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REVIEW ON VARIOUS FORMULATION STRATEGIES AND PATENTED TECHNOLOGIES OF ORAL DISINTEGRATING TABLETS

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Abstract

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The different dosage forms include tablets and capsules. The important drawback of these dosage forms for pediatric and geriatric patients is being difficulty in swallowing. Nearly 35% of the general population, especially the elderly patients and children suffer from dysphagia or difficulty in swallowing, which results in high incidence of ineffective therapy and non compliance. To overcome these problems, formulators have considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration, i.e., one, which disintegrates and dissolves rapidly (within 15 seconds) in saliva without the need for drinking water. This paper clearly describes various formulation strategies and also patented technologies of oral disintegrating tablets. This paper describes about the need for development of mouth dissolving tablets, and also lists out the various marketed products of oral disintegrating tablets.

Keywords

Mouth dissolving tablets, dysphagia, pediatric, geriatric, Zydis, quick dis, oroslov.

I. INTRODUCTION

Oral administration of drugs is the most convenient way of delivering the drugs. Almost 90% of the drugs available in the market are in the form of tablet. Tablets offer various advantages in both administration and production point of view. Compared to any other dosage form, tablets as well as capsule offer longer stability condition. (1)

Eventhough tablets and capsules offer various advantages, it also offer some drawbacks. One of those primary drawback is difficulty in swallowing or dysphagia, especially for children, elder people, mentally disabled person, coma patients etc. To overcome this drawback, various novel strategies have been adopted and also new dosage form have been developed. One among those dosage form is Oral Disintegration Tablet (2), which dissolve and disintegrate in mouth, within few seconds to minute of administration. Thus Oral disintegration tablets, dissolve rapidly in mouth, thus faster the absorption and ultimately rapid onset of action. Oral disintegrating tablets are otherwise referred to as mouth dissolving tablets, rapidly dissolving tablets, fast

dispersing tablets, quick disintegrating films, etc. This rapid disintegration can be achieved by means of superdisintegrants. These classes of tablets are intended to be taken as such without the need of water (3). These tablet when come in contact with saliva, gets broken down in small pieces and dissolved in saliva to form a semisolid mass (paste like consistency), which is then swallowed easily. (4)

Ideal properties of ODT

- It should possess sufficient strength to withstand the manufacturing process and do not fragile during subsequent handling
- Should not leave any residue in mouth and should give pleasant feel after administration (5)
- Should be adaptable to already existing machineries and conventional methods (6)
- Should be economic and cost effective
- It must disintegrate into the mouth within few seconds and require no water for administration . (7)

Advantages of ODT (8)

- ODT's are suitable for elderly patients and paediatrics who are not willing to swallow the tablets and also for the coma patients, mentally disabled person who are not able to swallow the tablets.
- Faster onset of action is achieved, as it disintegrates and dissolves within few seconds. (9)
- As some amount of drug get absorbed in the mouth, pharynx, and oesophagus, drug loss through first pass metabolism can be minimized. Ultimately bioavailability is increased.

II. NEED FOR THE DEVELOPMENT OF ODT (10)

Patient related factor (11)

Poor acceptance of already existing conventional drug delivery system payed the way for development of Non- invasive drug delivery system such as ODT

- ✓ It is mainly developed for pediatric and gediatric patients who were unable to swallow the tablets as such. (12)
- ✓ Woman undergoing radiation therapy for breast cancer not able to swallow H_2 blockers due to the nauseous effect of the radiation therapy.
- ✓ To overcome the risks associated with some conventional tablets such as choking, physical obstruction during oral intake of tablets. (13)
- ✓ Elder patients who are unable to take the daily dose of an antidepressant

Effectiveness factor (14)

Main reason for the development of ODT in effigacy point of view is due to improved bioavailability. The absorption may take place in buccal , pharyngeal or gastric region as drug gets dispersed in saliva. This will lead to by pass the hepatic metabolism. (15) The drug dose can be reduced, since the amount of drug that lost through first pass metabolism can be reduced ssignificantly.

