Review Article

A Review on: Orodispersible Tablet (ODT) Technology - A Novel Approach to Develop the Supergenerics

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ABSTRACT

Quality by Design (QbD) is modern comprehensive approach for developing the pharmaceutical drug products. While 'Super generics' emerges as economic strategy to develop the quality drug products at low cost. Though there is enormous amelioration in drug delivery, the oral route remains elite route for administration of therapeutic agents. Orodispersible Tablet (ODT) Technology is gaining more limelight due to reliable demand & accelerated product pipelines expansion. The highlighting trait of ODTs is economy and patient acceptance. The present article reviews all the aspects of ODTs which are necessary to develop the drug products as Super generics. The future prospective of ODTs in reference to QbD is also provided to bank the researchers & manufacturers towards ODTs.

Keywords: Critical Quality Attributes (CQA), Multifunctional Excipients, Orodispersible Tablets (ODT), Quality by Design (QbD), Super generics.

INTRODUCTION

According to the Joseph Juran, there are two definitions of Quality, the outcomes from his first definition is; "Product feature must meet the customers' demands", while the second definition is, "Product must be free from deficiencies". Both two definition of Joseph Juran has major impact on cost of the product.[1] International Conference on Harmonization (ICH) developed the Q8 R2 guideline for pharmaceutical development using risk based approach i.e. Quality by Design (QbD).[2] From January 2013, Food and Drug Administration demanding that generic manufactures must implement the QbD paradigm into their Abbreviated New Drug Application (ANDA), Module 3 Quality 3.2.P.2 Pharmaceutical Development.[3]

Today, many companies are engaged in doing research on developing the quality products at lower cost and due to this the term 'Super generics' is rise in pharmaceutical business models. Super generics are the developed patent expired drug products in terms of product delivery, design, application and efficient manufacturing process. It is possible to develop the Super generics inside the context of QbD.[4]

The most preferred route & dosage form for manufacturing the drug is oral route and tablet dosage form respectively. Dysphasia is remains the major dilemma for tablet dosage forms, hence to conquer this problem the Orodispersible Tablet Technology comes as a ray of hope.[5] Though the products manufactured using ODT form 1980s, in recent years the major pharma players are focusing on this technology due to its reliable demand & accelerated product pipelines expansion.[6] According to the United States Food and Drug Administration, "a solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of second, when place upon the tongue is known as orally disintegrating tablets".[7] While European Pharmacopoeia has used the term orodispersible tablets (ODT), which are the uncoated tablets, intended to be placed in the mouth where they disperse readily within 3 min before swallowing.[8] The ideal properties, drug selection criterion, advantages and disadvantages of the orodispersible tablets are described in Table 1.

Potential Formulation Challenges & Remedies for ODT's

Taste

The taste of drug isn't directly linked to safety and efficacy. But it has immense impact on patient acceptability. Hence, it is considered as Critical Quality Attribute (CQA) for those drugs having bitter or obnoxious taste. In order to achieve improved patient acceptability taste masking of drug should be carried out. Shaila Lewis *et al.* reviewed various techniques of taste masking, which develops drugs suitable to formulate as ODTs.[9, 10]

Disintegration Time

It is acknowledge as potential CQA for ODTs. A convenient arrangement of compression force setting is quick fix for achieving good mechanical strength with shorter disintegration time.[10]

Environmental Condition

Moisture, Temperature and Light become a CQA for ODTs containing deliquescent drugs or drugs whose degradation process gets accelerated due to moisture, temperature and light. A use of multifunctional excipients like COMPACTROL® is useful for providing stability to moisture sensitive drugs. The temperature conditions can be maintained during manufacturing, while supportive

packaging design also helps to overcome the stability problems due to environmental conditions.[9, 11]

Cost

It's one of the important credential for ODTs, due to which it has potential in super generic development. The cost reduction is possible for ODTs in areas like material, taste masking, processing and in packaging. Use of Multifunctional excipients, efficient process design, use of multifunctional instruments can leads in cost saving.[4, 9]

Multifunctional Excipients for ODT's

These are the class of excipients which provides additional functionalities in terms of flow ability, compressibility, particle size distribution, shape, porosity etc. Some products that have multiple roles in formulation also recognized as multifunctional excipients.[12] The examples of multifunctional excipients suitable for ODTs are illustrated in Table 2.

