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FORMULATION AND EVALUATION OF FAST MOUTH DISSOLVING TABLET OF AMLODIPINE BESYLATE USING DIFFERENT SUPER DISINTEGRANTS.

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ABSTRACT

Amlodipine besylate is a long-acting calcium channel blocker used to treat chronic stable angina, vasospastic angina and hypertension. Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution will increase by incorporating the drug in a fast dissolving dosage form. An attempt will be made to develop rapidly disintegrating oral tablets of Amlodipine Besylate by direct compression method. In this study, Fast Dissolving Tablet (FDT) was prepared using direct compression method using Crospovidone and Sodium starch glycolate as the super disintegrants. Amongst all formulations, formulation F3 prepared by a combination of both Crospovidone and Sodium starch glycolate showed least disintegrating time, and faster dissolution of 87%. Combination of super disintegrants were found to be better to formulate fast dissolving tablets of Amlodipine besylate.

Keywords: Fast Disintegrating tablet, Crospovidone, Sodium starch glycolate, Amlodipine Besylate

1.INTRODUCTION

Solid dosage forms are the most popular and widely preferred drug delivery system due to the advantages afforded both to the manufacturer and the patient (Abdelbary et al., 2004, Banker, 2005). Many patients find difficulty in swallowing tablets and hard gelatin capsules; consequently fail to take medication as prescribed which results in high incidence of non-compliance and ineffective therapy (Shailendra et al., 2012). Among the different types of tablets, emerged the concept of Fast dissolving tablet with the desire to provide the patients with more convenient means of taking their medication. Fast dissolving technology offers some unique advantages over conventional drug delivery systems in that it offers quick disintegration and dissolution of tablets. The tablet dissolves or disintegrates in the oral cavity even without drinking water (Ved et al., 2012).

The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration. The solutions containing the active ingredients are swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect (Dobetti et al., 2001). Target groups for oral FDTs are wide-ranging people of all ages who can have trouble in swallowing conventional tablets and capsules. This includes children and the elderly who either have trouble and cannot swallow or have not learned to swallow the conventional solid dosage forms. In addition, psychiatric patients as well as hospitalized or bedridden patients suffering from a variety of disorders such as stroke, thyroid disorders, Parkinson's disease and other neurological disorders such as multiple sclerosis and cerebral palsy (Sastry et al., 2000) also find difficulty in swallowing tablets and require 'fast-melt' tablets because of their physical condition. The convenience and ease of using FDTs is also important to normal consumers, with some adults preferring these dosage forms as they are easy to handle and swallow, can be taken without water and have a rapid onset of action (Ciper et al., 2006, Jeong et al., 2008). For example, patients and travellers with a limited access to water would also find such FDTs extremely beneficial (Sastry et al.,2000, Mizumoto et al., 2005). Besides improving patient compliance, FDTs have been investigated for their potential in increasing the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug (Ahmed et al., 2007, Corveleyn et al., 1998). Fast dissolving tablets are prepared by various techniques, mainly direct compression (Bi et al., 1996), lyophilization (Chandrasekhar et al., 2009) and compression molding (Ford, 1986); thus, they exhibit different disintegration behaviour. The basic approach used in the development of the fast-dissolving tablets is the use of superdisintegrants. Sodium starch glycolate, and crospovidone were screened in the present study. Another approach used in developing FDT is by maximizing the pore structure of the tablets. Freeze-drying and vacuum-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Usually superdisintegrants are added to a drug formulation to ease the breakup or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants (Abdelbary et al., 2004). Amlodipine besylate is a long-acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension (Brunton et al., 2005). Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by incorporating the drug in a fast dissolving dosage form (Sinko, 2006). The simplicity and cost effectiveness of the direct compression process have positioned this technique as an alternate to granulation technologies. In the present study we have developed an effective and stable FDT of Amlodipine besylate

formulated by wet granulation direct compression method with adequate hardness, low disintegration time and pleasant taste. Another purpose was to study the influence of superdisintegrants when used alone and in combination.

1.2Mouth dissolving tablet:

Definition

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintrigrates in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient‟s saliva along with the soluble andinsoluble excipients. 4-5These are also called melt-in-mouth tablets, porous tablets, oro- dispersible, quick dissolving or rapid disintegrating tablets.

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the mouth dissolving tablet (MDT) is the most widely preferred commercial products . The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules, Liquid preparations are administered by oral route . During the last decade, mouth dissolving tablet (MDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention. The MDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All MDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good MDTs varies from several seconds to about a minute . Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Mouth dissolving of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric

absorption when formulated as MDTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing .The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms.Tablet is still most popular conventional dosage forms existing today because of ease of self administration ,compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in wallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection.Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as “a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue.” Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute. The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking. In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability,convenience and patient compliance. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets. within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

1.2.1. Ideal properties of MDT

a. Not require water or other liquid to swallow.

b. Easily dissolve or disintegrate in saliva within a few seconds.

c. Have a pleasing taste.

d. Leave negligible or no residue in the mouth when administered.

e. Be portable and easy to transport.

f. Be able to be manufactured in a simple conventional manner within low cost.

g. Be less sensitive to environmental conditions like temperature, humidity etc

1.2.2. Salient features of MDT's

a) Ease of administration to pediatric, geriatric and psychiatric patients who refuse to swallow tablets.

b) To swallow the dosage form, water not required which is highly convenient feature for patients who are depressed.

c) Good mouth feel property helps to change the basic impression of bitter medication.

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

e) Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs.

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

1.2.3 Desired Criteria for MDT'S

Mouth Dissolving Tablets should

a) Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.

b) Be compatible with taste masking.

c) Be portable without fragility concern.

e) Leave minimal or no residue in the mouth after oral administration.

f) Exhibits low sensitivity to environmental conditions as humidity and temperature.

g) Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

1.2.4 Advantages of Mouth Dissolving Tablets

a) Leave minimal or no residue in mouth after administration.

b) Rapid drug therapy intervention.

c) Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.

d) Administration to such as pediatric, geriatric & psychiatric patients.

e) Achieve increased bioavailability/rapid absorption through pregastric absorption.

f) Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
g) Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.

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

i) It provides advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

j) High degree of vascularization, minimal enzymatic pool and passing of first pass metabolism increase bioavailability of drugs ideally suited for delivering drugs that are absorbed buccally.

1.2.5 Limitations of Mouth Dissolving Tablets

a) The tablets usually have insufficient mechanical strength. Hence, careful handling is required.

b) The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
c) Drugs with relatively larger doses are difficult to formulate into MDT. d) Patients who concurrently take anticholinergic medications & patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

1.2.6 Drug candidates suitable for Mouth dissolving tablets

Selection of drug candidate for MDT is a very crucial step while developing such dosage forms because of the following factors:

a) Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.

b) Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.

c) Patients with Sjogrens syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.

d) Drugs with a short half-life and frequent dosing.

e) Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.

f) The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g. selegiline, apomorphine, buspirone etc.

g) The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.

h) Drugs having ability to diffuse and partition into the epithelium o f the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

1.2.7Challenges in formulating Fast dissolving tablets:

1.2.7.1 Palatability

As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. Upon administration, it disintegrate or dissolve in patient‟s oral cavity, thus releasing the active ingredients which come in contact with the taste buds.Hence, taste-masking of the drugs becomes critical to patient compliance .

1.2.7.2 Mechanical strength

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, andoften requiring specialized peel-off blister packing that may add to the cost. Only Wow tab and durasolv technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi-dose bottles.

1.2.7.3 Hygroscopicity

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

1.2.7.4 Amount of drug

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

1.2.7.5 Aqueous solubility

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

1.2.7.6 Size of tablet

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

1.2.7.7 Faster disintegration

MDT's should disintegrate rapidly in matter of second.

1.2.7.8 Good packaging design

For protection of MDT's from moisture & other environmental hazards the packaging design should be considered early in development stages.

