

Formulation and Evaluation of Meclizine Hcl Orally Dispersible Tablets by using Natural Super Disintegrants

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Abstract

The present study is on Meclizine HCL orally disintegrating tablets. meclizine HCL is used for the treatment of many different types of bacterial infections such as bronchitis, sinusitis, tonsillitis, ear infections, skin infections, gonorrhoea, and urinary tract infections. meclizine HCL is a β -lactam type antibiotic. More specifically, it is a second-generation cephalosporin.

Natural super disintegrates like xanthum gum and algenic acid are added to the formula to increase its disintegration, Orodispensible tablets of Meclizine Hcl were formulated by the Natural Superdisintegrant addition method by direct compression technique. All the formulations were evaluated for disintegration time, hardness and friability, this Superdisintegrant addition method exhibits the lowest disintegration time 29 sec, hence it is ranked as the best among the methods. All the formulations were evaluated for weight variation 226.3, hardness 5.1 , friability0.29, drug content uniformity 99.5, wetting time 28 sec for in-vitro dissolution study. Among all the formulations containing naturally super disintegrates like algenic acid and xanthumgum was considered to be the best formulation, which release up to 99.6% of the drug in 20 mints.

Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. The DDS makes 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

Oral drug delivery has been known for decades as the most widely utilized routes of the administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration1. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population

along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and increase the flavor acceptability of bitter drugs by various groups of population. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.

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.



It is always the aim of a scientist or a dosage form designed 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.



Improved patient compliance has achieved enormous demand. Consequently the 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 the 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.

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.^{2,3}



But one important drawback of such dosage forms is dysplasia 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..^{2,3}

- Parkinsonism

- Motion sickness
- Unconsciousness
- Elderly patients
- Children
- Mentally disabled persons

- 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. Oro dispersible tablet that

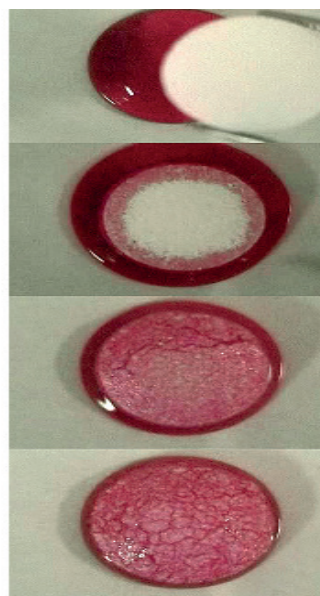
disintegrates and dissolves rapidly in the patient's mouth, within a 15 Sec-3 min without the need for drinking water or chewing. Most of the ODTs include certain super disintegrates and taste masking agents.



0.4 sec

1.5 sec

3.8 sec



• Ideal Properties of ODTs:^{4,5,6}

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function.

An ideal ODT should meet the following criteria:

- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds
- Has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- Allow high drug loading
- Has a pleasant mouth feel
- Is insensitive to environmental conditions such as humidity and temperature is adaptable and amenable to existing processes and packaging machineries.

1.2 Advantages of Orodispersible tablet:^{4,5,6}

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

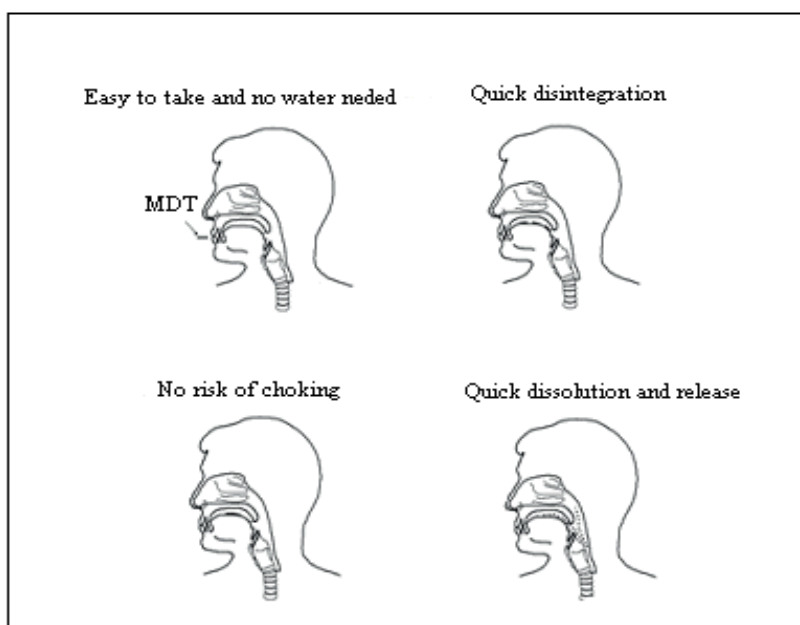


Figure 1: Figures showing Advantages of Orodispersible tablet

1.2. The need for development of ODT: ^{7,8,9}

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with the high cost of disease management.

1.2.1. Patient Factors:

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-Oz glass of water. These include the following

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms
- Patients who are unwilling to take solid preparation due to fear of choking
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eighty year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H₂-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of a typical antipsychotic.
- A patient with persistent nausea, who may be journeying, or has little or no access to water.

1.2.2. Effectiveness Factor:

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those

cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption of many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, 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 pre-gastric segments of GIT.

1.2.3. Manufacturing and Marketing Factors:

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. Launched Aricept ODT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its blockbuster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004²⁴. Marketers build a better brand and company image when they offer a unique, easy-to-take form that satisfies the need of an underserved patient population.

1.3. Significance:^{10,11}

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small pack size, and easy to handle by patients.
- No risk of obstruction of dosage forms, which is beneficial for traveling patients who do not have access to water.
- Easy to administer for pediatric, geriatric, and institutionalized patients (especially for mentally retarded and psychiatric patients)
- The rapid disintegration of tablet results in quick dissolution and rapid absorption, which provide rapid onset of action.
- Medication as “bitter pill” has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
- Bioavailability of drugs that are absorbed from the mouth, pharynx, and esophagus is increased. 3
- Pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

1.4. Challenges in Formulating ODTs: 10,11

1.4.1. Palatability:

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in the 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.

1.4.2. Mechanical strength:

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

1.4.3. 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.

1.4.4. Amount of drug:

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

1.4.5. 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 the loss of supporting structure

during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

1.4.6 Size of tablet:

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of the 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.

1.5 Criteria for Fast dissolving Drug Delivery System:12

The tablets should:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.
 - Be compatible with taste masking.
 - Be portable without fragility concern.
 - Have a pleasant mouth feel.
 - Leave minimum or no residue in the mouth after oral administration.
 - Exhibit low sensitive to environmental condition as temperature and humidity.
 - Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.
- ##### 1.6 Salient Feature of Orodispersible Drug Delivery System:13
- Ease of Administration for 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.
 - 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.
 - Rapid dissolution and absorption of the drug, which will produce quick onset of action.
 - 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.
 - Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
 - Good mouth feel property helps to change the perception of medication as the bitter pill particularly in the pediatric patient.
 - The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
 - New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.

- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantages of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.7 Main ingredients used in preparation of Orodispersible tablets: 14

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

Excipients balance the properties of the actives in Orodispersible tablets. 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

1.7.1. Super disintegrates:

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

Super disintegrates provide quick disintegration due to the combined effect of swelling and water absorption of 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. The optimum concentration of the superdisintegrant can be selected according to the 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 (crosscarmellose sodium), croscopolidone, microcrystalline cellulose, pregelatinised starch are some of the examples of disintegrates.

1.7.2. Sugar based excipients:

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having an unpleasant or bitter taste. And the basic requirement for designing ODTs is that the drug should not have a disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, Mannitol, Xylitol, dextrose, fructose, etc. Are mainly used. Indion-234 and Tulsion-335 were also utilized.

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 on the design of Oro dispersible tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, colors and flavors.

