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DEVELOPMENT OF ISOSORBIDE MONONITRATE FAST DISINTEGRATING TABLETS AND CHARACTERIZATION

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ABSTARCT

In the present work, an attempt has been made to develop fast disintegrating tablets of Isosorbide mononitrate Novel method of co processed super disintegrates technology was employed to formulate the tablets using co processed polymers like vivasol, polyplasdone. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. then checked for compatibility using FTIR and DSC studies. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F14 formulation showed maximum drug release i.e., 99.3% in 4 min hence it is considered as optimized formulation. The F14 formulation contains CP5 as super disintegrate in the concentration of 40 mg. (CP 5 contains Vivasole and polyplasdone XL in 3:1 ratio).

KEYWORDS: Isosorbide mononitrate, Co processed super disintegrates, Vivasole and polyplasdone XL.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical

scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance.[1]

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance.

Fig 1.1: Fast dissolving tablets.

It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Mouth Dissolving Tablet (MDT) is one among such approaches.

Fig 1.2: Mechanism of fast dissolving tablets.

Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.[2]

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms.

Fig 1.3: Commercial tablets.

But one important drawback of such dosage forms is Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc.

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water

To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 10 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

1.1 Ideal properties of a mouth dissolving tablet

Though nothing or nobody is ideal or perfect in this world, yet there are certain limits or characteristics that judge the nearness to perfection. A mouth dissolving tablet should:

1. Not require water or other liquid to swallow.
2. Easily dissolve or disintegrate in saliva within a few seconds.

3. Have a pleasing taste.
4. Leave negligible or no residue in the mouth when administered.
5. Be portable and able to tolerate the transportation stress.
6. Be able to be manufactured in a simple conventional manner within low cost.
7. Be less sensitive to environmental conditions like temperature, humidity etc.

1.2 Advantages of Mouth dissolving tablet

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosing as compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action.
5. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva, passing down into the stomach.
6. Advantageous over liquid medication in terms of administration as well as transportation.
7. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
8. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
9. Suitable for sustained/controlled release actives.

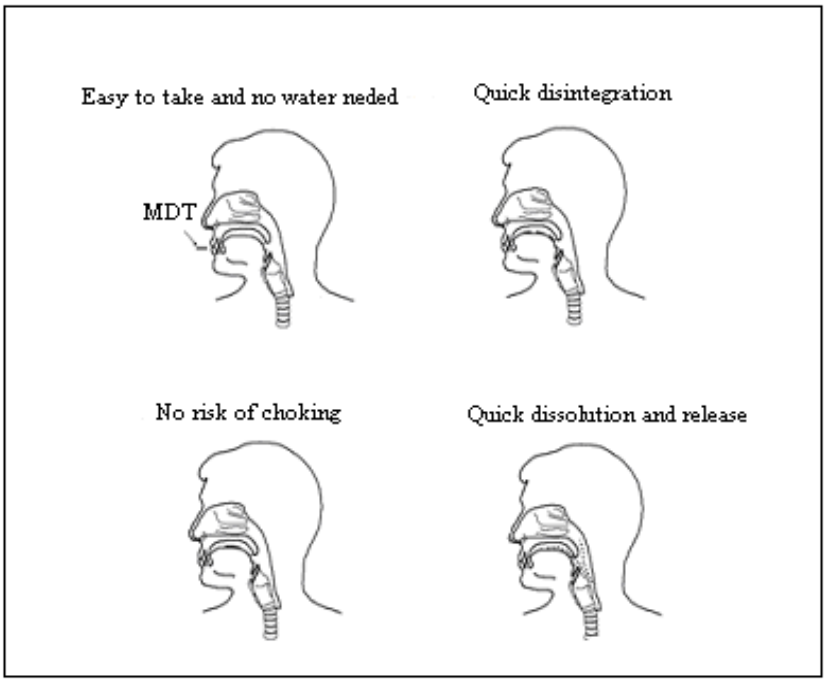

Figure 1.4: Figures showing Advantages of Mouth dissolving tablet.

1.3 Criteria for Fast dissolving Drug Delivery System

The tablets should

1. Not require water to swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
2. Be compatible with taste masking.
3. Be portable without fragility concern.
4. Have a pleasant mouth feel.
5. Leave minimum or no residue in the mouth after oral administration.
6. Exhibit low sensitive to environmental condition as temperature and humidity.
7. Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

1.4 Salient Feature of Fast Dissolving Drug Delivery System

1. Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
3. Rapid dissolution and absorption of the drug, which will produce quick onset of action.
4. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
5. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
6. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
7. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
8. New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
9. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
10. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

11. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.5 Main ingredients used in preparation of mouth dissolving tablets

Important ingredients that are used in the formulation of Fast dissolving tablet should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.[3]

Excipients balance the properties of the actives in FDDTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Binders keep the composition of these fast-melting tablets together during the compression stage. 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 30–35^{0}C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used. The most important ingredients of a mouth dissolving tablets are:

1.5.1. Super disintegrants

Use of disintegrants is the basic approach in development of mouth dissolving tablets. Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates.[4]

Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.