1.2.3 Various manufacturing techniques for MDT'S include:

- Lyophilization
- Moulding
- Direct Compression
- Cotton Candy Process
- Spray Drying
- Sublimation
- Mass Extrusion
- Nanonization
- Fast Dissolving Films

1.2.3.1 Freeze-Drying or Lyophilization

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

available for oxazepam, lorazepam, loperamide, and enalapril. ZT utilizes a unique freeze-drying process to manufacture finished dosage units which significantly differ from conventional oral systems.

The process involves the following steps:

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

Stage 2 - passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals which ensures that the tablets possess a porous matrix to facilitate the rapid disintegration property. These frozen units are then transferred to large-scale freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.

Stage 3 - Sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

Lyoc Lyoc technology lyophilizes, or "freeze-dries" an aqueous solution, suspension, or emulsion of an API and excipients. Lyoc‟s high degree of porosity yields shorter disintegration times than compressed tablets. The Lyoc manufacturing process produces a stable product without use of additives, preservatives or gelatins. This process is environmentally friendly and cost-effective because it doesn‟t require organic solvents. Lyoc technology is compatible with CIMA taste-masking techniques, customized release, high dosing and fixed-dose combination products.

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

1.2.3.1.1 Advantages

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

1.2.3.1.2 Disadvantages

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

1.2.3.2 Tablet Moulding

Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly.

Following are the different tablet moulding techniques:

- **Compression Moulding**
  Process This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.
- **Heat-Moulding**
  Process Heat-moulding process involves setting the molten mass containing a dispersed drug. This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.
- **Moulding by Vacuum Evaporation without Lyophilization**
  This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process.

1.2.3.3 Direct Compression (DC)

DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tabletting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugarbased excipients.

a)Disintegrants

In many MDT products based on DC process, the disintegrants mainly affect the rate of disintegration and hence dissolution which is further enhanced in the presence of water soluble excipients and effervescent agents. The introduction of superdisintegrants has increased the popularity of this technology. Tablet disintegration time can be optimized by focusing on the disintegrant concentration. Below a critical disintegrant concentration, tablet disintegration time becomes inversely proportional to disintegrant concentration. However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant. Another DC based technology; Flashtab contains coated crystals of drug and microgranules alongwith disintegrants. In this technology, two types of disintegrants are used: a disintegrating agent (e.g., modified cellulose), which has a high swelling force and a swelling agent (e.g., starch) which has a low swelling force. Bi et al. and Watanbe used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture MDTs wherein the ratio of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihara investigated the application of agar powder as a disintegrant due to its property of absorbing water and considerable swelling without forming a gel at physiological temperature.

b)Effervescent Agents

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

c)Sugar-Based Excipients

Another approach to manufacture MDTs by DC is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and

xylitol) which display high aqueous solubility and sweetness and hence, imparts taste masking and a pleasing mouth feel. Mizumoto et al., have classified sugar-based excipients into two types based on their mouldability and dissolution rate.

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

1.2.3.4 Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as „floss", made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such assucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva.

1.2.3.5 Spray-Drying

Allen et al., have used spray-drying for the production of MDTs. The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.

1.2.3.6 Sublimation

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

process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethene) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Makino et al., reported a method using water as a pore-forming material.

1.2.3.7 Mass-Extrusion

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

1.2.3.8 Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

1.2.3.9 Fast Dissolving Films

It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste.

1.2.4 . Patented Technologies Used For Manufacturing Mout Dissolving Tablets

1.2.4.1. Orasolv®.

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the FDTs. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light, and child resistance packing.

1.2.4.2. Durasolv®.

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants. Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in to bottles and blisters.

1.2.4.3. Wowtab®.

Yamanouchi patented this technology. WOW means with out water. This technology utilizes conventional granulation and tableting methods to produce FDTs employing low- and high-moldability saccharides. Low moldability saccharides are lactose, mannitol, glucose, sucrose,and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

1.2.4.4. Flashtab®.

Flashtab® tablets were developed by Prographarm, France. In this technique,most of the excipients are used as for conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles to produce a tablet that disintegrates in the mouth in one minute. Flashtab® matrix tablet contains a swelling agent such as modified starch or microcrystalline cellulose and a superdisintegrant such as

crospovidone or croscarmellose. The system may also contain a highly water soluble polyol such as mannitol, sorbitol, maltitol or xylitol with binding properties if no swelling agent is used. The direct coating procedure is used for taste masking of the active ingredient. In the Flashtab® technique, the excipients are first granulated using wet or dry granulation. Then they are mixed with coated drug particles and compressed into tablets using conventional processing equipment.

1.2.4.5. Zydis®.

Zydis® technique is owned by R P Scherer, a subsidiary of Cardinal Health.

A Zydis® tablet is produced by lyophilizing or freeze-drying the drug in a water soluble matrix material, usually consisting of gelatin. Freeze-drying is done in blisters, where sublimation removes water, which are then sealed and further packed. The resultant product is very porous, light and fragile and disintegrates immediately on contact with saliva.The Zydis® formulation is also self-preserving since the final water concentration in the freeze-dried product is very low and prevents microbial growth. The ideal drug candidates for Zydis® are the ones showing relatively low water solubility, with fine particles and good aqueous stability in the suspension. For water soluble drugs, the upper limit for drug loading is very low (approx. 60 mg). The basic problem of water soluble drugs is the formation of a eutectic mixture, which results in freezing point depression and formation of glossy solids on freezing, leading to supporting structure collapse during sublimation. This problem can be solved by adding a crystal forming agent such as mannitol.

1.2.4.6. Flashdose®.

Flashdose® technology was invented by Fuisz Technologies, USA, now owned by Biovail (Canada). Fuisz Technologies has developed three oral drug delivery systems that involve fast dissolution. The first two generations are quick-dissolving Soft Chew and EZ Chew tablets which require some chewing. Most recently Fuisz also developed Flashdose® technology, which uses a unique spinning mechanism to

produce a flash-like crystalline structure, much like cotton candy. These crystalline sugars can then incorporate APIs and be compressed into tablets. Flashdose® dosage form utilizes the shearform technique in association with CeformTM to mask the bitter taste of the medicament. CeformTM technique which produces uniform microspheres with very narrow particle size distribution has been patented by Fuisz. The shearform technology used in the preparation of the matrix is known as floss, which is made from a combination of excipients. The floss cotton candy-like fibers are made up of saccharides such as sucrose, dextrose, lactose and fructose. Sucrose required a temperature of 82–130 °C to be transformed into fibers while other polysaccharides such as polymaltodextrins and polydextrose require 30–40 % lower temperature than sucrose.

The Flashdose manufacturing process can be divided into four steps

1. Floss blend

Approximately 80% of sucrose in combination with mannitol or dextroseand 1% of surfactant (approx.) are blended to form the floss mixture, in which the surfactant acts as a crystallization enhancer for maintaining the structure and integrity of floss fibers. Also, the enhancer helps conversion of amorphous sugars into crystalline sugar. In this process, dispersed API is retained in the matrix by minimizing its migrationout of the mixture.

2. Floss processing

The floss formation machine consisting of a spinning head andheating element is similar to the cotton candy type. The matrix is produced by subjecting the carrier material to flash heat and flash flow processing. In the flash heat process, the carrier material is heated sufficiently to create the internal flow condition and then exit through the spinning head,which throws the floss by centrifugal force.Sufficient centrifugal force is generated by spinning head rotation at approximately 2000–3600 rpm. The heating blocks are positioned around the circumference of the crown and are outlined outside on the rim of the heaters. Narrowing the width of the aperture and increase in the path length of the existing material result in the production of fibers. The fibersproduced are usually amorphous.

3. Floss chopping and conditioning

The fibers are conditioned to smaller particle size in a high shear mixer granulator by chopping and rotation. The conditioning is performed by partial crystallization, which is carried out by spraying ethanol

(< 1 %) on the floss. The resultant evaporated floss fibers possess the cohesive properties and improved flow properties.

4. Tablet blend and compression

The resultant floss fibers are then blended with API along with other required tablet excipients and compressed into tablets. A modification of this process is a curing step. The curing step is added to improve the mechanical strength of the barely molded flash dose dosage form in plastic blister pack dispersion. The curing step involves exposure of the dosage form to elevated temperature and humidity conditions such as 40 °C and 85 % RH for 15 min. The curing step is carried out for crystallization of the floss material.

