FORMULATION DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLETS OF DILTIAZEM HYDROCHLORIDE BY DIRECT COMPRESSION METHOD

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

BRANCH I - PHARMACEUTICS

Submitted By

REGISTRATION No:261511153

Under the guidance of

Prof.Dr.M.Murugan, M.Pharm., Ph.D.,

Department of Pharmaceutics

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

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CERTIFICATE

This is to certify that the dissertation entitled "**Formulation Development and Evaluation of Mouth Dissolving Tablets of Diltiazem Hydrochloride by Direct Compression method"** submitted by **SAJU.R** (Reg No:261511153) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S.Pillay College of Pharmacy during the academic year 2016-2017.

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1. INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance.

To overcome this weakness, scientists have developed innovative drug delivery systems known as “melt in mouth” or “mouth dissolve (MD)” tablets. These are novel types of tablets that disintegrate/dissolve/disperse in saliva.

Their characteristic advantages such as administration without water, anywhere, anytime, lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water.

The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability, makes these tablets popular as a dosage form of choice in the current market.

A broad range of drugs cardiovascular, analgesics, narcoleptics, antihistamines, and antibiotics can be considered candidates for this dosage form.

Fast dissolving tablets are formulated by techniques like tablet molding, spray drying, lyophilization, sublimation and addition of disintegrants. Some of the patented technologies for preparation of fast dissolving tablets are Zydis,OraSolv, DuraSolv, Flash Dose, Wow tab (Without Water), and Flashtab[1].

These are novel types of tablets that dissolve/disintegrate/ disperse in saliva within few seconds without water. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem.

The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market.

Mouth dissolving tablets are also called as orodispersible tablets, fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets.

However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as ODTs. United States Food and Drug Administration (FDA) defined ODTs as “A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue[2].

DEFINITION

The Centre for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter seconds, when placed up on the tongue”. FDTs disintegrate and/or dissolve rapidly in the saliva without the need for water.

Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

Their growing importance was underlined recently when European Pharmacopoeia adopted the term “Orodispersible Tablet” as a tablet that to be placed in oral cavity where it disperses rapidly before swallowing.

SALIENT FEATURES OF FAST DISSOLVING DRUG DELIVERY SYSTEM:

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.

2. Requires no water.

3. Quick disintegration and dissolution of the dosage form.

4. Overcomes unacceptable taste of the drugs.

5. Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.

6. Allows high drug loading.

7. Ability to provide advantages of liquid medication in the form of solid preparation. Adaptable and amenable to existing processing and packaging machinery.

8. Cost-effective.

SIGNIFICANCE OF ORAL DISINTEGRATING TABLETS

Oral Disintegrating Tablets offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

Accurate dosing - Being unit solid dosage forms, provide luxury of accurate dosing, easy Portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

Enhanced bioavailability -
Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.

Rapid action –
Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

Patient compliance -
No need of water to swallow the dosage form. Hence, it is convenient for patient who are travelling and do not have immediate access to water.

Ease of administration -
Convenient to administer especially for geriatric, paediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

Obstruction free -
No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

Enhanced palatability -
Good mouths feel, especially for paediatric patients as taste masking technique is used to avoid the bitter taste of drug.

Simple packaging -
No specific packaging required. It can be packaged in push through blisters.

Business Avenue -
Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

Cost effective -
Conventional processing and packaging equipment's allow the manufacturing of tablets at low cost.

CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEM

1. Ease of administration: Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, and dysphasia.

2. Taste of the medicament: As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste bud and hence, masking of the drugs becomes critical to patient compliance.

3. Hygroscopicity: Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which called for special packaging.

4. Friability: In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging.

5. Mouth feel: Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit [3].

BENEFITS OF FAST DISSOLVING TABLETS:

- Administered without water, anywhere, any time.

- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are uncooperative, or are on reduced liquid intake plans or are nauseated.

- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

COMMON CONDITIONS FOR ODTS INDICATIONS

- Pain, fever, heartburn, diarrhea, migraine, anxiety, insomnia for fast faction.

- Parkinson's disease, Alzheimer's disease, psychosis, Schizophrenia, Hypertension, Cholesterol, Transplantation to improve patient's compliance.

- Cough, cold, allergy, pain, fever, ADHD that can be associated with pediatrics[4].

ADVANTAGES OF ODTS AS DRUG DELIVERY SYSTEM [4, 5, 6]

- Pregastric absorption from the mouth, pharynx, and esophagus as the saliva passes down into the stomach can result in enhancement of bioavailability which leads to a reduced dosage and improves the clinical performance and reduces the side effects [7, 8, 9, 12, 13, 15, 16.]

- ❖ It is useful for some conditions that need a rapid action such as motion sickness, sudden episodes of allergic attack or coughing

- ❖ Highly convenient for patients who are traveling anywhere, anytime and do not have instant access to water [7, 8, 11, 10, 12, 13.]

- ❖ Provide a suitable drug delivery for some drugs that have low molecular weight and are highly permeability[13].

- ❖ Due to rapid disintegration and dissolution time, orally dissolving tablets increase the bioavailability of insoluble and hydrophobic drugs

- ❖ Improve patient safety administration by avoiding the risk of chocking or suffocation during oral administration due to physical obstruction [7,9,12,13,16,17].

- ❖ ODTs have a unique feature by combining the advantage of solid and liquid dosage forms. They provide long term stability for the solid dosage form and high bioavailability as a liquid dosage form when placed on the mouth [7, 8, 10, 12].

- ❖ Useful for pediatric, geriatric and psychiatric patients because there is no need for chewing [8].

- ❖ Medications with a bitter taste have taken advantage of ODT technologies by the use of flavors and sweeteners to make them as pleasing as possible when they dissolve in the mouth

- ❖ ODT technologies show multipurpose utilization, therefore they are suitable for the development of enhanced products for veterinary medicines, OTC, as well as prescription medicines[17].

Limitation of Mouth Dissolving Tablets [8]

- ✓ Insufficient mechanical strength that make ODTs difficult to handle.

- ✓ Some of ODTs may leave unpleasant taste or gritty feel in the mouth if they not formulated properly.

Drug Selection Criteria [12, 19]

- ❖ Dose should be lower than 20 mg for FDT.
- ❖ Drug should be partially nonionized at pH in oral cavity.
- ❖ Drug should be diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferably >2)
- ❖ Drug should have to permeate through oral mucosal tissue.

Ideal Properties of MDTs[20]

They should

- ➢ Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- ➢ Be compatible with taste masking and other excipients.
- ➢ Have a pleasing mouth feel.
- ➢ Leave minimal or no residue in the mouth after oral administration.
- ➢ Have sufficient strength to withstand the rigors of the manufacturing process and
- ➢ Exhibit low sensitivity to environmental conditions such as humidity and temperature.

Techniques of MDT Formulation

The fast-dissolving property of the MDTs is attributed to quick ingress of water into tablet matrix resulting in rapid disintegration. Hence, the basic approaches to develop MDTs include:

Maximizing the porous structure of the tablet matrix.

- Incorporating the appropriate disintegrating agent/agents.
- Using highly water-soluble excipients in the formulation.

So far, several techniques have been developed on the basis of different principles. The resulting dosage forms vary on grounds like mechanical strength of the final product, drug and dosage form stability, mouth feel, taste, rate of dissolution and absorption from saliva, swallowability and overall bioavailability.

Table No:1 Shows the List of Some Patented Technologies.

Patented Technology	Basis of Technology	Technology developed by Company	Active Ingredient (Brand Names)
Zydis	Lyophilization	R.P.Scherer	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
Quicksolv	Lyophilization	Janssen pharmaceutics	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal MTab)
Orasolv	Direct Compression	Cima Labs,Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt), Hyoscyamine Sulfate.
Durasolv	Direct compression	Cima Labs, Inc.	(NuLev) Zolmitriptan (Zolmig ZMT)
Flashtab	Direct compression	Ethypharm	Ibuprofen (Nurofen FlashTab)
Wowtab	Direct compression	Yamanouchi Pharma Tech. Inc.	Famotidine (Gaster D)
Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetrizine, AdvaTab Paracetamol
Flashdose	Cotton Candy Process	Fuisz Technology, Ltd.	Tramadol HCl (Relivia Flash dose)
Oraquick	Micromask taste masking	KV Pharm.Co.,Inc.	Hyoscyamine SulfateODT
Ziplets	Direct compression	Eurand International	Ibuprofen (Cibalgina DueFast)
Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate (Spasfon Lyoc)

Various manufacturing techniques for MDDDS include:

1. Lyophilization
2. Moulding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying

6. Sublimation
7. Mass Extrusion
8. Nanonization
9. Fast Dissolving Films

Freeze-Drying or Lyophilization[21]

In freeze-drying process, the water is sublimed from the product after it is frozen. This technique forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture MDTs. Jaccard and Leyder used lyophilization to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs such as spironolactone and trolendomycin. Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug.

Zydis technology (ZT) is a patented technique which had been used for drugs like famotidine, loperamide, piroxicam, oxazepam, lorazepam, domeperidone, brompheniramine, olanzepine, ondansetron and rizatriptan. Thirteen products are currently available in the market, which had been manufactured using this technology. In U.S., the MDT products available are: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt- MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. In the worldwide market, Zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril [23].

ZT utilizes a unique freeze-drying process to manufacture finished dosage units which significantly differ from conventional oral systems [24]. The process involves the following steps:

Stage 1 - bulk preparation of an aqueous drug solution or suspension and its subsequent precise dosing into pre-formed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package.

Stage 2 - passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals which ensures that the tablets possess a porous matrix to facilitate the rapid disintegration property. These

frozen units are then transferred to large-scale freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.
Stage 3 - sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

Lyoc is a porous and solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus [14,25]. Its unusual properties are the result of its unique method of preparation, which involves freezing a thickened (paste like) emulsion containing the active as bulk or as coated microparticles. This product is capable of accommodating high dose and disintegrates rapidly but possesses poor mechanical strength.

Quicksolv is a porous solid form obtained by freezing an aqueous dispersion/solution of the drug containing matrix and then drying it by removing the water using excess of alcohol (solvent extraction)[26]. The final form disintegrates very rapidly but is limited to low drug content and can be used only for those drugs that are insoluble in the extraction solvent. The ideal drug characteristics required for this technology are relative low aqueous solubility, fine particle size < 50 µm [27, 28] and good aqueous stability in the suspension.

The maximum drug loading capacity for water insoluble and soluble drugs are 400 mg and 60 mg, respectively [12, 27]. The primary problems associated with water soluble drugs are the formation of eutectic mixtures resulting in freezing-point depression and the formation of a glassy solid on freezing which might collapse on drying due to loss of supporting structure during sublimation process [12, 13, 27].

MDTs manufactured using lyophilization process, usually contain excipients like polymers (e.g., gelatin, alginates and dextrin) to provide strength and rigidity to tablets; polysaccharides (e.g., mannitol and sorbitol) to impart crystallinity and hardness to the matrix and to improve palatability; collapse protectants (e.g., glycine) to prevent the product from shrinking in its packaging during manufacturing or storage; flocculating agents (e.g., xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulfate) to improve transmucosal permeability; pH adjusters (e.g. citric

acid etc.) to optimize chemical stability; flavors and sweeteners to improve patient compliance and water to ensure formation of porous units.

Advantages

The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouthfeel due to fast melting effect.

Disadvantages

Although being a fairly routine process, lyophilization has some disadvantages like it is a relatively expensive and time consuming process. Furthermore, the product obtained is poorly stable and fragile, rendering conventional packaging unsuitable.

Tablet Moulding

Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques:

Compression Moulding Process

This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution [15].

Heat-Moulding Process

Heat-moulding process involves setting the molten mass containing a dispersed drug . This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.

Moulding by Vacuum Evaporation without Lyophilization [30]

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a

solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process. Unlike lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the product. Pebley et al. evaporated the frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol or maltodextrin) and solvent in a tablet-shaped mould to design a MDT with a disintegration time of about 20 – 60 secs.

Tablets produced by moulding are solid dispersions. The drug, depending on its solubility in the carrier, exists either as discrete particles or microparticles dispersed in the matrix and is dissolved totally/partially to form a solid solution/dispersion in the carrier matrix.

Advantages

As the dispersion matrix is made from water-soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the moulding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale.

Disadvantage

As the moulded tablets have poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can increase the strength of the tablets but it would be at the cost of their disintegration time.

Direct Compression (DC)

DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tableting excipients with improved flow,

compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar based excipients.

Disintegrants

In many MDT products based on DC process, the disintegrants mainly affect the rate of disintegration and hence dissolution which is further enhanced in the presence of water soluble excipients and effervescent agents.

The introduction of superdisintegrants has increased the popularity of this technology [27]. Tablet disintegration time can be optimized by focusing on the disintegrants concentration. Below a critical disintegrant concentration, tablet disintegration time becomes inversely proportional to disintegrant concentration. However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant [22].

Another DC based technology; Flashtab contains coated crystals of drug and microgranules along with disintegrants[30]. In this technology, two types of disintegrants are used: a disintegrating agent (e.g., modified cellulose), which has a high swelling force and a swelling agent (e.g., starch) which has a low swelling force [30].

Bi et al. and Watanbe used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture MDTs wherein the ratio of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihara investigated the application of agar powder as a disintegrant due to its property of absorbing water and considerable swelling without forming a gel at physiological temperature.

Effervescent Agents

The evolution of CO2 as a disintegrating mechanism forms the basis of the patented Orasolv technology (OT) and is frequently used to develop over-the-counter formulations [26–30]. The product contains microparticles and is slightly effervescent in nature. Saliva activates the effervescent agent which causes the tablet to disintegrate. The OT had been utilized in fabrication of six marketed products: four Triaminic Softchew formulations, Tempra FirsTabs and Remeron SolTab.

The present technology uses the concept of effervescence to achieve fast-disintegration. In this technology, the microparticles are prepared by dispersing the drug

into a suitable polymer (ethyl cellulose, methyl cellulose, acrylate or methacrylic acid resins) along with other excipients (mannitol and magnesium oxide).

The drug and mannitol are added to the polymeric dispersion under stirring, followed by addition of magnesium oxide. Here, mannitol and magnesium oxide are known as release promoters as they aid in drug release from the polymeric coating. This mixture is then dried for one hour at 50 °C, delumped and dried for another hour at the same temperature.