Marketing factor (16)

It is crucial for the pharmaceutical industry to develop new drug delivery technologies to survive in their field. Pharmaceutical Manufacturers must develop new and improved dosage form for the drugs whose patent life is going to end. This will ultimately lead to unique product differentiation, extended market exclusivity, etc. (17)

III. FORMULATION TECHNIQUES:

Mass extrusion

This method utilizes mixture of solvents such as polyethylene glycol and methanol to form a softened mass. The active ingredients and other excipients are made softened using the above mentioned solvent mixture and extruded into cylindrical mass using extruder or syringe. Formed cylindrical mass is cut into tablets using previously heated blades. Thus tablets thus disintegrating in few seconds are formed using mass extrusion techniques. (18)

Spray drying (19)

Spray drying is employed to produce highly porous and fine powders. This method utilizes hydrolysed and non – hydrolysed gelatins (Supporting agents) , Sodium starch glycolate / Croscarmellose sodium as Disintegrants , mannitol as diluents. The disintegration behaviour is improved by using an acid or alkali material (20). Orally Disintegrating tablets prepared by this method shows disintegration time as 20 seconds.

Sublimation :

Volatile materials are compressed into tablets using any conventional methods. Compressed tablets are subjected to sublimation for removing volatile material to obtain extremely porous structure (21) .This porous structure is suitable for oral disintegrating form as water penetration is more rapid. Volatile materials employed in the formulation of ODT's are camphor, ammonium carbonate, ammonium bicarbonate, urea, menthol, thymol, fatty acid and adipic acid etc. The temperature employed for the sublimation of these volatile materials is 40 to 60 degree Celsius. ODT formulated using this sublimation technique shows disintegration time of 20 seconds. (22)

Moulding

Generally water soluble ingredients are employed for formulating molded tablets. The formulation procedure is same as that of procedure employed for manufacturing conventional tablets, except the fact that force employed for compressing ODT must be lower than the force employed for compressing conventional tablets. Thus less pressure is applied for formulating Orally disintegrating Tablets. This method is also called as Compression moulding. (23)

Generally molded tablets will posses low mechanical strength and my even tend to break during packaging and subsequent handling. If hardness enhancing agents are added, it will affect the disintegration time. Poor mechanical strength is the major drawback of this molding techniques.

Freeze drying:

Freeze drying or lyophilization is a technique defined as process of removal of water from the frozen product by sublimation. The active drug is dissolved in the polymeric solution and poured into the blister packs. This blister packs are allowed to pass through tunnel containing liquid nitrogen and allowed to freeze. The frozen blister packs are removed from the tunnel and kept in the refridgerator. This technique produces tablets with light weight and high porosity. In this method, water is sublimed after freezing. Since the equipment and processing steps are costly, this method is not widely used. And also another disadvantage of this method is that it produces product with less stability. (24)

Direct Compression

Direct compression is the cheapest and most employed technique for formulating ODT. It offers several advantages over other techniques. It can be formulated using commonly available excipients. It involves minimum processing steps and also found to be cost effective. (25)

The type and proportion of disintegrants added is the primary consideration in the formulation of MDT. The sugar based excipients are commonly used as diluents because of various advantages. Sugar based excipients are highly aqueous soluble and impart pleasant mouth feel. They are effective in taste masking due to their sweetness. Few examples of sugar based excipients are Maltose, dextrose, fructose, etc.

IV. CHALLENGES IN FORMULATION OF ODT

Mechanical Strength

Disintegration time depends on the mechanical strength of the tablet. If the mechanical strength of the tablets are more, the tablets will take more time to disintegrate. Not all the technologies produce tablet of high mechanical strength. Only few technologies such wowtab and durasolv produce tablet with sufficient mechanical strength.(26)

Taste masking

Since the tablet need to disintegrate and dissolve in mouth, it should have acceptable taste. Thus bitter drugs must need specialized coating and taste masking for formulating into ODT form. (27)

Mouth feel

ODT should not leave any particle our residue after disintegration. Mouth feel can be enhanced by adding coating agents such as menthol.

