DEVELOPMENT AND CHARACTERIZATION OF ORO DISPERSIBLE TABLETS OF DILTIAZEM HYDROCHLORIDE

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K.M.COLLEGE OF PHARMACY

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APRIL-2014

DEDICATED TO MY BELOVED PARENTS,WIFE AND FRIENDS

CERTIFICATE

This is certify that the dissertation entitled "**DEVELOPMENT AND CHARACTERIZATION OF ORO DISPERSIBLE TABLETS OF DILTIAZEM HYDROCHLORIDE"** submitted by **Mr. AZHAGUMANI D**, (**Reg.No.261210101**) in partial fulfilment for the award of Master of Pharmacy in Pharmaceutics under the Tamilnadu Dr.M.G.R Medical University, Chennai, done at **K.M.COLLEGE OF PHARMACY**, Madurai-625107, is a bonafide work carried out by his under my guidance and supervision during the academic year **APRIL-2014.** The dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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"The act of thanks giving does not exhibit ones sense of gratitude ,but the true tendency of leading a helping hand during emergency and the fact that every work has thousands of hands behind".

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AZHAGUMANI D

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INTRODUCTION

1. INTRODUCTION

The oral route of drug administration is the most important method for administering drugs for systemic effects. Except in certain cases the parenteral route is not routinely used for self administration, e.g. insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects. The parenteral route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless it is probable that at least 90% of all drugs used to provide systemic effects are administered by the oral route. When a new drug is discovered one of the first questions, a pharmaceutical company asks is whether or not the drug can be effectively administered forits intended effect by the oral route. Of drugs that are administered orally, solid oral dosage forms represent the preferred class of products. Tablets and capsules represent unit dosage forms in which usual dose of a drug has been accurately placed.

1.1 TABLETS: [1]

Tablets are solid preparation each containing a single dose of one or more active ingredients and are obtained by compressing uniform volumes of particles. The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the desired location and to have its chemical integrity protected to the point.

Tablets may vary in size, shape, weight, hardness, thickness, and disintegration characteristics and in other aspects, depending upon the intended use of the tablets and their method of manufacture.

1.2 TYPES OF TABLETS

1. Tablets ingested orally. e.g. standard compressed tablets, enteric coated tablets, delayed release tablets and mouth dissolving tablets
2. Tablets used in the oral cavity. e.g. buccal and sublingual tablets,
3. Tablets used to prepare solution. e.g. effervescent tablets
4. Tablets administered through other routes. e.g. vaginal tablets and implants

Recently Oro dispersible Drug Delivery Systems have started gaining popularity and acceptance as New Drug Delivery Systems.[2]

Since the development cost of a new chemical entity is very high, the Pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects.

Dysphagia (Difficulty in Swallowing) is seen to afflict nearly 35% of the general population and is common with all age groups. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, Aids, Head and neck radiation therapy and other neurological disorders including Cerebral palsy.[3]

Swallowing of solid dosage forms like Tablets / Capsules and improper dosing of suspension / emulsion may precipitate patient noncompliance with young individuals because of under developed muscular and nervous systems, psychiatric patients, non-cooperative patients and travellers who have little access to water.[4]

The approach to overcome these problems can be done by Formulating Oro dispersible Tablets.

1.3 HISTORICAL DEVELOPMENT OF FAST DISSOLVING TABLETS

Difficulty in swallowing (Dysphagia) is a common problem in all age groups, especially the elderly and pediatrics, because of physiological changes associated with these age groups. It is common to see those afflicted carrying a small device with them, which is used for crushing tablets, enabling easy ingestion. Other categories that experience problems using conventional oral dosage forms include are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack and coughing. Sometimes, it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of a novel type of solid oral dosage form called mouth-dissolving tablets, which disintegrate and dissolve rapidly in saliva without the need of the water. They are also known as Oro dispersible tablets, melt-in-mouth tablets, rapimelts, porous tablets, oro-dispersible, quick dissolving or rapidly disintegrating tablets.

Since 1986 when the Zydis® lyophilized, fast-dissolving dosage forms were first introduced, a number of other fast-dissolving formulations were developed, and the

technology is still improving. Using the concept of Gregory et al., Scherer has patented the Zydis technology. Using the freeze-drying process, this technology converts the mixture of active ingredient and water dispersible carrier materials into open matrix network that disintegrates rapidly.

The network is highly porous solid form, which allows rapid penetration of liquid and facilitates quick disintegration of the dosage unit. The freeze-drying approach produces the fastest dissolving tablets, but the process is expensive, and the resulting tablets are mechanically weak. The other most widely used method to manufacture these tablets is via regular compression that can produce tablets with higher mechanical strengths. The disintegration or melting time of the compressed tablets is not as fast as the freeze-dried dosage forms, but the compressed tablets provide many advantages, such as high mechanical strength facilitating their handling and processing. The technology of the compressed tablets is also making major improvements, producing tablets that can melt within several seconds in the mouth.

The fast-melting tablets present the combined benefits of a liquid formulation and a solid dosage form. They are easy to handle and ingestible as a liquid dosage form. An ideal fast-melting tablet should possess the following characteristics. The tablet should melt or disintegrate in the mouth within 60 seconds. The tablets should also be mechanically strong for easier handling, and the production cost should be similar to that of conventional tablets. The use of existing tablet machinery and procedures dictates the low production cost and has another advantage of producing mechanically strong tablets. The ideal fast-melting tablets should also be less sensitive to humidity, thus allowing multi-tablet packaging.

1.4 ORO DISPERSIBLE TABLETS[5]

Oro dispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed.

1.4.1 DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM[6]

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids .In dysphagia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.

- Swallowing of solid dosage form like tablet and capsules may produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphagia.
- Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.
- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.
- Cost of products is main factor as parenteral formulations are most costly and discomfort.

1.4.2 ADVANTAGES OF ORO DISPERSIBLE DOSAGE FORM[7]

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

- Requires no water intake.
- Quick disintegration and dissolution of dosage form.
- Overcomes unacceptable taste of the drugs.
- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
- Allows high drug loading.
- Faster onset of action.
- Convenient - ideal dosage form when fast relief required, for example, pain relief, migraine, or allergy.
- New business opportunities; line extension exclusivity of product promotion and patient life extension.

1.4.3 Requirements of Oro dispersible Tablets (ODT's) [2]

1. **Ease of Administration:**

   It should be easy to administer and handle for geriatrics and paediatrics.

2. **Taste of the Medicament:**

   It should include substances that would mask the bitter taste of the medicament, because the tablet dissolve or disintegrate in patient's mouth thus releasing the active ingredients which would come in contact with the taste buds and hence taste masking of the drug becomes critical to patients compliance.

3. **Hygroscopicity:**

   Since several Oro dispersible dosage forms are hygroscopic, they cannot maintain physical integrity under normal condition form humidity which calls for specialized product packaging.

4. **Friability:**

   In order to allow ODT's to dissolve in the mouth, they are made of either very porous and soft moulded 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 packing.

5. **Mouth feel:** Presence of any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. In such cases, flavours can be used which provides improved mouth fell perception.

6. Requires no water intake for administration.
7. They should allow high Drug loading.
8. They should leave minimal or no residue in the Mouth.
9. They should be manufactured using conventional tablets processing and packaging equipment at low cost.

1.4.4 Salient Features of Oro dispersible Tablets (ODT's)[2, 8]

Ease of administration for patients who are mentally ill, disabled and unco-operative.

1. No risk of choking.
2. Requires no water intake.
3. Overcomes unacceptable taste of the Drugs.
4. Allows high drug loading.
5. It leaves minimal or no residue in the mouth after administration.
6. Quick disintegration and dissolution of the dosage form.
7. Facilitates faster onset of therapeutic action.
8. Improved Bioavailability can be achieved.
9. Avoids First Pass Metabolism due to Pregastric absorption.
10. Enhanced Patient compliance.
11. Ability to provide advantages of liquid medication in the form of solid preparation.
12. Adaptable and ameanable to existing processing and packaging machinery.
13. Cost effective.

14. Rapid drug therapy intervention is possible.
15. Free of the risk of suffocation due to physical obstruction when swallowed thus offering improved safety.
16. Enhanced stability.
17. Optimum versatility with low manufacturing cost.
18. Ideal dosage form for Peadiatric and geriatric patients.
19. Promote New Business Opportunities like Product differentiation, Product – promotion, Patient extension and life cycle management.

1.4.5 Biopharmaceutical Considerations for Oro dispersible Tablets [4]

When a new drug delivery system is introduced, Biopharmaceutical factors like Metabolism and Excretion must be considered.

Pharmacokinetics:

After absorption, the drug attains therapeutic level and elicits pharmacological effect. So both rate and extent of absorption is important.

In conventional dosage forms, there is delay in disintegration and dissolution while ODT rapidly disintegrates in oral cavity and dissolution is fast.

Due to disintegration of ODT in mouth, absorption is started from mouth, phargnx and oesophagus. Some factors like age, gastro intestinal pH, blood flow through GIT are taken into consideration because elderly be considered as seperate unique medicate population.

1.Drug Disintegration:

It depends on factors like

- Tissue permeability
- Perfusion rate
- Binding of drug to tissues
- Disease state
- Drug interactions

In Geriatric patients decrease in lean body mass and total body water result in decreased volume of distribution (V_d) of lipid soluble drugs.

2. Duration and Intensity of action:

It depends on factors like

- Bio transformation
- Decrease in liver volume
- Regional blood flow to liver

Decrease in liver volume and regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half life of renally excreted drugs increased.

1.4.6 Bioavailability of Oro dispersible Tablets (ODT's) [9]

Disintegration and dissolution of ODT in oral cavity depends upon various factors like

- Method of manufacture
- Ingredients used for taste masking
- Physicochemical properties of the drug

While manufacture, batch to batch consistency should be ensured, patient's factors are also involved such as presence of amount of saliva in oral cavity and the extent of tongue movements etc.,

The disintegration time *in-vivo* can vary greatly depending on how the patient processes the drug product. The patient who actively moves the drug product with the tongue around the oral cavity experiences shortest disintegration time.

1.5 General Properties Of ODT's [10]

1) Excellent Mouth Feel

Disintegrants has narrow particle size distribution that imparts a smooth mouth feel to quick dissolve. Large particles tend to result in a gritty mouth feel that many consumers find objectionable. Therefore, smaller particles which are not felt in the mouth are preferred. These benefits are especially important in ODT.

2) Taste Masking [8]

Table: 1 Approaches have been taken to mask the unpleasant taste of drugs

Sensory approaches	* Using flavoring & sweetening agents * Inhibiting bitterness * Numbing of taste buds
Complexation & adsorption	* Complexation with Ion-exchange resins * Formation of Inclusion complexes with cyclodextrin derivatives * Adsorption of drugs onto clays or other adsorbents * Wax embedding of drugs
Chemical approaches	* Formation of Prodrugs * Formation of different Salts
Barrier approaches	* Using Viscosity modifiers * Using Emulsions * Using Liposomes * Using Microspheres

3.Fast Disintegration

When introduced into water, disintegrant which is used in ODT'S, quickly wicks water into its capillaries and swells which results in rapid disintegration. The disintegrant particles are granular and highly porous. This porous particle morphology allows for better wicking of liquid into the particle and tablet. This sugar disintegrant polymers does not form gels which could retard drug release or result in a gummy texture.

4) Tablet Hardness

To achieve rapid disintegration, ODT's are often porous and/or have low hardness and high friability. As a result, there can be a high level of tablet breakage unless special packaging systems are used. Therefore the challenge is to develop formulations with rapid disintegration and robust physical properties. Due to its unique particle morphology, the super disintegrant is a highly compressible material that increases tablet hardness and reduces friability.

ODT'S system comprises a low moisture that is convenient for doing, suitable for labelling and easy packing, handling and application. At the same time the rapid hydration rate facilitates an almost immediate softening of the ODT'S upon application in the oral cavity. The friability and strength of the tablet may be selected/modified to facilitate automatic rewinding, die punching and packaging during manufacturing.

1.6 SUPER DISINTEGRENTS[11]

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

Table: 2

List of super disintegrants and their mechanism of action

Name of disintegrant	Brand Name	Concentration (%)	Mechanism of action
Sodium Starch Glycolate	Explotab, Primogel	2-8%	Swelling
Micro Crystalline Cellulose	Avicel, Celex	2-15%	Water wicking
Cross linked povidone	Crospovidone	2-5%	Water wicking, swelling
Low substituted Hydroxy Propyl Cellulose	LH-11, LH-12 (Grades)	1-5%	Swelling
Crosscaramellose sodium	Ac-Di-Sol	1-3% - direct compression 2-4% - wet granulation	Wicking and swelling
Pre gelatinized Starch	Starch 1500	1-20%	Swelling

Advantages:

1. Effective in lower concentrations.
2. Less effect on compressibility and flow ability.

1.7 MECHANISM OF ACTION:

There are four major mechanisms for tablets disintegration as follows

1. Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart(Figure 1). Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

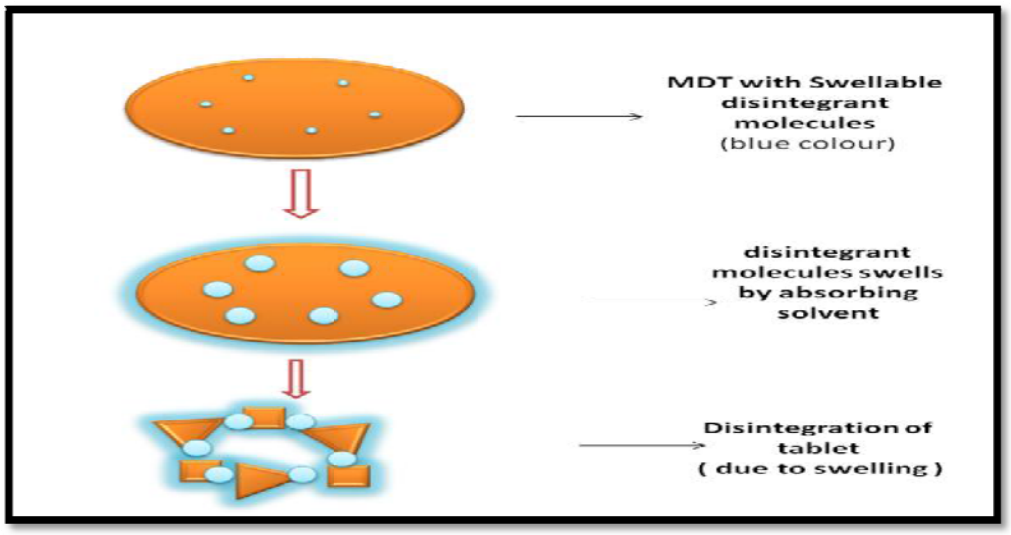

Figure 1: Swelling Mechanism of a Disintegrant

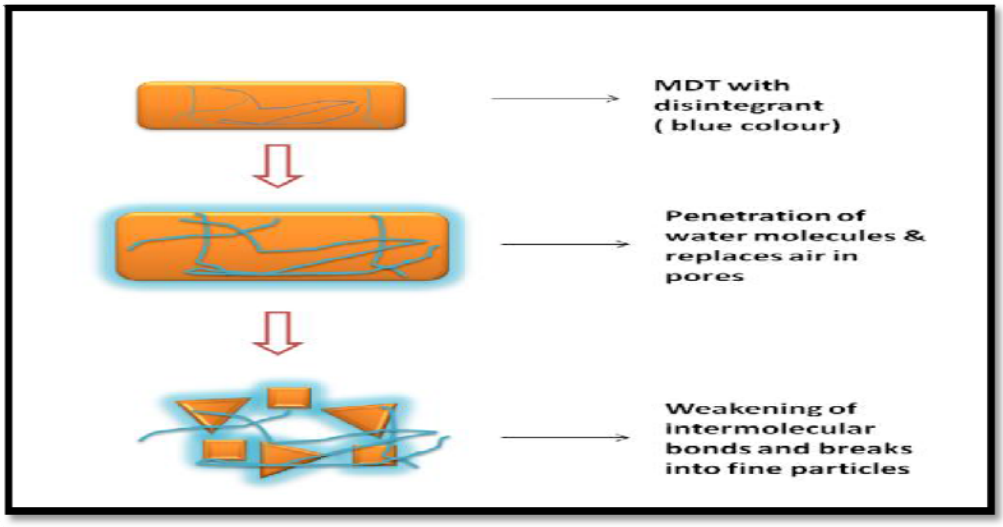

Figure 2: Wicking mechanism

2. Porosity and capillary action (Wicking):

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness &compressibility) themselves act to enhance porosity and provide these pathways into the tablet (Figure 2).Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

3. Disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with “non-swellable” disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets (Figure 3). The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Deformation:

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet (Figure 4). Starch grains are generally thought to be “elastic” in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be “energy rich” with this energy being released upon exposed to water.

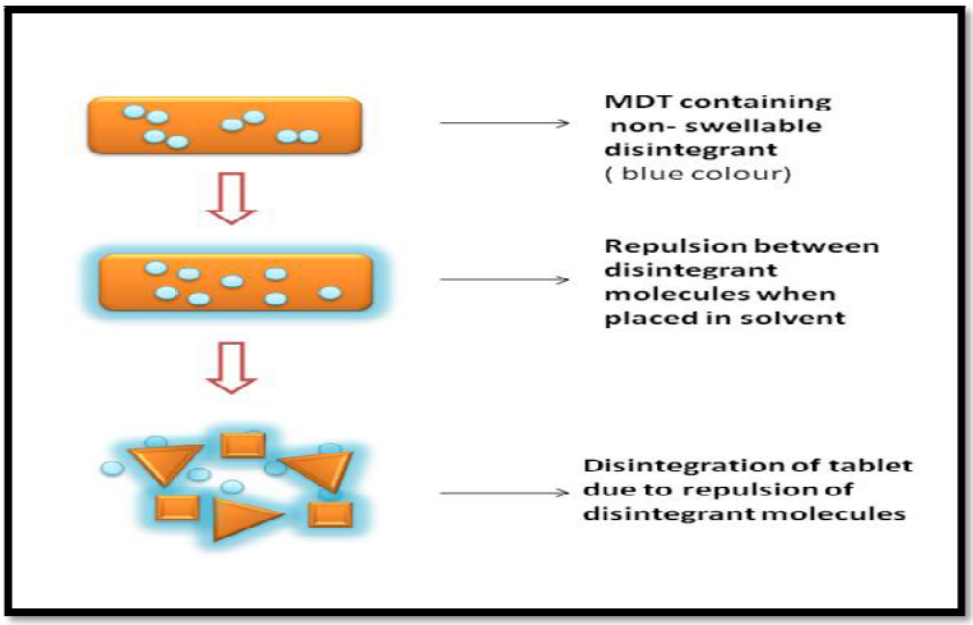

Figure 3: Repulsion mechanism of Disintegrant

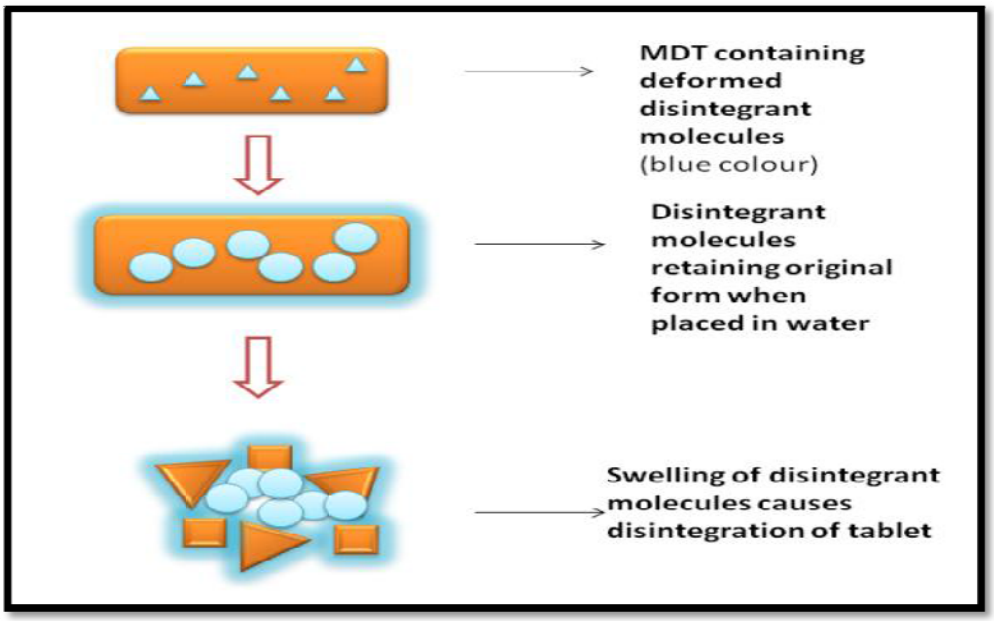

Figure 4: Deformation mechanism of Disintegrant

Mechanism of Drug Release from ODT's [9]

The drug releases from the ODT'S due to the action of super disintegrants like cros povidone, cros carmellose sodium, sodium Starch glycollate and polyvinyl pyrrolidone in the formulation.

superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. As an effect of swelling of superdisintegrant, the wetted surface of the carrier increases, which promotes wettability and dispersibility of the system and thereby enhance the disintegration and dissolution.

