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Mouth Dissolving Drug Delivery System: A Review

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Abstract: Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which include dysphagic, bed ridden, psychic, geriatric and paediatric patients. Research in developing orally disintegrating systems has been aimed at investigating excipients as well as technique to meet these challenges. Technologies used for manufacturing of orally disintegrating tablets are either conventional technologies or patented technologies. In conventional freeze drying, tablet molding, sublimation, spray drying etc. and in patented Zydis technology, Orasolv technology, Durasolv technology, Wowtab technology, Flashdose technology are important. Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution.
Keywords: MDDDS, ODT, Oral drug delivery.

Introduction

For the past one decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms[1].

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Should next generation drugs are predominantly protein or peptide based, tablets may no longer may be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by fast dissolving tablets which may

release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide[2,3,4,5,6,7,8,9]. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[10,11].

The problem can be resolved by the creation of rapidly dispersing or dissolving oral dosage forms (FDDS), which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[12]. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients[13]. In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of very porous and soft molded matrices or compressed into tablets with very low compression force[14,15,16]. The concept of Mouth Dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. FDTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well[12].

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)[1,17].

Definition

US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"[18].

Orally Disintegrating Tablet (ODT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less.

ODTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers, melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.[19].

Their growing importance was underlined recently when European Pharmacopoeia adopted the term " Orodispersible tablet" and described orally disintegrating tablets as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 min[12].

Difficulties with Existing Oral Dosage Form[12] :

1) Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.

2) Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.

3) Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult

4) Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.

5) Cost of products is main factor as parenteral formulations are most costly and discomfort.

Criteria for Fast dissolving Drug Delivery System[18,20,21]:

1) Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
2) Be compatible with taste masking.
3) Be portable without fragility concern.
4) Have a pleasant mouth feel.
5) Leave minimum or no residue in the mouth after oral administration.
6) Exhibit low sensitivity to environmental condition as temperature and humidity[20].
7) Allow high drug loading.
8) Be adaptable and amenable to existing processing and packaging machinery[21].
9) Less friable and have sufficient hardness.
10) Utilizes cost effective production method[18].

Salient Feature of Fast Dissolving Drug Delivery System[13, 20,22]:

- Ease of Administration to the patient who can not swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the
- clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability[20].
- Pregastric drug absorption avoids the first-pass metabolism; the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.[13].
- Rapid drug therapy intervention[22,23-29]

Selection of Drugs [19,30]:

The ideal characteristics of a drug for in vivo dissolution from an ODT include

- No bitter taste
- Dose lower than 20mg
- 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 (logp>1, or preferably>2)
- 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.

Factors to be Considered for Selection of Superdisintegrants[31,32] :

- **Disintegration**: The disintegrant must quickly wick saliva into the tablet to generate the volume stomach (pregastric absorption). In such cases bioavailability of drug is increased and improves

expantion and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

- **Compactability:** It is desirable to have ODT with acceptable hardness and less friability at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed.
- **Mouthfeel:** Large particals can result in a gritty feeling in mouth. Thus, small particales are preffered. If the tablet form a gel-like consistency on contact with water, However, it produces a gummy texture that many consumer find objectionable.
- **Flow:** In typical tablet formulation, suprdisintegrants are used at 2-5 wt % of the tablet formulation. With ODT formulation, disintegrant level can be significantly higher. At these higher use level, the flow properties of the disintegrant are more important because it make a greater contribution to the flow characteristics of the total blend[31].
- It should be effective at low concentration and have greater disintegrating efficienacy and they are more effective intragranularly[32].

Important Criteria for Excipient used in Formulation of ODTs[33]:

1) It must be able to disintegrate quickly.
2) Their individual properties should not affect the ODTs.
3) It should not have any interaction with drug and other excipieints.
4) It should not interfere in the efficacy and organoleptic properties of the product.
5) When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.
6) The metlting point of the excipients used should be in the range of 30-35ºC[34].
7) The binder may be in liquid, semi solid, solid or polymeric in nature.

Challenges in the Formulation of ODT[22]

1. Mechanical strength and disintegration time: It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

2. Taste masking: Effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

3. Mouth feel: The particles generated after disintegration of the ODT should be as small as possible. ODT should leave minimal or no residue in mouth after oral administration. Moreover addition of flavors and cooling agents like menthol improves the mouth feel.

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

5. Cost: The technology used for an ODT should be acceptable in terms of cost of the final product[35].

Limitations of Mouth Dissolving Tablets[20,22]:

- 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[20].
- Drugs with relatively larger doses are difficult to formulate into MDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for MDT. Similarly patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations[22].

Excipients Commonly used for FDT Preparation [14,19,32,36]

Mainly seen excipients in FDT are as per Table N0. 1 at least one disintegrant, a diluent, a lubricant and optionally swelling agent, a permeablizing agent, sweeteners and flavoring agents.