The material is then screened (8-mesh) and dried for one hour at 60 °C. The formed microparticles, effervescent agents and other excipients are blended and compressed into tablets at 1.0–2.0 kg hardness. The tablets obtained are fragile with in-vivo disintegration time of less than one minute. As the tablets are very soft, they are packed into aluminium blisters using a specially designed packaging system.

To reduce their friability, a novel method, known as particulate effervescent couple, had been developed. In this method the organic acid crystals are coated using a stoichiometrically low quantity of base material as compared to acid. The particle size of the organic acid crystals is carefully chosen to be greater than the base material so that base gets uniformly coated onto the acid crystals.

The coating process is initiated by the addition of a reaction initiator, which in this case, is purified water. The reaction is allowed to proceed only to an extent of completion of base coating on organic acid crystals. The required end-point for the reaction termination is determined by measuring CO2 evolution. The resulting effervescent couple can be used in tablet preparation by mixing with polymer-coated drug particles and other required excipients [31].

Though, the Orasolv tablet has the appearance of a traditional compressed tablet, they are lightly compressed and are weaker and more brittle than the conventional tablets. Therefore, a special handling and packaging system for Orasolv was developed [30]. An advantage of low degree of compaction is that the particle coating used for taste masking is not compromised by fracture during compression.

Durasolv, a second-generation technology was developed to produce robust MDTs. Durasolv has much higher mechanical strength than its predecessor due to use

of higher compaction pressure during compression. It is thus produced in a much faster and cost effective manner and can be packed in either traditional blister packs or vials.

The limitations of Durasolv is its low drug loading capacity and high compaction pressure which are not suitable for incorporation of taste masked coated pellets. Therefore, the Durasolv technology is best suited for relatively small doses of drug .

This technology has been applied in the fabrication of two products: NuLev and Zomig ZMT. However, the major drawback of effervescent excipients is their hygroscopicity which require control of humidity during processing and protection of the final product resulting in increase in the cost of the product.

Sugar-Based Excipients

Another approach to manufacture MDTs by DC is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness and hence, imparts taste masking and a pleasing mouth feel.

Mizumoto et al., have classified sugar-based excipients into two types based on their mouldability and dissolution rate.

Type I saccharides (e.g., lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type II saccharides (e.g., maltose and maltitol) exhibit high mouldability but low dissolution rate.

Mouldability is defined as the capacity of the compound to be compressed/ moulded and to dissolve. It does not refer to the formation of a true mould by melting or solvent wetting process. The mouldability of Type I saccharide can be improved by granulating it with a Type II saccharide solution.

The above technology forms the basis of WOWTAB which involves the use of fluidized bed granulation for the surface treatment of Type I saccharide with Type II saccharide. This technique has been used in the production of Benadryl Fast melt tablets. Here, 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 more stable to the environmental conditions

than the Zydis or Orasolv and is suitable for both conventional bottle and blister packaging.

The taste masking technology utilized in the WOWTAB is proprietary and claims to offer superior mouthfeel due to the patented smooth-melt action [26].

In the process of granulation, low mouldable sugar was coated with high mouldable sugar followed by a specific humidity treatment, to achieve fast disintegration. The resulting tablet had a hardness of 1.0–2.0 kg (tablet-size dependent) and presented a preferable disintegration time of 1–40 secs. Various classes of drugs can be incorporated into the above sugar combination to achieve a MDT with optimum performance characteristics. A preferable ratio of 5–10% w/w of high mouldable sugar was found to be sufficient to achieve the desired hardness and disintegration property [25].

A series of experiments had been conducted to develop a MDT using a combination of starch/cellulose and one or more water-soluble saccharides[27]. Erythritol was found to be the best saccharide because it displayed rapid disintegration, good tolerability, sweetening and a refreshing mouth feel due to its negative heat of solution.

Recently, the Ziplet technology was developed, which can be used for water insoluble drugs or drugs as coated microparticles. It was found that the addition of a suitable amount of a water-insoluble inorganic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the MDT and simultaneously maintained optimal disintegration even at low compression force and tablet hardness.

In fact, breakage of the tablet edges or formation of powder during manufacturing and opening of the blister pack is avoided because of its superior mechanical resistance. The use of water-insoluble inorganic excipients also offers better enhancement of disintegration characteristics in comparison to the most commonly used water-soluble sugars or salts. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in much longer disintegration time. As the soluble components dissolve on the tablet's outer layer, a concentrated viscous solution is formed, which reduces the rate of water diffusion into the tablet core.

Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs.

The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F.

However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation.

The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

I. Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture [29].

II. Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements.

In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature [30].

III. Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss .

IV. Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug along with other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

Spray-Drying

Allen et al.,have used spray-drying for the production of MDTs. The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant.

Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.

Sublimation

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation.

Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethene) have been used for this purpose.

Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Makino et al., reported a method using water as a pore-forming material.

Mass-Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste [25].

Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique .

The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs.

Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

Fast Dissolving Films

It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film.

This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

MDTs with Patented Taste Masking Technology

There are number of patented taste masking technologies which had been utilized to manufacture MDTs with acceptable taste. CIMA Labs' taste masking technique involving coating of drug with dissolution retarding excipient, Microcaps process involving microencapsulation by coacervation-phase seperation technique ,

Solutab technology involving coating of drug with sustained release agent followed by coating with enteric polymer and finally with mannitol [68] and blending of drug with cyclodextrins are some of the taste masking approaches applied in fabrication of MDTs.

One more formulation in this category is OraQuick formulation which produces microspheres, known as MicroMask, which has superior mouthfeel over other taste-masking alternatives. This process does not involve the use of solvents and therefore, leads to faster and more efficient production.

Moreover, relatively lower heat of production makes OraQuick appropriate for heat-sensitive drugs. The matrix that protects the drug in microencapsulated particles is more pliable which enables the tablets to be compressed with significant mechanical strength without disrupting the taste-masking property.

Alongwith good taste-masking ability, OraQuick also claims quick dissolution (in secs) of the MDT. This technology had also been utilized in the development of MDTs containing Hyoscyamine sulfate, which is a bitter tasting anticholinergic/antispasmodic drug.

AdvaTab technology utilizes a combination of Microcaps technology for taste masking and Diffuscap controlled release technology for the development of a highly differentiated controlled release MDT product [31].

2. REVIEW OF LITERATURE

1. Neena Bedi et.al, developed Formulation and Evaluation of Mouth Dissolving Tablets of OxcarbazepineTablets produced by direct compression method contain crospovidone as a superdisintegrant and aspartame as a sweetener. Solid dispersions of oxcarbazepine with polyvinylpyrrolidone K-30 and polyethylene glycol 6000 in different weight ratios were prepared with a view to increase its water solubility[32].

2. B. P. Patel et.al**,** developed Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine by effervescent, superdisintegrant addition and sublimation methods. All the three formulations were evaluated for disintegration time, hardness and friability, among these superdisintegrant addition method showed lowest disintegration time; hence it was selected for further studies. Further nine batches (B1-B9) were prepared by using crospovidone, croscarmellose sodium and L-HPC in different concentrations such as 5, 7.5 and 10%. All the formulations were evaluated for weight variation, hardness, friability, drug content, *in vitro* disintegration time, wetting time, *in vitro* dissolution. Formulation with 10% L-HPC showed the less disintegration time (25.3 s) and less wetting time (29.1 s). *In vitro* dissolution studies showed total drug release at the end of 6 min.

Keywords: Cinnarizine, *In vitro* disintegration time, mouth dissolving tablets, sublimation, wetting time[33].

3. Sharma V et.al, developed mouth dissolving tablet that disintegrates rapidly in mouth by using tasteless complex of Levocetirizine and Tulsion-335. Effect of different parameters such as swelling time, resin activation, drug resin ratio as well as stirring time was optimized by taste and percentage drug loading. Formulated DRC (Drug Resin Complex) was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction pattern. Tablets were formulated by wet granulation with PVP as binder, Sodium Starch Glycolate (SSG) and Crospovidone as super disintegrants. In these batches optimum hardness was achieved but disintegration time was found to be very high as ≥ 70 second, so further trials were planned by using different superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate (SSG) as well as

Crospovidone by wet granulation method. Tablets formulated with 7.5% crospovidone showed comparatively low disintegration time (25 sec), wetting time (20 sec) and friability (0.60 %) than the other batches. In present study we optimized the conditions required for maximum drug loading of Levocetirizine with Tulsion-335. Among different superdisintergants, crospovidone was found suitable with drug-resin complex to get the low disintegration time, wetting time and friability of tablets.

Keywords: Drug-resin complex; Levocetirizine; Superdisintegrant; Tulsion-335[34]

4. Goel H et.al, studied a variety of dosage forms like tablets, films, wafers, chewing gums, microparticles, nanoparticles etc. have been developed for enhancing the performance attributes in the orally disintegrating systems. Advancements in the technology arena for manufacturing these systems include the use of freeze drying, cotton candy, melt extrusion, sublimation, direct compression besides the classical wet granulation processes. Taste masking of active ingredients becomes essential in these systems because the drug is entirely released in the mouth. Fluid bed coating, agglomeration, pelletization and infusion methods have proven useful for this purpose. It is important to note that although, freeze dried and effervescent disintegrating systems rapidly disintegrate in contact with fluids, they do not generally exhibit the required mechanical strength. Similarly, the candy process cannot be used for thermolabile drugs. In the light of the paradoxical nature of the attributes desired in orally disintegrating systems (high mechanical strength and rapid disintegration), it becomes essential to study the innovations in this field and understand the intricacies of the different processes used for manufacturing these systems. This article attempts at discussing the patents relating to orally disintegrating systems with respect to the use of different formulation ingredients and technologies[35].

5. Chachin M et.al,studied pharmacological effect of Telmisartan (Micardis) is a potent, long-lasting, nonpeptide angiotensin II type-1 (AT(1)) receptor blocker (ARB) that is indicated for the treatment of essential hypertension. In receptor binding studies, telmisartan showed a high affinity and selectivity for the human AT(1) receptors

compared with AT(2) receptors and a slower dissociation rate from the human AT(1) receptor than those of ARBs. In isolated aorta rings, telmisartan was shown to be an insurmountable antagonist of AII-induced contractions. The inhibitory effects of telmisartan on AII-induced contraction persisted even after wash-out procedures. In animal models such as spontaneous hypertension rats and renovascular hypertensive rats, telmisartan produced the consistent reduction of blood pressure. Furthermore, there were no rebound phenomenon and no tolerance to the drug developed in the repeated oral administration. Telmisartan has a longer terminal elimination half-life (about 24 h) than the other ARBs. In patients with mild-moderate hypertension, trough/peak ratios for telmisartan were above 80%. In Japanese patients with mild-moderate hypertension, telmisartan produced a significant reduction in blood pressure (effective rate: 76.0%) with a good safety profile. Therefore, telmisartan is expected to be effective in the treatment of hypertension, producing sustained 24-h blood pressure control[36].

6.Chaudhari PD et. al, Studied the bitter taste of famotidine was masked using Eudragit in different ratio. The different superdisintegrants like Ac-di-sol and polyplasdone with their varying concentration used for disintegration of tablet in mouth. After dissolution study he concluded that all formulation showed faster release rate than marketed formulation[37] .

7.Takao M et. al., Tried to developed novel fast-disintegration tablet as a user friendly dosage form for the aged. Used mannitol, lactose, glucose, magnesium stearate as excipient. Prepared many formulations using different exicipients in different formulation, various parameters checked and compare. They concluded that tablet contain mannitol, glucose and lactose showed quick disintegration time, but very low hardness and tablet contain maltose and mannitol having high hardness but slow disintegration time[38].

8.Zhao N et. al., Compared disintegration efficiency and to developed a discriminating model for 3 classes of superdisintegrants represented of AC-Di- Sol, primoses and

polyplasdone X L 10. The study were thus provides a closer look at the functionality of superdisintegrants in promoting tablet disintegration and development of model formulation with examinated by videography and dissolution profile. AC-Di-Sol was found to disintegrate tablet rapidly into apparently primary particles. 3 disintegrants representing each of the 3 main classes of superdisintegrants differed in their ability to disintegrate model tablets into their primary particles[39].

9.Desai SA et. al., prepared o r d i s s o l v i n g tablets of promethazine hydrochloride were prepared by using superdisintegrant sodm starch glycolate and cross carmellose sodium by direct compression method. The prepared tablets were evaluated for uniformity of weight, tensile strength, content uniformity, hardness, friability, wetting time, invitro and invivo dispersion time and invitro drug release[40].

10.Nandgude TD et. al., Prepared diphenhydramine tannate fast dissolving tablet by wet granulation method after incorporating superdisintegrants like sodium glycolate and crospovidone in different concentration. The tablets are subjected to evaluation with post compressional parameters like weight variation, hardness and friability, tensile strength, water absorption ratio, *in-vitro* dispersion time, *in vivo* dispersion time. Concluded that conventional tablet show 100% release after 7 hrs where as mouth disintegration tablet achieved maximum release 3-4 hrs. Tablet containing SSG show superior organoleptic properties along with excellent *in-vitro* dispersion time[41].

11.Uddhav S et. al., Described manufacturing technologies for mouth dissolving tablets showing that incorporation of an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and improved patient compliance. In these studies they had described different types of technologies employed for the formulation of mouth dissolving tablets i.e. freeze drying, spray drying, sublimation and comparison of sugar based excipients with their dissolution rate and compressibility[42].

12.Shishu et. al., Prepared taste masked granules using aminoalkyl methacryl atecopolymer by the extrusion method and formula rapidly disintegrating tablet by direct compression method. The tablet prepared by using microcrystalline cellulose and sodium starch glycolate ate as disintegrant. Concluded that tablet had a good taste and rapidly disintegrated in the mouth were useful and practical for pediatric and geriatric population[43].

13.Sharma S et. al., Formulated promethazine theoclate solid dispersion with PEG 4000 by using optimized amount of superdisintegrant.A phase solubility method was used to evaluate the effect of various water-soluble polymers on aqueous solubility of promethazine theoclate.PEG 4000 was selected and solid dispersion were prepared by method of fusing[44] Chaudhari PD et. al., Formulated and evaluated taste masked orodispersible dosage form of levocetirizine. An attempt was made to mask the taste, by complexation technique using ion-exchange resin, tulsion 335 formulate in to a orodispersible dosage form. The drug loading onto ion exchange resin was optimized for concentration of resin, swelling time of resin, stirring time, pH of resin solution, stirring temperature. Shows bitter drug successfully taste masked using suitable ion exchange resin. The drug resin complex orodispersible tablets were formulated and the evaluated for drug content, content uniformity, weight variation, hardness, friability, water absorption ratio, in-*vitro and in-vivo drug* release[45].

