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Review Article

Formulation and Evaluation of Mouth Dissolving Tablets of Montelukast Sodium

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Abstract:

Convenience of administration and increased patient compliance are critical factors in the design of oral drug delivery systems, which continue to be the dominant route of drug delivery despite several drawbacks. Mouth dissolving tablets (MDTs) have grown in popularity over the past decade, and the sector has developed into a fast-growing segment of the pharmaceutical business. Due to the formulation's popularity and use, various MDT technologies have been developed. These procedures enable to dissolve in the mouth in five seconds without the need for chewing or water, which is very beneficial for children, geriatrics, and people who have difficulty swallowing tablets and capsules. By addressing swallowing difficulties and limited patient compliance, the formulation of an appropriate dose form for administration results in the production of mouth dissolving tablets. There are various traditional ways of preparation of MDTs, however new technologies have been created for the manufacturing of mouth dissolving tablets.

Keywords: MDTs, Montelukast Sodium

Introduction:

The oral route of drug administration is widely accepted for systemic delivery of therapeutic agents due to its precise dosage, low cost, non-invasive technique, and comfort management, which contribute to a high level of patient compliance, versatility in terms of drug type and dose, and suitability for scaling up[1,2]. Despite their many benefits, traditional tablets are seldom practical in real-world circumstances. Traditional tablets and capsules are difficult for elderly individuals to swallow. Additionally, individuals with acute nausea, paediatric patients, young toddlers, cerebrally challenged patients, and recalcitrant patients have difficulty swallowing tablets and capsules. Due to an inadequate development of muscle and neurological control, juvenile patients experience discomfort while ingesting solid dose forms[4-6]. These issues may be resolved by utilising a mouth dissolving tablet (MDT). Within seconds after placing the MDT under the tongue, it disintegrates and releases the medication. The disintegrating medication disperses readily in saliva and is absorbed into the stomach. MDT has a higher bioavailability when compared to typical solid dosage form[7,8].

Mouth Dissolving Tablets (MDTs)

According to the Food and Drug Administration (FDA), MDT is a tablet that dissolves within seconds of being placed on the tongue. After breakdown, DT forms gel-like compounds, which aid patients in easily ingesting their medications. According to the Pharmacopoeia, the disintegration period of MDT ranges from a few seconds and more than a minute[9-11].

Ideal Properties of MDTs[12, 13]

- Taste should be palatable.
- It should not need water to consume it.
- It should be in the mouth for no more than a few seconds.

- Should withstand handling and packing forces.
- Should leave pleasant after feel in mouth.
- Following administration of MDT, it is supposed to not leave any residues of tablets in the mouth.
- During transportation it resists the temperature and humidity.

Advantages of MDTs[14, 15]

- MDTs combine the benefits of tablets, capsules, and syrup dosage forms with extremely desirable qualities.
- **Precise dosing:** For elderly and paediatric patients, the MDT provides comfort and is an ideal replacement.
- **Improved bioavailability:** Because mouth dissolving tablets are absorbed directly from the mouth, throat, and oesophagus, their bioavailability is increased.
- **Prompt action:** Due to the quick disintegration and assimilation of the mouth dissolving tablets into the oral cavity, the therapeutic effect is initiated rapidly.
- **Patient compliance:** It is an appropriate dosage for patients who are wandering and do not have immediate access to water, since the MDTs does not need water to consume.
- **Effortlessness in administration:** Patients who have difficulty in swallowing tablets may benefit from using mouth dissolving tablets.
- **Obstruction free:** The MDT is regarded a more safe dose form since there is no danger of asphyxia in the airways during delivery.
- **Improved palatability:** The flavour masking agents are intended to make MDT more palatable, especially for young patients.
- **Easy packaging:** There is no need for specific packaging, and they may be put in push-through blisters.
- **Cost impressive:** The MDTs are cost effective owing to the use of conventional preparation and packaging equipment.

Salient Features of MDTs[12]

- MDT can be conveniently administered to paediatric and geriatric patients.
- It provides more precise and exact dosage than liquids.
- It has a fast beginning of effect owing to the drug's rapid disintegration.
- It increased the drug's bioavailability.

Disadvantage of MDTs[13]

MDT must be stored in a dry location because to its hygroscopic properties.
In rare circumstances, MDTs cause a tongue sensation.
Special packaging is required to ensure the stability of MDT.