1. Superdisintegrants

Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Swelling index of the super-disintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4h should be noted and swelling index is calculated by the formula.

Swelling Index =

[(Final volume - Initial volume)/initial volume)] X 100

Example: croscarmellose sodium, crospovidone, carmellose, carmellose calcium, sodium starch glycolate ion exchange resins (e.g. Indion 414) Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable

2. Binders

Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol.

Example**:** Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Acrylic polymers used are the ammonio-methacrylate copolymer, polyacrylate, and polymethacrylate.

3. Antistatic agent

An **antistatic agent** is a compound used for treatment of materials or their surfaces in order to reduce or eliminate buildup of static electricity generally caused by the triboelectric effect.

Example**:** colloidal silica (Aerosil), precipitated silica (Sylod.FP244), talc, maltodextrins, .beta-cyclodextrin etc[14].

4. Lubricants

Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

5. Flavours

Example**:** Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc[19].

6. Sweeteners

Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, sugars derivatives etc[32].

7. Fillers

Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

8. Surface active agents

Example**:** sodiumdoecylsulfate, sodiumlaurylsulfate, Tweens, Spans, polyoxyethylene stearate[6].

Table No. 1: Name and Weight Percentage of Various Excipients

Name of the excipients	Percentage used
Disintegrant	1-15%
Binder	5-10%
Anti static agent	0-10%
Diluents	0-85%

Taste Masking Methods[13,19,32,39]

The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in ODT formulations. Following methods are used in Taste masking is given in Table No. 2.

1) Simple wet granulation method or roller compaction of other excipients. Spray drying can also employed to shroud the drug.
2) Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc.[19,37,38]
3) Drug particles are coated directly.
4) Granulation of the drug with certain excipients fallowed by the polymer coating.
5) If the drug is tasteless or very low dose, direct blend of bulk drug substance into fast disintegrating matrix is straightforward[39,40].
6) Formation of pellets by extrusion spheronization.
7) Coacervation to form microencapsulated drug within a polymer[32].
8) Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.
9) Drug complexation with resinates are insoluble and no taste in oral cavity. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
10) Other methods include hot melt and supercritical fluids[19].
11) Adjustment of pH Values: Many drugs are less soluble at pH different from the pH value of the mouth, which is around 5.9. Solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug—sildenafil—dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone[13,41].

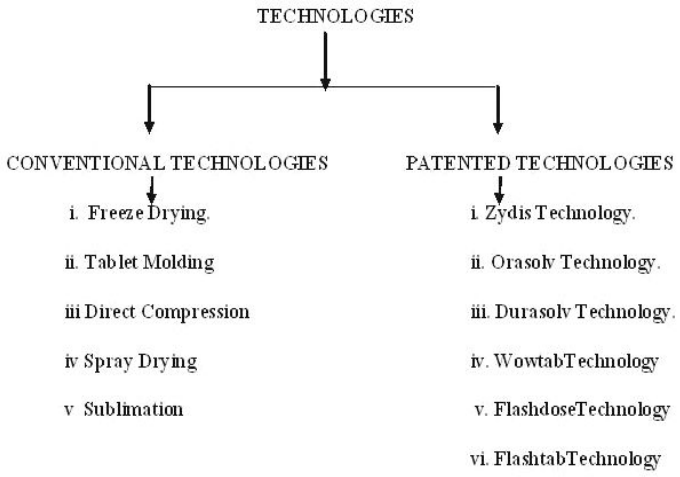
Excipients Updates for Orally Disintegrating Dosage Form[47]

Now a day different blends of excipients are available which can give disintegration property. Some novel disintegrants, modified sugar, modified sweeteners and some co-processed excipients blend are also developed which satisfying need of more than one excipient. The composition and characteristics of excipients are shown in Table No. 03

Technologies used to Manufacture Mouth Dissolving Tablets[12,14,21,22,50]

The technologies used to manufacture mouth dissolving tablets can be classified as:

Fig.



Conventional Technologies for ODTs[14,22,21]

1. Freeze drying

ZYDIS® (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. This method involves of drug in water soluble matrix, which is then transferred to the preformed blister with peelable foil, as the zydis units are not strong enough to withstand being pushed through the lidding foil of a conventional blister. Freeze drying is then done to remove water by sublimation. Incorporation of Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly (5sec.) and show improved absorption and bioavailability[14].

2. Moulding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution[14,48].

3. Spray Drying

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g.,

sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20sec. in an aqueous medium[14].

4. Sublimation[14,22,49]

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g. ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, phthalic anhydride, urea and urethene) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix.

5. Direct Compression Method (Disintegrant Addition)[21]

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level. The basic principle involved in formulating Fast-dissolving tablets by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.

Gas evolving disintegrants have been used to formulate fast dissolving tablets. The evolution of carbon dioxide as a disintegration mechanism called OROSOLV and DURASOLV have been described in two US Patents assigned to CIMA Lab.