14.Raghu NB ET. al., Studied on taste masking of drotaverine hydrochloride by the complexation technique. The drug loading process was optimized for taste masking and drug: resin ratio, the resinate was evaluated for bulk density, tap density, taste and characterization was done using DSC. The taste masked drotaverine complex was incorporated into palatable melt in mouth tablet and evaluated various quality control parameters. The mouth dissolve tablets had optimum physiochemical property with complete release of drug with 30 min[46].

15.Swamy PV et. al., Developed or dispersible tablet of meloxicam using different superdisintegrants. Combinations of sodium starch glycolate- croscarmellose sodium or sodium starch glycolate–crospovidone were used along with directly compressible mannitol. The prepared batches evaluated for hardness, friability, wetting time, water absorption ratio like various parameters. He concluded that the formulation prepared using 2% w/v sodium starch glycolate and 15% croscarmellose sodium was found better formulation compare to conventional tablet[47].

16.He X et.al.,Developed the rapidly dispersing tablet of a poorly wettable compound–formulation DOE and mechanistic study of effect of formulation excipient on wetting of celecoxib. In this work a tablet was placed in water and the turbidity of the resulting “dynamic” suspension was measured. They describe the novel method to enhance the dissolution rate for poorly soluble compounds by reduction in particle size, with screening formulation statistical design of experiments, mechanistic studies, optimization design of experiments and analytical methods like turbidity test, contact angle analysis, microscopic test[48].

17.Adamo F et. al., Developed eight formulations containing Ibuprofen in the form of orally disintegrating tablets. To prevent bitterness of drug he masked the taste of drug using taste masking agents. Aspartame used as a sweeter in formulation, mannitol used as a binder and explotab were added as superdisintegrant and compacted under low compression force. Dissolution profile suggest that the combined action of hydrophobic lecithin and coating delay the release of the drug from tablets with respect to when it is free or in the form of simple granules[49].

18.Setty CM et. al.,Developed fast dispersible Aceclofenac tablets and study the effect of superdisintegrants on wetting time, disintegration time, drug content, *in-vitro* release and stability parameter using direct compression technique. The parameters were tested for significance by using analysis of variance (ANOVA:Single factor). The stability study showed that tablet containing superdisintegrants were sensitive to high humidity condition. He also concluded that

although functional differences existed between the superdisintegrants, the fast dispersible aceclofenac tablets could be prepared by using any of the superdisintegrants used[50].

19.Mulla JA et. al., Prepared promethazine hydrochloride mouth disintegrating tablet that have been used for prevention of emesis and nausea using disintegrants like Ac-di-sol, explotab, polyplasdone and MCC along with other additives by directly compression techniques. It was observed that the concentration of the superdisintegrants had an effect on disintegration time and *in-vitro* dissolution time and *in-vitro* dissolution characteristics. Ac-di-sol was found to be better as compared to other superdisintegrants used in study[51].

20.Rampure MV et. al., Prepared rapidly disintegrating tablet at Alfuzosin by effervescent method using sodium bicarbonate and citric acid. Crospovidone, sodium starch glycolate and croscarmellose sodium used as superdisintegrants. The prepared tablet evaluated for different parameters and compare market product.He showed that the formulation containing crospovidone along with mixture at 24% w/w of sodium bicarbonate and 18% w/w citric acid as overall best formulation[52].

3. AIM & OBJECTIVE

3.1 AIM:

Formulation Development and Evaluation of Fast Dissolving Tablets of Diltiazem Hydrochloride by Direct Compression method.

3.2. Objectives:

In the present work, fast dissolving tablets of Diltiazem Hydrochloride are planned to prepare with an intention to improve disintegration, dissolution rate and bioavailability of drug by using some Superdisintegrants.

The fast dissolving tablet will be prepared by direct compression method are evaluated for various quality control tests for tablets such as hardness, friability, weight variation, drug content uniformity, disintegration and dissolution.

Fast dissolving tablets will also help in ease of administration because fast dissolving tablets give uniform dispersion product.

3.3 Justification:

Diltiazem is well absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability (compared to intravenous administration) of Diltiazem is approximately 40%.

Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine.

Fast dissolving tablets are formulated with an objective of improving disintegration and dissolution rate of the drug. Fast dissolving tablets are planned to prepare by using some super disintegrants. Super disintegrants are excipients used to promote rapid breakdown of oral solid dosage form to aid dissolution in vivo.

4. PLAN OF WORK

Preformulation Studies:

- Determination of Melting Point
- Determination of Solubility
- To Perform Drug -Excipients Compatibility
- To Perform Calibration By U.V
- To Perform Pre-Compression Studies**.**

Formulation studies:

- To formulate optimized formula
- Formulation of tablets by direct compression

Evaluation studies:

- Weight Variation
- Hardness
- Friability
- Percentage Porosity
- Drug Content Estimation
- Dispersion Time
- In-vitro Dissolution Studies

5. DRUG PROFILE

DILTIAZEM HYDROCHLORIDE[53]

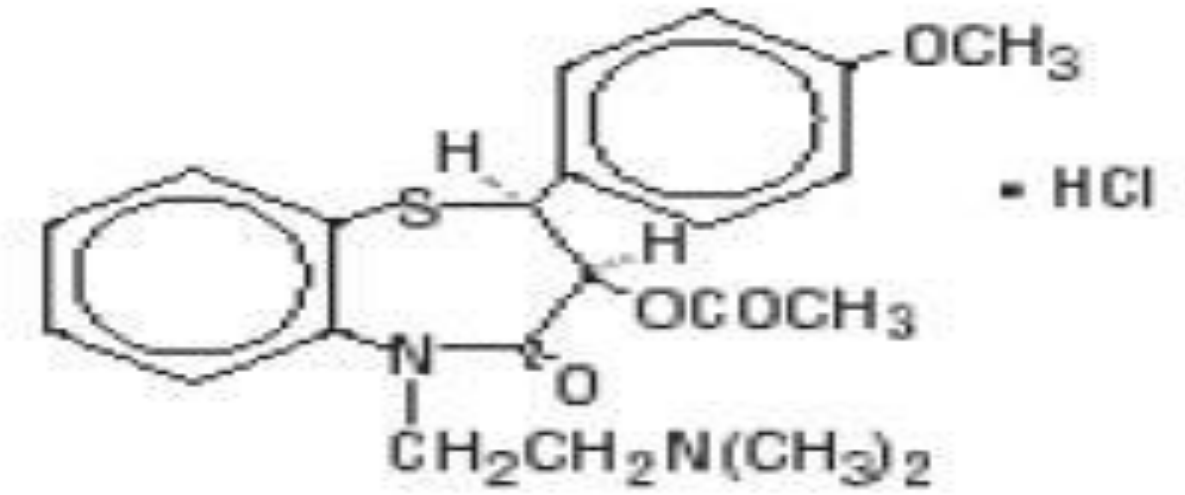
Chemical Name:

Chemically, Diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyl oxy)-5-[2- dimethylamino)ethyl] -2,3-dihydro-2-(4-methoxy phenyl) mono hydrochloride.

Molecular Formula: $C_{22}H_{26}N_2O_4S.HCl$

Molecular Weight: 450.99.

Structural Formula:



Description:

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform.

Diltiazem Hydrochloride - Clinical Pharmacology:

The therapeutic benefits of Diltiazem hydrochloride are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscles.

Mechanism of Action:-

Hypertension

Diltiazem HCl produces its antihypertensive effect primarily by relaxation of vascular smooth muscle with a resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina

Diltiazem HCl has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal workloads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by Diltiazem.

Hemodynamic and Electrophysiologic Effects

Like other calcium antagonists, Diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

Pharmacokinetics and Metabolism:-

Diltiazem is well absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability (compared to intravenous administration) of Diltiazem is approximately 40%.

Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine.

The plasma elimination half-life of Diltiazem is approximately 3.0 to 4.5 hours. Desacetyl Diltiazem, the major metabolite of Diltiazem, which is also present in the plasma at concentrations of 10% to 20% of the parent drug, is approximately 25% to 50% as potent a coronary vasodilator as Diltiazem.

Therapeutic blood levels of Diltiazem hydrochloride appear to be in the range of 40 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

Indications and Usage for Diltiazem:

Diltiazem Hydrochloride are indicated for the treatment of hypertension. Diltiazem hydrochloride may be used alone or in combination with other antihypertensive medications, such as diuretics.

Contraindications:

Diltiazem hydrochloride is contraindicated in:

- Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker;
- Patients with second or third degree av block except in the presence of a functioning ventricular pacemaker;
- Patients with hypotension (less than 90 mmhg systolic);
- Patients who have demonstrated hypersensitivity to the drug; and

- Patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

Drug Interactions:

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving Diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Diltiazem hydrochloride. As with all drugs, care should be exercised when treating patients with multiple medications.

Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of Diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism.

Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio such as cyclosporine, may require adjustment when starting or stopping concomitantly administered Diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Concomitant administration of Diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine, resulting in toxicity in some cases.

Diltiazem Hydrochloride Dosage and Administration:

Administration:-

Administer by direct IV injection, continuous IV infusion, or orally.

Oral Administration

Conventional Tablets

Administer tablets orally 3–4 times daily before meals and at bedtime.

Extended-release Capsules

Administer orally; directions for administration (e.g., frequency, whether to administer with or without food, potential for opening capsules and mixing with food) may vary by manufacturer and formulation; consult specific manufacturer's information for additional information.

Extended-release Tablets

Administer orally once daily without regard to meals. Tablet should be swallowed whole and not chewed or crushed.

Dosage:-

Available as diltiazem hydrochloride; dosage expressed in terms of the salt.

Warnings/Precautions:

Warnings:-

Cardiac Conduction

Potential for abnormally slow heart rate (particularly in patients with sick sinus syndrome) or second- or third-degree AV block.

Additive effects on cardiac conduction (e.g., prolonging AV node conduction) possible with concomitant use of diltiazem with β-adrenergic blocking agents or digoxin.

If high-degree AV block occurs in patients with sinus rhythm receiving IV diltiazem, discontinue the drug and institute appropriate supportive measures.

Heart Failure

Risk of heart failure, especially in those with preexisting ventricular impairment; limited experience in patients with impaired ventricular function receiving concomitant β-adrenergic blocking agents. Use with caution.

Hypotension

Possible symptomatic hypotension.

5.1. EXCIPIENT PROFILES[54,55,56]

5.1.1 CROSPOVIDONE:

Nonproprietary names:

BP: Crospovidone

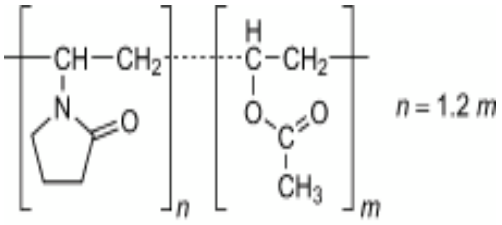
PhEur: Crospovidonum

USPNF: Crospovidone

Synonyms: Cross-linked povidone, polyvinyl pyrrolidone, PVPP,

Chemical name: 1-Ethenyl-2-pyrrolidinone homopolymer

Structural formula:



Functional category: Superdisintegrant.

Description: Crospovidone is a white to creamy- white,

Applications: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer.

5.1.2 CROSCARMELLOSE SODIUM (CCS):

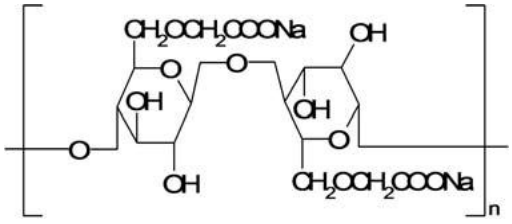
Nonproprietary Name: USPNF: Croscarmellose sodium.

Synonyms: Ac-Di-sol; cross-linked carboxy methylcellulose Sodium; Primellose

Functional category: Tablet and capsule disintegrants

Chemical name: Cellulose, carboxymethyl ether, sodium salt.

Structural formula:



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

Molecular weight: 90000-700000.

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

Application: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet and dry granulation methods.

5.1.3 SODIUM STARCH GLYCOLATE:

Synonyms: Explotab, Primogel.

Nonproprietary Name:

BP: Sodium starch glycolate

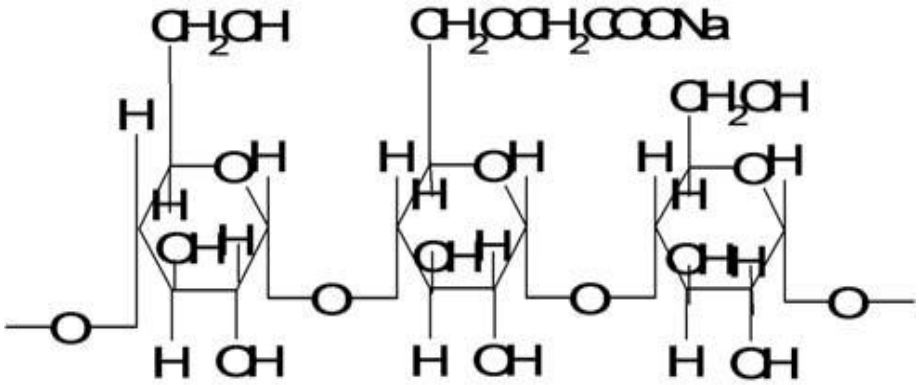
USPNF: Sodium starch glycolate

Functional category:Tablet and capsule disintegrant.

Chemical name: Sodium carboxymethyl starch.

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

Structural formula:



Solubility: Practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells up to 300 times its volume

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

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

5.1.4 MICROCRYSTALLINE CELLULOSE:

Nonproprietary name:

NF : Microcrystalline cellulose.

USP: Microcrystalline cellulose.

Functional category:Tablet and capsule diluents, tablet disintegrant, suspending and /or viscosity increasing agent.

