FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLET (ODT) OF CINNARIZINE
BY DIRECT COMPRESSION METHOD: A REVIEW

Avinash.K.Dhadve¹, Chander.P.Rathod²
¹Department of pharmaceutics, Nanded Pharmacy College Nanded, Maharashtra, India.
²Department of pharmaceutical chemistry, Nanded Pharmacy College Nanded, Maharashtra, India.

ARTICLE INFO

Article history
Received 14/10/2013
Available online
07/11/2013

Keywords
Oro-dispersible tablet;
Direct compression,
Cinnarizine;
Indion 414,
Polyplasdone XL,
Ac-di-sol, Primojel,
Motion sickness.

ABSTRACT

In a society in which people are living longer, drug dosage forms that can improve elderly patient compliance are needed. Many elderly patients having difficulty in swallowing tablets or capsules. In order to solve this problem, the development of solid dosage form that disintegrates rapidly or dissolves even when taken orally without water are being formulated anywhere, anytime lead to their suitability to geriatric and pediatric patients. Oro-dispersible tablet is a tablet to be placed in mouth where it disappears rapidly before swallowing. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. Cinnarizine is widely used in the treatment of motion sickness, vomiting, coughing during common cold, allergic conditions and bronchitis and vertigo. Finally it can be observed that the orodispersible tablet is ideal for elderly patients and patients consuming tablet in supine position without intake of liquid. This formulation has high patient compliance and should be tried with other drug candidates.

Please cite this article in press as Avinash. K. Dhadwe et.al. Formulation and evaluation of orodispersible tablet (ODT) of cinnarizine by direct compression method: a review. Indo American Journal of Pharm Research.2013:3(10).

Copy right © 2013 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
INTRODUCTION:
Orodispersible Drug Delivery System, as a novel dosage form, is different from the more traditional dosage forms. As the tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this, scientists have developed innovative drug delivery systems known as mouth dissolve tablets.

Objective of the study:
Orodispersible Drug Delivery System is a Novel Drug Delivery System aims to improve safety and efficacy of drug molecule as well as to achieve better patient compliance. Its significance can be shown as Administration without water, accuracy of dosage, ease palatability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and quick onset of action. Thus, with these tablets, disintegration time is greatly reduced and is rapidly dispersed or dissolved releasing the drug instantaneously. The drug may be absorbed from the mouth as the saliva passes down into the stomach. In these cases, rapid onset of action can be produced which may be beneficial in acute conditions of vomiting due to motion sickness, allergies. Also, drug loss by first pass metabolism can be greatly reduced. Due to such wide significance, Orodispersible drug delivery system, may lead to better patient compliance and good clinical output.

Cinnarizine is a H1 receptor antagonist widely used in the treatment of motion sickness, vomiting and vertigo. Cinnarizine is available in market in the form of immediate release tablets which is sold by various manufacturers under different brand names such as Stugeron, Cinzine, Verto, Cinar, Diznil, Syzeron etc. These forms, owing to the simplicity of use, are ideally suited for treatment of ambulatory patient. However, especially geriatric and paediatric patients experience difficulties of deglutition of tablets even together with intake of liquid.

Orodispersible tablets are also known as fast melt, fast dissolving, fast disintegrating, rapid-dissolve, or orally dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, for the patient compliance, rapid onset of action, increased bioavailability.

Although increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract. The proper choice of disintegrants and its consistency of performance are of critical importance to the formulation and development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth.

Salient Features of Orodispersible Drug Delivery System:
- Ease of administration for patient to swallow a tablet, such as pediatric and geriatric patient and psychiatric patients.
- Convenience of administration and accurate dose as compared to liquids.
- No need of water to swallow the dosage form, which is highly suitable feature for patients who are travelling and do not have immediate access to water.
- Good mouth feel property of ODDS helps to change the basic view of medication as bitter pill mainly for pediatric patients.
- Rapid drug therapy intervention is possible.
- The rapid the drug dissolution, quicker the absorption, which may produce rapid onset of action and ultimate clinical output.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is increased.
- Ability to provide advantage of liquid medications in the form of solid preparation.

Ideal drug Candidate for Orodispersible Tablets (ODTs):
The ideal characteristics of a drug for In-vivo dissolution from an ODT include –
- No bitter taste
- Dose lower than 30mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into epithelium of upper GIT(log p>1, or preferably>2)
- Ability to permeate oral mucosal tissue.

Drugs which are not suitable for ODTs:
- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
• Required controlled or sustained release.

Mechanism of action of Superdisintegrant:
Superdisintegrant is a substance or mixture of substances added to tablets to facilitate its break up or disintegration. The active constituents must be released from the tablet as efficiently as possible to allow its rapid action. The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on Capillary action, Swelling, Heat of wetting, Release of gases, Enzymatic reaction, Disintegrating particles/Particle repulsive forces, Deformation.