Aqueous solubility (28)

Water soluble drugs when incorporated in the formulation may tend to form eutetic mixture and may also lead to formation of glossy solid structure that may collapse during drying process. The collapse in the structure due to the formation of glassy structure can be prevented by incorporating various excipients such as mannitol to impart rigid structure.

Size of the tablet

The easiest size of the tablet for swallowing is considered as 7-8 mm, where as the easiest size for handling is greater than 8mm. Thus it is difficult for a manufacturer to formulate the tablet which is both easy to swallow and handle.

V. EVALUATION PARAMETER

Weight variation

20 tabeltes are weighed individually and average weight was calculated. The average weight was then compared to individual weight and weight variation was determined.

Friablility

The limit for friablility test as prescribed in the Pharmacoepias is not more than 1%, when performed at 25rpm for 4 minutes. It is often a great challenge for a manufacturer to maintain friablility within this limit since ODT should be formulated with minimum hardness suitable for achieving minimum disintegration time. This test is also not applicable for lyophilized tablets and suits only for the tablets produced by direct compression technique or moulding.

Moisture uptake study

Generally ODT contain high amount of hydrophilic excipients and may susceptible to moisture uptake. Thus it is necessary to perform moisture uptake study for ODT. Usually this study is performed in a desicator. Ten tablets are taken in a desicator along with CaCl2 and kept in the desicator for 24 hours. Make sure to ensure that all the tablets are completely dried. Then the tablets are weighed and exposed to Relative Humidity of 75% at room temperature for 2 weeks. Required amount of humidity can be attained with the help of saturated sodium chloride solution kept in the desicator.

After 2 weeks reweigh all the tablets and determine the percentage of increase in weight. Specialized manufacturing and packaging areas are required for the product with high moisture uptake. (29)

Wetting time.

The time required for complete wetting of tablets , when placed in an petridish containing water (water soluble dye) is said to be wetting time of the tablets. A tissue paper is cut into circular shape and fitted in petridish containing water soluble dye (0.5% eosin). A tablet was placed above the tissue paper and time required for the dye to wet the upper surface of the tablet was measured and it was considered as the wetting time of the tablets.

Water absorption study.

This study was conducted similar to that of wetting time study,instead water soluble dye water is used. A tissue paper was placed in petridish containing 6ml of water. Tablets was weighed and placed above the tissue paper. After the tablet was completely wet, remove it from the petridish and reweigh the tablets. Water absorption ratio was found by using the below mentioned formula

$$R = (Wa - Wb / Wb) \times 100$$

Where Wa and Wb are said to be weight of the tablet after and before absorption respectively. (30)

Tensile strength measurement.

Tensile strength is defined as force required to break the tablet when it is compressed in its radial direction. It is generally measured using hardness tester. Tensile strength measurement is not suitable for tablets prepared by lyophilization as it contains drug and excipients in its freeze dried state. The tablets prepared by moulding and direct compression are suitable for this test. Tensile strength should be low enough to ensure the minimal disintegration time of the tablets.

Disintegration test

Generally ODT disintegrates within a minute, i.e., 5 to 30 seconds. Disintegration test for ODT cannot be performed using standard procedure, which posses certain limitations. Thus modified method need to be followed for performing the disintegration test for ODT. This modified approach consist of a basket sinker in which the tablets need to be placed. The apparatus consist of 900 ml of water, maintained at 37^{o}C. The paddle was rotated at 100 rpm. The test was performed and the time required for complete disintegration of the tablets was determined. The tablets must disintegrate completely and must pass through the screen of sinker. (31)

Dissolution test.