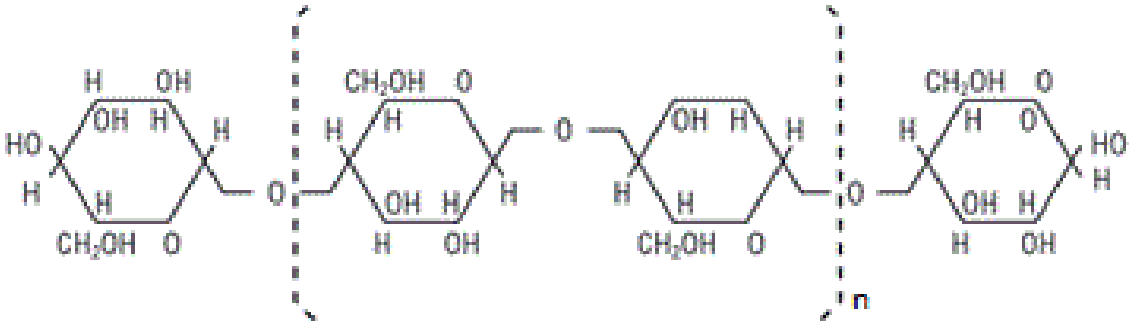
Synonyms: Cellulose gel: Crystalline cellulose: Avicel

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

Molecular weight:36,000(approx)

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

Structural Formula:



Microcrystalline cellulose

Density: Apparent density - 0.28g/cm^3

Tap density- 0.43g/cm^3

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

Incompatibilities: None cited in the literature.

Safety: Generally regarded as safe

Applications: Tablet binder/diluents (wet or dry granulation)

5.1.5 LACTOSE:

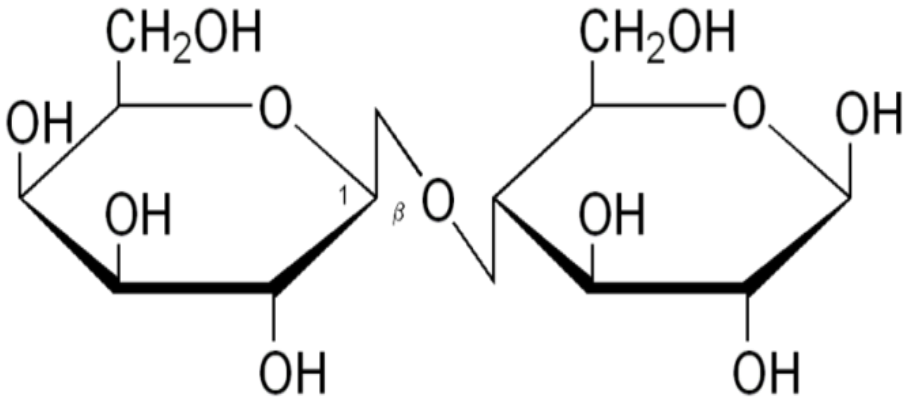
Synonyms: Fast-Flo, Microlose, milk sugar, Pharmatose, Tablettose.

Functional Category: Tablet and Capsule diluent.

Description: White to off-white crystalline particles powder, odorless.

Solubility: Freely soluble in water, practically insoluble in chloroform, ethanol and ether.

Structural Formula:



Applications: As filler or diluent in tablets (wet granulation and direct compression) and capsules, in lyophilized products and infant fed formula

Stability: Under humid conditions (80% RH and above)

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

Incompatibilities: A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown colored products.

Safety: An adverse reaction to lactose is largely attributed to lactose intolerance, which occurs in persons with a deficiency of the intestinal enzyme lactase.

5.1.6 TALC:

Nonproprietary name: Purified talc

Synonym: Powdered talc.

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

Description: Talc is very fine, white to greyish-white colored, odorless, hydrophobic, crystalline powder. It adheres readily to the skin, is soft to touch, and free from grittiness.

Functional category: Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant

Table No:2 Concentrations of talc to be used in various applications

Use	Concentration (%)
Dusting powder	90-99
Glidant and tablet lubricant	1-10
Tablet and capsule diluents	5-30

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

Incompatibilities: Incompatiblewithquaternary ammonium compounds

Safety: Following oral ingestion talc is not absorbed systemically and may be thus regardedasanessentially nontoxic material

Pharmaceutical applications: It is commonly used as lubricant in tablet and capsules.

5.1.7 MAGNESIUM STEARATE:

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt, stearic acid.

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

Molecular weight : 91.3

Structural Formula: $CH_3 (CH_2)_{16}COO)$

Functional Category: Tablet and capsule lubricant.

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

Stability and storage conditions: Magnesium stearate is stable and should stored in a well closed container in a cool, dry place

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

Application: magnesium stearate used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 % and 5.0 w/w. It is also used in barrier creams.

5.1.8 ASPARTAME:

Synonyms:(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid.

Nonproprietary Name:

BP: Aspartame

PhEur: Aspartame

USP-NF: Aspartame

Chemical Name: N-L-a-Aspartyl-L-phenylalanine 1-methyl ester

Empirical Formula : C14H18N2O5

Molecular Weight : 294.30

Description : Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste

Functional Category: Sweetening agent

Stability and Storage Conditions: Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L - phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness Stability in aqueous solutions has been enhanced by the addition of cyclodextrins,(4,5) and by the addition of polyethylene glycol 400 at pH 2.(6) However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents.

Applications: Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets (1, 2) powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

6. MATERIALS & METHODS

Table No: 3 Materials Used for Formulation of Diltiazem Hydrochloride

Sl.No.	Materials used	Source
1.	Diltiazem Hydrochloride	Pellsys pharma pvt limited, Hyderabad
2.	Croscarmellose sodium	Vijlak Pharma Limited, Hyderabad
3.	Crospovidone	Vijlak Pharma Limited, Hyderabad
4.	Sodium starch Glycolate	Vijlak Pharma Limited, Hyderabad
5.	Microcrystalline cellulose	Vijlak Pharma Limited, Hyderabad
6.	Magnesium Stearate	Oxford Laboratory, Mumbai.
7.	Talc	NR Chem, Mumbai.
8.	Lactose	Merck Specialties' limited., Mumbai
9.	Aspartame	Provizer Pharma, Hyderabad
10.	Menthol	Sagar Aromatics, Mumbai

Table No:4 Equipment Used for Formulation of Diltiazem Hydrochloride

Sl. No.	Equipment	Make / Model
1.	Tablet compression machine	Rimek, minipress 10 station rotary machine
2.	Hardness tester	Monsanto hardness tester, Servewell instruments and equipments pvt. ltd., Bangalore.
3.	Friability Test Apparatus	Classic Scientific , Maharastra
4.	Tablet Dissolution Test Apparatus	Electrolab Dissolution Apparatus, Mumbai
5.	UV visible spectrophotometer	PG Instruments limited, T-80 UV-VIS Spectrometer
6.	Digital Balance	Shimadzu, Shimadzu corporation, Japan
7.	pH meter	Hanna Instruments, Ranchi.
8.	FT-IR Spectrometer	Perkin Elmer Instruments, USA

6.1 Drug-Excipient Compatibility study (FTIR)[57]:

The study was designed to determine compatibility of drug with different co-processed excipients. Completely dried KBR and samples (drug and excipients) taken in 9:1 ratio and grinded for proper mixing. Sample was filled into the holes of stainless steel disk and sandwiched in the hydraulic press until pressure reaches 20,000 psi. After few seconds, pressure was released and pellet was collected. Then the pellet was inserted into the sample holder and run for the spectrum. FTIR

spectra of pure drug and excipients separately done to determine the compatibility. FTIR spectra of drug and excipients were obtained .The spectra were scanned over the wave number range of4000-400 cm^{-1}.

6.2. ANALYTICAL METHODS:

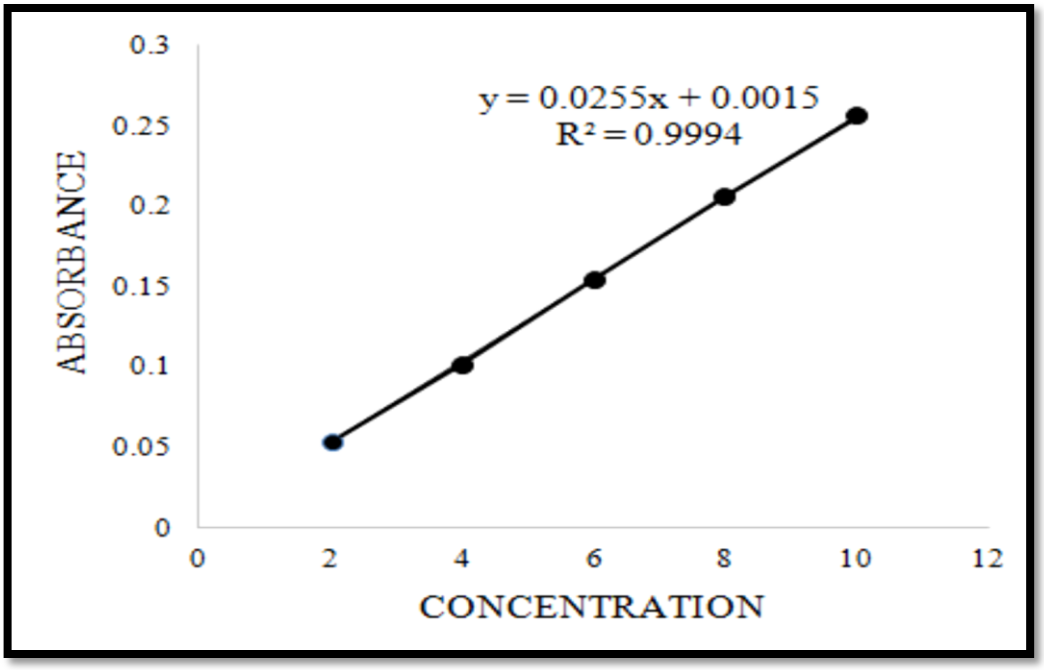
Preparation of pH 6.8 phosphate buffer[57]:

Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml[57].

Preparation of Calibration Curve of Diltiazem HCl in pH 6.8 phosphate buffer: 100mg of Diltiazem HCl was weighed accurately and dissolved in pH 6.8 phosphate buffer, which resulted in 1000 µg/ml. Then from the stock solution 100 µg/ml solution was prepared from this 2, 4, 6, 8, 10 µg/ml were prepared. The absorbances of the above dilutions were measured using UV-spectrophotometer at 236 nm using 6.8 pH phosphate buffer as blank. The conc. of corresponding absorbance was given below table. Standard curve was plotted by taking concentration on x-axis and absorbance on y-axis[57]. The results are given in table-5 and figure-1

Table No:5 Standard calibration curve of Diltiazem Hydrochloride in pH 6.8 phosphate buffer

Sl.No	Concentration mcg/ml	Absorbance at 236nm
1.	2	0.054
2.	4	0.101
3.	6	0.154
4.	8	0.205
5.	10	0.254



FigureNo:1 Calibration Curve of Diltiazem HCl in pH 6.8 phosphate buffer

B) PREPARATION OF DILTIAZEM HYDROCHLORIDE FAST DISSOLVING TABLET[58]

Diltiazem Hydrochloride fast dissolving tablet $DLTF_1$ to $DLTF_9$ were prepared by direct compression method and the detailed tablet composition was given in table-1. A total of tablets were prepared in every batch and the quantity for 60 tablets.

Method:

- All the ingredients were passed through 60 mesh sieve separately.
- Then drug and diluents separately taking small portion of both each time and blending it thoroughly to get uniform mixture.
- The granules were compressed using 8 mm size to get a tablet of 160 mg tablet weight using Rimek mini press machine

Table No:6 Materials used in the study with their property

Sl.No	Materials	Property
1.	Diltiazem Hydrochloride	Antihypertensive
2.	Crospovidone	Disintegrants
3.	Croscarmellose sodium	Disintegrants
4.	Sodium starch glycolate	Disintegrants
5.	Microcrystalline cellulose	Diluents
6.	Lactose	Diluents
7.	Talc	Glidant
8.	Magnesium stearate	Lubricant
9.	Aspartame	Sweetening agent
10.	Menthol	Flavouring agent

Table No:7 Parameters fixed for the Fast Dissolving Tablets

Sl. No.	Test	Limit
1.	Physical appearance	white, circular
2.	Diameter	7 mm
3.	Thickness	3mm
4.	Hardness	2-4 Kg
5.	Friability	NMT 1%
6.	Disintegration time	NMT 180 Sec

C)PRECOMPESSION STUDY[46, 47, 48]:

Angle of repose (θ) [46,48]:-

Angle of repose is defined as the maximum angle possible between the

surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = h/r$

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

Where,

θ is the angle of repose,

h is height of pile

r is radius of the base of pile

Different ranges of flow ability in terms of angle of repose (Table No. 9) are given below.

Table No:8 Relationship between angle of repose (θ) and flow properties.

Angle of Repose (θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable or poor

Method:

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

Bulk density:-

Bulk density is defined as the mass of a powder divided by the bulk

volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec interval. The tapping was continued until no further change in volume was noted. The LBD and TBD can be calculated using following formula,

$$LBD = \frac{\text{Weight of powder}}{\text{Volume of powder before tapping}} \quad \ldots\ldots\ (a)$$

$$TBD = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}} \quad \ldots\ldots\ (b)$$

POST-COMPRESSION PARAMETERS:

All the formulation of Diltiazem Hydrochloride prepared were evaluated for the following physical and chemical parameters

Physical Parameters:-

Size and shape: The tablet formulated was circular in shape with 7 mm diameter.

Organoleptic Characters:-

Colour: Diltiazem Hydrochloride fast dissolving tablets were found to be white in colour.

TABLET PROPERTIES:

Hardness test:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test:-

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

The friability of tablets was determined by using Veego Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{\text{Initial weight - Final weight}}{\text{Intial weight}} \times 100 \quad \ldots\ldots\ldots\ldots (d)$$

Friability of tablets less than 1% is considered acceptable.

Weight variation test[49]:-

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table No:9 Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5

In all the formulations the tablet weight was more than130mg and less than 324 mg, hence 7.5% maximum difference allowed.

Drug Content Uniformity:

Five tablets were weighed and crushed with pestle in a mortar. The fine powder was weighed to get a100mg (equivalent to 60mg Diltiazem HCl) and transferred to 250 ml conical flask containing 100 ml of 6.8 pH phosphate buffer stirred for 45 min in an sonicator then the solution was filtered and it was analyzed by UV spectrophotometrically at 236 nm and drug content was determined.

Disintegration Time:

Disintegration time is the time required for a tablet to break into granules of specified size (or smaller), under carefully specified test conditions. Six tablets were placed in each of the tubes and run the apparatus using phosphate buffer 6.8 pH which is maintained at 37±2 ºC. The time required for complete passage of tablet

fragments through the sieve #10 was considered as the disintegration time of the tablet.