1.8 Basic Approaches Of Designing ODT's [1, 2, 4]

To ensure the tablets Oro dispersible attribute, water must quickly egress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. This can be achieved by

a. Maximizing the porous structure of the tablet matrix
b. Incorporating the appropriate disintegrating agent
c. Using highly water soluble excipients in the formulation.

Conventional Techniques

1) Tablet moulding
2) Direct compression
3) Spray drying
4) Sublimation
5) Freeze drying (or) Lyophilization
6) Mass extrusion
7) Taste masking
8) Use of sugar based excipients

1) Tablet Moulding:

Moulded tablets are usually prepared by different moulding techniques.

A. Compression moulding:

The powder mixture previously moistened with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

B. Heat moulding:

The moulded forms can be obtained directly from a molten matrix in which the drug is dispersed / dissolved.

C. No vacuum Lyophilization:

In this process at standard pressure the solvent from a drug solution or suspension is evaporated.

Tablets produced by moulding are solid dispersion. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases is absorbed through the mucosal lining of the mouth.[1] The tablets prepared by moulding offer more rapid disintegration and improved taste as the dispersion matrix is made from water soluble excipients (sugars).[4]

Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.[1]

2) Direct Compression

It is the easiest way to manufacture tablets. Low manufacturing cost, conventional equipments, commonly available excipients and a limited number of processing steps lead this technique to be a preferable one. High doses can be accommodated and final weight of tablet can easily exceed that of other production methods.

Addition of disintegrants in ODT's leads to quick disintegration of tablets and hence improves dissolution. In many Oro dispersible tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution.

The disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents.The optimum concentration of superdisintegrant can be selected according to critical concentration of the disintegrant. Below this concentration the tablet disintegration time is inversely proportional to the concentration of superdisintegrant, whereas if concentration of superdisintegrant incorporated in tablet is above the critical concentration, the disintegration time remains approximately constant or even increases.

3) Spray Drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during the process. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredient and compressed into tablet, which disintegrated in less than 20 seconds when immersed in an aqueous medium.

4) Sublimation

Compressed tablets composed of water soluble excipients as tablet matrix often do not dissolve rapidly due to low porosity. ODT'S having porous structure and sufficient mechanical strength, which dissolves quickly have been developed using urea, ammonium carbonate, camphor, naphthalene, tablet excipients and finally compressed the blend. Porous structure is generated by sublimation of volatile oil.

5) Freeze Drying / Lyophilization

A process in which water is sublimated from the product after freezing is called Freeze drying.

Lyophilization results in preparations which are highly porous with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

The use of Freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

6) Mass Extrusion

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

7) Taste Masking:

Taste masking is an essential requirement for Melt-in-Mouth Tablets for commercial success.

Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers like Eudragit E, Eudragit L-55 and Eudragit RL.

8) Use Of Sugar Based Excipients

Sugar based excipients (eg : sorbitol, mannitol, dextrose, xylitol, fructose etc) have been used as bulk agents. Aqueous solubility and sweetness impart pleasing mouth feel and good taste masking. But no sugar based materials have fast dissolution rate and good compressibility and/or compactibility. However technologies are developed to make use of the sugar based excipients in the design of ODT's.

1.9 PATENTED TECHNOLOGIES [1, 4, 5]

1) Zydis Technology:

Zydis is a unique freeze dried oral solid dosage form that can be swallowed without water as it dissolves instantly on tongue in less than 3 seconds. A zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin, dextran or alginates. Water is used during the process to produce porous units for rapid disintegration. The zydis formulation is also self preserving because the final water concentration in the freeze dried product is too low to allow for microbial growth.

A major claim of the zydis product is increased bioavailability because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of Pregastric absorption from this formulation.

The product is very light weight and fragile and must be dispensed in a special peelable blister pack. The zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water and is very sensitive to degradation at humidities greater than 65%.

2) Orasolv Technology

It is CIMA lab's first Oro dispersible formulation. The tablets are prepared by direct compression technique at low compression force inorder to minimize oral disintegration and

dissolution time. Orasolv technology is an example of slightly effervescent tablet that rapidly dissolves in mouth. The active medicament is taste masked and dispersed in saliva due to the action of effervescent agents. It provides a pleasant sensation of effervescence in mouth of the patient. Their disintegration time is less than 30 seconds. The major disadvantage of orasolv technology is its low mechanical strength. The tablets produced are soft and friable and need to be packed in specially designed pack.

3) Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. It is an appropriate technology for products requiring low amounts of active ingredients.

4) Wowtab Technology

It is patented by Yamanouchi. Wow means “without water” In this process, the active ingredient is mixed with a low mouldability saccharide and granulated with
a high mouldability saccharide and compressed to obtain a rapidly melting strong tablet. The wowtab product dissolves quickly in 15 seconds or less.

5) Flash Dose Technology (Ceform Technology)

It is patented by Fusiz laboratories. It utilizes a unique spinning mechanism to produce a floss like crystalline structure, much like cotton candy. This crystalline sugar can incorporate the active drug then compressed into a tablet. The final product has a very high surface area for dissolution. Once placed on the tongue it disperses and dissolves quickly.

6) Flash Tab Technology

It is patented by Prographarm labs. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in mouth within one minute. This technology utilizes the conventional tabletting technology.

7) Oraquick Technology

The Oraquick Oro dispersible tablet formulation utilizes a patented taste masking technology by K.V. Pharmaceutical company, who claim that its taste masking technology i.e Microsphere technology (Micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Tablets with significant mechanical strength without disrupting taste masking are obtained after compression. Oraquick claims quick dissolution in a matter of seconds with good taste masking.

8) Quick-Dis Technology

It is a novel intra oral Oro dispersible drug delivery system invented by Lavipharm Laboratories. It is a thin, flexible and quick dissolving film placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. It can be packed in unit dose pouches to multiple dose blister packages.

For a quick diss film of thickness 2mm, the disintegration time is 5-10 seconds and the dissolving time is around 30 seconds in aqueous media. The typical release profile of an active ingredient exhibited by this system is 50% released within 30 seconds and 95% within 1 minute.

9) Nanocrystal Technology

Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter which are produced by milling the drug substance using wet milling technique. This technology provides for cost effective manufacturing processes that utilize conventional, scalable unit operations, wide range of doses (upto 200mg of API per unit), use of conventional, compendial inactive components and employment of non moisture sensitive inactives.

Nano crystal colloidal dispersions of drug substance are combined with water soluble ingredients, filled into blisters and lyophilized. The resultant wafers are remarkably robust yet dissolve in very small quantities of water in seconds.

1.10 LIST OF PRODUCTS CATEGORIZED BY TECHNOLOGY

ZYDIS PRODUCTS[12]

Claritin Reditab

Micronized loratadine (10 mg), citric acid, gelatin, mannitol, mint flavor.

Feldene Melt

Piroxicam (10 or 20 mg), gelatin, mannitol, aspartame, citric anhydrous

Maxalt-MLT

Rizatriptan (5 or 10 mg), gelatin, mannitol, aspartame, peppermint flavor

Pepcid RPD

Famotidine (20 or 40 mg), gelatin, mannitol, aspartame

ZyprexaZydis

Olanzapine (5, 10, 15 or 20 mg), gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium

Zofran ODT

Ondansetron (4 or 8mg), aspartame, gelatin, mannitol, methlparaben sodium, propylparaben sodium, strawberry flavour.

Dimetapp Quick Dissolve Chidern's Cold and Allergy Tablets (OTC)

Active ingredient: Loratadine.

ORASOLV PRODUCTS

RemeronSoltab

Mirtazepine (15, 30, or 45 mg), aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavor.

TempraFirstTabs

Acetaminophen (80 or 160 mg), inactive ingredients including mannitol (currently available in Canada).

DURASOLV PRODUCTS

NuLev

Hyoscyamine sulfate (0.125 mg), aspartame, colloidal silicon dioxide, crospovidone, mint flavoring, magnesium stearate, mannitol, microcrystalline cellulose

Zomig ZMT

*Zolmitriptan (2.5 mg),*mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavor

Triaminic Softchew(OTC)

Active ingredients: Chlorpheniramine, Dexomethorphan.

WOWTAB PRODUCTS

Benadryl Allergy & Sinus Fastmelt (OTC)

Active ingredients: Diphenhydramine citrate, pseudophidrine HCL.

Children's Benadryl Allergy & Cold Fastmelt (OTC)

Active ingredients: Diphenhydramine + Pseudoephidrine (12.5mg+30mg, 19mg+30mg).

Table No: 3

MARKETED FORM OF ORO DISPERSIBLE TABLETS[13]

Technologies	Trade Name	Ingredient	Category	Manufacturer
Freeze Drying	Feldene Fast melt	Piroxicam	Antirheumatic non-steroidal	Pfizer Inc., NY, USA
	Claritin Redi Tab	Loratidine	Antihistamine	Schering Plough Corp.,
	MaxaltMLT	Rizatriptan	Antimigraine	Kenilworth, USA
	Zyprexia	Olanzapine	Antipsychotic	Merck & Co., NJ, USA
	Pepeid RPD	Famotidine	Antihistamine	Eli LiIIy, Indianapolis, USA.
	Zofran CDT	Ondansetron	5-HT3 Antagonist	Merck & Co., NJ, USA
	Zornig-ZMT	Zolmitriptan	Antimigraine	GlaxoWellcome, Middlesex, UK
	ZelaparTM	Selegilline	Antipsychotic	
	TempraQuicklets	Acetaminophen	Antipyretic	
	Febrectol	Paracetamol		
Disintegrant Addition	Nimulid MDT			

Sugar Based Excipient	Torrox MT Olanexlnstab Romilast Benadryl Fastmett	Nimesulide Rofecoxib Olanzapine Montelukast Diphenhydramine & Pseudoephedrine	Antipyretic Antipyretic COX-2 Inhibitor NSAID Antipsychotic Antiastharnatic Antialtergic	AstraZeneca, Wilmington, USA Amarin Corp., London, UK Bristol Myers Squibb, NY, USA Prographarm, Chateauneuf, France Panacea Biotech, New-Delhi, India . Torrent Pharmaceuticals Ahmedabad, India Ranbaxy Labs Ltd., New-Delhi, India Ranbaxy Labs Ltd., New-Delhi, India Warner Lambert, NJ, USA

LITERATURE REVIEW

2.LITERATURE REVIEW

Rajan et al.,[14](2012) prepared the fast disintegrating tablets of Diclofenac sodium by direct compression method. Six formulation of different concentrations of superdisintegrants were prepared.*In-vitro* drug release studies were conducted two formulations with concentration of croscarmellose sodium and crospovidone showed excellent disintegrants property.

Mayank P et al.,[15](2011) prepared fast dissolving tablets of Lorazepam by direct compression method. Disintegration time and drug release was taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for post-compression parameters,*in-vitro* and dissolution drug release profile. The formulated tablets had good appearance and better drug release properties as compared to marketed conventional tablets. Croscarmellose sodium in the concentration of 12% showed shorter disintegration time in 33sec shows 95.99% drug release within 10min was selected as optimized formulation.

Ganesh K.G et al.,[16](2010) prepared the fast dissolving tablets of Chlorpromazine HCL by direct compression method using superdisintegrants, the fast dissolving tablet formulation showed enhanced drug release.

Aravind K.S et al.,[17](2010) prepared fast dissolving tablets of Salbutamol sulphate by direct compression method using super disintegrating agents like Ac-di-sol, poly plasdone, primojel, and MCC,mannitol were used as diluents. The formulations containing Ac-di-sol as superdisintegrating agent showed rapid disintegration time as compared to other formulations.

Sudhir B et al.,[18](2010) formulated fast dissolving tablets of Aceclofenac by using super disintegrants like sodium starch glycolate. The tablets were evaluated for post-compression parameters, *in- vitro* dissolution studies. All formulations showed disintegration time in the range of 12.22 to 27.25 seconds along with rapid *in-vitro* dissolution. The fast dissolving tablets showed enhanced dissolution, taste masking and hence better patient compliance.

Shishu et al.,[19](2010) developed taste masked microsphere of ornidazole from eudragit E-100 by solvent evaporation technique using sodium starch glycolate.

Keng et al.,[20](2010) developed Rizatriptan benzoate mouth dissolving tabletby using super disintegrating agents like crospovidone, Indion 414 and Indion 234 by direct compression method.

N.G Nagendrarao et al.,[21](2010) formulated metoprolo tartrate by sublimation methodby using super disintegrating agents like sodium starch glycolate, crospovidone, croscarmellose sodium, indion-414.

Prabhu H et al.,[22](2009) prepared Cinnarazine fast dissolving tablets by direct compression method by using natural superdisintegrants.The drug and polymer interaction were evaluated using FTIR. All polymers and excipients used were compatible with the drug. It was found that results pre-compression parameters and post compression parameters were found to be satisfactory. The time taken for the *in-vitro* disintegration and *in-vitro* dispersion were found to be within limits. *In-vitro* drug release showed almost 90% of the drug was released from all formulations within 15min, thus crospovidone and treated agar proved to be best disintegrants.

Kawtikwar P.S et al.,[23](2009) prepared fast dissolving tablets of Tizanidine Hydrochloride using superdisintegrants. They carried out disintegration time studies were found to be 22sec. Tablets prepared by addition of superdisintegrants had less disintegration time than those prepared by sublimation method.

Jain et al.,[24](2009) developed fast dissolving tablets of valsartan using different superdisintegrants by direct compression method. Evaluated the prepared tablets for post-compression parameters and *in-vitro* dissolution. Tablets were evaluated for disintegration time. Tablets containing crospovidone showed least wetting time and showed fast disintegration time. The drug release from fast dissolving tablets increased with increasing concentration of superdisintegrants.

Anupama K et al.,[25](2009) prepared mouth dissolving tablets of Oxcarbazepine by directcompression method using crospovidone as a superdisintegrant and aspartame as sweetener. Solid dispersions of oxcarbazepine with polyvinylpyrrolidine and polyethylene glycol 6000 were prepared. Solid dispersions with polyvinylpyrrolidone K-30 in 1:2 ratios of drug carrier showed maximum drug release and hence compressed with other excipients. Oxcarbazepine tablets prepared using solid dispersion technology was found to have good technological properties and reproducible drug dissolution profiles.

Nagendrakumar D et al.,[26](2009) prepared fast dissolving tablet of fexofenadine HCL by effervescent method using crospovidone, croscarmellose sodium, sodium starch glycolate as super disintegrating agents.

MallikarjunaSetty et al.,[27](2008) designed the fast dispersible Aceclofenac tablet and the effect of functionality of super disintegrating agents by direct compression method. Effect of

super disintigrants such as croscarmellose sodium, sodium starch glycolate, crospovidone on wetting time, disintegration time, drug content, in-vitro release has been studied. Disintegration and dissolution parameter decreased with increased in level of disintegrates.

T V Rao et al.,[28](2008) worked on the cefadroxil dispersible tablets by direct compression technique using super disintegrating agents as crospovidone, croscarmellose sodium, sodium starch glycolate. The tablets were evaluated for hardness, friability, disintegration, dissolution time, wetting time and water absorption ratio.

S. Shirsand et al.,[29](2008) designed fast dissolving tablet of clonazepam by direct compression method using crospovidone, croscarmellose sodium and sodium starch glycolate, micro crystalline cellulose, mannitol.

SajalkumarJha et al.,[30](2008) developed melt in mouth dissolved tablet of Halopridol by direct compression method using super disintegrating agents like croscarmellose sodium, sodium starch glycolate, crospovidone.

R. C. Doijad et al.,[31](2008) formulated mouth dissolving tablet of Granisetron by wet granulation method using PVPk-32 and different super disintegrating agents like Avicel101. Almost 80% of the drugs were released from all formulations within 60sec.

Aithal. K et al.,[32](2006) developed once daily fast dissolving tablet of GranisetronHcl by direct compression method using super disintegrating agent formulation containing crospovidone and croscarmellose sodium shows shortest disintegrating time.

M.M. Patel et al.,[33](2006) developed fast disintegrating valdecoxib tablet containing solid dispersion of voldecoxib with mannitol, PEG-4000 and poly vinyl pyrrolidine K-12. Poly vinyl pyrrolidine K-12 showed maximum drug release.

Halakatti P.K et al.,[34](2006) developed rapidly disintegrating tablet of domperidone by mass extrution technique and treated agar method by using sodium starch glycolate as super disintegrating agent.

Sreenivas et al.,[35](2006) developed the formulation and evaluation of ondansetron HCL fast dissolving tablet by using super disintegrating agent like sodium starch glycolate and crospovidone, croscarmellose by direct compression method.

I.S. Ahmed et.al., [36] **(2006)** designed fast dissolving Ketoprofen tablet using Freeze drying in blisters technique. The tablets were evaluated for saturation solubility and dissolution characteristics on comparison with the plain drug and physical mixture. Results showed increase in solubility and also 95% of Ketoprofen in fast dissolving tablet dissolved within 5 minutes.

Marzia cirri et.al.,[37](2005) developed fast dissolving tablets of Flurbiprofen cyclodextrin system. Beta cyclo dextrin, methyl-beta-cyclodextrin and Hydroxy ethyl-beta-cyclo dextrin were evaluated. All formulations containing drug cyclodextrin systems gave a higher drug dissolved amount than the corresponding ones with drug alone.

Devi V.K. et. al.,[38](2006) developed Orodispersible Fluconazole tablets with two different volatilizable compounds like camphor and ammonium chloride by wet granulation method and the tablets were evaluated and the best formulations chosen were compared with

marketed conventional tablets. The formulated tablets exhibited instantaneous disintegration compared to marketed tablets.

Halakatti P.K. et.al.,[39](2006) developed Rapidly disintegrating tablets of Domperidone by mass extrusion technique and treated agar method. The time taken for *in-vitro* disintegration, *in-vivo* disintegration and *in-vivo* dispersion were found in the range of 8-20 sec, 11-25 sec and 17-32 sec. respectively.

Shirwaikar A.et.al.,[40](2006) developed once daily fast dissolving tablets of Granisetron-HCL by Direct Compression method using superdisintegrants. Formulations containing Crospovidone and Croscarmellose Sodium shows shortest disintegration time.

D.M. Patel et.al.,[41](2006) developed fast dissolving Valdecoxib tablets containing solid dispersion of Valdecoxib with Mannitol, Polyethylene glycol-4000 and Polyvinyl pyrrolidone k-12. Valdecoxib solid dispersion with Polyvinyl pyrrolidone K-12 showed maximum drug release.