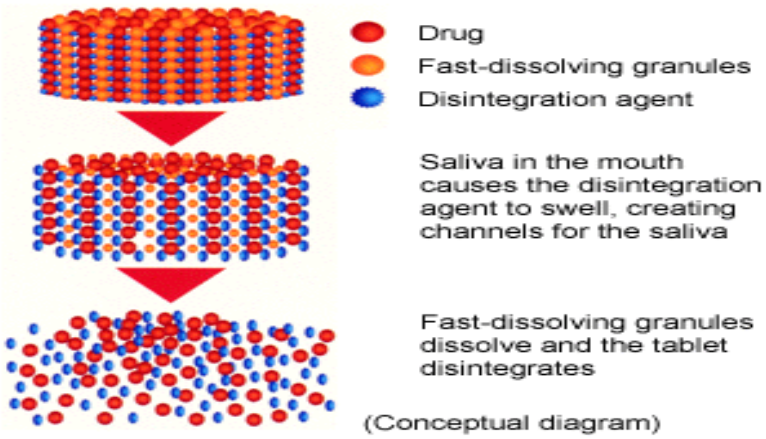

Figure 1.5: Mechanism of fast-dissolving tablets.

The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases Sodium starch glycolate, Ac-di-sol(crosscaremellose sodium), crosspovidone, microcrystalline cellulose, pregelatinised starch are some of examples of disintegrants.

1.5.2. Sugar based excipients

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing MDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, Mannitol, xylitol, dextrose, fructose, etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking. But not all sugar-based materials have fast dissolution rate and good compressibility or compatibility. However technologies are developed to make use of the sugar based excipients in the design of fast dissolving tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavors.[5]

1.6 Mechanism of action of disintegrants

The tablet breaks to primary particles by one or more of the mechanisms listed below:

1.6.1 By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tabletting 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.

1.6.2 By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

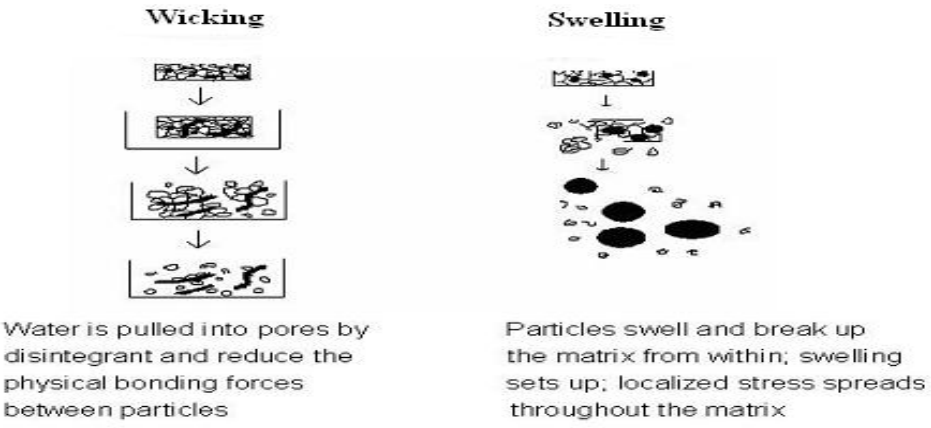

Figure 1.6: Disintegration of Tablet by Wicking and Swelling.

1.6.3 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 cannot describe the action of most modern disintegrating agents.

1.6.4 Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Scientists have proposed a particle repulsion theory based on the observation that non-swelling 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.

1.6.5 Due to deformation

Researchers had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

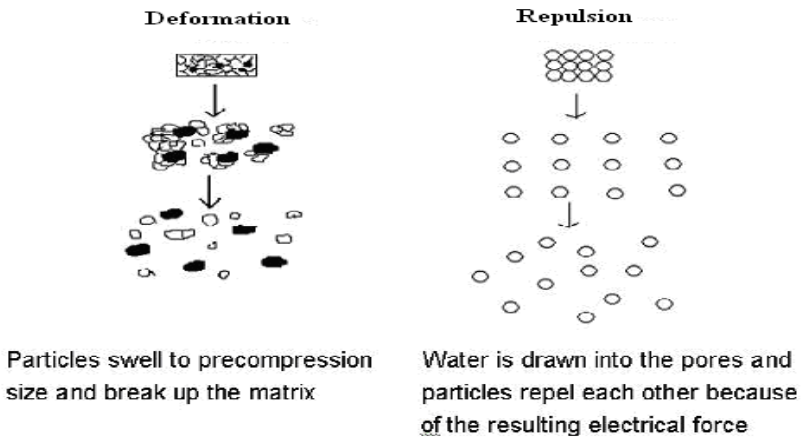

Figure 1.7: Disintegration by Deformation and Repulsion.

1.6.6 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.

1.6.7 By enzymatic reaction

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

1.7 Various Approaches for Fast Dissolving Tablets

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.[6-8]

Various technologies used in the manufacture of Fast dissolving tablets include:

- Freeze –drying or lyophilization
- Spray drying
- Direct compresion
- Moulding
- Mass extrusion

1.7.1 Freeze-drying

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. In this process, water is sublimated from the product after freezing. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is carried out to reduce the moisture to around 4% w/w of dry product. Finally, secondary drying is done to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapsed temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature, instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva. However the use of freeze-drying is limited due to high cost of equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

1.7.2 Spray drying

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. Allen and Wang used this technique to prepare mouth-dissolving tablets, which disintegrated within 20 sec.

