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Review Article

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Current Scientific Advances in Oral Disintegrating Tablets (ODTS)

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ABSTRACT

Various pharmaceutical therapeutic agents are given to patients to produce its effects to the systemic circulation. Among the various dosage forms, oral route is still preferred by the patients for administration of drug. Drugs administration from an oral route is the most preferred due to several advantages over others route. It has a high rate of patient compliance as compared to other routes. Apart from the patient's convenient, it is also available at very low price. Many groups of patients like children, elderly, mental retarded, patients having difficulties in swallowing or low intake capacity of food and water. To avoid such conditions or limitations, a novel pharmaceutical technology have been developed as Oral disintegrating tablets (ODTs). ODTs can be broadly defined as a category of oral solid dosage forms, which disintegrate in mouth or oral cavity within a minute without any presence of water at very fast or rapid speed. Apart from above mentioned limitations, it is also preferred, when the patients is travelling or have very little access to water. This review depicts the various aspects of ODTs formulation and technologies developed.

Keywords: Oral disintegrating tablets (ODTs); Fast dissolving tablet (FDTs); Sublimation

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INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. Due to greater stability, smaller bulk, accurate dose and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms [1]. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form. Moreover the most promising NCEs [2], despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window [3]. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Approximately, 70% of new chemical entities (NCE) in the drug discovery have shown poor aqueous solubility and nearly 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100 μg/mL) [4]. Moreover, approximately 90% of drugs in development phase are reported to be poorly soluble drugs [5]. Oral drug delivery systems present a major challenge for the poorly soluble drugs especially those belonging to the Class II and IV of Biopharmaceutics Classification System (BCS) [6]. The BCS class II drugs readily permeate biological membranes, making their maximum solubility and/or dissolution rate in the gastrointestinal tract (GIT) the rate-limiting steps to their absorption [7]. The poor aqueous solubility, low and variable bioavailability and high intra- and inter-subject variability of such drugs lead to low plasma-drug concentration, thereby rendering them unavailable at the receptor site to elicit a desired pharmacological response [8]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability (BCS class II drugs) [9]. By improving the solubility of these drugs, it is possible to enhance their bioavailability and reduce the dose [10].

Fast disintegrating tablets has taken a new dimension over the past decade and is increasingly enhancing the solubility and bioavailability of pre-existing lipophilic drugs as well as the therapeutically active NCE [11].
Amidon et al., introduced BCS classifications of drug candidates into one of four categories based on their solubility and intestinal permeability, responsible for controlling drug absorption (Figure 1) [12]. The concept of BCS has been used not only by the regulatory agencies for biowaiver but also for formulation design from early to clinical stages of drug development [13]. A typical representation of the BCS is depicted below.

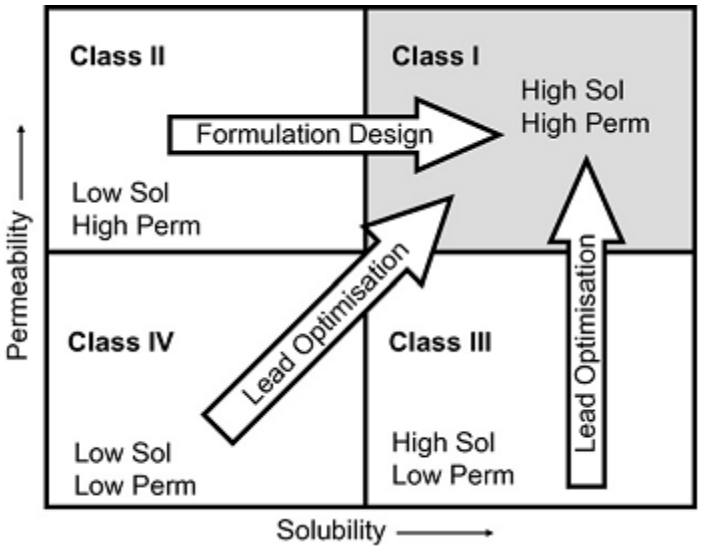

Figure 1: A typical representation of the BCS (Pouton, 2006)

Advantages of Oral Disintegrating Tablets (ODTs)

