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A REVIEW ON: FORMULATION, TECHNOLOGICAL AND BENEFICIAL ASPECTS OF ORAL DISPERSIBLE TABLETS

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ABSTRACT:

This review is about oral dispersible tablets a novel approach in drug delivery systems that are now a day's more focused in formulation world, and laid a new path that, helped the patients to build their compliance level with the therapy, also reduced the cost and ease the administration especially in case of pediatrics and geriatrics. Oral dispersible tablets are advantageous for pediatric, geriatric mentally ill, nausea patients who have difficulty in swallowing conventional tablets and capsules. Using various excipients, evaluation tests marketed formulation and drugs used in the research area. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia. Their growing importance has been underlined recently when European Pharmacopoeia adopted the term "Oral dispersible Tablet" as tablet that is to be place in the mouth where it disperses rapidly before swallowing. When ODTs are put on tongue they disintegrate instantaneously, releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form.

Introduction:

Oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage forms, but several limitations of that kind of dosage forms like choking and swelling discomfort in geriatric and pediatric patients [1,2]. Formulation of drugs into a presentable form is the basic requirement and need of today. Dosage form is a mean of drug delivery system, used for the application of drug to a

living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having different type of drug delivery mechanisms. These classical/modern dosage forms have some advantages and disadvantages therefore the development of an ideal drug delivery system is a big challenge to the pharmacist in the presence scenario. In order to get the desired effect the drug should be

delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected [3]. An Oral route of drug administration have wide acceptance up 50-60% of total dosage form. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importance patient compliance [4]. The U.S food and drug administration center for drug evaluation and research (CDER) defines, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue. The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules [6]. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamics characteristics of drugs.

These dosage forms disintegrate within 30 sec with very less quantity of water. This can be achieved by addition of various super disintegrants like Croscarmellose sodium, Cross povidone, sodium starch glycolate [5]. These tablets are also called as Orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts [6].

NEED OF INNOVATIVE DRUG DELIVERY SYSTEM

The orally administered drug delivery is still considered as a standard system in pharmaceuticals field and still considered safest, convenient and economical method of administration providing best route for patient compliance[7], however in case of tablet and

capsule having a common drawback of difficulty in swallowing leading to poor compliance specially in geriatrics[8]. To improve compliance and making the administration convenient, design of new dosage forms gained significant importance. Conventional oral drug delivery present a drug with quick and full release that may go as such without producing the desired effect may be due to the presence of food, Ph of the stomach, enzymatic degradation, change in GIT motility as so forth, giving not enough time to get absorbed[9,10]. Recently much light is being put on the area of designing drug delivery systems bearing organoleptic elegance and maximum patient acceptability in pediatrics and geriatric groups[11-13]. A lot of innovative work is being done on drug delivery in which oral route is preferred because of ease of administration, cost effective therapy, self medication and noninvasive method leading to patient compliance to a higher level[14]. Tablet coating is one of the parameter in drug delivery designing applied to minimize the bad tasting and side effects while enhancing elegance and drug bioavailability[15].

SUITABILITY OF DRUGS FOR ORAL DISPERSABLE TABLETS:

For developing ODT of a specific drug several factors should be kept forth while selecting drug, excipients and formulation method. These are as follows: Drugs to be used for sustained action are not suitable candidate for ODT. Drugs having very disagreeable taste are not suitable like clopidogrel. Patients suffering from Sjogren's syndrome and those with less saliva secretion and not suitable for ODT dosage form. Drugs of very short half life and requiring frequent dosing are not appropriate candidate. Patients on anticholinergic therapy are not suitable for ODT. Drugs showing altered pharmacokinetic behavior if formulated in such dosage form with respect to their conventional dosage form are not suitable, like selegiline, apomorphine and buspirone. Drugs producing considerable amounts of toxic metabolites on first pass metabolism and in GIT and having substantial absorption in oral and pregastric areas are good candidates. Drugs permeable to upper GIT and oral mucosal epithelial cell lining are considered good candidates for ODT [16].

SALIENT FEATURE OF FAST DISSOLVING DRUG DELIVERY SYSTEM [17,18,19,20,21]

- 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 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 stomach. In such cases bioavailability of drug is increased.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- 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.