Technologies for Formulation of ODT's

There are many conventional technologies like Lyophilization, Spray drying, Molding, Sublimation, Direct Compression, Mass extrusion, Melt granulation, Wet granulation, Dry granulation, Phase transition process, Sintering, Disintegrant addition.[13] The conventional technologies which having the potential to develop super generics are described as follows:

Direct Compression

The most astonishing trait of direct compression is its simplicity and hence economy. A tablet produced through direct compression disintegrates into their primary particles rather than granular aggregates. The resultant increase in surface area available for dissolution should result in faster drug release.[14] A wide range of excipients including multifunctional excipients are available for direct compression.[12]

Disintegrant Addition

It is one of the accessible techniques for formulating an ODT due to its easy implementation and low cost. A selection of proper concentration of single superdisintegrant or blend of superdisintegrant is important. Mohanachandran PS *et al.* reviewed various superdisintegrants that can be used in ODT formulations.[9]

Patented Technologies for Formulation of ODT's

The Zydis (Catalent Pharma Solutions, Somerset, NJ) Lyophilization technology provided the early approved ODT in the United States in 1996. Due to this there is rise of various patented technologies for ODTs.[15] The patented technologies for ODTs are presented in Table 3.

Evaluation Parameters for ODT's

Despite of copious techniques had been developed for ODTs, but apart from European Pharmacopoeia (EP), no standardization techniques had been described in other pharmacopoeias for evaluation of ODTs.

Weight Variation Test

This test is carried out as per Indian pharmacopoeia using 20 tablets and electronic weighing balance.[9]

Tablet Tensile Strength

It is the force measured using tablet hardness tester, which is required to break the tablet by compressing it in radial direction. It is calculated as:

$$T=2F/\pi dt$$

Where, T is Tensile Strength, F is crushing load, d is diameter of tablet & t is thickness of tablet. The measurement of tablet tensile strength is relevant for ODTs formulated by direct compression or molding methods but not useful for evaluation of those formulated using techniques like lyophilization and flashdose.[16, 17]

Table 1: Ideal Properties, Convenient Drug Candidates, Inadmissible Drug Candidates, Promising Advantages and Disadvantages of Orodispersible Tablets.[9, 13, 25-26]

Parameter	Description
Ideal Properties	➢ Cost effective manufacturing is possible. ➢ Heightened Patient Acceptability. ➢ Enables conceivable high drug loading. ➢ Raised overall bioavailability. ➢ Exhibit flat sensitivity to environmental conditions like moisture and temperature.
Convenient Drug Candidates	➢ Acceptable taste profile, stability in saliva and water and good permeation property. ➢ Low drug dose & small to moderate molecular weight.
Inadmissible Drug Candidates	➢ Possible to achieve taste masking ➢ Short half life and frequent dosing. ➢ Demanding modified release
Promising Advantages	➢ Wide patient acceptance. ➢ Accurate dosing, Rapid onset of action and with enhanced bioavailability. ➢ Low production cost. ➢ Ability to raise market capturing opportunities due to product differentiation, product promotion, brand extension.
Disadvantages	➢ Moisture and Photosensitivity of certain drugs is main hurdle during manufacturing. ➢ Low drug dose requirements. ➢ Packaging requirements.

Thickness

It is relevant parameter in reproducing appearance and also in counting by using filling equipment. The thickness of ODTs is measured using vernier caliper.[9]

Friability

It is considerable challenge for manufacturer in order keep friability within 1% but at the same time it should

meet the requirements of tablet mechanical strength and disintegration time limit. Like tablet tensile strength, the friability test is used for evaluating ODTs prepared using direct compression or molding but not for lyophilization and flash dose techniques.[18]

Disintegration time

The determination of disintegration time is appears to be method dependent in case of ODTs. As per EP, the disintegration time for ODTs is measured using the conventional disintegration test apparatus. The time limit as per EP for ODTs is 3 minutes. To overcome the issues with the conventional disintegration test, many researchers modified the disintegration test for ODTs. Bi Y *et al*. recommended use of modified dissolution apparatus. Motohiro *et al*. used the wire cloth to perform the disintegration test. Fu *et al*. carried out disintegration test on shaking water bath. Morita *et al*. developed the disintegration apparatus which is equipped with charge coupled device (CCD) camera. Narazaki *et al*. carried out disintegration test with rotary shaft method. Bose Corporation designed an instrument 'ElectroForce®3100' with an objective to simulate disintegration condition of in mouth. el-Arini SK *et al*. used texture analysis apparatus to measure the disintegration time.[18]

Table 2: Multifunctional Excipients that are extensively for ODTs.[11-12, 24]

Multi functional Excipient	Property
Galen IQ	Filler, Binder, Sweetener, Granulating Agent.
PEARLITOL® Flash	Filler, Sweetener (*No Superdisintegrant is needed)
MCC SANAQ® burst	Filler, Binder and Superdisintegrant
Kollidon® CL SF	Superdisintegrant and Solubilizer
StarLac®	Diluent and Superdisintegrant
F-MELT®	Diluent and Superdisintegrant
Parteck® ODT	Diluent and useful in taste masking
COMPACTROL®	Filler and Stabilizer
PanExcea™ MHC300G	Filler, Binder and Disintegrant

