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REVIEW: ORAL FAST DISINTEGRATION TABLET

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ABSTRACT
Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spray drying and use of disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times, and dissolution are also discussed.

KEYWORDS: Fast dissolving tablets, freeze drying, spray drying, taste masking.

INTRODUCTION

Fast Disintegrating Tablets

United States Food and drug administration defined fast disintegrating tablet as "a solid dosage form containing medicinal substance or active ingredient which disintegrate fast usually within a few seconds when placed upon the tongue." FDTs differ from traditional tablets as they are designed to be dissolved on the tongue rather than swallowed whole. Fast disintegrating tablets are also known as mouth-disintegrating tablets, melt-in mouth tablets, Orodispersible tablets, porous tablets, quick dissolving tablets, fast dissolving tablets.[1]

According to US Food and Drug Administration 2008 publications of guidance are:

1. FDTs should have an In vitro disintegrating time of approximately 30 sec or less.
2. Generally, the FDT tablet weight should not exceed 500 mg, although the combine influence of stable weight, size and component solubility all factor into the acceptability of an ODT for both patients and regulators.

Recent advances in novel drug delivery system aim to enhance safety and toxicity of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast dissolving tablets. Fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for paediatric and geriatric patient. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients who experience difficulties in swallowing traditional oral solid-dosage forms. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds.[2]

Fast dissolving tablets are a perfect fit for all of these patients. The FDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All FDTs approved by the Food and Drug Administration are classified as orally disintegrating tablets.

Recently, the European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that is to be placed in oral cavity where it disperse rapidly before swallowing.

The major advantage of FDT formulation is that it combines the advantage of both liquid and conventional tablet formulation cavity and also due to pregastric

absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets Drug delivery systems are a strategic tool for expanding markets, extending product life cycles and generating opportunities.[3]

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors.[4]

ADVANTAGES OF FDTS[5]

- Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- 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 provide improved patient compliance. Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and Manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.
- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and esophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Good mouth feels, especially for paediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.
- Minimum risk of suffocation in air ways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.
- Conventional processing and packaging equipments allow the manufacturing of tablets at low cos

Limitations To Fdt[6]

- Drugs with relatively large doses are difficult to formulatento FDTs.
- Patients who concurrently take anti-cholinergic medications may not be the best candidates for FDTs.
- Tablets usually have insufficient mechanical strength. Hence, it requires careful packaging and handling.
- Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- They are more susceptible to degradation by humidity and temperature.
- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- FDT requires special packaging for properly stabilization & safety of stable product.
- Drugs difficult to formulate into FDT with relatively larger doses.
- Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates of FDTs.

The Need for Development of Oral Fast Disintegration Tablets[7]

Patient factors: Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an8-oz glass of water. These include the following

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Paediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.

Effectiveness factor: Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improves for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre gastric segments of GIT.

Selection of Drugs For Fdts[8]

For the selection of drug, there are following criteria;

- No bitter taste.
- Dose lower than 20mg.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially unionized at the oral cavities pH.
- Oral mucosal tissue can be permeated.

- Ability to permeate oral mucosa.
- At least partially non-ionized at the oral cavity.
- Have the ability to diffuse and partition into the epithelium of the upper GI.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half-life and frequent dosing drugs are unsuitable for FDT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odour drugs are unsuitable for FDT.

Challenges In Formulating Fdts[9-10]

Palatability: Most of the drugs are unpalatable. Fast dissolving tablet usually contain medicament in taste mask form which upon administration, disintegrates or dissolves in patient's oral cavity.

Mechanical strength: In order to allow fast dissolving tablets to disintegrate in the oral cavity, they are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force

Hygroscopicity: Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity.

Amount of drug: The application of technologies used for orally disintegrating tablets is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.

Aqueous solubility: Water-soluble drugs pose various formulation challenges because they form eutectic mixtures

Size of tablet: The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Taste masking: As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste- masked form. Delivery systems disintegrate or dissolve in patient's oral cavity.

Mouth feel: FDTs should not disintegrate into larger particles in the oral cavity.

Sensitivity to environmental conditions: FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water.[4]

Significance of Fdts[11]

Oral Disintegrating Tablets offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include -

- Accurate Dosing
- Enhanced bioavailability
- Rapid action
- Patient compliance
- Ease of administration
- Obstruction free
- Enhanced palatability
- Simple packaging
- Business Avenue
- Cost effective

Mechanism[12,13]

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet Disintegrates are important excipients of the tablet formulation, they are always added to tablet to induce breakup of tablet when they are comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrates. The objectives behind addition of disintegrates are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together.