Due to its ease and convenient in availability to different group of patients, it is preferred. As it's an advance pharmaceutical technology, so it come to a market with improved taste, stability, increased bioavailability and better drug efficacy. It is also available at very low-cost and at variable dose. It has been assumed in literature that after few years more than half of the patients would like to prefer ODTs over the other oral solid dosage form [14]. The Food and Drug Administration (FDA) has approved all the fast disintegrating tablets and it is classified as orally disintegrating tablets [15].
Fast dissolving tablets are an emerging and one of the most common used solid dosage form with widely accepted by the different category of patients. It has been widely accepted due to its easy manufacturing process, accuracy in its dose, it's easy management by patients, bioavailability, long-time stability and requirement of small size packaging materials [16]. Due to its numerous benefits over liquid dosage form, such as it can be easily administrated to the patients without any risk of suffocation resultant on or after physical obstruction by a dosage form [17].
Fast dissolving tablet (FDTs) falls in the category of the novel dosage or drug delivery form. It is vastly accepted by aged people, paediatric, physically disabled or challenged people and bedridden patients because of its convenient and no need or requirement of water to take or swallow. It is mainly preferred by the patients of nausea, asthma, Parkinson's disorder and the patients facing the problems like trouble in swallowing (dysphagia) [18].
As the demand of FDTs are increasing day-by-day, so its application need to be stretched to its more extensive form to the patients on the basis of daily intake of medicaments and drug-dosage regimen. By considering the major pharmaceutical industry's point of view in mind, we can say that FDTs offer a life cycle management to the patients at very cheap and affordable cost [19]. This availability of dosage form means that drug is available to the last user i.e. patients in a form of novel or new dosage forms. Due to disintegration of tablets in the oral cavity of mouth, drugs may get absorbed in the buccal cavity, gastric and pharyngeal regions [20]. Due to its rapid and fast drug-release in the mouth, bioavailability of drugs will increase. As the absorption of drug follow pre-gastric drug absorption path, because of that the first-pass drug metabolism of the drug is absent. As the tablets are available in the form of new dosage form, the dose of drug can be reduced as per convenient. The dose of the drug can also be reduced if the drug is lost from hepatic metabolism.

FDTs has numerous advantages and widely accepted being recognized by the people at both level (industry and academia). Due to its improved patient's compliance it is most preferred as a primary technology.

Advantages of Fast Dissolving Tablets are Summarised in Following Points:

1. There is no requirement of water for intake of medicaments. Due to absence of water intake, it gives convenient feature for the patient who are on journey or don't have an immediate availability of water.
2. FDTs can be easily administered to the elderly, paediatric and mental patients.
3. Accuracy in dose intake as compared to liquid dosage form.
4. It offers fast onset of action, due to its high rate of disintegration, dissolution and absorption of the drug in the body.
5. It can increase the drug-loading capacity.
6. It creates favourable circumstances, which increase the chances of accuracy and easy administration along with convenient transportation.
7. The manufacturing process is fast and on large scale due to its simple and more efficient techniques.
8. It offers improved drug-safety profile.

Manufacturing Technology

There are numerous patented and non-patented preparation methods or technology are available for the development of ODTs [21].

These technologies are following:

- Lyophilization
- Molding
- Cotton candy process
- Direct compression technique
- Spray drying
- Mass extrusion
- Nanonization
- Sublimation
- Fast dissolving films.

Patented Technologies Include

- Zydis®
- Durasolv®
- Orasolv®
- Wowtab®
- Flashtab®

Direct Compression Tablets Manufacturing Technique

Direct compression is considered to be one of the most preferable, standard, low-cost method of tablets preparation with less time-consuming. This method of tablets preparation is preferred by both by academicians and pharmaceutical manufacturers. In most of the pharmaceutical companies conventional manufacturing equipments and regularly easily available ingredients are used. The direct compression method following are commonly used [22]:

1) Blending Ingredients
2) Sieve Blends
3) Mix Blend/Lubrication
4) Compress Blends

Direct compression method can be useful in manufacturing of FDTs by selecting an appropriate combination of drug: excipients ratio. This appropriate ratio of drug and excipients will provide fast disintegration with good physical resistance. In the preparation of FDTs technique based on sugar-excipients have broadly been accepted as bulking agents. It is widely accepted because of its elevated and fast solubility in aqueous or water with sweet in taste. Sweet taste pleas mouth-feel good and mask the bitter taste of drug. To mask the taste of the drug, in most of the prepared formulations of FDTs are incorporated with sugar or some sweetening materials as an excipient of formulations [23].

Direct compression is one of the simplest, most profitable processes of tablets manufacture. Due to its easy and convenient preparation method of tablets, which mainly require excellent characteristics of powder. Among the various characteristics; powder features like excellent powder flow with good compressibility and

compactability [24]. Addition of super-disintegrants increases the rate of tablets disintegration and drug dissolution in the body [25].

