IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

# DESIGN DEVELOPMENT AND EVALUATION OF ORO DISPERSIBLE TABLET OF FEXOFENADINE

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**ABSRACT:**

To develop Orodispersible tablets (ODTs) of fexofenadine hydrochloride using three different superdisntegrants in various ratios and to compare their disintegration properties. Direct compression technique was used for the preparation of ODTs. Mannitol and Avicel CE-15 (microcrystalline cellulose and guar gum) were used as direct compression diluents. The disintegration time of tablets using each polymer (superdisintegrant) was evaluated as well as other tablet properties including weight fluctuation, hardness, friability, wetting time and water absorption.

**KEY WORDS:** Croscarmellose sodium, Direct compression, Fexofenadine, Orodispersible tablets.

## INTRODUCTION:

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules [1,2]. One important drawback of such dosage forms is Dysphagia, or difficulty in swallowing is common among all age groups. Common complaints about the difficulty in swallowing tablets are size, surface, and taste of tablets. Geriatric and pediatric patients and traveling patients, who may not have ready access to water, are most in need of easy swallowing dosage forms [3]. To fulfil these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as ODTs which disintegrate rapidly in saliva, usually within a matter of seconds, without the need to take it water. Drug dissolution and absorption, as well as onset of clinical effect and drug bioavailability, may be significantly greater than those as compared with conventional dosage forms [4-6]. ODTs releases the medicament in the mouth for absorption through local Oro mucosal tissue and through pre-gastric (oral cavity, pharynx, and oesophagus), gastric (stomach), and post-gastric (small and large intestine) segments of gastrointestinal tract (GIT) [7]. ODTs are also called as Orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapid melts. However, of all the above terms,

United States pharmacopoeia (USP) approved these dosage forms as ODTs. The European Pharmacopoeia has used the term Orodispersible tablet for tablets that disperses readily within 3 minutes in the mouth before swallowing [3]. United States Food and Drug Administration defined ODT as "A solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute [8].

**IDEAL PROPERTIES OF ORODISPERSIBLE TABLETS [9]:**

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds • High drug loading
- Be compatible with taste masking and other excipients
- Have a pleasing mouth feel
- Leave minimal or no residue in the mouth after oral administration
- Exhibit low sensitivity towards environmental conditions such as humidity and temperature
- Be adaptable and amenable to existing processing and packaging machinery.

**ADVANTAGES OF ORODISPERSIBLE TABLETS [10]:**

- Administration to patients who cannot swallow, like the elderly, stroke victims and bedridden patients; patients who should not swallow, like renal failure patients; and patients who refuse to swallow, such as paediatrics, geriatric and psychiatric patients
- Patient's compliance for disabled bed ridden patients and for traveling and busy people, who do not have ready access to water
- Good mouth feel property helps to change the basic view of medication as "bitter pill," particularly for paediatric patients due to improved taste of bitter drugs
- The convenience of administration and accurate dosing as compared to liquid Formulations
- Benefit of liquid medication in the form of solid preparation
- More rapid drug absorption from the pre-gastric area, i.e., mouth, pharynx and oesophagus which may produce rapid onset of action
- Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent life extension.

**DISADVANTAGE OF ORODISPERSIBLE TABLETS**

- Orodispersible is hygroscopic in nature so must be keep in dry place
- Sometime it possesses mouth feeling
- ODT requires special packaging for properly stabilization and safety of stable product
- Dose uniformity is a technical challenge.[9 10 11]

**SELECTION OF THE ODTS DRUG CANDIDATES [12] :**

- Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms:
- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g., selegiline, apomorphine, buspirone, etc.
- The drugs that produce a significant number of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT
- Drugs are having the ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for ODT formulations
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs
- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for ODT formulations
- Drugs which are having a short half-life and needs frequent dosing, which are very bitter or either having unacceptable taste whose taste masking cannot be achieved or which require controlled or sustained release are inappropriate for ODT formulation.

**CHALLENGES IN THE FORMULATION OF ODTS:**

**Mechanical strength and disintegration time:**

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile, and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. It is very natural that increasing the mechanical strength will delay the disintegration time. Hence, a good compromise between these two parameters is always essential [13].

**Tastes masking:** Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in the mouth will seriously affect patient compliance and acceptance for the dosage form. Hence, effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity [13].

**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 loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented using various matrix-forming excipients such as mannitol that can induce crystallinity and hence, impart rigidity to the amorphous composite [14].

**Size of tablets**:

The degree of ease when taking tablets 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 [14].

**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. According to USP generally, the ODT tablet weight should not exceed 500 mg. For lyophilized dosage form, the drug dose should be lower than 400 mg for insoluble drug and <60 mg for soluble drug. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers [9].

