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An Over View on Patented Technologies of Orodispersible Tablets

Review Article

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Abstract

Orodispersible tablets are dissolved rapidly in the saliva without the need of water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Other ingredients to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. Oro or mouth dissolving tablets have been formulated for pediatric, geriatric and bedridden patients and for active patients who are busy and travelling and may not have access to water orally dispersible tablets (ODTs) have received ever increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. This article describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In this review describes in detail about ODT technologies based on lyophilization, molding, sublimation, spray drying, mass extrusion and direct compression. Several techniques have been developed in the recent years, to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the technologies available and the advances made so far in the field of fabrication of orally dissolving tablets. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique patented technologies like Zydis, Orasolv, Durasolv, Flashtab, Flash dose and Wowtab, Lyoc, Pharmaburst technology, Frosta technology, OraQuick, Quick-Dis Technology, Sheaform Technology, Ceform Technology, Nano technology, Advatab.

Key Words: Oro dispersible , Patented technologies, Super disintegrants

Introduction

The oral route of administration is considered as the most widely accepted route because of its convenience, self-administration, compactness and ease of manufacturing. During the last decade, several new advanced technologies have been introduced for the formulation of ODTs (Orodispersible Tablets) with very interesting features, like extremely low disintegration time, excellent taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients.

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Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue[1]. Orodispersible tablets are also known as "Mouth dissolving tablets", "Orally disintegrating tablets", "Melt in mouth", "Fast dissolving drug delivery", "Rapimelts", "Porous tablets", "Quick dissolving tablets" etc[2]. Recently ODT terminology has been approved by United States of Pharmacopoeia, British Pharmacopoeia[3] and Centre for Drug Evaluation and Research (CDER). US FDA defined ODTs as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue". European pharmacopoeia also adopted the term "orodispersible tablet" as a tablet that is to be placed in the mouth where it disperses, rapidly before swallowing despite various terminologies used. Recently, ODT have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance especially in elderly and children. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable or brittle, which are difficult to handle, often requiring specialized peel off blister packaging. Along with the rapid market growth of ODT products, the technologies, too, have advanced considerably over the years.

The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs. Companies such as Eurand can produce pleasant tasting tablets, overcoming the common problem of poor drug taste compromising the benefits of an ODT. In addition, some companies is developing controlled release ODTs, significantly broadening the applications of this dosage form. A key reason that companies choose an ODT over other delivery technologies is that it is a relatively easy and often less risky delivery option to develop. Since the route of administration remains the same, ODTs that are formulated as bioequivalent line extensions or generic versions of an existing oral dosage form have minimal clinical requirements to gain approval. First generation ODTs are commonly characterized by high porosity, low density and low hardness, making them brittle and difficult to handle. As a result, they often require blister packaging, which is less convenient for patients than bottles and entails high production costs. Freeze dried ODTs are especially friable, making them difficult to package conventionally and raising questions about storage stability[4].

Furthermore, it is difficult to use traditional flavours and sugars to mask poor tasting APIs with first generation ODTs, which restricts their application to non bitter APIs. The common approach is to use flavouring and sweetening agents to overpower the taste rather than neutralize it. Today, there are only a few technologies on the market that provide effective taste masking capabilities, which requires a physical barrier between the API and the taste buds. One such technique is coacervation (encapsulation). As the ODT market matures, pharmaceutical companies are seeking additional capabilities from these dosage forms. These include higher API loading, more effective taste masking, controlled release capability.

THE NEED FOR DEVELOPMENT OF ORODISPERSIBLE TABLETS [5,6]

The need for non-invasive delivery systems persists due to patient`s poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Patient factors

Orodispersible dosage forms are particularly suitable for patients, for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric 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 diarrhoea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients.

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 improved 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.

Manufacturing and marketing factors

As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and undertreated patient populations.

Characteristics and Formulation Challenges of ODTs

The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows water absorption faster with maintenance of higher mechanical strength.

ODTs should have low sensitivity to moisture for greater stability. A good package design or other strategy should be created to prevent ODTs from various environmental conditions. For the ideal ODTs technology, the drug properties should not significantly affect the tablet property for example; the solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of a drug can significantly affect the final characteristics of tablets, such as porosity, tablet strength, disintegration and dissolution As the ODTs dissolve or disintegrate in the patien`s mouth, the drug will be partially dissolved in close proximity to the taste buds. Thus, the taste inside the mouth becomes critical for patient acceptance. When the drug is tasteless or does not have an undesirable taste, taste masking techniques does not become so important. The taste masking technology should not affect the ODT formulation[7].