1.7.3 Direct compresion

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by direct compresion creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.

1.7.4 Moulding

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion. Different moulding techniques can be used to prepare mouth-dissolving tablets:

a) **Compression moulding:** The powder mixture previously wetted with a solvent like Ethanol/water is compressed into mould plates to form a wetted mass.
b) **Heat moulding:** A molten matrix in which drug is dissolved or dispersed can be directly moulded into Mouth dissolving tablets.
c) **No vacuum lyophilization:** This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

Moulded tablets having porous structure, which facilitates rapid disintegration and easy dissolution. Moulded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But moulded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrolidone can increase mechanical strength.

1.7.5 Mass extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

1.7.6 Direct compression

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets due to certain advantages:

- High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- Easiest way to manufacture the tablets.
- Conventional equipment and commonly available excipients are use
- A limited number of processing steps are involved.
- Cost-effectiveness.

Disintegration and solubilzation of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents. Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

1.8 Technologies for MDT

Several technologies are available for preparing Mouth dissolving tablets. But some commercially useful technologies are.[9-10]

1.8.1 Zydis technology

'Zydis' is the first mouth dissolving dosage form in the market. It is a unique freeze-dried tablet in which the active drug is incorporated in a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water by direct compresion. Zydis matrix is made up of a number of ingredients in order to obtain different objectives. SUPER DISINTEGRANTS such as gelatin, dextran or alginates are added to impart strength during

handling. These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart crystallinity, elegance and hardness. Various gums may be added to prevent sedimentation of dispersed drug particles. Water is used as a medium to ensure the formation of a porous dosage form. Collapse protectants like glycine may be used to prevent shrinkage of dosage form during freeze drying and long-term storage. If necessary, suspending agents and pH adjusting agents may be used. Preservatives may also be added to prevent microbial growth. Zydis products are packed in blister packs to protect the formulation from environmental moisture. A secondary moisture proof foil punch is often required as this dosage form is very moisture sensitive. When put into the mouth, Zydis unit quickly disintegrates and dissolves in saliva.

Drawbacks

1. A water insoluble drug can be incorporated only upto 400 mg per tablet or less. On the other hand water-soluble drug can be incorporated only upto 60mg.
2. Relatively expensive and time-consuming process.
3. Fragility and poor stability of dosage form during storage under stressful conditions.

1.8.2 Orasolv technology

It is CIMA lab's first mouth dissolving formulation. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipment are used for preparation of tablets. Less force of compaction is used for manufacturing so as to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

1.8.3 Durasolv Technology

This too has been developed by CIMA labs. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tabletting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.

1.8.4 Wowtab Technology

Yamanauchi pharmaceutical company patented this technology. 'wow' means "without water". The active ingredients may constitute upto 50% w/w of the tablet. In this technique,

saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed.

Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldabiity saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 seconds or less. Wowtab product can be packed in both into conventional bottle and blister packs.

1.8.5 Flashdose Technology

This technology is patented by Fuisz. This system uses the combination of both Shearform and Ceform technologies in order to mask the bitter taste of the drug. A sugar based matrix, called 'Floss' is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation.

Drawbacks

1. The dosage form can accommodate only upto 600 mg of drug.
2. Tablets produced are highly friable, soft and moisture sensitive. Therefore specialized packing is required.

1.8.6 Flashtab Technology

Prographarm labs have a patent over this technology. In this technology, microgranules of the taste-masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion- spheronisation. All these processes utilize conventional tabletting technology. These taste-masked micro crystals of active drug, disintegrating agent, a swelling agent and other excipients like soluble diluents etc are compressed to form a multi-particulate tablet that disintegrates rapidly.

1.8.7 Shearform Technology

In this technology, a shearform matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass

to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. The flowing mass comes out through the spinning head that flings the floss. The produced floss is amorphous in nature. So by various techniques, it is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it.

1.9 Selection of drug candidates for mouth dissolving tablets.[11]

Several factors must be considered when selecting drug candidates for delivery as MDT dosage forms. In general,

- MDT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the MDT occurs in the post-gastric GIT segments, similar to the conventional oral dosage form.
- But this scenario may not always be the case. MDT may have varying degrees of pre-gastric absorption and thus, the pharmacokinetic profile (including the maximum plasma concentration, time to achieve maximal plasma concentration, and area under the plasma concentration time curve of an equal dose of an MDT and a conventional oral dosage form) will vary. Therefore, the MDT will not be bioequivalent to the conventional oral dosage form.
- Examples are cited in the literature in which the pharmacokinetic profiles and bioavailabilities of the same dose of drug in an MDT are not bioequivalent to the conventional oral dosage form.
- For example, MDT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.
- It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both.
- If significantly higher plasma levels and systemic exposure have been observed, pre-gastric absorption leading to the avoidance of first-pass metabolism may play an important role.
- This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for a MDT.

- For example, safety profiles may be improved for drugs that produce significant amounts 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.

1.9.1 Some of promising Drug candidates for mouth dissolving tablets

Antibacterial agents: Ciprofloxacin, tetracycline, azithromycin, erythromycin, rifampicin, penicillin, doxycyclin, clarithromycin, nalidixic acid, nitrofurantoin, trimethoprim, sulphacetamide, sulphadiazine.