Potential Drug Candidates[16,17]

- Anti-migraine
- Anti-psychotic (Neuroleptics)
- Cardiovascular drugs
- Drugs for erectile dysfunction
- NSAIDs,
- Anti-emetics,
- Anti-histaminics,

Manufacturing and marketing factors

In today's competitive environment, pharmaceutical manufacturers are increasingly focused on dosage forms that are readily tolerated by patients. MDT is deemed more comfortable for patients because to its ease of administration[18]. Manufacturing procedures may influence the physical qualities of mouth dissolving tablets.

Challenges in formulating mouth dissolving tablets[19]

1. Palatability

Tablets, in general, are unpleasant; often, MDT includes the medication in a flavor-masked form. When MDT is put on the tongue, it disintegrates fast and the active components make their way to the taste receptors. As a result, masking the undesirable taste of active substances is very challenging for patient compliance.

2. Mechanical strength

MDTs are friable due to their construction from very porous and soft moulded matrices. However, it is quite stubborn when it comes to tablet management. As a result, MDT needs specific peel-off blister packaging for storage. This packaging of MDT may result in an increase in cost. By using the Wow tab and durasolv procedures, the MDT may become firm and stable.

This enables the tablet to be packaged in multi-dose bottles.

3. Hygroscopicity

MDT is mostly hygroscopic in nature, which makes it very difficult to keep its physical properties under standard temperature and humidity circumstances. However, it requires specialised packaging to protect the tablets, which adds to the product's cost.

4. Amount of drug

MDT formulation techniques are quite restricted. Tablets in lyophilized dosage forms containing less than 400 mg of insoluble active ingredients and 60 mg of soluble active elements. This characteristic may make MDT preparation more challenging.

5. Aqueous solubility

MDT is typically water soluble because to the medicament and substance utilised in its production. Because of its water solubility, formulation is very difficult to create. This issue may be resolved by the use of matrix-forming dosage forms.

6. Size of tablet

The tablet's size has an effect on how it is administered. According to scientific evidence, the size of MDT should be 7-8 mm for optimal swallowing. However, it is quite difficult to manage tablets with a diameter of less than 8 mm.

Ingredients for mouth dissolving tablets[20]

MDT is prepared with chemicals that promote rapid drug release from tablets, resulting in faster dissolving. This section includes both active and inactive substances.

1. Drug

The concluding characteristics of a medicament for oral breakdown and pregastric absorption from MDTs are as follows:

- No bitter taste
- Active ingredients are less than 20 mg
- Easily solubilize in saliva
- Permeate to absorb in oral mucosal tissue

2. Excipients

Integral elements need an awareness of the nature of inactive substances that might obstruct interaction with the API. When these excipients are added to MDT throughout the manufacturing process, they impart the necessary organoleptic properties and product efficacy. Thus, the cost and nature of excipients play a considerable role in its selection.

3.Binders

Binders are used to hold excipients and active ingredients together in a variety of dosage forms. The right selection of binders is critical in the formulation of MDT to retain the tablets' physical properties. Binders such as polyethylene glycol are utilised in the MDT formulations. They might be liquid or semi-solid or a mixture of various molecular weights. Acacia, Tragacanth, Starch paste, and Cellulose (natural binders); HPMC, Hydroxy Propyl Cellulose, PVP, Polyethylene Glycol (PEG), Polymethacrylates, and Polyvinyl Alcohols (synthetic/semi-synthetic polymers).

4. Bulking materials

The bulking ingredient is included into the MDT as a diluent and filler. These compounds may improve the textural characteristics of MDT, hence increasing its breakdown in the mouth. Sucrose-based bulking agents are recommended in this dosage form. Among them, mannitol has a high solubility in water and a favourable sensory impression. The MDT is composed of between 10% and 90% bulking agent by weight of the final tablet formulation.

5. Lubricants

While lubricants such as aerosil, talc, and magnesium stearate are not required excipients, they do eliminate the roughness. This may also aid in the passage of medication from the oral cavity to the belly. Lubricants aid in the formation of a more pleasant MDT once it dissolves on the tongue.

6. Flavours and sweeteners

Flavors and sweeteners enhance the palatability and acceptability of the items. It contributes to the overpowering harshness and unpalatable taste of the excipients in MDT. MDT's organoleptic properties are enhanced with the addition of flavour derived from synthetic and natural sources. Sugar, dextrose, and

fructose are all utilised as sweeteners and are readily accessible on the market. Sucralose, sodium saccharin, and aspartame are all non-nutritive sweeteners.

