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An Insight into Fast Dissolving Tablets

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ABSTRACT

Fast dissolving tablets (FDTs) are unit solid dosage forms that are administered orally and often used for juvenile and geriatric patients who have difficulty in swallowing. Another advantage of FDTs is that they do not require water thereby, increases patient compliance. Direct compression, freeze-drying, spray drying, melt granulation, sublimation, mass extrusion, etc., are some of the processes used to make FDTs. Since FDTs disintegrates and dissolves fastly, they show the rapid onset of action and the production method parameters need to be optimized accordingly with the critical product parameters. The most extensively used production methods as well as evaluation tests for FDTs are discussed in this study.

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INTRODUCTION:

The most important route for drug delivery is the oral route. It has many advantages like patient compliance, less manufacturing cost and cost-effective. FDTs is one of the best methods for the drugs to be administered through the oral route [1]. FDTs can be defined as "solid dosage forms containing medicinal substances which disintegrate rapidly usually within seconds when placed in oral cavity" by USFDA CDER in orange book [2].These dosage forms are mainly useful for patients who are bedridden and mentally retarded. FDTs are single unit dosage forms that disintegrate within a few seconds i.e., <30 seconds or <one minute. Soon after the administration, the drug absorbs into the body and shows an immediate onset of action. They can be easily retrieved from the mouth and can be used in emergencies [1]. FDTs can be formulated by multiple techniques like spray drying, wet granulation, moulding, sublimation, direct compression, lyophilization, etc. various super disintegrants like croscaramellose sodium, sodium starch glycolate, crospovidone, xanthan gum, etc. are used [3] . After administration, the drug gets absorbed through the oral cavity and enters into systemic circulation via a jugular vein [4]. As per the recent market evaluation, most of the population prefers FDTs (70-80%) [2].

IDEAL CHARACTERISTICS:

1. It should disintegrate within a few seconds i.e., less than 30seconds.
2. It should exhibit a pleasant mouth feel after administration.
3. The tablet should withstand different environmental conditions like temperature, humidity and should exhibit low sensitivity.
4. FDTs can be manufactured by using different conventional methods at a low cost [5].
5. No requirement of water for oral administration of tablet because it gets dispersed within seconds [6].
6. It should be patient compliance.
7. FDTs must be cost-effective [7].
8. It should not leave any residue in the mouth [8].
9. Should be compatible with other excipients [9].

ADVANTAGES:

1. Dose accuracy can be maintained.
2. Shows a rapid onset of action.
3. It is easy to administer and is convenient for pediatric, geriatric patients.
4. Low sensitivity to environmental conditions [10].
5. Shows more bioavailability [1].
6. More stable at different temperatures because the drug remains in solid dosage form until the administration of tablet into the oral cavity [11].
7. Rapid rate of drug absorption is possible because of pre-gastric absorption from the mouth, pharynx, and oesophagus [12].

LIMITATIONS:

1. FDTs are hygroscopic in nature, so care must be taken during storage.
2. It requires special packaging material for proper safety and stabilization [3].
3. Less mechanical strength.
4. Shows an unpleasant taste [13].
5. Shows grittiness if it is not properly formulated.
6. FDTs are not suitable for persons with decreased saliva.
7. Bitter taste drugs cannot be formulated as FDTs hence need to mask the taste of the drug [14].
8. FDTs are manufactured with low compression force hence making the tablet more fragile and brittle [15].

FACTORS EFFECTING ORAL ABSORPTION [16, 5, 8, 13]:

