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Formulation Development of Fast Dissolving Tablets

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ABSTRACT

Since the previous decade, oral administration has received substantially more attention for the treatment or management of disorders. Mouth dissolving tablets (MDTs), a novel idea in oral delivery, are now widely used. Mouth dissolving tablets are solid dosage forms that dissolve and release the active ingredient when placed in the mouth for a short period of time without the use of water. Geriatric, pediatric, and bedridden patients are particularly affected by it since they have swallowing issues, as do those with dysphasia. It is more convenient for traveler's and those who do not have easy access to water. Various technologies use super disintegrants to make mouth dissolving pills. Because of higher patient compliance, mouth dissolving tablets are more reliable than traditional dosage forms such as tablets and capsules. The improvement in this subject enables the development of a more cost-effective and efficient method of disease management while avoiding many issues associated with other delivery systems. DEFINITION: A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrants in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, repimelts, porous tablets, Orodispersible, quick dissolving, or rapid disintegrating tablets.

I. INTRODUCTION:

Recent developments in technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous, or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrants in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient.

These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development ofMDT is the use of super disintegrants like Cross linked carboxymethyl cellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.

The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjectto first pass metabolism is reduced as compared to standard tablets Different types of technologies have been employed for the formulation of mouth dissolving tablets viz freeze-drying, Tablet Molding, Direct Compression

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Method, spray drying and sublimation Technologyetc. have been tried by researchers to maximize the pore structure of tablet matrix.

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containingmedicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water.

IDEAL PROPERTIES:

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablets using conventional processing and packaging equipment.
- It should not require any liquid or water to show its action.
- Be portable without fragility concern.
- More rapid drug absorption from the pre-gastric area i.e., mouth, pharynx and oesophagus which may produce rapid onset of action.

ADAVANTAGES:

- Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
- Increases onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Conventional processing and packaging equipment's allow the manufacturing of tablets at low cost.
- Good mouth feels, especially for pediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.
- The FDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water and thus provides improved patient compliance.
- Minimum risk of suffocation in airways due to physical obstruction, when FDTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.

DISADVANTAGES:

- The major disadvantages of FDTs are related to the mechanical strength of tablets.
- FDT are very porous and soft molded metrics or compressed in a tablet with low

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compression, which makes tablet friable and brittle which difficult to handle.

- Major drawback of this system is high cost, time consuming procedure and fragility, making conventional packing inappropriate for packing this dosage form and stability issues under stress condition.
- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- MDT requires special packaging for proper stabilization & safety of stable product.
- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Mechanism of Action:

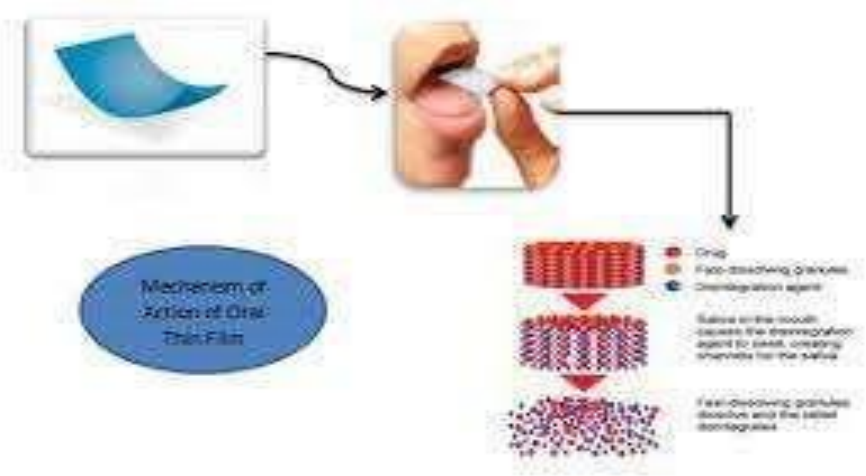
The four major mechanisms for tablet disintegration are as following-:

Swelling:

When tablet comes in contact with water then swelling occurs and thus adhesiveness of other ingredients of the tablet is lost, causing the tablet disintegration.

Due to repulsive forces:

-Another mechanism of disintegration attempts the swelling of tablet made with„nonswellable" disintegrants. Nonswelling particles also cause disintegration of tablets. Generation of electric repulsive forces between particles promotes the disintegration of tablets and water is required for it.



Deformation

-The super disintegrants get deformed during tablet compression and upon contact with water they regain their normal structure which causes an increase in size of deformed particles resulting in the breaking of tablet.

Porosity and Capillary Action (Wicking)-

Due to the porous nature of the tablet, the liquid is drawn (wicking action) into the tablet through capillary action, thus the inter-particulate bonds get ruptured causing disintegration of tablet.