1.8. Mechanism of action of disintegrates:

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

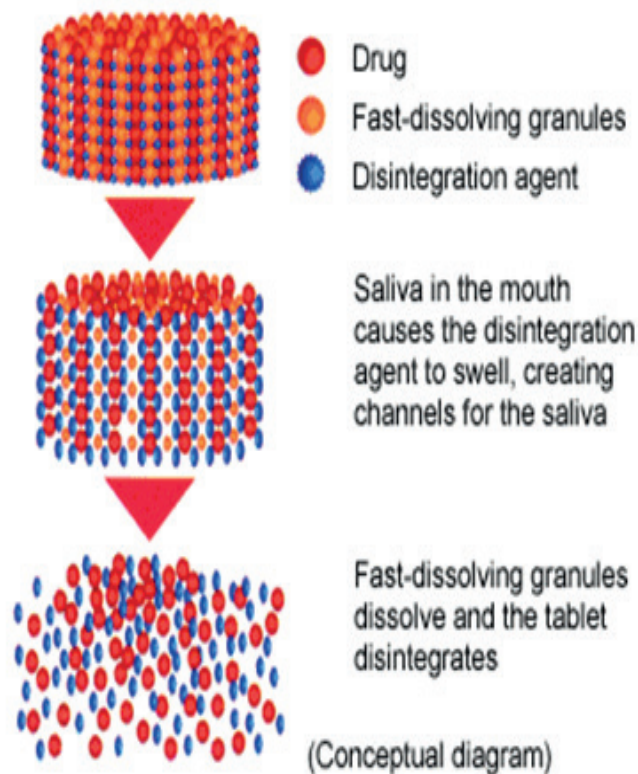


Figure 2: Mechanism of fast-dissolving tablets:

1.8.1 By capillary action:

Disintegration by capillary action is always the first step. When we put the tablet in 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 tabulating 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.

1.8.2 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 slow down.

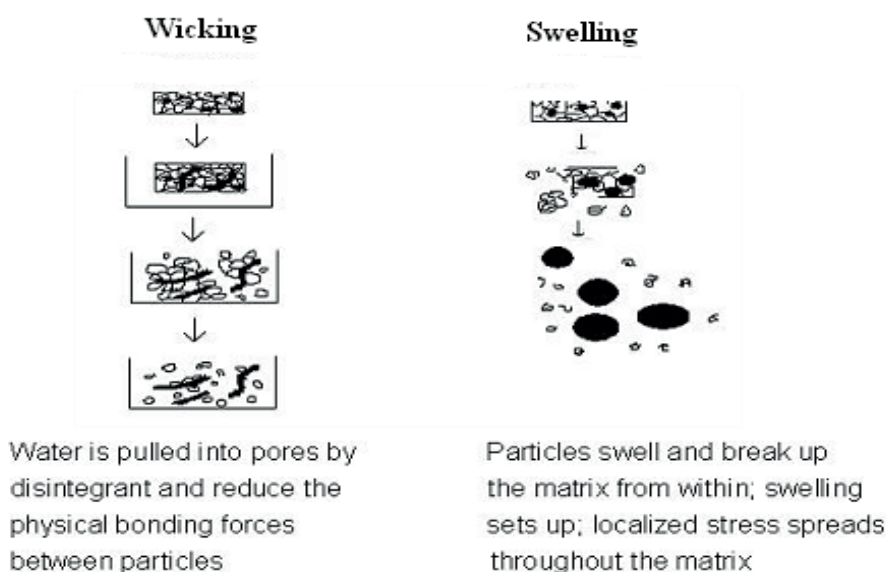


Figure 3: Disintegration of Tablet by Wicking and Swelling

1.8.3 Because of heat of wetting (or expansion):

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

1.8.4 Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablets made with 'non-swelling' disintegrates. 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.

1.8.5 Due to deformation:

Researchers have proven 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.

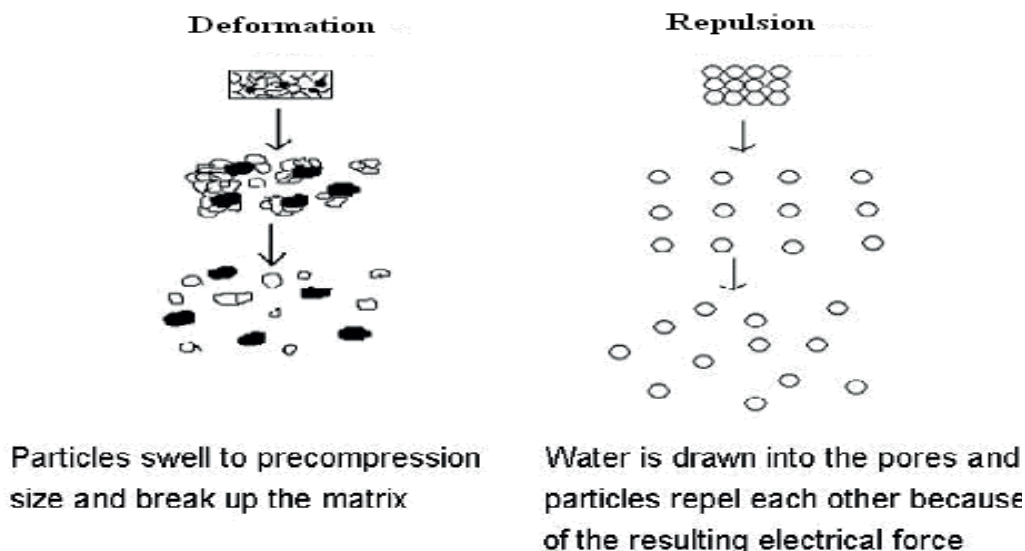


Figure 4: Disintegration by Deformation and Repulsion

1.8.6 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 disintegrates are highly sensitive to small changes in humidity level and temperature, strict control of the environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

1.8.7 By enzymatic reaction:

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

1.9. Various Technologies Used In The Manufacture Of Orodispensible Tablets: 13,14

The performance of orodispersible tablets depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water

into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop orodispersible tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Following technologies have been used by various researchers to prepare orodispersible tablets:

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

1.9.1 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 the high cost of equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

- 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 ingredients and compressed into tablets. Allen and Wang used this technique to prepare mouth-dissolving tablets, which disintegrated within 20 Sec.

Direct compression:

This process involves the addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc, to other excipients and the compression of blend into a tablet. Removal of volatile material by direct compression 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 a pore forming agents. Oro dispersible tablets with highly porous structure and good mechanical strength have been developed by this method.

- 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, the 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 of-

fer 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.

Mass extrusion:

In this technique, a blend of active drug and other ingredients is softened using a 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.

- Direct compression¹⁴

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 used
- A limited number of processing steps are involved.
- Cost-effectiveness.

Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrates, 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 disintegrate 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.

1.10 Patented Technologies for ODT:

Several technologies are available for preparing Oro dispersible tablets. But some commercially useful technologies are:

1.10.1 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 into a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water by direct compression. Zydis matrix is made up of a number of ingredients in order to obtain different objectives. SUPER DISINTEGRANTS such as gelatin, dextran or agents 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

protects like glycerin 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. Zydys 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, Zydys unit quickly disintegrates and dissolves in saliva.

Drawbacks:

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

1.10.2 Orasolv technology:

It is CIMA lab's first Orodispersible formulation. This technology involves taste masking of active drug. The effervescent disintegrating agent is also used. Conventional blenders and tablet equipment are used for preparation of tablets. The 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 packaging system.

1.10.3 Durasolv Technology:

This tool 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 drugs, fillers and a lubricant prepare the tablet. Conventional tabulating 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.

1.10.4 Wowtab Technology:

Yamanouchi pharmaceutical company patented this technology. 'Wow' means "without water". The active ingredients may constitute up to 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mutability is the capacity of a compound to be compressed.

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

1.10.5 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:

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

1.10.6 Flashtab Technology:

Prographarm labs have a patent over this technology. In this technology, microgranules of the taste-masked, active drug is used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion- spheronisation. All these processes utilize conventional tableting 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.

1.10.7 Shearform Technology:

In this technology, a shearform matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subject 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.

1.11. Problems in Tablet manufacturing:

- Lamination: Separation of a tablet into two or more distinct horizontal layers.
- Capping: Partial or complete separation of top or bottom crowns of a tablet.
- Chipping: Breaking of tablet edges during compression or coating.
- Cracking: Fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracks'.
- Picking: In picking the tablet material adheres to the surface of the punches resulting in tablets with a pitted surface instead of a smooth surface.
- Sticking: The tablet material adheres to the die wall.
- Mottling: Unequal distribution of color on the surface of colored tablets.

- Blotting: Appearance of light or dark spots of color on the tablet surface.

1.12. Approaches for Masking Taste:

Orally disintegrating tablet, which disintegrate or dissolve in the saliva and produce a positive or a negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays critical role in formulating ODT. The negative taste sensation of drugs can be reduced or eliminated by various approaches studied, which include the addition of sweeteners and flavors, encapsulating the unpleasant drug in to micro particles and adjustment of pH.

1.12.1. Incorporation of Sweeteners and Flavors:

Maximum patient acceptability with ODT is seeing if they provide pleasant taste and mouth feel. To provide this property in tablets various sweeteners and flavors are employed. Usually sugar-based excipients are used as they are highly water soluble and dissolve quickly in saliva and provide pleasant taste and mouth feel to the final product. Mannitol is most widely used excipient in formulating ODT. Aspartame and citric acid are most commonly used along with various flavors such as mint flavor, orange flavor, strawberry flavor, peppermint flavor to produce pleasant taste, and mouth feel.