***In-vitro* dissolution Studies:**

The release rate of Diltiazem HCl tablets was determined using USP Dissolution type II testing apparatus (paddle type). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium previously maintained at 37 ± 0.5ºC and at 50 rpm. After completion of each specified time interval, aliquots of 5ml was withdrawn from the dissolution media and the samples were replaced with fresh dissolution medium. After filtration and samples are diluted and absorbance was noted at 236 nm using UV visible spectrophotometer and percentage of drug release was calculated.

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

Apparatus used	: Dissolution test apparatus (type II)
Dissolution medium	: pH 6.8 phosphate buffer
Dissolution medium Volume	: 900ml
Temperature	: 37 ±0.5°C
Speed of basket paddle	: 50 rpm
Sampling intervals	: 1 min
Sample withdraw	: 5 ml
Absorbance measured	: 236 nm

Drug polymer interaction studies: FTIR STUDIES:

IR spectra for pure drug, formulations Diltiazem Hydrochloride, Crospovidone and DLTF6 were recorded in a Fourier transform infrared (FTIR) spectrophotometer with KBr pellets.

Table No: 10 Formulation of Diltiazem Hydrochloride Fast Dissolving Tablets Prepared By Direct Compression Method

Ingredients (mg)	$DLTF_1$	$DLTF_2$	$DLTF_3$	$DLTF_4$	$DLTF_5$	$DLTF_6$	$DLTF_7$	$DLTF_8$	$DLTF_9$
Diltiazem Hydrochloride	20	20	20	20	20	20	20	20	20
Croscarmellose sodium	1.6	4.8	8.0	----	----	----	----	----	----
Crospovidone	----	----	----	3.2	6.4	8.0	----	----	----
Sodium starch glycolate	----	----	----	----	----	----	6.4	9.6	12.8
Microcrystalline cellulose	48.8	44.8	42.4	47.4	44	45.6	44	41.6	37.6
Lactose	80	80	80	80	80	80	80	80	80
Talc	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Mg stearate	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Aspartame	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Menthol	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Total weight in (mg)	160	160	160	160	160	160	160	160	160

Table No:11 Formulation of Diltiazem Hydrochloride Fast Dissolving Tablets Prepared By Direct Compression Method (For 60 Tablets)

Ingredients (mg)	DLTF1	DLTF2	DLTF3	DLTF4	DLTF5	DLTF6	DLTF7	DLTF8	DLTF9
Diltiazem Hydrochloride	1200	1200	1200	1200	1200	1200	1200	1200	1200
Croscarmellose sodium	96	288	480	----	----	----	----	----	----
Crospovidone	----	----	----	192	384	480	----	----	----
Sodium starch glycolate	----	----	----	----	----	----	384	576	768
Microcrystalline cellulose	3120	2928	2736	3030	2832	2736	2832	2640	2448
Lactose	4800	4800	4800	4800	4800	4800	4800	4800	4800
Talc	192	192	192	192	192	192	192	192	192
Magnesium stearate	192	192	192	192	192	192	192	192	192
Menthol	3	3	3	3	3	3	3	3	3
Total weight in (mg)	9600	9600	9600	9600	9600	9600	9600	9600	9600

7. RESULTS AND DISCUSSION

RESULTS:

PRE-FORMULATION STUDIES:

SOLUBILITY:It is soluble in water, methanol and chloroform.

MELTING POINT: 262^0 C

7.1 Results of Granule Parameter Evaluation:

Table No:12 Granule Parameters for Diltiazem Hydrochloride Formulation

Formulation Code	Bulk Density gm/cc	Tapped Density	Angle of Repose θ=h/r	Percentage Porosity
$DLTF_1$	0.53	1.27	28.32	56
$DLTF_2$	0.52	1.45	29.08	57
$DLTF_3$	0.55	1.23	30.21	56
$DLTF_4$	0.54	1.09	30.11	56.5
$DLTF_5$	0.51	1.23	28.43	57
$DLTF_6$	0.50	1.87	30.38	56.8
$DLTF_7$	0.53	1.45	31.03	56.9
$DLTF_8$	0.54	1.78	28.10	56
$DLTF_9$	0.52	1.67	26.28	56.4

7.2Hardness Test Result

Table No:13 Hardness Test for Diltiazem Hydrochloride Formulation

Formulation code	Hardness in* Kg/cm^2 ±SD
$DLTF_1$	3.2±0.12
$DLTF_2$	3.23 ±0.28
$DLTF_3$	3.34 ±0.12
$DLTF_4$	3.23 ±0.24
$DLTF_5$	2.9 ±0.36
$DLTF_6$	2.8±0.32
$DLTF_7$	3.1±0.12
$DLTF_8$	2.91 ±0.01
$DLTF_9$	2.95 ±0.14

*** Average of three determinations**

7.3Friability Test Results

Table No:14 Friability test for Diltiazem Hydrochloride Formulation

Formulation code	Friability (%)
$DLTF_1$	0.64
$DLTF_2$	0.66
$DLTF_3$	0.67
$DLTF_4$	0.62
$DLTF_5$	0.5
$DLTF_6$	0.59
$DLTF_7$	0.53
$DLTF_8$	0.62
$DLTF_9$	0.61

7.4 In Vitro Dispersion Time

Table No:15 In Vitro Dispersion Time for Diltiazem Hydrochloride Formulation

Formulation code	Time in seconds ±SD
DLTF1	75.0±2.5
DLTF2	60.0±1.4
DLTF3	35.0±1.8
DLTF4	55.0±0.7
DLTF5	38.0±0.4
DLTF6	15.0±0.5
DLTF7	110.0±1.1
DLTF8	85.0±1.4
DLTF9	68.0±0.7

Table No:16 **Weight Variation of Diltiazem Hydrochloride Formulation**

Sl.No	DLTF1			DLTF2			DLTF3		
	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
1	161	1.3	0.81	164	4.4	2.7	163	2.2	1.36
2	162	2.3	1.4	162	2.4	1.49	162	1.2	0.74
3	159	0.7	0.43	158	2.4	1.49	162	1.2	0.74
4	164	4.3	2.69	160	0.4	0.24	160	0.8	0.49
5	157	2.7	1.69	158	2.4	1.49	160	0.8	0.49
6	158	1.7	1.06	158	2.4	1.49	163	2.2	1.36
7	160	0.3	0.187	159	1.4	0.87	162	1.2	0.74
8	158	1.7	1.06	160	0.4	0.24	159	1.8	1.11
9	160	0.3	0.187	162	2.4	1.49	157	3.8	2.36
10	158	1.7	1.06	163	3.4	2.11	160	0.8	0.49
	Average of 10 Tablets 159.7 mg			Average of 10 Tablets 160.4 mg			Average of 10 Tablets 160.8mg		

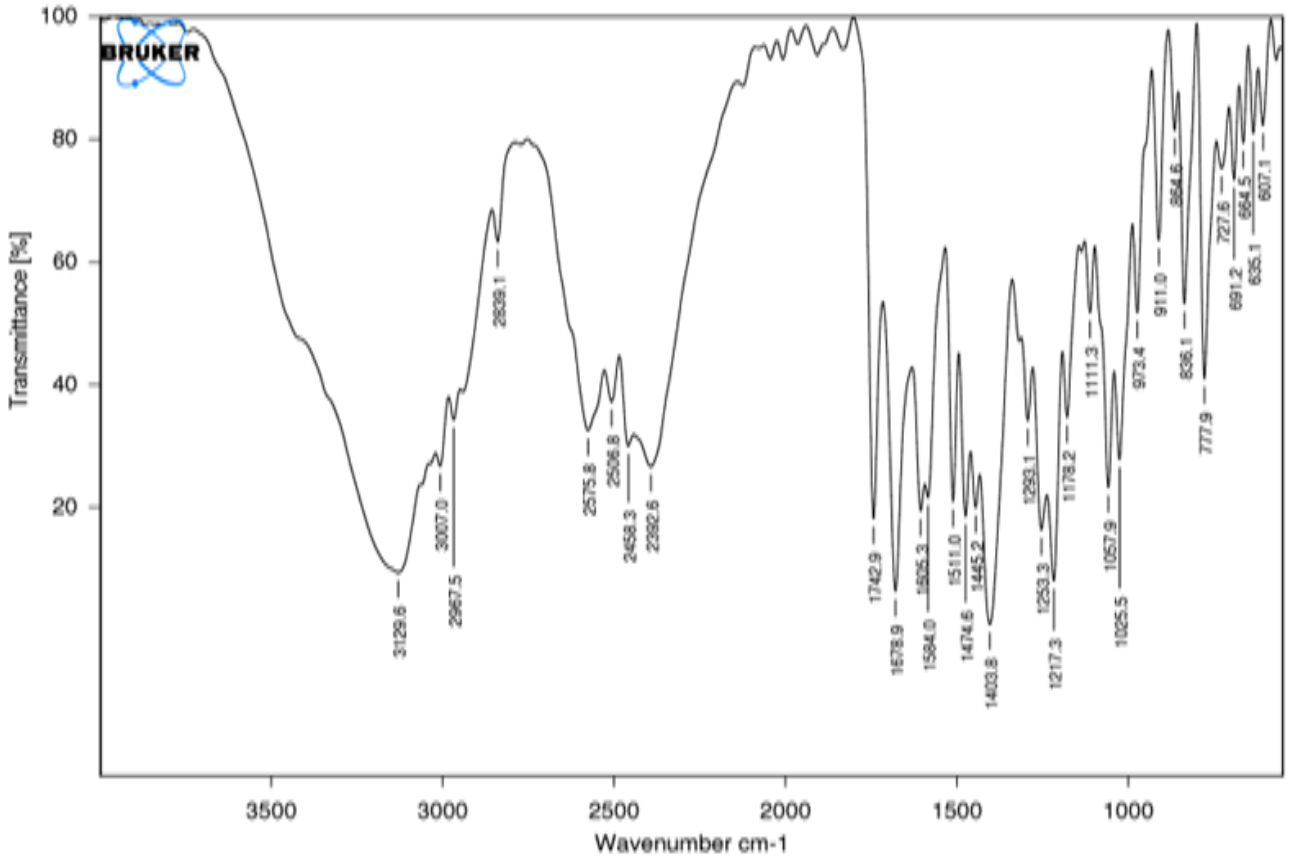
Table No:17 Weight Variation of Diltiazem Hydrochloride Formulation

Sl. No	DLTF4			DLTF5			DLTF6		
	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
1	160	1.1	0.68	160	0.7	0.43	162	0.8	0.49
2	165	4.1	2.54	162	1.3	0.80	163	1.8	1.11
3	158	2.9	1.80	164	3.3	2.05	161	0.2	0.12
4	160	0.9	0.55	162	1.3	0.80	162	0.8	0.49
5	162	1.1	0.68	162	1.3	0.80	162	0.8	0.49
6	163	2.1	1.30	161	0.3	0.18	163	1.8	1.11
7	163	2.1	1.30	159	1.7	1.05	158	3.2	1.98
8	157	3.9	2.42	158	2.7	1.68	159	2.2	1.36
9	159	1.9	1.18	157	3.7	2.30	160	1.2	0.74
10	160	0.9	0.55	162	1.3	0.80	162	0.8	0.49
	Average of 10 Tablets160.9 mg			Average of 10 Tablets 160.7mg			Average of 10 Tablets161.2 mg		

Table No:18 Weight Variation of Diltiazem Hydrochloride Formulation

Sl. No	DLTF7			DLTF8			DLTF9		
	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation	Weight in mgs	Difference in weight	Percent Deviation
1	161	0.8	0.49	160	0.1	0.06	162	1.3	0.80
2	162	1.8	1.12	159	1.1	0.68	163	2.3	1.43
3	163	2.8	1.74	157	3.1	1.93	159	1.7	1.05
4	159	1.2	0.74	162	1.9	1.18	158	2.7	1.68
5	158	2.2	1.37	163	2.9	1.81	162	1.3	0.80
6	157	3.2	1.99	159	1.1	0.68	163	2.3	1.43
7	159	1.2	0.74	157	3.1	1.93	158	2.7	1.68
8	160	0.2	0.12	159	1.1	0.68	159	1.7	1.05
9	161	0.8	0.49	163	2.9	1.81	161	0.3	0.18
10	162	1.8	1.12	162	1.9	1.18	162	1.3	0.80
	Average of 10 Tablets 160.2 mg			Average of 10 Tablets 160.1 mg			Average of 10 Tablets 160.7 mg		