7. Superdisintegrants

When added to a MDT, superdisintegrants aid in the disintegration of the solid mass when put in saliva. They are productive at low concentrations, have the least influence on compressibility and outpouring capacity. Sodium starch glycolate, croscarmellose sodium, crospovidone, and low substituted hydroxyl propyl cellulose are some of the superdisintegrants.

Mechanism of action

Following are the major processes for tablets disintegration mentioned below:

1. Swelling

When MDT comes into touch with water, the excipients begin to expand, impairing the adhesion of other constituents. The chemicals begin to break down, followed by the tablets disintegrating. The porosity of the tablet is critical in this process of breakdown.

2. Porousness and capillary action (Wicking)

The disintegrants in this scenario disintegrate the MDT through porosity and capillary action. When the MDT is dissolved in water, it enters into the tablets and replenishes the aerate occupied by the pieces. This absorbs air, so weakening the intermolecular link and causing the tablets to crumble into little pieces.

3. Disintegrating particle by repulsive forces

Guyot-Hermann proposed a particle repulsion explanation for this nonswellable disintegrant, which also results in tablet disintegration. During the investigation, the author discovered that when electric repulsive interactions between particles are generated, it results in the breakdown of tablets, which requires water.

Technology for mouth dissolving Tablets

When MDT is dissolved in water, it immediately penetrates the matrix of tablets. This matrix forms a spongy structure that disintegrates rapidly. By using an appropriate dissolving agent, the matrix tablets' spongy structure may be enhanced. These very polar-soluble excipients are used in the preparation. Subsequent typical procedures employed by many scientists to produce oral dissolving tablets include the following:

1. Lyophilization
2. Moulding
3. Sublimation
4. Direct Compression
5. Spray Drying
6. Mass extrusion
7. Nanonization
8. Melt Granulation
9. Cotton Candy Process
10. Phase transition process
11. Three – dimensional Printing (3DP)

1. Lyophilization or freeze-drying

The freeze-drying process results in a shapeless spongy material that dissolves rapidly. The carrier employed is critical in liquefying the active ingredient when it is dissolved in water. Following that, the blend is weighed for the desired dosage and inserted into the blister pack wells. The solution is then frozen dry by passing it through a liquid nitrogen freezing tunnel. Following that, chilled pustule flocks are stored in cooled cabinets to continue the chill drying process. Aluminum foil is used to seal the blisters. Finally, the MDT blisters are packaged[21]. The primary disadvantages of lyophilization are the high cost of equipment and processing[22].

2. Moulding

Tablets disintegrate and dissolve rapidly in this approach owing to the presence of water-soluble components. MDTs are made by compressing the wet powder combination and melting it into a tablet. Compression is used less often in this procedure than it is in regular tablet densification. Following that, the solvent is evaporated from the mixture by withering in the air. The MDT created using this process retained its porous structure, which aids in dosage dissolution. The primary disadvantages of this technique are decreased mechanical strength and inadequate flavour masking[23–25].

3. Sublimation

This process employs highly evaporative chemicals such as benzoic acid, ammonium bicarbonate, camphor, ammonium carbonate, urea, and

naphthalene. These chemicals are introduced because they evaporate more quickly than the other excipients used in tablets. Following processing, the resulting mix is compacted into tablets. Sublimation evaporates the volatile components of the MDT, resulting in a spongy matrix over the tablets. MDTs synthesised using this technology has a particularly penetrating character and dissolves in saliva in less than 15 seconds.

4. Direct compression

This technique utilises compounds that are extremely evaporative, such as benzoic acid, ammonium bicarbonate, camphor, ammonium carbonate, urea, and naphthalene. These compounds are included because they evaporate more rapidly than the other excipients used in tablet manufacturing. The final mixture is crushed into tablets during processing. Sublimation evaporates the MDT's volatile components, leaving a spongy matrix on top of the tablets. MDTs synthesised with this method exhibit a high degree of penetration and dissolve in saliva in less than 15 seconds [23,24,25].

5. Spray drying

MDT is made utilising starch hydrolysate, dextrose, fructose, xylitol, isomelt, sorbitol, polydextrose, maltose, and mannitol as expanding substitutes. The aqueous solubility and sweetness of the bulking agent are really desired. Additionally, this kind of bulking ingredient hides undesirable flavours and gives a pleasing mouthfeel[26,27].