Anthelmintics: Albendazole, mebendazole, thiabendazole, livermectin, praziquantel, pyrantel embonate, dichlorophen, etc.

Antidepressants: Trimipramine maleate, nortriptyline HCl, trazodone HCl, amoxapine, mianserin HCl.

Antidiabetics: Glibenclamide, glipizide, tolbutamide, tolazamide, gliclazide, chlorpropamide, etc.

Analgesics and anti-inflammatory agents: Diclofenac sodium, ibuprofen, flurbiprofen, ketoprofen, naproxen, mefenamic acid, meclofenamic acid, indomethacin, nabumetone, piroxicam, oxyphenbutazone, phenylbutazone, etc.

Antihypertensives: Amlodipine, carvedilol, diltiazem, felodipine, minoxidil, nifedipine, prazosin HCl, nimodipine, terazosin HCl, etc.

Antiarrhythmic agents: Disopyramide, quinidine sulphate, amiodarone HCl, etc.

Antihistamines: Acrivastine, cetrizine, cinnarizine, loratadine, fexofenadine, triprolidine, etc.

Anxiolytics, sedatives, hypnotics and neuroleptics: Alprazolam, diazepam, amylobarbitone, chlorpromazine, clotiazepam, chlordiazepoxide, clozapine, flurazepam, lorazepam, haloperidol, nitrazepam, oxazepam, midazolam, droperidole, phenobarbitone, thioridazine, triazolam, prochlorperazine, etc.

Diuretics: Acetazolamide, clorthiazide, amiloride, furosemide, spironolactone, bumetanide, ethacrynic acid, etc.

Gastro-intestinal agents: Cimetidine, ranitidine HCl, famotidine, domperidone, loperamide, mesalazine, sulphasalazine, omeprazole, lansoprazole, ondansetron HCl, granisetron HCl, etc.

Corticosteroids: Betamethasone, beclomethasone, cortisone acetate, hydrocortisone, dexamethasone, fluticasone propionate, prednisone, prednisolone, methyl prednisolone, etc.

Antifungal agents: Amphotericin, fluconazole, itraconazole, miconazole, ketoconazole, terconazole, econazole nitrate, nyastatine, griseofulvin, etc.

Antiprotozoal agents: metronidazole, tinidazole, omidazole, benznidazole, clioquinol, decoquinate, etc.

1.1 Some commercially available mouth dissolving tablets.

Trade name	Active drug	Manufacturer
Nimulid-MD	Nimesulide	Panacea Biotech, New Delhi, India
Feldene Fast Melt	Piroxicam	Pfizer Inc., NY, U.S.A
Zyrof Meltab	Rofecoxib	Zydus, Cadila, India
Pepcid RPD	Famotidine	Merck and Co., NJ, U.S.A
Romilast	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Torrox MT	Rofecoxib	Torrent Pharmaceuticals, Ahmedabad, India
Olanex Instab	Olanzapine	Ranbaxy Labs Ltd., New Delhi, India
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Mosid-MT	Mosapride citrate	Torrent Pharmaceuticals, Ahmedabad, India
Febrectol	Paracetamol	Prographarm, Chateauneuf, France

Coprocessed super disintegrates.[12]

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual5. Co-processing excipients lead to the formulation of excipient granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, andreduced lubricant sensitivity6. Several co-processed superdisintegrants are commercially available: Ludipress (lactose monohydrate, polyvinylpyrrolidone and crospovidone), Starlac(lactose and maize starch), Starcap 1500 (corn starch and pregelatinized starch), Ran Explo-C (microcrystalline

cellulose, silica and crospovidone), Ran Explo-S (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G (microcrystalline cellulose, hydroxy propyl methyl cellulose and crospovidone.

METHODOLOGY

6.1. PREFORMULATION STUDIES

The goals of the preformulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

6.2 Determination of absorption maximum (λ_{max})

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance. Isosorbide mononitrate was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in 6.8 pH phosphate buffer and the final volume was made up to 100 ml with 6.8 pH phosphate buffer to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with 6.8 pH phosphate buffer to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Construction of Isosorbide mononitrate calibration curve with phosphate buffer PH 6.8:

100mg of Isosorbide mononitrate was dissolved in 100ml of 6.8 pH phosphate buffer to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 1ml was taken and diluted to 100ml with)6.8 pH phosphate buffer to give a concentration of 0.01mg/ml (10µgm/ml). From this stock solution aliquots of 0.5, 1, 1.5,2 and 2.5ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with)6.8 pH phosphate bufferto produce concentration of 5, 10,1,20 and 25µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 290 nm.

6.3. Drug- excipient compatibility studies by FT-IR

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about $8t/in^2$. The spectra were recorded over the wave number of 8000 to $400cm^{-1}$.

6.4. Flow properties

Angle of Repose

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula: $\Theta = \tan^{-1} H/R$

Θ=angle of repose

H=height of powder cone, R=radius of powder cone

Angle of Repose less than 30^0 shows the free flowing property of the material.