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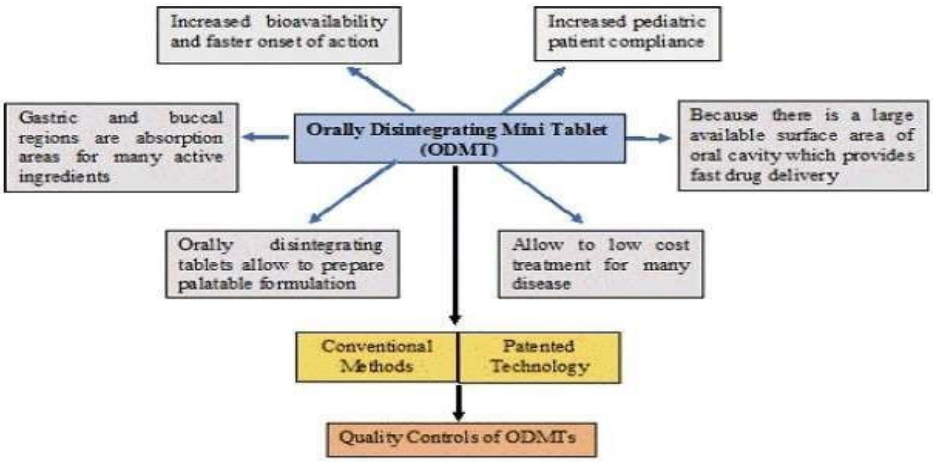
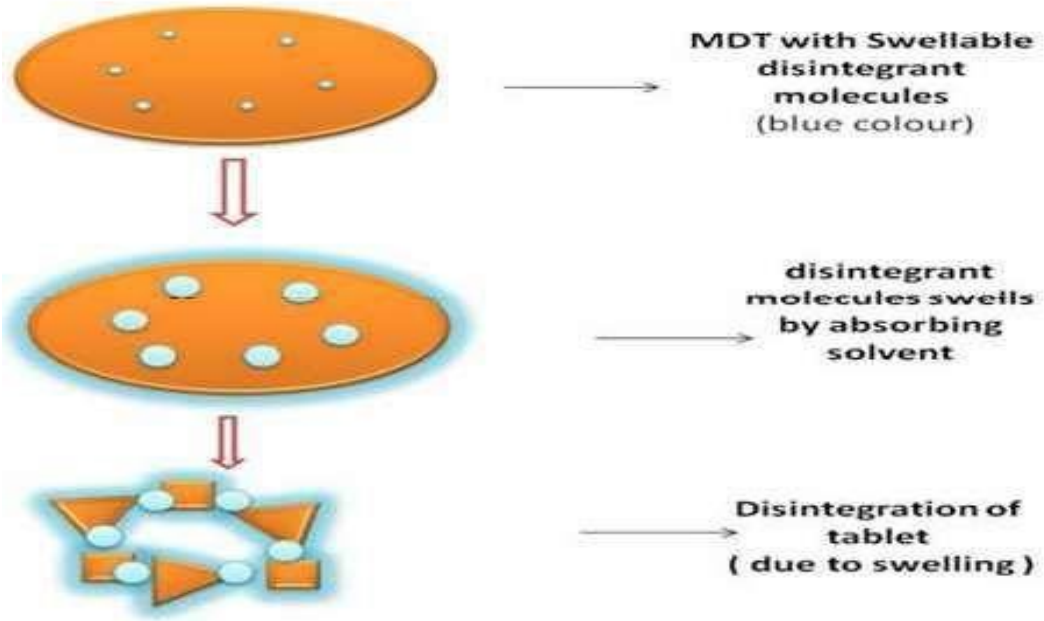


Enzymatic reaction:

Some enzymes present in the body also act as disintegrants. These enzymes reduce the binding ability of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or enhance absorption of water leads to an enormous increase in the volume of granules to improve disintegration.