Drug Selection Criteria [8,9]

- The ideal characteristics of a drug for in vivo dissolution from an ODT include:-
  - ✓ No bitter taste.
  - ✓ Small to moderate molecular weight.
  - ✓ Good stability in water and saliva.
  - ✓ Partially non-ionized at the oral cavities pH.
  - ✓ Ability to diffuse and partition into the epithelium of the upper GIT.
  - ✓ Ability to permeate oral mucosal tissue.
- Unsuitable drug characteristic for ODT:-

- ✓ Short half-life and frequent dosing.
- ✓ Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- ✓ Required controlled or sustained release.

Desired Criteria For ODTs [10,11,12]

- ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking technologies should be adopted for bitter drugs.
- Exhibit low sensitivity to environment condition such as humidity and temperature.
- ODTs should dissolve / disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug and excipients property should not affect the orally disintegrating tablets
- Be portable and without fragility concern.

Advantages of orodispersible drug delivery systems [13,14,15]

Fast dissolving technology offers:

- ➢ Improved compliance/added convenience
- ➢ No water needed
- ➢ Can be designed to leave minimal or no residue in mouth after administration and also to provide a pleasant mouth feel.
- ➢ Chewing is not needed ,
- ➢ Better taste obtained by taste masking
- ➢ Improved stability, low sensitivity to environmental condition
- ➢ Administration to the patients who cannot swallow, such as the elderly, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- ➢ Rapid drug therapy intervention.
- ➢ Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
- ➢ Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- ➢ Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.

The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

Disadvantages[16]**:**

- ➢ Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- ➢ Some time it possesses mouth feeling.
- ➢ ODT requires special packaging for proper stabilization & safety of stable product.

New Generation Of ODTs [1,17,18]

New generation of ODTs available today, is one that can be combined with a proprietary process to improve taste masking, allow a modified release profile, and enhance bio availability. As a result, formulators can taste mask even extremely poor tasting drugs, use high doses of API, and expand the range of therapeutic applications.

These ODTs comprises of rapidly dispersing microgranules, a direct compression blend and an external tablet lubrication method. The result is an ODT with excellent physical robustness, mouth feel, and disintegration properties. The tablets dissolve in 15 to 30 seconds (depending on dosage strength) and produce a smooth, pleasant tasting mixture of API granules and carrier that is easy to swallow. The tablets are made on standard presses, accept printing on both sides, typically have a friability of less than 0.5 percent, and can be packaged in bottles or blister packs. Combining micro encapsulation with ODT technology effectively can masks bitter APIs and can be applied to soluble and poorly soluble substances, as well as to high dose products. One technology is based on coacervation, a coating technique that encapsulates individual drug particles completely and provides superior taste masking. The coacervation process places a uniform coating of polymeric membranes of varying thicknesses and porosities directly to dry crystals or granules, creating particles that are typically 150 to 300 microns. The membranes create an inert barrier between the API and the taste buds and a stabilization barrier between the API and the tablet excipients. This coacervation technique has taste masked a wide range of extremely poor tasting drugs, including zolpidem (for insomnia), sumatriptan (for migraines), ranitidine (for gastro esophageal reflux)

First –Generation ODTs [1,19,20]

While first generation ODT technologies produce tablets that dissolve rapidly in the mouth, provide convenience and ease of swallowing and have had success in the market, some of them fall disorder), and cetirizine (for allergic rhinitis). It has also been applied to theophylline, ibuprofen, acetaminophen, pseudoephedrine, and products on the market that have incorporated the technique include Children's Chewable Advil, Rulid (roxithromycin) and the Benadryl line of products.

One of the biggest challenges for an ODT that uses taste masking polymers is achieving

bioequivalence with the conventional form (reference product).The polymers can impede API release in the gastrointestinal (GI) tract, delaying the onset of action. Using a micro encapsulation technique restricts dissolution of the API in the mouth, but allows rapid dissolution in the GI tract, thus overcoming the bio equivalence obstacle as given in figure 1.