6. Mass extrusion

The mass extrusion procedure is used to combine the desired amount of active mixture with water soluble polyethylene glycol and methanol. Following that, muted aggregate is extracted using a syringe to create a barrel shape for the goods, which is then cut into even parts using a hot blade to produce tablets. Additionally, these dried barrels were employed to spread the pieces in order to disguise their acrid flavour and create a pleasant flavour of tablets[28,29].

7. Nanonization

Milling procedures are used to decrease the size of active substances to nanoparticles. After nanodrugs are stabilised, they are integrated into MDTs[12].

8. Melt granulation

The hydrophilic waxy binders use in melt granulation process for the preparation of MDTs.

9. Cotton candy process

The cotton candy approach is used to generate MDTs that comprise amorphous saccharides or polysaccharides. The whole process is carried out concurrently by the use of flash liquefying and centrifugal force. Candy components include active chemicals and excipients. The mixes are then compacted into MDTs. Compression requires a greater pressure, which might result in an increase in processing temperature. The high temperature limit eliminates this method's advantage for thermally stable substances[30].

10. Phase transition process

MDTs are produced using the phase transition procedure. This approach combines sugar alcohols with low and high melting points. No particular equipment is required for the preparation of the MDTs.

11. Three dimensional printing (3DP)

The 3DP method is used to manufacture MDTs by applying rapid prototyping (RP) technology. In this method the MDTs prepare can fast dissolve as compared to other technology.

Approaches for masking taste

In the present environment, paediatric and geriatric patients experience discomfort while consuming tablets due to the bitter and unpleasant taste of the medication. As a result, it is vital to hide the harsh taste of the medicine. This may improve the patient's acceptability. To improve acceptance, it is believed that the oral dose form should be less bitter. Various approaches have been developed in recent years to lessen the bitterness of tablets and to increase the palatability of MDTs.

Two approaches are often used to mask the bitter taste of the active substances. The first approach dissolves the medicine in saliva, and then equilibrium between decreased solubility and bioavailability occurs. The second technique is used to alter the way a medication interacts with taste receptors. The ideal flavour masking process and preparation should result in the following [31]:

- Machines and transforming phases should be lowest
- Least quantity of excipients required for an superlative formulation
- It does not produce any adverse and side effect
- Excipient should be easily available
- Reduces the manufacturing cost
- The processing can be done at room temperature
- It can be prepared easily and rapid

Methods to taste masking

Numerous strategies are available to mask the undesirable taste of the dosage forms. Several of them include:

- Coating of medicament fragments with inactive agents
- The solid dispersion system, microencapsulation
- Multiple emulsions
- Inclusion complexes
- Ion exchange resins
- The mass extrusion method (dispersion coating)
- Prodrugs[32].

Evaluation of mouth dissolving tablet

After complete formulation of mouth dissolving tablets it valuation is required for the quality assessment of tablets. Following methods can be applied to check the survival of tablets.

A. Precompression evaluation parameters of MDTs

1. Angle of Repose

It can be measured by the funnel method. It is used to determine flow property of the excipients. It is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose. A funnel is filled to the brim and the test sample is allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet is taken to measure the area of pile, thereby evaluating the flow ability of the granules. Height of the pile is also measured.

$\tan \theta = H / R$

$\theta = \tan^{-1} (H/R)$

Where, is the angle of repose H being height of pile

R, is radius of the base of pile

2. Bulk Density

It can be determined by using formula;

Bulk density = M/V

M – Mass of the blend

V – Tapped volume of the blend

3. Tapped Density

Tapped density is calculated by the formula:

Tapped Density = M/V_t

M – Mass of the blend

V_t – Bulk volume of the blend

Both the parameter is used to assess the porosity of the powder. This property can help in determining the settling of powder.

4. Carr's Index

It represents the powder flow properties. Weighed amt. of powder is taken. This powder is transfer to measuring cylinder and the volume of powder is noted as bulk volume from that by using weight of powder bulk density is calculated. Now according to IP powder is tapped 100 times manually and the volume of powder is noted as tapped volume. It can be computed by the formula;

Carr's Index = $(D_t-D_b)/ D_t$ X 100

D_t – tapped density of the powder

D_b – bulk density of the powder

5. Hausner's Ratio

It also reveals the flow properties of powder.

Hausner's Ratio= Tapped density/ Bulk density

B. Post compression evaluation parameters of MDTs

1. Shape and Size

MDTs' physical characteristics, including their dimensions and appearance, may be monitored and adjusted. Ten tablets may be used to determine the width of a tablet using digital vernier callipers.