1.2.4.7. Oraquick

Oraquick formulation was developed by utilizing patented taste maskingtechnologies such as FlavourTech and MicroMask. In MicroMask technology, the taste masking process is done by incorporating the drug into the matrix microsphere and KV Pharmaceutical claims that MicroMask has good taste masking compared to Flavour Tech. In Oraquick® technique, tablets are prepared by dissolving the sugar (sucrose, mannitol,sorbitol, xylose, dextrose, fructose or mannose) and protein (albumin or gelatin) ina suitable solvent such as water, ethanol, isopropyl alcohol and ethanol-water mixture.The matrix solution is then spray-dried to give highly porous granules. Porosity of the resultant granules depends upon the quantity of solvent used in the process.

1.2.4.8. Lyoc

Lyoc technique is owned by Cephalon Corporation. CIMA is a subsidiaryof Cephalon and it currently manages the Lyoc R&D efforts. This was the first freeze drying technique used for the manufacturing of ODTs. The liquid solution or suspension preparation involves fillers, thickening agents, surfactants, non-volatile flavouring agents and sweeteners along with APIs. The resultant homogeneous liquid is placed in blister cavities and subjected to freeze-drying. Lyoc® tablets do not contain preservatives. To prevent inhomogeneity due to sedimentation during this process, the formulation requires a large proportion of undissolved inert filler (mannitol) in order to increase the viscosity of the in process suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets, with disintegration rates comparable to the loosely compressed oral melt formulations.

1.2.4.9. Advatab

Advatab® tablets disintegrate rapidly in the mouth, typically in less than 30 s to allow for convenient oral drug administrationwithout water. These tablets are especially suited to patients that experience difficulty in swallowing capsules and tablets. Advatab® is different from other ODT technologies in that it can be combined with Eurand's complimentary particle technologies like Microcaps ® (world leading taste masking technology) and

1.2.4.10. Diffucaps (controlled release technology).

A combination of Advatab and Microcaps creates products that offer the dualadvantage of a patient's preference together with superior taste and smooth mouth feel.This is critical advantage as the unpleasant taste of drugs restricts application of other ODT technologies. **1.2.4.11. Frosta® (Akina).**

The Frosta® approach utilizes conventional wet granulation processingand tablet machines for extremely cost effective production of fast-melting tablets. In this technique, plastic granules are formulated and compressed at low pressure to produce strong tablets with high porosity. Plastic granules are composed of three components porous and plastic material, water penetration enhancer and binder. The processinvolves mixing of the porous plastic material with water penetration enhancer followed by granulation with binder. The tablets obtained have excellent hardness and rapid disintegration time, ranging from 15 to 30 s depending on the size of the tablet.

1.2.4.12. Quick-Dis Technology

The novel intraoral drug delivery system, trademarkedQuick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible and quick-dissolving film (81). The film is produced by the solvent casting method. In this technique, water-soluble hydrocolloids like gelatin, pectin, gum acacia, gum arabic, hydroxypropylmethylcelluloseor starch were completely dissolved in water to form a homogenous viscous solution. Other ingredients such as emulsifying agents, solubilizingagents, wetting agents, taste-modifying agents, plasticizers, water-soluble inert fillers, preservatives, buffering agents, coloring agents, and stabilizers along with APIs were dissolved in a small portion of aqueous solvent using a high-shear processor. The active mixture was then added to the viscous hydrocolloid solution to form a homogeneous viscous solution.. The Quick-Dis™ drug delivery system can be dispensed in various packaging configurations,ranging from unit-dose pouches to multiple-dose blister packages.

1.2.4.13. Nanocrystal Technology/nanomelt

For mouth dissolving tablets, Elan's proprietary Nanocrystal® technologyimproves compound activity and final product characteristics. Decreasing the particle size increases the surface area, which in turn leads to an increase in the dissolution rate and this is the main principle behind the Nanocrystal™ technology. This technique is especially used for poorly water-soluble drugs. Nanocrystal™ particles are nano-sized drug substances, typically less than 1000 nm in diameter, which are produced by milling using a proprietary wet milling technique and are stabilized against agglomeration tocreate a suspension that behaves like a solution. Nanocrystal™ orally dissolving technology provides for:

1. Pharmacokinetic benefits, which mainly include bioavailability of orally Administered nanoparticles (< 2 mm) in the form of a rapidly disintegrating tablet matrix;

2. Product differentiation based upon a combination of proprietary and patent-protectedtechnology elements;

3. Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters);

4. Wide range of doses (up to 200 mg of API per unit);

5. Use of conventional, compendial inactive components;

6. Employment of non-moisture sensitive inactives.

Nanocrystal colloidal dispersions of drug substance are combined with water soluble,generally regarded as safe (GRAS) ingredients, filled into blisters and lyophilized. The resultant wafers dissolve in very small quantities of water in seconds. This approach is mainly used when working with highly potent or hazardous materials because itavoids a number of manufacturing steps such as granulation, blending and tableting,which generate large quantities of aerosolized powder and constitute a much higher risk of toxicity.

1.2.5. Ingredients used in MDT

1.2.5.1. superdisintegrants

Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. The natural superdisintegrants involve various natural substances like gums, mucilages, and other substances of natural origin which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Some natural substances like gum karaya, modified starch and agar have been used in the formulation of FDT‟s. Mucilage of natural origin is preferred over semisynthetic and synthetic substances because they are comparatively cheaper, abundantly available, nonirritating and nontoxic in nature.

Selection criteria for superdisintegrant

Although superdisintegrants primarily affect the rate of disintegration, but when used at high levels it can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate superdisintegrants for a particular formulation should:

a. Proceed for rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.

b. Be compactable enough to produce less friable tablets.

c. Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.

d. Have good flow, since it improves the flow characteristics of total blend.

1.2.5.1.1. Mechanisms of Super-Disintegrants

There are seven major mechanisms for tablets disintegration as follows

1.2.5.1.1.1 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. 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.

1.2.5.1.1.2 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. 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.

1.2.5.1.1.3 Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegratn attempts to explain the swelling of tablet made with „nonswellable" disintegrants. Guyot-Hermann and Ringard53 have proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. 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.

1.2.5.1.1.4 Due to deformation

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

1.2.5.1.1.5 Because of heat of wetting (air expansion)

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

1.2.5.1.1.6 Due to release of gases

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

1.2.5.1.1.7 By enzymatic reaction

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

1.2.5.2 Taste-masking agents

Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

a. Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.

b. Granulating the drug and coating with a taste masking polymer.

c. Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.

d. Complexation by the use of inclusion in cyclodextrins.

e. Psychological modulation of bitterness.

f. Coacervation to form microencapsulated drug within a polymer.

g. Formation of pellets by extrusion spheronization.

1.2.5.3 Sweeteners

Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products,although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are: Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, Glycerin, sugars derivatives etc.

Disintegrating agents are substances routinely included in the tablet formulations to aid in the break up of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.

1.2.5.4 Binders

Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–350C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

Example: Binders commonly used are cellulosic polymers such as ethylcellulose, hydroxypropylcellulos (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures povidones, polyvinyl alcohols, and acrylic polymers. Acrylic polymers used are the ammoniomethacrylate copolymer, polyacrylate, and polymethacrylate.

1.2.5.5 Antistatic agent

An antistatic agent is a compound used for treatment of materials or their surfaces in order to reduce or eliminate buildup of static electricity generally caused by the triboelectric effect. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling.

Example: colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non micronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearylfumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant.

1.2.5.6 Lubricants

Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach. Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

1.2.5.7 Flavours

Example**:** Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc.

1.2.5.8 Fillers

Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

1.2.5.9 Surface active agents

Example: sodiumdoecylsulfate, sodiumlaurylsulfate, Tweens, Spans, polyoxyethylene stearate.