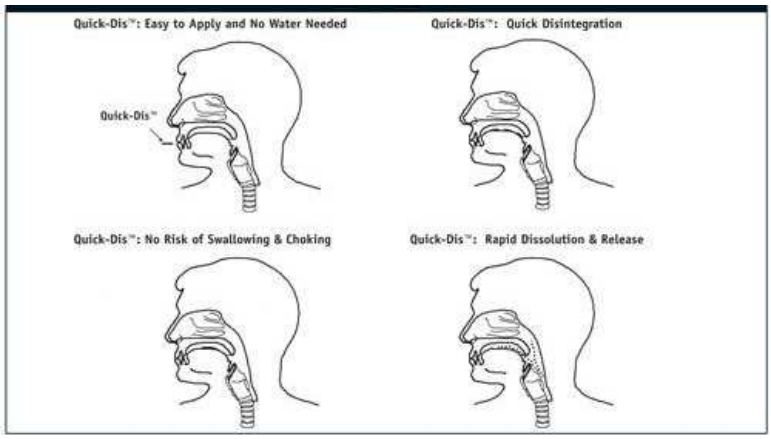

Figure 1: Advantages Of Orodispersible Drug Delivery Systems

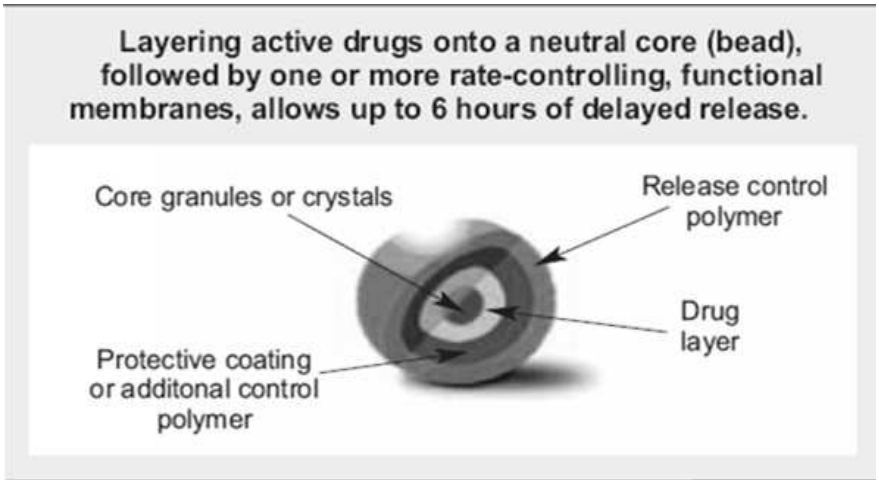

Figure 2: New generation ODTs

Controlled release Combining ODTs with specialized functional Polymers and coating processes can lead to ODTs with sustained modified and customized release profiles. It is even possible to combine release profiles in a single dose. Typical of these approaches are micro encapsulation and multiparticulate coating technologies, which allow formulators to create modified release polymer layers around API particles. These particles are flexible enough for compression without breakage or loss of the modified release properties and small enough to provide good mouth feel. Adjusting the coating parameters (thickness, composition, porosity, pH modifying agents and number of layers) changes the desired plasma profile.

Technologies Used For Manufacturing of orodispersible Tablets:

Various technologies used in the manufacture of Mouth dissolving Tablets include:

I. Conventional technologies
II. Patented technologies

I. CONVENTIONAL TECHNOLOGIES [1,21]

Freeze-Drying:

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. First of all, the material is frozen to bring it below its eutectic point. Then drying is carried out to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. However the use of freeze-drying is limited due to high cost of equipment and processing, low mechanical strength, poor stability at higher temperature and humidity.[22,23,24]

Sublimation:

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, menthol, ammonium bicarbonate, benzoic acid, hexamethylene tetramine, naphthalene, phthalic anhydride, etc. to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores (Figure 1) in tablet structure, due to which tablet dissolves when comes in contact with saliva. Mouth dissolving tablets with highly porosity exhibit good mechanical strength and have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

Direct Compression

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance.

Molding

Molded tablets, usually prepared from soluble ingredients, by compressing a powder mixture which is moistened with a solvent, into mould plates to form a wetted mass. Recently, molded forms have been prepared directly from a molten matrix, in which the drug is dissolved or dispersed or by evaporating the solvent from a drug solution or suspension at a standard pressure. Usually molded tablets are compressed at a lower pressure than are conventional tablets, and posses a porous structure that hastens dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Unfortunately, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases.[25]

Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder 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. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with different super disintegrategrants e.g. sodium starch glycolate, croscarmellose sodium and crosspovidone etc.[26]

Melt Granulation [27]

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. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

Phase Transistion Process [28]

Kuno *et al* proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique ODT were produced by compressing powder containing erythrito (melting point: 122 °C) and xylitol (meltingpoint: 93 - 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compactibility.

II. PATENTED TECHNOLOGIES [29,30,31,32]

ZYDIS Technology:

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

DURASOLV Technology: [33]

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring small amounts of active ingredients.

ORASOLV Technology:

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to prepare the tablets. The tablets prepared are soft and friable and packed in specially designed pick and place system.

FLASH DOSE Technology:

This technology is based on the preparation of sugar based matrix known as floss, which is made from a combination of excipients either alone or in combination of drugs. Two platform fuisz technologies called Shearform or Ceform are currently being utilized in preparation of wide range of oral disintegrating product.

