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A Review: Mouth Dissolving Tablets for Motion Sickness

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ABSTRACT

The oral route is the most preferred route for administration of various drugs because it is regarded as the safest, most convenient and economical route. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients is the difficulty to swallow. For this reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention are ideal. Recently researchers developed the mouth dissolving tablet (MDT) with improved patient compliance and convenience for kinetosis (motion sickness). MDTs are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. These mouth dissolving tablets are ingested without the addition of water because they melted in the buccal cavity. Mouth dissolving tablets are also called as Fast-dissolving tablets, melt-in-mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick-dissolving, etc. The key to successful drug delivery application is based on meeting unmet need or benefit of use of the chosen system, that's why a technology selection process will be most successful when considering clinical, technical, medical and business benefits. Bringing these factors together, the selected drug delivery system will significantly enhance patient compliance and market acceptance.

INTRODUCTION

Motion sickness is a common syndrome that occurs upon exposure to certain types of motion. It is thought to be caused by a conflict between the vestibular, visual, and other proprioceptive systems. Although nausea is a common symptom, it is often preceded by stomach awareness, malaise, cold sweat, drowsiness, and irritability[1]. Lots of yawning can be the first sign of motion sickness and some people get more and more irritable. Motion sickness is a syndrome that occurs when a patient is exposed to certain types of motion like travel by car, train, airplane, or boat and usually resolves soon after its cessation. It is a common response to motion stimuli during travel. Although nausea is a common symptom, the syndrome includes symptoms ranging from vague malaise to completely incapacitating illness. These symptoms, which can affect the patient's recreation, employment, and personal safety, can occur within minutes of experiencing motion and can last for several hours after its cessation.

Early self-diagnosis should be emphasized, and patients should be counseled about behavioral and pharmacologic strategies to prevent motion sickness before traveling. Patients should learn to identify situations that will lead to motion sickness and control the amount of unpleasant motion they are exposed to by avoiding difficult conditions while traveling or by positioning themselves in the most stable part of the vehicle. Slow, intermittent exposure to the motion can control symptoms. Other behavioral strategies include watching the true visual horizon, steering the vehicle, tilting their head into turns, or lying down with their eyes closed. Patients should also try to reduce other sources of physical, mental, and emotional discomfort.

