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AN EMERGING TREND IN ORAL DRUG DELIVERY TECHNOLOGY: RAPID DISINTEGRATING TABLETS

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Abstract

Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Rapid Disintegrating Tablets (RDT) which are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. RDT can be applicable in difficulty in swallowing (Dysphagia) or chewing solid dosage forms to pediatrics, geriatrics, mentally ill, uncooperative and nauseated patients. RDT is much more advantageous because of ease of administration, enhanced bioavailability, masking the unpleasant taste of drug, etc. Many patented technologies have been developed such as Zydis, Orasolv, Durasolv, WOWTAB, FlashDose, Nanocrystal technology etc. There are many conventional techniques used in manufacturing of RDT such as direct compression, tablet moulding, freeze drying, sublimation etc. RDT can be administered for large number of drugs. The prepared blend can be evaluated for preformulation studies and the prepared tablets are then evaluated for quality control tests. With the help of RDT, the objective of the patient compliance can be satisfactorily achieved.

Key Words: Rapid Disintegrating Tablets (RDT); Salient features; Patented technologies; Conventional Techniques; Evaluation.

Introduction

Rapid disintegrating tablets (RDT) are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. When this type of tablet is placed into the mouth, the saliva will serve to rapidly disintegrate the tablet[1,2,3]. The faster the drug into solution quicker the absorption and onset of clinical effect. RDT release drug in the mouth for absorption through local oromucosal tissues and through pregastric (i.e., oral cavity, pharynx and esophagus), gastric (i.e, stomach) and postgastric (i.e., small and large intestine)[4,5]. In such cases, the bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs are significantly greater than those observed from conventional dosage forms. RDT can be applicable in difficulty in swallowing (Dysphagia) or chewing solid dosage forms to pediatrics, geriatrics, mentally ill, uncooperative and nauseated patients.[6]

Rapid disintegrating tablets (RDT) are also known as 'fast dissolving', 'mouth dissolving', 'rapid-dissolve', 'quick disintegrating', 'orally disintegrating', 'rapimelt', 'fast melts', 'orodispersible', 'melt-in-mouth', 'quick dissolving', 'porous tablets', 'EFVDAS' or 'Effervescent Drug Absorption System'[7].

Recently Orally disintegrating (OD) tablet technology has been approved by United States Pharmacopoeia (USP), Centre for Drug Evaluation and Research (CDER). USFDA defined OD tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term "Oro Dispersible Tablet"[8].

The aim of rapid disintegrating tablets (RDT) drug delivery is to produce good-tasting tablets that disintegrate in a reasonable time

without the need for water. Drugs have varying levels of bitterness and dosage. It may be acceptable to have a small amount of drug taste present in the final product. Clearly, patient compliance must be taken into account when developing any new drug products and this is where RDT products have a clear benefit for patients[9].

Mechanism

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet (Figure 1).

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together[10] (Figure 2).

Salient Features[2,11,12,13]

- Ease of administration which improves patient compliance.
- 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 of water.
- Rapid dissolution of drug and absorption, which may produce rapid 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 drugs is increased.
- Good chemical stability and allows high drug loading.

Figure 1: Schematic Representation of Tablet Disintegration and Subsequent Drug issolution

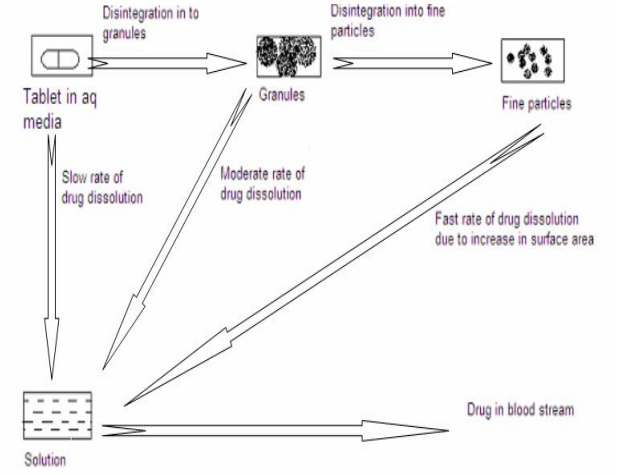
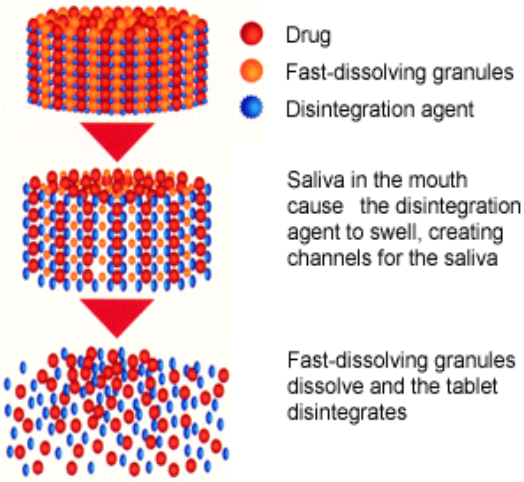