Table 4 :list of super disintegrants

Superdisintegrants	Example	Mechanism Of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX®	Crosslinked cellulose	Swells 4-8 folds in < 10 seconds. -Swelling and	Swells in two dimensions. -Direct compression or

Primellose®Solutab ® Vivasol®L-HPC		wicking both.	granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	Swells very little andreturns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		Does not contain any starch or sugar. Used in nutritionalproducts.
Soy polysaccharides Emcosoy®		-Wicking action	Highlyporous,Optimu m concentration is between 20-40%

2. LITERATURE REVIEW

1.Sonali J. Shah et al (74) The aim of the study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, mannitol used as diluent and aspartame as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants, like croscarmellose sodium, sodium starch glycolate and crospovidone. Tramadol hydrochloride, a centrally acting synthetic opioid analgesic, was selected as the active pharmaceutical ingredient in the study.

2. Solanki et al (2011) formulated and evaluated aceclofenac fast-disintegrating tablets. The wet granulation and direct compression method were utilized to fabricate the fast dissolving tablets. The fast-disintegrating tablets were manufactured by incorporating diverse concentration of excipients and diluents. The physical and chemical properties of tablets were evaluated. The dissolution of drug was performed in buffer Phosphate buffered Saline (PBS) pH 7.4. From outcomes of study, it has been concluded that direct

compression of formulation C3 produces better dissolution than the wet granulation of formulation F2. The formulation F3 and C3 released 89.69% and 75.37% drug in 90 minutes respectively.

3.Masareddy et al (2011) developed Tizanidine HCl mouth dissolving tablets. The hardness, friability, in vitro disintegration time and in vitro drug release were evaluated for formulated tablets. Formulation F-3 prepared by addition of co-processed excipient base in the ratio of 1:3 showed minimum disintegration time of 9.15±0.04 s and the higher amounts of drug release of 93.75% at the end of 15 min. Granules obtained by spray drying technique were found to be more spherical, which improved its flow property and was supported by scanning electron microscope studies.

4.Kumar et al (2011) designed and prepared Felodipine fast disintegrating tablets. The direct compression method was utilized to manufacture the tablets. The fast disintegrating tablets were fabricated by using crospovidone as super-disintegrant and microcrystalline cellulose. Additionally mannitol was added to mask the bitter taste. The physicochemical studies were performed for formulated tablets. The results of physicochemical indicate satisfactorily value. Moreover the formulation does not produce any drug excipient

5.Sharma et al (2010) developed Levocetirizine mouth dissolving tablet by employing wet granulation method. The PVP as binder was used o prepared the MDTS. Moreover the sodium starch glycolate and Crospovidone as super disintegrants tablets were used to improve disintegration of tablets. The value of disintegration time, wetting time and friability of formulation containing 7.5% crospovidone produces comparatively lower than the other formulation. The formulation containing crospovidone as superdisintegrant produced suitable drug-resin complex to obtain the low disintegration time, wetting time and friability of tablets.

6.Keny et al (2010) formulated mouth disintegrating tablets of Rizatriptan benzoate by employing direct compression method. The super disintegrant were used in formulation of tablets. The physicochemical studies were performed for tablets. The assay of tablets was done by high performance liquid chromatography. From the outcomes of study, it has been concluded that the formulation containing .

3. NEED OF WORK

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration , compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing.

Combination treatment for hypertension is individualized. It gives the best possible control of blood pressure with fewest side effects. Different combination of drug in varing dosages are used to treat hypertension. Sometimes using lower doses of one or more drug in combination can minimize side effects. Fix dose combination regimens consisting of a calcium channel blocker and an angiotensin II type I receptor blocker represent a new addition to the available antihypertensive treatment options.

4. AIM AND OBJECTIVE

AIM :

FORMULATION AND EVALUATION OF FAST MOUTH DISSOLVING TABLET OF AMLODIPINE BESYLATE USING DIFFERENT SUPERDISINTEGRANTS.

OBJECTIVE :

1.To develop the MDT's of Amlodipine Besylate with faster disintegration using the different superdisintegrats.

2.To carry out preformulation studies.

3.To design and develop fast dissolving tablet by wet granulation method

4.To carry out morphological characteristics of the drug.

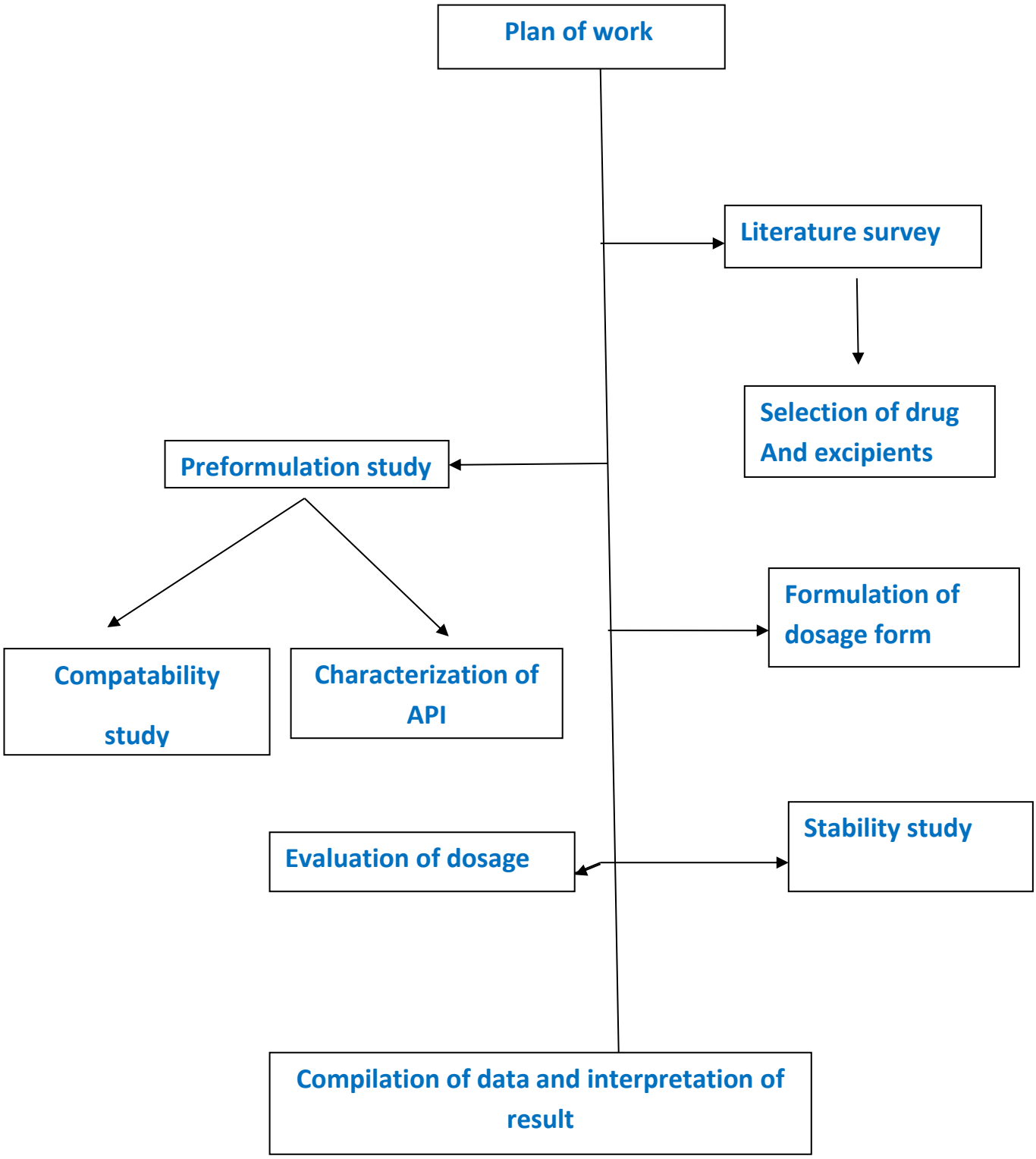
5.To carry out in-vitro release study using USP II dissolution test apparatus.

1. To evaluate in-vitro dissolution time of formulation.
2. To carry out stability studies.
3. To carry out evaluation study.