Chaudhari P.D.et.al.,[42](2005) formulated and evaluate fast dissolving tablets of Famotidine,which is bitter in taste and has low bioavailability (40-45%). Bitter taste of Famotidine was masked using Drug : Eudragit E100 in different ratios (1:1-1:10). The formulation containing 2% Ac-Di-Sol and Polyplasdone showed 91.89% and 101.07% release respectively in 12 minutes.

Kaushik. D.et.al.,[43](2004) formulated and evaluate Olanzapine mouth dissolving tablets by effervescent formulation approach sodium bicarbonate and citric acid were used as effervescent agents and their ratio in the formulation was optimized. The study revealed that

10:8 ratio of sodium bicarbonate and citric acid in the Olanzapine mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile.

Mishra. D.N.et.al.,[44](2005) designed rapidly disintegrating oral tablets of Valdecoxib using various super disintegrants following Direct compression technique. All the formulations showed disintegration time of less than 60 seconds along with rapid *in-vitro* dissolution.

A.A. Shirwaikar et.al.,[45](2004) developed fast disintegrating tablets of Atenolol by Dry granulation method using three superdisintegrants like Ac-Di-Sol, Polyplasdone-XL & Explotab Ac-Di-Sol proved to be the best among the three and showed satisfactory results at $3kg/cm^2$ hardness.

Kuchekar B.S.et.al.,[46](2004) designed mouth dissolving tablets of Salbutamol sulphate by factorial design technique using superdisintegrants like Sodium starch glycolate, Croscarmellose sodium and Treated agar, Microcrystalline cellulose as diluent. Formulations containing Sodium starch glycolate along with other super disingrants showed rapid *in-vitro* and *in-vivo* dispersion time.

Nayak. S.M.et.al,[47](2004) designed fast dissolving tablets for Promethazine theoclate using Effervescent melt, Superdisintegrant addition and Melt technologies. Tablets from Effervescent melt and Superdisintegrant addition technique released 92% and 89% of the drug at the end of 10 minutes.

Mane Avinash. R.et.al.,[48](2003) prepared mouth dissolving tablets of Domperidone using a meltable binder polyethylene glycol-4000, a diluent mannitol and a component which sublimes readily like camphor/ammonium carbonate. Two of the formulations having 40%

w/w of ammonium carbonate and 20%w/w of camphor were found to be exhibiting disintegrating time of 19.66 seconds and 21.33seconds.

Amin. P.D.et. al.,[49](2005) designed fast disintegrating dosage form of Ofloxacin and Metronidazole Benzoate using cationic exchange resins. Taste evaluation of the tablets showed complete masking of the bitterness of Ofloxacin.

H.S. Mahajan et al., [50](2005) designed Rapidly disintegrating tablets of Piroxicam for elderly patients using super disintegrants like Sodium starch glycolate,cros carmellose sodium, low substituted propyl cellulose and microcrystalline cellulose [Avicel pH-102] was used as diluent. The tablets exhibited rapid disintegration and faster release rate of Piroxicam.

Sreenivas S.A et.al.,[51](2006) formulated and evaluate Ondansetron-HCL directly compressed mouth disintegrating tablets using disintegrants like crospovidone, croscarmellose sodium, pregelatinized starch, sodium starch glycolate and L-HPC were used along with other additives. Results suggests that a 10% disintegrant concentration is suitable for the preparation of ondansetron HCL mouth disintegrating tablets and the tablets containing crospovidone and croscarinellose, sodium are the best.

Mishra. D.N.et.al.,[52](2006) designed rapidly disintegrating oral tablets of Meloxicam using superdisintegrants like Ac-Di-So1, Sodium starch glycolate, low molecular weight hydroxy propyl methyl cellulose. The disintegration time in the oral cavity was also tested and was found to be around 1 minute.

S. Pandey et.al., [53](2003) designed to optimize fast dissolving dosage forms of Diclofenac sodium by rapidly disintegrating agents like Crosslinked carboxymethyl cellulose, Sodium starch glycolate and Croslinked povidone in different concentrations. Tablets containing Cross linked carboxy methyl cellulose showed better disintegrating character along with rapid release (90% drug release in 10 minute).

B.S. Kuchekar et.al.,[54](2004) designed mouth dissolve tablets of Diltiazem hydrochloride using disintegrants like Sodium starch glycolate, Carboxymethyl cellulose sodium and Treated agar by direct compression method. Almost 90% of drug were released from all formulations within 10 minutes.

J.K. Lalla et.al.,[55](2004) designed fast dissolving Rofecoxib tablets with cyclodextrin using Ball milling technique and evaluated using DSC. The fast dissolving tablet composition with 25mg equivalent Rofecoxib showed complete release of Rofecoxib in 12 minutes as compared to 20% drug release from the conventional release marketed tablets during the same period.

Rajanna S.G. et.al.,[56](2006) designed and characterization of orodispersible Valdecoxib tablets using Mass extrusion technique and Sublimation method. The disintegration was achieved within 30 seconds from all the formulations prepared by both methods when observed in the saliva of healthy volunteers. The *in-vitro* dissolution was almost 90% within 15 minutes for all formulations.

Shishu et.al., [57](2005) Prepared and evaluate fast disintegrating oral dosage forms of Diazepam and Chlorpheniramine maleate using Microcrystalline cellulose as directly compressible filler binder and sodium starch glycolate as super disintegrant panel testing

data collected from 20 healthy volunteers indicate successful formulation of oral fast disintegrating tablets which had good taste and disintegrated in the oral cavity within 30 seconds.

Srinivasa Rao. M. et.al., [58](2005) designed orally disintegrating tablets of Nimesulide by direct compression method using crospovidone, cros carmellose sodium and sodium starch glycolate as super disintegrants. In all formulations cumulative % drug release increased with time and 99% of drug was released in 60 minutes. Croscarmellose sodium formulations showed faster drug release when compared to the Cros povidone and Sodium starch glycolate formulations.

Vandana B. Patravale et.al., [59](2005) developed taste masked resonates of the Quinine sulphate drug using ion exchange resins. The taste masked complex was then formulated into a prototype suspension base and evaluated for various quality control parameters. Taste evaluation showed complete masking of the bitterness of the drug. *In-vitro* release studies revealed complete drug elution from the complex after a period of 30 min in pH-1.2 buffer.

Mashru R.C. et.al., [60](2005) prepared and optimize the fast dissolving film of Salbutamol sulphate prepared using Solvent evaporation technique containing Polyvinylalcohol, Glycerol and Mannitol. Multiple regression analysis and polynomial regression analysis were carried out. The experimental results indicated that polymer concentration, plasticizer concentration and filler concentration had complex effects on film mechanical behaviour and % drug release.

Mukesh. Gohel. et.al., [61](2004) designed to develop mouth dissolve tablets of Nimesulide. Granule containing Nimesulide, Camphor, Crospovidone and lactose were prepared by wet

granulation technique and the tablets were evaluated for percentage friability, wetting time and disintegration time. 3^2 full factorial designs was used to investigate the joint influence of 2 formulation variables, amount of Camphor and Crospovidone. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating form tablets should be prepared using an optimium concentration of camphor and a higher percentage of Crospovidone.

Kakasaheb R. Mahadik et.al., [62](2000) studied on New drug delivery systems for elderly with improved patient compliance and optimizing dosage regimen. Oral new drug delivery systems like jelly preparation, rapidly disintegrating oral tablets and fast dissolving dosage form are some of the examples of drug delivery systems specifically developed for geriatric patients.

D.M. Patel et al., [63](2004) designed studies in formulation of orodispersible tablets of Rofecoxib using Sodium starch glycolate, Crospovidone and Croscarmellose sodium along with mannitol as diluent and the tablets were evaluated.

Suresh Bandari et.al.,[64](2006) studied on Development and evaluation of orally disintegrating tablets of Domperidone by direct compression technique employing three super disintegrants in 4,6 and 8% concentrations and evaluated for thickness, hardness, friability, assay, disintegration time, drug release studies, wetting time, water absorption ratio and disintegration in oral cavity. Drug release studies revealed that with increase in the concentration of superdisintegrant the cumulative % drug release increased with time and 99% of drug was released in first five minutes in all the formulations.

Khushwant. S. Yadav et.al., [65](2006) designed and *in-vitro* and *in-vivo* evaluation of orodispersible tablets of Ondansetron-HCL with the aim to provide quick onset of action in the condition of emesis. The results suggest that the formulated tablet was a rapidly disintegrating tablet have an ease of administration along with increased bioavailability.

Gandhi et.al., [66](2006) designed taste masking and development of a rapid disintegrating oral dosage form of Gatifloxacin-Sesquihydrate using Resin. The results suggested that the formulation of oral fast disintegrating tablets which had good taste and disintegrated in oral cavity within 21 seconds.

Shirsand S.B. et.al., [67](2006) designed preparation of orodispersible tablets of Meloxicam by sublimation and effervescent methods with a view to enhance patient compliance formulation prepared by effervescent method emerged as the overall best formulation.

Nagendra Kumar D. et.al., [68](2006) designed development of quick dissolve tablets of Tenoxicam by direct compression, sublimation and effervescent techniques and evaluted. Tablets prepared by effervescent method containing 12% w/w each of sodium bicarbonate and anhydrous citric acid were found to be promising.

Arun Shirwaikar et.al., [69](2006) designed formulation and evaluation of fast dissolving tablets of Granisetron-Hcl by Direct compression method. The tablets prepared with smaller sized camphor particles were found to disintegrate faster than the tablets prepared with larger sized camphor particles.

Marina Koland et.al., [70](2006) Studied on design of fast mouth dissolving tablets of Terbutaline sulphate and their characterization. The tablets were prepared using 3 different technologies viz. by Effervescent formulation approach with addition of citric acid and

sodium bicarbonate as effervescing agents, by the addition of superdisintegrants such as Sodium starch glycolate along with other disintegrants such as SCMC and PVP, by sublimation method using subliming agents such as camphor and ammonium carbonate in different ratios. FMDT of Terbutaline sulphate can be successfully formulated by sublimation method.

S.L. Raut et.al., [71](2006) designed evaluation of Bamboo manna as super disintegrant in mouth dissolving tablet. Disintegration rate of Paracetamol formulation containing natural disintegrant Bamboo manna and Paracetamol formulation containing Sodium starch glycolate were compared for their pharmaceutical properties. Bamboo manna is proved to be economical disintegrant in formulation of mouth dissolving tablets with Sodium starch glycolate.

Jain S.P. et.al., [72](2006) designed mouth dissolving tablets of Fexofenadine – HCL by taste masked drug resin complex by granulation technique using excipients like super disintegrants, sweeteners and lubricants. The results suggests that Fexofenadine HCL could be successfully taste masked by complexation.

R. Senthil Prabhu, et. al.,[73](2005) designed Fabrication and Characterization of Melt-in-Mouth tablets of Valdecoxib to increase the bioavailability of the drug by Direct compression method using various superdisintegrants like Sodium starch glycolate, Cros carmellose sodium, Crospovidone, Polyvinyl pyrollidone and Beta cyclodextrin. Then the tablets were evaluated. In all batches of tablets Cumulative amount of drug release increased with time.

Amin P.D et al., [74](2005) designed disintegration dosage form of ofloxacin and metronidazole Benzoate using cationic exchange resins. Taste evaluation of the tablets showed complete masking of the bitterness of ofloxacin.

Mishra D.N et al., [75](2005) designed rapidly disintegrating oral tablet of valdecoxib using various super disintegrating agents following direct compression technique. All the formulations showed disintegration time 60sec along with in-vitro dissolution rate.

Anroop B, Nair et al., [76](2005) designed controlled release matrix uncoated tablets of enalapril maleate using HPMC. Two grades of HPMC (K_{100} and K_4 M) in different properties were used to prepare tablets by direct compression technique.

Kaushik.D et al., [77](2004) studied the fast dissolving tablets of olanzapine by effervescent formulation approach using different ratios of sodium bicarbonate and citric acid and reported 10:8 ratio of sodium bicarbonate and citric acid in the olanzapine MDT shows good palatability and quick dissolving profile.

Kuchekar B et al., [78](2004) studied the formulation of salbutamol sulphate by direct compression using sodium starch glycolate, Crospovidone, treated agar as superdisintegrants and reported sodium starch glycolate exhibiting rapid dispersion than other superdisintegrant.

Nayak S.M et al., [79](2004) studied the FDT of promethazine theoclate using effervescent melt, super disintegration addition and melt technologies. The effervescent melt and super disintegration addition techniques releases 92% and 89% of the drug at the end 10mins respectively.

Gohel M et al., [80](2004) designed mouth dissolving tablets of Nimesulide using vacuum drying technique. The sublimation of camphor from tablets by vacuum drying results faster disintegration.

Chandrashekar .N.S et al.,[81](2004) studied the fast dissolving tablets containing novel gas-evolving disintegrant. The relative efficiency of improvement was in the range of Crospovidone> ac-di-sol >primojel.

Kasture V.S[33] et al., [82](2004) studied the Spectrometric method for simultanesous estimation of oflaxacin and ornidazole in tablet dosage form.

A.A. Shirwaiker et al., [83](2004) developed disintegrating tablet of atenolol by dry granulation method using three super disintegrates like AC-Di-Sol proved to be the best among the three and showed satisfactory results at $3kg/cm^3$ hardness.

J.K. Lalla et al., [84](2004) designed fast disintegrating Rofecoxib tablet with β- cyclodextrin using ball milling technique and evaluated using DSC. The fast disintegrating tablet composition with 25mg equivalent Rofecoxib in 12min is compared to 20% drug release from the conventional release marketed tablet during the same period.

H.S. Mahajon et al., [85](2004) designed mouth dissolving tablet of sumatriptan succinate using disintegrating agents like sodium starch glycolate, carboxy methyl cellulose sodium, and treated sugar by direct compression method. Almost 90% of the drugs were released from all formulations within 10 mins.

Shenoy .V et al., [86](2003) studied the fast dissolving tablets diclofenac sodium using direct compression after incorporating rapid disintegrants such as sodium starch glycolate, Crospovidone, croscarmellose sodium. Croscarmellose sodium is better for the formulation of FDT of diclofenac sodium.

Robinson Joseph et al., [87](2003) reported the effervescent granulations of narcotics, antibacterial agents , antiviral agents, anxiolytic agents, a cholesterol lowering agent, an alpha adrenergic blocking agent and synthetic antibacterial agents and the preparation of MDT from effervescent granules.

Andaleeb Ahmed et al., [88](2003) described the key ingredients used in the formulation of fast dissolving tablets and about the technologies used in preparations.

Chandrasekhar et al., [89](2003) studied the analysation of mouth dissolving tablets using revolution technology with E-tongue apparatus.

B.P. Panda et al., [90](2003) studied nimesulide mouth fast dissolving effervescent tablets. Formulation containing 15% of the effervescent ingredients divided as internal disintegrants and external disintegrants in the ratio of 2:1 is the best acceptable fast dissolving dosage form.

Poornima D et al., [91](2002) studied the fast dissolving tablets of taste masked complex of roxithromycin. The taste masking of roxithromycinviz granulation with eudragit E100 and complexation with ion exchange resin and compressing with superdisintegrant.

Schiermeiers S,et. al., [92](2002) studied the formulation of ibuprofen fast dissolving tablets by direct compression method.

Sheetalmalke et al., [93](2002) formulated oxcarbazepine fast dissolving tablet by using Avicel PH 102 as a diluents and Ac- di – sol as a super disintegrating agent by wet granulation method.

AIM OF THE WORK

3.1 AIM OF THE WORK

The aim of the proposed work was to formulate and characterize Oro dispersible tablets (ODT) of Diltiazem Hydrochloride for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension in elderly patients.

ODT of Diltiazem hydrochloride which when placed in the tongue disintegrates or dissolves rapidly in the saliva without the need of drinking water.

As tablet disintegrates in the mouth, this could enhance the clinical effect of the drug through Pregastric absorption from the mouth, pharynx and oesophagus. This leads to an increase in bioavailability by avoiding first pass liver metabolism. Diltiazem hydrochloride is a new generation calcium channel blocker with peripheral and coronary vasodilator properties, which is used in the management of classical, and vasospastic angina pectoris and also in the treatment of essential hypertension. The plasma half-life following a single oral dose is 3-4 hrs. The success of a therapy depends on selection of the appropriate delivery system as much as it depends on the drug itself. Thus diltiazem hydrochloride is chosen as a suitable candidate for Oro dispersible tablets drug delivery system.

Hence ODT of Diltiazem hydrochloride has been developed with the goal of speeding absorption and onset of effect compared to standard Diltiazem hydrochloride tablets with the following objectives.

- To provide convenient dosing
- To achieve rapid dissolution rate for the drug.
- To improve the bioavailability of the drug.
- To facilitate faster onset of therapeutic action.
- To make easier administration for geriatrics, mentally ill patients and dysphagia patients.

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PLAN OF THE WORK

3.2 PLAN OF THE WORK

Present work was carried out to design and evaluate the Oro dispersible tablets.

The study was proposed to carry out in the following stages.

- Preformulation studies
- Construction of standard curve for Diltiazem hydrochloride.
- Fabrication of Oro dispersible tablets of Diltiazem hydrochloride .
- Evaluation of Oro dispersible tablets
- Comparative *in-vitro* drug release studies with Marketed samples of the same drug.
- *In-vitro* drug release studies.
- Stability studies
- Investigation of drug release kinetics

3.3 SCHEME FOR MECHANISM ORO DISPERSIBLE TABLET.

Oro dispersible tablets

↓

Placed in tongue

↓

Instantaneous Disintegration in mouth

↓

Rapid drug dispersion/ dissolution in saliva

↓

Pre-gastric absorption

↓

Avoids frist pass metabolism

↓

Increase in Bio availability

↓

Faster onset of action

METHOD

4. METHOD

4.1 MATERIALS USED

Sl. No.	Materials	Suppliers
1.	Diltiazem hydrochloride	Nicholas Piramal India Ltd
2.	Crospovidone (Polyplasdone XL)	Micro labs, Hosur
3.	Croscarmellose Sodium (Ac-Di-Sol)	Signet chemical corporation, Mumbai
4.	Sodium starch glycolate (Glycolys)	Signet chemical corporation, Mumbai
5.	Colloidal silicon dioxide (Aerosil)	Micro labs, Hosur
6.	Mannitol-DC	Micro labs, Hosur
7.	Micro crystalline cellulose powder (Avicel PH-102)	S.D. Fine chemicals, Boisar
8.	Saccharin Sodium	S.D. Fine chemicals, Boisar
9.	Magnesium stearate	S.D. Fine chemicals, Boisar
10.	Potassium dihydrogen Phosphate (AR)	S.D. Fine chemicals, Boisar
11.	Sodium hydroxide (AR)	S.D Fine chemicals, Boisar

Table: 4 MATERIALS USED

4.1.2 INSTRUMENTS USED

S.No	Instruments	Suppliers
1	Single pan electronic balance	Shimadzu corporation, Japan
2.	pH meter	Elico
3.	Single Beam UV-visible Spectrophotometer	1201,Shimadzu corporation, Japan
4.	FTIR spectrophotometer	Perkin. Elmer, Germany
5.	Dissolution apparatus	Disso 2000, Lab India, Chennai
6.	Disintegration tester	Electrolab, Chennai
7.	Friability test apparatus	Roche Friabilator
8.	Vernier calipers	Mitutoyo Corps, Japan
9.	Hardness Tester	Monsanto
10.	16 station Rotary Tablet compression machine	Cadmach, India
11.	Sieves	Goston, India
12.	Stability chamber	Osworld, Mumbai

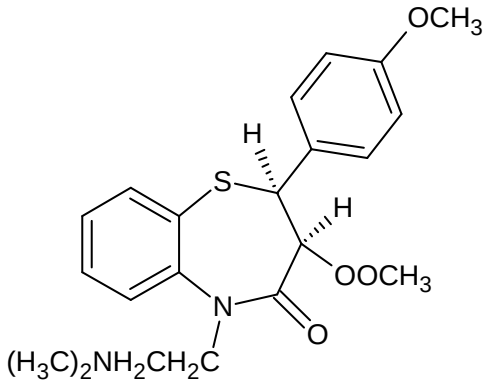
Table: 5 INSTRUMENTS USED

4.2 DRUG PROFILE

DILTIAZEM HYDROCHLORIDE[94]

Drug Name: Diltiazem hydrochloride

Structure:



Molecular formula: $C_{22}H_{26}N_2O_4S.HCL$

Molecular Weight: 414.52

Category: Antianginal, Calcium channel blocker

Description:

White crystalline powder / small crystals

Solubility:

Freely soluble in water, methanol, chloroform and formaldehyde. Insoluble in benzene.