Flash dose has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets; prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as “Floss”. Shearform matrices are prepared by flash heat processing.

WOWTAB Technology:

Wowtab Technology is patented by Yamanouchi Pharmaceutical Company WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

FLASHTAB Technology:

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion-spheronisation. All the processing utilized conventional tableting technology.

CEFORM Technology:

In this, microspheres containing active ingredient are prepared. The manufacturing process involves placing a dry powder, containing either substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into precision engineered, and rapidly spinning machine. The centrifugal force throws dry blend at high speed through small, heated openings. The resultant microburst of heat liquifies the drug blend to form sphere. The microspheres are blended or compressed into preselected oral delivery dosage form. The microspheres can be incorporated into a wide range of fast dissolving dosage forms such as flash dose or spoon dose, EZ chew.

SHEARFORM Technology:

The technology is based on the preparation of floss that is also known as “Shearform Matrix”, which is produced by subjecting a feed stock containing a sugar carrrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.[34]

COTTON CANDY:

Cotton candy process is known as candy floss process this technique forms the basis of flash dose (Fuisz technologies, Chantilly,VA). In this technology, saccharides or polysaccharides are processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The floss is then partially recrystallised to impart a good flow properties and compressibility. The floss then can be milled and blended with active ingredient and other excipients and finally that compressed into MDT. Advantages of this process are that the tablet can be accommodate high doses and posses satisfactory mechanical strength. The candyfloss are hygroscopic, hence; their manufacturing requires control of humidity conditions.

Superdisintegrants

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. Different types of superdisintegrants are used in the formulation of orodispersible tablets. Some of the superdisintegrants, their commercially available grades and their mechanism of action are mentioned in the below table.[35]

Superdisintegrants	Commercially available grades	Mechanism of action	Special comment
Crosslinked cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC.	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.	Swells in two dimensions. Direct compression or Granulation Starch free.
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature so get porous tablet.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix.
Crosslinked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action.	Promote disintegration in both dry or wet granulation.
Soy polysaccharides	Emcosoy®		Does not contain any starch or Sugar. Used in nutritional products.
Calcium silicate		Wicking action.	Highly porous, Light weight,

TABLE 1: List of supersisintegrants

CONCLUSION

The ODTs have potential advantages over conventional oral dosage forms with their improved patient compliance; convenience, bioavailability and rapid onset of action which drawn the attention of many manufactures over a decade. ODT's formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth. Various types of superdisintegrants, disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it 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 disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. Disintegrants expand and dissolve when wet causing the tablet to break apart and releasing the active ingredients for absorption. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution.

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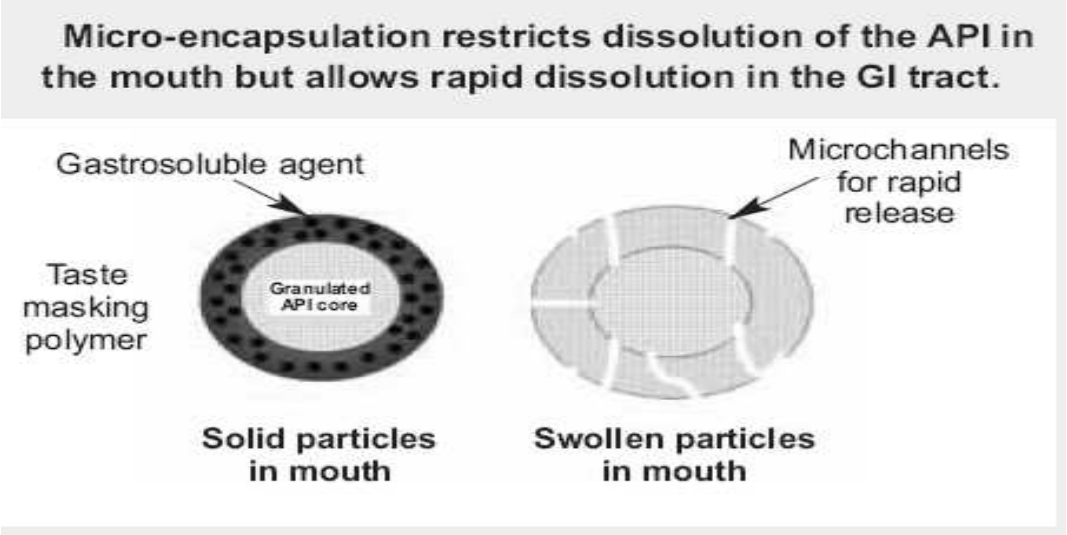

Figure 3: Microencapsulation restricts dissolution of API in mouth but allows rapid dissolution in the GI Tract