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Review Article

Oral Dispersible Tablet: A Popular Growing Technology

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ABSTRACT:

Oral Dispersible tablets are well recognised dosage forms presented in the market. Since their introduction to the market in the 1980s, ODTs have become one of the fastest growing segments of the oral drug delivery industry, and their product pipeline is rapidly expanding. An orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited amount of over-the-counter (OTC) and prescription medications. ODTs is one such novel approach to increase consumer acceptance by virtue of self-administration without water or chewing which disintegrate or dissolve rapidly in the mouth (saliva) within few seconds.The various advantages that they offer to the patients in terms of massive revenues by line extension of products include a variety of advantages. The development of oral dispersible tablets has been formulated for paediatric, geriatric, and bed rest patients and for those people as well as patients who may not have access to water with improved therapeutic efficacy and patient compliance. Several formulations provide an opportunity for product line extension especially for elderly persons will have difficulties in taking conventional oral dosage forms because of hand tremors and dysphasia and swallowing problem in young individuals due to under developed muscular and nervous systems. This article gives a brief review on the ideal properties, significance, characteristics, limitation, choice of drug candidates, challenges in formulation, the fabrication of Oro-dispersible tablets with a detailed concept of fabricating technologies, patented technologies as well as emerging trends or technologies and Evaluation tests of ODTs.

Key words: *Orodispersible tablets, Method of preparation, Patented Technology, Future Prospective*

INTRODUCTION:

Drug delivery systems (DDS) are a strategic tool for expanding markets indications, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. As there are various routes of drug delivery systems to the body, the oral delivery is considered as one of the golden standard in the pharmaceutical industry where it is regarded as the safe, convenient, and most economical method of drug delivery having the patient compliance from the elderly. Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue [1]. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing (Dysphagia). ODTs are useful among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications [2, 3].Orally disintegrating tablets are also called as

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orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs [4-7]. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia [8-11].Recently, European Pharmacopoeia has used the term orodispersible tablet for those tablets which disperses readily and within 3 min in mouth before swallowing. 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.The US food and drug administration centre for drug evaluation and research defines in the "orange book" ODTs as a solid dosage form containing medicinal substance which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue [12, 13].These tablets in contrast with conventional dosage forms (tablets and capsules) which takes several minutes to dissolve in mouth, ODTs disintegrates and dissolves in the mouth in less than 60 seconds and hence produce a rapid action. These tablets releases the medicament in the mouth for absorption through local oro-mucosal tissue and through pre-gastric (Oral cavity, Pharynx, and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of Gastro Intestinal Tract (GIT) [14-17]. 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 [18].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.

Ideal Characteristics of ODT's: [19-21]

- Exhibit low sensitivity to environmental conditions as humidity and temperature,
- Should dissolve or disintegrate in the mouth rapidly without aid of water in matter of seconds and without swallowing.
- Should maintain physical integrity and possess no friable loss with sufficient mechanical strength.
- Should have a pleasant mouth feel.
- Should leave minimum or no residue in the mouth after oral administration.
- Should exhibit low sensitive to environmental condition as temperature and humidity.
- Should allow high drug loading capacity.
- Should be adaptable and amenable to the existing processing and packaging machinery at low costs.
- Small to moderate molecular weight.
- Good solubility in water and saliva.
- Partially non-ionized at the oral cavity pH.
- Ability to diffuse and partition in to the epithelium of the upper GIT logp more than1 or preferably more than 2.
- Ability to permeate oral mucosal tissue
- The fast disintegration usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.
- The excipients should have high wettability, and the tablet structure should also have a highly porous network for fast dissolution.
- The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing.
- A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking

technology should provide drugs without grittiness and with good mouth feel.

- The amount of taste masking materials used in the ODTs formulation should be kept a slow as possible to avoid excessive increase in tablet size.
- Drug properties for example; the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density should not affect the final ODT sperformance and characteristics such as tablet strength and disintegration.

Significance of Oro-dispersible tablets:[22-23]

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and ease of handling by patients.
- No risk of obstruction of dosage form as rapidly dissolves in saliva.
- Administration without water, anywhere and anytime, hence beneficial for traveling patients who do not have access to water.
- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Medication as "bitter pill" has changed by excellent mouth feel property produced by the use of flavors and sweeteners in ODTs.
- Suitable for delivering relatively low-molecular weight and highly permeable drugs.
- Requires minimum number of ingredients and so it is cost effective dosage form.
- Solid oral delivery systems do not require sterile conditions, so less expensive to manufacture.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Bioavailability of drug is increased as some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach.
- Pre-gastric absorption of drugs avoids hepatic metabolism which can results in improved bioavailability which results of reduced dosage with improved clinical performance through the reduction of unwanted effects.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided and thus provided improved safety.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action is required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

Advantages of Oro-dispersible tablets:[24-31]

- ODTs have all the advantages of solid dosage forms; they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- ODTs have the advantages of liquid formulations such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form.
- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- No risk of obstruction of dosage form and 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 disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- The tablets disintegrate inside the mouth; drugs may be absorbed in the buccal, pharyngeal, and gastric regions (pregastric absorption). Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible.
- Hence drugs like anti-anginal, antiasthmatics, anti-allergics and NSAIDs and other emergency drugs can be administered.