1.12.2. Encapsulation or Coating of Drugs:

Some of the unpleasant drugs cannot be masked by incorporation of sweeteners and flavors, in such cases, alternative method of masking the taste is by encapsulating or coating the drug. In fact, this process retards or inhibits dissolution and solubilization of the drug, which allows time for particles to pass from mouth before the taste is perceived in the mouth.

VARIOUS TECHNIQUES UTILIZED INCLUDE

- The CIMA'S taste masking technique uses a coating of drug with the dissolution retarding material.
- Phase separation approach for taste-masked microcapsules.
- Microspheres process used microencapsulation technology.
- Extrusion method.
- Micromask technology used casting or spin congealing melt dispersions or solution of the drug in a molten blend of materials.
- Flashtab technology.
- Solutab technology involves coating drug with sustained release agents, which are finally coated with enteric polymers and further with menthol.
- Blending with Cyclodextrins.

- Coating crystals, granules, and pellets with aqueous dispersions of methacrylic acid polymers.

1.13 Some of promising Drug candidates for Orodispersible tablets:

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

Anthelmintics: Albendazole, mebendazole, thiabendazole, ivermectin, 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, oxphenbutazone, phenylbutazone, etc.

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

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

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

Anxiolytics, sedatives, hypnotics and neuroleptics: Alprazolam, diazepam, amylobarbitone, chlorpromazine, clonazepam, chlor-diazepoxide, clozapine, flurazepam, lorazepam, haloperidol, nitrzapam, oxazepam, midazolam, droperidol, phenobarbitone, thioridazine, triazolam, prochlorperazine, etc.

Diuretics: Acetazolamide, chlorthiazide, 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, decoquinol, etc.

1.14 Some commercially available Orodispersible tablets:

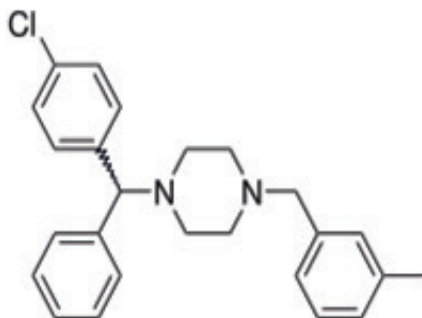
TRADE NAME	ACTIVE DRUG	MANUFACTURER
Nimulid-MD	Nimesulide	Panacea Biotech, New Delhi, India
Feldene Fast Melt	Piroxicam	Pfizer Inc., NY, U.S.A
Zyrof Meltab	Rofecoxib	Zydus, Cadila, India
Pepcid RPD	Famotidine	Merck and Co., NJ, U.S.A
Romilast	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Torrox MT	Rofecoxib	Torrent Pharmaceuticals, Ahmedabad, India
Olanex Ins tab	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, Chateaufort, France

MATERIALS**5.1 Materials:****Table 1: List of materials used**

S. No	Name of ingredients	Functional category	Suppliers
1	Meclizine HCL	API	Natco Pharma Ltd, Hyderabad
2	Mannitol	Diluent	Rankem Limited, Mumbai, India
3	Microcrystalline cellulose	Suspending agent	Rankem Limited, Mumbai, India
4	Sodium alginate	Super Disintegrant	Rankem Limited, Mumbai, India
5	Magnesium stearate	Lubricant	Rankem Limited, Mumbai, India
6	Xanthan gum	Super Disintegrant	Rankem Limited, Mumbai, India

Table 2: List of equipments used

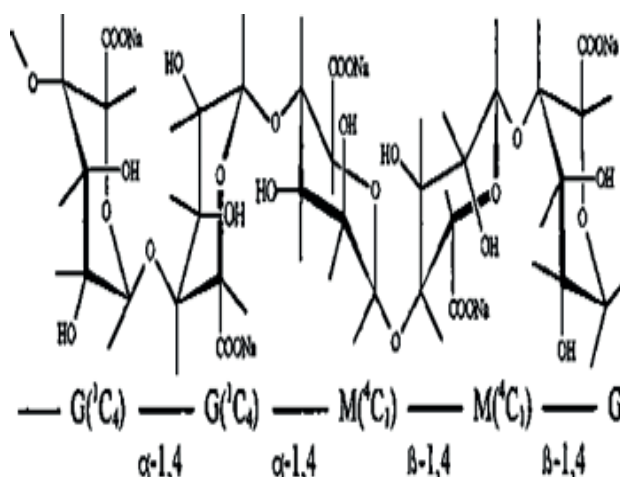
S. No	Name of ingredients	Functional category
1	Tablet Dissolution Tester	Sisco, Mumbai.
2	Sonicator	Prima Instruments Pvt., Ltd., Mumbai.
3	Digital pH meter	ELICO Ltd., Mumbai.
4	UV-Vis Spectrophotometer	Shimadzu (Asia Pacific) PTE Ltd.
5	Monosanto tablet hardness tester	Electrolab, Mumbai.
6	Tablet Friability Tester	Electrolab, Mumbai.
7	Tablet Disintegrator	Electrolab, Mumbai.
8	Tap Density Apparatus	Electrolab, Mumbai.
9	Electronic Weighing Balance	Essae, Mumbai.
10	Tablet Machine Mini press II	Cadmach, Mumbai.
11	Vernier Callipers	Mitutoyo-Digimatic, Mumbai.

DRUG PROFILE:**Generic Name: Meclizine HCl****Chemical structure:****Chemical Name:** (RS) -1-[(4-chlorophenyl) (phenyl) methyl]-4-(3-methylbenzyl) piperazine**Molecular Formula:** C₂₅H₂₇ClN₂**Molecular weight:** 390.948 GM/Mol**Category:** Is An Antihistamine Considered to be an Antiemetic.**Appearance:** white powder.**Solubility:** It is insoluble in water and alcohols, but soluble in 0.1 NNaOH; it is freely soluble in dimethylformamide.**BCS classification;** II**Melting point:** 208-2090c.**pKa:** 5.9.**Absorption:** Gastrointestinal absorption is uniform, rapid, and essentially complete.**Bioavailability:** 100% for regular formulation, 90% for extended-release formulation.**Half life:** 2 to 5 hours.**Protein binding:** 98-99%, primarily to albumin.**Metabolism:** Hepatic hydroxylation.**Elimination:** Renal and faecal.**Mechanism of action:**

Meclizine is an antagonist of H₁ receptors. It possesses anticholinergic, central nervous system depressant, and local anesthetic effects. Its antibiotic and antivertigo effects are not fully understood, but its central anticholinergic properties are partially responsible. The drug depresses labyrinth excitability and vestibular stimulation, and it may affect the medullary chemoreceptor trigger zone.

Side/adverse effect:

Some common side effects such as drowsiness, dry mouth, and tiredness may occur. Meclizine has been shown to have fewer dry mouth side effects than the traditional treatment for motion sickness, transdermal scopolamine. A very serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction may include: rash, itching/swelling, severe dizziness, and/or trouble breathing



Formula weight:**Structural unit:** 198.11 (theoretical)

222 (actual average)

Macromolecule: 10,000 - 600,000 (typical average)**Description:**

It occurs as white to yellowish brown filamentous, grainy, granular or powdered forms.

Functional uses:

Stabilizer, thickener, gelling agent, emulsifier.

Solubility:

Dissolves slowly in water, forming a viscous solution; insoluble in ethanol and ether

- Precipitate formation with calcium chloride.
- Precipitate formation with ammonium sulphate.
- Sodium: Passes test.
- Purity: Loss on drying: Not more than 15% (105°, 4h).
- Water-insoluble matter: Not more than 2% on the dried basis.
- Arsenic: Not more than 3 mg/kg.
- Lead: Not more than 5 mg/kg. Prepare a sample solution as directed for organic compounds in the Limit Test, using 5 mg of lead ion (Pb) in the control.
- Microbiological criteria: Total plate count: Not more than 5,000 colonies per gram. Initially prepare a 10-1 dilution by adding a 50 g sample to 450 ml of Butterfield's phosphate buffered dilution water and homogenizing in a high speed

blender.

Yeasts and moulds: Not more than 500 colonies per gram.

Coliforms: Negative by test.

Salmonella: Negative by test.