EXCIPIENTS REQUIRED IN FORMULATING ODTs

Excipients used in ODTs contain one superdisintegrant, a diluent/bulking agent, a lubricant and optionally swelling agent, a permeabilizing agent

(depending upon drug nature), sweeteners and flavorings agents. Names of excipients classes and their percentages are given in Table 1[22].

TABLE 1: DRUGS THAT CAN BE INTEGRATED IN ORAL DISPERSABLE TABLETS

Categories	Drugs
Analgesics and anti inflammatory agents	Piroxicam, ibuprofen, ketoprofen, sulindac
Antiepileptics	Carbamazepine, methsuximide, phenytoin
Antifungal agents	Clotrimazole, amphotericin, griseofulvin
Antimalarial	Chlorquine, mefloquine, proguanil
Antigoutagents	Allopurinol, probenecid, sulphinyprazole
Antibacterial agents	Clarithromycin, ciprofloxacin, erythromycin
Antineoplastic agents	Chlorambucil, methotrexate, cyclosporine
Diuretics	Acetazolamide, amiloride, chlorthalidone,
Antiparkinsonism agents	Bromocriptine mesylate, lysuride maleate
Anxiolytic, sedatives,	Alprazolam, chlordiazepoxide, meprobamate,
Local anaesthetics	Lidocaine
Nutritional agents	Vitamin A, Vitamin D, Vitamin K, Vitamin E,

TECHNIQUES FOR PREPARING ORAL DISPERSIBLE TABLETS

TABLE 2: NAMES AND WEIGHT PERCENTAGE OF VARIOUS MAJOR EXCIPIENTS

Name of the excipients	Percentage used
Superdisintegrants	1–15
Binder	5–10
Antistatic agent	0–10
Diluents	0–8

DIRECT COMPRESSION:

The most easiest and cost effective way to prepare tablets. Conventional compression machines with common ingredients are used, by limited number of processing steps. Microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) are used to manufacture rapidly disintegrating tablets. Rapid disintegration can also be achieved by adding effervescent material in a tablet to generate carbon dioxide, which also helps in taste masking of a drug. Major drawback of effervescent form, is hygroscopicity i.e., the ability to absorb atmospheric moisture. Sometime super disintegrants are added in

optimal concentration, to achieve good oral dispersibility with pleasant feeling. Common examples of superdisintegrants include sodium starch glycolate, croscopolidone, alginic acid, calcium silicate and crosscarmellose. They provide rapid disintegration by swelling due to water absorption [23]. Characteristics of direct compression are cost effective, much similar to the conventional dosage form with an exception of containing high amount of disintegrants in some cases which can result in low tablet hardness [23].

LYOPHILIZATION / FREEZE-DRYING

Formation of porous product in freeze-drying process is exploited in formulating ODTs. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. However, the MDTs formed by Lyophilization have low mechanical strength, poor stability at higher temperature, and humidity. Major drawback of this system is high cost, time consuming procedure and fragility, making conventional packing inappropriate for packing this dosage form and stability issues under stress condition [24].

MOLDING 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 increase dissolution. Tablets are designed using hydrophilic ingredients, with the aim to get maximum drug dissolution. Powder mass is wetted with hydro alcoholic solvent and compressed into dosage form. The solvent system is then allowed to evaporate. Taste of drug particles is developed by spray congealing the molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol with

an active ingredient into lactose based tablet triturate [25].

COTTON CANDY PROCESS

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimics cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharine by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODTs [25].

SPRAY DRYING

This technique is based upon a particulate support matrix that 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 ingredient and compressed into tablet. Allen and Wang have employed spray drying technique to prepare Orodispersible tablets. In this method ingredients are integrated by hydrolyzed and nonhydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution [26]. Characteristics of spray-drying method is this method gives rapid dissolution (within 20 seconds) when dosage form gets in contact with aqueous medium [26].

MASS-EXTRUSION:

In this the mixed ingredients are softened by water soluble ingredient i.e. polyethylene glycol, using methanol as solvent, passing through an extruder to form thin cylinders. Which further get sliced with heated blade to form small tablets [27]. Characteristics of this method is these products can be used to mask bitter tasting drugs making small granules thus enhancing oral bioavailability [27].

SUBLIMATION

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet. The volatile material is evolved by reduced pressure and applying slight temperature leaving the mass in porous forms [28]. Characteristics of sublimation method are, they are porous in nature, solvents like cyclohexane and benzene can be used [28].