- The pre-gastric 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. Hence drugs which metabolised by first pass effect or metabolised by gastric enzymes, can alsobe administered.
- From the pharmaceutical industry's point of view, ODTs can provide new dosage for msas a life cycle management tool for drugs near the end of their patent life.

Limitations of Oro dispersible drug delivery system:[32]

- The tablets usually have insufficient mechanical strength. Hence, it requires careful packaging and handling.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Difficulty in developing extremely high doses (typically in excess of 500 mg) and extensive taste masking of bitter tasting actives.

Challenges in development of ODTs:[33-36]

Palatability:
It is a formidable challenge for formulation scientists to mask the taste of bittertastingdrugs selected for ODT. As most drugs are unpalatable, orally disintegrating drugdelivery systems usually contain the medicament in a taste masked form. Hence, tastemasking of the drugs become critical to patient compliance.

Mechanical strength:
In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous or soft-moulded matrices or compressed in to tablets with very low compression force, which makes the tablets friable or brittle, and difficult to handle. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi dose bottles, such as Wowtab by Yamanouchi Shaklee, and Durasolv by CIMA labs.

Hygroscopicity /moisture sensitivity:
Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Dose/Amount of drug:
The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. Molecules requiring high doses present mainly three challenges to the development of fast dissolve dosage forms; a) taste masking of active ingredient, b) mouth feel or grittiness and c) tablet size. These challenges are not unrelated because most drugs require taste masking, the amount of taste masking materials used in different dosage forms will depend on the drugs degree of bitterness relative to its dose, which will in turn affect the final tablet size.

Aqueous solubility:
Water-soluble drugs pose various formulation difficulties because they form eutectic mixture, which result in freezing point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse can be prevented by using matrix-forming excipients such as mannitol that can induce Crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet:
The degree of ease when taking a tablet depends on the 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.

First generation ODTs:[37-41]

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 short in terms of

taste masking and the accommodating high dosesand because most first-generation technologies can handle only low amounts of APIs, their therapeutic applications are limited and are used only in immediate-release applications.

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. Furthermore, it's 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, low friability,cost-effective development, and more packaging options.

New generation of ODTs:[37-41]

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 micro-granules, 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 onto dry crystals or granules, creating particles that are typically150 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 ofextremely poor-tasting drugs, including zolpidem (for insomnia),sumatriptan (for migraines), ranitidine.It has also been applied to theophylline, ibuprofen, acetaminophen.

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 amicro-encapsulation technique restricts dissolution of the API in the mouth, but allows rapid dissolution in the GI tract, thus over coming the bio-equivalence obstacle as given in figure 1.

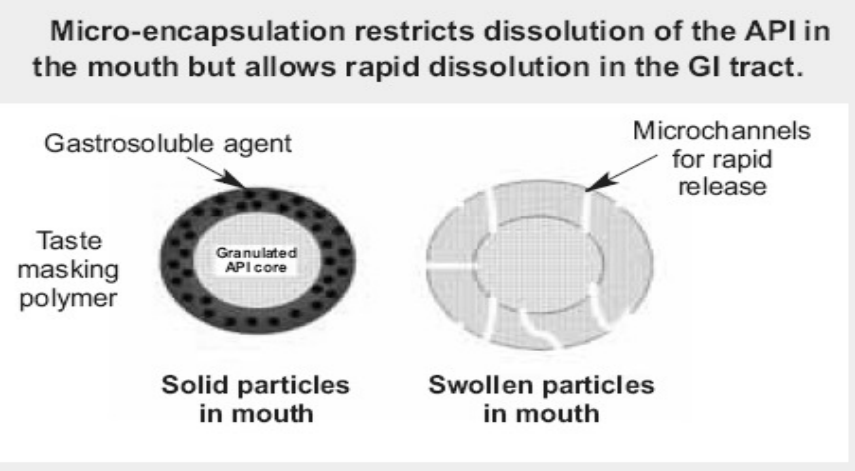

Figure 1: Microencapsulation restricts dissolution of API in mouth but allows rapid dissolution in the GI Tract

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.

Some technologies provides sustained release by layering active drugs onto a neutral core (bead), followed by one or more rate controlling, functional membranes Allowing up to 6 hours of delayed release as given in figure 2, these layered beads can be less than 500 microns in very robust ODTs.