Identification tests: Precipitate formation with calcium chloride:

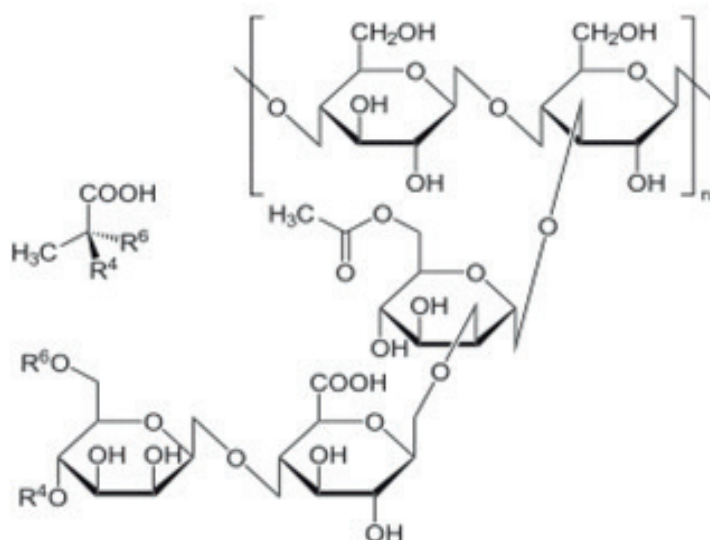
To a 0.5% solution of the sample in sodium hydroxide TS add one-fifth of its volume of a 2.5% solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes sodium alginate from gum Arabic, sodium carboxy methyl cellulose, carrageenan, gelatin, gum ghatti, karaya gum, carob bean gum, methyl cellulose and tragacanth gum.

Precipitate formation with ammonium sulfate:

To a 0.5% solution of the sample in sodium hydroxide TS add one-half of its volume of a saturated solution of ammonium sulfate. No precipitate is formed. This test distinguishes sodium alginate from agar, sodium carboxy methyl cellulose, carrageenan, de-esterified pectin, gelatin, carob bean gum, methyl cellulose and starch.

5.1.2. XANTHAN GUM 17

Xanthan gum is a polysaccharide, derived from the bacterial coat of *Xanthomonas campestris*, used as a food additive and a rheology modifier, commonly used as a food thickening agent (in salad dressings, for example) and a stabilizer (in cosmetic products, for example, to prevent ingredients from separating). It is produced by fermentation of glucose, sucrose, or lactose by the *Xanthomonas campestris* bacterium. After a fermentation period, the polysaccharide is precipitated from a growth medium with isopropyl alcohol, dried, and ground into a fine powder. Later, it is added to a liquid medium to form the gum.

Structural Formula:

Preparation:

The polysaccharide is prepared by inoculating a sterile aqueous solution of carbohydrate(s), a source of nitrogen, dipotassium phosphate, and some trace elements. The medium is well-aerated and stirred, and the polymer is produced extracellularly into the medium. The final concentration of xanthan produced will vary greatly depending on the method of production, a strain of bacteria, and random variation. After fermentation that can vary in time from one to four days, the polymer is precipitated from the medium by the addition of isopropyl alcohol and dried and milled to give a powder that is readily soluble in water or brine. In the United States, a pound of cheese creates 9 pounds of a byproduct called whey, for which the USDA sought to find more uses. Whey is composed of water and lactose, so the researchers developed a strain of *X. Campestris* that would grow on whey rather than glucose. The newly developed lactose-utilizing bacteria produced 30 g/Lt of xanthan gum for every 40 g/lot of whey powder. Whey-derived xanthan gum is commonly used in many commercial products, such as shampoos and salad dressings.

Properties:

Xanthan is a white to cream colored free flowing powder, soluble in both hot and cold water to give viscous solutions at low concentrations. Its industrial importance is based upon its ability to control the rheology of water based systems. Even at low concentrations xanthan gum solutions show a high viscosity in comparison with other polysaccharide solutions. This property makes it a very effective thickener and stabilizer.

Xanthan gum solutions are highly Pseudoplastic i.e. Even after high shear rates the initial viscosity is rebuilt immediately. No hysteresis is evident, i.e., Shear thinning and recovery are instantaneous. This pseudo- plasticity enhances sensory qualities (mouth feel, flavor release etc.) In final products and guarantees

high degree mix-, pump- and pourability.

Xanthan gum solutions are very resistant to pH variations, i.e. They are stable in both alkaline and acidic conditions. Between pH 1 to 13, the viscosity of xanthan solution is practically constant. At pH 9 or above, xanthan is gradually deacetylated, but this has little effect on its solution properties.

The viscosity of aqueous solutions of xanthan is nearly independent of temperature over a wide range. The viscosity of a xanthan solution is virtually unaffected by temperatures from freezing point to the boiling point of pure water. Thus the rheological properties of the final products remain stable irrespective of been kept in a refrigerator, stored at room temperature or heated. Pharmaceutical

Applications: Super disintegrate

5.1.3. MICROCRYSTALLINE CELLULOSE (Avicel PH 102) 17

Nonproprietary Name:

NF: Microcrystalline Cellulose

USP: Microcrystalline Cellulose

Functional Category:

Tablet and capsule diluent, tablet disintegrant, suspending and/or viscosity increasing agent.

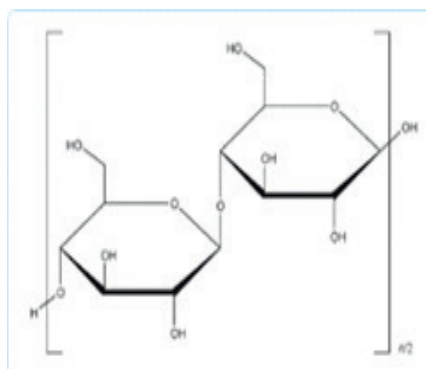
Synonyms:

Cellulose gel: Crystalline cellulose: Avicel PH101, 102,

Chemical names: Cellulose

CAS Registry Number: 9004-34-6

Empirical formula: (C₆H₁₀O₅)_n=220 Molecular weight: 36,000 (approx)

Structure:

Description:

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

Density:

Apparent density 0.28g/cm³

Tap density 0.43g/cm³

Solubility:

Insoluble in water, dilute acids and most organic solvents, slightly soluble in

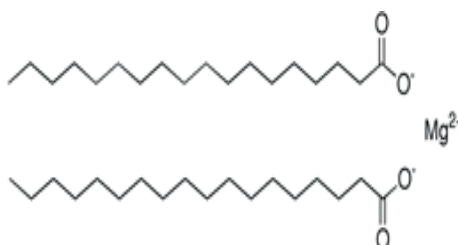
5% w/v NaOH solution,

Stability and Storage Conditions:

Stable, hygroscopic. Store in a well closed container.

Incompatibilities:

None cited in the literature.

Structural Formula:**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.

Stability and Storage Conditions:

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

Incompatibilities:

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

Safety:

Magnesium stearate is widely used as a pharmaceutical excipi-

Safety:

Generally regarded as safe.

Applications:

Tablet binder/diluent, disintegrant, Tablet glidant

5.1.4 Magnesium Stearate 17

Nonproprietary Names:

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur: Magnesium Stearate USP-NF: Magnesium Stearate

Synonyms:

Dibasic magnesium stearate, magnesium distearate, magnesia stearates, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt, Synpro 90.

Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

ent and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst case daily intake and heavy metal composition. Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled. Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

5.1.5.Mannitol 17**Nonproprietary Names:**

BP: Mannitol,JP: D-Mannitol,PhEur: Mannitolum,USP: Mannitol

Synonyms:

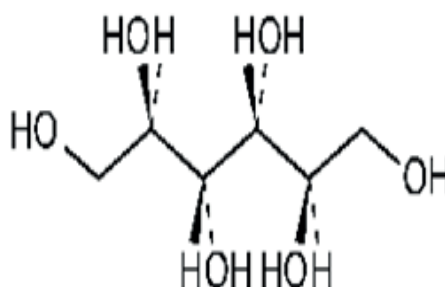
Cordycepic acid, PharmMannidex, E421, manna sugar,D-man-

nite, mannite, Mannogem, Pearlitol.

D-Mannitol [69-65-8]

Chemical Name and CAS Registry Number:

Structural Formula:



Functional Category:

Diluent, diluent for lyophilized preparations, sweetening agent, tablet and capsule diluents, tonicity agent.

Applications in Pharmaceutical Formulation or Technology:

The monitor is widely used in pharmaceutical formulations and food products. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. It is also used as a diluent in rapidly dispersing oral dosage forms. Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure.

Description:

Mannitol is D-mannitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol show polymorphism.

Stability and Storage Conditions:

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/ml and 30 mg/ml concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with Xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation. The monitor was found to reduce the oral bioavailability of cimetidine compared to sucrose

Safety:

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables, the product label should bear the statement 'excessive consumption may have a laxative effect'. The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient. An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.

METHODOLOGY

5.2. Preformulation Studies: ^{18, 20, 25}

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system. Preformulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients prior formulation.