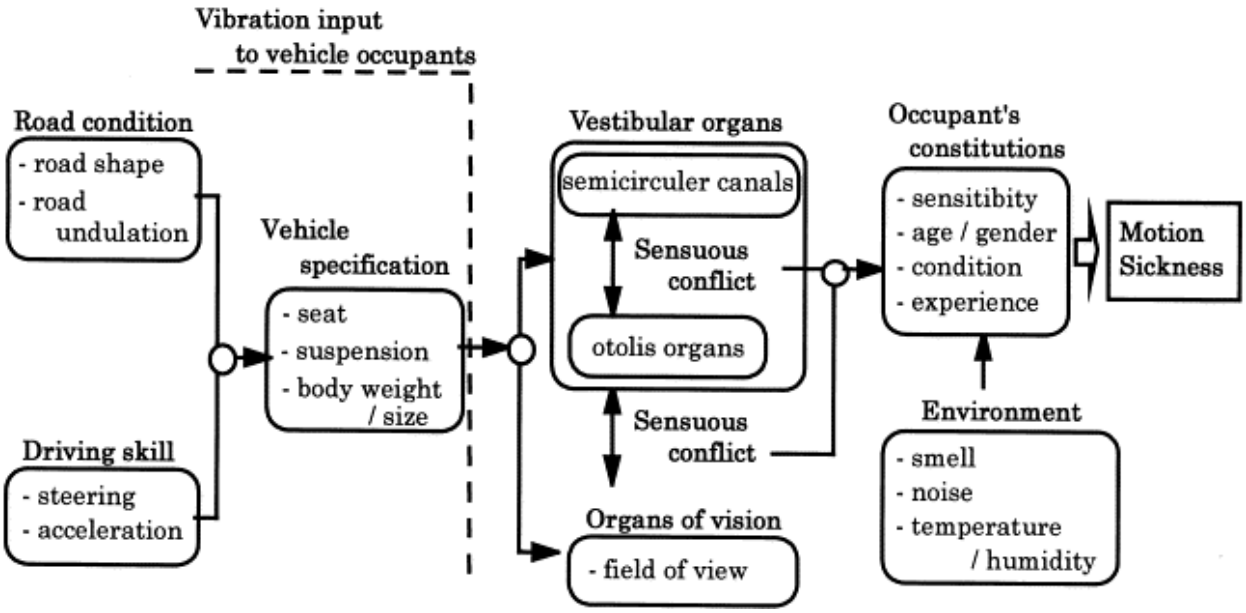

Figure no.1. Mechanism of motion sickness

Most people with motion sickness do not need to consult their doctor to treat Motion sickness. Laboratory testing also is not required. Before taking these medications, read the precautions because many of these drugs have side effects, like, drowsiness, dry mouth, blurry vision, and occasionally disorientation[2]. Treatment for motion sickness can consist of medical treatment; simple changes their environment, for example, get fresh air. Some people with motion sickness respond well to biofeedback training and relaxation techniques. Alternative medications for the treatment of motion sickness are ginger, peppermint, and tea. Some people respond to acupuncture. People who drive vehicles or operate heavy equipment should not take these medications.

First-generation antihistamines, although sedating, are also effective. Nonsedating antihistamines, ondansetron, and ginger root are not effective in the prevention and treatment of motion sickness[3].

MOUTH DISSOLVING TABLETS

Drug Delivery Systems (DDS) is a strategic tool for improving markets/indications, extending product life cycles and introducing opportunities. DDS makes a good contribution to world pharmaceutical sales through market segmentation and is moving quickly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters applicable to their

performance. Despite incredible advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of the low cost of therapy, ease of administration, accurate dosage, self-medication, pain prevention, flexibility, leading to high levels of patient compliance. Tablets and capsules are the most accepted dosage forms. But one important disadvantage of such dosage forms is difficulty in swallowing. This disorder is also associated with several conditions like:

- Parkinsonism
- Motion sickness
- Unconsciousness
- Elderly patients
- Children
- Mentally disabled persons
- Unavailability of water.

Improved patient compliance has achieved vast demand. Consequently, demand for their technologies is also growing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus on the development of new drug delivery systems for already presented drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) aim for the same by formulating a dosage form, suitable to be administered to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a fast dissolving drug delivery system, i.e. Mouth Dissolving Tablet (MDT).

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need for drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15s to 3min. Most of the MDTs include certain superdisintegrants and taste masking agents.

IDEAL PROPERTIES OF MDT[4]

Mouth dissolving tablets are particularly suitable for patients, who have difficulty to swallow conventional tablets with a glass of water.

A mouth dissolving tablet should

- Not require water or other liquid to swallow.
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.

ADVANTAGES OF MDT

- Patients who are not interested to take solid preparation due to fear of choking.
- Patients who are undergoing treatment for cancer may feel too nauseous to swallow H_2-blocker.
- A patient with continual nausea, who may be in the journey, or has little or no access to water.
- No need of water to swallow the tablet.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose, and improved clinical performance by reducing side effects[5].
- Accurate dosing as compared to liquids.

➢ Dissolution and absorption of the drug are fast, offering rapid onset of action.

➢ Bioavailability of drugs is improved as some drugs are absorbed from mouth, pharynx, and esophagus through saliva passing down into the stomach.

➢ First pass metabolism is reduced, thus offering improved bioavailability and thus reduced the dose and side effects.

➢ Free of risk of suffocation due to physical obstruction when swallowed, thus contribute to improved safety.

➢ More amount of drug can be loaded.