Melting Point:

Melts at above 210^{o}C with decomposition

Standards: Diltiazem is (+) is C 2,3,4,5 tetra hydro -5- (2 dimethyl amino ethyl) -2- (-4 methoxy phenyl) 4-oxobenzene (6) thiazepin-3yl acetate monohydrochloride. It contains not

less than 98.3% and not more than 101.9% $C_{22}H_{21}N_2O_4S_2HCl$ calculated with reference to dried substance.

Therapeutic uses

Variant angina:

Variant angina is as a result of reduction in blood flow. The drug can attenuate ergonovine-induced vasospasm in patient with variant angina

Exertional angina:

Effective in the treatment of exertional or exercise induced angina. The utility of this agent results in an increase in blood flow due to coronary arterial dilation.

Unstable angina:

It is a recurrent angina, associated with minimal exertion. It is prolonged and frequent. Coronary flow is severely restricted and it is likely that vasospasm also occurs in some patients.

Other uses: Antiarrythmic

Dose:

Given orally (30mg) 4 times daily, usual dose in 60 mg three times daily. Sustained release preparation is given twice daily.

Pharmacokinetics

Diltiazem is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration, but undergoes extensive first pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations.

Diltiazem is around 50% bound to plasma protein. It is extensively metabolized in the liver, one of the metabolites desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. The plasma half-life is 3-4 hours. Approximately 60% of the dose is excreted in the bile and 35-40% in the urine, 2-4% as unchanged diltiazem.

Adverse effects

1. Depression of cardiac conduction, atrioventricular block
2. Headache, dizziness, ankle oedema, flushing, hypotension, nausea and gastrointestinal discomfort.
3. There have been reports of hyperactivity sometimes with associated psychiatric symptoms. Gynaecomastia has also been reported.

Precautions

1. Diltiazem should be administered with caution to patients with pre-existing hypertension and probably along to those with impaired left ventricular function due to the potential negative ionotropic properties of diltiazem.
2. Treatment should commence with reduced doses in elderly patients and with impaired liver or kidney function.
3. Diltiazem should be used in pregnant women only if the potential benefit justifies the potential risk to the foetus.

Indication

Chronic stable angina, unstable angina, variant angina

Contraindication

Sick sinus syndrome, 2nd or 3rd degree AV block hypotension (systolic pressure < 90Mm Hg)

Commercially available dosage form

Angizem (Sunpharma) : 30mg and 60mg

Dilgard (Cipla) : 30mg

Dilzem (Torrent) : 30mg and 60mg

Sustained release dosage forms

Angizem CD (Sun pharma) : 90mg and 120mg

Dilcontin XL (Modi Mundi Pharma) : 90mg and 180mg

Dilzem SR (Torrent) : 90mg

4.3 EXCIPIENTS LITERATURE [95]

4.3.1 CROSPOVIDONE

Synonyms:

Crosslinked povidone; polyplasdone XL, Polyplasdone XL-10.

Chemical Name:

1- Ethenyl-2-Pyrrolidinone homopolymer

Functional Category:

Tablet disintegrant

Description:

Crospovidone is a white to creamy white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties:

Density : 1.22 g/cm^3

Solubility : Practically insoluble in water and most common organic solvents

Stability and Storage Conditions:

Crospovidone is hygroscopic. So it should be stored in an airtight container in a cool, dry place.

Safety:

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as nontoxic and non-irritant material.

Applications:

- Crospovidone is a water insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct compression.
- Cros povidone can be used to enhance the solubility of poorly soluble drugs in co-evaporation technique.

4.3.2 CROSCARMELLOSE SODIUM

Synonyms:

Ac-Di-Sol, Crosslinked carboxymethyl cellulose-sodium, modified cellulose gum, primellose, solutab.

Chemical Name:

Cellulose, Carboxy methyl ether, sodium salt, Crosslinked.

Functional Category:

Tablet and capsule disintegrant.

Description:

Croscarmellose sodium occurs as an odorless, white, colored powder.

Typical Properties:

Density (bulk) : 048 g/cm^3

Density (tapped) : 0.67 g/cm^3

Solubility:

Insoluble in water, although Cros carmellose sodium rapidly swells to 4-8 times its original volume on contact with water.

Stability and Storage Conditions:

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

Safety:

It is regarded as an essentially non-toxic and non-irritant material. However oral consumption of large amounts of Cros carmellose sodium may have a laxative effect although the quantities used in solid dosage formulations are unlikely to cause such problems.

Applications:

Cros carmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, cros carmellose sodium may be used in both direct compression and wet granulation process. Concentrations of upto 5% w/w of cros carmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression.

4.3.3 SODIUM STARCH GLYCOLATE

Synonyms:

Carboxy methyl starch, Sodium salt, Explotab, Primojel.

Chemical Name:

Sodium carboxymethyl starch

Functional Category:

Tablet and capsule disintegrant

Description:

It is a white to off-white, odorless, tasteless, free flowing powder. It consits of oval or spherical granules, 30-100 m in diameter with some less spherical granules ranging from 1-35 in diameter.

Typical Properties:

Aciditiy / Alkalinity : pH = 3.0 – 5.0%

Density (Bulk) : 0.85 g/cm^3 for primojel.

Melting Point:Does not melt, but chars at approximately 200^oC

Solubility:

Sparingly soluble in ethanol (95%) practically insoluble in water at a concentration of 2% w/v, it disperses in cold water and settles in the form of a highly hydrated layer.

Stability and Storage Conditions:

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

Incompatibilities:

It is incompatible with ascorbic acid.

Safety:

It is widely used in oral pharmaceutical formulation and is generally regarded as a non-toxic and non-irritant material. However oral ingestion of large quantities may be harmful.

Applications:

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulation. It is commonly used in tablets prepared by either direct compression or wet granulation processes. The usual concentration employed in a formulation is between 2-8%, 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. It has also been investigated for use as a suspending vehicle.

4.3.4 MICROCRYSTALLINE CELLULOSE

Synonyms:

Avicel, Emcocel and Tabulose

Functional Category:

Adsorbent, suspending agent, tablet and capsule diluent, disintegrant

Description:

White coloured, odourless, tasteless, crystalline powder composed of porous particles.

Typical properties:

Solubility:

It is insoluble in water, slightly soluble in 5% w/v sodium hydroxide solution

pH = 5.0 – 7.0

Melting point : Chars at 260 – 270^{o}C

Moisture Content:

It is hygroscopic in nature, moisture content is less than 5% w/w.

Density (Bulk): 0.337 g/cm^{3}

Density (Tapped):0.478 g/cm^3

Stability and Storage Conditions:

Should be stored in well – closed container and kept in a cool and dry place.

Incompatibilities:

Incompatible with strong oxidizing agents

Safety:

It is widely used in oral pharmaceutical formulations and food products and is generally regarded as non-toxic and non-irritant material

Applications

It is widely used as a diluent in oral tablets and capsules. It is used in both wet granutation and direct compression process.It is also used as tablet disintegrant.

4.3.5 COLLOIDAL SILICON DIOXIDE

Synonyms:

Aerosil, cab-o-sil, colloidal silica, fumed silica

Description:

It is submicroscopic fumed silica with a particle size of about 15nm. It is a light, loose, bluish-white coloured, odorless, tasteless, nongritty amorphous powder.

Functional Category:

Adsorbent, anticaking agents, glidant, suspending agent, tablet disintegrant, viscosity increasing agent

Typical properties:

Solubility:

It is insoluble in water, organic solvents, and acids, except hydrofluoric acid. It is soluble in hot solution of alkali hydroxide.

Density (Bulk): 0.029 – 0.042 g/cm^3

Density (Tapped): 0.050 g/cm^3

Stability and Storage Conditions:

It is hygroscopic and absorbs large quantities of water without liquefying.so it should be stored in well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with diethyl stilbosterol preparations.

Safety:

It is widely used in oral and topical pharmaceutical formulations and is generally regarded as a non-toxic and non-irritant material. Intraperitoneal and subcutaneous injection may produce local tissue reactions and / or granulomas.

Applications:

It is widely used in Pharmaceuticals, cosmetics and food products. It is mainly used as a glidant for tabletting form, also used to stabilize emulsion and as a thixotropic thickening and suspending agent in gels and semisolid preparations. It is also used as tablet disintegrant.

4.3.6 MANNITOL

Synonyms:

Cordycepic acid; E421; 1,2,3,4,5,6 – hexanehexol; manita; manna sugar; mannite; pearlitol.

Chemical Name :D-Mannitol

Functional Category:

Sweetening agent, tablet and capsule disintegrant, tonicity agent, vehicle for lyophilized preparations.

Description:

It is a white, odorless, crystalline powder or free flowing granules. It has a sweet taste.

Solubility:

It is soluble in alkalis at 20°C, 1 in 5.5 parts is soluble in water at 20°C.

Stability and Storage Conditions:

It is stable in the dry state and in aqueous solutions. The bulk material must be stored in well closed containers in a cool, dry place.

Incompatibilities:

It is incompatible with xylitol infusion and forms complexes with some metals (Fe, Al, Cu).

Safety:

Mannitol when consumed orally in large quantities laxative effects may occur. An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.

Applications: Mannitol is widely used in pharmaceutical formulations as a diluent (10 – 90 % w/v) in tablet formulations,Where it is of particular value since it is not hygroscopic and may thus be used with moisture sensitive active ingredients.

Mannitol may be used in direct compression tablet applications. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness and mouth feel.

4.3.7 MAGNESIUM STEARATE

Synonyms:

Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate

Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Functional Category:

Tablet and capsule lubricant

Typical properties:

Solubility:

It is insoluble in water, ethanol and ether, slightly soluble in warm benzene and warm ethanol.

Melting point : 117 – 150°c

Density (tapped): 0.286 g/cm^3

Density (bulk) : 0.159 g/cm^3

Stability and Storage Conditions:

It should be stored in a well – closed container in a cool, dry place. It is a stable compound.

Incompatibilities:

Imcompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

Safety:

It is widely used in pharmaceutical formulations and is generally regarded as a non-toxic material. However oral consumption of large quantity may result in some laxative effect or mucosal irritation.

Applications:

It is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet at concentration between 0.25 – 5.0%.

4.3.8 SACCHARIN SODIUM

Synonyms:

1,2-Benzisothiazoline- 3- one 1,1-dioxide, sodium salt, Britsol, Crystallose, Degutan; E954, Kristallose, sodium-o-benzosulfimide, soluble gluside, soluble saccharin, sucaryl, sucromat; syncal s.

Chemical Name:

1,2 –Benzisothiazol-3 (2H)-one 1,1-dioxide sodium salt.

Functional Category:

Sweetening agent

Description:

It occurs as a white, odorless or faintly aromatic, efflorescent, crystalline power. It has an intensely sweet taste.

Typical properties:

Melting Point: Decomposes upon heating

Solubility:

It is soluble in pH 7.0 buffer at 1 in 1.21 at 25^{o}C soluble in water at 1 in 1.2 at 25^{o}C.

Stability and Storage Conditions:

It is stable under the normal range of conditions employed in formulations. It should be stored in a well-closed container in a cool,dry, place.

Safety:

It is regarded as a safe intense sweetener. The WHO has set a temporary daily intake of upto 2.5 mg / kg body weight for saccharin, including its salts.

Applications:

It is an intense sweetening agent used in beverages, food products, table top sweeteners and pharmaceutical formulations such as tablets,Powders, medicated confectionery, gels, suspensions and liquids.

Sweetening power is approximately 300 times that of sucrose. Saccharin sodium enhances flavor systems and may be used to mask some unpleasant taste characteristics.

RESEARCH ENVISAGED

5. EXPERIMENTAL INVESTIGATION

5.1 CONSTRUCTION OF STANDARD CURVE OF DILTIAZEM HYDROCHLORIDE BY UV-SPECTROSCOPY METHOD

Method of preparation of Sorenson's buffer pH 6.8 [96]

1. Preparation of 0.2 M Potassium dihydrogen phosphate solution (Primary solution):

   27.218 grams of Potassium dihydrogen phosphate was weighed and dissovled in small quantity of distilled water and the volume was made upto one litre with distilled water.

2. Preparation of 0.2 M Sodium hydroxide solution (secondary solution):

   8 grams of sodium hydroxide was weighed and dissolved in distilled water and made upto one litre with distilled water.

From the primary solution 50ml and from the secondary solution 22.4ml was taken and made upto 200ml with distilled water to get sorenson's buffer and the pH was checked and adjusted to 6.8.

Procedure for Construction of Standard Curve[97]

Primary stock solution

100mg of diltiazem hydrochloride was accurately weighed and dissolved in buffer pH 6.8 and then made up to 100ml a concentration of 1000 mcg/ml.

Secondary stock solution

1 ml of the primary stock solution was diluted with buffer pH 6.8 to get a concentration of 10 mcg/ml.

Sample solution

From the secondary stock solution aliquots ranging from 1ml to 10ml were pipetted out and diluted to 10ml with buffer to get the concentration of 1mcg/ml to 10mcg/ml. The absorbance was measured at 237 nm against blank.

Then a caliberation curve was plotted taking concentration on X-axis and absorbance on Y – axis.

Table:6. Standard Curve for Diltiazem hydrochloride using by using UV-Spectroscopy Method

Sl.No.	Concentration (µg/ml)	Absorbance
1	1	0.061
2	2	0.121
3	3	0.159
4	4	0.225
5	5	0.283
6	6	0.335
7	7	0.401
8	8	0.458
9	9	0.523
10	10	0.571

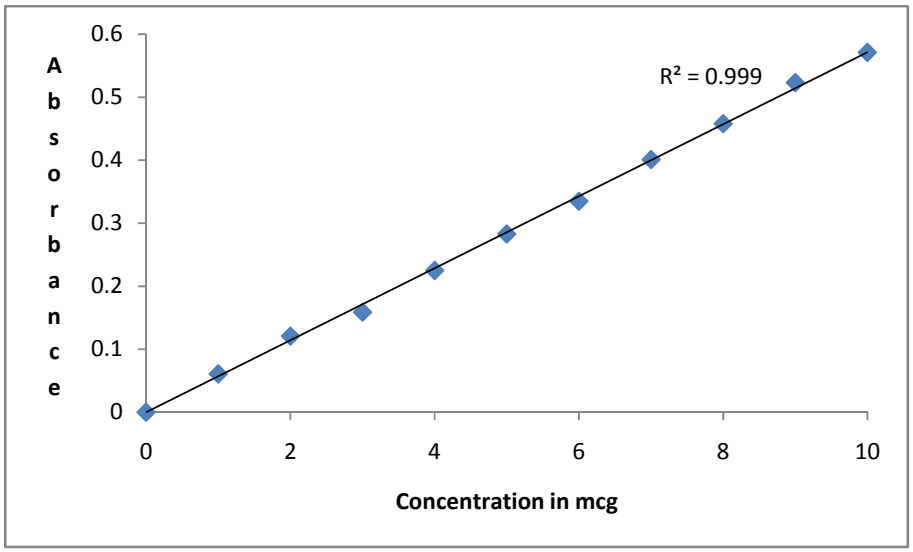


Fig.5: Standard Curve For Diltiazem Hydrochloride by UV-Method

5.2 PRE FORMULATION STUDIES[98,99]

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage form.

1. Drug – Excipients compatibility studies

About 50mg of Diltiazem hydrochloride with various excipients in 1 : 1 ratio in glass vials were taken and kept at various accelerated condition (30°C / 65% RH, 40°C / 75% RH and 60°C / 80% RH) in stability chamber [osworld stability chamber, India] It is carried out for one month in open and closed glass vials. Samples were withdrawn at the intervals of 1,2,3,4,5,6,7,14,21 and 30 days and physical characteristics like colour change if any was recorded. Finally the mixtures with no colour change were selected for Formulation development.

2. Angle of Repose (θ)

It is defined as the maximum angle that can be obtained between the free standing of a powder heap and the horizontal plane which is given by the equation

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

θ - Angle of repose

h – Height of the pile

r – Radius of the base of the conical pile

3. Loss on Drying

It was done in Electronic loss on Drying [LOD] apparatus [Sartorius, Germany]. Weighed quantity of 1 gram of sample was placed in the pan and the temperature was increased up to 500^{o}C and the loss on drying in percentage was noted.

4. Bulk Density, Tapped Density, Hausner Ratio and Carr's Index

Weighed quantity of powder blend was taken in a graduated cylinder and the bulk volume (V_b) was measured, and weight of the blend (M) was determined. The measuring cylinder containing known mass of powder blend was tapped for a fixed time and the tapped volume (V_t) occupied in the cylinder and the weight of the blend (M) was measured. From that bulk density, tapped density, Hausner bulk ratio and carr's index were calculated.

Bulk density (e_b) = $\frac{M}{V_b}$

Tapped density (e_t) = $\frac{M}{V_t}$

Hausner ratio = $\frac{e_t}{e_b}$

$$\text{Carr's index (I)} = \frac{e_b - e_t}{e_t} x100$$

5. Infrared Spectroscopic Studies

Identification of the pure drug and super disintegrants were performed using Infrared spectroscopy.

Pressed Pellet Technique

Sample and potassium bromide in the ratio of 1 : 100 were placed in a clean agate mortar and triturated well and the powder mixture is compressed in a mini press to get pellets. The pellet is placed in the sampling area of FTIR spectrophotometer and peaks obtained were identified.

5.3 FABRICATION OF ORO DISPERSIBLE TABLETS OF DILTIAZEM HYDROCHLORIDE

Direct Compression Method

In this formulation of ODT of Diltiazem hydrochloride, Each superdisintegrant was employed in three concentrations (5,10 and 15%). The composition of ODT of Diltiazem hydrochloride was shown in Table: 1. weighed quantities of along with appropriate concentrations of superdisintegrant, mannitol-D, microcrystalline cellulose, colloidal silicon dioxide, saccharin sodium were weighed and mixed in geometric progression in a dry and clean mortar. Then the blend was passed through sieve No : 60. Then magnesium stearate was added and mixed well.

The dry blend was compressed into tablets using 8 mm punches in a 16 Station Rotary Tablet Machine [Cadmach, India]. Then the Fabricated tablets were evaluated for

thickness, diameter, hardness, friability, wetting time, water adsorption ratio, weight variation test, drug content uniformity, uniformity of dispersion, *In- vitro* dispersion time, *In- vitro* disintegration time, *In-vitro* dissolution studies, Moisture uptake studies, and Stability studies.

EXPERIMENTAL INVESTIGATIONS

TABLE : 7. COMPOSITION OF ORO DISPERSIBLE TABLETS (ODT'S) OF DILTIAZEM HYDROCHLORIDE

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem Hydrochloride	30	30	30	30	30	30	30	30	30
SSG	5%	10%	15%	-	-	-	-	-	-
CCS	-	-	-	5%	10%	15%	-	-	-
CP	-	-	-	-	-	-	5%	10%	15%
MCC (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mannitol	15	15	15	15	15	15	15	15	15
Aerosil	3	3	3	3	3	3	3	3	3
Saccharin sodium	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2

5.4 EVALUATION OF ORO DISPERSIBLE TABLETS (ODT's)[100-102]

(a) Thickness and Diameter

The thickness and diameter of the tablets were carried out using vernier calipers (Mitutoyo corps, Japan). Five tablets were used for the above tests from each batch and results were expressed in millimeters.