Pharmacokinetics

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution while RDT is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of RDT in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

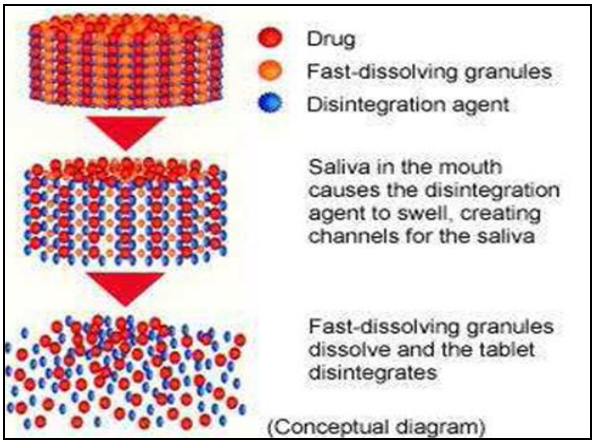

Fig no: 1 Mechanisms of FDTs.

Pharmacodynamics

Drug reception interaction impaired in elderly as well as ion young adults due to development of organ. Decreased ability of body to respond baro reflexive stimuli, cardiac output and orthostatic hypotension may see in taking anti-hypertensive like prazosin. Decreased sensitivity of CVS to beta adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illness is often present in elderly, which is also taken into consideration while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patients.

MENUFECTURE TECHNOLOGIES OF FDTS[13-14]

A) Conventional Technologies

Freeze drying technology: Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth

Tablet Molding: Molding process is of two type's 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 moulded plates to form a wetted mass (compression moulding).

Cotton Candy Process: The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shear form technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. solubilisation of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

Nanonization: A recently developed Nano melt technology involves reduction in the particle size of drug to Nano size by milling the drug using a proprietary wet-milling technique. The Nano crystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs.

Phase transition 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

Three-dimensional Printing (3DP): Three-dimensional printing is a rapid prototyping technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large over all pore volume.

Melt granulation: Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able 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.

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.[7]

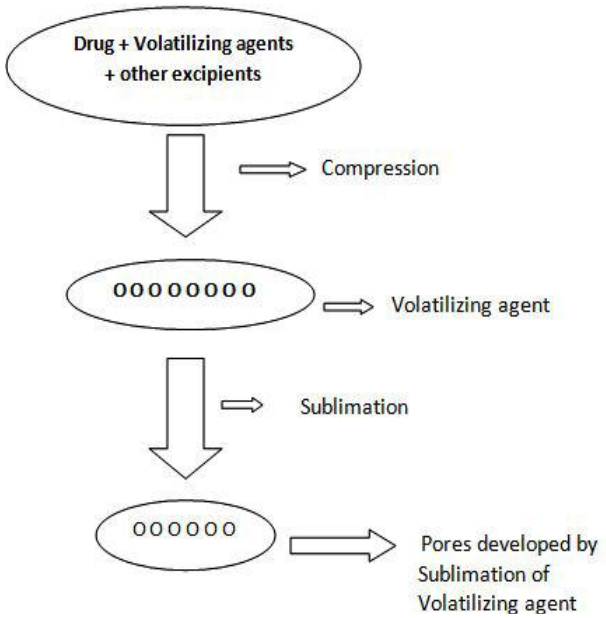

Fig: 2: Schematic Diagram of Sublimation Technique for Preparation of FDT.

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods.[8]

Spray drying

In this technique, gelatin can be used as supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmelloseor crosspovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.[10-15]

Disintegrant Addition

Disintegrant addition technique is one popular and cost-effective technique for formulating Fast-dissolving tablets because of its easy implementation. The basic principle involved in is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.[16]

MARKETED PRODUCTS OF FDT

Table 1.2: List of Commercially Available Oral Fast Disintegrating Tablets.[4]

Brand Name	Active Drug	Manufacturer
Benadryl	Diphenhydramine & pseudoephedrine	Warner Lambert, NY, USA
MouthmeltClaritin redi Tab	Loratidine	Schering plough Corp., USA
Olanexinstab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Feldenmouth melt	Piroxicam	Pfiser Inc., NY, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Zofran ODT	Ondensetron	GlaxoWellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA

Mechanism of Action of Superdisintegrants

By Swelling: It is a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. When it comes in contact with water it swell, the adhesiveness of other ingredients in a tablet is overcome causing the tablet fall apart as in figure 1.eg: Sodium starchglycolate.

Capillary Action: Disintegrant that do not swell they act through porosity and capillary action. Tablet porosity: provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) the3mselves enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.