Patented Technologies for ODTs[12,50]

1. Zydis Technology[12]

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

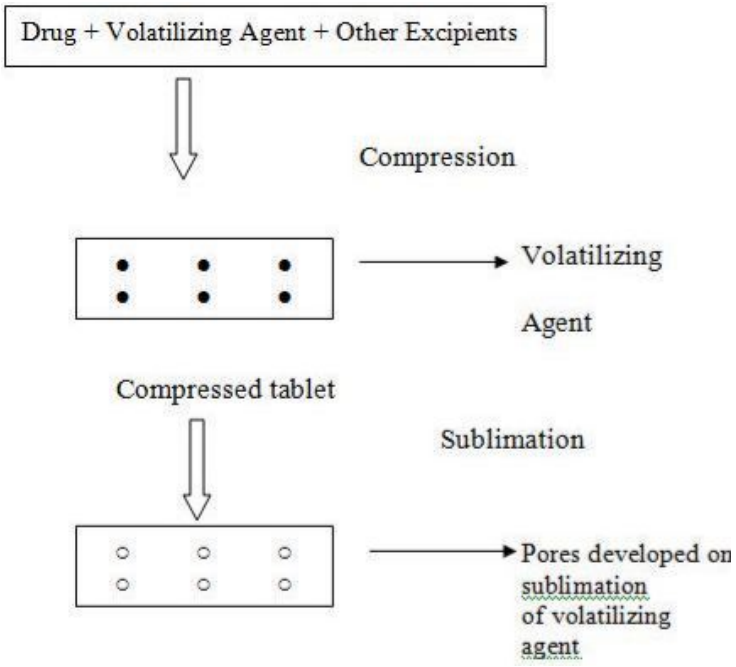


Fig.: Steps Involved in Sublimation[14,22]

2. Durasolv Technology[12]
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.

3. Orasolv Technology[12]
Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique.

4. Wowtab Technology[12]
Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. 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.

5. Flash Dose Technology[12]
Flash dose technology has been patented by Fuisz. Flash dose tablets consist of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

6. Flashtab Technology[12]
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 tabletting technology.[2]

Table No. 2: Technologies Used for Masking the Taste of Active Ingredients[42,43-46].

Technology	Excipients	Active Ingredient	Method
Fluidized bed coating	Methyl cellulose (MC), Acesulfame(AS), HPMC	Northindrone, tamoxifen, caffeine, acetaminophen, rilmazafone HCl	-MC and AS solution charged to fluidized bed drier containing sieved northindrone. -Internal temperature maintained at 115°F - Coating completed in 3 min.
Agglomeration process	Sweetener:- Sodium saccharin; acesulfeme Dry blend;- HPMC Silica dioxide Polythiazide	Polythiazide	-Sweetener solution sprayed on dry blend to form agglomerated granules - Wet mixture was dried in a convection oven at 103°F for 17 hrs. -Dried product size reduced, sieved (#100)
Pelletization process	Dry Blend:- Aspartame, HPC and Gum arabic	Loratidine	- Crushed ice was mixed with dry blend mixture to form spherical particles. - Wet spherical particles were dried in a tray drier at 55°C
Infusion method	Dry blend:- Sucralose, Fluoxetine and Polyvinyl pyrrolidone	Fluoxetine	-Propylene glycol: water (40:60) was used to mix dry blend, HPMC was added. Mixing was continued at high speed for 3 min. The particles obtained were screened (#100)

Table No. 3: Composition and Characteristics of Excipients

Excipient	Composition and characteristics
Ludiflash	Coprocesed blend of 90% Mannitol, 5% Kollidon® CL-SF(Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate)
F-MELT	Coprocesed blend of carbohydrates, disintegrant and inorganic ingredients. F-melt are commercially available Type C &Type M
Modified chitosan with silicon dioxide	Co precipitation of chitosan and silica, It acts as superdisintegrant and filler
Orocell 200 and Orocell 400	Spheronised mannitol with a binder, filler and carrier property Orocell 200 with 90% mannitol (<315µm) Orocell 400 with 90% mannitol (<500µm)
Pearlitol SD	Spheronised granulated mannitol Pearlitol® 100SD, Mean diameter: 100µm Pearlitol® 200SD Mean diameter 180µm Sweetening power about 40% that of sucrose
Glucidex IT	Agglomerated spray dried range of maltodextrins
Polacrillin Potassium	Potassium salt of a cross linked polymer derived from methacrylic acid and divinyl benzene

7. Oraquick Technology[12]

The Oraquick fast dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as Micro Mask. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable

8. Nanocrystal Technology

Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds[50].

Conclusion

Orally disintegrating tablets have better patient acceptance and offer improved biopharmaceutical properties, improved efficacy and better safty as compared with conventional oral dosage forms. Recent trends of patient oriented dosage form to achieve patient compliance. The number of formulation related factors contributes to the significant amount of non-compliance and hence there is a need to design patient oriented drug delivery system.

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