(b) Hardness Test [63, 64]

Tablets require a certain amount of strength or hardness and resistance to Friability to with stand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester, five tablets from each batch were used for hardness studies and results were expressed in Kg/cm^2.

(c) Weight variation Test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance [Ax, Shimadzu – corporation, Japan] and the average weight was calculated. The uniformity of weight was determined according to I.P. Specification. As per I.P. not more than two of individual weights would deviate from average weight by more than 5% and none deviates by more than twice that percentage.

(d) Friability Test

The friability of the tablet was determined using Roche friabilator. It is expressed in percentage (%). 20 tablets were initially weighed ($W_{initial}$) and transferred in to the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes. The tablets are weighed again (W_{final}). The % Friability was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

$F \rightarrow$ % Friability

(e) Wetting Time

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients.

A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step for disintegration process to take place.

Method :

A piece of tissue paper folded twice was placed in a small Petridish (internal diameter = 6.5cm) containing 6ml of water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. Three trials for each batch were performed and standard deviation was also determined.

(f) Water Absorption ratio

A piece of tissue paper folded twice was placed in a small Petridish (internal diameter = 6.5cm) containing 6ml of water. A tablet was placed on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

$W_a \rightarrow$ weight of tablet after water absorption

$W_b \rightarrow$ weight of tablet before water absorption

(g) Uniformity of dispersion test

Two tablets from each batch were seperately kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22mesh. The tablets were considered to pass the test if no residue remained on the screen.

(h) Drug Content uniformity test

Powder equivalent to 50mg of Diltiazem hydrochloride was dissolved in sorenson's buffer pH 6.8, sufficient dilutions were made. Absorbance of the resulting solution was measured at 237 nm using Shimadzu [UV-1201] spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated. Procedure was repeated by using four more tablets from the same formulation and the average value of all five tablets were calculated.

(i) **Moisture Uptake Test**

Ten tablets from each formulation were kept in desiccators, over calcium-chloride at 37^{o}C for 24 hours. The tablets were then weighed and exposed to 75% RH, at room temperature for two weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as a control (without superdisintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

(j) *IN – VITRO* DRUG RELEASE STUDIES

(I) *In- Vitro* Dispersion Time

In-vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in-vitro* dispersion time was performed.

(II) *In – Vitro* Disintegration Time

The disintegration time of the tablets was determined as per Indian Pharmacopoeial monograph. The test was carried out using Tablet disintegration apparatus.

Six tablets from each batch were placed and one liter of distilled water was used as the disintegration medium. The time required to obtain complete disintegration of all the six tablets was noted.

(III) *In – Vitro* Dissolution Studies

In-vitro drug release studies for the Oro dispersible tablets of Diltiazem hydrochloride was studied using Dissolution apparatus II USP XX1 model [Paddle type] for the fabricated batches. 650ml of sorenson's buffer solution [pH 6.8] was used as the dissolution medium. The tablet was placed in the dissolution medium and rotated at a speed of 50 rpm maintained at a temperature of 37 ± 0.5^{o}C.

1ml of sample was withdrawn at periodic intervals 1st, 2nd, 4th, 6th, 8th and 10th minutes and was made upto 10ml with sorenson's buffer solution. 1ml of

fresh dissolution medium [maintained at the same temperature] was replaced after each time of withdrawal of samples.

The samples were analyzed spectrophotometrically at 237 nm for the drug content against the respective buffer blank. The mean percentage of Diltiazem hydrochloride released at various time intervals was calculated from standard graph and plotted against time.

5.5 Comparative *In – Vitro* Drug Release Studies For The Optimizied Formulation F_8 [CP-10%] With Marketed Diltiazem hydrochloride Tablets[29].

Compare the drug release rates of the fabricated Oro dispersible tablets [CP – 10%] with that of the commercially available tablets of Diltiazem hydrochloride DILZEM [Torrent] was selected as a choice and dissolution studies were carried out. 1ml sample were withdrawn periodically and proceeded for the previous mentioned standard analysis by UV – method.

5.6 Stability Studies

Stability studies were carried out for the optimized formulation F_8 [CP-10%]. The samples were packed in an aluminum foil placed in an tightly closed plastic container and kept at 4°C in refrigerator, 40°C / 75% RH in stability chamber [osworld, Mumbai] and 60°C in Incubator for 1 month according to ICH guidelines. At the interval of 15 days, the tablets were withdrawn and evaluated for Thickness, Diameter, Hardness, Friability, weight variation, content uniformity and disintegration time.

The *In-vitro* dissolution study was carried out for 3 month at the interval of 1 month.

5.7 Kinetics of Drug release

The optimized formulation F_8 [CP -10%] was subjected to kinetic treatment to assess the order of drug release.

A plot of Logarithm of percentage of drug remaining to be released versus time would be linear if the rate of drug release follows First order kinetics

The linear equation for first order drug release plot is

$$\log C = \text{Log } C_o - \frac{Kt}{2.303}$$

C = concentration remaining at time 't'

C_o = original concentration

t = time

k = release rate.

RESULTS & DISCUSSION

6. RESULTS AND DISCUSSION

Pre Formulation Studies

1. Drug – Excipients compatibility studies

Diltiazem hydrochloride was subjected to Drug – Excipients compatibility studies with various excipients like cros povidone, cros carmellose sodium, sodium starch glycolate, povidone, microcrystalline cellulose, Mannitol, Magnesium stearate, Saccharin sodium and colloidal silicon dioxide. The mixtures have shown no colour change.

2. Angle of repose

The angle of repose for the powder blends of all batches exhibits good flow properties.

3. Loss on Drying

The moisture content has influence on tableting process in various aspects like sticking and also affect the moisture sensitive excipients like povidone, cros povidone, cros carmellose sodium and sodium starch glycolate.

The loss on drying for various batches of powder blends varies from 1.53 to 2.09. Hence excipient like Colloidal silicon dioxide [Aerosil] was selected to maintain the moisture content.

4. Bulk Density, Tapped Density, Hausner Ratio and Carr's Index

Bulk Density, Tapped Density, Hausner Ratio and Carr's Index were studied. From the obtained Bulk density and Tap density values Hausner ratio and Carr's index were calculated. Since the Hausner ratio was less than 1.25% for all batches of powder blends, the flow property was good. Also the Carr's index was below 15% for all batches of powder blends, the flow property was good.

The results for Angle of repose, Loss on Drying, Bulk Density, Tapped Density, Hausner ratio and Carr's Index were predicted in Table.4.

TABLE : 8. PHYSICAL CHARACTERISTICS OF POWDER BLENDS

Sl. No	Parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Bulk density (g/ml)	0.58 ± 0.37	0.58 ± 0.54	0.58 ± 0.26	0.56 ± 0.91	0.56 ± 0.36	0.56 ± 0.41	0.55 ± 0.39	0.55 ± 0.98	0.55 ± 0.75
2	Tapped density(g/ml)	0.643 ± 0.035	0.649 ± 0.04	0.646 ± 0.09	0.646 ± 0.08	0.646 ± 0.19	0.647 ± 0.03	0.634 ± 0.04	0.636 ± 0.05	0.634 ± 0.03
3	Hausner ratio	1.106 ± 0.24	1.111 ± 0.57	1.107 ± 0.39	1.147 ± 0.18	1.152 ± 0.28	1.152 ± 0.36	1.144 ± 0.18	1.156 ± 0.17	1.143 ± 0.11
4	Carr's index (%)	9.63 ± 0.35	10.02 ± 0.41	9.69 ± 0.87	12.84 ± 1.12	13.24 ± 1.06	13.22 ± 0.78	12.59 ± 0.67	.13.50 ± 0.81	12.55 ± 0.59
5	Angle of repose (θ)	23°.83 ± 0.35	23°.12 ± 0.41	23°.61 ± 0.68	22°.20 ± 0.69	22°.05 ± 0.39	22°.31 ± 0.38	21°.20 ± 0.31	21°.32 ± 0.64	21°.53 ± 0.36
6	Loss on drying	1.97 ± 0.18	1.86 ± 0.25	1.89 ± 0.05	1.82 ± 0.09	1.76 ± 0.11	1.77 ± 0.07	2.32 ± 0.03	2.41 ± 0.01	2.38 ± 0.28

TABLE NO: 9. PHYSICAL CHARACTERISTICS OF GRANULES

Sl No	Parameters	F 1	F 2	F 3	F4	F 5	F6	F 7	F 8	F9
1	Bulk density (g/ml)	0.58 ± 0.38	0.60 ± 0.58	0.59 ± 0.64	0.59 ± 0.43	0.58 ± 0.26	0.56 ± 0.61	0.55 ± 0.65	0.57 ± 0.39	0.58 ± 0.61
2	Angle ofrepose (0)	28.2 ± 0.03	29.3 ± 0.15	29.3 ± 0.04	27.3 ± 0.30	30.2 ± 0.900	28.5 ± 0.910	26.2 ± 0.32	25.3 ± 0.412	28.1 ± 0.412
3	Tap density (g/ml)	0.69 ± 0.02	0.68 ± 0.09	0.67 ± 0.12	0.66 ± 0.007	0.68 ± 0.08	0.65 ± 0.06	0.64 ± 0.07	0.66 ± 0.009	0.65 ± 0.05
4.	carr's index	14.7 ± 0.34	13.6 ± 0.29	14.9 ± 0.61	13.63 ± 0.24	14.7 ± 0.31	13.9 ± 0.48	14.5 ± 0.48	13.6 ± 0.42	13.8 ± 0.17
5.	Hausner ratio	1.18 ± 0.12	1.14 ± 0.18	1.3 ± 0.36	1.15 ± 0.54	1.17 ± 0.15	1.16 ± 0.18	1.16 ± 0.21	1.16 ± 0.34	1.15 ± 0.14

5. Infra Red Spectroscopic Studies

By using FT IR technique, Diltiazem hydrochloride and superdisintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate and povidone were identified by the frequency of the obtained peaks.

The Interpretation of the Infrared spectrum of the drug and superdisintegrants are as follows.

Table : 10. IR Spectra of Diltiazem hydrochloride

Frequency cm^{-1}	Groups Assigned
3034	Aromatic C – H stretching
3005	Aliphatic C – H stretching
2842	O – CH_3 C-H stretching
2388	Amine HCl N – H stretching
1743	Acetate C = O stretching
1678	Lactam C = O stretching
1606	C = O stretching
1474	C – H bending
837	O – substituted aromatic C – H out of plane deformation
777	P – substituted aromatic C – H out of plane deformation

Table : 11 IR Spectra of formulation

Frequency (cm^{-1})	Groups Assigned
3005	Aliphatic C – H stretching
2842	O – CH_3 C-H stretching
2388	Amine HCl N – H stretching
1743	Acetate C = O stretching
1678	Lactam C = O stretching
1606	C = O stretching
1474	C – H bending
837	O – substituted aromatic C – H out of plane deformation

Fig : 6 IR Spectra of Diltiazem hydrochloride

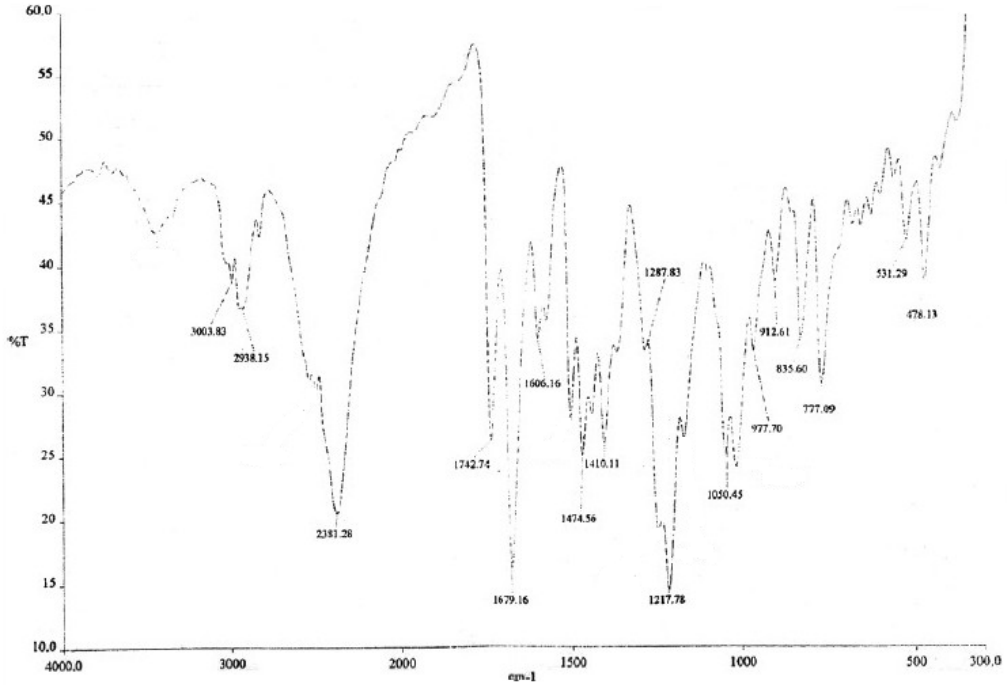
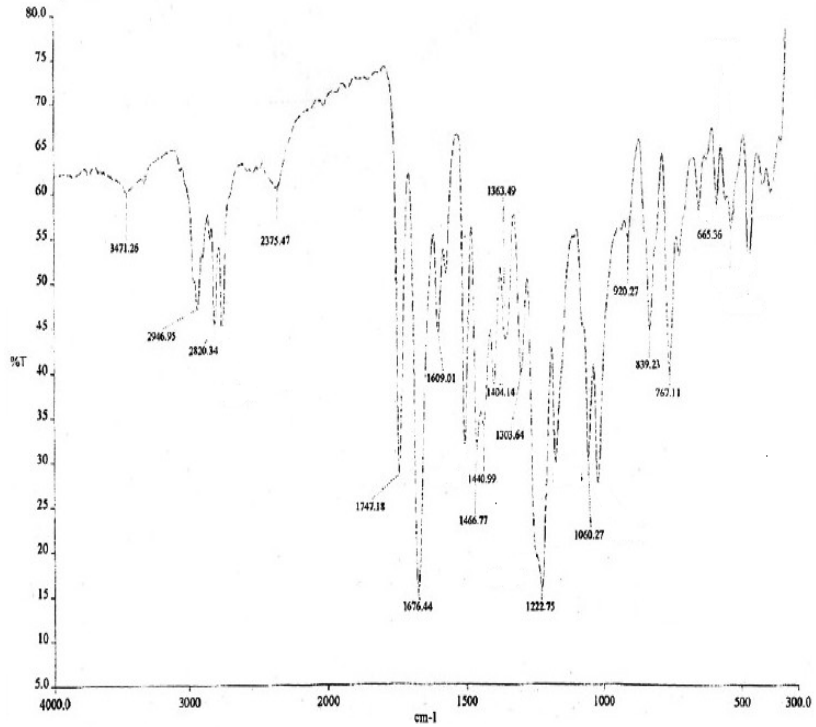


Fig : 7 IR Spectra of formulation



EVALUATION OF FABRICATED TABLETS

a) Thickness, Diameter and Hardness

The Thickness and Diameter of the tablets were found in the range of 3.09 ± 0.08 to 3.31 ± 0.21 and 7.89 ± 0.08 to 8.11 ± 0.12. The Hardness of the different formulations ranged from 3.8 to 3.9 Kg/cm^2.

Table : 12. Thickness, Diameter and Hardness data of the tablets

Formulation Code	Batch	Thickness(mm) ± S.D [n=5]	Diameter(mm) ± S.D [n = 5]	Hardness[Kg/cm^2] ± S.D [n = 5]
F_1	SSG – 5%	3.14 ± 0.09	8.11 ± 0.20	3.8 ± 0.32
F_2	SSG – 10%	3.18 ± 0.12	8.02 ± 0.49	3.8 ± 0.64
F_3	SSG – 15%	3.19 ± 0.18	7.96 ± 0.52	3.9 ± 0.71
F_4	CCS – 5%	3.21 ± 0.09	7.92 ± 0.62	3.8 ± 0.47
F_5	CCS – 10%	3.20 ± 0.22	8.03 ± 0.81	3.8 ± 0.39
F_6	CCS 15%	3.18 ± 0.19	8.02 ± 0.3	3.8 ± 0.62
F_7	CP -5%	3.22 ± 0.40	7.98 ± 0.32	3.9 ± 0.81
F_8	CP – 10%	3.26 ± 0.36	7.91 ± 0.14	3.9 ± 0.76
F_9	CP – 15%	3.30 ± 0.28	8.03 ± 0.32	3.9 ± 0.82

b) Friability and Weight Variation Test

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P. Limit. Mostly the variation was within ± 1%. All the formulations exhibited less than 1% Friability and was within the I.P. Limit.

Table : 13. Friability and Weight Variation Data of the Tablets.

Formulation Code	Batch	Friability (%)	WeightVariation(mg) ± S.D
F_1	SSG – 5%	0.383	249.75 ± 1.10
F_2	SSG – 10%	0.387	249.85 ± 0.48
F_3	SSG – 15%	0.372	249.10 ± 0.62
F_4	CCS – 5%	0.361	249.85 ± 0.67
F_5	CCS – 10%	0.351	249.37 ± 0.38
F_6	CCS 15%	0.361	249.80 ± 0.45
F_7	CP -5%	0.382	249.60 ± 0.67
F_8	CP – 10%	0.441	250.12 ± 1.18
F_9	CP – 15%	0.421	250.03 ± 1.18

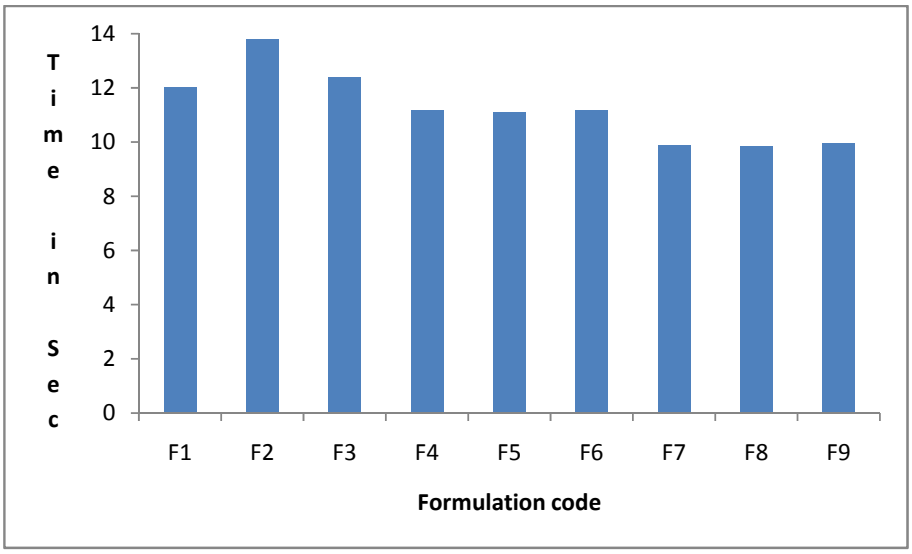
c) Wetting Time and Water Absorption Ratio

The results of Wetting time and Water absorption ratio are presented in Table.14. The Wetting time ranges from 9.76 sec [CP-15%] to 13.78 [SSG-10%] sec and water absorption ratio ranges from 69.13[CP-5%] to 84.42 [SSG-15%]

Table: 14. Wetting Time and Water Absorption Ratio Data of the Tablets

Formulation Code	Batch	Wetting Time [sec]	Water Absorption Ratio
F_1	SSG – 5%	12.02 ± 0.23	80. 56
F_2	SSG – 10%	13.78 ± 0.32	80.83
F_3	SSG – 15%	12.39 ± 0.27	81.42
F_4	CCS – 5%	11.16 ± 0.04	76.25
F_5	CCS – 10%	11.11 ± 0.02	75.79
F_6	CCS – 15%	11.16 ± 0.08	74.52
F_7	CP -5%	9.87 ± 0.01	69.41
F_8	CP – 10%	9.84 ± 0.15	69.13
F_9	CP – 15%	9.96 ± 0.01	69.16

FIG.8. DETERMINATION OF WETTING TIME OF VARIOUS FORMULATIONS OF ODT's OF DILTIAZEM HYDROCHLORIDE



d) Test for Uniformity of Dispersion

The results of Test For Uniformity of Dispersion are presented in Table : 13

Table : 15 Uniformity of Dispersion Data of Tablets

Formulation Code	Batch	Residue remaining on Screen	Result
F_1	SSG – 5%	NIL	PASS
F_2	SSG – 10%	NIL	PASS
F_3	SSG – 15%	NIL	PASS
F_4	CCS – 5%	NIL	PASS
F_5	CCS – 10%	NIL	PASS
F_6	CCS – 15%	NIL	PASS
F_7	CP– 5%	NIL	PASS
F_8	CP – 10%	NIL	PASS
F_9	CP – 15%	NIL	PASS

All batches of tablets posses good uniformity of dispersion.

e) Test for Uniformity of Drug Content

The content uniformity test for Diltiazem hydrochloride was carried out. The results was found to be 99.98 ± 0.071% [SSG – 10%] to 100.01 ± 0.21% [CCS – 5%]. The results were found to be within the I.P. Limits [90%-110%]. It shows that the drug was distributed uniformly throughout the tablets.