Figure No:2 IR Spectrum of Pure Drug Diltiazem Hydrochloride



IR Spectrum of Pure Drug Diltiazem Hydrochloride

Figure No:3 IR Spectrum of Formulation DLTF6

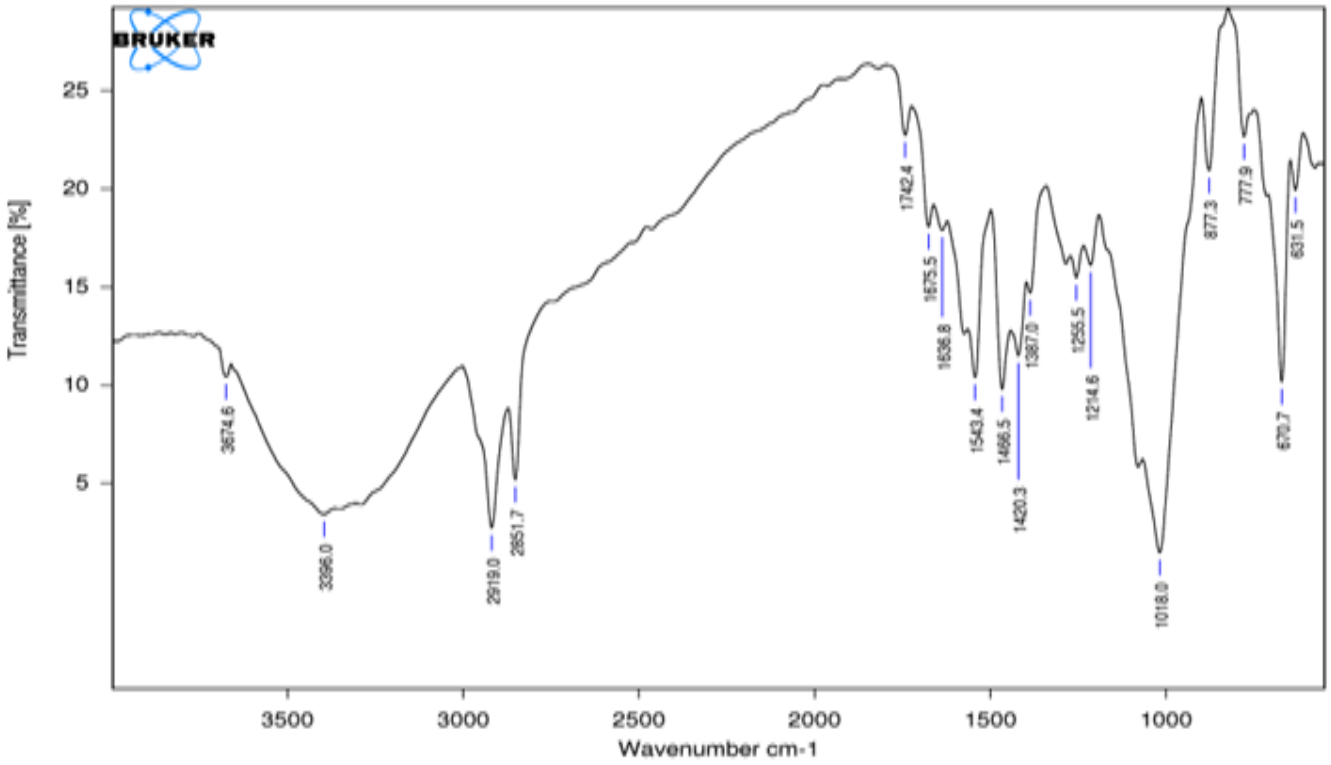


Table No:19 Drug Content of Diltiazem Hydrochloride Formulation

Sl. No.	Formulation code	Average Content (%) ± SD
1	DLTF1	99.5 ± 0.175
2	DLTF2	100.0 ± 0.275
3	DLTF3	97.0 ± 0.175
4	DLTF4	96.0 ± 0.436
5	DLTF5	99.3 ± 0.354
6	DLTF6	99.0 ± 0.154
7	DLTF7	95.5 ± 0.265
8	DLTF8	99.5 ± 0.241
9	DLTF9	97.0 ± 0.156

Table No:20 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF1

Time in Minute	% Drug Release ± SD
01	15.3 ± 0.12
02	27.0 ± 0.32
03	39.78 ± 0.12
04	48.95 ± 0.32
05	60.12 ± 0.21
06	72.90 ± 0.16
07	81.9 ± 0.55
08	91.8 ± 0.34
09	94.5 ± 0.16
10	97.02 ± 0.44

Figure No:4 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet $DLTF_1$

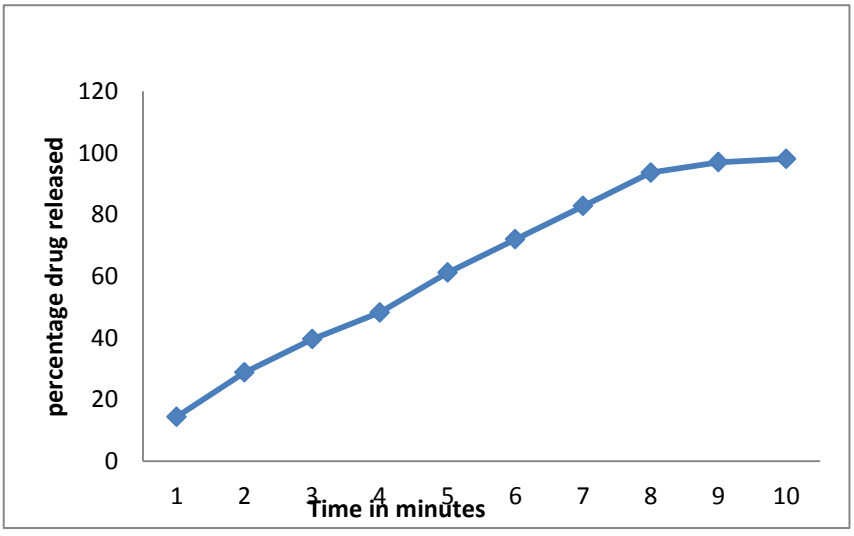


Table No:21 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF2

Time in Minute	%Drug Release ±SD
01	14.4 ± 0.12
02	28.8 ± 0.34
03	39.6 ± 0.56
04	48.24 ± 0.45
05	61.2 ± 0.66
06	72.0 ± 0.68
07	82.8 ± 0.43
08	93.6 ± 0.12
09	97.02 ± 0.13
10	98.1 ± 0.01

Figure No:5 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF2

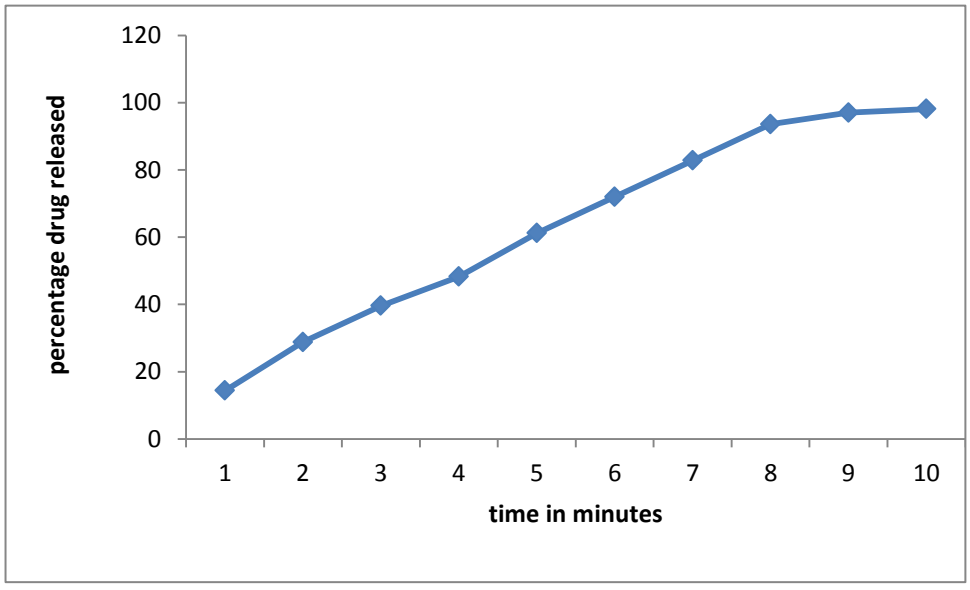


Table No:22 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF3

Time in Minute	%Drug Release ±SD
01	16.56 ± 0.32
02	34.2 ± 0.12
03	47.16 ± 0.32
04	57.78 ± 0.44
05	75.60 ± 0.45
06	84.42 ± 0.43
07	95.58 ± 0.23
08	98.82 ± 0.72
09	98.82 ± 0.12
10	98.82 ± 0.10

Figure No:6 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF3

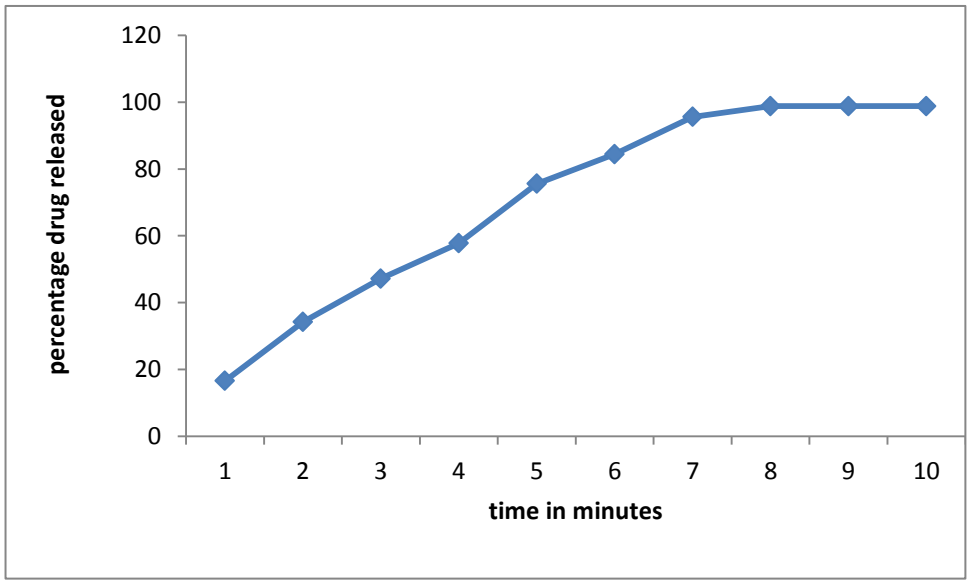


Table No:23 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF4

Time In Minute	% Drug Release ±SD
01	20.66 ± 0.22
02	41.58 ± 0.23
03	57.78 ± 0.55
04	72.0 ± 0.45
05	82.80 ± 0.88
06	86.76 ± 0.12
07	90.00 ± 0.14
08	93.60 ± 0.16
09	95.40 ± 0.24
10	97.74 ± 0.12

Figure No:7 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF4

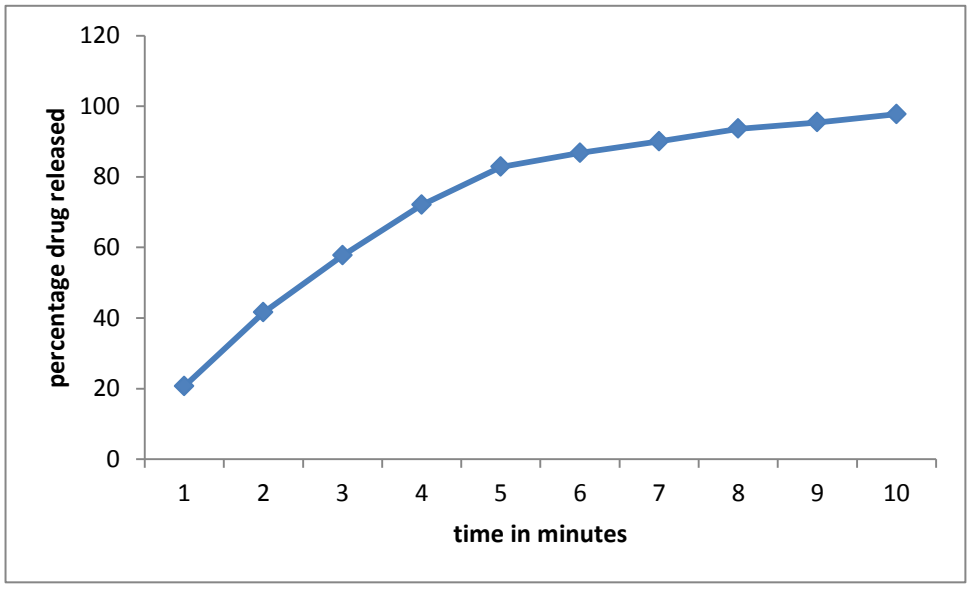


Table No:24 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF5

Time in Minute	% Drug Release ±SD
01	21.78 ± 0.22
02	41.94 ± 0.23
03	59.94 ± 0.22
04	73.62 ± 0.36
05	83.16 ± 0.24
06	88.38 ± 0.14
07	91.98 ± 0.16
08	95.22 ± 0.18
09	96.3 ± 0.16
10	98.46 ± 0.01

Figure No:8 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF5

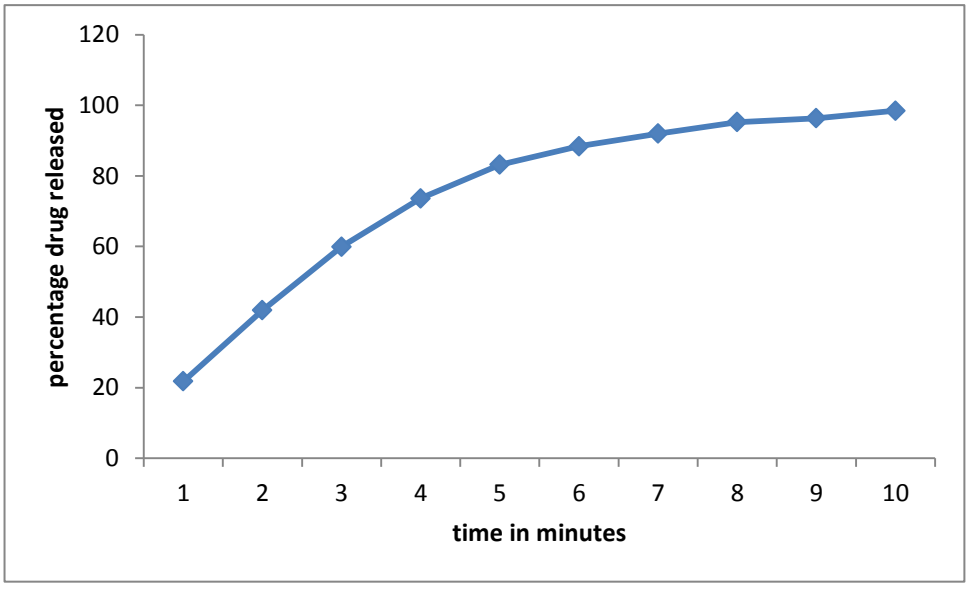


Table No:25 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF6

Time in Minute	% Drug Release ±SD
01	25.92±0.44
02	52.02±0.46
03	74.52±0.12
04	82.56±0.5
05	89.12±0.8
06	91.78±1.0
07	93.24±0.11
08	99.9 ±0.00

FigureNo:9 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF6

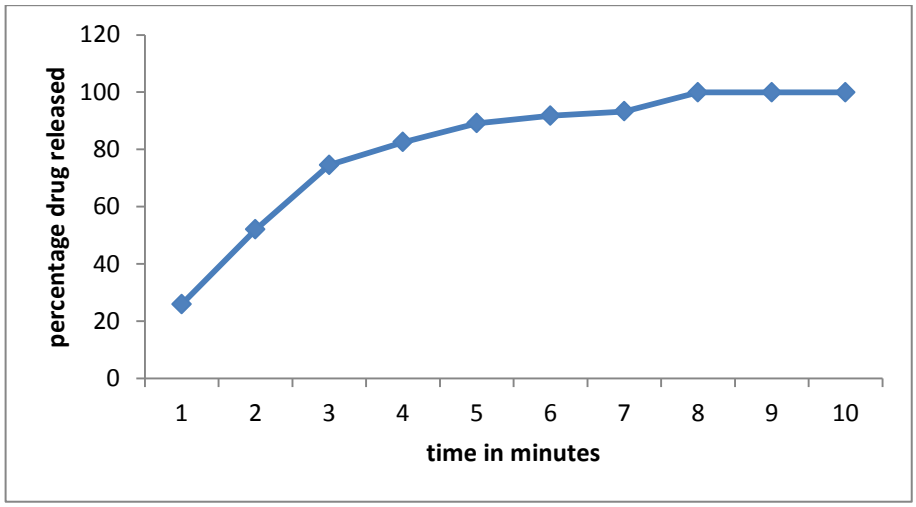


Table No:26 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF7

Time in Minute	% Drug Release ±SD
01	13.86 ± 0.13
02	26.10 ± 0.43
03	43.74 ± 0.65
04	55.80 ± 0.24
05	58.86 ± 0.64
06	63.90 ± 0.12
07	75.96 ± 0.24
08	88.92 ± 0.42
09	93.24 ± 0.31
10	94.14 ± 0.52