Tablet Molding

Tablets prepared by molding techniques are replaced by direct compression technique. Tablets molding techniques are mainly preferred at lab scale or for small batch size production. For the preparation of tablets by this technique, water-soluble additives are used. Due to addition of these water-soluble additives dissolution of the drug gets rapidand complete in mouth only. This process of tablets preparation is very tedious and time-consuming. For the preparation of tablets from tablets molding technique all ingredients (drug:excipients) of the formulation are passed through fine mesh. After complete sieving, then this dry blend is wetted with a hydroalcoholic solvent. After complete blending then it is compressed into tablets by applying low compression forces. The solvent which are present inside the tablets during manufacturing process are removed by air-drying method. The prepared molded tablets contain a porous like structure, which helps to enhances the rate ofdisintegration and dissolution profile of the drug further increases bioavailability of the drug. In the preparation of molded tablets low mechanical strength are applied. Different types of binding agents (sucrose, polyvinyl pyrrolidone) and cellulosic polymers (hydroxylpropyl methylcellulose) are used in the preparation of tablets to provide the mechanical strength [26].
There is very little scope of taste masking from this molded tablets preparation technique. It is used to mask the unpalatable taste of the medicament, the drug to be incorporated has to be pre-treated with different techniques available like flavor addition, spray congealing or micro-particulate system of the drug [27].

Spray Drying Method
In spray drying approachof FDTs preparation method, gelatin is considered as one of the most preferred supporting agent and act as a matrix, crospovidone, croscarmellose, sodium starch glycolate are used as superdisintegrants and mannitol as a bulking agent. Spray drying techniques offer rapidly or fast dissolving or disintegrating tablets to the patients. This procedure or principle of fast disintegrating tablets work on a particulate matrix support system. Tablets which are prepared by spray drying technique encompass of an aqueous or watery composition substances as a support matrix along with other components. These components arefine powder with highly porous in nature. All these ingredients are mixed properly with active pharmaceutical ingredients. After complete mixing it is compressed in to tablets [28].
Allen and Wang (1997) followed spray-drying technique for the preparation of fast dissolving tablets. They developed formulation by using bulking agent (mannitol), support matrix (hydrolyzed and non-hydrolyzedgelatin), disintegrant (sodium starch glycolate), acidic material (citric acid) and alkali material (e.g. $NaHCO_3$). These ingredients are used to enhance disintegration and dissolution profile of the drug. Tablets start disintegrating in less than 20 seconds, in which spray-drying preparation method are used. It disintegrates in less than 20 s in which aqueous medium is used [29].

Lyophilization
Lyophilizationis is also known as Freeze drying technique. It is process to which water is completely removed from the tablets after it's frozen. This lyophilizationtechnique offers more rapid rate of drug disintegration or dissolution as compared to than other available preparation technique. Lyophilization offers glossy amorphous structure to the bulking agent and sometimes to the drugs also. Tablets prepared from lyophilization technique are highly porous in nature, with a very high surface area. Due to its high porous nature and large surface area it helps drug to dissolve fast and rapid. Due to this it showed improved and good rate and extent of absorption of the drug from its dosage form. Lyophilization technique is mostly preferable to drugs which are very heat sensitive and biological products. Due to its high fragile in nature and low mechanical strength, it is very difficult to handle. It has very poor stability on storage under stressed conditions [30].

Sublimation

Tablets prepared from compression technique are mainly composed of excipients, which are highly water-insoluble in nature. Due to its low porosity, it does not dissolve fast in water. To avoid such problems and increase the solubility and porosity, there is a need to focus on such problem. Tablets prepared by sublimation technique required additional sublime salt (ammonium acetate, ammonium bicarbonate and ammonium carbonate). These sublime salts are added to the tabletting component. All the components are mixed properly till homogenous mixtures are obtained. All the components which are used for preparation of FDTs are mixed uniformly to obtain a significantly homogenous or uniform mixture. Sublime salts are volatilized from the

homogenous mixture. Pores are created in the tablets after removal of sublime salt. Pores in tablets help in fast disintegration of tablets, when it comes in contact with saliva [31].