**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 [9]

**Mouth feel** :

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after the disintegration of the ODTs should be as small as possible. Moreover, addition of flavours and cooling agents like menthol improve the mouth feel. [13]

**Good packaging design:**

For the protection of ODTs from moisture and other environmental hazards, the package design should be considered early in the development stages. [14]

**Various Methods of Preparation of Or dispersible Tablets:**

There are several methods for the preparation of Oro dispersible tablets but the prepared products vary in their properties depending on the method of preparation. The properties in which they vary are mechanical strength of the tablets, swallowability, bioavailability, drug dissolution in saliva, stability, and to some extent taste.[15] Various process of manufacturing of Or dispersible tablets are moulding, compaction, spray-drying, freeze-drying, and some special methods are melt granulation, phase transition, and sublimation.

**Moulding process:**

Tablets formed by moulding process are highly porous in structure, resulting in high rate of disintegration and dissolution. This process includes moistening, dissolving, or dispersing the drugs with a solvent then moulding the moist mixture into tablets by applying lower pressure in compression moulding, but always lower than the conventional tablet compression. The powder mixture may be sieved prior to the preparation in order to increase the dissolution.[17] Moulded tablets have low mechanical strength, which results in erosion and breakage during handling.

**Compaction methods:**

Conventional methods for the preparation of tablets such as dry granulation, wet granulation, and direct compression are also exist for the preparation of Orodispersible tablets. Some important super disintegrants, which are used during preparation of Orodispersible tablets, are cross povidone, croscarmellose sodium, sodium alginate, acrylic acid derivatives.[18,19] Baclofen Orodispersible tablets were prepared by direct compression method using cross povidone and sodium starch glycolate as super disintegrants.[20] Even Orodispersible tablets of Carbamazepine were prepared by this method having microcrystalline cellulose and cross povidone (2%-10%).[21] In all the cases it has been found that preparation by compression method along with addition of super disintegrants in correct concentration obey all the properties of orodispersible tablets.[20,21]

**Spray-drying method:**

Here, Orodispersible tablets are made up of hydrolysed or unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulk agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Sometimes in order to improve the disintegration and dissolution, citric acid and sodium bicarbonate are used. Finally, the formulation is spray-dried in a spray drier. Orodispersible tablets prepared through this method are disintegrated in less than 20s. [22,23]

**Freeze-drying method:**

This is a very popular process for the preparation of Orodispersible tablets. Tablets prepared by this process have low mechanical strength, poor stability at higher temperature and humidity, but glossy amorphous structure resulting in highly porous, lightweight product. There are various patents on this particular technology. [16]

**Some methods of preparations:**

**Melt granulation:**

It is a unique method for the preparation of Orodispersible tablets by incorporating superpolystate.[24] Super polystates are hydrophilic waxy binders with a melting point 33-37°C and Hydrophilic –Lipophilic Balance value is 9. They play a dual role as a binder that increases the physical resistance of the tablets and also as a disintegrants, which help the tablet to melt in the mouth, and solubilize rapidly leaving no residue in the mouth. Superpolystate were introduced in the formulation of Orodispersible tablets by melt-granulation method. Here, granules are formed by the molten form of this material. Crystallized paracetamol was used as a model drug along with mannitol and croscarmellose sodium.

**Phase transition process:**

Kuno *et al*. [25] investigated this process by compressing powder containing two sugars alcohols. One with high and another with low melting point, and they are heated at a temperature between their melting point and then compressed finally in order to get the tablets. Example of sugar alcohols are erythritol (m.p. 122°C), xylitol (m.p. 93-95°C), trehalose (97°C), and mannitol (166°C). After heating, tablet hardness was increased due to an increase in interparticle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

**Sublimation:**

In this process, subliming material 'camphor' is used. It was sublimed in vacuum at 80°C for 30 min after preparation of tablets. Here, also tablets prepared are porous in nature. In conventional types, sometimes rapid disintegration does not occur. Therefore, in order to improve porosity, volatile substance camphor is added in the preparation, which gets sublimed from the formed tablet.[26]

**Effervescent method:**

Orodispersible tablets are also prepared by effervescent method by mixing sodium bicarbonate and tartaric acid of concentration 12% (w/w) along with super disintegrants like pregelatinized starch, sodium starch glycolate, crospovidone, and croscarmellose. First, sodium bicarbonate and tartaric acid were preheated at a temperature of 80°C to remove absorbed/residual moisture and thoroughly mixed in the motor. Finally, the blends are compressed in the punch. [27,28]

**APPROACHES FOR TASTE MASKING:**

There are various drugs which do not taste good. Since Orodispersible tablets dissolve in mouth, so proper taste-masking is very much essential, especially in the case of bitter taste drugs, e.g., metronidazole.[29] Various approaches have been explored in order to mask the bitter or any other bad taste of the drugs which include addition of sweeteners and flavours or encapsulating the unpleasant drugs into the microparticles or by the adjustment of pH.[15] In masking the bitter taste of metronidazole, Mohire *et al*,[29] used three approaches as addition of sweetener like sodium saccharin, formation of complex and finally by numbness of the tongue. A complex was prepared by triturating drug and *Glycyrrhiza glabra* extract in a ratio of 1:3 in the presence of a solvent, and numbness of tongue is carried out by adding eugenol to the drug and disintegrating mixture. They found good results in the case of the complex formation of drug with *G. glabra*. However, the most popular and general approach is the addition of sweeteners and flavours. Highly water soluble and quickly dissolvable sugar-based excipients are mannitol, aspartame, and citric acid. Flavours are mint, orange, peppermint, and strawberry.[29] Encapsulation or coating of drugs is another method where the bad taste can be masked]. [30,31]

