersion with different carriers and sublimation method)

Precompressional parameters, angle of repose, percentage compressibility and Hausner's ratio studies indicated that most of the formulation showed fair and good flow properties.

Postcompressional parameters, hardness, friability, disintegration time, wetting time, drug content, dissolution studies and stability parameters were studied. Tablets kept for stability study at (40 ± 2^0 C/75± 5% RH) for 3 months. Tablets prepared by solid dispersion with Mannitol showed slightly higher hardness than other tablets prepared by solid dispersion with Povidone and Pva, while that of tablets prepared by Camphor sublimation method showed least. Friability of tablets ranged between 0.21-0.64%. Drug content of tablets ranged between 95.91-102.00%.

Tablets containing solid dispersion with Povidone of ratio 1:4 (P3), with Pva of ratio 1:4 (E3) and with Mannitol of ratio 1:9 (M4) yielded best results in terms of dissolution rate. Tablets prepared by sublimation method containing 40% Camphor (C5) yielded best result in terms of dissolution rate.

XRD analysis revealed that there was a formation of amorphous form in all solid dispersions. FT-IR studies revealed that, there was no incompatibility of the drug with the excipients used.

Disintegration time of tablets prepared by solid dispersion using mannitol, increased significantly ($p<0.05$) and that of those tablets prepared by sublimation method decreased significantly ($p<0.05$) after stability studies.

CONCLUSION

From this study, it can be concluded that dissolution rate of felodipine could be enhanced by tablets containing solid dispersion and sublimation technique.

Tablets prepared by sublimation method showed least disintegration times as compared with other tablets prepared by solid dispersion method. Tablets prepared by sublimation method showed best dissolution rate than the other tablets prepared by solid dispersion method.

Here we have succeeded in formulating fast dissolving formulation for Felodipine which are cost effective and have patient compliance.

Success of the present study recommends a detailed investigation in to *in-vivo* studies for its effective use in clinical practice.

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