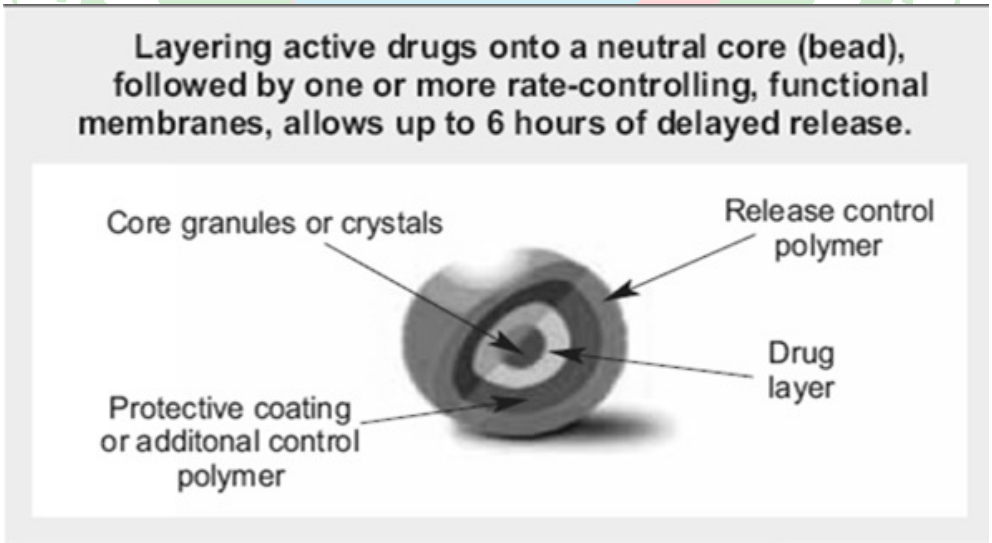

Figure 2: Layers active drugs onto a neutral core and rate controlling membranes.

Formulation consideration in ODTs:[42-43]

Diluents:

Diluents are most commonly selected from cellulose derivatives and preferably

microcrystalline cellulose, starches, lactose & preferably mannitol.

Binders:

Generally, binders are used to keep the composition of tablets together with the drug during compression stage. The right selection of a binder or combination of binders is essential to maintain integrity and stability of the tablet. The temperature of the excipients should be preferably around 30-35^{0}C for faster melting property. Further its incorporation imparts smooth texture &disintegration characteristics to the system. Binders can be either liquid, semi -solid or solid or mixtures of vary ingmolecular weights such polyethylene glycol. Commonly used binders are cellulosic polymers, povidones, and polyvinyl alcohols.

Super disintegrants:

Oro dispersible tablet requires faster disintegration and dissolution. In-order, to achieve faster disintegration, Super disintegrants is used in formulating ODTs. The super disintegrant used should be effective at low concentrations and have greater disintegrating efficiency and should be more effective intra-granularly. The only problem is that it is hygroscopic therefore not used with moisture sensitive drugs. Super disintegrants acts by swelling and due to swelling pressure exerted in the outer or radial directions, it causes the tablet to burst or accelerates the water absorption leading to enormous increase in the volume of granules to promote disintegration.

Taste-masking agents:

Taste masking of the drug can be done by preventing the exposure of drug to the tongue rough processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulating in polymer systems or by complexation.

Some of the approaches of taste-masking are

- Layering the drug onto inert beads using a binder followed by coating with taste-masking polymer.
- Granulating the drug & coating with a taste-masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- Complexation using Inclusion complexes like cyclodextrins.
- Psychological modulation of bitterness.
- Coacervation to form micro capsulated drug within a polymer.
- Formation of pellets by extrusion spheronization.

Sweeteners:

Sucrose and other natural sweeteners, such as sorbitol, can be used in ODTs, although artificial sweetening agentsare customary. However, the applications of artificial sweeteners are restricted by Health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in the fast disintegrating tablet. Earlier cyclamates and cyclamic acid were the artificial sweeteners of the choice, but their use has now been restricted. And some of the commonly used sweeteners are: Sorbitol, Mannitol, Hydrogenated starch hydrolysate, Maltitol solution, Maltitol, Xylitol, Erythritol, Glycerin, Sucrose, Fructose, Maltose etc.

Lubricants:

Commonly used lubricants are magnesium stearate,stearic acid, sodium stearyl fumerate, micronizedpolyoxyethylene glycol (Macrogol 6000), leucine andsodium benzoate.

Glidant:

Colloidal silica (Aerosil), precipitated silica, micronized/non-micronized talc, maltodextrins etc. are used asglidant.

APPROACHES FOR PREPARATION OF ODTs:

Melt Granulation: [44]

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

Phase transition: [45]

It is identified 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. MDTs by phase transition are prepared by heating sugar alcohols using Erythritol (melting point 122°C), xylitol (melting point 93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation: [46]

The key for rapid disintegration of mouth dissolving tablets is the presence of a high porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and pthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

Tablet moulding: [47]

Moulded 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. Moulding process is of three types i.e., solvent method, heat method and No vacuum lyophilisation.

Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in the moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. And this process is similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat moulding process**[48]**uses an agar solution as a binder and a blister packaging well as a mould to manufacture a tablet. The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

No-vacuum lyophilization is done by evaporating the solvent from a drug solution or suspension at standard pressure. 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.

Freeze Drying: [49]

Freeze drying is the process in which water is sublimed from the product after it is frozen. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilisation process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. 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. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability.

Mass Extrusion: [50]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

Spray Drying: [51-53]

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets. Gelatine can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or Croscarmellose 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).This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Direct Compression: [54-58]

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. Directly compressed tablet's disintegration and solubilisation depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance. Direct Compression technique can now be applied to preparation of ODT because of the availability of improved excipients especially super disintegrants and sugar based excipients.

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. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

Sugar Based Excipients

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 mouth feel. There are two types of sugar-based excipients on the basis of moulding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Nanonization: [59]

In this process, the particles of the drug are reduced in the size to nanoparticles by milling the drug in the proprietary wet milling process. The agglomeration can be prevented by surface adsorption of the nanocrystals. These are then compressed & changed into a tablet. This technique is advantageous for less water soluble drugs. The bioavailability of the drug is increased as the disintegration time is reduced to a significant extent.