Table : 16 Uniformity of Drug content Data of the Tablets.

Formulation Code	Batch	Drug Content (%)± S.D	No.of Tablets Outside 90% – 110% Limit
F_1	SSG – 5%	99.97 ± 0.069	NIL
F_2	SSG – 10%	99.99 ± 0.074	NIL
F_3	SSG – 15%	99.98 ± 0.12	NIL
F_4	CCS – 5%	100.01 ± 0.20	NIL
F_5	CCS – 10%	100.01 ± 0.14	NIL
F_6	CCS 15%	99.99 ± 0.08	NIL
F_7	CP -5%	99.98 ± 0.03	NIL
F_8	CP – 10%	99.99 ± 0.06	NIL
F_9	CP – 15%	100.01 ± 0.03	NIL

f) Moisture Uptake by Various Formulations of Oro dispersible Tablets: (ODT's)

The moisture uptake test was conducted for various formulations of Oro dispersible tablets of Diltiazem hydrochloride. Any difference in moisture uptake among various formulations may be due to difference in type or concentration of super disintegrant added.

From the observations, it is evident that water uptake of super disintegrant follows the order SSG > CCS > CP.

***(j) IN – VITRO* DRUG RELEASE STUDIES**

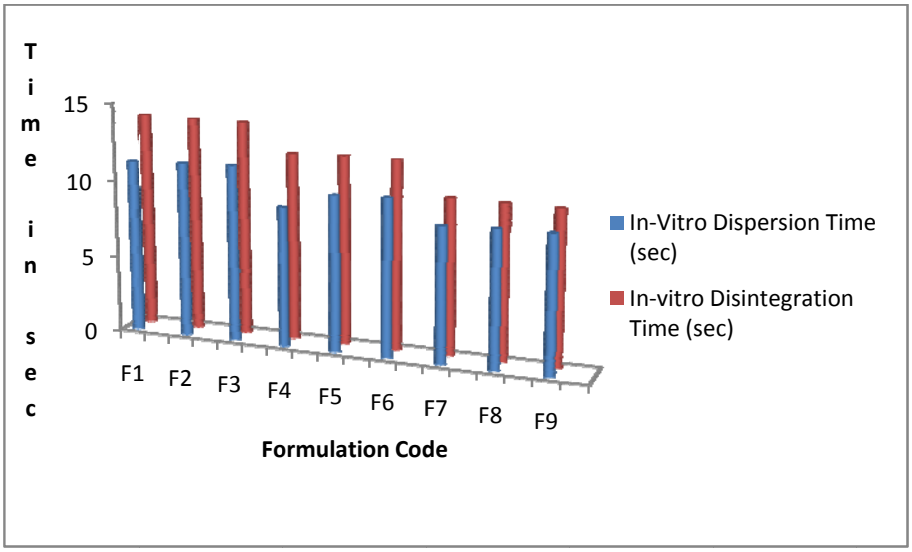
(I) & (II) *In – vitro* Dispersion Time and *In – vitro* Disintegration Time

The results of *In-vitro* dispersion time and *In-vitro* disintegration time ranges from 8.79 sec [CP –5%] to 13.49 sec [PVP–15%] and 10.04 sec [CP – 15%] to 17.31 sec [PVP–15%]

Table: 17. *In-vitro* Dispersion Time and *In-vitro* Disintegration Time Data of the tablets

Formulation Code	Batch	*In-Vitro* Dispersion Time (sec) ± S.D [n = 3]	*In-vitro* Disintegration Time (sec) ± S.D. [n=6]
F_1	SSG – 5%	11.16 ± 0.13	13.82 ± 0.11
F_2	SSG– 10%	11.27 ± 0.06	13.79 ± 0.13
F_3	SSG– 15%	11.38 ± 0.01	13.80 ± 0.18
F_4	CCS – 5%	9.01 ± 0.02	12.08 ± 0.14
F_5	CCS–10%	10.06 ± 0.01	12.19 ± 0.19
F_6	CCS–15%	10.19 ± 0.04	12.21 ± 0.12
F_7	CP –5%	8.79 ± 0.06	10.10 ± 0.02
F_8	CP – 10%	8.91 ± 0.03	10.08 ± 0.21
F_9	CP – 15%	8.94 ± 0.08	10.04 ± 0.04

The *In-vitro* dispersion time was minimum (8.79 sec to 8.94 sec) with Cros povidone containing batches and maximum (11.16 sec to 11.38 sec) with SSG containing batches. The *In-vitro* disintegration time was rapid [10.04 sec to 10.10 sec] with Cros povidone containing batches and delayed [13.79 sec to 13.82 sec] with SSG containing batches. The rapid disintegration may be due to rapid uptake of water from the medium, swelling and burst effect.



(III) *In – Vitro* Dissolution Studies

Dissolution apparatus II USP XXI model was used to carried out the *in-vitro* drug release studies on the prepared batches of Oro dispersible tablets. 650 ml of Sorenson's buffer solution (pH-6.8) was used as the dissolution medium. The tablet was placed in the bowel and the paddle was rotated at 50 rpm. The temperature of the dissolution medium was maintained at $37^{o}C \pm 0.5^{o}C$.

Analysis of Samples :

1ml of sample was withdrawn at periodic intervals 1st, 2nd, 4th, 6th, 8th and 10th minutes and was made up to 10ml with Sorenson's buffer solution. 1ml of Fresh dissolution medium was replaced after each time of withdrawl of sample. The samples were analyzed spectro photometrically at 228 nm for the drug content against the respective buffer blank. The mean percentage of Diltiazem hydrochloride released at various time intervals was calculated and plotted against time.

The results of the dissolution data for various formulations of ODT's of Diltiazem hydrochloride are presented in Table 17 to 28.

***In – vitro* Dissolution Studies**

Table : 17 Dissolution data of F_1 [SSG-5%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	18.2	60.61	60.61
2	2	18.32	63.07	63.16
3	4	21.45	71.5	71.60
4	6	22.10	73.67	73.78
5	8	24.05	80.14	80.25
6	10	24.05	81	81.12

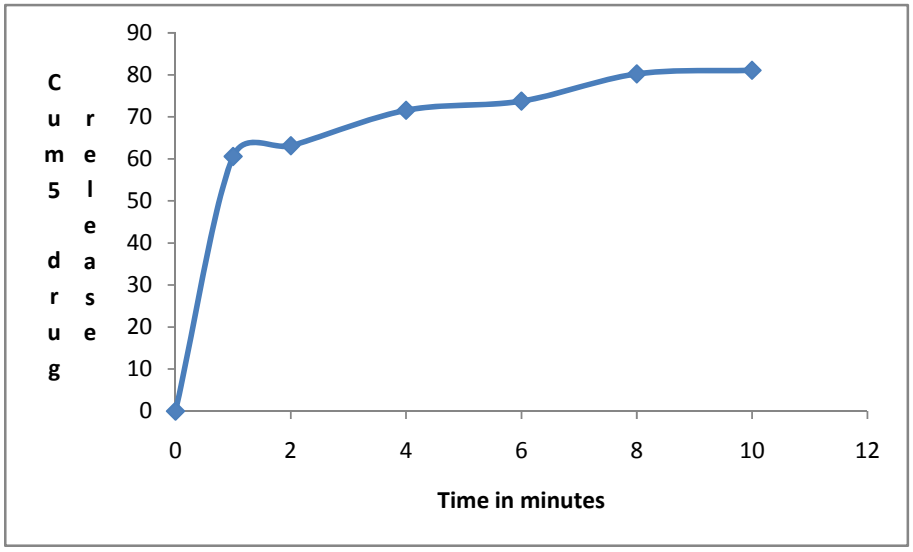


Fig.6: Dissolution Profile of Formulation F_1 [SSG-5%]

Table : 18 Dissolution data of F_2 [SSG -10%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	18.92	63.07	63.07
2	2	20.8	69.33	69.43
3	4	22.1	73.67	73.78
4	6	23.4	78	78.11
5	8	24.7	82.35	82.47
6	10	25.35	84.5	84.63

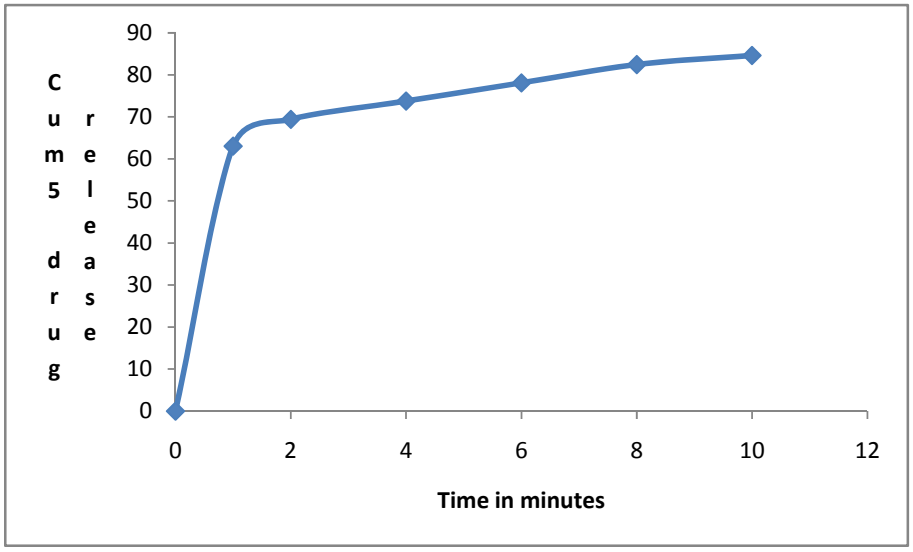


Fig.7: Dissolution Profile of Formulation F_2 [SSG-10%]

Table : 19 Dissolution data of F_3 [SSG -15%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	21.45	71.5	71.5
2	2	22.1	73.67	73.78
3	4	24.05	80.17	80.28
4	6	25.02	83.42	83.54
5	8	26.65	89.83	89.96
6	10	27.63	92.1	92.24

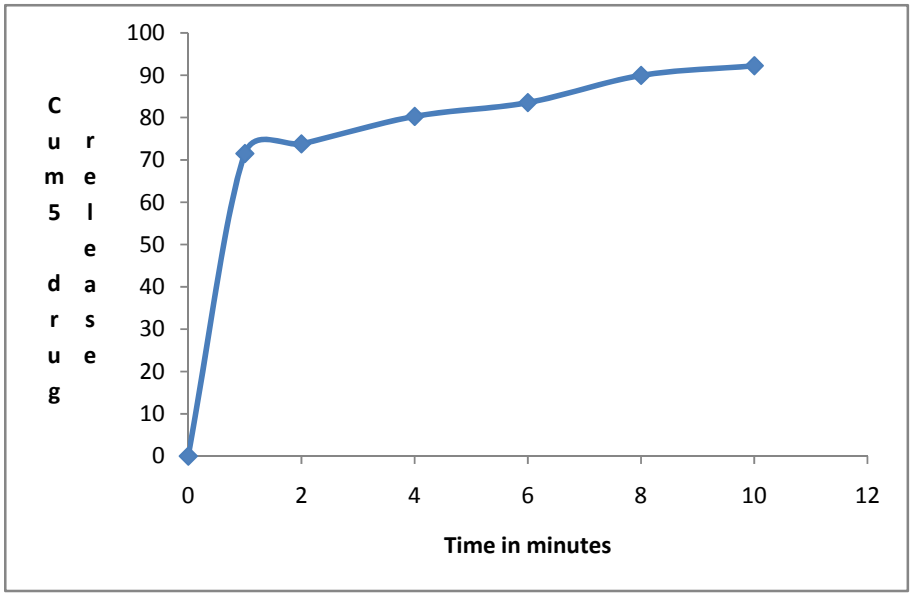


Fig.8 Dissolution Profile of Formulation F_3 [SSG-15%]

Table : 20 Dissolution data of F_4 [CCS -5%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	20.8	69.33	69.33
2	2	22.6	73.67	73.78
3	4	24.05	80.17	80.28
4	6	25.35	84.5	84.62
5	8	26.97	89.91	90.04
6	10	27.63	92.1	92.24

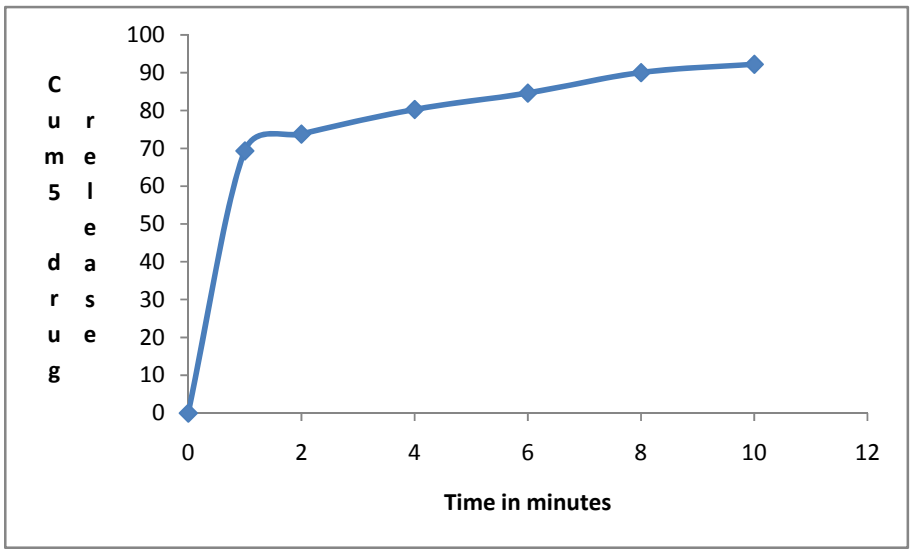


Fig.9: Dissolution Profile of Formulation F_4 [CCS-5%]

Table : 21 Dissolution data of F_5 [CCS -10%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	21.77	72.58	72.58
2	2	24.05	80.17	80.28
3	4	25.35	84.5	84.62
4	6	27.3	91	91.13
5	8	27.95	93.16	93.30
6	10	28.6	95.33	95.47

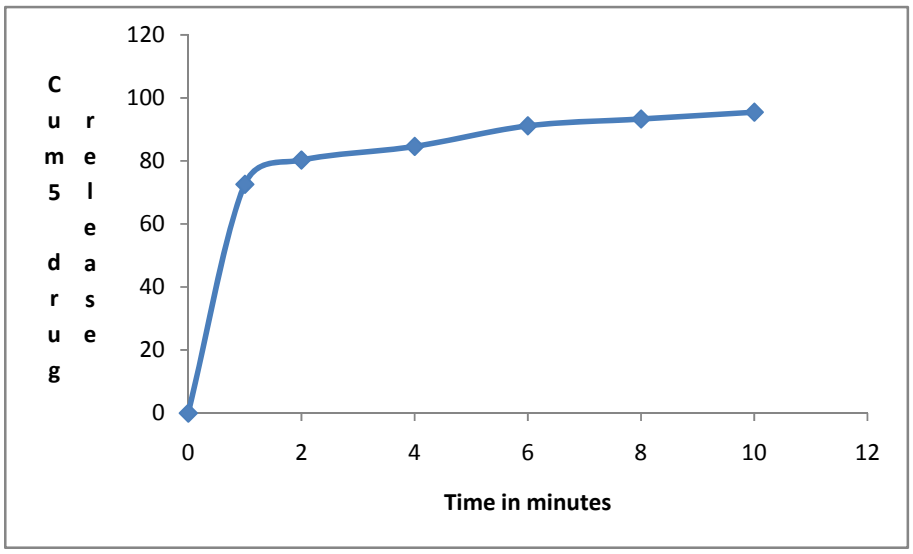


Fig.10: Dissolution Profile of Formulation F_5 [CCS-10%]

Table : 22 Dissolution data of F_6 [CCS-15%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	23.4	78	78
2	2	25.35	84.5	84.62
3	4	26	86.67	86.80
4	6	27.63	92.1	92.23
5	8	28.6	95.33	95.47
6	10	29.25	97.5	97.65

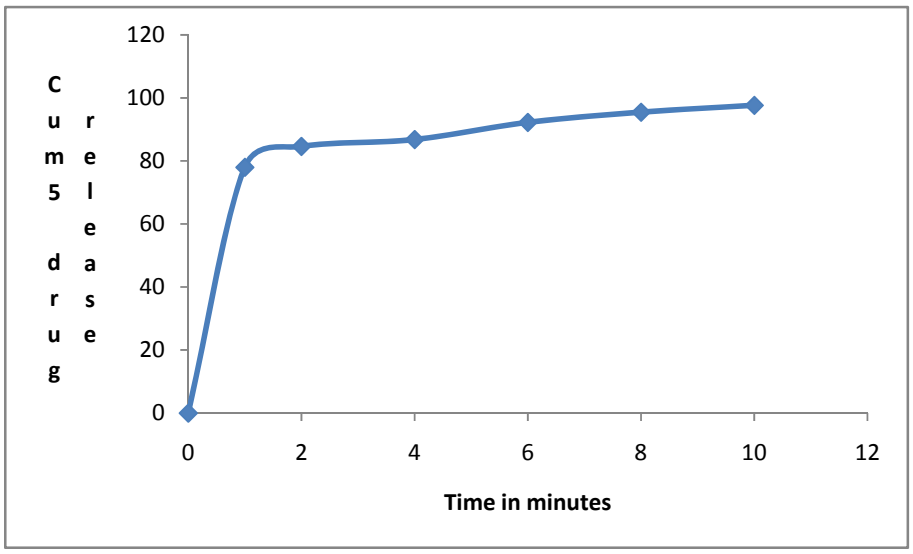


Fig.11: Dissolution Profile of Formulation F_6 [CCS-15%]

Table : 23 Dissolution data of F_7 [CP-5%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.25	81.25
2	2	25.35	84.5	84.62
3	4	26.97	89.91	90.04
4	6	28.27	94.25	94.39
5	8	28.92	96.41	96.55
6	10	29.25	97.5	97.65