Table 1: list of factors effecting oral absorption

S.NO	FACTORS	INFERENCE
1.	Lipophilicity of drug	For more absorption, the drug must possess high lipid solubility.
2.	pH and pKa of saliva	For high absorption, the drug must be in an unionized state at salivary pH.
3.	Binding to the oral mucosa	Drugs should not bind to the oral mucosa.
4.	Partition coefficient	Drugs with low partition coefficient value (40-2000) are formulated as FDTs.
5.	Solubility in salivary secretion	Drug must be soluble in salivary fluids.
6.	Thickness of oral mucosa	The thickness of buccal mucosa (500-800 micrometer) which is higher when compared to the oral mucosa (100-200 micrometer).
7.	Drug dose	The dose of the drug must be less than 20mg.
8.	Patient factors	• Mentally retarded patients • Bed ridden patients • Psychiatric patients • Pediatric patients Cannot swallow the drug easily.
9.	Marketing and manufacturing factors	As the drug patent gets expired pharmaceutical companies will develop a new generic drug, hence this leads to increased revenue and can also target the under-treated patient population.
10.	Effectiveness factor	Rapid onset of action and increasing the bioavailability are majorly considered while formulating FDTs.
11.	Taste	The tablets should not be bitter in taste.
12.	Undesired	Drugs with a short half-life, frequent dosing will affect the oral absorption.

SALIENT FEATURES OF FDTs:

1. FDTs give a good mouth feel especially for pediatric patients.

2. Rapid onset of action can be seen in case of cough, allergic conditions, and motion sickness.

3. Fast disintegration shows a quick onset of action.

4. Drug recovery is possible in case of emergencies.

5. Bioavailability can be improved by pre-gastric absorption if any, as a result of reduced dose clinical efficiency can be increased with fewer side effects.

6. New opportunities can be seen in the case of patent extension, product promotion, product differentiation, and lifecycle management [4].

7. FDTs can be administered easily to patients who are unable to swallow [14].

CHALLENGES AND CHARACTERISTICS IN FORMULATING FDT'S [2, 17]:

Table 2: list of challenges in formulating FDT's

S.NO	CHALLENGES	DESCRIPTION
1.	Masking of taste	The majority of drugs are bitter in taste, hence taste masking is a main criteria for bitter drugs.
2.	Palatability	Taste masking must be done for the tablets, as majority of the drugs are unpalatable.
3.	Mechanical strength and disintegration time	An increase in the mechanical strength leads to a delay in the disintegration time of tablet, as the FDTs are formulated to get disintegration time within 30 seconds. So, the main criteria in formulating FDTs is maintaining the good mechanical strength.
4.	Environmental sensitivity	The tablet should show less sensitivity to environmental conditions like temperature and humidity.
5.	Mouth feel	The tablet should disintegrate into smaller

		particles after administration into the oral cavity and it should not leave any residue in the mouth.
6.	Drug dose	The drug dose must be <60mg for soluble drugs and <400mg for insoluble drugs hence this parameter is a major challenge in formulating FDTs.
7.	Size of the tablet	The ease of administration depends on the size of the tablet. The size of the tablet to follow is 7-8mm, hence tablet size is difficult to formulate.
8.	Aqueous solubility	Aqueous soluble drugs form glassy solid structures resulting in collapse and also forms eutectic mixtures. So collapse can be prevented by using mannitol which can increase crystallinity.
9.	Drug properties	Solubility, hydrophilicity, particle size of a drug may affect FDTs formulation

EXCIPIENTS USED IN FDT'S FORMULATION [18, 9, 17]:

Table 3: list of excipients

S,NO	NAME OF THE EXCIPIENTS	PERCENTAGE	EXAMPLES
1.	Super disintegrants	1-20%	Microcrystalline cellulose, sodium starch glycolate, alginic acid, croscaramellose sodium, crospovidone
2.	Binder	6-10%	Polyvinyl pyrrolidine, acacia, gelatin
3.	Diluents	1-80%	Mannitol, spray dried lactose
4.	Polymers	1-10%	PEG 6000, PVP K-30, Cyclodextrin

Super disintegrants:

The use of disintegrants is the major approach while formulating FDTs. Disintegrants play a major role in dissolution and disintegration. The optimum concentration of disintegrants should be used for high dissolution and rapid disintegration. Due to swelling and wicking

properties, super disintegrants show quick disintegration. Some of the disintegrants used are sodium starch glycolate(SSG), croscaramellose sodium(CCS), crospovidone(CP), microcrystalline cellulose(MCC), pregelatinized starch.

Mechanism of super disintegrants:

If the concentration of super disintegrant is above the critical concentration, the disintegration time increases or remains constant and if it is below the critical concentration, disintegration time may increase or decrease concerning concentration of super disintegrant.