Cotton candy process:

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. The candy floss matrix is grinded and blended with drug and excipients and then compressed to ODT. This process is more helpful for high doses of drug and also increases mechanical strength of tablet. But high temperature process limits the use of this process.

Floss blend

The floss mix is prepared by blending the 80% sucrose in combination with mannitol/ dextrose and 1% surfactant. The surfactant maintains the structural integrity of the floss fibres by acting as crystallization enhancer. This process helps in retaining the dispersed drug in the matrix, thereby, minimizes the migration out of the mixture.

***Floss processing*[60]**

The floss formation machine uses flash heat & 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 (2000-3600 rpm) that flings the floss under centrifugal force & draws into long & thin floss fibres, which are usually amorphous in nature.

Floss chopping & conditioning:

In this, fibres are converted into smaller particles in high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) on to the floss and subsequently evaporated it to impart improved flow & cohesive properties to the floss. This is called as Conditioning.

***Blending & Compression*[61]**

The chopped & conditioned floss fibres are blended with drug & other excipients and compressed into tablets. Exposure of the dosage forms to elevate temperature and humidity conditions (400C & 85% RH for 15mins) improve the mechanical strength of tablets due to expected crystallization of floss material that results in binding & bridging, to improve the structural strength of the dosage form.

PATENTED TECHNOLOGIES FOR ODT FORMULATION:

Zydis Technology: [62,63]

Using concept of Gregory *et al*. Scherer has patented the Zydis technology. Zydis, the best known of the fastdissolving/disintegrating tablet preparations, and was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrixusually consisting of gelatine. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, butinstead peel the film back to release the tablet. The Zydisformulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be asubstantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience. The amount of drug that could be incorporated should generally be less than 60 mg for soluble drugs. The particle size of the insoluble drugs should be less than 50mm and not more than 200mm to prevent sedimentation during processing. There are some disadvantages to the Zydis technology. The process of freeze-drying is a relatively expensive manufacturing process. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidity. It readily absorbs water, and is very sensitive to degradation at humidity greater than 65%.

Durasolv Technology: [64-67]

Durasolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. DuraSolv has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during tableting. DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. This technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, Durasolv technology is best suited for formulations including relatively small doses of active compound. The tablets made by this technology consist of a drug, fillers and a lubricant and prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Due to higher force of compaction used, tablets prepared are rigid.

Orasolv Technology: [68]

Orasolv® is Cima's first orally disintegrating dosage form. It based on direct compression of an effervescent agent and taste masked drug. The use of effervescence causes a tablet to disintegrate rapidly in less than 1 min on contact with water or saliva leaving coated drug powder. This technique is frequently used to develop over the counter formulations. This technology can accommodate a wide range of active ingredient from 1 mg to 500 mg. The effervescence occurs due to chemical reaction between organic acid such as citric acid, maleic acid and a base such as sodium bicarbonate, potassium bicarbonate,

bicarbonate, which result in generation of CO_2. Effervescent disintegration agents evolve gas by means of chemical reaction called effervescent couple. Carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate, and acids like citric, tartaric, fumaric, adipic and succinic are used. Microparticles, effervescent agents and other ingredient such as flavours, sweeteners, colorants and lubricants are blended and compressed at a low degree of compaction.

Flash Dose Technology: [69-70]

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, Flash Dose. The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shearform matrix termed as "floss". Shearform matricesare prepared by flash heat processing and are of two types.

Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol. Dual floss consists of a first shear form carrier material (termed "base floss",contains a carrier and at least one sugar alcohol generally sorbitol), and a second shearform binder matrix("binder floss", contains a carrier and xylitol).

Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a flosslike material, small spheres of saccharide scan be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as CEFORM and serves as an alternative method of taste masking.

Wow Tab Technology: [71]

The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "Wit out Water". It has just been introduced into the U.S. The Wow tab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharides (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the Wow tab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the Wow tab is proprietary, but claims to offer superior mouth feel due to the patented SMOOTHMELT action. The Wow tab product dissolves quickly in 15 seconds or less

Flashtab Technology: [38]

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystal. Drug micro-granules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystal of microgranules of the active ingredient is added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tableting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

Advatab Technology:

Advatab is a new generation ODT. In this technology the lubricant is dispensed ontoeach tablet by using a spray during the production process. Advatab is produce using 30 times less hydrophobic lubricant and 405 stronger than conventional tablets. This technology can handle high drug loading and coated drug particles.

Ceform technology:

This technology involves preparation of microspheres of the active drug. Drug material alone or in combination with other pharmaceutical substances, and excipients is placed into a precision engineered rapidly spinning machine. The centrifugal force comes into action, which throws the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The microspheres thus formed are compressed into tablets. As the drug and excipients both can be processed simultaneously, it creates a unique microenvironment in which the materials can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability.