It is identical to that of dissolution test those performed for conventional tablets. Dissolution media and other specification should be based on the individual monographs of the drug substance. The most common choice employed for the dissolution test of ODT is USP II dissolution apparatus (paddle type). (32) The paddle speed commonly used is 50 rpm and the commonly employed dissolution media is 0.1 M HCl and the buffer with pH 4.5 to 6.8

VI. MARKETED PRODUCTS

6.1 Some of the marketed formulations of ODT with their indications are mentioned below.

S.No	Brand name	Drug	Indications	Category
1.	Alavert	Loratidine	Runny nose, sneezing	Antihistamine
2.	Olanex instab	Olanzapine	Bipolar disorder, schizophrenia	Atypical antipsychotics
3.	Cibalginadue Fast	Ibuprofen	Muscular pain, headache, toothache etc	NSAID's
4.	Lonazep MD	Olanzapine	Bipolar disorder and Schizophrenia	Atypical antipsychotic
5.	Zontec MD	Cetrizine	Allergic conditions, hay fever, cold	Antihistamine
6.	Zofran MD	Ondansetron	Chemotherapy induced nausea and vomiting	serotonin 5-HT_3 receptor antagonists
7.	Zyprexia	Olanzapine	Schizophrenia	Antipsychotics
8.	Vomidon MD	Domeperidone	treatment of indigestion, nausea, and vomiting	Anti emetic and prokinetic
9.	Mosid MD	Mosapride	gastroesophageal reflux disease.	gastrointestinal agents,'
10	Kazolid MD	Nimusulide	headache, migraine, nerve pain, toothache	NSAID's
11	Ugesic	Piroxicam	osteoarthritis, rheumatoid arthritis), such as inflammation, swelling, stiffness, and joint pain.	NSAID's
12	Romilast	Monteleukast	treatment of asthma and allergic rhinitis	Anti asthmatic
13	Ondem MD	Ondansetron	Nausea and vomiting	

				serotonin 5-HT_3 receptor antagonist
14	Pepcid	Famotidine	Treatment of peptic ulcer and heart burn	H2 receptor antagonist
15	Nurofen	Ibuprofen	Muscular pain, headache, toothache etc	NSAID's
16	Niravam	Alprazolam	Anxiety and pain disorders	Benzodiazepines

VII. PATENTED TECHNOLOGIES

Zydis Technology

This technology utilizes lyophilization technique, in which the water is removed from the product by sublimation and subjected to freeze drying. The tablets are packed in blisters and sealed. The tablets produced by this technology are usually porous, light and disintegrate immediately. Drugs with low water solubility and high aqueous stability are ideal candidates for zydis technology. If highly water soluble ingredients are added in the formulation, collapse in the structure may occur. For that purpose collapse protectants such as glycerine is added. Mannitol is incorporated to impart crystanity and thus preventing the structure from collapsing. (33)

The major disadvantage of this technology is, poor stability of freeze dried product at high temperatures and relative humidity. It is also considerably expensive techniques.

Oroslov technology

This was developed by CIMA labs. The tablets produced by this technology mainly composed of 2 components, (i) active ingredient which is taste masked and (ii) effervescent disintegrants which on contact with saliva, releases CO_2 producing effervescence and ultimately releasing taste masked active ingredient . This technology utilizes direct compression technique, employing very low compression force and tablets thus produced are friable, requiring specialized packing. Taste masking is achieved by means of 2 things, one by coating the powder and another by effervescence.(34)

Duraslov technology

It is the second generation ODT formulation of CIMA Labs. Unlike Oroslov technology, tablets produced this technology possess high mechanical strength and usually produced by employing high compression force. The main components of these tablets are non- direct compressible diluents like mannitol, sorbital, dextrose, lactose etc., and lubricants. These non- direct compressible diluents dissolve very quickly and also free from gritty particles.(35) This technology is only suitable for drug with low dose. Since they are formulated by using high compression force, high drug doses are not suitable. The tablets are packed normally in a conventional blister package and tablets of this technology usually disintegrate within 60 seconds.(36)