Figure No:10 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF7

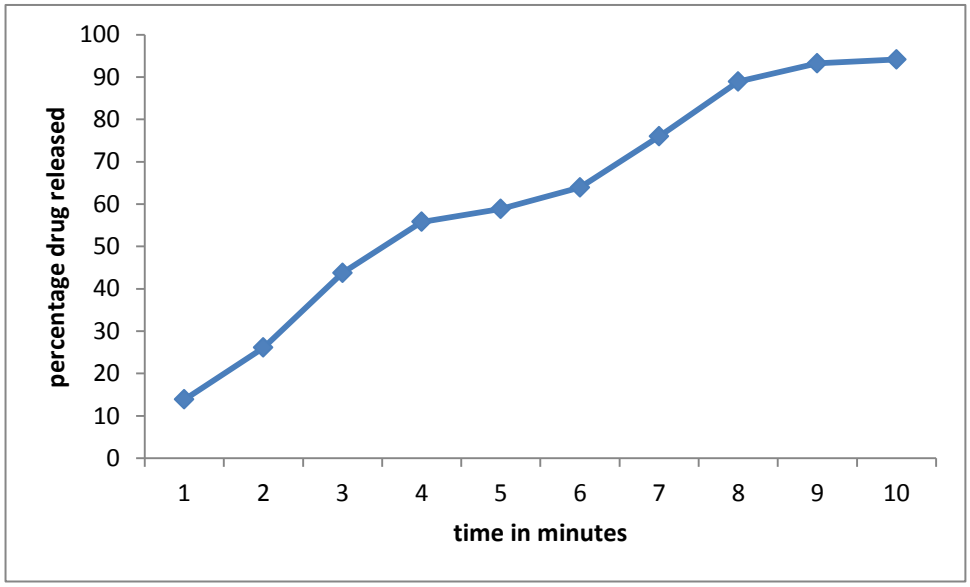


Table No:27 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF8

Time in Minute	% Drug Release ±SD
01	11.88 ± 0.78
02	23.94 ± 0.64
03	34.74 ± 0.44
04	47.16 ± 0.22
05	56.52 ± 0.42
06	68.04 ± 0.12
07	79.38 ± 0.14
08	85.86 ± 0.16
09	91.08 ± 0.99
10	94.68 ± 0.11

Figure No:11 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF8

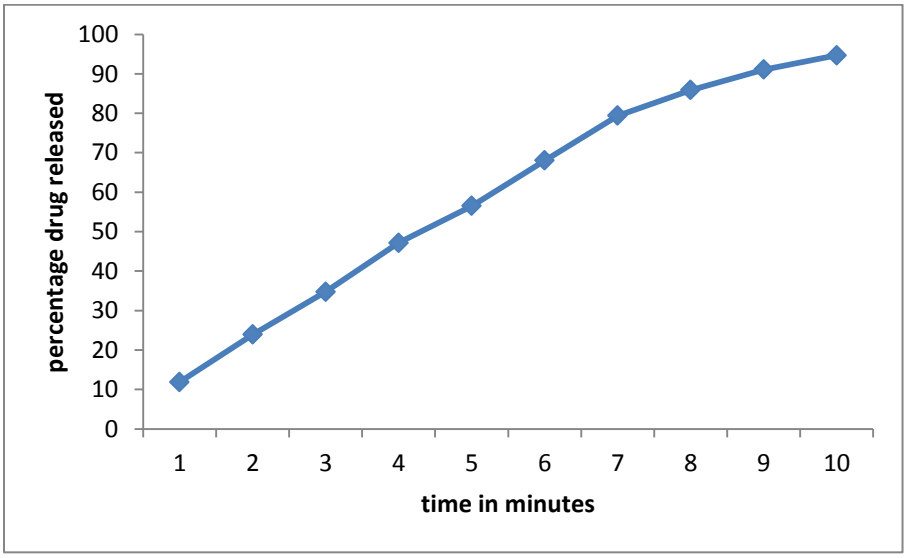


Table No:28 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet DLTF9

Time in Minute	% Drug Release ±SD
01	12.96 ± 0.33
02	25.92 ± 0.36
03	41.76 ± 0.23
04	53.64 ± 0.12
05	68.04 ± 0.12
06	79.38 ± 0.24
07	89.82 ± 0.16
08	93.78 ± 0.18
09	94.32 ± 0.03
10	95.08 ± 0.03

Figure No:12 In-vitro Drug Release of Diltiazem Hydrochloride Fast Dissolving Tablet DLTF9

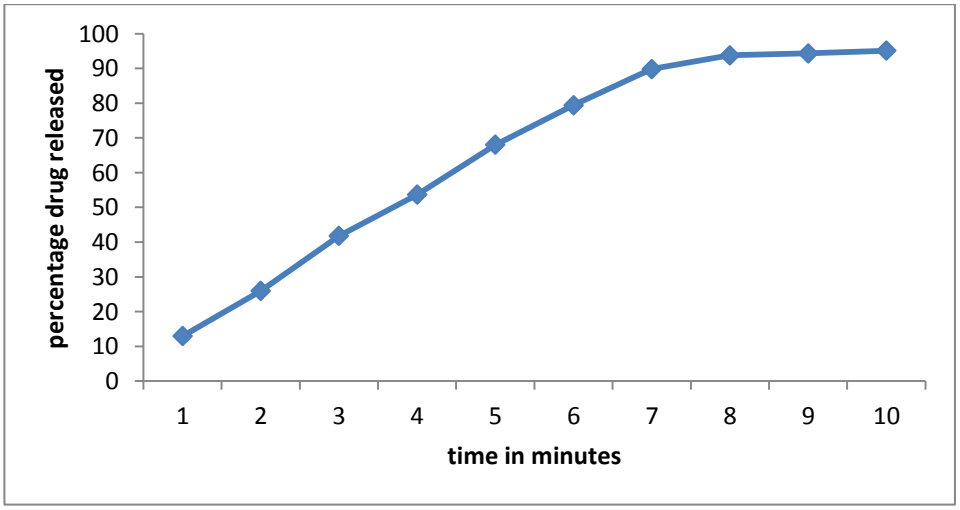


Table No:29 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet $DLTF_1$ to DLTF9

Time	DLTF1 (%)	DLTF2 (%)	DLTF3 (%)	DLTF4 (%)	DLTF5 (%)	DLTF6 (%)	DLTF7 (%)	DLTF8 (%)	DLTF9 (%)
1	15.3±0.12	14.4±0.12	16.56±0.32	20.66±0.22	21.78±0.22	25.92±0.44	13.86±0.13	11.88078	12.96±0.33
2	27.0±0.32	28.8±0.34	34.2 ±0.12	41.58±0.23	41.94±0.23	52.02±0.46	26.10±0.43	23.940.64	25.92±0.36
3	39.78±0.12	39.6±0.56	47.16±0.32	57.78±0.55	59.94±0.22	74.52±0.12	43.74±0.65	34.74± 0.4	41.76±0.23
4	48.95±0.32	48.24±0.4	57.78±0.44	72.0±0.45	73.62±0.36	82.56±0.5	55.80±0.24	47.16± 0.2	53.64±0.12
5	60.12±0.21	61.2±0.66	75.60±0.45	82.80±0.88	83.16±0.24	89.12±0.8	58.86±0.64	56.52± 0.4	68.04±0.12
6	72.90±0.16	72.0±0.68	84.42±0.43	86.76±0.12	88.38±0.14	91.78±1.0	63.90±0.12	68.04± 0.1	79.38±0.24
7	81.9±0.55	82.8±0.43	95.58±0.23	90.00±0.14	91.98±0.16	93.24±0.11	75.96±0.24	79.38± 0.1	89.82±0.16
8	91.8 ±0.34	93.6±0.12	98.82±0.72	93.60±0.16	95.22±0.18	99.9 ±0.00	88.92±0.42	85.86± 0.1	93.78±0.18
9	94.5±0.16	97.02±0.1	98.82±0.12	95.40±0.24	96.3±0.16	99.9 ±0.00	93.24±0.31	91.08± 0.9	94.32±0.03
10	97.02±0.44	98.1±0.01	98.82±0.10	97.74±0.12	98.46±0.01	99.9 ±0.00	94.14±0.52	94.68± 0.1	95.08 ± 0.03

Figure No:13 In-vitro Drug Release of Diltiazem Hydrochloride Fast dissolving Tablet $DLTF_1$ to DLTF9

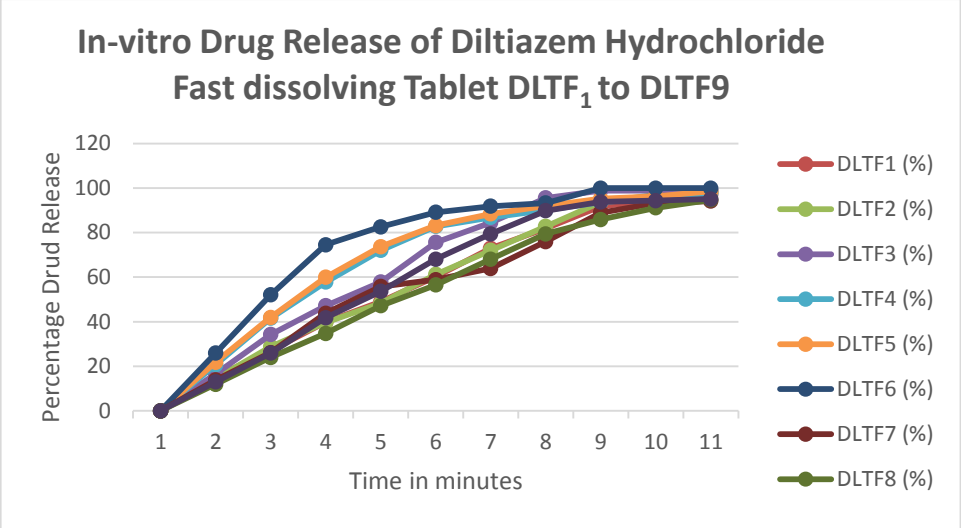


Table No:30 Time required to dissolve 70% of the drug with various Diltiazem Hydrochloride fast dissolving tablet

Sl. No	Formulation Code	T70%(min)
1	$DLTF_1$	4.3
2	$DLTF_2$	4.5
3	$DLTF_3$	4.4
4	$DLTF_4$	3.8
5	$DLTF_5$	3.4
6	$DLTF_6$	2.8
7	$DLTF_7$	6.3
8	$DLTF_8$	6.5
9	$DLTF_9$	5.9

DISCUSSION

Diltiazem Hydrochloride is an angiotensin II receptor antagonist and is used for treatment of essential Hypertension. Croscarmellose sodium, Crospovidone and Sodium starch glycolate were used in different concentration to prepare Fast dissolving tablets.

All the formulations prepared were evaluated for precompression parameters like Bulk density, Tapped density, Angle of Repose and Percentage porosity and are given in table. The angle of repose for all formulation was found to be less than 30° indicating free flowing granules. All the Fast dissolving tablets were found to be elegant without any chipping, capping and sticking.

Fast dissolving tablets so prepared were evaluated for post-compression parameters like Hardness, Friability, Drug content uniformity, weight variation, In-Vitro Dispersion, and In-Vitro Drug release studies. Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of the tablet is in the 2.8-4.0.Kg/cm^2. Tablets of each batch were evaluated for percentage friability. The results suggest that the friability will withstand the rigors which occurred during packing, transportation and shipping etc. Because of their low percentage friability is less than one.

Drug content uniformity study was carried out on the tablets of every batch. The results were showed that there was uniform distribution of the drug throughout the batch.

Drug Polymer Interaction Study:

The probability/possibility of drug polymer interaction was studied by Infrared Spectroscopy using KBr pellet method. The Infrared Spectra of Pure drug Diltiazem Hydrochloride shows a characteristics peak at different frequencies which are as follows.

- Peak at 1667.24cm^{-1} is due to C=O stretching.

- Peak at 1422 cm^{-1} is due to C=N stretching.

- Peak2957.79cm^{-1} is due to C-H stretching.

- Peak at 1582.76 cm^{-1} is due to C=C stretching.

The spectra of the formulation scanned showed following peaks.

- Peak at 1661.73 cm^{-1} is due to C=O stretching.

- Peak at 1438.25 cm^{-1} is due to C=N stretching.

- Peak at 2976.52 cm^{-1} is due to C-H stretching.

When the peaks of the formulation spectra compared with the peak of Diltiazem Hydrochloride Pure Drug Spectra, the characteristic peak of Pure Drug were retained indicating the intactness of the drug in the formulation prepared.

Tablets of every batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately 160mg and it is in between 80 - 320mg. So the permissible limit is ± 7.5%. The results of the test showed that, the tablets were weighing in the range of limit.

Three tablets of each batch were evaluated for In-Vitro Dispersion time test. The results showed that the tablets so prepared were disintegrating and dispersing in the time range of 15 to 110 seconds. The tablets of the batch $DLTF_6$ prepared using 8mg of Crospovidone showed Faster disintegration is within 15 seconds.

Finally, the tablets were evaluated for In-Vitro drug release studies for a period

of 10 minutes and the results were shown in the table 17-28. In all the cases a minimum of 91% of the drug was released within 10 minutes, among the various formulation prepared the batch/tablets of the composition drug Diltiazem Hydrochloride and Crospovidone (8mg) $DLTF_6$ released 99% of the drug within 8 minute.

The improved drug release was mainly due to the increased In-Vitro dispersion which is due to the addition /inclusion of super disintegrant. $t_{70\%}$ value of the drug was released within a minimum time of 3 minutes.