Nanocrystal technology: [72-73]

For fast dissolving tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nano-meters (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

NanoCrystal™ Fast dissolving technology provides for:

Pharmacokinetic benefits of orally administered nanoparticles(<2 microns) in the form of a rapidly disintegrating tablet matrix,

Product differentiation based upon a combination of proprietary and patent protected technology elements

Cost-effective manufacturing processes that utilize conventional, scalable unit operations

Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters)

Wide range of doses (up to 200mg of API per unit)

Use of conventional, compendial inactive components

Employment of non-moisture sensitive inactives

Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

Orodis Technology:[74]

There are several technologies to consider for orally disintegrating tablets. Orodis® is compressed technology, beside a fast disintegration time in the mouth (15 to 30 seconds) it has many advantages against other technologies.

Hard tablets, not fragile- easy to handle

No specific packing required, can be packaged in push –through blisters

Smooth mouth-feel

Pleasant taste- incorporation of taste masking agents and flavours

All the materials meets USP and EP standards

Conventional manufacturing equipment – not difficult to transfer to final production site.

Cost effective.

Melt Ease Technology: [74]

Newer technology developed by nutrition formulators, which allow stable dissolution in less than five sec (average 400mg tablet) this is the best mechanism available to ensure compliance and increase sales in two important markets, children and the elderly for many nutritional supplements at a very marginal development cost effect in specific formulations, including taste masking and sustained release on certain ingredients.

EVALUATION PARAMETERS OF ORO DISPERSIBLE TABLETS:

Weight variation test: [75]

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test. 20 tablets were selected at random and average weights were determined. Then individual tablets are weighed and the individual weight was compared with the average.

Calculate the average weight of tablets =
Total weight of tablets
Number of tablets

Hardness: [75]

Hardness of MDTs tablets were evaluated by using "Monsanto hardness tester". Tester consists of a barrel containing a compressible spring held between two plungers. Lower plunger is placed in contact with tablet &a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a guage in the barrel to indicate the force.

Friability:[75]

Roche friability is used to measure the friability of the tablets .It rotates at rate of 25 rpm.10 tablets are weighed collectively and placed in the chamber of friabilator. In the friabilator, the tablets are exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4min), the tablets are taken out from the friabilator and intact tablets are again weighed collectively.

Percentage friability is determined by using the formula,

Friability = (W1-W2)/W1×100

Where,

W1 = weight of tablets before test

W2 = weight of tablets after test

Content Uniformity test: [76]

Ten tablets were used in this test, where each one was crushed and transferred into a 100 ml volumetric flask. The flasks were brought to volume by phosphate buffer pH 6.8. The flasks were placed onto a sonicator till complete dissolution; 1 ml of the solution was filtered through a Millipore filter of 0.45 µm pore size then introduced into a 25 ml volumetric flask which was completed to volume by phosphate buffer. The absorbance of the solution was measured using a UV-visible spectrophotometer against the blank buffer. The tablets meet the test if the mean drug content lies within the specified range of the labelled potency.

In- vitro Disintegration test:

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen which was immersed in water bath at 37 ± 2^0C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the Pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

Modified Dissolution apparatus for Disintegration time: [77]

Three tablets per batch were evaluated for disintegration time by employing a modified dissolution apparatus. Instead of the disintegration apparatus described in JP XII, a modified dissolution apparatus (JP XII paddle method) was employed. Simulated salivary fluid (900 ml), maintained at 37±0.5^{0}C was stirred with a paddle at 100 rpm. Disintegration time was recorded when all the fragments of the disintegrated tablet passed through the screen of the basket.

In-vitro dispersion test:[78]

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. In- vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and in-vitro dispersion time was performed.

Wetting time:[79]

Ten ml of water soluble dye, eosin solution is added to petridish containing five circular filter papers of 10 cm diameter. Tablets were carefully placed on the surface of the filter paper and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results were presented as mean value of three determinations (± SD).

In-vitro Dissolution studies:[80,81]

In-vitro dissolution studies of the mouth dissolving tablets were performed according to USP XXIII Type-II dissolution employing a paddle stirrer at 50 rpm using 900 ml of simulated salivary fluid pH 6.8 at 37±0.5°C as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with equalvolume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance by UV-Visible spectrophotometer. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates.

Particle packaging index (PPI): [82]

Particle packaging index was calculated on FDTs compressed to its maximum extend by modifying the method. It is an indicator of compactness of powder. The particle packaging index is a ratio of density of tablet to density of particles. Density of tablets (tablet) was determined using the following formula;

$$\text{Density(tablet)} = \frac{\text{Weight of tablet}}{\Pi * \text{radius of tablet} * 2 * \text{thickness of tablet}}$$

Moisture Uptake Studies: [83]

Ten tablets from each formulation were kept in desiccator over calcium chloride at 370C for 24 h. Then the tablets were weighed and exposed to 75% relative humidity (using saturated sodium chloride solution) at room temperature for 2 weeks. One tablet without super disintegrant as control was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded. The results were presented as mean value of three determinations (± SD).

Tablet Porosity Measurement:[83]

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative eassessment of the degree of water penetration in the formulation, responsible for its fast disintegration.

