World Journal of Pharmaceutical research

Volume 2, Issue 6, 3025-3036. Review Article ISSN 2277 – 7105

PROSPECTIVE PLANNING FOR DEVELOPING ORALLY DISINTEGRATING DOSAGE FORMS

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Article Received on
18 August 2013,

Revised on 25 Sept. 2013,
Accepted on 30 October 2013

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ABSTRACT

Objective of work be projecting prospective planning to be following while developing orally disintegrating dosage forms (ODDFs). These dosage forms were exploited for improving their performance and patient compliance. Development of product is aiming to have a process producing optimised and acceptable product with reproducible quality and performance, throughout its shelf life and life cycle. This being difficult task requires proper planning with extensive knowledge. Publications projecting prospective planning for their development are scarce. This manuscript will assist researchers while developing them with wished performance.

KEYWORDS: Disintegrating, development, dosage form, orally, planning.

INTRODUCTION

Drug delivery systems had been a key contributor to global pharmaceutical sales. Increased cost and complications associated with development of a new drug molecule be compelling pharmaceutical companies to develop new dosage forms for existing drug molecules. Development of cost effective dosage form with improved safety and efficacy be requiring for survival of company, regardless of their size. [1-4]

The act of developing dosage form is segmenting and extending market, and is moving rapidly. By this manufacturer have markets with exclusivity while offering their patient

population a more convenient dosage form having unique product differentiation and value-added product line extension, or extending patent protection. [1-5]

Oral route of administration possesses acceptance up to 50-60% of total dosage forms. [3, 4] Consensus on ODDFs is that more than 50% of patient population have preference, 70% ask for and purchase it, or more than 80% prefer comparing regular tablets or liquids. [4] Their market is expanding over the years with concomitant approval of terminology relating ODDFs by United States Pharmacopoeia, British/European Pharmacopoeia and other pharmacopoeias. [4-8]

ODDFs synonyms for orodispersible, orally disintegrating, mouth/quick/fast-dissolving, and rapi/fast-melt tablets; fast dissolving drug delivery system; and freeze-dried wafers. These terminologies are official in several countries. [4, 9]

This class of dosage forms are very much admired and indicated for dysphagic, geriatric, paediatric, bed-ridden, travelling and psychotic patients; and for getting better palatability of bitter drugs. [9, 10] Advancement of technologies is resulting robust and versatile products with improved performances. This efficiently sustains or controls delivery and masks taste, and broadening their applications. [5]

Amount of drug, palatability, mouth feel effect, aqueous solubility, pharmacokinetics, mechanical strength, size of tablet, stability, and overall cost determines selection of process and performance of product. Several methodologies adopted to address these issues. Each method has specific technicalities and utility, and limitations. These facts create ambiguities in selecting an appropriate system, for developing them. [4, 11-14]

Said facts demand for presenting prospective action plan on development of ODDFs. Knowledge on methods of preparing, their utility and inherent technicality and limitations is prerequisite. Presented information will help researchers while designing an efficient system with wished performance.

ORALLY DISINTEGRATING DOSAGE FORMS

Freeze-dried wafer and tablets are the preferred form for grooming ODDFs. Orally disintegrating tablets disintegrates rapidly (within seconds) upon placing on tongue, without requiring water for swallowing. [7] While quick/fast/rapid/mouth–dissolving/melting tablet, orodispersing or fast-dissolving multiparticulate tablet dissolves within 60 seconds. These

tablets were physically robust and can be packaged in multi-dose containers. Freeze-dried wafer is quick-dissolving, fragile, thin-matrix dosage form. These packaged in unit-dose, and intended to get dissolved or dispersed in the saliva within oral cavity. [4]

They may be grouped as first or second-generation. First-generation one fails in terms of taste masking and holding high dose of drug. These characterised by high porosity and brittleness, and, low density and hardness. They are difficult to handle and often requires blister or specialised packaging that increases production costs and inconveniency. New-generation one improves taste masking, offers high drug loading and modified-release profile, enhances bio-availability, decreases friability, and provides cost-effective product with more packaging options. These comprises of rapidly dispersing microgranules, a directly compressible blend, and an external tablet lubrication method thereby resulting product with excellent physical robustness and wished friability (< 0.5%). They have mouth-feel and improved disintegration properties, accept printing on both sides with standard presses, and can be packaged in bottles or blister packs. Also they yield a smooth and pleasant tasting mixture of drug and carrier that is easy to swallow. [4, 12, 13]

These improve patient compliance and convenience. [2, 4, 11, 14] They are cost effective with lower production, packaging and distribution costs comparing commercially available liquid products. Provides flexibility of dosing and can be an immediate and/or controlled release type. [4] These enhance bioavailability and therapeutic benefit of drugs undergoing gastric and first pass hepatic metabolism and or whose significant fraction getting absorbed in oral cavity and pregastric segments of gastrointestinal tract (GIT). [4] Pharmaceutical company consider it as a strategic tool for expanding markets or indications; managing life cycles of existing and established drug molecule with low investment and risk, and minimal clinical requirements to gain approval; generating opportunities; and competing products in competitive therapeutic categories. [4, 5] However these dosage forms are unsuitable for drugs with relatively larger doses, and for patients with Sjögren's syndrome, dryness of mouth or who concurrently take anticholinergic medications. [4]

Drug contained in the ODDFs gets released, dissolved, or dispersed in the saliva that subsequently swallowed without water. Consequently the drug(s) was absorbed across the GIT and enter the blood stream. [7, 15]

Ideal ODDFs should dissolve/disperse/disintegrate in mouth within a matter of seconds, leaving minimum or no residue, without chewing and requiring water and in mouth. They have to allow high drug loading in cost effective way and be offering immediate-/ controlled-/ sustained-release profile. These must be capable in taste masking with improved palatability and pleasant mouth feel property. Must have adequate mechanical strength, to resist rigors of manufacturing practice and post manufacturing handling. Should have improved stability and be adaptable and amenable to conventional processing and packaging equipments, and also high speed machinery. [4]

Exploitable method and technology in developing ODDFs include conventional and patented technologies. Basic principle involved in said method or technology are freeze drying or lyophilisation, sublimation, mass extrusion, moulding, direct compression, disintegrant addition, spray drying and sublimation, cotton-candy process, oral films/wafers, nanocrystal, and so on. [1, 2, 4, 16] Information on conventional and patented technology used for devising ODDFs provided with Figure-1.

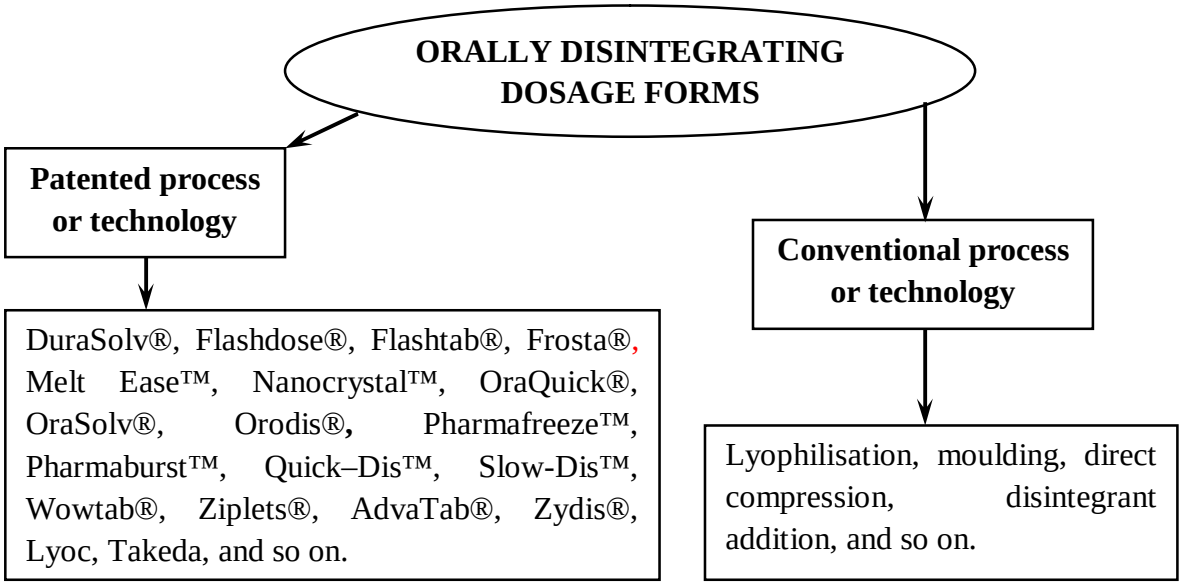

Figure-1: Depicts conventional and patented technologies used for devising ODDFs.

All these approaches are aims for having a porous system enabling quick ingress of water into matrix. Porous tablet obtainable with incorporation of apposite disintegrant and or using highly water soluble excipients in their formulation. [4] Amalgamation of microencapsulation and multi-particulate coating technology effectively masks obnoxious taste of drug and can be applied to soluble and poorly soluble substances, as well as to high-dose products. [4, 16]

Stated technologies differ from each other by mechanism and process. These resulting variation in mechanical strength, stability of drug and dosage form, mouth feel and taste, swallow-ability, drug dissolution rate in saliva, rate of absorption from saliva, and bioavailability. [4, 16]

Hurdles in their development

Quality and quantity of drug plays crucially while developing formulation of ODDFs. Ideally drug be diffusing and partitioning into the epithelium of the upper GIT, and be having log P value more than 1 and preferably more than 2. They should have oral mucosal tissue permeability. [17] Quantity of drug to be get loaded in the dosage form was a challenging affair specifically for a fast-dissolving oral films or wafers. [4]

Water-soluble drugs forming eutectic mixtures forms glassy and may collapse during the sublimation process, whilst insoluble one may settle out prior to freeze drying and creates content non-uniformity issues. [14, 18]

Palatability issue has to be skilfully addressed, as patient acceptance and success depends on taste not with speed of disintegration. [4, 11, 19] Upon disintegration they should leave minimum or no residue in the oral cavity.

Prospective planning for developing them

Prospering tablets with adequate strength can be obtainable following granulation method, moulding method, special excipients methods, or compaction and subsequent treatment methods.

Tablets obtainable with conventional tablet press were very wise option. These have low manufacturing cost, and can be easily developed and scaled-up with existing infrastructure and facilities. Considered as an easiest way to manufacture orodispersible tablets using common excipients involving minimum processing steps and utilising conventional equipment. These can accommodate high dose of drug. [4, 20, 21]

These tablets contain disintegrants and sugar-based excipients. Inclusion of superdisintegrants is preferred option. Understanding their properties ought to improving efficiency of tablets. List of superdisintegrants provided with Table-2. Alternately, disintegrants resulting disintegration of tablets following effervescence can be used. They bear advantage of partial taste masking of obnoxious drug. Hygroscopicity is the major

drawback of effervescent system, thus requiring protection of final product and controlling humidity during manufacture. [22-26] Inclusion of sugar-based excipients imparts taste masking and mouth-feel effect. Exploited sugar-based excipients are dextrose, fructose, isomalt, maltose, maltitok, mannitol, polydextrose, starch hydrolyse, sorbitol, xylitol and so on. [4, 20, 21]

Table-2: Superdisintegrants used in preparing orally disintegrating tablets. [21]

Sl. No.	Compound Name	Brand Name
01	Sodium carboxymethyl starch	Sodium starch glycollate
02	Cross linked polyvinyl pyrrolidone or 1-Ethenyl-2-pyrrolidinone homopolymer	Crospovidone
03	Hydroxypropyl cellulose	Klucel
04	Hydroxypropyl methylcellulose	Hypromellose
05	Crosslinked carboxymethyl ether cellulose sodium salt	Ac-di-sol
06	Microcrystalline cellulose	Avicel

Novel fast dissolving formulation comprise of at least one water soluble sugar, and non-sugar sweetener in fast release and slow release (mucoadhesive) form along with pharmaceutically active agent(s). [4]

Moulded tablets are less compact and highly porous with hasten dissolution comparing compressed tablets. These, in general, have insufficient mechanical strength thus prone to erosion and breakage during handling and notching of blister packs. [15, 27]

These tablets are obtainable by compression-moulding, heat-moulding, or no-vacuum lyophilisation method. Compression-moulding involves moistening of the powder blend with a hydro-alcoholic solvent followed by moulding under pressure lower than that of conventional one and subsequent solvent removal by air-drying. [4]

Heat-moulding involves setting of molten mass containing dispersion of drug and sugar (mannitol or lactose) in agar solution (as a binder) in a blister packaging well (as a mould). Their subsequent solidification at room temperature forms a jelly which upon drying at -30^{0}C under vacuum yields tablet. [28]

No-vacuum lyophilisation involves evaporation of solvent from the solution or suspension of drug at standard pressure. [29] Frozen mixture; containing solution or suspension of drug(s), and a carbohydrate and a gum; to be kept in mould having tablet shape prior to lyophilisation. Exploitable gums are xanthan, tragacanth, guar, carageenan, or acacia; whilst carbohydrates are maltodextrin, maltose, mannitol, lactose, or dextrose. [15, 27]

Sublimation or lyophilisation method is suited for heat sensitive drugs and biological. [30, 31] The process results a preparation that is very porous with high specific surface area. These formulation uses mannitol, erythritol, glucose, sucrose, xylitol as a matrix former. [30, 32] Tablets primed by said method were fragile and possess low mechanical strength. They are difficult to handle, dissolves rapidly, exhibits improved absorption and bioavailability, and demonstrate reduced stability. [4, 33] Porous matrix can be obtainable by inclusion of volatile ingredients that get removed by sublimation. Volatile ingredients used for this purpose are ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were used. [34-36]

In extrusion method, softened blend of active, in liquefied mixture of aqueous soluble polyethylene glycol and methanol, was extruded through the extruder or syringe. Resulted cylindrical product was cut into even segments with heated blade to form tablets or pellets. [4] Highly porous fine powders containing drugs can be obtainable following spray-drying method. This method uses formulation containing hydrolysed and un-hydrolysed gelatine as a supporting agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrants. [37] Their disintegration and dissolution be improving further by the inclusion of an effervescence system. Resulted porous powder has to be blended with excepients prior to compress. These tablets disintegrate within 20 second. [30, 37-43]

Microencapsulation is considered as novel method for getting microparticles loaded with drug. Resulting microparticles be flexible enough for compression without breakage or loss of the modified release properties and small enough to offer good mouth feel. [38]

Granules, particles, pellets or tablets may be suitably coated for masking bitterness of bitter tasting drugs or modifying release profile of drug. Alternately, multi-particulate coating technologies can be followed for getting coated granules, particles or pellets. [4, 38]

Adoption of specialised coating processes and or inclusion of specialised functional polymers has been resulting sustained, modified, or customized release profiles of drugs. Variation in the coating parameters (thickness, number of layers, composition, porosity, and, pH modifying agents) modifies release profile and plasma drug profile. Coacervation method is able to lay directly a uniform polymeric membrane of varying thicknesses and porosities onto dry crystals or granules. Resulting particles have size of 150 to 300 microns. [4, 38]

Microencapsulation and multi-particulate coating restrains dissolution of drug in mouth but allows rapid dissolution in GIT. Coating creates an inert barrier between drug and excipients or taste buds thereby stabilising formulation along with taste masking. However balancing taste masking and wished release profile is prerequisite. [4, 38]

Taste masked formulation segments of ODDFs constitute 22% of forecasted oral drug delivery market value of $52 billion which have opportunity for new enhanced oral products arising within this market segment. [4, 14, 15]

Evaluation of ODDFs

The success of formulation depends upon their performance. They should have assured safety and efficacy, and peak profile up to the end of shelf-life, at defined storage conditions. This assurance can be achievable through evaluation of product. Which will enable in maintaining inter and intra batch uniformity. Followings are the important parameters for evaluating product efficacy and efficiently.

Appearance (colour, shape and size), resistance to crushing of tablet or hardness or crushing strength test, friability, uniformity of weight (mass) or weight variation test, wetting time, *in-vitro* disintegration test, *in-vitro* release study/dissolution test, *in-vitro* release kinetic studies, statistical evaluation, and data fitting, moisture uptake studies, *in-vivo* disintegration time, [4, 6, 15, 45-47] For newer or bioequivalent line extension product clinical studies, pharmacokinetic studies, and stability studies, are prerequisite. [4, 18, 38, 47]

Generally ODDFs were formulated as a bioequivalent line extension of an existing oral dosage form. However these may have varying degrees of pregastric absorption and will not be bioequivalent to reference product and differences in the pharmacokinetic profiles will be pragmatic. [18, 38] They lead to difficulties in finding a discriminating dissolution test method, associated with very short disintegration tine with respect to its counterparts. [4] Use of taste-

masking and release modifying polymers creates challenges in achieving bioequivalence referring reference one, which impede drug release in the GIT and delays onset of action.

CONCLUSION

ODDFs have better patient acceptance and compliance. They may offer improved biopharmaceutical properties and efficacy, and better safety. Availability of new technologies in combination with strong market acceptance and patient demand had created promising potentiality for these products. With persistent development of latest excipients, one can expect the materialisation of more novel technologies in the days to come.

Researches in this segment should be directed for developing products with existing disintegrants and disintegrants from different coating polymers by their modifications; optimisation of blend of disintegrants or excipients; improvise upon existing technology. Besides these research should be performed for improving their palatability and patient compliance; selecting and developing proper packaging material and system for improving stability; and developing cost effective product.

Broadening their uses should be done by developing formulation for macromolecules. Achieving modified-release profiles within the ease of ODDFs with better patient compliance and ultimate clinical output was the challenges.

The degree of ease in administering a tablet depends on its size. Convenient size of tablet should be minimum 8 mm. Technology used for manufacturing them should be tolerable in terms of cost of the final product. Patented method necessitates special technologies and specific packaging leading to remarkably increase in the cost. Overall ODDFs have great potential for patentability.

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