2. Weight variation of MDT

The objective of the weight variation test is to ensure -good manufacturing practices (GMP), appropriate size of the tablets and the content uniformity of the formulation. The United States Pharmacopoeia (USP) provides criteria for tablet weight variation of intact dosage units. All the brands complied with the compendial specification for uniformity of weight which states that tablets weighing 130 mg or less, weights of not more than tablets should not differ from the average weight by more than 10% and none deviates by more than twice that percentage. In all the formulations the tablet weight is more than130mg and less than 324 mg, hence 7.5% maximum difference allowed.

3. Thickness variation

The screw gauze micrometer is used to determine the thickness of the tablets. The thickness of tablets calculated by measuring the size of ten tablets and it means value indicate the thickness of individual tablets.

4. Hardness

Tablets are classified according to their hardness, which shows the amount of force needed to split them. Monsanto's hardness tester, Pfizer's hardness tester, and others are used to determine the tablet's hardness. Hardness is measured in kilogrammes or pounds. The amount of pressure necessary to shatter the tablets is dependent on their hardness (kg/cm2). Consistency between the derived values and the standard value is required. Three tablets are randomly picked from each formulation and the mean and standard deviation values are calculated.

5. Friability

The friability of the tablet is determined using the friability test instrument. Friability is used to determine the amount to which tablets break during physical stress situations such as packing, transportation, and so on. Twenty tablets are initially weighed (Initial) and transferred into friabilator. The friabilator is operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets are weighed again (Final). The % weight reduction is estimated by comparing the pre- and post-operative weights of six tablets.

6. Wetting time

The ratio of wetting time to water absorption is a critical criterion in evaluating mouth dissolving tablets. The filter paper is placed in Petridish containing water soluble dye solution (Sorenson's buffer pH 6.8). After that, tablets are laid on the paper and the duration required for entire damping of the tablet is determined.

7. Disintegration time

The disintegration time of six randomly chosen tablets is determined using a disintegration test equipment. In this, one evaluated the average time needed for disintegration and then compared it to industry standards[33]. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1 N HCL maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured and recorded.

8. Drug Content

The drug content is calculated by triturating the three tablets in a mortar with pestle to get fine powder. Taken powder equivalent weight of one tablet and is dissolved in pH 6.8 phosphate. Measure the absorbance of diluted sample of drug at respective wavelength, using UV-Visible Spectrophotometer. The drug content is calculated by using standard calibration curve.

9. Dissolution test

Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablet, capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness**.** The dissolution is used to determine the release of drug from tablets. The various solvent can use for dissolution of tablets. The solvents are as follows:

- 0.1N HCl
- Buffers
- Saline water
- Water

Dissolution rate is studied by using I.P. type-I apparatus(50 rmp) using 900ml of 0.1 N HCl as dissolution medium. Temperature of the dissolution medium is maintained at 37± 0.5°C, aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution is measured by UV spectrophotometric method at 296 nm and concentration of the drug is determined from standard calibration curve.

10. Accelerated stability

The MDTs are used to special packing so that it can avoid moisture contamination. As per ICH guidelines, before post marketing of the MDTs it required to pass the stability test. The tablets can kept in following temperature to checks its stability:

- 40 ± 1 °C
- 50 ± 1°c
- 37 ± ° C and Relative Humidity= 75% ± 5%[33,34,35]

Conclusion

MDTs are dosage forms which are prepared to dissolve rapidly in the saliva generally within few seconds. MDTs provide lot of advantages over conventional dosage forms such as improved efficacy, bioavailability, rapid onset of action, better patient compliance. Particularly, MDTs give more comfort to pediatric and geriatric patients. MDTs can be formulated by several methods based on the drug and additives used. Usually MDTs consists less mechanical strength. But by applying some new technologies and additives MDTs with sufficient mechanical strength can be formulated.

The basic fundamental utilised in the development of the mouth dissolving tablet is to maximize its pore structure. Vacuum drying and freeze-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is inconvenient and yields a fragile and hygroscopic product. Therefore, a vacuum-drying technique is adopted in the present investigation after addition of a subliming agent to improve porosity of the tablets. Even bitter drugs can be added in MDTs by using taste masking agents. The research for MDTs is still going on. MDTs give wide marketing also which makes the dosage form successful in the market. Many drugs will be prepared as MDTs in future for its market potential.

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