FUTURE PROSPECTIVE: [84-87]

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. The tablet is the most widely utilised oral dosage form. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the ODT. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. A number of ODT are commercially available for human use using technologies developed by pharmaceutical companies such as Cardinal Healthcare, Jannsen Pharmaceutical, Bioavail, and Eurand, Zydus, Yamanouchi. However, these technologies use either expensive processing technology producing fragile tablets that require costly specialised packaging or use conventional tableting procedures which give longer than desired disintegration & still require specialised

packaging. Dr Zeibun Ramtoola and her team at the Royal College of Surgeons in Ireland have addressed the above shortcomings by developing a novel, cost effective one step ODT manufacturing process using conventional tableting technology for the production of robust tablets suitable for conventional packaging. This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. "supergenerics" for veterinary or human application. The oral drug delivery market was estimated to be worth $35bn in 2006 & forecast to reach $52bn by 2010 with a CAGR of 10%. Of this, the ODT, taste masked & micro emulsion formulation segments constitute a 22% share with an expected CAGR of 17% to 2010. There is a clear opportunity for new enhanced oral products arising within this market segment. ODT technologies entered the market in the 1980s, they have grown steadily in demand and importance, and their product pipeline is rapidly expanding. In 2004, ODT products generated revenues of well over $2 billion, an increase of 20% over 2003, according to a 2005 report by Technology Catalysts International. With multiple new consumer health and prescription product launches in recent years, the ODT market was predicted to easily reach $3 billion in 2006, including brands and generics. The market continues to grow 20% each year, with a growing penetration of generic ODTs.

CONCLUSION:

The ODTs have potential advantages over conventional dosage forms, with their improved patient compliance; convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. Their characteristic advantages such as administration without water, anywhere, anytime lead totheir increased patient compliance in today's scenario of hectic life. As they have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. Thus ODT may be developed for most of the available drugs in near future. Such products provide opportunity for the product line extension in the market place and extension of patent term of innovator. Due to this wide significance of ODT, this drug delivery system may lead to better patient compliance and ultimate clinical output. Future might witness many more classes of drugs developed in the form of ODT.

REFERENCES:

1. Sreenivas SA. Orodispersible tablets: New- fangled drug delivery system- A Review. Indian J.Pharm.Educ.Res, 2005; 39(4): 177-181.
2. Lindgren S, Janzon L. Dysphagia: Prevalence of swallowing complaints and clinical finding. *Med Clin North Am,*1993; 77:3-5.
3. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery: A review. *Pharm Sci Technol Today,*2000;3:138-145.
4. Simone Schiermeier, Peter Christian Schmidt. Fast dispersible ibuprofen tablets. European Journal of Pharmaceutical Sciences, 2002; 15, 295-305.
5. Ciper M, Bodmeier R. Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity. Eur. J. Pharm. Biopharm, 2006; 62, 178–184.
6. Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Terada K. Formulation design of a novel fast disintegrating tablet. Int. J.Pharm, 2005; 306, 83–90.
7. Seager H. Drug delivery products and the Zydis fast dissolving dosage form. J. Pharm. Pharmacol, 1998; 50.
8. Rakesh RK. Orally Disintegrating Tablets novel tablets novel approach to drug delivery. Pharma Review 2004; 2(12): 34-6.
9. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets: a novel drug delivery system. Pharma Times 2003; 35:1-8.
10. Brown D. Orally disintegrating tablets – taste over speed. Drug Delivery Technology. http://www.drugdeliverytech.com/cgibin/articles.cgi?idArticle=164.
11. Klauke J. Dissolution testing of orally disintegrating tablets. Retrieved from www.dissolutiontech.com.
12. Fu Y, Yang S, Jeong SH, Kimura S, Park K, Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies, Crit Rev Ther Drug Carr Sys, 2004; 21, 433-476.
13. Suresh Bandari, Rajendar kumar Mitta palli, Ramesh Gannu, Yamsani Madhusudan Rao. Orodispersible tablets: An overview.Asian Journal of pharmaceutics; Jan 2008.
14. Shyamala B, Narmada GY. Rapid dissolving tablets: A Novel Dosage Forms. The Indian Pharmacist (2002); 13(8): 09-12.
15. Porter SC. Novel drug delivery: Review of Recent Trends with oral Solid Dosage Forms. American Pharm. Rev. (2001); 85:28-35.
16. Bradoo R, Shahani S, Deewan B, Sudarshan S. Orally Disintegrating Drug Delivery System. J Am. Med. Assoc. India (2001); 4(10):27-31.
17. Bi YX, Sunada H, Yonezawa Y, Danjo K.Evaluation of Rapidly Disintegrating Tablets Prepared by a Direct Compression Method .Drug Dev Ind Pharm (1999) ; 25:571-581.