5. PLAN OF WORK

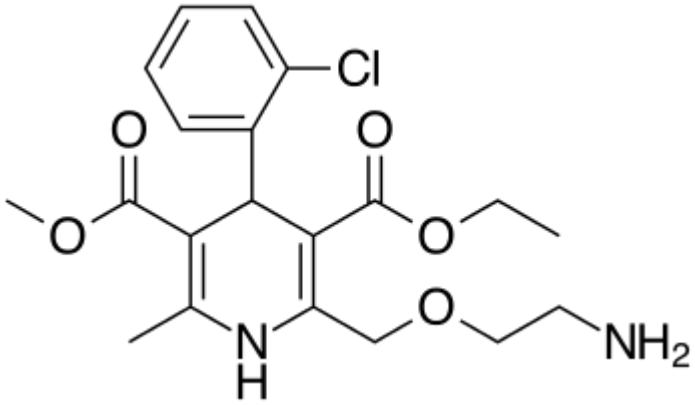
- **Literature survey**
  - Selection of drug and excipients
- **Preformulation studies**
  - Analytical characterization of the drug
  - Infrared spectroscopy
  - Compatability study using dsc
  - Flow properties study
- **Formulation development**
- **Evaluation of tablets**
  - Tablet characteristics
  - In – vitro drug release study
- **Compilation of data and interpretation of result**

Flow chart of Plan of work



6. DRUG AND EXCIPIENTS PROFILE

Amlodipine besylate



Synonyms

Amlodipinum , 3-Ethyl-5-methyl(+-)-2-(2-aminoethoxymethyl)-4-(O-chlorophenyl)-1 , (+-)-2-[(2-aminoethoxy)methyl]-4-(o- chlorophenyl)-1

Molecular formula :- $C_{26}H_{31}ClN_2O_8S$

Molecular weight:- 567.1

Category

Antihypertensive Agents , Vasodilator Agents , Calcium Channel Blockers.

Dose

Usual Adult Amlodipine Dose for Hypertension: Initial dose: 5mg orally once a day Maintenance dose: 5 to 10 mg orally once a day Small or fragile patients may be started on 2.5 mg orally once a day.

Description

This compound belongs to the class of organic compounds known as dihydropyridinecarboxylic acids and derivatives. These are compounds containing a dihydropyridine moiety bearing a carboxylic acids group.

Melting point:- 178^0c

Pharmacodynamics

Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T –type. It was widely accepted that DHP CCBs target L-type calcium channels , the major channel in muscle cells that mediate contraction; however , some studies have indicated that amlodipine also binds to and inhibits N-type calcium channel. Similar to other DHP CCBs, amlodipine binds directly to inactive L-type calcium channel stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations , inactive channel are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives amlodipine additional arterial selectivity. At therapeutic sub-toxic concentrations , amlodipine has little effect on cardiac myocytes and conduction cells.

Mechanism of action

Amlodipine decrease arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Calcium ions entering the cell through these channels bind to calmodulin . Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phsporylation of the regulatory light chain subunit of myosin , a key step in muscle contraction signal amplification is achieved by calcium induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and result in vasodilatation the vasodilatory effects of amlodipine result in an overall decrease in BP. Amlodipine is a long acting CCB that may be used to treat mild to moderate essential hypertension and exertion related angina (Chronic stable angina) . another possible mechanism is that amlodipine inhibites vascular smooth muscle carbonic anhydrase I activity causing cellular pH increase which may be involved in regulating intercellular calcium influx through calcium channels.

Pharmacokinetics

Absorption

Amlodipine is slowely and almost completely absorb from the gastrointestinal track . Peak plasma concentration are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90% . Absorption is not affected by food .

Metabolism

Hepatic metabiolized extensively (90%) to inactive metabolites via the cytochrome P450 3A4 isozyme**.**

Half life

30 – 50 hours

Protein binding

97.5 %

Route of administration

Amlodipine is extensively (about 90%) converted to inactive metabolite via hepatic metabolism with 10 % of the parent compound and 60% of the metabolite excreted in the urin .

Solubility

It is slightly soluble in water freely soluble in methanol , sparingle soluble in ethanol and slightly soluble in 2- propanol .

Storage

Store protected from moistur.

Croscarmellose sodium

Nonproprietary Names

• BP: Croscarmellose sodium

• PhEur: Carmellosum natricum conexum

• USPNF: Croscarmellose sodium

Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum;

Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

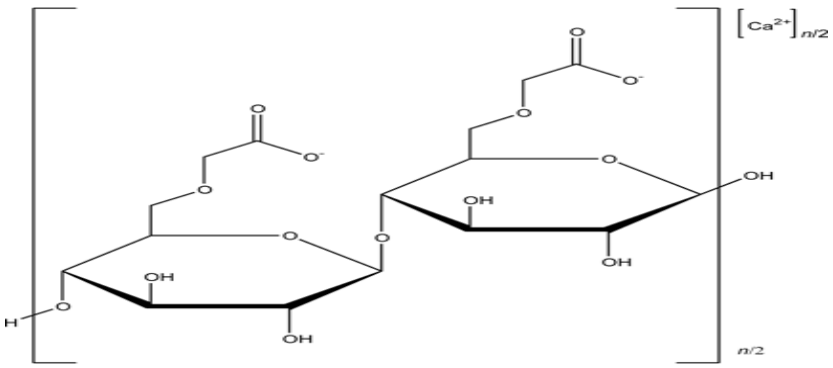
Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Empirical Formula and Molecular Weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,1,2 tablets,3–13 and granules. In tablet formulations, croscarmellose sodium may be used in both direct-

compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.11,12 Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table 5: Uses of croscarmellose sodium.

Use	Concentration (%)
Disintegrant in capsules	10-25
Disintegrant in tablets	0.5-5.0

Description

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Typical Properties

Acidity/alkalinity

pH = 5.0–7.0 in aqueous dispersions.

Bonding index

0.0456

Brittle fracture index

0.1000

Density (bulk)

0.529 g/cm3 for Ac-Di-Sol

Density (tapped)

0.819 g/cm3 for Ac-Di-Sol

Density (true)

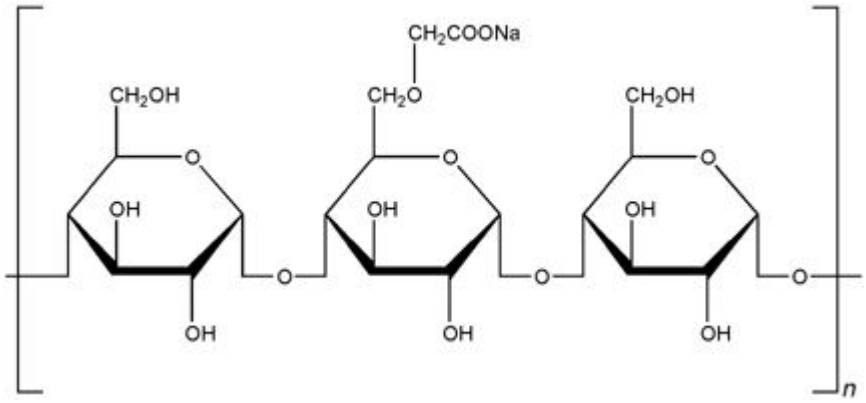
1.543 g/cm3 for Ac-Di-Sol

Stability and Storage Conditions

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

SODIUM STARCH GLYCOLATE

Structure



Synonyms

Carboxymethyl starch, sodium salt, Exploso, Explotab, Glycolys, Primojel, starch carboxymethyl ether, sodium salt, Tablo, Vivastar P.

Chemical Name

Sodium carboxymethyl starch

Empirical Formula and Molecular Weight

The USPNF 23 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium. The PhEur 2005 describes three types of material: Types A and B occur as the sodium salt of a cross-linked partly O-carboxymethylated potato starch, containing 2.8–4.2% and 2.0–3.4% of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly O-carboxymethylated starch containing 2.8–5.0% sodium.

The JP, PhEur and USPNF monographs have been harmonised for Type A and Type B variants.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking.

The molecular weight is typically 5 × 105–1 × 106.

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either directcompression or wet-granulation processes.The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter.

Typical Properties

Acidity/alkalinity

pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3% w/v aqueous dispersion. See Section 18.