Mass Extrusion

Hot melt extrusion enhances solubility of the drug by producing an increased-energy form of the drug through the combination of different manufacturing process and by using different grades of excipients having different chemical properties. The resulting or obtained mass product from this process is called an extrudate. After obtaining the extrudate, it isagain processed to obtained final dosage form. This re-processed mixer helps to achieve the final dosage form as FDTs as of desired profile. Sherry *et al*., (2008) patented the melt extrusion preparation technique of ODTs of paracetamol and NSAID. The preparation method involved number of steps. Firstly, dry blend of sugar alcohol along with drugs and other excipients are obtained. This dry blend powder mixture was heated in the temperature ranging from 100°C-165°C in an extruder. Due to constant heating of extruder, alcohol sugarstart melted. This obtained resultant mass contains partially or fully molten sugar alcohol (mannitol, xylitol, sorbitol etc). And the non-molten sugar alcohol is naproxen, diclofenac, ibuprofen or paracetamol. After this some additional elective excipients were poured on stainless-steel tray, which were cooled after pouring on tray, it was kept few minutes to cool down. The obtained molten mass mixtures get solidified within less than a minute or 60 seconds. The obtained solid mixtures were further milled by passing it through a cone mill which was close-fitting with a creen with a rounded shape hole having diameter of 1 mm. The granules were obtained, and it was blended with some extra-granular components like di-calcium phosphate, colloidal silicon dioxide, stearic acid, magnesium, microcrystalline cellulose, stearate and lactosein a mixing blender. The obtained blended mass was again fed to a rotary tablet punching machine. It was compressed into FDTs by applying compaction force in the range of 4 kN to 14 kN. Tablets obtained from fully melted xylitol was robust than others tablets obtained by conventional dry blending process [32].

Disintegrants Used in Preparation of FDTS

It has been reported in literature that disintegrants play an import role in preparation of fast disintegrating tablets. It has been published in patent, where it has been suggested to use single disintegrants or use of combination of disintegrants. A report has been summarized by Dobetti. It has been summarized that there are different categories of non-effervescent disintegrantsare used in the pharmaceutical industries [33].

Starch and Modified Starches

In this category of disintegrants arE mainly natural like starch of potato and maize; directly compressible starch is starch 1500. The modified form of starch is carboxymethyl starch and sodium starch glycolate and starch derivatives like amylose.

i. Cross-linked polyvinylpyrrolidone
ii. Microcrystalline cellulose
iii. Alginic acid and sodium alginate
iv. Modified cellulose starch: cross-linked sodium carboxymethylcellulose
v. Methacrylic acid-divinylbenzene copolymer salts

In addition to these recently some superdisintegrant with a unique porous structure has been reported. These are poly (acrylic acid), superporous hydrogel (SPH) microparticles [34]. To reduce the disintegration time of FDTs wicking agents were added. It has been reported that the poly (acrylic acid) SPH microparticles are swellable in nature and it can swell more than 80 times in triple distilled water. It can also swell in pH 6.8 phosphate buffer solution at fifty time's higher rate. The dimension of SPH microparticle had some more important effects on the time of disintegration and its tensile strength of prepared ketoprofen loaded FDTs. Disintegration time of the microparticle was found to be less than aminute with size range of 75–106 μm of microparticle. Tensile strength of the microparticlewas found to be very less or decreased as the size of SPH microparticle decreased. Size of the microparticlewas decreased from 180-250 μm to 25-44 μm [35].

However, in some cases the tensile strength of the prepared FDTs was found to be increased as the size of the microparticle was decreased. It is mainly, when the sizes of the microparticles were found to be smaller than 25 μm [36]. It was suggested that the size of an optimal microparticle should be in the range of 75–106 μm. The FDTs made of SPH microparticle in the range of 75-106 μm showed the fastest disintegration time (15.0 ± 2.0 s) and higher tensile strength (84.4± 4.1 N/cm^2).

Inorganic Excipients Used in Preparation of FDTs

Dobetti, prepared FDTs by taking some inorganic water insoluble excipients as the key components. They patented their preparation technique. They reported that disintegration of prepared FDTs was affected by the quantity of the insoluble inorganic ingredients used along with disintegrant. The time to disintegrate the tablets mainly depends on the ratio of relative weight between the water-soluble and water-insoluble excipients. This is best for the excipients which are water-soluble in nature. It was suggested that sufficient compression might be applied to form tablets with strong tensile strength and low friability in their formulations [37]. The disintegration time remains the same and it is not affected by the high compression force.

Substantially Water Insoluble Components

In this category of classification following group includes:

- Coated and uncoated drugs; which are water-insoluble in nature
- Lubricants and glidants which are insoluble in water.
- Water-Insoluble excipients include insoluble inorganic salt or organic filler.

Substantially Soluble Components

It consists of flavouring agents, compressible sugars, binders, sweeteners, and surfactant. Examples include starch of maize, modified starch, cross-linked polyvinyl pyrrolidone and sodium carboxymethyl cellulose. It has been reported that the disintegration time will increase at very fast rate as the amount of insoluble components will decrease. If small quantities of active pharmaceutical ingredients will be used in the prepared formulation, the disintegration time could be optimized by including insoluble fillers like silicon dioxide and microcrystalline cellulose. It can also be optimized by increasing the amount of insoluble inorganic excipients and calcium salts such as dibasic calcium phosphate [38].