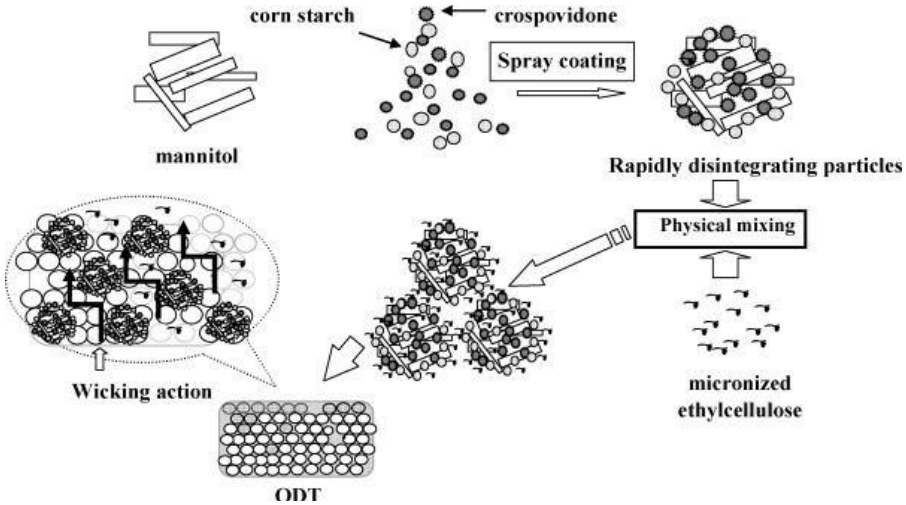

Fig: no 3: Capillary Action.

Due to heat of wetting: The capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

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.

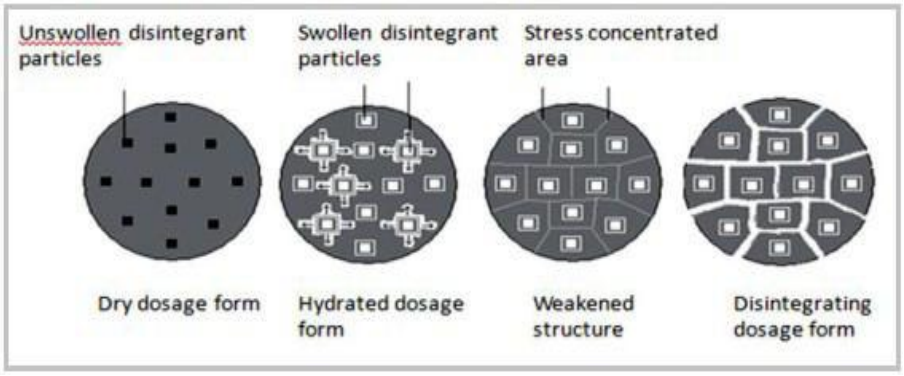

Fig no 4: Enzymatic reaction.

Due to release of gases: Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets.

Deformation: Starch grains are generally "elastic" in nature means that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, when the Compression forces involved in tableting applied, and then these grains are deformed permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

Acid base reaction (Chemical reaction): By internal liberation of CO_2 in water due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water tablet quickly broken apart. The tablet disintegrates due to generation of pressure within the tablet. Due to liberation in CO_2 gas, the dissolution of active pharmaceutical ingredients in water as well as taste masking effect is increased. As these disintegrants are highly sensitive to small changes in temperature and humidity level, control of environment must be required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation. The effervescent blend is added immediately before compression or can be added into two separate fraction of formulation.

Electrostatic repulsion: Guyot-Hermann has proposed a particle repulsion theory on the basis of his theory he observed that the particle with no swelling action also causes disintegration of tablets. Mechanism of disintegration based on electric repulsive forces between particles and water is required for it as shown in figure. Researchers found that repulsion is secondary to wicking.[17]

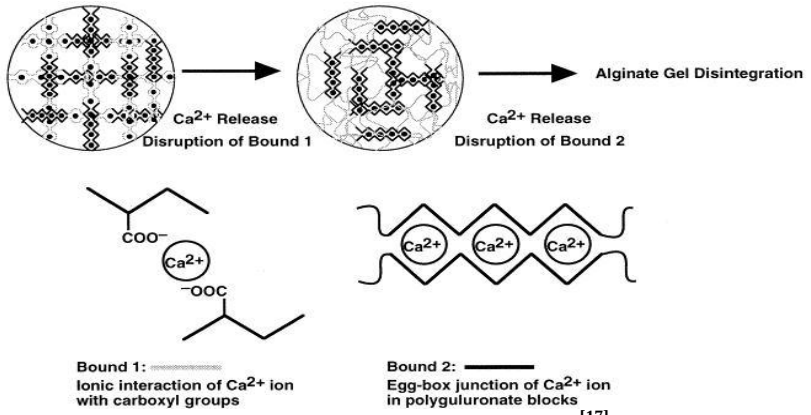

Fig no 5: Electrostatic repulsion.[17]

CONCLUSION

Quick-dispersing oral drug delivery systems are defined as oral drug delivery systems that when placed in the mouth dissolve or disintegrate within a few seconds to a few minutes and do not require water to aid swallowing. The FDT dosage forms are ideal for many groups of patients including geriatrics, pediatrics, and those people who have difficulty swallowing. An important benefit of FDT dosage forms is the ability to provide the advantages of a liquid medication in the form of a solid preparation. This feature enables the patient to take the dose as directed at any time without water and inconvenience. There is clear medical need and clinical benefits provided by these technologies and products.

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