Ash

≤15% for Explotab

Density (bulk)

0.756 g/cm3;

0.75 g/cm3 for Explotab;

0.81 g/cm3 for Primojel;

0.67 g/cm3 for Tablo.

Density (tapped)

0.945 g/cm3;

0.88 g/cm3 for Explotab;

0.98 g/cm3 for Primojel;

0.83 g/cm3 for Tablo.

Density (true)

1.443 g/cm3

1.51 g/cm3 for Explotab;

1.56 g/cm3 for Primojel;

1.49 g/cm3 for Tablo.

Melting point

does not melt, but chars at approximately 200°C.

Particle size distribution

100% of particles less than 106 μm in size. Average particle size is 35–55 μm for Explotab.

Solubility

sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.

Swelling capacity

in water, sodium starch glycolate swells to up to 300 times its volume.

Viscosity (dynamic)

≤200 mPa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties.23–25 Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it

is stored at moderate temperatures and humidity.

TALC

Nonproprietary Names

BP: Purified talc

JP: Talc

PhEur: Talcum

USP: Talc

Synonyms

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

Chemical Name and CAS Registry Number

Talc [14807-96-6]

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents

Table 6. : use and concentration of talc

Use	**Concentration**(%)
Dusting powder	90.00-99.00
Glidant and tablet lubricant	01.00-10.00
Tablet and capsule diluent	05.00-30.0

although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets;8 and as an adsorbant.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; . Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder; Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description

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

Typical Properties

Acidity/alkalinity

pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs)

1.0–1.5

Moisture content

talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution

varies with the source and grade of material. Two typical grades are ≥99% through a 74 μm (#200 mesh) or ≥99% through a 44 μm (#325 mesh).

Refractive index

n20

D = 1.54–1.59

Solubility

practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity

2.7–2.8

Specific surface area

2.41–2.42 m2/g

Stability and Storage Conditions

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

Incompatibilities

Incompatible with quaternary ammonium compounds.

SACCHARIN SODIUM

Nonproprietary Names

BP: Saccharin sodium

JP: Saccharin sodium

PhEur: Saccharinum natricum

USP: Saccharin sodium

Synonyms

1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; Crystallose; E954; sodium obenzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

Chemical Name and CAS Registry Number

1,2-Benzisothiazol-3(2H)-one 1,1-dioxide, sodium salt [6155-57-3] for the dehydrate [128-44-9] for the anhydrous material

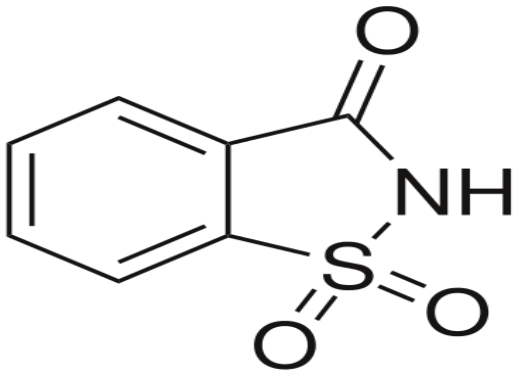
Empirical Formula and Molecular Weight

C7H4NNaO3S 205.16

C7H4NNaO3S·⅔H2O (84%) 217.24

C7H4NNaO3S·2H2O (76%) 241.19

Structural formula



Applications in Pharmaceutical Formulation or Technology

Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners, and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes

Table 7: Uses of saccharin sodium

Use	**Concentration (%)**
Dental paste/gel 0.12–0.3	0.12-0.3
IM/IV injections	0.9
Oral solution	0.075-0.6
Oral syrup	0.04-0.25

It is also used in vitamin preparations. Saccharin sodium is considerably more soluble in water than saccharin, and is more frequently used in pharmaceutical formulations. Its sweetening power is approximately 300 times that of sucrose. Saccharin sodium enhances flavor systems and may be used to mask some unpleasant taste characteristics. Injection of saccharin sodium has been used to measure the arm-to-tongue circulation time.

Description

Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population. Saccharin sodium can contain variable amounts of water.

Properties

Unless stated, data refer to either 76% or 84% saccharin sodium.

Acidity/alkalinity

pH = 6.6 (10% w/v aqueous solution)

Density (bulk)

0.8–1.1 g/cm3 (76% saccharin sodium);

0.86 g/cm3 (84% saccharin sodium).

Density (particle)

1.70 g/cm3 (84% saccharin sodium)

Density (tapped)

0.9–1.2 g/cm3 (76% saccharin sodium);

0.96 g/cm3 (84% saccharin sodium).

Melting point

decomposes upon heating.

Moisture content

saccharin sodium 76% contains 14.5% w/w water; saccharin sodium 84% contains 5.5% w/w water. During drying, water evolution occurs in two distinct phases. The 76% material dries under ambient conditions to approximately 5.5% moisture (84% saccharin sodium).

Stability and Storage Conditions

Saccharin sodium is stable under the normal range of conditions employed in formulations. Only when it is exposed to a high temperature (125°C) at a low pH (pH 2) for over 1 hour does significant decomposition

occur. The 84% grade is the most stable form of saccharin sodium since the 76% form will dry further under ambient conditions. Saccharin sodium should be stored in a well-closed container in a cool, dry place.away heating.

MICROCRYSTALLINE CELLULOSE

Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name and CAS Registry Number

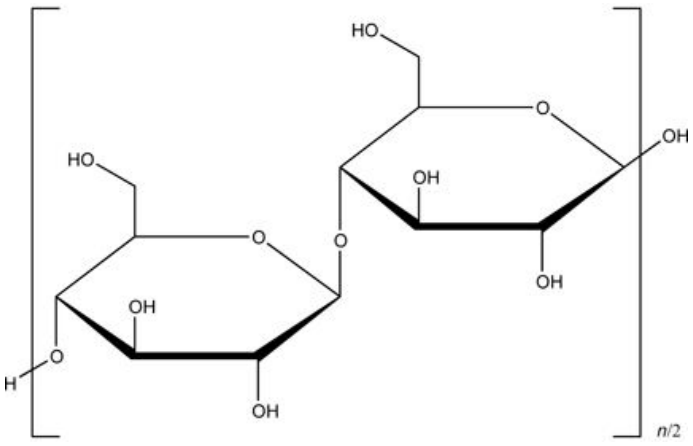
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

where n ≈ 220.

Structural Formula



Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and directcompression processes.In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 8: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluents	20–90

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties

Angle of repose

49° for Ceolus KG; 34.4° for Emcocel 90M.

Density (bulk)

0.337 g/cm3; 0.32 g/cm3 for Avicel PH-101;10 0.29 g/cm3 for Emcocel 90M; 0.29 g/cm3

Density (tapped)

0.478 g/cm3; 0.45 g/cm3 for Avicel PH-101; 0.35 g/cm3 for Emcocel 90M.9

Density (true)

1.512–1.668 g/cm3

Flowability

1.41 g/s for Emcocel 90M

Melting point

chars at 260–270°C.

Moisture content

typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic

Solubility

slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place,

MAGNESIUM STEARATE

Nonproprietary Names

BP: Magnesium stearate JP: Magnesium stearate PhEur: Magnesii stearas USPNF: Magnesium stearate

Synonyms

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

Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight

C36H70MgO4 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula

[CH3(CH2)16COO]2Mg

Functional Category

Tablet and capsule lubricant

Applications in Pharmaceutical Formulation or Technology

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

Description

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

Typical Properties

Crystalline forms

high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk)

0.159 g/cm3

Density (tapped)

0.286 g/cm3

Density (true)

1.092 g/cm3

Flash point

250°C

Flowability

poorly flowing, cohesive powder.

Melting range

117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).