Table 6.1: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Loose bulk Density (LBD)

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$Df = M / Vp$$

Where, Df = bulk density

M = weight of sample in grams

Vp = final volume of powder in cm^3

Tapped bulk density (TBD)

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 if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was 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

$$Do = M / Vp$$

Where, Do = Tapped density,

M = weight of sample in grams

Vp = final volume of powder after tapping in cm^3

Carr's consolidation index

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

Where, ρ_b is the bulk density, ρ_t is the tapped bulk density

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Table 6.2: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$$H = \rho_{b/} \rho_b$$

Where, ρ_b is the bulk density

ρ_b is the tapped bulk density

Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

6.5. Formulation of Fast dissolving tablets of Isosorbide mononitrate:

Preparation of co processed super disintegrates:

Co processed super disintegrates were prepared by using sodium Vivasole and polyplasdone XL. The super disintegrates were mixed in different concentrations and labeled as CP1,CP2,CP3.The blend of super disintegrates was mixed thoroughly for a period of 15 min, collected and used for preparing formulations in different concentrations.

CP = Coprocessed super disintegrate

Table 6.3: Composition of co processed super disintegrates.

Ingredients	CP1	CP2	CP3	CP4	CP5
Vivasol (mg)	500	500	500	1500	1000
Polyplasdone XL (mg)	500	1000	1500	500	500

Preparation of tablets

Composition of Isosorbide mononitrate Fast dissolving Tablet by direct compression is shown in table 6.4. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-10 station with 6mm flat punch, B tooling. Each tablet contains 10 mg Isosorbide mononitrate and other pharmaceutical ingredients.

Table no. 6.4. Composition of various tablet formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Isosorbide mononitrate (mg)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
CP 1(mg)	20	40	60	-	-	-	-	-	-	-	-	-	-	-	-
CP 2(mg)	-	-	-	20	40	60	-	-	-	-	-	-	-	-	-
CP 3(mg)	-	-	-	-	-	-	20	40	60	-	-	-	-	-	-
CP 4 (mg)	-	-	-	-	-	-	-	-	-	20	40	60	-	-	-
CP 5(mg)	-	-	-	-	-	-	-	-	-	-	-	-	20	40	60
Mg St(mg)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc(mg)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

6.6. POST COMPRESSION PARAMETERS

Evaluation of tablets

Shape and colour

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test

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

Table no.6.5.Limits of Weight variation.

Average Weight Of Tablet(mg)	%deviation
130mg or less	10
> 130or <324	7.5
> 324	5

Drug Content estimation

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

10 tablets were weighed and triturated. The tablet triturate equivalent to 50 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2. Absorbance was read at 290 nm against the reagent blank, and the concentrations of drug in µg/ ml was determined by using the regression equation.

Drug content in mg / tablet = conc. µg/ml * dilution factor /1000

% Drug content = drug content in mg * 100 / label claim.

***In -vitro* dissolution studies**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 500ml of 6.8 pH phosphate buffer at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Isosorbide mononitrate by measuring absorbance at 290 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of 6.8 pH phosphate buffer. Details:

Apparatus used	:	USP II Lab India DS 800
Dissolution Medium	:	6.8 pH phosphate buffer
Dissolution Medium volume	:	500ml
Temperature	:	37^0C
Speed of paddle	:	50rpm
Sampling Intervals	:	2, 4, 6, 8, 10, 15, 20,25 and 30 min
Sample withdrawn	:	5ml
Absorbance measured	:	290 nm.

MATERIALS

Table 5.1: List of Materials Used.

Name of the material	Source
Isosorbide mononitrate	NATCO laboratory
Microcrystalline cellulose	Signet Chemical Corporation, Mumbai, India.
Vivasole	Merck Specialities Pvt Ltd, Mumbai, India.
Polyplasdone XL	Merck Specialities Pvt Ltd, Mumbai, India.
Magnesium stearate	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

Table 5.2: List of Equipment's used.

Name of the Equipment	Manufacturer
Weighing Balance	Wensar
Tablet Compression Machine (Multistation)	Karnavati Limited, India.
Hardness tester	Monsanto, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
DissolutionApparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.

RESULTS AND DISCUSSION

7.1. Standard Calibration curve of Isosorbide mononitrate

Table 7.1: Concentration and absorbance obtained for calibration curve of Isosorbide mononitrate in 6.8 pH phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 290 nm)
1	0	0
2	5	0.106
3	10	0.177
4	15	0.265
5	20	0.344
6	25	0.431

It was found that the estimation of Isosorbide mononitrate by UV spectrophotometric method at λ_{max} 290.0 nm in 6.8 pH phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1.

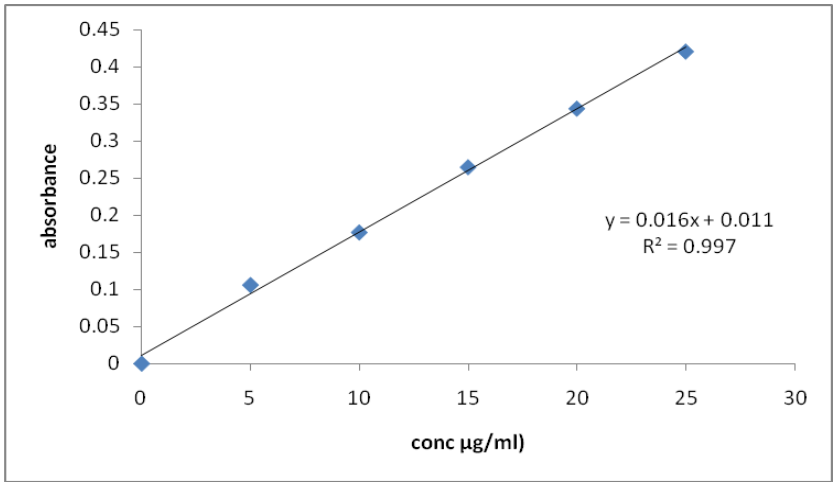

Fig 7.1: Standard graph of Isosorbide mononitrate 6.8 pH phosphate buffer.