Table 3: Patented Technologies for ODTs and their marketed preparations[9, 25, 27]

Technology and its inventor	Key features
Zydis® Technology- R.P.Scherer	- Most successful technology on the market with more than 20 marketed products. - Tablet disintegrates within 10 seconds. Shelf life of 2-3 years. - Robust, can withstand transport and handling Basic formulation components are: matrix former, structure former, structure promoter, sweetener, flavors, colors and pH modifiers. - Marketed Preparations: Grazax®ODT, Maxalt® MLT, Xilopar® 1.25, Zofran® Zydis, Claritin®Reditabs® Pepcid®RPD etc.
Lyopan® Fast Dissolve Technology- University Basel and Pantec, a Swiss company linked to Rohrer	- Process involves dosing powder into blisters and then adding a small amount of water, prior to freezing to bind the unit together. It is then frozen and dried like Zydis® Fast Dissolve Tablets. - Tablet disintegrates within 10 seconds. - Increased option for taste masking. - Enables formulation of molecules at higher dose (>200mg).
Flashdose® Technology- Dr. Richard Fuisz Fuisz Technologies	- Floss-like crystalline structure, much like cotton candy, disintegrates within 1 min. - Flashdose tablets of powder or coated mini particles disperse rapidly, can accommodate high active doses, and possess satisfactory mechanical strength. - Marketed Preparation: Ralivia™ Flashdose®
WOWTAB®- Yamanouchi Pharma Technologies, Inc.	- Products can be taken without water. Combination of low-mouldability and high mouldability saccharides. - Marketed Preparations: Gaster D, Benadryl Allergy & Sinus Fastmelt (OTC)
OraSolv®- CIMA Labs	-Exclusive two fold taste masking. -Tablet disintegrates within minute. -Marketed Preparations: Remeron SolTab, Tempra® First Tab, and Triaminic SoftChew.
DuraSolv®- CIMA Labs	-Mechanically better than OraSolv. -Disintegration time is 5-45 seconds. -Unseemly with larger doses. -Marketed Preparations: NuLev and Zomig® ZMT.
FlashTab®- Ethypharm	-Drug in nanocrystal form is compressed using Conventional Tableting Method. -Marketed Preparation: Neurofen Flash Tab.
OraQuick Technology- KV Pharmaceutical Co., Inc.	-Use of patented MircoMask technique in formulation. -Suitable for thermolabile drugs. -Marketed Preparation: Hyoscyamine Sulphate ODT
QuickSolv- Janseen	-Freeze dried tablets, disintegrates within 10 seconds. -Marketed Preparation: Propulsid QuickSolv®, Risperdal Quicklet™.
AdvaTab- Eurand	- Effective taste masking. -Microcap and Diffuscap CR technology. -Tablets disintegrates within 30 seconds -Marketed Preparation: AdvaTab Cetrizine®.
Lyoc®- Framalyoc	- Freeze dried wafer, disintegrates within 10 seconds. -Absence of preservatives. -Marketed Preparation: Spansfon Lyoc®

Fineness of Dispersion

This test is to estimate the grittiness arise due to disintegration/dispersion of ODTs in coarse particles. This qualitative test is indicated in EP. This test is performed by placing 2 tablets in 100ml water and stir until tablet is completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 mm.[18]

Wetting Time and Water Absorption Ratio

Bi Y *et al*. studied wetting time and water absorption ratio by using a piece of double folded tissue paper placed in a Petri plate containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined by calculation as:

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

Where, Wa is the weight of tablet after water absorption and Wb is the weight of tablet before water absorption.[19]

Effectiveness of Taste Masking

The sensation of taste is a subjective property and thus as far as patient acceptability is concern, taste and mouth-feel are major quality attributes. The evaluation of effectiveness of taste masking is carried out using both *in-vitro* and *in-vivo* methods.