8. SUMMARY

- In some cases of Hypertension Quick onset of action is desired, the Fast dissolving tablets plays a vital role. Fast dissolving tablets have much number of advantages over the conventional tablets like rapid disintegration, faster dissolution, Ease of administration and quick onset of action etc.

- In the present research work, Diltiazem Hydrochloride Fast dissolving tablets were prepared using Super disintegrants like Croscarmellose sodium, Crospovidone and Sodium starch Glycolate in different concentrations by Direct Compression method.

- Diltiazem Hydrochloride Fast dissolving Tablets prepared were evaluated for Pre-compressional and Post-compressional parameters. The Pre-compressional parameters evaluated are bulk density, true density, angle of repose and percent porosity; where the angle of repose of all the formulations is below 30^{o} indicating free flowing.

- Post-compression parameters like Hardness, weight variation, Percent friability, In-Vitro dispersion, Drug content uniformity and In-vitro drug release studies were carried out for all the formulation. All the Formulation given the result within the official limits.

- The drug and excipients interaction study is carried out by taking Infrared Spectrum of Pure drug and Best formulation ($DLTF_6$). There is no change in the structure indicating drug is in intact form.

- Formulation $DLTF_6$ in which Crospovidone (8mg) used, shows less Dissolution time i.e. 15 seconds and highest Dissolution rate 99.9% release in 8 minutes which is considered as Formulation among all.

9. CONCLUSION

The concepts of formulating Fast Dissolving Tablets of Diltiazem Hydrochloride offers a suitable practical approach in serving desired objectives of faster disintegration and dissolution characteristics.

In the present work, Fast dissolving tablets of Diltiazem Hydrochloride were prepared by Direct Compression Technique using Crospovidone, Croscarmellose Sodium starch glycolate as Super disintegrants. All the Fast dissolving tablets of Diltiazem Hydrochloride prepared were subjected to Drug content Uniformity, weight variation, Hardness, Thickness, Friability, Disintegration and Dissolution studies.

- Precompression parameters like Bulk density, Tapped density, percentage Porosity, Angle of repose. The result of angle of repose indicates free flowing characteristics of granules.

- Hardness of the tablet of every batch was in the range of 2.8 to 4.0Kg/cm^2

- Friability of all the tablets was less than 1%.

- Weight variation test results of every batch showed that the weight of each tablet of the batch tested was within the range ±7.5%.

- All the tablets formulated using Croscarmellose sodium, Crospovidone and Sodium starch glycolate disintegrated within 3minutes fulfilling the official limits of the Fast dissolving tablets.

- IR Spectral analysis suggests that the characteristic peaks of the Pure drug Diltiazem Hydrochloride exist in the Spectra of Formulation prepared indicting the intactness of the drug is in intimate contact with the additives. It has not undergone any chemical interaction with the excipients used in

the development of Diltiazem Hydrochloride Fast dissolving tablets.

- Drug content uniformity study results showed that the drug Diltiazem Hydrochloride was uniformly distributed throughout the formulation of every batch.

- t_{70}% value that is the time required /taken to the release 70% of the drug were determined for every batch, the formulation $DLTF_6$ shows every low t_{70}% i.e. 2.6minutes to release 70% of the drug.

- Finally, we can conclude that, among various formulations prepared, the Fast dissolving tablets prepared, using Crospovidone (8mg) $DLTF_6$, disintegrated rapidly and gave highest dissolution of Diltiazem Hydrochloride within a short period of time.

10. REFERENCES

1.Biswajit Basu, Abhishek Bagadiya, Sagar Makwana, Vora Vipul, Devraj Batt, And Abhay Dharamsi. Formulation and Evaluation Of Fast Dissolving Tablets Of Cinnarizine Using Superdisintegrant Blends And Subliming Material. J Adv Pharm Technol Res. 2011 Oct-Dec; 2(4): 266–273.

2. Alok Kumar Gupta, Anuj Mittal and Prof. K. K. Jha. Fast Dissolving Tablet- A Review. Www.Thepharmajournal.Com. Vol. 1 No. 1 2012.

3. *Narendra Sharma et. al.,* Fast Dissolving Tablets As Novel Dosage Form. *Int. J. Res. Dev. Pharm. L. Sci. August-September, 2012, 1(3), 90-104.*

4. Ghosh, T., A. Ghosh, and D. Prasad, *A Review On New Generation Orodispersible Tablets And Its Future Prospective.* International Journal of Pharmacy and Pharmaceutical Sciences, 2011. **3**(1): p. 1.

5. Seager, H., *Drug-delivery Products and the Zydis Fast-dissolving Dosage Form*.* Journal of pharmacy and pharmacology, 1998. **50**(4): p. 375-382.

6. Slowson, M. and S. Slowson, *What to do when patients cannot swallow their medications.* Pharm Times, 1985. **51**: p. 90-96.

7. Rani Thakur, R. and A. Verma, *Mouth Dissolving Tablets- Preparation Characterization and Evaluation:An Overview.* Journal of Pharmacy Research, 2012. **5**(2): p. 993-1000.

8. Dixit, S., et al., *Fast Dissolving Tablet-A Promising Approach For Drug Delivery: A Review.* Journal of Pharmacy Research, 2012. **5**(3): p. 1508-1513.

9. Pahwa, R., et al., *Orally disintegrating tablets-Friendly to pediatrics and geriatrics.* Archives of applied science research, 2010. **2**(2): p. 35-48.

10. Bhowmik, D., et al., *Fast dissolving tablet: An overview.* Journal of chemical and Pharmaceutical Research, 2009. **1**(1): p. 163-177.

11. Gauri, S. and G. Kumar, *Fast dissolving drug delivery and its technologies.* The pharma innovation, 2012. **1**(2): p. 34-39.

12. Prabhakar, V., et al., *Fast Dissolving Tablets: An Overview.* International Journal of Pharmaceutical Sciences: Review and Research, 2012. **16**(1): p. 17.

13. Shinde, G. and B.S. Rathinaraj, *New generation of orodispersible tablets: recent advances and future propects.* International Journal of Advances in Pharmaceutical Sciences, 2011. **2**(1).

14. Bandari, S., et al., *Orodispersible tablets: An overview.* Asian journal of pharmaceutics, 2008. **2**(1): p. 2.

15. Shukla, D., et al., *Mouth dissolving tablets I: An overview of formulation technology.* Sci Pharm, 2009. **77**(2): p. 309-326.

16. Bandari, S., et al., *Orodispersible tablets: An overview.* Asian journal of pharmaceutics, 2008. **2**(1): p. 2.

17. Pahwa, R. and N. Gupta, *Superdisintegrants in the Development of Orally Disintegrating Tablets: A Review.* Int. J. Pharm. Sci. Res, 2011. **2**: p. 2767-2780.

18. Harmon, T.M. and E. MBA, *Orally Disintegrating Tablets: A Valuable Life Cycle Management Strategy.* Pharmaceutical commerce, March, 2007.

19. Kuchekar, B., A.C. Badhan, and H. Mahajan, *Mouth dissolving tablets: A novel drug delivery system.* Pharma times, 2003. **35**(7).

20. Parakh SR, Gothoskar AV.A review of mouth dissolving tablet technologies. Pharm Technol. 2003; 27: 92-100.

21. Kuchekar B S, Atul C Badhan, Mahajan HS.Mouth dissolving tablets: a novel drug delivery system.Pharma Times. 2003; 35: 7–9.

22. Corveleyn S, Remon JP.Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorothiazideas a model drug.Int J Pharm. 1997; 152: 215–225.doi:10.1016/S0378-5173 (97) 00092-6

23. Corveleyn S, Remon JP.Freeze-dried disintegrating tablets.US Patent 6,010,719. 2000 Jan 4.

24. Gregory GKE, Ho D.Pharmaceutical dosage form packages.US Patent 4,305,502. 1981 Dec 15.

25. Gregory GKE, Peach JM, Du Mayna JD.Articles for carrying chemicals.US Patent 4,371,516. 1983 Feb 1.

26. Yarwood R, Kearney P, Thompson A.Process for preparing solid pharmaceutical dosage forms. US Patent 5,738,875. 1998 Apr 14.

27. Devrajan PV, Gore SP.Melt-in-mouth tablets: innovative oral drug delivery system.Express Pharm Pulse. 2000; 7: 16-–6.

28. Zydis® fast dissolve technology- Optimize your product’s market potential in less than 3 seconds.http://www.catalent.com/drug/oral/zydis/zydis.pdf

29. Gole D, Savall T, Lyou-fu G, Dale W, Paul K, Davies JD.Taste-masked resinate and preparation thereof.US Patent application 20050036977. 2005 Feb 17.

30. Pebley WS, Jager NE, Thompson SJ.Rapidly disintegrating tablet.US Patent 5, 298, 261. 1994 March 29.

31. D. Shukla *et al.* Mouth Dissolving Tablets I: An Overview of Formulation Technology. Sci Pharm. 2009; 76; 309–326.

32.Neena Bedi et.al, Formulation And Evaluation Of Mouth Dissolving Tablets Of Oxcarbazepine .Int. J. of Pharmacy and Pharmaceutical Sciences, Vol. 1, Suppl 1, Nov.-Dec. 2009.

33.B.P.Patel et.al, Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine. Indian J Pharm Sci. 2010 Jul-Aug; 72(4): 522–525.

34. Sharma V et.al, Iran J Pharm Res. Formulation and evaluation of taste masked mouth dissolving tablets of levocetirizine hydrochloride.2012 Spring;11(2):457-63.

35. Goel H et.al,Orally disintegrating systems: innovations in formulation and technology.Recent Pat Drug Deliv Formul. 2008;2(3):258-74.

36. Chachin M et.al.Pharmacological and clinical profile of telmisartan, a selective angiotensin II type-1 receptor blocker. Nihon Yakurigaku Zasshi. 2004 Jul;124(1):31-9.

37. Chaudhari PD, Chaudhari SP, Kolhes R, Dave KV ,More DM. Formulation and evaluation fast dissolving tablets of famotidine. Indian Drugs. 2005 Oct 10; 42(10): 641-9.

38. Takao M, Yoshinori M, Takeshi Y, Katsuhide T. Formulation design of novel fast-disintegrating tablets. Int J Pharm. 2005 Oct 27; 306: 83-90.

39. Zhao NA, Larry LA. Studied functionality comparison of three classes of

superdisintegrants in promoting aspirin tablet disintegration and dissolution. AAPS Pharm Sci Tech. 2005 Dec 12; 6(4): 634-40.

40. Desai SA, Kharade SV, Petkar KC, Kuchekar BS. Orodissolving tablets of promethazine hydrochloride. Indian J Pharm Educ Res. 2006 July; 40(3): 172-4.

41. Nandgude TD, SaifeeM, Bhise KS.Formulation and evaluation of fast disintegrating tablets of diphenhydramine tannate. Asian. J. Pharm.2006 Oct; 1(1): 41-5.

42. Udhav S, Bagul .Manufacturing Technologies for Mouth Dissolving Tablets.Phrmainfo. net.2006:1-7.

43. Shishu , Bhatti A, Singh T. Preparation of tablets rapidly disintegrating in saliva containing bitter taste-asked granules by compression method. Indian. J. Pharm. sci. 2007 Jan 15; 69 (1): 80-4.

44. Sharma S, Gupta GD, Jain CP, Naruka PS. Development and evaluation of carvedilol fast dissolving tablets using superdisintegrates and solid dispersion technique. The Pharma Review. 2007 Aug: 164-8.

45. Chaudhari PD, Chaudhari SP, Lanke SD, Patel N. Formulation and in vitro evaluation of taste masked Orodispersible dosage form of lavocetirizine dihydrochloride. Indian J Pharm Educ Res. 2007 Oct; 42(4): 319-7.

46. Raghu NB, Rao L, Amin PD.Studies of taste masking drotaverine hydrochloride and its formulation. Indian Drugs. 2007 Nov; 44(11): 848-1.

47. Swamy PV, Areefulla SH, Shirand SB, Gandra S, Prashant B.Orodispersible tablets of meloxicam using disintegrant blend for improved efficacy. Indian J Pharm Sci. 2007 Nov; 69(6): 836-40.

48. He X, Barone MR, Marsac PJ, Sperry DC. Development of rapidly dispersing tablet of a poorly wettable compound –formulation DOE and mechanistic study of effect of formulation excipient on wetting of celecoxib.2008 Jan 22;353:176-6.

49. Adamo F, Valentina B, Ceschel GC, Celestino R. Fast dispersible/ slow releasing ibuprofen tablets. Eur J Pharm Bio. 2008 Jan; 69: 331.

50. Shetty MC, Prasad DV, Gupta RM. development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrants. Indian J Pharm Sci.

51. Mulla JA, Dasankoppa FS, Villas GJ, Sholapur HP. Fast dissolving tablet of promethazine: A novel oral formulation for the treatment of fractionated radiotherapy induced nausea and emesis. Indian Drugs. 2008 Apr 24; 45(4): 314-7.

52. Rampure MV, Raju SA, Shirsand SB, Swamy PV and Nagendrakumar.Rapidly disintegrating oral tablets of alfuzosin. The Pharma Review. 2008 Aug: 140-2.

53. https://www.drugs.com/

54. Rawe RC, Sheskey PG, Owen SC. Handbook of Pharmaceutical Excipient, 5th Edn, 2006: pp 202,701,132,385,429,767.

55. Handbook of Pharmaceutical Excipients, 2nd Edition (Wade A, Jsweller P, Eds). The American Pharmaceutical Association, Washington, 1994.

56. Larry L augsburger, Albert W Brezecko and Umang Shahia.Encyclopedia of Pharmaceutical Technology, 2nd Ed., Vol. 3, 2002. P.No 2623.

57. M.Sunitha Reddy*, Niveditha Kore And S. Muhammad Fazal Ul Haq.Formulation and Evaluation of Diltiazem Hcl Fast Dissolving Tablets Using Different Co-Processed Excipients By Direct Compression Method. International Journal of Pharmaceutical Sciences and Research. *2017; Vol. 8(7): 2853-2861*

58. K.V.Chaudhari, P.D. Gaikwad, V.H Bankar, S.P. Pawar. Development and Validation for simultaneous estimation of Diltiazem Hydrochloride and Atorvastatin Calcium in bulk and tablet dosage form. *International Journal of Pharmacy and Technology* June2010:Vol.2.P.No 255-264.