The tablet blend was tested for angle of repose, bulk density,

tapped density, Carr's index, Hausner's ratio.

Angle of repose: ^{19, 20, 25}

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by the fixed funnel method and is the measure of the flow ability of powder/granules. A funnel with 10 mm inner diameter of the stem was fixed at a height of 2 cm. Over the platform.

About 10 mg of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the

radius of the powder cone was measured.

Angle of repose was calculated from the average radius, using the following formula.

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

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

Flow properties corresponding to Angle of repose

Table 3: Angle of repose range

Angle of repose	Type of flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

The higher the angle of repose the rougher and more irregular is the surface of the particles.

Bulk and Tapped Density: ^{19, 25}

An accurately weighed quantity of the granules (w) that was previously passed through # 40 was carefully poured into the graduated cylinder and the volume (vo) was measured. The graduated measuring cylinder was tapped for 100 times and after that, the volume (VF) was measured and continued the operation till the two consecutive readings were equal. Bulk density and tapped density determine the floating capacity of the formulation. The bulk density and tapped density were calculated using the formulas below

$$\text{Bulk density} = w/v_o$$

$$\text{Tapped density} = w/VF$$

Table 4: Compressibility Index range ^{19, 20, 25}

% Compressibility	Flow description
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Where, w - Weight of powder

v_o - Initial volume.

VF - Final volume.

Percentage compressibility:

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simplest methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility or compressibility index.

Compressibility measures give idea about flow property of the granules as per Carr's index which is as follows.

Hausner's ratio: ^{19, 20, 25}

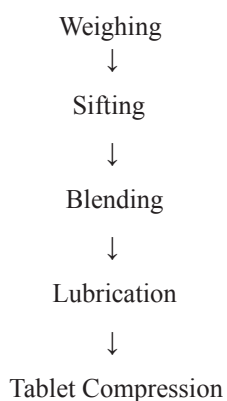
It provides an indication of the degree of densification which could result from the vibration of the feed hopper.

Table 5: Hausner's ratio range

Hausner's ratio	Type of flow
<1.25	Good flow
1.25 – 1.5	Moderate
>1.5	Poor fellow

Method of manufacturing Meclizine Hcl tablets: ^{26, 27}**Direct Compression Method:**

The tablet Meclizine Hcl dispersible tablets were prepared by direct compression method by using 7.5mm oval punches & with a break line on one side. The flow chart for direct compression method is given below

Flow chart for Meclizine Hcl dispersible tablet by the direct compression method:**5.2.5. Preparation of Meclizine Hcl tablets: 24****Table 6: Limits for Weight variation**

Dosage form	Average weight of tablet (mg)	% deviation
Uncoated and film coated tablets	80 mg or less	10
	More than 80 mg but not less than 250 mg	7.5
	250 mg or more	5

5.3.3 Hardness Test:

The crushing load which is the force required to break the tablet in the radial direction was measured using Electrolab hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in KP or kg/cm².

5.3.4 Variability:

If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. Four tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g was taken. The

Tablets of Meclizine Hcl (230mg) were prepared by direct compression method employing microcrystalline cellulose as a binder, Mannitol as diluent, Magnesium stearate as lubricants. Three series of tablets were made in each case, in one series, organic acid and xanthum gum as a natural super disintegrates.

All the ingredients were weighed accurately and compressed into tablets on the tablet punching machine (Cad mach machinery Co Pvt Ltd.) With a hardness of 3 kg/cm² using 7.5 mm round and oval punches.

5.3. Post formulation Studies: ^{21, 22, 23}**5.3.1 Thickness:**

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale (Mitutoyo- Digimatic) and the average thickness was determined in mm. The tablet thickness should be controlled within a $\pm 5\%$ variation of a standard.

5.3.2 Weight Variation:

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the IP specifications if not more, than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

tablets were rotated in the Roche Friabilator for 100 revolutions at 25 RPM. The tablets were disgusted and reweighed. The percentage friability should be not more than 1% w/w according to IP and 0.5% w/w according to USP of the tablets being tested.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\% \text{ Friability} = [(W_0 - W_f) / W_0] \times 100$$

W₀ = Initial weight of the tablets

W f = Final weight of the tablets

5.3.5 Disintegration Time:

The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at $37 \pm 20^\circ\text{C}$. Six tablets were placed in each of the tubes and the time required for the complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 Sec.

5.3.6 Dissolution Studies:

The dissolution test was carried out in USP Apparatus Type II (paddle). The samples were drawn at 5, 10, 15, 20, 25 and 30. The fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Preparation of Dissolution Medium: 24

a. Preparation of 0.1N HCl / pH 1.2 buffers:

Place 85ml of 0.2M HCl dissolved in 1000ml of water.

b. Preparation of pH 6.8 buffer:

Place 22.4 ml of 0.2M NaOH in 1000ml of distilled water.

5.4. Preparation of standard curve:

The standard calibration curve of Meclizine Hcl in 0.1 N HCl was prepared. First dissolve 100mg of pure drug in 100ml, 0.1 N HCl buffer this is the primary stock solution. From the above primary stock solution pipette out 10ml of solution and again make up to 100ml this is the secondary stock solution. From this secondary stock solution different concentrations of Meclizine Hcl (2, 6, 10, 14, 18, 22, 26, 30 $\mu\text{g}/\text{mL}$) in 0.1 N HCl buffer were prepared & observance of these solutions measured at 281 NM by spectrophotometrically (Shimadzu-1700, UV/Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution.

5.5. Wetting Time:

A piece of tissue paper folded double was placed in clean and dry petri plates containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.

5.6. Stability Studies: 27, 28

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Accelerated study: The product is subjected to accelerated stability studies at $40\text{C} \pm 2\text{C} / 75\% \pm 5\% \text{RH}$ for 6 months.

5.7 Storage conditions for stability studies

Table 7: Storage conditions for stability studies

S. No.	Storage Condition	Test Period
1	$40\text{C} \pm 2\text{C} / 75\% \pm 5\% \text{RH}$	1st month
		2nd month
		3rdmonth
2	$25\text{C} \pm 2\text{C} / 60\% \pm 5\% \text{RH}$	1st month
		2nd month
		3rdmonth

Table 8: Formulation of Meclizine Hcl tablets

By varying the proportion of alginic acid and xanthan gum of formulation different ratios design into 6 batches which is summarized in the table.

Table 8: Formulation of Meclizine Hcl tablets

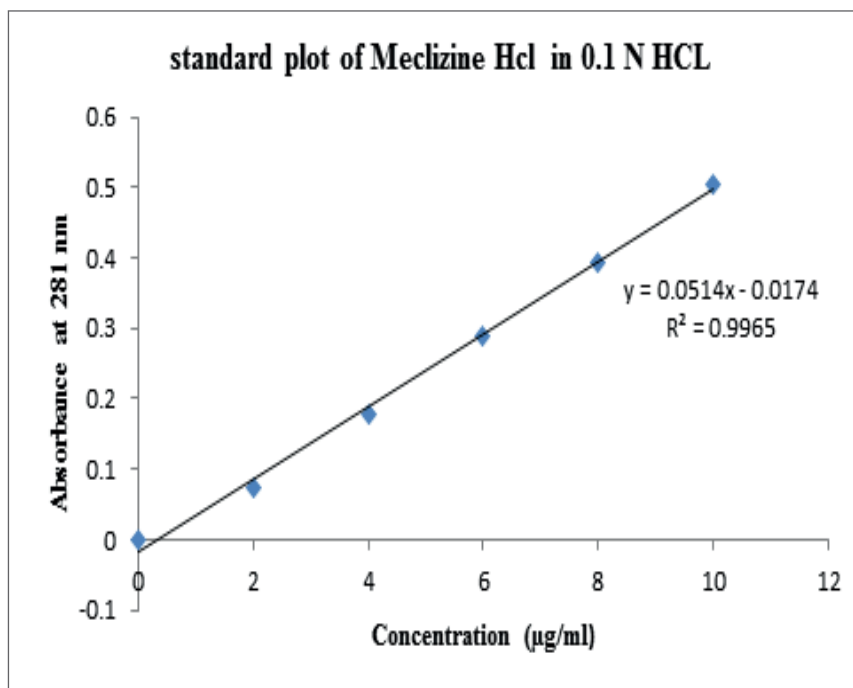
S.No	EXCIPIENTS (Mg)	Formulations					
		F1	F2	F3	F4	F5	F6
5 – 15	Drug	150	150	150	150	150	150
12 – 16	Mannitol	10	10	10	10	10	10
18 – 21	MCC	60	59	60	59	58	58
23 – 35	Magnesium stearate	9	9	9	9	9	9
35 – 38	Xanthan gum	1	2	-	-	1	2
> 40	Sodium alginate	-	-	1	2	2	1