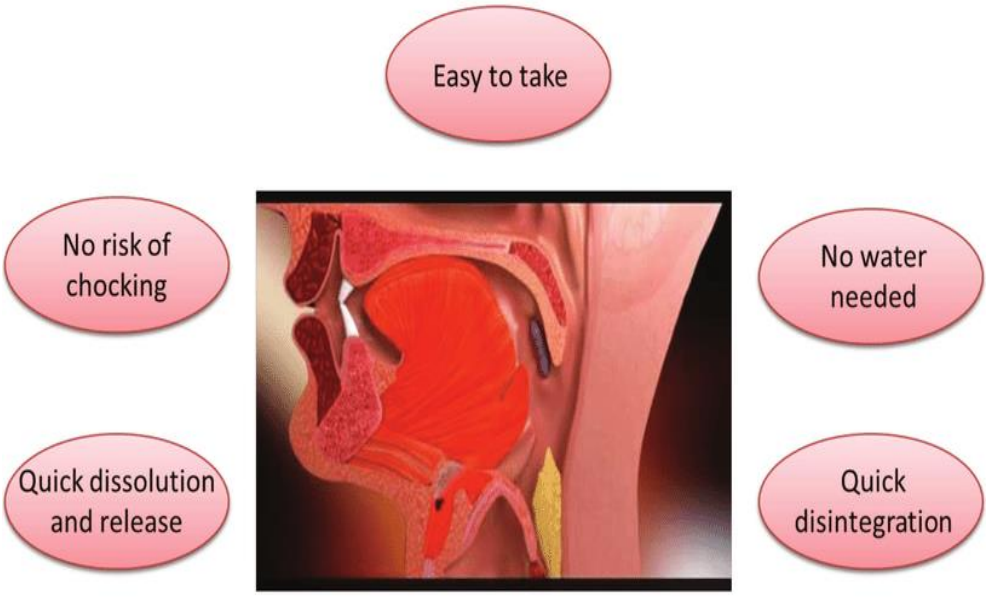

Figure no. 2. Advantages of MDT[6]

LIMITATIONS OF MDT

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

➢ The tablets may leave an unpleasant taste and/or grittiness in the mouth if not formulated properly.

FORMULATION OF MDT

Important ingredients that are used in the formulation of MDTs should allow rapid release of the drug, resulting in quicker dissolution. This includes both the actives and the excipients.

Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients, and effervescent agents. Excipients balance the properties of the actives in MDTs. 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 problem that wants to be addressed by formulators. The function of excipients is important in the formulation of mouth dissolving tablets. Binders keep the composition of these mouth dissolving tablets together during the compression stage.

The right selection of a binder or combination of binders is important to maintain the disintegration and release of the tablet. Binders can either be liquid, semi solid. The selection of a binder is crucial in a mouth dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients.

Super disintegrants

Use of disintegrants is the basic approach in the development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT. It is necessary to choose a suitable disintegrant, in an optimum concentration to ensure quick disintegration and high dissolution rates. Super disintegrants provide quick disintegration due to the combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, it promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution[7]. 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 the concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Sodium starch glycolate, Ac-di-sol (cross carmellose sodium), crospovidone, microcrystalline cellulose, pregelatinized starch are some of the examples of disintegrants.

Mechanism of action of disintegrants

The tablet disintegrates into small particles by the following mechanisms:-

- By capillary action
- By swelling
- Sublimation
- Due to the release of gases
- By enzymatic action
- Due to disintegrating particle/particle repulsive forces
- Due to deformation

By capillary action

Disintegration by capillary action is always the primary step. When the tablet in a suitable aqueous medium, the medium penetrates the tablet and weakens the intermolecular bond and breaks the tablet into small particles. Water penetrates the tablet depends upon hydrophilicity of the drug /additives. For these types of disintegrants, upholding of spongy structure and decrease interfacial tension towards aqueous fluid is essential which helps in disintegration by forming a hydrophilic network around the drug particles.

By swelling

The most commonly accepted mechanism of action for tablet disintegration by swelling. Tablets with high porosity give poor disintegration due to inadequate swelling force[8]. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

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.

Sublimation

The principle involves in the process is the addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and compressed into a tablet. Removal of volatile material by sublimation produce pores in tablet core, due to this tablet dissolves when comes in contact with saliva. Additionally, several solvents like cyclohexane, benzene, etc can also be used as pore-forming agents. Mouth dissolving tablets prepared with sublimation technique have a highly porous structure and good mechanical strength.

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 the active ingredient and compressed into a tablet. Allen and Wang used this technique to prepare mouth-dissolving tablets, which disintegrated within the 20s.

Molding

Tablets manufactured by this method are solid dispersions. The physical form of the drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as disaggregate particles or microparticles in the matrix[9]. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion.

Different molding techniques can be used to prepare mouth-dissolving tablets:-

Compression molding:

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

Heat molding:

A molten matrix in which drug is dissolved or dispersed can be directly molded into Mouth dissolving tablets.

No vacuum lyophilization:

This process involves evaporation of solvent from a drug solution or suspension at standard pressure. Molded tablets possess a porous structure, which facilitates rapid disintegration and easy dissolution of tablets. Molded tablets offer improved taste due to water-soluble sugars present in the dispersion matrix. But molded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs[10]. However, adding sucrose, acacia or polyvinylpyrrolidone 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 mask their bitter taste.