Solubility

practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions

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

7.MATERIAL AND INSTRUMENTS

Table :List of instruments and their manufacturers

Sr.no	Instrument / Machine	Make
1	UV vis spectrophotometer	Jasco
2	Hot air oven	Lab Line
3	Tablet compression machine	Lab press
4	Disintegration apparatus	Veego
5	Dissolution apparatus	Electro Lab
6	Friability test apparatus	Rolex
7	Monsanto hardness tester	Dolphin
8	Ultra sonicator	Schimadzu
9	Electronic Balance	Schimadzu

Table : List of materials and their suppliers

Sr. no	Chemical and reagents	Suppliers
1	Croscarmellose sodium	Nulife pharmaceuticals Ltd
2	Sodium starch glycolate	Ozone international
3	Microcystalline cellulose	Loba chemie Pvt,Ltd
4	Magnesium stearate	Loba chemie Pvt,Ltd
5	Talc	Loba chemie Pvt,Ltd
6	Sachharin sodium	S.D.fine chem. Ltd
7	Mannitol	Qualigens fine chemicals

8.EXPERIMENTAL WORK

8.1 Preformulation Study

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance.

The following parameters were checked for determining the purity of drug.

8.1.1 Melting Point

8.1.2 Physical Appearance

8.1.3 Calibration curve of Amlodipine besylate

8.1.3.1 Determination of Amlodipine besylate λmax of in phosphate buffer PH 6.8 solution:

Amlodipine besylate in phosphate buffer PH 6.8 solution taken separately in 100 ml of volumetric flask (10 mg in 100 ml) .from the stock solution 2ml diluted up to the 10 ml to get 20 µg/ml solution. prepared in phosphate buffer PH 6.8 solution and scanned between 200- 400 nm . the absorption maxima selected and use for further study.

Solution A (100µg/ml) : 10 mg of Amlodipine besylate were accurately weighed and transferred into a 100 ml volumetric flask separately, the drug was then dissolved and diluted up to the mark with phosphate buffer PH 6.8 solution.

Solution B: from solution A 0.5, 1.0, 1.5, 2.0, 2.5 ml were transferred to 10ml volumetric flask and diluted up to the mark with phosphate buffer PH 6.8 solution to contain 5, 10, 15, 20, 25 µg/ml of Amlodipine besylate.The a bsorbance was measured in the UV- visible spectrophotometer at 237 nm for using phosphate buffer PH 6.8 solution as blank and graph of concentration versus absorbance was plotted and data were subjected to linear regression analysis in Microsoft excel was plotted and data were subjected to linear regression analysis in Microsoft excel.

8.1.4 I.R Spectroscopy –

In the present study FTIR spectra of the were recorded using a FTIR spectrophotometer.

8.2. Physical Properties

The following tests were performed for Amlodipine besylate.

8.2.1. Bulk density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml. This was determined by pouring an accurately weighed quantity of blend into a graduated cylinder and then the volume and weight was measured.

Db= M/Vb

Where,

Bulk density = Db,

Weight of powder = M

Volume of packing = Vb

8.2.2. Tapped density (Dt)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/mL and is given by

Dt = M / Vt

Where,

M - the mass of powder

Vt - the tapped volume of the powder.

8.2.3 Compressibility index (carr's Index)

The compressibility index (Carr's Index) was determined by using following equation,

Carr's Index (%) = [(Dt – Db) × 100] / Dt

Where,

Dt - the tapped density of the powder

Db - the bulk density of the powder

Table 11: Relationship between % compressibility and flow ability

Compressibility (%)	**Flow ability**
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
< 40	Very very poor

8.2.4 Angle of repose (q)

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation,

$$\tan(\theta) = h/r$$

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

Where,

θ - the angle of repose.

h - the height in cmsr -the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

Table12: Angle of repose as an indication of powder flow properties

S. No.	Angle of repose (°)	Type of flow
1	< 20	Excellent
2	20-30	Good
3	30-34	Passable
4	> 34	Very poor

8.2.5 Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. Hosner ratio is the ratio of tapped density to bulk density, i.e.,

Hausner ratio = Dt / Db

Where,

Dt - the tapped density and

Db - the bulk density.

Table 13: Hausner ratio as an indication of powder flow properties

Hausner ratio	flow properties
less than 1.18,	Excellent
1.19,	Good
1.25,	Passable
1.3- 1.5	poor

greater the 1.5	Very poor

8.3.Formulation approach of amlodipine besylate MDT's

- ✓ Amlodipine besylate MDT's was prepared by wet granulation – direct compression . The different concentration of superdisintegrants crosscarmellose sodium, sodium starch glycolate, were used.

- ✓ The formulation were subjected to the evaluation i.e thikness, hardness, friability, wetting time, water absorption ratio, disintegrating time, invitro drug release.

8.4.FORMULATION AND EVALUATION OF FAST MOUTH DISSOLVING TABLET OF AMLODIPINE BESYLATE USING DIFFERENT SUPERDISINTEGRANTS.

Formulation of Amlodipine besylate tablets were prepared by wet granulation direct compression technique.Tablets ingredients were accurately weighed. These powder wer then passed through sieve . The blend was compressed using single punch tablet machine.

S.N.	Ingredient in mg/Tablet	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Amlodipine besylate	10	10	10	10	10	10	10	10	10
2	Crosscarmilose sellulose	5	10	15	-	-	-	2.5	5	7.5
3	Sodium starch glycolate	-	-	-	5	10	15	2.5	5	7.5
4	Starch	7	7	7	7	7	7	7	7	7
5	Microcrystalline cellulose	21.5	16.5	11.5	21.5	16.5	11.5	21.5	16.5	11.5

6	Sodium sachharide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Talc	2	2	2	2	2	2	2	2	2
8	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
9	Vanilla	1	1	1	1	1	1	1	1	1
10	Zink oxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table: Preparation of FAST MOUTH DISSOLVING TABLET OF AMLODIPINE BESYLATE USING DIFFERENT SUPERDISINTEGRANTS mouth dissolving tablet

Method of preparation of tablet- Wet granulation- direct compression method.

8.5. Evaluation of the Amlodipine besylate granules:

8.5.1. Particle size distribution

The size and size distribution of the granules produced was determined by agitation for 10 min with a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve, a particle size distribution graph was plotted from which the median diameter was determined.

8.5.2. Bulk density

15 g granules blend introduced into a dry 100 ml cylinder, without compacting. The granules was carefully levelled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the following formula

$\rho bulk = M / Vo$……..(1)

Where, ρbulk = Apparent bulk density, M = Weight of the sample, Vo = Apparent volume of powder.

8.5.3 Tapped density

A suitable amount of granules was placed in a 100 ml measuring cylinder. After absorbing its initial volume, the sample was tapped 500 times initially followed by an additional taps of 750 times until the difference between succeeding measurement is less than 2% and then tapped volume, was measured, to the

nearest graduated unit. Tapped density was calculated using equation [9]. ρtab = M / Vf ……....(2)

Where, ρtab = Tapped Density, M = Weight of the sample, Vf = Tapped volume of powder

8.5.4 Hausner's ratio

Hausner's ratio is the ratio of tapped to bulk density and was calculated by using the following equation.

Hausner's Ratio = ρtab/ρbulk……(3)

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.6 showing moderate flow properties, cohesive powder and more than 1.5 poor flow .

8.5.5 Angle of repose

The angle of repose was determined by allowing granules to flow through a funnel and fall freely onto a graph paper on a horizontal surface. The height and diameter of the resulting cone were measured and the angle of repose is calculated from this equation:

tan Ø = h / r…….(4)

Where

h is the height of the powder cone and r is the radius of the powder cone

h is the height of the powder cone and r is the radius of the powder cone

Values for angle of repose ≤ 30° usually indicate a free flowing material and angles ≥ 40° suggest a poorly flowing material, 25- 30 show excellent flow properties, 31-35 show good flow properties, 36-40 show fair flow properties and 41-45 showing passable flow properties.

8.5.6. Moisture content

Titration method was used to determine the water content. With the Karl Fischer (KF) titration both free and bound water can be determined [10]. Around 50 ml of methanol was taken in the titration vessel of Karl Fischer titrator and titrated with the Karl Fischer reagent to end point. In a dry mortar the granules

were ground to fine powder. Weighed accurately about 0.5 g of the sample and transferred quickly to the titration vessel, stirred to dissolve and titrated with the Karl Fischer reagent to end point.