Results

Calibration curve for Meclizine Hcl 0.1N HCL:

Table 9: Standard plot for Meclizine Hcl in 0.1N HCl

Concentration (µg/ml)	Absorbance at 243nm
2	0.0073
4	0.177
6	0.288
8	0.395
10	0.504

**Fig 5: Standard plot of Meclizine Hcl in 0.1N HCL**

Preformulation studies of Meclizine Hcl orally Disintegrating Tablets:**Table 10: Preformulation studies of Meclizine Hcl**

Formulation	Angle of repose (°)	Bulk density (GM/cm ²)	Tapped density (GM/cm ³)	Hausner's ratio	Compressibility index (%)
F1	24.55±1.052	0.633±0.007	0.721±0.009	1.136±0.22	12.23±1.033
F2	24.58±0.921	0.626±0.010	0.731±0.006	1.30±0.014	14.44±1.031
F3	23.92±1.435	0.635±0.007	0.727±0.011	1.14±0.021	14.29±1.123
F4	24.38±0.722	0.633±0.002	0.733±0.005	1.15±0.021	13.58±1.632
F5	22.96±1.495	0.633±0.006	0.728±0.012	1.14±0.014	12.98±1.102
F6	24.55±0.868	0.629±0.002	0.724±0.008	1.14±0.025	13.18±1.851

All values were expressed as mean ± S.D; Number of trails (n) = 3

Post compression parameters:**Table 11: Evaluation of Meclizine Hcl tablets**

Formulation code	Weight variation (mg)	Hardness (kg/cm ³)	Thickness (mm)	friability (%)
MRKT	240±0.51	4.7±0.32	3.4±0.32	0.5±0.11
+F1	228.3±0.15	4.0±0.05	3.1±0.85	0.25±0.21
F2	226.6±0.15	4.8±0.10	3.3±1.04	0.30±0.25
F3	232±0.23	4.1±0.10	3.1±0.86	0.27±0.02
F4	230±0.52	4.1±0.10	3.0±0.85	0.28±0.01
F5	228.3±0.52	4.2±0.05	3.2±0.74	0.29±0.16
F6	226.3±0.20	4.8±0.05	3.4±0.90	0.29±0.13

Table 12: Evaluation of Meclizine Hcl Tablets:

Formulation code	Wetting time (Sec)	Disintegration time (Sec)	Content uniformity (%)
MRKT	35±0.5	38±0.5	101.10±0.1
+F1	37±0.4	39±0.4	100.08±0.01
F2	31±0.5	32±0.5	99.38±0.23
F3	39±0.5	41±0.3	99.32±0.15
F4	34±0.3	36±0.2	100.82±0.4
F5	30±0.6	30±0.4	99.48±0.2
F6	28±0.5	29±0.4	99.5±0.6

All values were expressed as mean ± S.D; Number of trails (n) = 3

In vitro dissolution studies:**Table 13: In vitro drug release for all formulations:**

				% Drug released				
Time	MRKT	F1	F2	F3	F4	F5	F6	
0	0	0	0	0	0	0	0	
5	48±0.2	49±0.43	44±0.23	44±0.22	50±0.31	56±0.61	62±0.12	
10	62±0.3	68±0.34	58±0.16	69±0.41	69±0.43	74±0.59	80±0.23	
15	74±0.3	79±0.36	71±0.21	79±0.35	76±0.55	89±0.26	89±0.24	
20	86±0.2	85±0.27	88±0.43	86±0.47	89±0.29	95±0.29	99.6±0.41	
25	92±0.4	96±0.50	94±0.63	97±0.28	98±0.27	100.4±0.31	100.6±0.25	
30	100±0.5	101±0.19	100.8±0.23	100.1±0.29	101.2±0.41	101.3±0.29	101.2±0.48	

All values were expressed as mean ± S.D; Number of trails (n) = 3

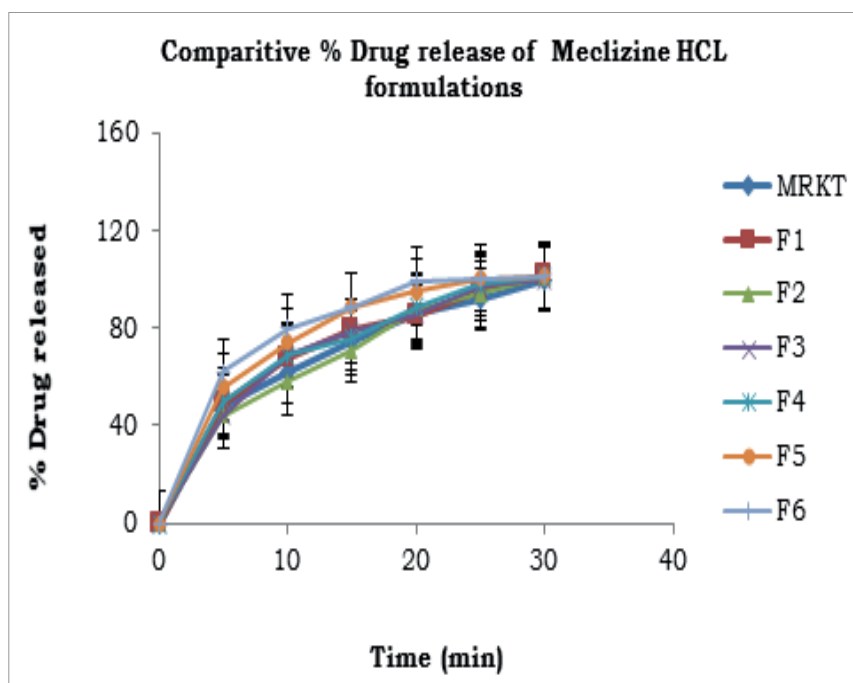


Fig 6: Plot for in vitro drug release for all formulations

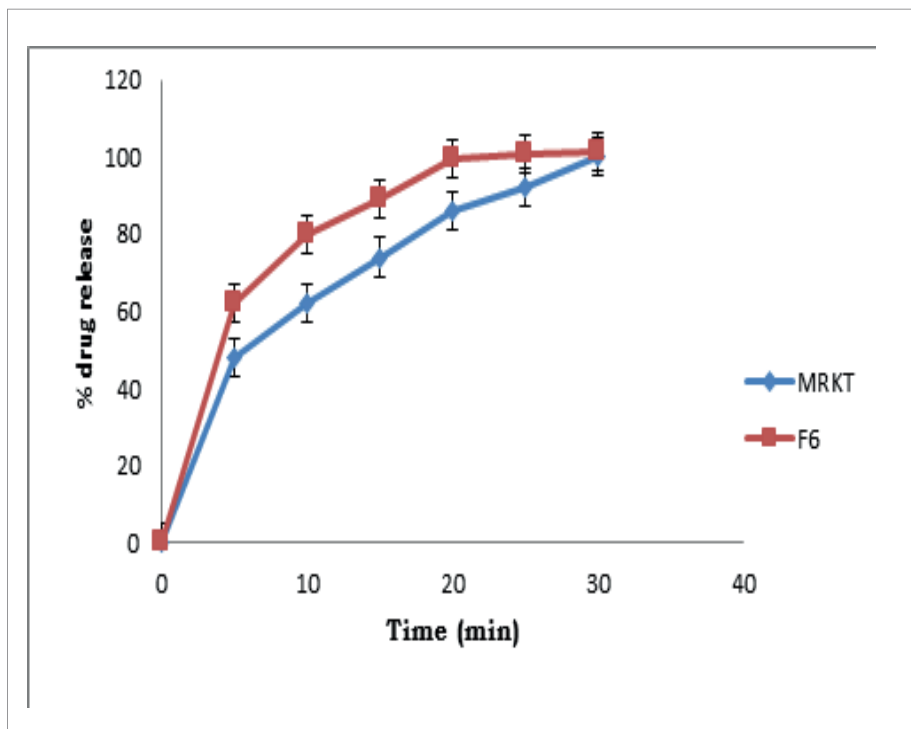


Table 2: P-values for gender differences in a Fig 7: Plot for in vitro drug release for marketed and F6 formulations cyclated ghrelin levels