**EXCIPIENTS USED IN ODT's PREPARATION:**

Excipients used in ODTs contain at least one superdisintegrant, diluents, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings [32]

**SUPER DISINTEGRANTS**:

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrates i.e., Superdisintegrant which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. This superdisntegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

**BULKING MATERIALS:**

Bulking materials are significant in the formulation of fast-dissolving tablets. The material contributes functions of a diluents, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolysate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

**LUBRICANTS:**

Though not essential excipients can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

**TASTE MASKING:**

The materials for taste-masking purpose have often been classified depending upon the basic taste. Flavouring and perfuming agents can be obtained from either natural or synthetic sources. • Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices, and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups, or spirit. Apart from these conventional materials, many compositions have been found to show effective taste-masking abilities with improved flavour such as alkaline earth oxide, alkaline earth hydroxide, or an alkaline hydroxide. Another composition includes phosphorylated amino acid such as phosphotyrosine, phosphoserine, and phosphothreonine

and mixtures thereof. Anethole effectively masked bitter taste as well as the aftertaste of zinc, which is used in treating the common cold. Clove oil and calcium carbonate, which has been found to be particularly useful to mask the unpalatable active in formulations which are intended to be chewed or dissolve in mouth prior to ingestion in solution. [33]

**EMULSIFYING AGENT**:

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast dissolving tablet formulation, including alkyl sulphates, propylene glycol esters, lecithin, sucrose esters and others.These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition [34]

**EVALUATION OF ORO DISPERSIBLE TABLETS:**

The mixture of powder was evaluated for bulk density, tapped density, Car's index, Hausner's ratio and angle of repose. The tablets were evaluated for thickness, hardness, friability, weight variation test, drug content and release rate In-Vitro studies. (35)

1. **General Appearance**: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, Taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. **Size and Shape**: The size and shape of the tablet can be dimensionally described, monitored and controlled.

3. **Tablet thickness**: Tablet thickness can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier Callipers [38].

4. **Weight variation**: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

5. **Hardness**: The fracture strength, which is defined as the force required to breaking a tablet by radial compression is measured with a tablet hardness tester (Monsanto hardness tester). It is expressed in kg/cm2.[36]

6. **Friability**: The friability of sample of six tablets is measured using a Roche Friabilator. This device subject the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm

and dropping the tablets at a height of 6 inches in each revolution. Six pre-weight tablets are rotated at 25 rpm for 4 minutes. The tablets are then reweighed after removal of fines using 60 mesh screens and the percentage of weight loss is calculated [37]. % Friability = (Loss in weight /Initial weight) ×100

7. **Wetting time**: Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured. [38]

**8. Disintegration Time**: The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds 28. Modified Disintegration Test: The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a Petridis (10 diameter) was filled with 10 ml of water. The tablet was carefully put in the centre of petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

**9. In-Vitro Dispersion Time Test**: To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined. [40]

**10. Dissolution test**: The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used. [41]

**11. In vivo clinical studies**: In vivo studies show the actual action of ODT in the oral-oesophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The investigation using gamma scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage form is rapid. The oesophageal transit time and stomach emptying time are comparable to those of traditional dosage forms i.e., tablets, capsules, or liquid forms. [42]

**12. Disintegration in oral cavity**: The time required for complete disintegration of tablets in mouth is obtained from six healthy volunteers, who have given tablets from optimum formulation.

13. **Accelerated stability study**: The Orally disintegrating tablets are packed in suitable packaging and stored under the following condition for a period as prescribed by ICH guideline for accelerated studies.

**A.** 40 ± 10C

**A.** 50 ± 10C

**B.** 37 ± 10C and Relative Humidity = 75%± 5%

The tablets are withdrawn after a period of 15days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegration, and Dissolution etc.) and drug content. The data obtained is fitted into first order equation to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the self-life at 25 $^0$C. **(43)**

**CONCLUSION:**

Orodispersible tablets have potential advantages over conventional solid dosage form. This drug delivery is one of the great inventions of all the novel drug-delivery systems. They have improved patient compliance, convenience, bioavailability, and rapid onset of action. However, common people are not much aware of this delivery system. Therefore, pharmacists are responsible to spread the knowledge regarding this system. It is the duty of the pharmacist to counsel the patients regarding its use, advantages, storage and maintenance. This dosage form should be handled carefully since they do not have sufficient mechanical strength. Patients who suffer from dryness of mouth should not be prescribed Orodispersible tablets, since minimum volume of saliva is necessary for it to disintegrate/dissolution. This dosage form is very much suitable for children having no primary teeth and for geriatric patients who have lost their teeth permanently. Thus, in near future, it is expected that this delivery system will get much importance as that of conventional delivery.

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