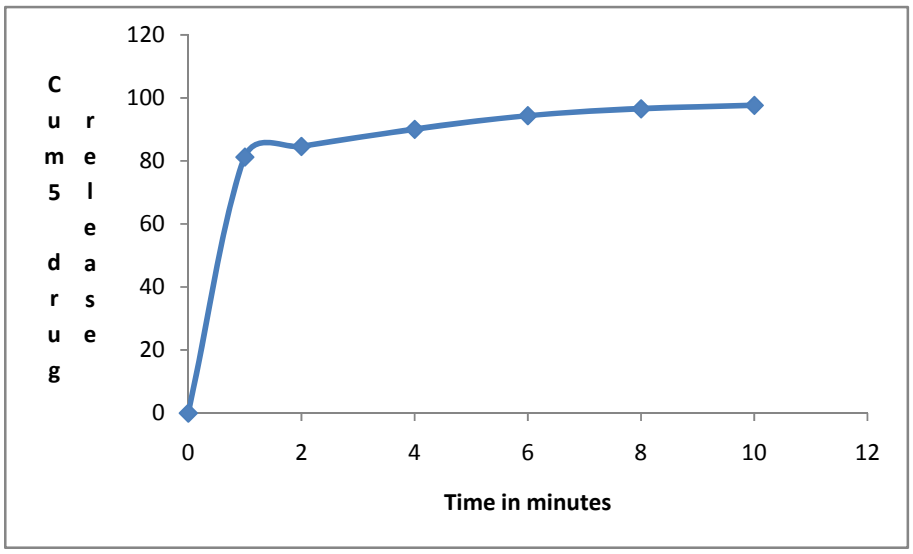


Fig.12 : Dissolution Profile of Formulation F_7 [CP-5%]

Table : 24 Dissolution data of F_8 [CP-10%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.25	81.25
2	2	25.35	84.5	84.62
3	4	26.65	88.43	88.56
4	6	27.95	93.16	93.30
5	8	29.25	97.5	97.64
6	10	29.9	99.66	99.81

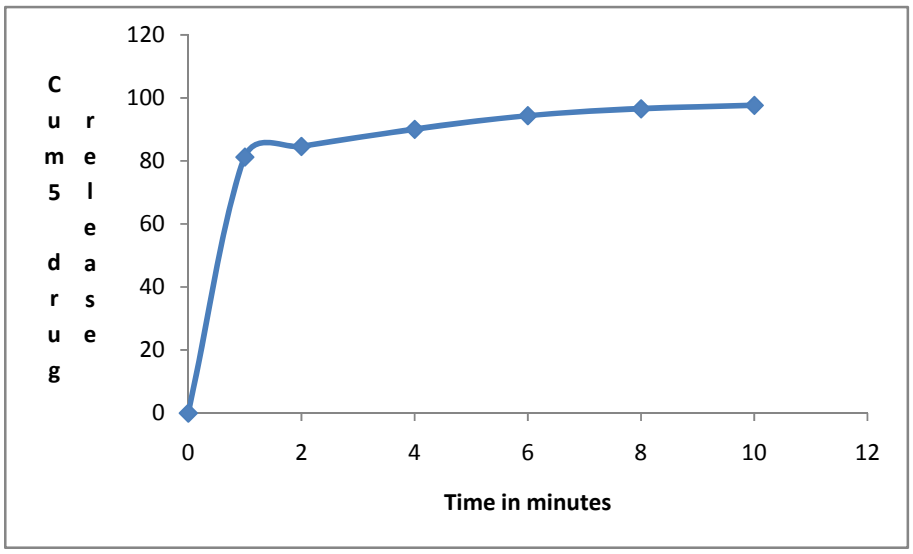


Fig.13 : Dissolution Profile of Formulation F_8 [CP-10%]

Table : 25 Dissolution data of F_9 [CP-15%]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	23.7	79.08	79.08
2	2	25.02	83.42	83.54
3	4	26	86.67	86.80
4	6	27.3	91	91.13
5	8	27.95	93.16	93.30
6	10	28.92	96.41	96.55

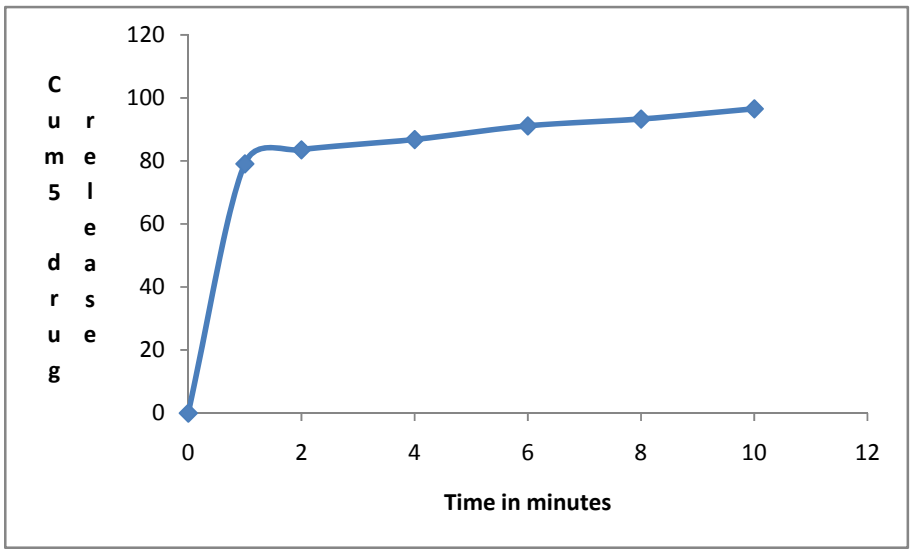


Fig.14 : Dissolution Profile of Formulation F_9 [CP-15%]

Formulation F_1[SSG-5%], F_2[SSG-10%] and F_3[SSG-15%]

Formulation F_1, F_2 and F_3 releases 81.12%, 84.63% and 92.24% drug respectively at the end of 10 minutes. The percentage of drug release increased with increased concentration of Sodium Starch Glycolate (SSG) from 5 to 15%.

The higher dissolution rates observed with SSG may be due to rapid disintegration and fine dispersion of particles formed after disintegration.

Formulation F_4[CCS-5%], F_5[CCS-10%] and F_5[CCS-15%]

Formulation F_4, F_5 and F_6 release 92.24%, 95.47% and 97.65% respectively at the end of 10 minutes. The percentage of drug release increased with increased Concentration of Cros Carmellose Sodium (CCS) from 5 to 15%.

The higher dissolution rates observed with CCS may be due its strong swelling power which exerts sufficient hydrodynamic pressure which inturn facilitates complete and rapid disintegration.

Formulation F_7[CP-5%], F_8[CP-10%] and F_9[CP-15%]

Formulations F_7, F_8, and F_9 releases 97.65%, 99.81% and 96.55% drug respectively at the end of 10 minutes [Ref.Table 23 – 25, Fig 12 - 14]

The percentage of drug release increased with increased concentration of superdisintegrant. From 5 to 10% on increasing the concentration of superdisintgrant from 10 to 15%. The percentage of drug release declines.

In case of polyplasdone XL [CP] up to 10% w/w concentration, there was steady increase dissolution rate with concentration. Therefore 10% w/w concentration is optimum for polyplasdone XL [CP].

The higher dissolution rates observed upto the optimum concentration [10% w/w] may be due to highly porous structure of the super disintegrant which facilitates faster water uptake and hence faster disintegration, easy break down of particles and rapid absorption of drug into the dissolution medium.

Decrease in dissolution rate with increase in concentration may be due to the blockade of pores resulting in interior of tablets inaccessible to water.[20]

Order of Enhancement of Dissolution rate with Various Super disintegrants

In the formulation of ODT's of Diltiazem hydrochloride various super disintegrants like Cros Povidone [CP], Cros Carmellose Sodium [CCS] and Sodium Starch Glycolate [SSG] were employed.

The order of enhancement of the dissolution rate with various super disintegrants was found to be CP > CCS > SSG.

From the overall observations, formulation F_8 containing 10%w/w concentration of Cros povidone was considered to be the optimized formulation which releases upto 99.81% of the drug in ten minutes.

(V) Comparative *In-vitro* Drug Release Studies for the Optimized Formulation F_8 [Cp – 10%] With Marketed Sample of the Same Drug [Suminat]

The *In-vitro* Drug release profiles for the optimized formulation F_8[CP-10%] was compared with Dilzem [Torrent]

At the end of ten minutes of *in-vitro* dissolution study only 48.49% of the drug was released from Dilzem whereas 99.81% of the drug was released from the optimized formulation F_8 [CP-10%].

Table : 30 *In-vitro* Dissolution data for Dilzem

Sl.No	Time in min	Cumulative % drug release	
		F8	Marketted product
1	1	81.25	12.35
2	2	84.62	19.28
3	4	88.56	31.14
4	6	93.30	38.24
5	8	97.64	43.85
6	10	99.81	48.49

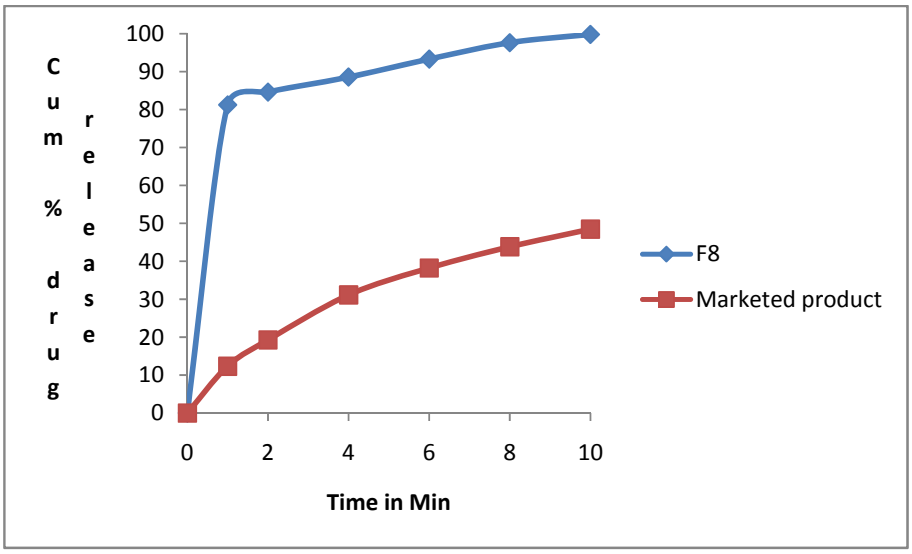


Fig.19 : Dissolution Profile of Formulation F_8 [CP-10 %] compared with Dilzem

The results obtained from the data given in Table.28 reveals that enhanced dissolution characteristics of the formulation F_8[CP-10%] which may be due to the high wicking action of Cros Povidone which makes the tablets to swell and facilitates quick disintegration of the tablets.

(VI) Stability Studies

The optimized formulations F_8[CP-10%] was subjected to stability studies for 3 month at 40°C / 75% RH in stability chamber [Osworld, Mumbai], 8°C in Refrigerator and 60°C in Incubator. At the interval of 30 days, the tablets were withdrawn and evaluated for Thickness, Diameter, Hardness, Friability, weight variation, content uniformity and disintegration time. All the parameters have not shown much variation when compared to the initial data and the results were within the limits.

The *in-vitro* dissolution studies were carried out for 3 months at the interval of 30 days. The release profiles were not affected by exposing to higher temperature and the specified humidity conditions.

Table : 31 Dissolution data of F_8 A.S [CP – 10%] [After 1 month at 4°C]

Sl.No	Time in min	Amount of drug release in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.25	81.25
2	2	25.35	84.5	84.62
3	4	26.65	88.43	88.56
4	6	27.95	93.16	93.30
5	8	29.25	97.5	97.64
6	10	29.9	99.66	99.81

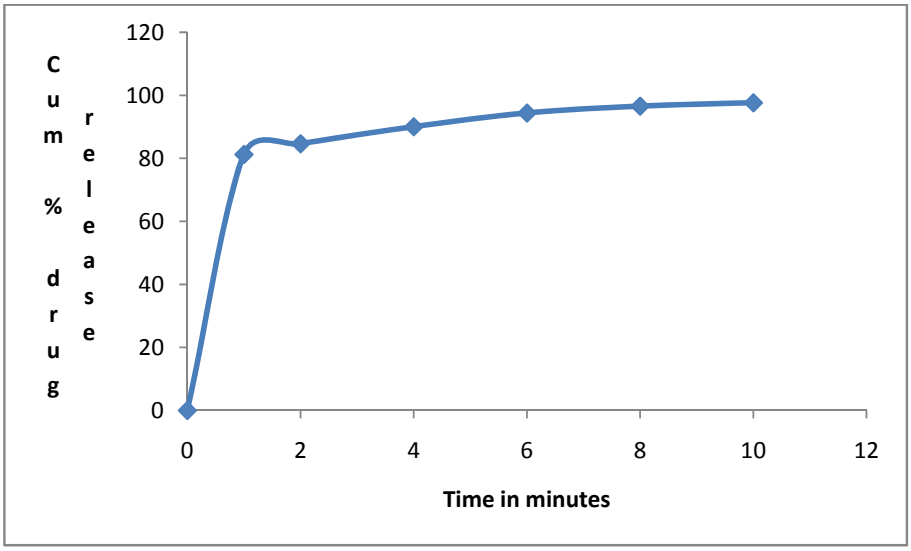


Fig.20: Dissolution profile of F_8 A.S [CP – 10%] [After 1 month at 4°C]

Table : 32 Dissolution data of F_8 [CP – 10%] [After 2 month at 4°C]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.25	81.25
2	2	25.35	84.5	84.62
3	4	26.65	88.43	88.56
4	6	27.95	93.16	93.30
5	8	29.25	97.5	97.64
6	10	29.9	99.66	99.81

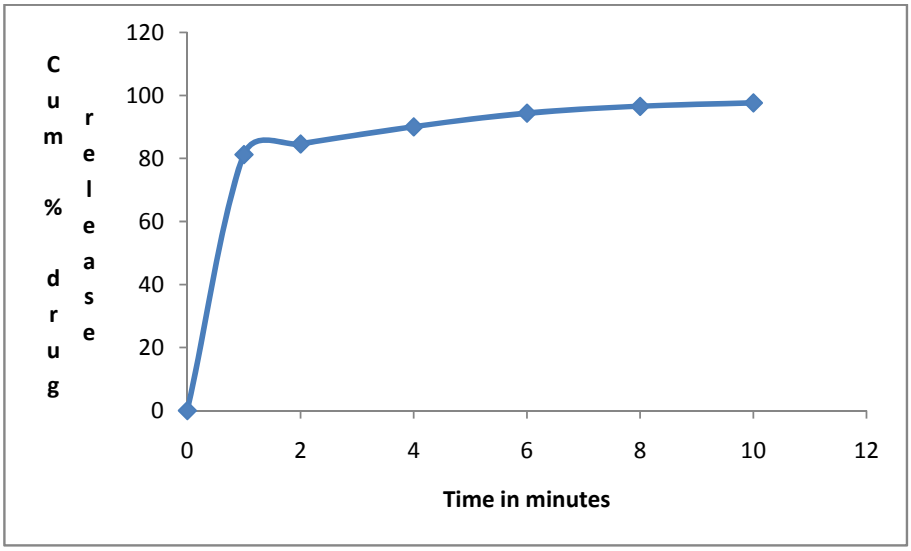


Fig.21:Dissolution profile of F_8 A.S [CP – 10%] [After 2 months at 4°C]

Table : 33 Dissolution data of F_8[CP 10%] [After 3 months at 4°C]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.23	81.23
2	2	25.35	84.50	84.62
3	4	26.00	86.66	86.79
4	6	28.60	95.33	95.46
5	8	29.25	97.50	97.65
6	10	29.90	99.67	99.82

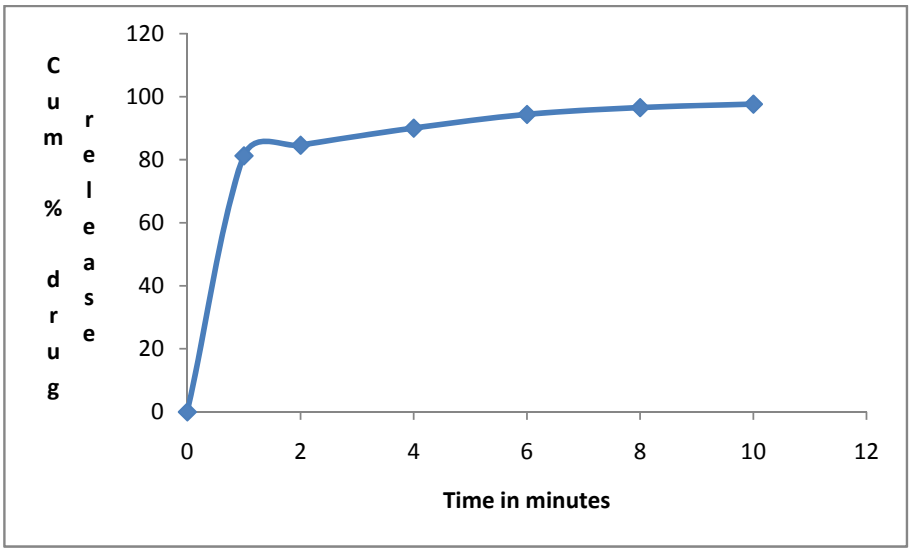


Fig.22:Dissolution profile of F_8 A.S [CP – 10%] [After 3 months at 4°C]

Table : 34 Dissolution data of F_8[CP -10%] [After 1 month at room temperature]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.25	81.25
2	2	25.35	84.5	84.62
3	4	26.65	88.43	88.56
4	6	27.95	93.16	93.30
5	8	29.25	97.5	97.64
6	10	29.9	99.66	99.81

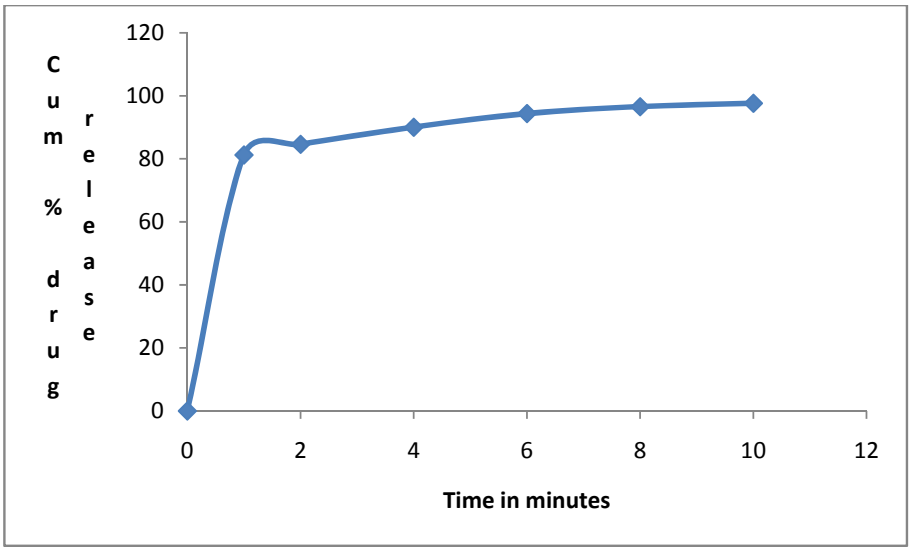


Fig.23:Dissolution profile of F_8 A.S [CP – 10%] [After 1 month at room temperature]

Table : 35 Dissolution data of F_8[CP – 10%] [After 2 months at room temperature]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	24.37	81.23	81.23
2	2	25.35	84.50	84.62
3	4	26.65	88.43	88.56
4	6	27.30	91.00	91.14
5	8	28.60	95.33	95.47
6	10	29.90	99.67	99.82