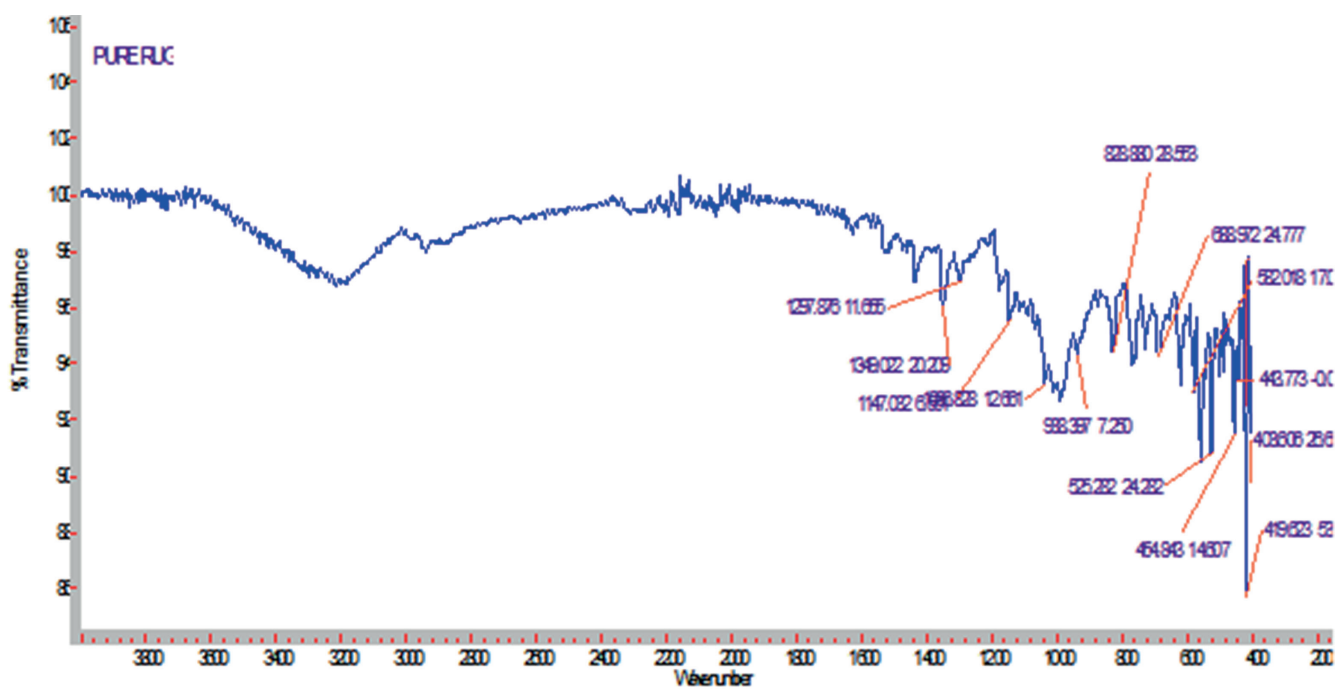


Figure 8: FT-IR Spectrum of Meclizine HCl pure drug.