By Capillary Action:
Disintegration of tablet by capillary action is always the first step. When we put the tablet into suitable aqueous medium then it penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug or excipients.

By Swelling:
The most widely accepted general mechanism of action for tablet disintegration is swelling tablets with high porosity show poor disintegration time due to lack of adequate swelling force. On the other hand, satisfactory swelling force is exerted in the tablet with low porosity. It is useful to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again decreases.

Because of Heat of Wetting (Air Expansion):
When disintegrants with exothermic properties gets wetted, local stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation is limited to only some types of disintegrants.

Due to Release of Gases:
Carbon dioxide released within tablets on wetting is due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The generation of pressure causes disintegration of tablet. This effervescent mixture is used when pharmacist needs to formulate fast disintegrating tablet. As these disintegrants are very sensitive to small changes in humidity level, temperature and control of environment is required during formulation of the tablets. The effervescent blend is also added immediately before compression or can be added into two separate fraction of formulation.

By Enzymatic Reaction:
Enzymes present in the body also act as disintegrants which destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction, it causes tablet to rupture or the accelerated absorption of water leading to an increase in the volume of granules helps for disintegration.

Due to Disintegrating Particle/ Particle Repulsive Forces:
Another mechanism of disintegration explains the swelling of tablet made with non - swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Due to Deformation:
Hess had proved that during tablet compression, disintegrated particles get collapsed and get into their normal structure when they come in contact with aqueous media. Sometimes, the swelling capacity of starch was improved when granules were extensively deformed during direct compression. This increase in size of the collapsed particles produces a breakup of the tablet. This may be a mechanism of starch. (7,9)

Common methods for Addition of Superdisintegrants:
Superdisintegrants are added in tablet granulation to prepare compressed tablet to break or disintegrate when placed in aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:
I. Internal Addition (Intragranular)
II. External Addition (Extragranular)
III. Partly Internal and External

Selection of Superdisintegrants:
General characteristics for selection of Superdisintegrants:
• It should produce quick disintegration when tablet dissolves in saliva.
• It should be compatible to produce less-friable tablets.
• It should be able to produce good mouth feel to the patient.
• It should have good flow to improve the flowability of the total blend. (10)
Factors influencing Action of Superdisintegrants:
1. Percentage of disintegrants present in the tablets
2. Types of substances present in the tablets
3. Combination of disintegrants
4. Presence of surfactants
5. Hardness of the tablets
6. Nature of Drug substances
7. Mixing and Screening

Technologies of preparation of ODTs:
There are several techniques to manufacture these tablets namely freeze drying, moulding and compressing wet powders to construct high porous structure. Table 1.1 shows different patented products manufactured by these technologies. But direct compression is the most convenient and economical way to produce tablet with sufficient structural integrity. Following technologies are commonly used to prepare ODT:
- Freeze-drying
- Moulding
- Direct compression
- Ziplets technology

**Freeze-drying:**
In freeze-drying, drug is physically entrapped in a water soluble matrix, which is freeze-dried to produce a tablet that dissolve rapidly in less than 5 sec when placed in mouth. Lyophilized tablets show a very porous structure which causes quick penetration of saliva in the pores when placed in oral cavity.

**Moulding:**
Moulding is done by two methods compression moulding and heat moulding. Compression moulding tablets are prepared by compressing a powdered mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass. In heat moulding the drug is dissolved or dispersed in a molten matrix. No-vacuum lyophilization is a new technique in which evaporation of solvent from a drug solution or suspension is done at standard pressure. Tablets produced by moulding are solid dispersions, having advantage of very rapid dissolution (5 to 15 sec) and can load high dose. The major disadvantages are high cost of production, weak mechanical strength and possible limitation in stability.

**Direct compression:**
Direct compression is the easiest way to manufacture tablet in low manufacturing cost. It uses conventional equipment, commonly available excipients, high dose accommodation, and limited number of process steps. This article mainly covers the excipients required to produce orodispersible tablet by direct compression method. The disintegration time is in general satisfactory, although the disintegration efficacy is strongly affected by tablet size and hardness. Breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus all result from insufficient physical strength.

**Ziplets technology:**
Recently Eurand (Pessano con Bornago, Italy) developed the Ziplets technology, which can be used with water insoluble compounds as both bulk actives and as coated micro particles (the latter containing soluble and/or insoluble drugs). Coated granules are easy alternatives for laboratory purpose. It was found that the addition of a suitable amount of water-insoluble organic excipients combined with one or more effective disintegrants imparted an excellent physical resistance to the ODT, and simultaneously maintained optimal disintegration, even at low compression forces and tablet hardnesses. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in a much longer disintegration time. As the soluble components dissolve on the tablet’s outer layer, the rate of the water diffusion into the tablet core decreases because of the formation of concentrated viscous solutions. Other methods used to prepare ODT are Cotton Candy Method (Fuisz Technology), Mass-Extrusion, Spray Drying, Lyophilization etc. Table 1.2 shows different marketed ODT products in India.
Motion sickness is a very common disturbance of the inner ear that is caused by repeated motion such as from the swell of the sea, the movement of a car, the motion of a plane in turbulent air, etc. In the inner ear (which is also called the labyrinth), motion sickness affects the sense of balance and equilibrium and hence, the sense of spatial orientation.

