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Review Article

A REVIEW ON ORODISINTEGRATING TABLETS

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Orally disintegrating tablets (ODTs) as well as critical issues during evaluation of ODTs such as bioequivalence and challenges and limitations of ODTs and finally present and the future of ODTs. ODTs have received ever- increasing demand and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water. When ODTs are put on tongue they disintegrate instantaneously, releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia. Their growing importance has been underlined recently when European Pharmacopoeia adopted the term “Orodispersible Tablet” as tablet that is to be place in the mouth where it disperses rapidly before swallowing. ODTs have some challenges but solutions to overcome these challenges were shown in this paper.

Keywords: Taste masking; orally disintegrating: Orodispersible; Tablets; Fast; Advantages

INTRODUCTION

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid dosage form. The undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. Hence forth aggressively bitter tasting drugs like the fluoroquinolone antibiotics, penicillins, macrolide antibiotics, and non-steroidal anti inflammatory drugs are candidates for taste masking. Without changing its safety and efficacy, a drugs taste has to be masked and techniques are being adapted to meet this need, especially for the paediatric and juveniles patients[1].

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable

to provide the drug either in a chewable solid form or a liquid dosage form. The undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. Chemoreceptors on the Tongue Taste are the brain's interpretation of chemicals that trigger receptors on the tongue, which are housed in the taste buds. Molecule interacts with taste receptor on the tongue to give taste sensation, when they dissolve in saliva. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste.[2,3]

Four fundamental sensations of taste have been described: Sweet and salty, mainly at the tip. Sour, at the sides, Bitter at the back.

TASTE MASKING TECHNOLOGIES:

Multiple factors, including costs, medical condition, and complexity of regimen, play a role in adherence rates. Lack of patient adherence often leads to worsening health and poor outcomes and increases costs across the healthcare system. Taste masking can contribute to improved drug acceptability and medication adherence, particularly in pediatric, geriatric, and other special patient populations.[4] When the taste and palatability of a drug product's active pharmaceutical ingredient (API) is likely to be unpleasant to patients or when the dosage form has a high degree of interaction with patients' taste buds (such as with chewable and orally disintegrating tablets, gums, and gummies), taste masking is likely to be beneficial for the formulator, the key initial consideration is the level of masking required, which depends on the API and the dosage form design. In some cases, the API is only slightly bitter and can be masked easily with flavors and sweeteners; in other cases, the API has a very bitter taste requiring additional taste-masking techniques. For general use tablets, which the patient swallows whole, an immediate-release film coating is typically sufficient to mask an unpleasant API. With bitter APIs, however, even a small amount of exposure is sufficient to give the patient a perception of bad taste. In these cases, formulators should consider using a barrier membrane coating or other alternative technique to mask the taste of the drug particles or granules.[5,6]

Dosage strength may dictate whether a specific taste-masking formulation strategy is suitable. Low-dose APIs are easiest to mask, while high-dose APIs pose a problem simply because more material (and a greater surface area) needs to be masked. This is especially true for formulations with fast-dissolving bases, which may leave patients with a mouthful of coated API particles that produce a gritty mouthfeel. These particles can also get stuck between the patients' teeth, producing a lingering grittiness and bitterness as further chewing breaks the coated particles. In pediatric formulations, the dose is generally small enough to allow flexibility with respect to the taste-masking approach.[7]

The physicochemical properties of an API also play an important role when selecting a taste-masking technology. For example, certain APIs have lower solubility at different pH values. Adding an alkalizing agent (such as sodium bicarbonate) or an acidifying agent (such as citric acid) can reduce solubility in the mouth, minimizing taste perception. You can also use a lower- solubility form of an API to reduce or eliminate poor taste. With a lower-solubility form of ranitidine base, the bitter taste can be adequately masked by flavors and sweeteners, but for more soluble forms of ranitidine (such as ranitidine hydrochloride), flavors and sweeteners may not be sufficient, particularly if the dosage form is an orally disintegrating tablet (ODT).[8]

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug.

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

An ideal taste masking process and formulation should have the following properties.[9]

- Involve least number of Equipments and processing steps.
- Effectively mask taste with as few excipients which are economically and easily available.
- No adverse effect on drug bioavailability.
- Least manufacturing cost.
- Can be carried out at room temperature.
- Require excipients that have high margin of safety.
- Rapid and easy to prepare.

Factors that are taken into consideration during the taste-masking formulation process include:

- Extent of the bitter taste of the API.
- Required dose load.

- Drug particulate shape and size distribution.
- Drug solubility and ionic characteristics.
- Required disintegration and dissolution rate of the finished product.
- Desired bioavailability.
- Desired release profile.
- Required dosage form.

Factors affecting selection of taste masking technology Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions.[10]

Orally Disintegrating Tablets

Orally disintegrating tablets have been developed and new ODT technologies compensate many pharmaceuticals and patients' needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia. Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance.[11]

ODTs are being named as orodispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. There are some definitions that made by pharmacopeias and agency as follows: Orodispersible tablets have been placed in the mouth where they disperse fast before being swallowed and they are uncoated tablets. Orodispersible tablets disintegrate within 180 seconds when the disintegration tests have been conducted up to the test for disintegration of tablets.[12]

Orally disintegrating tablets are intended to disintegrate fast in the mouth to provide dispersion before being swallowed where the active ingredient is intended for gastrointestinal delivery and/or absorption. A solid dosage form containing active ingredients which disintegrates fast, usually within seconds, when put on the tongue. In addition to those definitions, FDA recommends that, orally disintegrating tablets should be considered as solid oral preparations that disintegrate fast in mouth, with an in-vitro disintegration time of approximately less than or equal to 30 seconds, when the disintegration test conducted to the United States Pharmacopeia (USP) disintegration test method or

alternative.[13,14]

Products of ODT technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding.

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Catalent Pharma Solutions (formerly Scherer DDS) in UK, Cima Labs in the US and Takeda Pharmaceutical Company in Japan are some of the initiators for the development of ODTs.[15]

The first ODT which got approval from the US Food and Drug Administration (FDA) was a Zydis ODT formation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998.[16]

The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing.[17]

The Need for Development of ODTS

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 high cost of disease management.

Patient factors[18]

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 eight-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 an atypical antipsychotic
- A patient with persistent nausea, who may be journey, or has little or no access to water

Effectiveness factor[19]

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for 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 pregastric segments of GIT.

Manufacturing and marketing factors[20]

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, unique product differentiation, value-added 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.

CHALLENGES IN FORMULATING ODTS

Palatability[21,22]

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 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.

Mechanical strength[23,24]

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, 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.

Hygroscopicity[25]

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.

Amount of drug[26,27]

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.

Aqueous solubility[28,29]

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

Size of tablet[30]

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

Approaches to ODTs Development[31,32]

The fast disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to develop rapidly dissolving oral dosage forms include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. As is often the case, a technology that is originally developed to address a particular administration need can quickly become adopted as part of a pharmaceutical company's product life cycle management strategy, which is precisely what has happened with ODT technologies.

The technologies that have been used by various researchers to prepare orally disintegrating dosage forms include: Freeze-Drying or Lyophilization, Molding, Direct Compression, Disintegrant addition, Sublimation, Spray Drying, Mass Extrusion,

Cotton-candy process, Nano Crystal TM Technology, Oral films/wafers.

Future Prospects

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharma-ceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide.

CONCLUSION

Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of ODTs for product line extensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come.

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