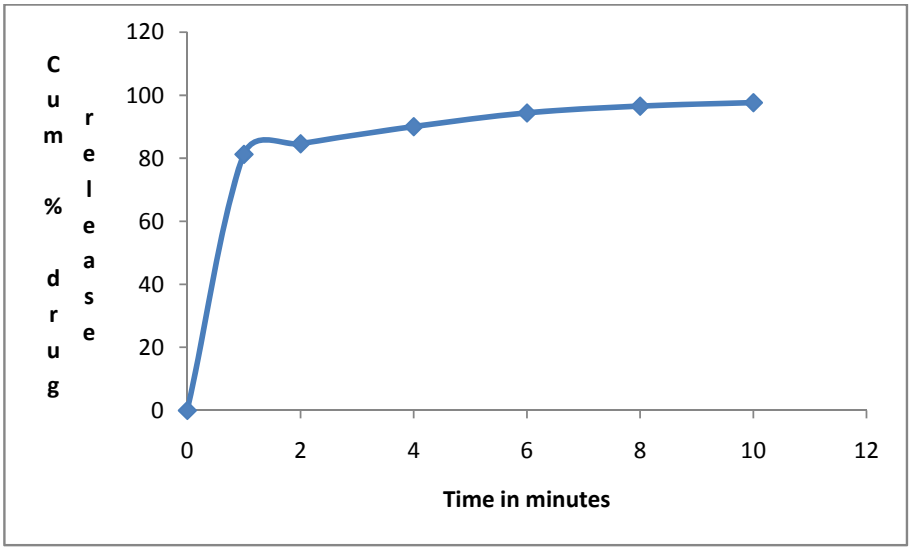


Fig.24:Dissolution profile of F_8 A.S [CP – 10%] [After 2 months at room temperature]

Table : 36 Dissolution data of F_8[CP – 10%] [After 3 months at room temperature]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	23.40	78.00	78.00
2	2	25.35	84.50	84.62
3	4	26.00	86.67	86.80
4	6	27.30	91.00	91.13
5	8	29.25	97.50	97.64
6	10	29.90	99.67	99.82

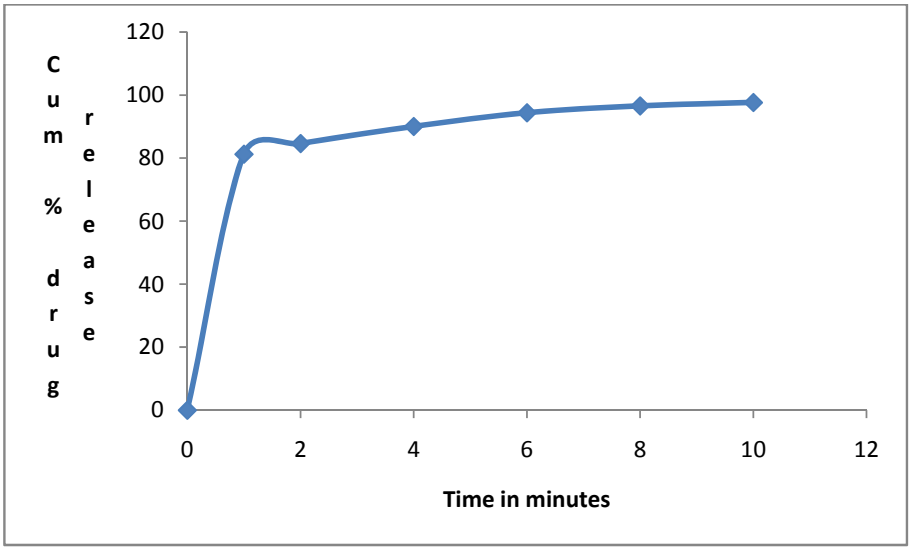


Fig.25:Dissolution profile of F_8 A.S [CP – 10%] [After 3 months at room temperature]

Table : 37 Dissolution data of F_8[CP – 10%] [After 1 month at 45°C/ 75%RH]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	23.40	78.00	78.00
2	2	25.35	84.50	84.62
3	4	26.65	88.43	88.56
4	6	27.30	91.00	91.14
5	8	28.60	95.33	95.47
6	10	29.90	99.66	99.80

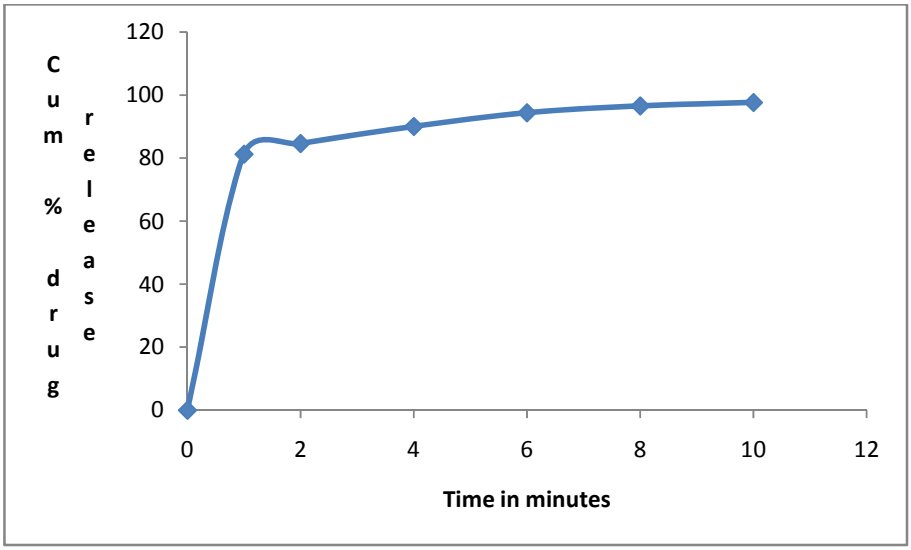


Fig.26:Dissolution profile of F_8 A.S [CP – 10%] [After 1 month at 45°C/ 75%RH]

Table : 38 Dissolution data of F_8[CP – 10%] [After 2 months at 45°C/ 75%RH]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	22.75	75.80	75.80
2	2	24.70	82.33	82.44
3	4	26.00	86.67	86.80
4	6	27.30	91.00	91.13
5	8	28.60	95.33	95.47
6	10	29.57	98.58	98.73

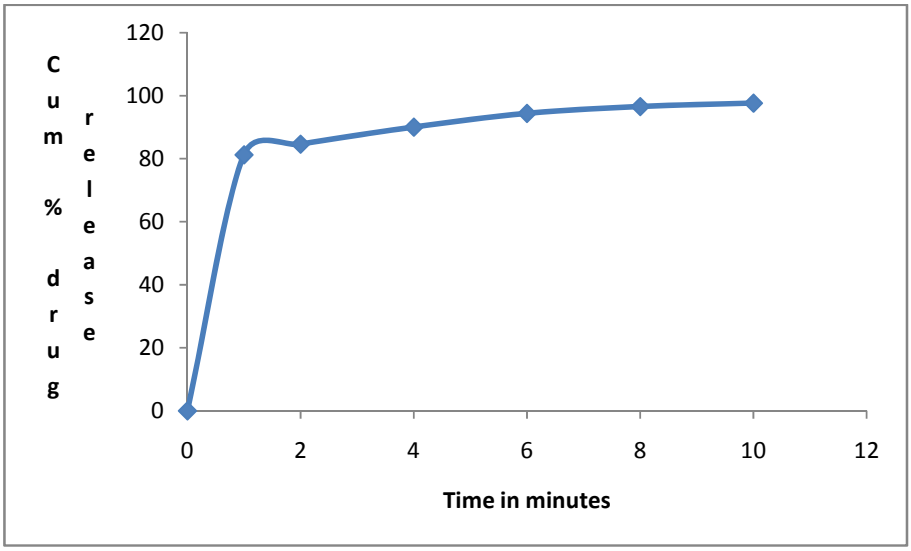


Fig.27:Dissolution profile of F_8 A.S [CP – 10%] [After 2 months at 45°C/ 75%RH]

Table : 39 Dissolution data of F_8[CP – 10%] [After 3 months at 45°C/ 75%RH]

Sl.No	Time in min	Drug concentration in mg	Percentage drug release (%)	Cumulative % drug release
1	1	22.75	75.80	75.80
2	2	24.05	80.17	80.29
3	4	25.35	84.50	84.62
4	6	26.65	88.43	88.56
5	8	27.95	93.16	93.30
6	10	29.25	97.50	97.64

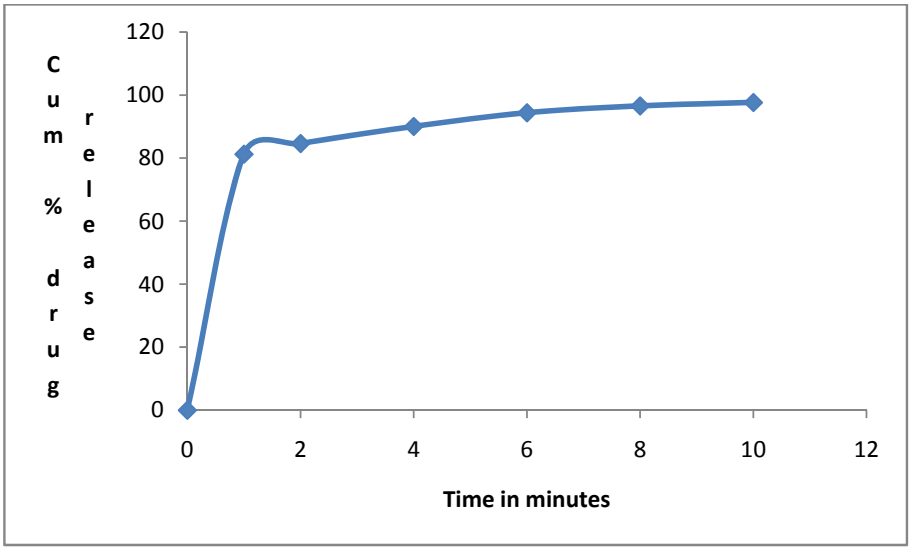


Fig.28:Dissolution profile of F_8 A.S [CP – 10%] [After 3 months at 45°C/ 75%RH]

The optimized formulation F8 did not show any significant changes in drug release profile, hardness, friability, weight variations after the period of 3 months. Hence it can be concluded that the optimized batch F8 is stable at an accelerated storage conditions.

KINETICS OF DRUG RELEASE

A plot of percentage of drug remaining verses time would be linear. If the drug release follows zero order kinetics [i.e. concentration independent release].

The linear equation for zero order drug release plot is.

$$Ct = C_0 – Kt$$

Where

Ct= concentration remaining at time t.

C_0= Original concentration.

T = Time.

K = Release rate.

A plot of log concentration of drug remaining verses time would be linear, if the drug release follows first order kinetics [i.e. concentration dependent].

The linear equation for first order drug release plot is.

$$Log\ C = Log\ C_0 – Kt/2.303$$

Since the polymers used for preparing Oro dispersible tablets are soluble in the medium, was assumed that the drug release data obtained in dissolution for optimized formulation was treated accordingly to first order equation.

The optimized formulation F_8 [CP -10%] upon kinetic treatment releases the drug by first order kinetics.

A plot of Logarithm of percentage of drug remaining to be released versus time showed linearity.From the plot, correlation coefficient and slope value was found to be 0.857.

The values obtain signify that the drug release follows first order kinetics (i.e. concentration dependent release).

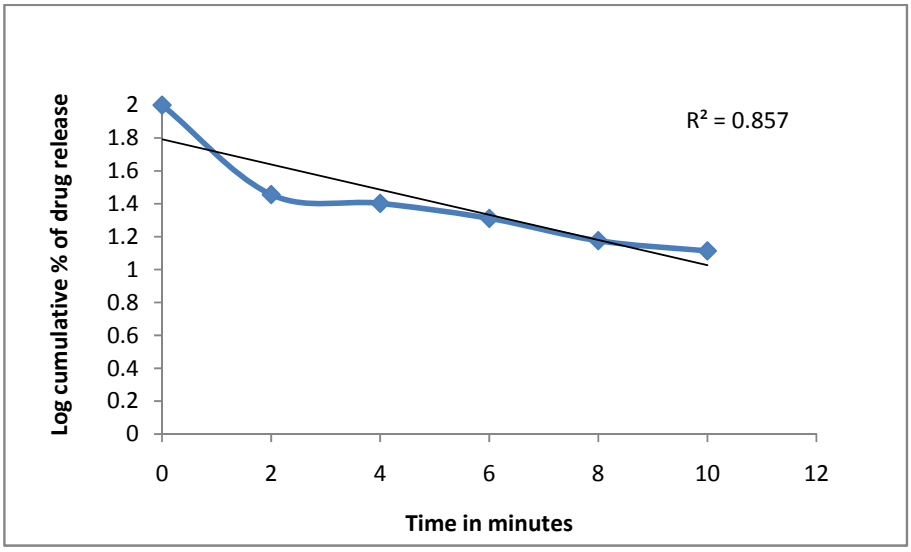


Fig.29: Plot of Log % of Drug remaining to be released Versus Time IN F8

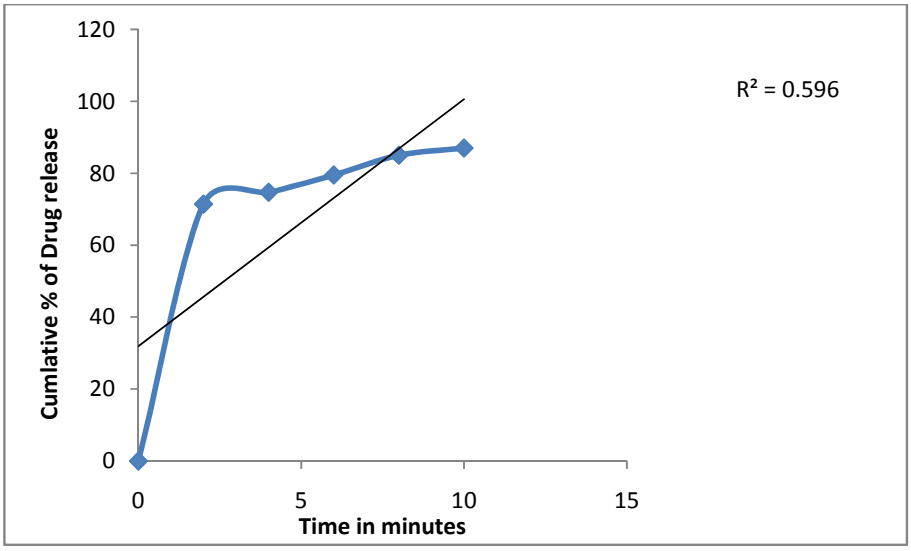


Fig 30 Plot Of Zero Order Drug Release In F8

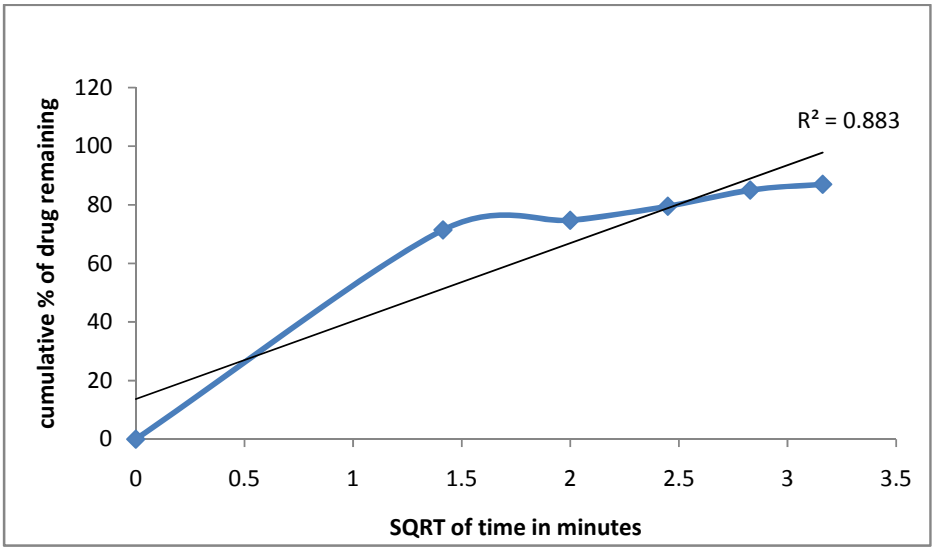


FIG NO 31 PLOT OF HIGUCHI IN F8

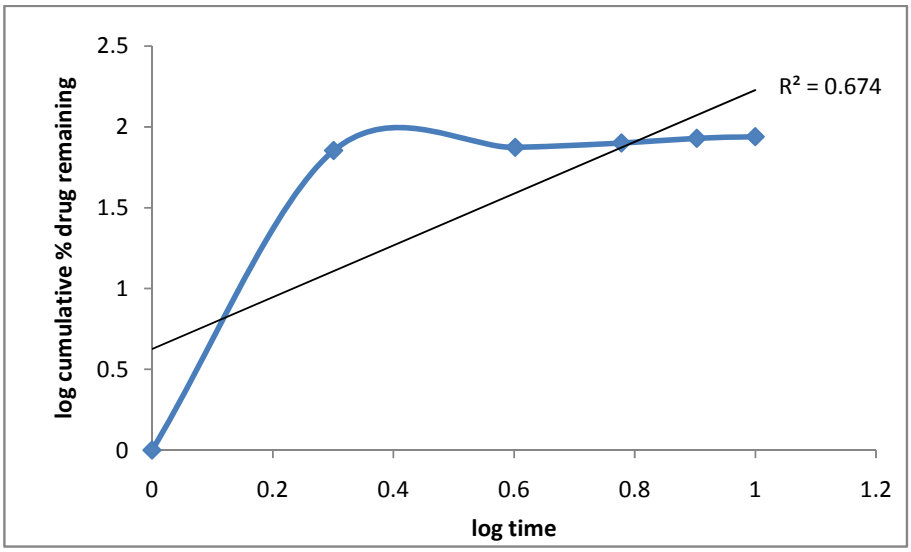


FIG 32. PLOT OF PEPPA'S IN F8

Discussion on kinetic studies:

To know the drug release from the formulation F9, data obtained from the in-vitro dissolution studies was fitted into Zero order, First order, Higuchi, Korsmeyer-peppas equations.

First order kinetics plot:

The graph was plotted between log cumulative % drug remaining and time. Formulation F9 was best explained by first order kinetics and regression value is 0.857 showed that drug release relationship with concentration of the drug.

Zero order kinetics plot:

The graph was plotted between cumulative % drug release and time. Formulation F9 was best explained by first order kinetics and regression value is 0.596 showed that drug release doesn't relationship with concentration of the drug.

Higuchi plot:

The graph was plotted between cumulative % drug remaining and square root of time. The regression value is 0.883 that clearly indicating that drug releasing mechanism was predominantly controlled by Diffusion mechanism.

Korsmeyer - peppas plot:

The graph was plotted between log cumulative % of drug remaining and log time. The regression value was 0.674. This indicates the drug release follow fickian diffusion.

CONCLUSION

CONCLUSION

The oro dispersible Tablets (ODT's) of Diltiazem hydrochloride were prepared by Direct compression method using various super disintegrants. Formulation **F_8** containing 10%w/v concentration of Cros Povidone with appropriate amount of other excipients were considered to be the optimized formulation with the desired drug release.

The oro dispersible Tablet formulation of Diltiazem hydrochloride provides instant relief for migraine sufferers and helps them to resume their normal function as soon as possible. All formulation were found to have homogenic drug distribution with excellent content uniformity. F8 batch contains 10% CP was optimized.

Comparative drug release study revealed that the formulated Oro dispersible tablets [ODT's] release drug more rapidly than the marketed sample.

The results of stability studies revealed that the formulation F_8 showed no significant variations in all the parameters and was stable for a period of 3 months.

The optimized formulation F_8 was found to follow First order kinetics, which was revealed by the linearity shown from the plot of logarithm of drug remaining to be released versus time.

In future, the developed formulation F_8 can be subjected to Bioequivalence study and suitability to the market can be decided based on that.

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BIBLIOGRAPHY

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