Characteristics Features of Orally Disintegrating Tablet

Orally disintegrating tablets allow wettability in nature due to its porous in nature. As the compression force is very low, it permits for water to influence the superdisintegrants. It perpetuates a swelling effect in ODTs which in results permits ODTs to disintegrate at very high and rapid rate [39]. Hardness of the ODTs is less than 30 Newtons. This hardness allows ODTs for its rapid disintegration. Along with the rapid rate of disintegration, it also maintains he mechanical strength for the production and distribution of tablets.

Bioavailability

When the ODTs disintegrate in the oral cavity of the mouth, it permits a higher degree of rate and extent of absorption i.e. bioavailability of the drug from its dosage form. It acts by reducing the amount of drug, which rapidly undergo first-pass metabolism. logP value was found to be more than 1 in an ideal conditions [40]. ODTs diffuse into the epithelium layer of cells of the upper part of human gastrointestinal tract (GIT). Due to its diffusion in the upper part of GIT, ODTs have a more rapid or fast onset of action. Drug is absorbed at very rapid or fast rate because the saliva moves from the oral cavity of mouth to the gastrointestinal tract of human [41].

Polymers play an important role in novel or control release pharmaceutical effects. Enteric coatings are preferred in formulation and it helps and prevents drug release in gastric pH. Due to use of gastric pH enteric polymers, it helps tablets to stable in low pH. Tablets start eroding when the pH of the intestine becomes more basic such as the intestinal environment [42].

Palatability

Palatability is an important characteristic feature of an oral drug delivery systems. As the main aim of any prepared formulation is to provide patient compliance. It is dependent on favourable or good taste of ODTs, which is further determined by the target patients. As the taste of the many APIs is bitter and offensive. To mask the bitter taste of the drug, it requires different type of sweetening and flavouring agents. By using different types of sweetening and flavouring agent, it can be masked and make easily available for patients. In some cases, the drug is excessive bitter in nature like diphenhydramine HCl. To mask the excessive bitterness of the drug and provide patient compliance, it requires coating [43].

By using micro-encapsulation technique, we can incorporate cyclodextrinsin soluble and poorly soluble substances.

Coacervation is considered to be one of the best coating technique that provides superior taste masking against unpleasant taste of APIs [44].

Mass Extrusion

This technique was used in order to soften the actives blends. To obtain the soft active blends solvent mixture of water soluble polyethylene glycol was used along with used methanol. The expulsion of unstiffened soft mass passes via syringe. After passing from the syringe, it produces a cylindrical needle shape of the mass into identical segments. It is produced by using heated blade to form the FDTs tablets. If the taste of drug is bitter, then the dried cylinder can also be used to coat granules for taste masking [45].

Taste Masking

Different types of taste masking techniques are used to hide or mask an unpleasant, bitter and bad taste of the drug. For taste masking of the drug microencapsulation technique is used. For microencapsulation of drug different types of pH sensitive acrylic polymers like Eudragit L-55, Eudragit Eand Eudragit RL are used. To overcome the bad taste of drug different types of methods like solvent evaporation and solvent extraction are used. These polymers are used to mask the bitter taste of the drug. Apart from the taste mask, it also fastenthe disintegration and dissolution rate of the APIs. This increase rate of dissolution further increases the bioavailability of the prepared ODTs as compared to other conventional tablets. A novel method for taste masking of macrolides was reported by using monoglycerides. Selection of materials used in preparation ODTs depends upon the unpleasant or bitter taste of the drugs. They have very low melting point which helps to form good elaborate film, very easily soluble in intestine [46].

CONCLUSIONS

Fast disintegrating tablets have possible advantages over usual dosage forms, with improved patient observance, convenience, bioavailability and rapid onset of action. They are good substitute for drug delivery to geriatric and paediatric patients. They have major advantages of both solid and liquid dosage forms, as they remain solid during storage, which assist in stability of dosage forms and transform into liquid form within few seconds after its administration. Thus FDT has great scope for being immediate drug delivery.

It is generally used for the treatment of different diseases. It is safe well tolerated. As the development a new drug molecule is time consuming and costly affair, the research is being concentrated on the development new dosage forms of the existing drug molecules for having better patient acceptance and compliance, this approach provided an option for the utilization of fast oral disintegrating delivery systems. Orally disintegrating tablets system has several advantages as compared to traditional systems such as fast dissolution, quick absorption through oral mucosa and allowing complete disintegration before swallowing for quick therapeutic action. Thus, this review project, have been attempted to explore the benefits of such delivery system over the conventional system.

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