18. Harmon TM. Orally Disintegrating Tablets: A Valuable Life Cycle Management Strategy". Pharmaceutical Commerce, March (2007), available online www.pharmaceuticalcommerce.com.
19. Shukla D, Chakraborty S, Mouth Dissolving Tablets I: An Overview of Formulation Technology, Sci Pharm. (2009); 76; 309–326.
20. Yamamoto Y, Fujii M, Watanabe K, Tsukamoto M, Shibata Y, Kondoh M, Watanabe Y: Effect of powder characteristics on oral tablet disintegration. International Journal of Pharmaceutics 2009; 365: 116-120.
21. Abdelbary A, Elshafeey AH, Zidan G: Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine. Carbohydrate Polymers 2009; 77: 799–806.
22. Patel P B, Fast Dissolving Drug Delivery Systems: Pharmainfo.net, (2006) ; 4 (4):1-7.
23. Bhomik D, Krishnakanth CB, Chandria RH, Fast dissolving tablet: an overview, J Chem pharm Res, 1(1), 2009, 163-177.
24. Behnke K, Sogaard J, Martin S, Bauml J, Ravindran AV, Agren H, etal. Mirtazapine orally disintegrating tablet versus sertraline: A prospective onset of action study. J Clin Psychopharmacol 2003; 23:358-364.
25. Clarke A, Brewer F, Johnson ES, Mallard N, Hartig F, Taylor S, *et al.* A new formulation of selegiline: Improved bioavailability and selectivity for MAO-B inhibition. *J Neural Transm* 2003; 110:124-5.
26. Prajapati BG, Ratnakar N. A review on recent patents on fast dissolving drug delivery system, Int J pharmtech Res. 2009; 1(3), 790-798.
27. Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R, Gupta N. Orally disintegrating tablet: formulation, preparation techniques and evaluation. J Applied pharm sci, 2011; 1(4), 35-45.
28. Biradar SS, Bhagavati ST. Fast dissolving Drug DeliverySystem: A brief overview. The Internet Journal ofpharmacology 2006; 4(2):1531-2972.
29. Slowson M, Slowson S. "What to do when patients cannotswallow their medications". Pharm. Times 1985; 51: 90-6.
30. Seager H. Drug-deliver Products and the Zydis Fast-dissolvingDosage Form. J. Pharm. and Pharmacol 1998; 50: 375-382.
31. Reddy LH, Ghose, B., Rajneesh. Indian J. Pharm. Sci 2002;64(4): 331-336.
32. Bangale GS, Yadav GJ, Shinde GV, Rathinaraj BS, New generation of orodispersible tablets : Recent advances and future prospects. International Journal of Pharmacy and Pharmaceutical Science Research 2011; 1(2): 52-62.
33. Deshmukh KR, Patel V, Verma S, Pandey AK, Devagan P. A review on mouth dissolving tablet techniques, Int J Res Ayurveda pharm, 2011; 2(1), 66-74.
34. Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R,Gupta N. Orally disintegrating tablet: formulation, preparationtechniques and evaluation.J Applied pharm sci, 2011; 1(4), 35-45.
35. Reddy DRB, Ram CVSS, Kumar KSB, Reddy VY, Rapimelts: a review,J pharm Biomedical sci, 6(6), 2011, 1- 8.
36. Puttlingaiah L, Kavitha K, Mani TT. Fast disintegrating tablets: an overview of formulation techniques and evaluation. Res Jpharmaceu. Biolog, Chem Sci, 2011; 2(2), 589-601.
37. Harmon TM. Beyond the First Generation of Orally Disintegrating Tablets. Emerging Technology. Tablets and Capsules, 3rd Sep (2006).
38. Dobetti L. Fast Melting Tablets: Developments and Technologies: Pharmaceutical Technology. Drug Delivery.(2001) : 44-50.
39. Technology Catalysts International, "Oral Fast-Dissolving Drug Delivery: Technologies, Market Analysis, & Business Opportunities." August (2003).
40. Hamilton E, Lutz E.Orally Disintegrating tablets. Drug Delivery Technology. January (2005).
41. Tanmoy ghosh, Amitava ghosh. A Review on New Generation Orodispersible Tablets and its Future Prospective. Int. J.Pharm. Sci, (2011) ; 3,(1) :1-7.
42. Shaikh S, Khirsagar RV, Quazi A, Fast disintegrating tablets: anoverview of formulation and technologies, Int J pharm pharm sci,2(3), 2010, 9-15.
43. Yarwood R, Kearnery P and Thompson A., Process for preparing solid pharmaceuticaldosage form. US Patent # 5,738,895 ;1998.
44. Piccerelle P, The preparation of orally disintegrating tablets using a hydrophilic waxy binder, Int J Pharm, 278, 2004, 423-33.
45. Kuno Y, Kojima M, Ando S, Nakagami H, Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols, J Control Release, 105, 2005, 16-22.
46. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M, Newmethod of preparing high porosity rapidly saliva solublecompressed tablets using mannitol with camphor: A subliming material, Int J Pharm, 152, 1997, 127-31.
47. Bhomik D, Chiranjib, Jaiswal J, Dubey V, Chandria M, Fast dissolving tablets: a review on revolution of novel drug deliverysystem and new market opportunities, Der pharmacia Lettre, 1(2), 2009, 262-276.
48. Kaur T, Gill B, Kumar S, Guptha GD, Mouth dissolving tablets: a novel approach to drug delivery, Int J current pharm Res, 3(1),2011, 1-7
49. Habib W, Khankari RK, Hontz J, Fast-dissolve drug delivery systems,Crit Rev The Drug Carrier Sys, 17, 2000, 61-72.
50. Bhaskaran S, Narmada GV, Rapid Dissolving tablet A Novel dosage form, Indian Pharmacist, 1, 2002, 9-12.
51. Allen LV, Wang B, Process for making a particulate support matrix for making a rapidly dissolving dosage form, US Patent, 6207199,2001.
52. Allen LV, Wang B, Process for making a particulate support matrix for making a rapidly dissolving tablet. US Patent, 5587180, 1996.
53. Allen LV, Wang B, Davis LD, Rapidly dissolving tablet, US Patent 5807576, 1998.
54. Rishi RK, The pharma review, 2, 2004, 32.
55. Makino T, Yamad M, Kikutaj, US Patent. 5939091,1998.
56. Bolhuis KG, Zuurman, Wrierikte PHG, Eur. J. Pharm, 5, 1997, 63.
57. Kintsch KN, Hagen A, Manz E, US Patent. 134943, 1979.
58. Heinemann Hand Rotte W, US Patent 3,885,026, 1976.
59. Gajare GG, Bakliwal SR, Rane BR, Gujrathi NA, Pawar SP, Mouth dissolving tablets: a review, Int J pharm Res Dev, 3(6), 2001, 280-296.
60. Meyers GL, Battist GE, Fuisz RC, Process and apparatus for making rapidly dissolving dosage units and product there form, PCT PatentWC 95/34293-A1, 1995.
61. Kumar MD, Sethi P, Kheri R, Sarogi GK, Singh AK. Orally disintegrating tablets: a review. Int Res J pharm. 2(4), 2011, 16- 22
62. Rish RK. A review on fast dissolving tablets techniques. The Pharma Review 2004; 2: 32.