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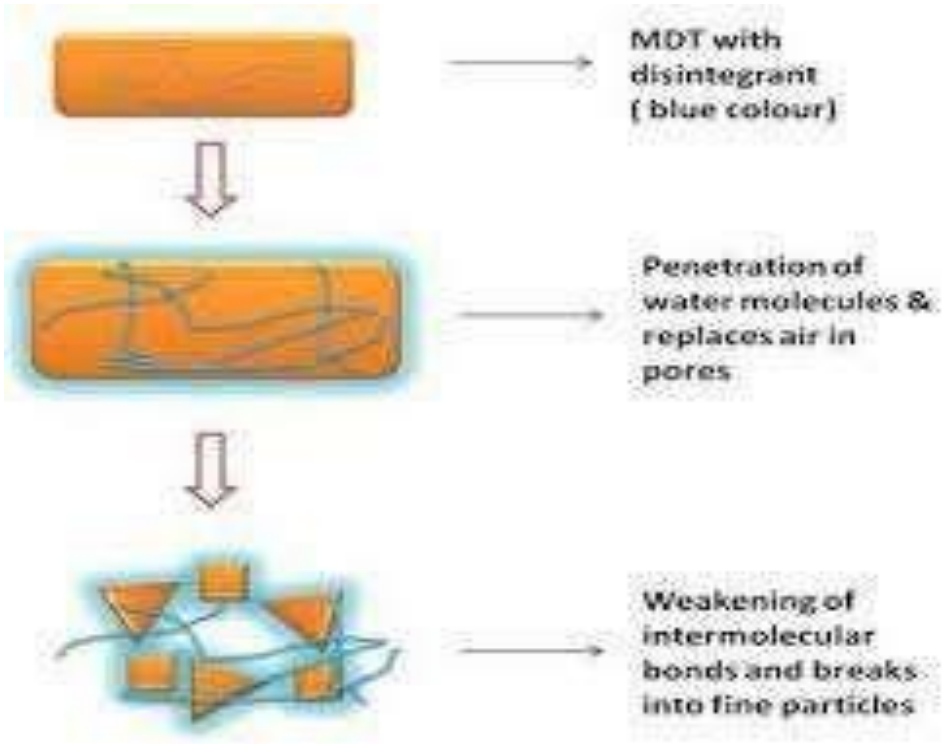

DRUGS TO BE IN CORPORATED IN FAST DISSOLVING TABLETS:

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Anthelmintics:
Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.

Anti-Arrhythmic Agents:
Amiodarone, Disopyramide, Flecainide Acetate, Quinidine sulphate.

Anti-bacterial Agents:
Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Tetracycline, Trimethoprim.

Anti-coagulants:
Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

Antidepressants:
Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate., Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide. Anti-Epileptics: Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine,valproic acid.

Anti-Hypertensive Agents:
Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.

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Anti-Fungal Agents:
Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, Undecanoic Acid.

Anti-Gout Agents:
Sulphinpyrazone, Allopurinoc, probenecid.

Anti-Malarial:
Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.

Anti-Migraine Agents:
Dihydroergotamine Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate,

Anti-Muscarinic Agents:
Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide.

Anti Protozoal Agents:
Benznidazole, Clioquinol, Deco quinate, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.

Anti-Thyroid Agents:
Carbimazole, Propylthiouracil. Anxiolytic, Sedatives,

Corticosteroids:
Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Fluticasone Propionatu, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.

Diuretics:
Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid.
Histamine H, -Receptor Antagonists:

Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Dimenhydrinate,
Flunarizine, Loratadine, Meclozine, Oxatomide, Terfenadine, Triprolidine.

METHODOLOGY IN FORMULATING FAST DISSOLVING TABLET:-
1.Melt granulation:

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

2.Phase transversion process:

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min.

3.Sublimation:

In this method, a subliming material like camphor , is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously

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existed in the compressed mannitol tablets prior to sublimation of the camphor.

4.Three-dimensional Printing (3DP) :

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding material.

5. Mass Extrusion:

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

6. Spray Drying:

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitola s a bulking agent and sodium starch glycolate or cross carmellose or crospovidone are used as super disintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a super disintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate).

7. Cotton Candy Process:

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association withCeform . TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs.

a) Floss Blend:

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers.This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

b) Floss Processing:

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in ‘cotton-candy’ formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material.

c) Floss Chopping and Conditioning:

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

d) Blending and Compression:

Finally, the chopped and conditioned floss fibers are blended with the drug along with other required excipients and compressed into tablets. This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

8. Tablet Molding:

Molding process is of two types’ i.e., solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding).

The solvent is then removed by air-drying. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which

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increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

9. Lyophilization or Freeze-Drying:

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs.

10.Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially super disintegrants and sugar based excipients.

a) Super disintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence the dissolution.

b) Sugar based:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types based on molding and dissolution rate.

11.Nanonization:

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water soluble drugs.

II. CONCLUSION

It is developing a novel, cost effective one step FDDT manufacturing process using conventional tableting technology for the production of robust tablets suitable for conventional packaging. The advantages of the proposed method have easy adaptability in industry &practical applications in the areas of quick disintegration and dissolution enhancement. The formulation prepared with Crospovidone was offered relatively rapid release of Ibuprofen when compared with other super disintegrants used in this investigation. Statistically significant difference between dissolution efficiencies (DE) of Ibuprofen tablets formulated with different super disintegrants was observed. A new tablet dosage format, the fast-dissolving tablet has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid.

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