7.2 Evaluation Parameters for Fast Dissolving Tablets of Isosorbide mononitrate

7.2.1 Pre-compression parameters

The data's were shown in Table 7.2.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends was fall in the range of 13.06% to 18.18%. The Hausner ration was fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 7.2: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.45±0.03	0.55±0.04	18.18±0.01	1.22±0.09	27.91±0.09
F_2	0.47±0.06	0.55±0.03	14.54±0.04	1.17±0.07	28.23±0.06
F_3	0.50±0.04	0.58±0.06	13.79±0.03	1.16±0.06	29.34±0.04
F_4	0.46±0.07	0.55±0.01	16.36±0.06	1.19±0.03	26.71±0.06
F_5	0.50±0.01	0.58±0.06	13.79±0.04	1.16±0.06	29.34±0.03
F_6	0.47±0.06	0.55±0.04	14.54±0.07	1.17±0.03	28.23±0.01
F_7	0.50±0.04	0.58±0.07	13.79±0.03	1.16±0.01	29.34±0.07
F_8	0.41±0.09	0.50±0.03	18.34±0.06	1.21±0.07	26.78±0.09
F_9	0.41±0.03	0.50±0.04	18.02±0.07	1.21±0.06	26.78±0.09
F10	0.45±0.09	0.55±0.03	18.18±0.04	1.22±0.09	25.85±0.06
F11	0.48±0.01	0.57±0.07	15.78±0.03	1.18±0.04	27.45±0.01
F12	0.46±0.07	0.54±0.03	14.81±0.06	1.17±0.03	28.12±0.04
F13	0.49±0.03	0.58±0.06	15.51±0.01	1.18±0.04	27.02±0.03
F14	0.51±0.04	0.59±0.03	13.55±0.04	1.15±0.03	26.36±0.09
F15	0.41±0.09	0.49±0.04	16.32±0.03	1.19±0.09	28.75±0.09

7.2.2. Post compression Parameters

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.3. The average weight of the tablet is approximately in range of 307 to 298.5, so the permissible limit is ±5% (>250mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 7.3. The results showed that the hardness of the tablets is in range of 2.0 to 2.5 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.3. The result showed that thickness of the tablet is raging from 4.56 to 5.34.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7.3. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time

Tablets of each batch were evaluated for in vitro disintegration time and the data's were shown in the Table 7.3. The results showed that the disintegration time of prepared tablets were in the range of 17 to 25.33 seconds.

Assay

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 - 100.26 %.

Invitro Dissolution studies

Table 7.4: Invitro dissolution data.

Time (Min)	F1	F2	F3	F4	F5	F6	F7
2	25.4±0.3	31.7±0.05	40.8±0.9	24.3±0.9	39.5±0.6	44.9±0.3	35.2±0.7
4	39.6±0.05	40.5±0.3	56.72±0.05	31.6±0.6	56.3±0.3	58.4±0.6	50.2±0.3
6	48.6±0.6	51.9±0.9	76.16±0.3	49.3±0.05	76.2±0.9	63.1±0.3	62.1±0.6
8	54.3±0.9	62.4±0.6	87.4±0.7	58.3±0.3	89.7±0.3	79.7±0.6	73.5±0.3
10	66.4±0.7	79.1±0.3	98.5±0.6	74.3±0.7	97.8±0.3	89.3±0.05	80.4±0.9
15	73.1±0.3	85.5±0.7		88.1±0.6		98.9±0.3	89.3±0.05
20	80.6±0.7	95.2±0.6		97.6±0.7			94.2±0.3
25	91.5±0.6						100.2±0.7
30	97.86±0.9						

Time (Min)	F8	F9	F10	F11	F12	F13	F14	F15
2	44.2±0.7	53.2±0.4	43.7±0.9	54.2±0.4	75.2±0.9	53.2±0.4	79.3±0.7	83.1±0.4
4	52.1±0.4	66.2±0.7	55.2±0.4	70.3±0.6	85.3±0.4	60.2±0.7	99.3±0.4	96.3±0.7
6	64.9±0.2	79.3±0.6	74.2±0.7	86.3±0.6	99.3±0.7	75.3±0.9		
8	75.3±0.6	85.2±0.2	89.3±0.6	97.3±0.7		94.3±0.2		
10	87.3±0.9	98.2±0.9	95.3±0.9					
15	96.2±0.2							
20								
25								
30								

Invitro dissolution studies were carried out by using 500ml of 6.8 pH phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations were given in the Table 7.4.