MELT GRANULATION

By Melt granulation, it is formulated by addition of hydrophilic waxy binder (super polystate) PEG-6-stearate. This binder possesses dual action; increasing physical strength it also enhances the disintegration. Drugs such as griseofulvin can be easily administered in such dosage form [29]. Characteristics of compaction method is that it rapidly melts in mouth leaving no residue [29].

FAST DISSOLVING FILMS:

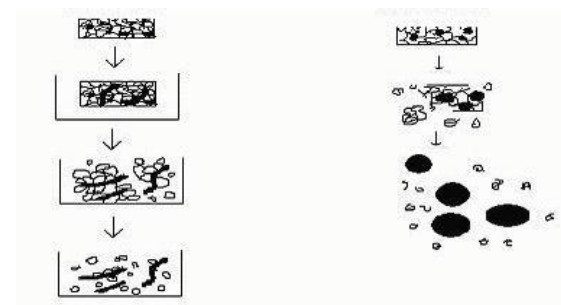
It contains a nonaqueous solution having water soluble film forming polymers (pullulan, carboxymethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate.), a drug and other taste masking agent which are used to develop a film as solvent evaporates. In case of bitter tasting drugs resin adsorbate or coated micro particles of a drug can be used into a film [30]. Characteristics: These are thin films of 2×2 inches dimensions; dissolve fast within 5 seconds, leaving a good after taste [30].

SUPERDISINTEGRANTS

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of Superdisintegrants are Crosscarmellose, Crospovidone and sodium starch Glycolate, which are a cross linked cellulose, cross-linked polymer and a cross linked starch respectively. The proper choice of

disintegrant and its consistency of performance are critical to formulation development of such tablets. Microcrystalline cellulose and low substituted hydroxyl propyl cellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch Glycolate, Crospovidone and Crosscarmellose are some of the popular superdisintegrants [31].

MECHANISM OF SUPERDISINTEGRANTS [31]



WICKING SWELLING

Fig. 1.0: Disintegration by wicking and swelling process

SWELLING

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

POROSITY AND CAPILLARY ACTION (WICKING)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on table ting conditions. For these types of disintegrates maintenance of porous structure and low interfacial

tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

DUE TO DEFORMATION

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied. Disintegration of tablets by deformation and repulsion.

SUGAR-BASED EXCIPIENTS

Sorbitol, Mannitol, dextrose, xylitol, fructose, maltose, isomalt and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar based materials.

PATENTED TECHNOLOGIES FOR ORAL DISPERSIBLE TABLETS 32, 33, 34, 35, 36

ZYDIS TECHNOLOGY

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The Zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystalline, elegance and hardness, saccharides such as Mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to

prevent sedimentation of dispersed drug particles in the manufacturing process.

ORASOLV TECHNOLOGY

In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

DURASOLV TECHNOLOGY

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

WOW TAB TECHNOLOGY

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 (e.g. lactose, glucose, and Mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligo saccharides) and compressed into tablet.

FLASH DOSE TECHNOLOGY

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

FLASH TAB TECHNOLOGY

Tablet prepared by this system consists of an active ingredient in the form of micro crystals.

FUTURE ASPECTS OF ODTs

Some new quality control methods can be developed to determine the technological aspects of orally disintegrating tablets to define the characteristics of ODTs [37]. It would be an innovative improvement in the ODT technology when development of ODTs with

controlled release properties that can deliver drugs which has short half-lives like 12–24 hours. The added convenience and compliance of such formulations will be used more immensely [38]. In addition, the ability to formulate drugs in large doses will bring another important technological advance. In general, the ODT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle. ODT formulations that require fewer excipients than the drug itself will be a break through [39]. ODT technologies are in progress, but development of formulation of ODTs that contains lipophilic active pharmaceutical ingredients is a challenge. New ODT technology should be developed to find a solution for this problem [40]. As far as seen in the literature there is not much delayed release ODTs in the market.

APPLICATIONS OF ODTs

Numbers of drugs are being marketed applying different methods of formulating ODTs. Orally disintegrating tablets have many advantages compared with the other oral dosage forms, such as better bioavailability, better patient compliance, and improved efficacy. Nevertheless formulation challenges such as limited tablet weight, disintegration time, friability, manufacturing technology, and packaging should be considered. Orally disintegrating tablets may be evaluated as a first choice for pediatrics and geriatrics – situations that parenteral cannot be used especially for central nervous system, gastrointestinal system disorders and pain.

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