Quick Dis technology

Quick Dis technology utilizes solvent casting method to form oral dissolving film. This film majorly consist of hydrocolloids such as HPMC, gelatin, starch, acacia etc. These hydrocolloids are dissolved in water to form viscous solution. All other excipients (emulsifying agent, wetting agent, buffering agent, preservative) along with API are dissolved in aqueous solvent. Then the resultant solution is added to the viscous solution of hydrocolloids and subjected to degassing process under vacuum. The degassed solution is coated over casting film and dried. This Quick Dis film takes only 5 to 10 seconds for disintegration. This film is placed in the tongue (floor of the tongue), where it release the active drug and produce either local or systemic action.(37)

Flash tab technology

Prographarm (France) invented flash tab technology. This technology utilizes the combination of both disintegrating agent and swelling agent, which aid in rapid disintegration dissolution. The excipients employed are usually of conventional excipients and manufacturing also involves conventional methods. All the excipients including disintegrants, swelling agents, etc., are first granulated and these granulated materials are compressed into tablets by incorporating active ingredients.(38) Active ingredients are incorporated at the final stage of manufacturing. Disintegrants employed in this technology are Croscarmallose, Crospovidone, Microcrystalline cellulose, etc.

Wow tab technology

Wow- tab technology was invented by Yamanouchi Pharma. The word wow stands for ‘ Without water ‘. The tablets usually composed of combination of both low and high mouldability saccharides and formulated by conventional method such as granulation followed by compression.(39)

The saccharides are of 2 types

(i) low mouldability saccharides which produces tablets of hardness (0-2 kg), which includes glucose, lactose, mannitol, etc.,

(ii) high mouldability saccharides which produces tablets of hardness greater than 2kg.

Here in this technology, the active ingredients are first mixed with low mouldability saccharides and granulated. The granulated materials is then compressed into tablets using high mouldability saccharides. The tablets thus produced disintegrates and dissolved within 15 seconds.

Lyoc technology (40)

Lyoc technology was introduced by Cephalon corporation. This was the first technology to use freeze drying techniques for manufacturing of ODT. The active ingredients are mixed along with fillers, thickeners, sweeteners etc., to form a liquid solution or suspension. The liquid solution is then sealed in blisters and allowed to freeze drying. There may be chances of inhomogenicity in the formulation which may occur due to sedimentation of particles. (41) To overcome this, mannitol is added in large quantities which ultimately increase the viscosity of the solution. This technology does not utilize preservatives in their formulation.

Advatab technology

Eurand Pharma invented and patented the advatab technology. This technology differs from other technologies of ODT in a way, that it incorporates the lubricant externally on to the tablet surface during manufacturing, thus producing durable tablets without using high compression force. Bitter tasted drugs are taste masked by micro encapsulation techniques. Thus bitter tasted drug which are not formulated using other technologies can be formulated with this technology. This technique uses the combination of both Diffucaps (controlled release technology) and Microcaps (taste masking technology) which produces tablets with smooth mouth feel and superior taste. Though the tablets produced by this technology are hard, it does not affect the disintegration of the tablets. (42)

VIII. CONCLUSION

Oral disintegrating tablets offer improved efficacy as well as biopharmaceutical properties and also possess better patient compliance as that of conventional tablets. Initially they are available in the market only for geriatric and pediatric use, mainly to overcome the difficulties facing while swallowing the tablets. But over the decade, the marketed formulations ODT are available for cold, allergy, etc. The reason behind this growth is availability of new patented technologies and also better market acceptance. (43)

Since it satisfies the patient demand, it is considered as the promising dosage formed as compared to that of conventional dosage form and also found to be more effective. In the field of developing pharmaceutical industry and also more novel excipients, we can expect more novel technologies and growth in the field of ODT in future. (44)

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