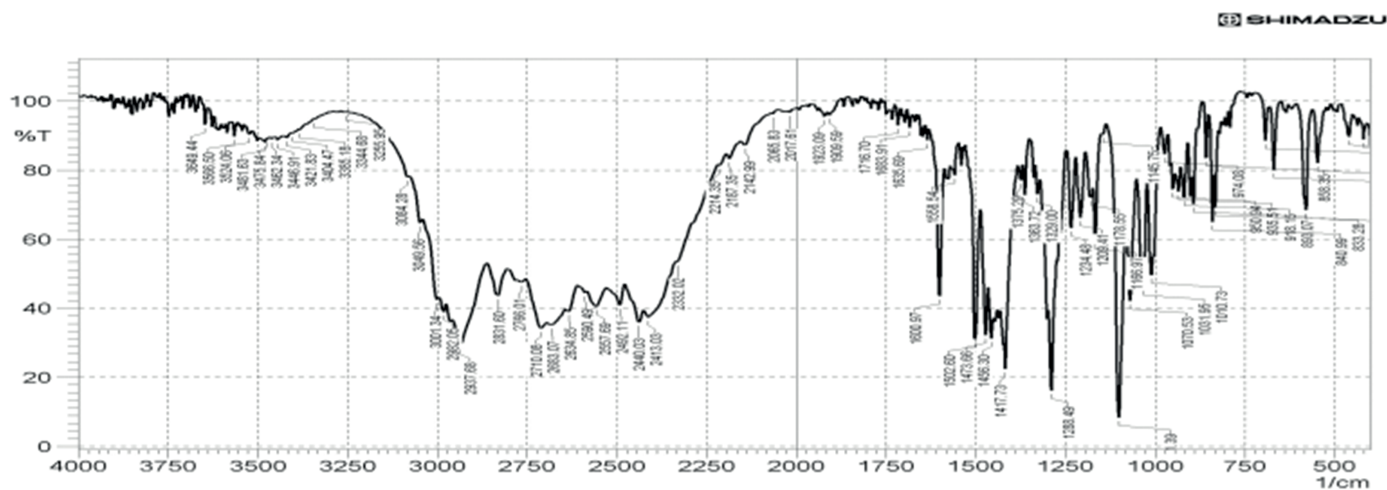


Figure 9: FT-IR Spectrum of Meclizine Hcl and xanthan gum

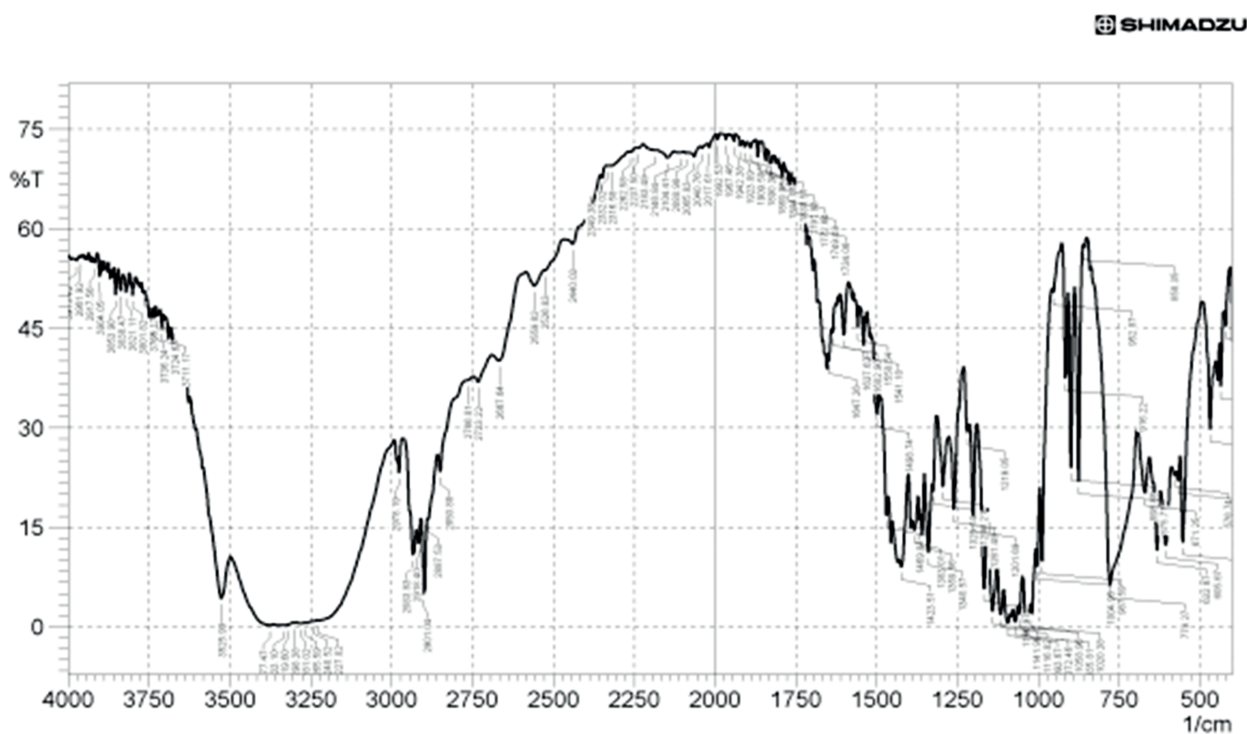


Figure 10: FT-IR Spectrum of Meclizine Hcl and sodium alginate

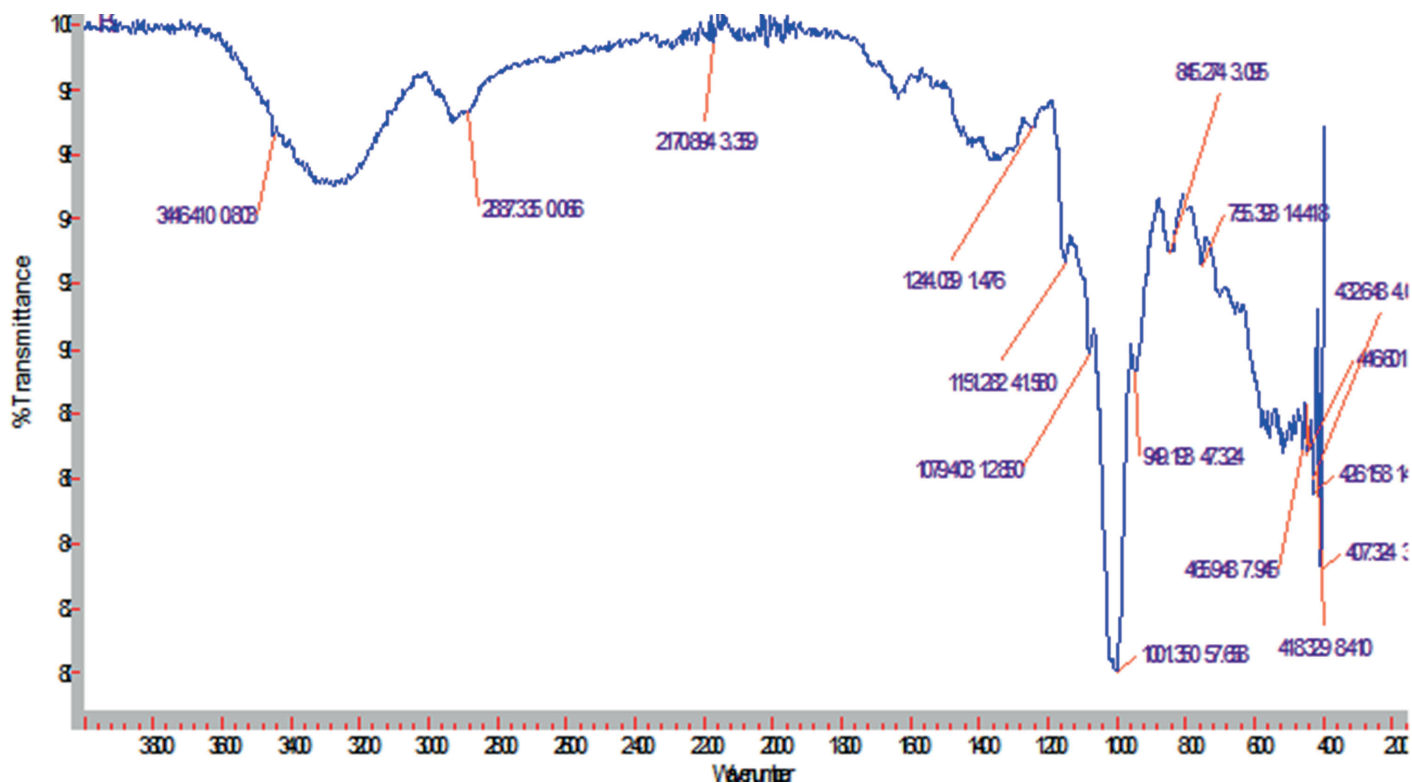


Figure 11: FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions. Hence, they were compatible.

Discussion of Results

Preformulation studies:

Bulk characteristics of Meclizine Hcl granules:

- Angle of repose of granules is in the range of 22.96 ± 1.49 to 24.58 ± 0.92
- Bulk density was in the range of 0.626 ± 0.01 to $0.633 \pm 0.007 \text{ gm/cm}^3$.
- Apparent density was in the range of 0.721 ± 0.009 to $0.733 \pm 0.005 \text{ gm/cm}^3$.
- Percentage compressibility was in the range of 12.23 ± 1.633 to $14.44 \pm 1.031\%$.
- Hausner's ratio was in the range of 1.136 ± 0.021 to 1.30 ± 0.014 .

From the above results it was observed that F5 formulation having better bulk characteristics than compared to remaining formulations.

Evaluation of Oral Orodispersible Tablets of Meclizine Hcl:

Meclizine Hcl orodispersible tablets were compressed with 7.5 mm round shaped standard punch.

Weight variation was found to be in the range of 226– 240 mg. Thickness was found to be 3.0 - 3.4, hardness was found to be in the range 4.0-4.8 kg/cm² indicating good mechanical strength, friability was within the USP limits, drug content was found to be within 99.5- 101.10% which is acceptable limits, in vitro

disintegration time of the tablet were evaluated and found to be between 30 Sec. Weight variation was in the range 226- 240 mg.

Dissolution test:

The dissolution results show that there was a hike in the dissolution velocity of the tablets.

The maximum drug release was observed at 20 min which is acceptable and more than the marketed sample. Formulation F6 having a higher concentration of xanthan gum showed more drug release.

Discussion of results:

- Weight variation was in the range of 226.3 ± 1.6 to 240.0 ± 1.5 mg.
- Hardness was in the range of 4.0 ± 0.05 to 4.8 ± 0.1
- Weight variation and hardness of Meclizine Hcl Tablets were within range.
- Percentage friability of tablet was evaluated in 100rpm and tablet passed the friability test.
- Tablets from each batch showed uniformity of weight as per IP limits. Each sample was analyzed in triplicate ($n = 3$).
- Content uniformity was made as per IP and the values were satisfactory.
- Wetting time was in the range of 30 to 39.3 such as wetting time increases disintegration time of tablet decreases.

Wetting time of combination of superdisintegrants shows lower values, hence higher disintegration time. Formulations containing of xanthan gum showed somewhat lower wetting time than combination batches hence showed satisfactory disintegration time. Formulations containing of alginic acid showed very low wetting time compared to other formulations hence showed very less disintegration time than other formulations.

- Disintegration Time of tablets was evaluated and was found to be in the range of 29 ± 1 to 41 ± 1.52 . Higher disintegration time was for f5 and f6 formulations respectively because of combination of superdisintegrants. Formulations containing of xanthan gum in higher quantity showed the good disintegration time. Formulations containing of alginic acid showed lesser disintegration time compared with other formulations.

In vitro dissolution studies:

Superdisintegrants has a dominant role in disintegration as well as drug release from orodispersible tablets. Both of superdisintegrants are chosen in the present work were natural superdisintegrants hence all the formulations showed better and satisfactory drug release profile. Due to the swelling and the wicking action of both the superdisintegrants the tablets showed better disintegration time, which in turn showed good drug release from tablet formulations.

The Dissolution study of various batches from F1- F6 shows that Meclizine Hcl release from tablets containing combination of both alginic acid and xanthan gum at higher concentrations showed higher drug release. As the concentration of xanthan gum decreased it showed lower drug release in combination batch. The formulation F2 which contain only 2 mg of xanthan gum showed 94% of drug release and the formulation F4 containing 2mg of sodium alginate showed 98% of drug release within 25 min. Drug release for formulations F1 and F3 which contain 1mg of xanthan gum and 1mg of sodium alginate have 96% and 97% drug release within 25 min respectively.

Further, we can say that as concentration of superdisintegrants increases, it causes higher % of drug release.

Summary

The Study was undertaken with an aim to formulate orodispersible tablets of Meclizine Hcl by using natural superdisintegrants like Xanthan gum and alginic acid.

Different formulations were prepared varying the superdisintegrant concentration. Preformulation study of the tablet blend was carried out, the tablet blends showed good flowing properties directing for the further course of formulation.

The tablets were prepared by direct compression method by 7.5 mm, round shaped, B tooling punch.

Tablet blend was evaluated for post formulation studies like hardness, weight variation, friability, wetting time, in vitro disintegration time and in vitro dissolution, stability studies.

The hardness was found to be in the range of 4.0 -4.8 kg/cm². Weight variation was found to be in the range of 226 – 240 mg. Friability was NMT 0.5% meeting the USP limits. Wetting time

was found to be within 30 sec.

Among the formulations using xanthan gum, F1 formulation with 0.6% xanthan gum shown faster drug release (96%) within 25minutes and among formulations with sodium alginate, F4 formulation with 1.2% sodium alginate shown faster drug release (98%) in 25 minutes. In case of mixed formulations, F6 formulation is 1.2% of xanthan gum and 0.6% of sodium alginate showed maximum drug release (99.6%) within 20 minutes.

Conclusion

In the present work, an attempt has been made to develop fast disintegrating tablets of meclizine Hcl. Natural disintegrants such as sodium alginate and xanthan gum were selected as super disintegrates. All the formulations were prepared by direct compression method and the blend of all the formulations shown good 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 IP limits. Among all the formulations, F6 formulation containing concentration of 1.2% xanthan gum and 0.6% sodium alginate showed higher percentage drug release i.e. 62% within 5 minutes, hence the F6 formulation was considered to be the best formulation showing fast drug release.

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