Table 4: mechanism of super disintegrants

S.NO	MECHANISM	EXAMPLES OF SUPER DISINTEGRANTS
1.	Wicking and swelling	Crosslinked alginic acid, crosslinked PVP
2.	Wicking	Cross linked cellulose, cross linked PVP, calcium silicate
3.	Swelling	Cross linked starch

TECHNOLOGIES FOR PREPARATION OF FDTs [9, 5]:

These are classified into 2 categories:-

a. Non-patented technology: include direct compression, spray drying, lyophilization, melt granulation, mass extrusion and sublimation.

b. Patented technology: include Dura-solv, Flash-dose, Wow tab, Zydis and Ora-solv technologies

NON-PATENTED TECHNOLOGIES

Table 5: list of non-patented technologies

S.NO	METHODS	INFERENCE
1.	Direct compression	It is the easiest and preferable method for compression of tablet. It is described as the process in which powder/ granules are directly compressed into a tablet without modifying the physical nature of the material. The optimum concentration of diluents, super disintegrants, lubricants results in rapid disintegration of the tablet.
2.	Spray drying	Fine powder with high porous nature can be produced from spray drying. Formulation obtained from this process contain un-hydrolyzed and hydrolyzed gelatin as supporting material, SSG or CP or CCS as super disintegrants, mannitol as diluent/filler.
3.	Lyophilization	This method is applicable for thermolabile drugs. Drying is performed at low temperature and by sublimation technique, water is removed. The tablets obtained by this technique are more sensitive, thereby need special packaging. The major limitation of freeze drying is having poor stability when exposed to stress conditions.
4.	Melt granulation	This technique uses materials that are effective as granulating fluids when they are in molten state. To solidify the molten materials, agglomerated powders must be cooled.
5.	Mass extrusion	The powder blend is passed through an extruder to obtain a cylindrical extrude. Water miscible polymers and methanol are utilized to soften active blend solvent mixture. Later, these extrude are made into even segments by using a heated blade to form tablets.
6.	Sublimation	Dissolution is rate-limiting due to low porosity, hence it reduces the water permeation into the matrix. So, volatile substances are combined with tablets of high porosity. In the present technique, ammonium bicarbonate, urea, urethane, etc can be incorporated as sublimating agents.

PATENTED TECHNOLOGIES:

Table 6: list of patented technologies

S.NO	METHOD	INFERENCE
1.	Dura-solv	It is a patented technique of CIMA labs. Tablets prepared by this technology contain drug, diluent and lubricant. For compression of tablet, low compression force is used, direct compression methods and conventional equipment is employed, and hence leads to reduction in the production cost.
2.	Flash-dose	It is a patented technology of FUISZ. It consists of floss which acts as self-binding shear from matrix which is prepared by flash heating process.
3.	Wow-tab	Combination of high and low mouldability saccharide are used to prepare a tablet and obtaining a product possessing proper hardness and achieve better dissolution.
4.	Zydis	This technology utilize a special freeze drying method which involves preparation of drug solution by using vaccum mixer. The drug solution was placed in a vessel and filled into blister pockets. The formulations prepared by this technique have poor stability at high temperature and humidity.
5.	Ora-solv	This technology utilizes taste masked drug particulate in the formulation which enhance tablet disintegration time. Effervescence is observed when the drug components combines with water.
6.	Flash-tab	Granular excipients and coated crystals of drug are compressed to prepare a tablet. Swelling and disintegrating agents are two main mechanisms involving in this technology. Swelling agents such as starch, microcrystalline cellulose are used. Disintegrating agents like CMC are used to compress the tablet.