Motion sickness is the uncomfortable dizziness, nausea, and vomiting that people experience when their sense of balance and equilibrium is disturbed by constant motion. Riding in car, aboard a ship or boat, or riding on a swing all cause stimulation of the vestibular system and visual stimulation that often leads to discomfort. The precise etiology of motion remains a mystery. The classic “sensory conflict” explanation posed by Reason and Brand and supported by subsequent studies, suggest motion sickness is triggered when the brain interprets sensory messages regarding movement as inharmonious. Motion sickness is not a disorder. It is a normal response to an abnormal stimulus. All types of motion sickness are due to the same basic problem: a disagreement between what you see and what the body is programmed to believe.

This is the same sort of sensory disturbance that might result from eating toxic or spoiled foods. The body is programmed in this case to get rid of the food as fast as possible. This is why motion sickness causes vomiting. About 33% of people are susceptible to motion sickness even in mild circumstances such as being on a boat in calm water, although nearly 66% of people are susceptible in more severe conditions. Approximately 50% of the astronauts in the U.S. space program have suffered from space sickness. Individuals and animals without a functional vestibular system are immune to motion sickness.
Antihistamines are most widely used in allergic rhinitis, anaphylaxis, asthma, conjunctivitis, coughs and cold, and various allergic conditions (allergic rhinitis, pruriitis, urticaria, nausea, vomiting) and these are often chosen for initial therapy. Antihistamines should be given, prophylactically. In the anticipation of a reaction, to achieve maximum response, it should be taken regularly by sensitive patients.

H₄-antagonists defined as those drugs that competitively inhibit the action of histamine on tissues containing H₄-receptors. They also display an array of other pharmacologic activities that contribute towards therapeutic application and adverse reactions. Many of the first generation agents function as antagonist at muscarinic receptors and to lesser extent, adrenergic, serotoninergic and dopamine receptors.

The drugs readily available for motion sickness are Dimenhydrinate, Cinnarizine, Meclizine, Scopolamine etc. Sedating anti-histamine medications such as Promethazine work quite well for motion sickness, although they can cause significant drowsiness.

Cinnarizine, chemically 1-[(di (phenyl) methyl]-4-(3-phenylprop-2-enyl) piperazine is an anti-histaminic drug which is mainly used for the control of vomiting due to motion sickness and vertigo. It is the most effective drug for management of motion sickness which is selective calcium antagonist inhibiting the influx of calcium intracellularly. Its acceptable taste makes that an ideal drug candidate for orodispersible tablet. Cinnarizine is having ‘melt-in-the-mouth’ texture rather than being bitter or chalky so it is the most suitable candidate for orodispersible tablet. Cinnarizine is available in the market in the form of Immediate Release Tablet under the various brand names such as Stugeron, Cinzine, Vergo, Cinaz, Diznil, Syzeron etc. As on date there is no orodispersible tablet of Cinnarizine available in the market therefore an attempt has been made to develop orodispersible tablet of Cinnarizine.

The present investigation was aimed to develop such a orodispersible dosage form for Cinnarizine by simple and cost effective direct compression technique. Indion 414, Polyplasdone XL, Ac-di-sol and Primojel were used as Superdisintegrants on account of their well established production technology by direct compression.

EVALUATIONS OF ODTs:
Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness
A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

Friability:
To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

The friability (f) was calculated by:

\[ f = 100 \times \left(1 - \frac{W}{W_0}\right) \]

Wetting time and water absorption ratio:
Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure.[29] Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (Wb).The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, R can be the determined according to the following equation. \[ R = 100 \times \frac{(W_a-W_b)}{W_b} \]

Moisture uptake studies:
Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 370°C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

www.iajpr.com
Disintegration test:
The time for disintegration of ODTs is generally <1min and actual the disintegration time that patients can experience ranges from 5 to 30s. 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 test for ODT should mimic disintegration in mouth with in salivary contents.

Dissolution test:
The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized.

To obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets.

CONCLUSION:
Orally disintegrating tablets have potential advantages over conventional dosage forms, with improved patient compliance, convenience, bioavailability and rapid onset of action. They are a very good alternative for drug delivery to geriatric and pediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in shelf stability of dosage forms and transform into liquid form within few seconds after its administration. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

ABBREVIATIONS: ODT- Orodispersible Tablet, ODDS- Orodispersible Drug Delivery System, USP- United States Pharmacopeia

REFERENCES: