Advance Research in Pharmaceuticals and Biologicals

(A Peer Reviewed International Journal for Pharmaceutical and Allied Research)

ISSN 2250-0774 USA CODEN: ARPBGZ

RECENT PATENTS AND PATENTED (COMMERCIAL) TECHNOLOGIES OF FAST DISSOLVING TABLET-A REVIEW

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Received : 11/03/2014 **Revised : 19/03/2014** **Accepted : 23/03/2014**

ABSTRACT:
Sometimes people experience inconveniences in swallowing conventional dosage forms that can rapidly dissolve or disintegrate tablets in the oral cavity have attracted a great deal of attention. Newly designed fast dissolving tablets and techniques used to enhance the solubility and dissolution rate and to improve patient compliance for all age groups. Fast dissolving tablet is solid dosage forms that can be disintegrate into smaller granules without need of water within a few seconds in the mouth. This review describes various patented fast dissolving technologies are Zydis, Orasolv, Wowtab, Flashtab, Advatab, Ziplets, Pharmaburst, Nanocrystal/nanomelt, Frosta, Dispersible tablet technology, Oraquick, Quick-dis, Lyo, Quicksolv, Flashdose, Shearform, Ceform, Advantol 200, EFVDAS, Multiflash, Takeda, Daiichi, Novartis, Nippon Shinyaku technology used to enhance the FDT properties. This article makes an effort to achieve or complete discussing the patents relating to fast disintegrating systems with respect to the use of different ingredients, formulation and technologies.

Keywords: Fast dissolving tablet, Patented technology, Disintegration time, Recent patents

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INTRODUCTION

Oral drug delivery system has been in demand for decades, as the most preferred route of administration. For the past two decades, there has been an enhanced demand for more patient compliant dosage forms. As a result, the demands for their technologies have been increasing three fold annually. Since the development cost of a new chemical entity is very high, pharmaceutical companies are focusing on new drug delivery systems for existing drug with an improved efficacy and bioavailability[1]. The oral route of administration is the most important method of administering drugs for systemic effects. This route is preferred due to its manifold advantages such as: ease of ingestion, pain avoidance, versatility, patient compliance and accurate dosing[2, 3].

Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people[4]. To overcome these problems, fast dissolving tablets (FDT) have been developed, which has good hardness, easy administration, dose uniformity and serves as the best choice of dosage form for pediatrics, geriatrics, bedridden and travelling patients. FDTs are also known as "rapid melting, oro-dispersible, porous tablet, rapid dissolving or melt in mouth tablets". Fast dissolving tablets can define as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth within 15 second to 3 minutes[5, 6].

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a few seconds, when placed upon the tongue." Drug delivery

through oral route has been the best route of administration since decades. Dispersible tablets are uncoated tablets that produce a uniform dispersion or suspension in water at room temperature without stirring. It is the most widely used routes of administration for the systemic delivery of drugs via various dosage forms. However USP approved these dosage forms as ODTs[7].

IDEAL PROPERTIES OF FDT

- It should not require any liquid or water for oral administration[8, 9].
- Leave minimal or no residue in mouth after administration of the table[10].
- Exhibit less sensitivity to environmental conditions (temperature and humidity) [10].
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and which may produce rapid onset of action[11, 12].
- Have a pleasing mouth feel[10].
- Low cost manufacture of tablets using conventional processing and packaging equipment[10].

PATENTED TECHNOLOGY FOR FAST DISSOLVING TABLET

1) Zydis® technology (Cardinal Health Inc.)
2) Orasolv® technology (Cima Labs, Inc.)
3) Durasolv® technology (Cima Labs, Inc.)
4) Wowtab® technology (Yamanouchi Pharma Technologies, Inc.)
5) Flashtab® technology (Prographarm Labs)
6) Advatab™ technology (Eurand)
7) Ziplets technology (Eurand)
8) Pharmaburst technology (SPI Pharma, New Castle)
9) Nanocrystal/nanomelt™ technology (Elan Corporation)
10) Frosta ® technology (Akina)
11) Dispersible tablet technology (Lek Yugoslavia)
12) Oraquick® technology (KV Pharmaceutical Co. Inc.)
13) Quick-dis ™ technology (Lavipharm)
14) Lyoc ® technology (Cephalon Corporation)
15) Quicksolv™ technology (Janssen Pharmaceuticals)
16) Flashdose ® technology (Fuisz Technologies, Ltd.)
17) Shearform™ technology
18) Ceform™ technology (Fuisz Technology Ltd., USA)
19) Advantol™ 200
20) EFVDAS technology (Elan Corporation)
21) Multiflash technology (Prographarm)
22) Takeda technology ® (Osaka, Japan)
23) Novartis technology (Basel, Switzerland)
24) Nippon Shinyaku technology (Kyoto, Japan)
25) Daiichi technology (Tokyo, Japan)

Zydis technology

This is one new and first marketed technology of mouth dissolving tablets. The tablet of this technology is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. Thus the tablet dissolves in the mouth within seconds after placement on the tongue. The tablet of the Zydis is light in weight, transparent and also fragile. The tablet is packed in a special blister packing. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. Thus, this product dissolve on the tongue in 2 to 3 seconds and also self preserving as final water content is too low. As this product showing fastest dispersion and maximum dissolution which results in increased bioavailability and also there will be pregastric absorption from this Zydis tablet. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions[13, 14].

Orasolv technology

OraSolv technology produces tablets by low compression pressure, utilizes effervescence material. This technology utilizes conventional manufacturing equipment. The effervescence material causes the dosage form to quickly disintegrate following contact with water or saliva. The widely used effervescence disintegration pair includes an acid source and carbonate source. The acid source include malic acid, tartaric acid, fumaric acid, adipic acid, citric acid and carbonate source include sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate. The carbon dioxide evolved from the reaction (occurred between acid and carbonate) may provide some fizzing sensation like positive organoleptic sensation. However, current technology uses this concept in a modified fashion to prepare fast disintegrating dosage forms[15-17].

Durasolv technology

The DuraSolv technology has a formulation similar to the OraSolv technology, combining taste masked drug microparticles with or without a low effervescence-containing formulation, was developed by CIMA labs, consist of a drug, fillers and the lubricants[18]. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner[19].

Wowtab technology

Wowtab Technology is patented by "Yamanouchi Pharmaceutical Co. "WOW" means "Without Water". In this process the active ingredient is mixed with a low mould ability saccharide and granulated with a high

mould ability saccharide is used up to 50% w/w of the compressed tablet[20]. The tablets produced by Wowtab technique offers superior mouth feel due to the smooth melt action. It is suitable for both conventional bottle and blister packaging. But more stable to the environment than other techniques[21].

Flashtab technology

Flashtab technology is patented by Ethypharm, Saint Cloud. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets[22]. Drug micro granules may be prepared by using the conventional techniques. Reticulated polyvinyl pyrrolidine or carboxy methylcellulose are used as disintegrating agents and swelling agents like that carboxy methyl cellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starches, etc are used. All the processing utilized the conventional tableting technology, and the tablets produced have good mechanical strength and disintegration time less than 1 min[23].

Advatab technology

Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds and administered without water. Advatab is distinct from other FDTs technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcaps taste masking technology and its Diffucaps, controlled release technology[24-26]. The combination product of Advatab and Microcaps has advantages such as ideal dosage form with superior taste and soft mouth feel but the disadvantage is taste masking of unpleasant drug[27].

Ziplets technology

In Ziplet technology water insoluble drugs or drugs as coated microparticles are used. The addition of a suitable amount of water-insoluble inorganic excipients combined with disintegrants imparted an excellent physical resistance to the ODT and simultaneously maintained optimal disintegration[28]. The use of water-insoluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily of water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed which reduces the rate of water diffusion into the tablet core[29].

Pharmaburst technology

Pharmaburst technology was developed by SPI Pharma. This technology uses co-processed excipients to prepare FDT that, depending on the type of active ingredient and loading up to 700 mg, dissolves within 30–40 seconds. The method involves a dry blend of a drug, flavor and lubricant that are compressed into tablets on a standard tablet press under normal temperature and humidity conditions. The prepared tablets can be packaged in blister packs or bottle[30].

Nanocrystal technology

This is patented by Elan, King of Prussia. This technology is based on the principle that surface area increases with decrease in particle size, which leads to an increase in dissolution rate. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling[30]. Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blister pockets[31].

Frosta technology

Frosta (Akina) technology is not the first FMT technology developed based on the compression method, it is unique because it combines two contradicting properties into one formulation: fast disintegration and high mechanical strength. The Frosta technology is based on the compression of highly plastic granules at low pressures to prepare FMTs[32]. The highly plastic granules are composed of three components: a plastic material, a wet binder and a water-penetration enhancer. FMTs produce by Frosta technology have less disintegration time with low processing cost[33].

Dispersible tablet technology

In this technology improvement in dissolution rate is achieved by incorporation of 8-10% of organic acids and disintegrating agents. Disintegrating facilitates rapid swelling and good wetting capabilities to tablets that results in quick disintegration. Lek Yugoslavia patents this technology. Disintegrants include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethylcellulose and cyclodextrins which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature[34].

Oraquick technology

The Oraquick fast dissolving/disintegrating tablets formulation utilizes a patented taste masking technology. This taste masking process does not utilize solvents of any kind, so leads to faster and more efficient production. During processing low-heat is produced so this technique is suitable for heat sensitive drugs. KV pharmaceuticals claim that the matrix that surrounds and protects the drug powder in microencapsulated particle is more liable. This technique gives tablets with good taste masking and quick dissolution in matter of seconds[35].

Quick-dis technology
The novel intraoral drug delivery system, Quick-Dis, is Lavipharm's proprietary patented technology and is a thin, flexible and quick-dissolving film[36]. The film is produced by the solvent casting method. In this technique, water-soluble hydrocolloids and other ingredients used with APIs were dissolved in a small portion of aqueous solvent using a high-shear processor. The active mixture was then added to the viscous hydrocolloid solution to form a homogeneous viscous solution. This viscous solution was degassed under vacuum and the solution was then coated on a casting film. The coated film was subsequently dry into an oven. The dry film was then cut into the desired shape and size for the intended application[37].

Lyoc ® technology
Lyoc technique is owned by Cephalon Corporation. Lyoc utilizes a freeze-drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. The liquid solution or suspension preparation evolves fillers, thickening agents, surfactant, non-volatile flavoring agents, and sweeteners along with drug. This homogeneous liquid is placed in blister cavities and subjected to freeze-drying. To prevent in homogeneity by sedimentation during this process, to require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the in process suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates are comparable to loosely compressed fast melt formulations[38].

Quicksolv technology
The Quicksolv technology (Janssen, a subsidiary of Johnson, New Brunswick, NJ) an aqueous dispersion of the API and matrix components is first formed and then frozen. Water removing from the frozen matrix can be performed either by lyophilization or submerging frozen product in alcohol (solvent extraction) to produce a dry unit. The product formed has uniform porosity and adequate strength for handling[39]. The ideal drug characteristics required for this technology are relative low aqueous solubility, fine particle size <50 µm[40, 41] and good aqueous stability in the suspension.

Flashdose technology
Flash does technology has been patented by Fuisz. Flash dose tablets consist of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing[42, 43]. Tablets are made by direct compression technique. The final product has a very high surface area for dissolution and it disperses/dissolves quickly once placed on the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics to the product can be altered greatly[44].

Shearform technology
The shearform technology is based on preparation of floss which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to rapid solubilisation of sugars in presence of saliva. The recrystallized matrix is then blended with the drug along with other excipients and compressed into tablets. So, to improve the mechanical strength the tablets are exposed to elevated temperature and high humidity (40°C and 85% RH for 15 minutes [45-47].

Ceform technology
In Ceform technology, micro spheres containing active ingredient are prepared. The essence of Ceform micro sphere manufacturing process involves placing dry powder, containing pure drug and excipients rapidly into a spinning machine and carefully controlled temperature of the resultant microburst of liquefied the drug blend to form a sphere without adversely affecting drug stability. The microsphere are then blended and/or compressed into the pre-selected oral delivery dosage form[48].

Advantol 200
Advantol 200 is developed by SPI Pharmaceutical it uses directly compressible excipient to produce "Soft-Melt" tablet by involving co-processing technology. The tablets are produced by conventional technique and equipment. The tablets produced are robust with good mechanical strength[49].

EFVDAS technology
EFVDAS or Effervescent Drug Absorption System is a drug delivery technology that has both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use[49, 50].

Multiflash technology
Multiflash is a multi-unit tablet comprised of coated microgranules and FDT_S excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water[51].

Takeda technology
The wetted mass was compressed at low pressure and subsequently dried to produce porous tablets with sufficient mechanical strength. The disintegration time was about 30–50 seconds in the mouth. In a patent by Novartis Consumer Health (Basel, Switzerland), the

drug solution or suspension was dispersed into molds. The solvent was removed from the units usually by heating, pressure reduction, or microwave radiation[52].

Novartis technology

Novartis Consumer Health (Basel, Switzerland) also has filed a patent application for tablets prepared by dispensing the drug solution or suspension into moulds, evaporating the solvent from the units (usually achieved by heating, pressure reduction, or microwave radiation), and then optionally sealing the dried units directly in the mould[53].

Nippon Shinyaku technology

Nippon Shinyaku (Kyoto, Japan) compression-moulds and dries a kneaded mixture containing the drug and a water-soluble sugar[54]. This process is claimed to impart sufficient physicochemical stability to the tablet, good appearance, and an oral cavity dissolution time of less than 30 s.

Daiichi

Daiichi (Tokyo, Japan) performed a series of experiments to develop an FMT of moderate strength, using a combination of starch or cellulose and one or more water-soluble saccharides. Erythritol was found to be the sugar for this type of formulation, showing rapid disintegration that was negligibly affected by tablet hardness; good tolerability and sweetening; and a refreshing mouth sensation because of its endothermic dissolution heat. Tablets are produced by compressing a powder containing two sugar alcohols with high and low melting points. Before the heating process, the tablets do not have sufficient hardness because of the low compatibility. The tablet hardness is increased after the heating process. A combination of two sugar alcohols and the heating process is needed to prepare FDT tablets with sufficient hardness. Tablet hardness is related to the increase of inter-particle bonds or the bonding surface area in tablets induced by the phase of the lower melting point sugar alcohol. Manufacturing of FDT tablets by the present method can be performed without any special apparatus[55].

RECENT PATENTS ON FAST DISSOLVING TECHNOLOGY

Janos Szamosi, Kevin Scott Kinter et al (2013) filed US patent for fast dissolving tablets which dissolve rapidly in the mouth and provide an excellent mouth feel. The tablets of the invention comprised a compound which melts at about 37°C. or lower, it was found that the prepared tablets have low hardness, high stability and it generally comprised few insoluble disintegrates which may causes a gritty or chalky sensation in the mouth. The tablets of the invention may be produce convenient and economically feasible processes [56].

Evangelos Karavas, Efthimios Koutris et al (2013) invented to provide a fast dissolving tablet comprised a therapeutically effective amount of a phosphate binding polymer, such as sevelamer or pharmaceutically acceptable salt or derivative thereof, as the active ingredient. They exhibited a limited swelling in the oral cavity, have pleasant taste and mouth feel, high phosphate binding capacity with fast binding kinetics and require limited amount of water intake. A process for the preparation thereof is also provided[57].

Pilgaonkar, Pratibha S. (2013) has invented taste-masked orally disintegrating tablets of memantine hydrochloride related to a solid pharmaceutical composition comprised memantine, which dissolved or disintegrated in the oral cavity preferably within about 60 seconds. They have optimal mechanical strength but also control the release of taste-masked memantine and pharmaceutically acceptable excipients[58].

Sang Yeob Park, Hye Jung Lim (2013) invented highly robust fast-disintegrating tablet and process for manufactured by a wet-granulation method. Tablet comprised slightly wetted granules comprised a spray-dried mannitol and a sucrose binder manufactured by conventional pharmaceutical equipment; and the product has fast disintegrability as well as high hardness[59].

Cifter, Türkyilmaz (2012) invented to a silicon dioxide free orally disintegrated tablet and formulated of zolmitriptan or a pharmaceutically acceptable salt thereof comprising magnesium carbonate heavy and sodium stearyl fumarate with one or more pharmaceutically acceptable excipient. It has surprisingly been found that the specific combination of magnesium carbonate heavy and sodium stearyl fumarate with the active ingredient zolmitriptan results a synergistic effect over the disintegration time and mechanical strength (such as; hardness and friability) of the orally disintegrated tablet formulation[60].

Sanjay Boldhane, Kuldeep Bhokare (2012) invented a fast dissolving pharmaceutical composition comprised lornoxicam or pharmaceutically acceptable salts thereof as an active ingredient along with at least one alkalinizer, one organic acid and one pharmaceutically acceptable excipient. Improved the rate and extent of absorption of oral formulations of compounds has been the subject of substantial research composition exhibits a dissolution profile[61].

Regina Schueller, Stefan Toegel (2012) invented fast disintegrated compositions comprised nabilone and randomly methylated beta cyclodextrin (RAMEB). It has been surprisingly shown that the solubility of Nabilone was highly increased when RAMEB was used as

complex-forming agent, methods for increased the bioavailability of Nabilone[62].

Jin-Wang Lai, Vijaya Swaminathan (2012) filled rapid dissolved tablet compositions for vaginal administration. A rapid dissolve tablet comprised rapidly dispersing microgranules comprised one or more active pharmaceutical ingredients suitable for vaginal route of administration, one or more polymeric excipients having a dual property of acting as a binder as well as a bioadhesive material, one or more sugar alcohols or saccharides, and one or more disintegrants, methods of making and using such compositions for therapy via topical action or systemic absorption, as well as uterine targeting. Invented to this tablet rapidly disintegrate upon insertion into the vagina of a patient, forming a viscous drug suspension that rapidly and widely spreads to coat the vaginal mucosa with the drug suspension/solution[63].

CONCLUSION

Fast dissolving tablets (FDTs) are emerging trend in novel drug delivery systems and have increased the acceptance advantages over conventional dosage forms, with their improved patient compliance, provide a rapid onset of action and increase bioavailability. Though considerable research has been done in the formulation development and technologies for FDTs, more intensive investigations are to be carried out in this promising area to result in newer cost effective technologies and better products. The information given in above article will provide the details about the techniques and methods that are available for the manufacturing of fast dissolving tablets and will be helpful to the young researchers in the field of pharmacy.

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