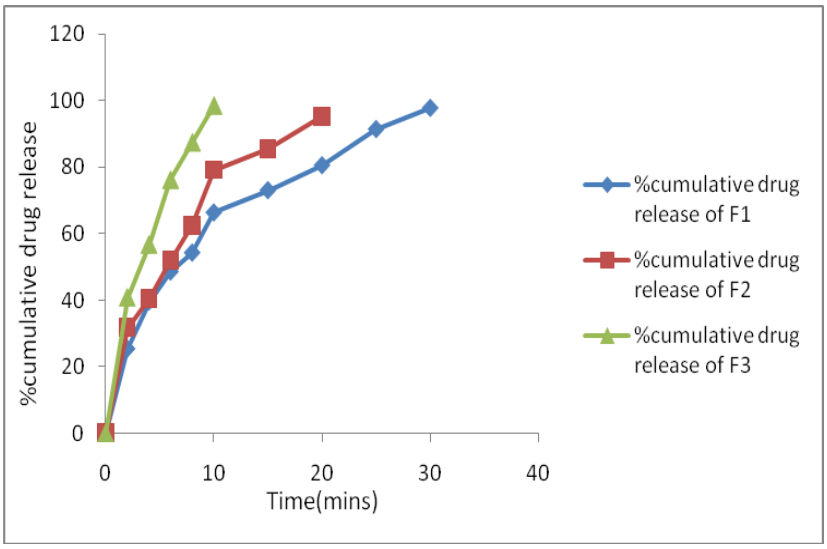

Fig 7.2: Dissolution profile of formulations prepared with CP1 as super disintegrate.

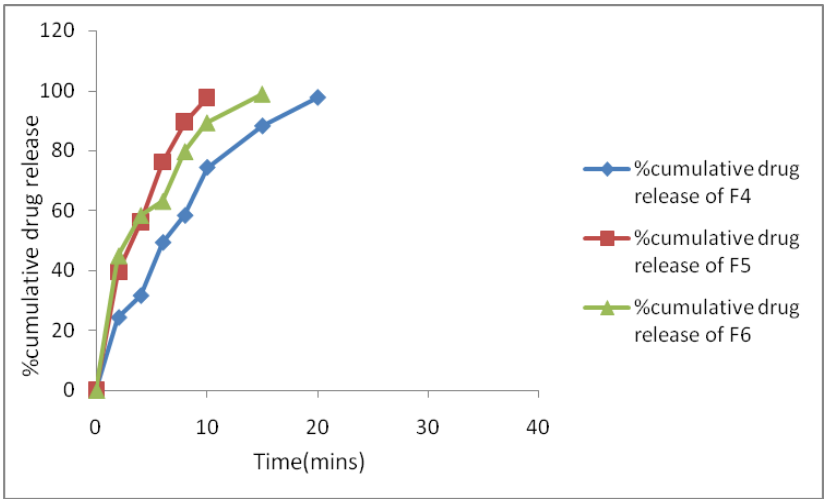

Fig 7.3: Dissolution profile of formulations prepared with CP2 as super disintegrate.

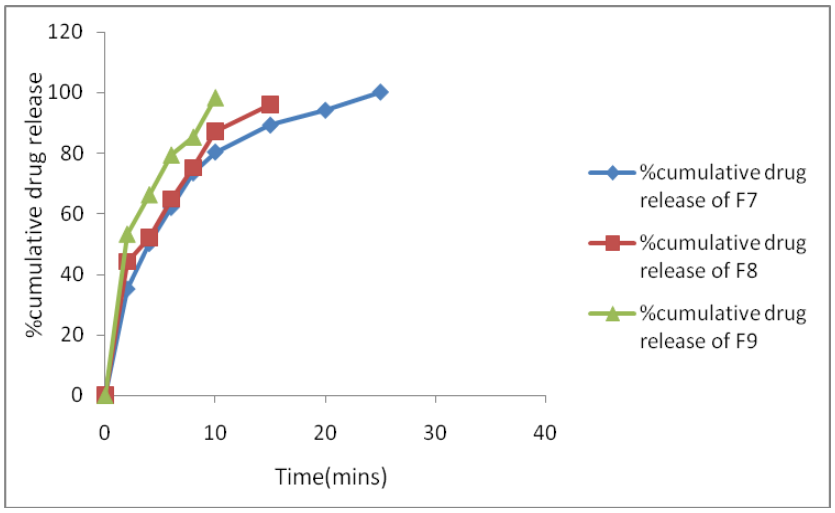

Fig 7.4: Dissolution profile of formulations prepared with CP3 as super disintegrate.

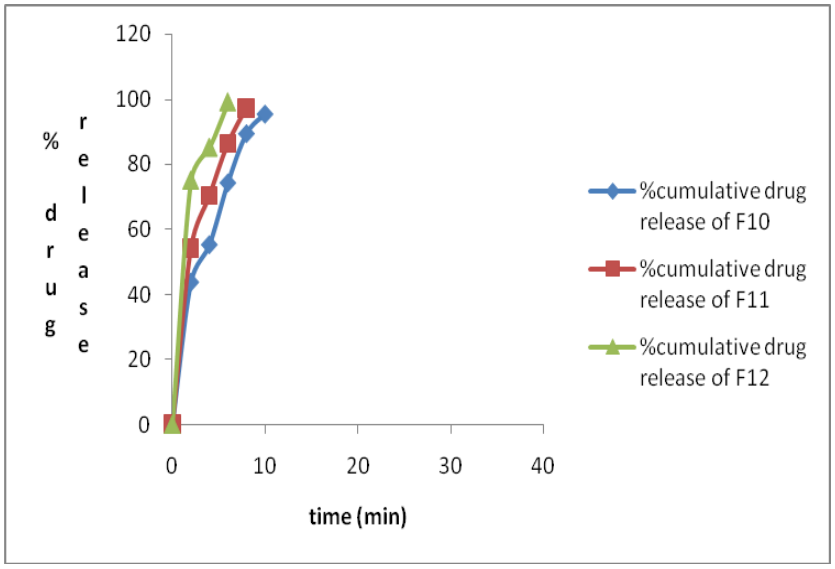

Fig 7.5: Dissolution profile of formulations prepared with CP4 as super disintegrate.