DRUGS USED IN FDT'S [3, 19]:

Table 7: list of drugs

S.NO	CATEGORY	DRUG EXAMPLES
1.	Anti-epileptics	Phenytoin, valproic acid
2.	Anti-gout agents	Probencid, allopurinol
3.	Analgesics	Ibuprofen, mefenamic acid
4.	Diuretics	Spironolactone,acetazolamide
5.	Anti-thyroid agents	Carbimazole
6.	Local anaesthetics	Lidocaine
7.	Anxiolytic agents	Lorazepam, alprazolam
8.	Anti-hypertensive agents	Amlodipine
9.	Anti-fungal agents	Miconazole, clotrimazole
10.	Anti-malarial agents	Chloroquine, pyrimethamine
11.	Anti-bacterial agents	Doxycycline,tetracycline
12.	Nutritional agents	Vitamin A,B,D
13.	Gastro-intestinal agents	Ranitidine, famotidine, domperidone, mesalazine, thymoquinone

EVALUATION TESTS [18, 16, 7, 20]:

1. General appearance: Tablet size, shape, color, odor, taste, surface morphology are evaluated.

2. Size and shape: Size and shape must be considered and monitored.

3. Thickness of tablet: 10 tablets were weighed from each formulation and the thickness was measured by using a digital screw gauge micrometer.

4. Weight variation: 20 tablets were selected and weighed randomly from each formulation. As per I.P, the weight variation specification is shown in the following table:

Table 8: list of weight variation of the tablet

S.NO	AVERAGE WEIGHT OF THE TABLET	PERCENTAGE DEVIATION
1.	<80mg	±10
2.	80mg-250mg	±7.5
3.	>250mg	±5

5. Hardness: It is defined as the force required to break the tablet and was measured by using a Monsanto hardness tester. It was expressed in kg/cm^2.

6. Friability: It was determined by using Roche's friabilator.20 tablets were weighed and placed in the friabilator, the chamber revolves at 25 rpm and drops a tablet at a height of 6inches for each revolution. This was subject to 100 revolutions. The friability was given by the formulae:

$$F= W_1-W_2 / W_1$$

Where, W_1= weight of the tablet before friability

W_2= weight of the tablet after friability

7. Wetting time: This method was used to measure the tablet wetting time. A 2 folded tissue paper (12 cm x 10.75cm) was placed in a petri dish containing 6ml of Sorenson's pH 6.8 buffer, then a tablet was placed on the paper and complete wetting of the tablet was measured.

8. In-vitro disintegration test:

It was measured by placing a tablet in a beaker containing buffer. 3 tablets from each formulation were selected and disintegration time was measured.

9. In-vitro dissolution test:

This was performed by using USP type II apparatus (paddle) at 50 rpm. A suitable buffer was selected as dissolution media and the temperature was maintained at 37±5°C. 5ml of sample was withdrawn at specific time intervals and was filtered. The amount of drug dissolved will be determined using UV spectrophotometer by measuring the absorbance of the sample.

10. Stability testing:

Tablets were placed in suitable packaging material and were stored at different temperatures as prescribed by ICH guidelines for accelerated studies.

35±1°C

45±1°C

37±1°C and RH 75±5%

The tablets were analyzed for physical characteristics such as hardness, friability, disintegration, dissolution, etc, and percentage of drug content after 15 days.

PATENTED TECHNOLOGIES AND THE DRUGS USED [16]:

Table 9: list of patented technologies and the drugs

S.NO	TECHNOLOGY	PATENT OWNER	PROCESS INVOLVED	DRUGS USED
1.	Flash-tab	Ethypharm	Lyophilization	Ibuprofen
2.	Flash-dose	Fuisz	Cotton candy process	Tramadol HCL
3.	Zydis	R.P. scherer INC	Lyophilization	Loratidine
4.	Dura-solv	Cima labs INC	Moulding	Hyoscyamine sulphate
5.	Wow-tab	Yamanouchi pharma technology INC	Compressed moulded tablets	Famotidine
6.	Ora-solv	Cima labs INC	Compressed tabs	Paracetamol

CONCLUSION:

FDTs are rapidly evolving technology that offers significant advantages in terms of lifecycle management, development timelines, patient convenience, and marketability. By keeping a close eye on technological advancements, pharmaceutical companies can benefit from new technologies. FDTs are useful for expanding product lines with the ongoing development of new technologies, one can anticipate the emergence of pharmacological excipients. In the days, ahead there will be more unique technologies for FDTs; they have been successfully marketed with a pleasant taste and quick release time, qualities of release with the rapid acceptance of FDTs by the public and the market. The dosage form appears to be promising as does the product pipeline, which continues to expand at a high rate. FDTs can improve patient compliance and shows a rapid onset of action with enhanced bioavailability.

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