Moisture content = V * F * 100/Weight of sample (mg)……..(5)

Where, F= factor of Karl Fischer reagent, V=volume in ml of Karl Fischer reagent consumed for sample titration.

8.6. Post Compression Study

a)Thickness

b)Wt. Variation

c) Hardness

d)Friability

e)Disintegration time[sec]

f)Wetting time[sec]

g)Water absorption ratio

***h)In Vitro*drug Release**

i)Drug content

j)Stability

a) Thickness Test

The thickness in millimeters was measured individually for 10 tablets by using a digital Venire caliper. The average thickness and standard deviation was reported.

b)Weight Variation Test

The 20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The I.P allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table16 Percentage Deviation In Weight Variation

Sr. No	Average weight of a tablet	Percentage deviation
1	130 mg or less	10
2	More than 130 mg and less than 324 mg	7.5
3	324 mg or more	5

c) Hardness Test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping.

Method: The hardness of the tablets was determined using Monsanto Hardness tester. It was expressed in Kg/cm2. Tablets were randomly picked from formulation and place into the Monsanto hardness tester and the mean and standard deviation values were calculated.

d) Friability Test

It is the phenomenon where by tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Rolex Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed and transferred into friabilator and then it was operated at 28 rpm for 4 minutes. Friability was determined

Formula-

Friability =Initial wt. – final wt. / Initial wt. ×100

e) Disintegration Test

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a

group of tablets to disintegrate into particles which will pass through a 10 # mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms84

f) Wetting time

Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time.

g) Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on paper & the time required for complete wetting was measured. The wetted tablet was then weighted. Water absorption ratio R was determined using following equation,

$$R=10\ (Wa/Wb)$$

Where,

Wb- Wt. of tablet before absorption

Wa- wt. of tablet after absorption

h)In vitro dissolution study (Dissolution test)

Medium: Phosphate buffer pH 6.8

Apparatus: USP XXIV type II (paddle)

Speed: 50 rpm

Temperature: 37oC ± 0.5oC

Sampling: 10, 20, 30 and 45 min

Dissolution medium: 900 ml phosphate buffer

pH 6.8

Preparation of sample solution:

Dissolution apparatus was set as per parameters. Tablets were put in each dissolution vessel and dissolution was carried out. Five ml of solution at the end of fixed intervals were withdrawn. The solution was filtered through whatmann filter paper.

UV-VIS measurement:

The tablets were analyzed UV spectrophotometrically and the absorbance were recorded at 237 nm using UV spectrophotometer against a dissolution medium as a blank.

9. RESULT AND DISCUSSION

9.1 PREFORMULATION STUDY

9.1.1 Physical characteristic of Amlodipine besylate

Table No:17 Physical characteristic of Amlodipine besylate

Sr.no	Test	Observation	Inference
1	Colour	White	Complies
2	Odour	Odourless	Complies
3	Surface Nature	Powder	Complies

9.1.2 Melting point of Amlodipine besylate

Table No:18 Melting point of Amlodipine besylate

Sr no	Std M.P of Amlodipine besylate	Practically found M.P of Amlodipine besylate	Inference
1	178-179	179-180	Complies

Melting point of was found in the range of. While as per standard literature, it is reported to be. So it can be concluded that Amlodipine besylate was in a pure state.

9.1.3 Analytical methodology

9.1.3 U.V spectrophotometric analysis

The λ max of pure Amlodipine besylate was found at 237 nm.

Since all absorbance taken at 237nm in a Phosphate buffer.

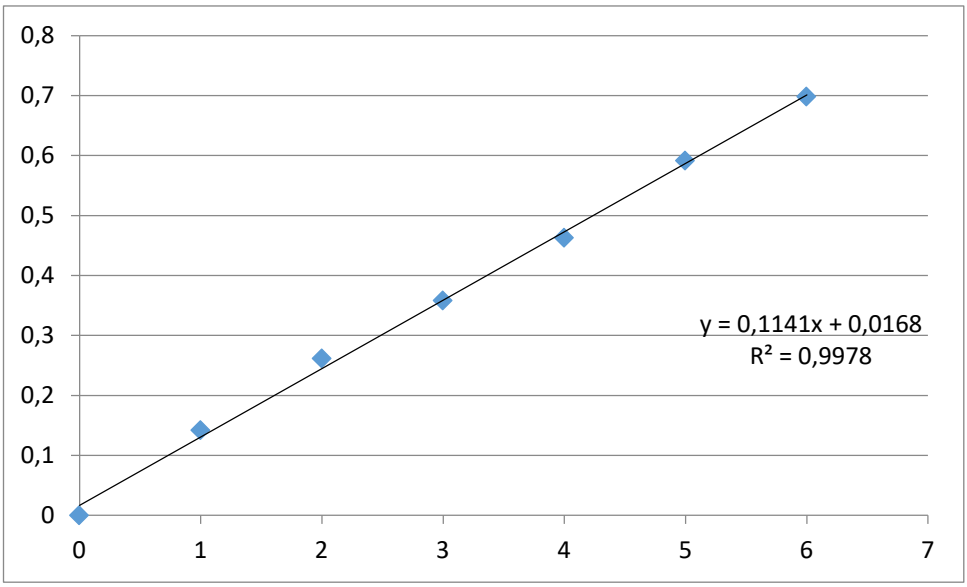
Fig. λmax of Amlodipine Besylate

Table Standard calibration curve of Amlodipine besylate

Sr No.	Concentration	Absorbance
1	0	0.000
2	5	0.1420
3	10	0.2612
4	15	0.3578
5	20	0.4624
6	25	0.5911
7	30	0.6980

Table

Sr no	λmax (nm)	Solvent used	Regression equation
1	237 nm	6.8 phosphate buffer	y =



9.1.4 I.R. Spectroscopy

Fig. I.R. spectra of Amlodipine besylate

9.2 Physical Properties

The following parameters were evaluated for Amlodipine besylate

Table : Physical properties of drug and excipients

Material	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner ratio	Angle of repose (degree)
Amlodipine besylate	0.32	0.38	15.79	1.18	29.12
CCS	0.29	0.35	16.85	1.20	25.21
SSG	0.33	0.39	15.38	1.18	26.40
MCC	0.39	0.45	13.33	1.15	28.13

9.3 Evaluation of Granules

Table: Evaluation parameters of granules of all formulations F1-F9

Formulations	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index(%)	Hausner ratio	Angle of repose (degrre)
F1	0.30	0.34	11.76	1.13	24.51
F2	0.32	0.37	13.51	1.15	24.82
F3	0.29	0.35	17.14	1.20	25.90
F4	0.31	0.37	16.21	1.19	25.43
F5	0.33	0.36	8.3	1.09	25.74
F6	0.30	0.35	14.28	1.16	26.13
F7	0.29	0.34	14.70	1.17	27.31
F8	0.30	0.36	16.66	1.2	25.12
F9	0.28	0.32	12.5	1.14	24.23

All formulations i.e. F1-F9 were evaluated for the blend property like bulk density, tapped density, carr's index, Hausner ratio and angle of repose.

The bulk density of all formulations was in the range of 0.29-0.33 gm/ml. The tapped density of all was range of 0.32-0.37 gm/ml. the carr's index of formulations was range of 8.3-17.14% which was considered as good flow property. The angle of repose for all formulation was in the range of 24.23-27.31degree , the angle of repose less then 30 indicating good flow property . Hausner ratio below 1.19 indicating good compression characteristics. All these result indicate that the powder blend posses satisfactory flow and compression properties.

9.4 Preparation of Amlodipine Besylate tablet

9.4.1 Evaluation of tablet

Table Evaluation parameter for MDT's

Formulations	Weight variation (%)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	50.01	6.8mm	3.4		100.1
F2	50.20	7mm	3.2		100.2
F3	51.10	7mm	3.2		100.2
F4	51.00	6.8mm	3.3		100.5
F5	49.50	6.7mm	3.3		99.9
F6	48.85	7mm	3.2		100.1
F7	50.5	7.1mm	3.2		100.1
F8	52.70	7.1mm	3.1		100.2
F9	51.00	6.9mm	3.3		100.1