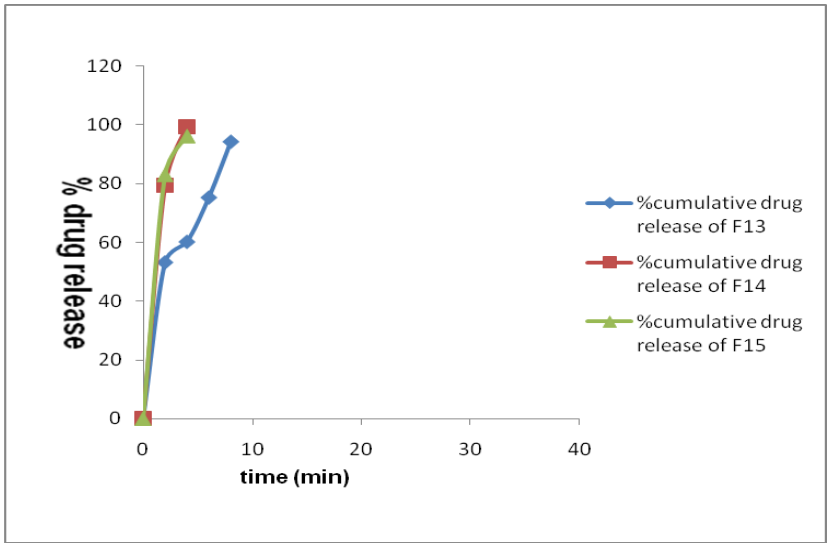

Fig 7.6: Dissolution profile of formulations prepared with CP5 as super disintegrate.

From the tabular column 7.4 it was evident that the formulations prepared with super disintegrate CP5 showed maximum % drug release in 4 min i.e.99.3%, 96.3% (F13, F14) formulations and the concentration of super disintegrate is 30mg,45 mg). So the principle of coproceesed super disintegrates was found to be useful to produce oro dispersible tablets.F13 formulation was considered as optimized formulation as it contains less concentration of super disintegrate.

Fourier Transform-Infrared Spectroscopy

Fig 7.7: FTIR of pure drug.

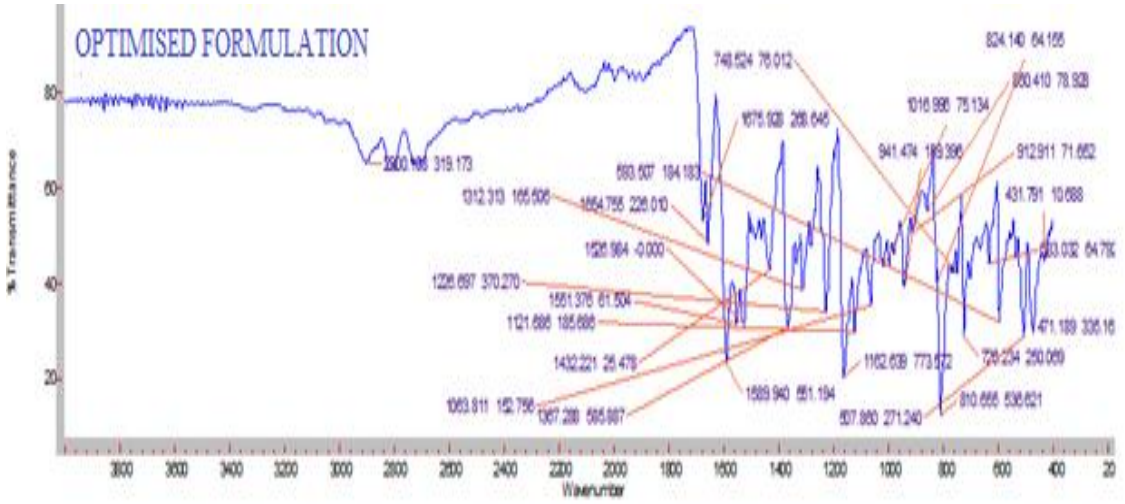

Fig 7.8: FTIR of optimized formulation.

Observation: by observing the spectrum it was observed that there is no change in the characteristic peaks of the pure drug and polymers it shows the compatibility between the pure drug and optimized formulation.

CONCLUSION

In the present work, an attempt has been made to develop fast disintegrating tablets of Isosorbide mononitrate. Novel method of co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F14 formulation showed maximum drug release i.e., 99.3% in 4 min hence it is considered as optimized formulation. The F14 formulation contains CP5 as super disintegrate in the concentration of 30 mg. (CP 5 contains Vivasole and polyplasdone XL in 3:1 ratio).

Conflict of Interest

The authors declare that they have no conflict of interest.

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