In-vitro method for evaluation of effectiveness of taste masking

Shukla D *et al*. developed an *in-vitro* method for evaluation of taste masked resinate of Risperidone and its orally disintegrating tablets.[20] "E-tongue" technology is favored now days for evaluation of taste masking. Alpha MOS an analytical instrument company developed this E-tongue technology. In similar to the human tongue, E-tongue not only assesses basic tastes like bitter, sweet, sour, salty and umami but also all other gustatory components like metallic, pungent, astringent, etc.[21]

In-vivo method for evaluation of effectiveness of taste masking

It is most favored method for evaluating taste masking. The *in-vivo* taste assessment consists of a double blind crossover study, carried out on a trained taste panel of healthy volunteers with sound organoleptic senses. Hughes L, discusses ways to evaluate the effectiveness of taste-masking in the development of pharmaceutical products.[22]

Moisture Uptake Study

In order to achieve faster disintegration, hydrophilic excipients are favored. Most of the hydrophilic excipients are susceptible to moisture uptake, upon moisture absorption the tablet integrity, surface texture gets affected. Hence moisture uptake study is strongly favored as evaluation parameter for ODTs. Avani Amin *et al*. shaded light on moisture uptake study for ODTs.[18]

In-vitro drug release

The current process of dissolution could be extended to *in-vitro* evaluation of ODTs. The dissolution conditions for reference listed drugs available in United States Pharmacopoeia (USP) can be applied for in-vitro studies to correlate drug release in *in-vivo* conditions. 0.1N HCl, pH 4.5 and pH6.8 phosphate buffers should be used as dissolution medium. To carry out dissolution testing, the USP-apparatus II (paddle) with paddle rotation speed of 50 rpm is suitable. For ODTs which disintegrate into particles having floating tendency, the USP-apparatus I (basket) with basket rotation speed of 100 rpm may seem some application.[18]

Packaging of ODT'S

The packaging is considered as the last step of manufacturing and first step of marketing. The choice of packaging material for ODTs is imperative part from manufacturers point. The packaging of ODTs should be carrying out in such way that it protects the physical integrity of ODTs and also it should create differentiation from other dosage form. The packaging is easiest way which creates product differentiation and patients' acceptance. The critical factors considered during packaging are the environmental conditions and hardness of ODTs. The peelable closure is of choice for fragile ODTs, but blister packing is also favored. The packaging integrity test should be performed for final dosage form.[23]

Regulatory Status for ODT'S

Despite of having three regulatory pathways for drug approval in US, most of the ODTs are approved through 505 (b) (2) pathways. A 505(b) (2) is a new drug application (NDA) which contains full safety and effectiveness reports, but allows at least some of the information required for approval to come from studies not conducted by or for applicant. This method gains approval for new drugs in a fraction of the time and cost required by traditional paths. The 505(b) (2) is the approval pathway for products developed through 'supergenerics'[4].

Target Quality Attributes for Orodispersible Tablets

As a part of QbD, a manufacturer has to identify potential critical quality attributes (CQA) of drug product. Target quality attributes for ODTs and their justification are given below;[15, 24]

Appearance

Color and shape should be acceptable by patient and absence of visual defects should be the target for ODTs. Color and shape are not directly linked with safety and efficacy, but it has impact on patient acceptability. Thus formulator target is to ensure patient acceptability.[25]

Odour

Similar to appearance, a noticeable odour is not directly linked to safety and efficacy, but odour can affect patient acceptability. The formulator should select those excipients having no odour or having pleasant flavour, no use of organic solvents during manufacturing process.

Taste

The taste profile should be appropriate for target patient population. Minimum intensity and duration of basic tastes and gustatory components with absence of gritty consistency is desirable.

Tablet Weight

The weight limits for ODTs is <500mg (finished product) and manufacturer should follow the guidelines recommended by FDA.

Hardness

It is the potential CQA for ODTs. Hardness has an impact on disintegration, and friability. This CQA should be investigated during manufacturing and hardness level should be targeted in such a way that it provides good mechanical strength and shorten disintegration time.

Disintegration Time

It is potential CQA for ODTs. The disintegration time is achieved in such a way that ODT disintegrate/disperse within seconds when placed on tongue without need for chewing or water. The FDA or European Pharmacopoeia guidance is recommended for setting the target disintegration time.

Dissolution

It is also potential CQA as failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. Hence formulator should investigate this CQA during product development. The US or EP pharmacopoeia guidance is recommended for dissolution.

Dose range and accuracy

It should meet the standards set for product. As per recommendation for solid dosage forms, dose range and accuracy for ODTs is targeted and determined.

Pharmacokinetic Profile

The ODTs should meet the requirements for drug product. As ODT products do not require administration of water, it may be required to perform bioequivalence studies with and without water depending upon the nature of the drug. Most ODTs are bioequivalent to conventional dosage forms, but some meet specific drug delivery requirements.

Robustness

The target is set in such a way that the physical integrity of ODT is maintained during packaging, transport and patient handling. The guidance recommended for solid oral dosage forms is applicable for this attribute.

CONCLUSION

The development of ODTs as super generics is within the capability of both innovator and generic manufacturers provided the regulatory frameworks are also innovative in the context of a Risk based approach. It is possible to establish the ODTs developed as super generics as new brand identity as well as product's superiority in global market. The ODTs should be developed to focus on areas of unmet medical needs.

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