63. Adel M, Semreen MK, Qato KM, et al. fast dissolving dosage forms-.technique. Pharm Tech 2005; 2: 68-75.
64. Indurwade NH, Rajyaguru TH, Nakhat PD. Novel Approach – Fast Dissolving Tablets. Indian Drugs 2002; 39(8):405-409.
65. Hirani JJ, Rathod DA, Vadalia KR. Orally Disintegrating Tablets: A Review. Tropical Journal of Pharmaceutical Research April 2009; 8 (2): 161-167.
66. Kundu S, Sahoo PK. Recent Trends In The Developments of Orally Disintegrating Tablet Technology. Pharma Times April 2008; 40(4): 11-20
67. Bhowmik D, Chiranjib.B, Krishnakanth, Pankaj, Chandira RM. Journal of Chemical and Pharmaceutical Research 2009; 1(1): 163-167.
68. Mizumoto T, Masuda Y, Kajiyama A, Yanagisawa M, Nysadham JR. Tablets quickly disintegrating in the oral cavity and process for producing the same. US Patent 6,589,554; 1999.
69. Dobetti L. Fast Disintegrating tablets. PCT Patent WO 99/44580-A1; **1999**.
70. Caramella C. Int J Pharm Techno Prod Mfr. 1984; 5:1-5.
71. Allen LV, Wang B, Davis JD, et al. US patent NO. 5, 807, 567, 1998.
72. National institute of neurological disorders and stroke, National institute of health.**2007**,06-25.
73. Onalli A. Fast melt tablets and and method of making same. US Patent 5,807,577; **1998**.
74. Tanmoy ghosh, amitava ghosh, devi Prasad. A review on new generation orodispersible tablets and its futureProspective. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(1), 1-7.
75. Indian Pharmacopoeia, Vol.1, Govt. of India, Ministry of Health and Family Welfare, 2007, 182.
76. Udhav S, Bagul. Manufacturing Technologies for Mouth DissolvingTablets. Pharma info. net. 2006, 1-7.
77. Bi Y, Akinobu O, "Evaluation of a compressed tablet rapidly disintegrating in the oral cavity", Chem.Pharm. Bull, 44, 1995,2011-17.
78. Gohel MC, Parikh RK, Brahmbhatt BK, Shah AR, Preparation and assessment of novel co-processed super disintegrants consisting of crospovidone and sodium starch glycolate: A technical note, AAPSPharm Sci Tech, 8(1), 2007, Article 9:E1-E7.
79. Jacob S, Shirwarkar AA, Joseph A, Srinivasan KK, Novel coprocessed excipients of mannitol and microcrystalline cellulose forpreparing fast dissolving tablets of glipizide, Ind J Pharm Sci, 69(5), 2007, 633-9.
80. Mashru RC, Sutariya VB, Sankalia MG, Parikh PP, Development and evaluation of fast-dissolving film of salbutamol sulphate, Drug DevInd Pharm, 35, 2005, 25–34.
81. Uddhav Bagul, Kishore Gujar, Nancy Patel, Sanjeevani Aphale, Shalaka Dhat, Formulation and Evaluation of Sublimed Fast MeltTablets of Levocetirizine Dihydrochloride, Int J Pharm Sci, 2, 2010,76–80.
82. Michael, U., and Okor, RS, Effect of humidity on the disintegrant property of cellulose. Part II: A technical note, AAPS PharmSciTech, 6(1), 2005, E31–E34.
83. Shukla D, Chakraborthy S, Singh S, Mishra B, Mouth dissolving tablets: an overview of formulation technology, Scientiapharmaceutica, 73, 2009, 309-32
84. Seager H. Drug-deliver Products and the Zydis Fast-dissolving Dosage Form. J. Pharm. and Pharmacol 1998; 50: 375-82.
85. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolvingtablets. Pharma. Tech 2000; 24(6): 52-8.
86. Bradoo R, Shahani S, Poojary S, Deewan B, Sudarshan S. JAMA India 2001; 4(10): 27-31.
87. Bhaskaran S, Narmada G V. Rapid dissolving tablet A novel dosage form Indian Pharmacist 2002; 1(2): 9-12.