Direct compression

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

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

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLETS

Table no. 1. Patented technologies for mouth dissolving tablets

Sr. No.	Patented technologies	Inventers
01	Zydis technology	Zydis
02	Takeda technology	Takeda (Osaka, Japan)
03	Novartis technology	Novartis consumer health
04	Nippon shinyaku technology	Nippon shinyaku
05	Flashtab[11]	Ethypharm
06	Wowtab[12]	Yamanouchi
07	Daiichi	Daiichi
08	Orasolv	Cima labs
09	Ziplets	Eurand
10	Lyoc	Pharmalyoc
11	Nanocrystal technology[13]	Elan, king of prussia
12	Pharmaburst	SPI pharma
13	Advantol	Akina
14	Frosta	Lavipharm laboratories, inc.

EVALUATION OF MOUTH DISSOLVING TABLETS

MDTs formulations have to be evaluated for the following evaluation tests.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness

Tablet thickness is an important characteristic in reproducing the appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using a micrometer.

Uniformity of weight

As per IP, 20 tablets were taken and their weight was determined individually and totally on a digital weighing balance. The average weight of one tablet was determined from the total weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Table. No 2. Limits of weight variation test

The average weight of Tablets (mg)	Limit (%)
130 or less	+/- 10.0
130-324	+/- 7.5
More than 324	+/- 5.0

Tablet hardness

The hardness of the tablet is defined as the force applied across the surface of the tablet to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, shipping and handling before usage depends on its hardness[14]. The hardness of the tablet of each formulation was determined using Monsanto Hardness tester and Pfizer hardness tester.

Friability

It is measured by the mechanical strength of tablets. Roche friabilator was used to determine the friability. A pre weighed de dusted tablet was placed in the friabilator. It consists of a plastic-chamber that revolves at 25rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes (100rpm). At the end of test tablets were dusted and reweighed, the loss in the weight of the tablet is the measure of friability and is expressed in percentage as;

% Friability = loss in weight / initial weight x 100

***In vitro* disintegration test**

The test was carried out on 6 tablets using the apparatus specified in IP 1996. Distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for

complete disintegration of the tablet with no palatable mass remaining in the apparatus which was measured in seconds[15].

Wetting time

A piece of tissue paper (12cm X 10.75cm) folded twice was placed in a small petridish (ID = 6.5cm) containing 6ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

FUTURE PROSPECTS OF MDT

Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. Also, MDTs may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that has limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in MDTs may be absorbed in the pregastric sites of highly permeable buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low-molecular weight and highly permeable drugs. Future possibilities for improvements in MDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized[16].

Table 3. List of marketed mouth dissolving tablet for motion sickness

Sr. No.	Trade name	Active constituent
1	Zofran	Ondansetron
2	Meclizine	Meclizine hydrochloride
3	Equate	Dimenhydrinate
4	Stemetil MD	Prochlorperazine
5	Etizest-1 MD	Domperidone
6	Scopace	Scopolamine
7	Dimen	Diphenhydramine
8	Domeperon	Domperidone
9	Avomine MD	Promethazine

CONCLUSION

Mouth dissolving tablets constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The pediatric and geriatric populations are the primary. Targets, as both the groups found it difficult to swallow conventional tablets. The availability of the various technologies and manifold advantages of mouth dissolving tablets will surely increase its popularity shortly. Recent trends of patient-oriented practices demand the design of patient-oriented dosage form to achieve patient compliance. The number of formulation related factors contributes to the significant amount of non-compliance and hence there is a need to design a patient-oriented drug delivery system. Mouth dissolving tablets are ideal for many groups of the patient including geriatrics, pediatrics, and psychiatrists and for those people who have difficulty in swallowing. By using such manufacturing technologies, many drugs can be formulated in the form of a mouth dissolving tablets to provide the advantages of liquid medication in the form of solid preparation. Motion sickness, a common problem of travelers is a condition in which a disagreement exists between visually perceived movement and the vestibular system's sense of movements. The key to successful drug delivery application is based on meeting unmet need or benefit of use of the chosen system, that’s why a technology selection process will be most successful when considering clinical, technical, medical and business benefits. Bringing

these four factors together, the selected drug delivery system will significantly enhance patient compliance and market acceptance.

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