Figure 2: Mechanism of Disintegration



- Can be designed to leave minimal or no residue in the mouth and also good mouth feel property helps to change the basic view of medication as 'bitter pill', particularly for pediatric patients.
- Overcomes unacceptable taste of the drugs.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- New business opportunities: line and patient-life extension, exclusivity of product promotion.

Characteristics[11,13]

Taste of the medicament

As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredient which comes in contact with the taste buds and hence, taste masking of the drugs becomes important for patient compliance.

Hygroscopicity

Several rapid disintegrating drug delivery systems 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.

Friability

In order to allow the tablets to dissolve rapidly in the mouth, they are made of either porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as WOWTAB® by Yamanouchi-Shaklee and Durasolv® by CIMA labs.

Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe. Effervescence can be added to aid disintegration and improved mouth feel by reducing the 'dryness' of a product.

Patented Technologies[3,5,7,14,15]

Some of these patented technologies are shown in Table 1.

Zydis Technology

Using the concept of Gregory et al., R.P.Scherer has patented zydis technology. Zydis is a unique freeze-dried oral solid dosage form that can be swallowed without water as it dissolves instantly on tongue in less than 5 seconds. The drug is physically trapped in a water-soluble matrix, and then freeze-dried to produce a product that rapidly dissolves. The matrix consists of water-soluble saccharides and polymer (gelatin, dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. Water is used during the process to produce porous units for rapid disintegration. Various gums are used to eliminate the sedimentation problem of dispersed drugs. Glycine is used to prevent the shrinkage of zydis unit during the process and in long-term storage. As the zydis dosage form is weak in physical strength, unit is contained in peelable blister pack, which allows removal of product without damaging it.

Orasolv Technology

CIMA labs have developed Orasolv technology. The system essentially makes tablets that contain taste masked active ingredients and effervescent disintegrating agent which on contact with saliva, rapidly disintegrates and releases the taste mask active ingredient. The tablets made by direct compression at very low compression force in order to minimize oral dissolution time. The tablets so produced are soft and friable and are packaged specially designed pick and place system. The taste masking associated with Orasolv formulation is two folds. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; coating the drug powder and effervescence are means of taste masking in Orasolv.

Durasolv Technology

Durasolv is CIMA's second generation fast dissolving tablet formulation. Produced in a similar fashion to that of orasolv, durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction produced during tabletting. The durasolv product is thus produced in a faster and more cost effective manner. One disadvantage of durasolv is that the technology is not compatible with larger doses of active

ingredients, because formulation is subjected to high pressures on compaction. Durasolv is currently available in two products nulev and zorlip.

WOWTAB Technology

WOWTAB technology is patented by Yamanouchi Wow means "without water". WOWTAB is an intrabuccally soluble, compressed tablet consisting of granules made with saccharides of low and high mouldability. The combination of high and low mouldability is used to obtain a tablet of adequate hardness and fast dissolution rate. Mouldability is the capacity of the compound to be compressed. Low mouldablity means the compounds show reduced compressibility for tabletting and rapid dissolution rate. But in case of high mouldability compounds this context is reversed. In this the active ingredient is mixed with low mouldability saccharides and granulated with high mouldability saccharides and then compressed into tablet. The wowtab formulation is stable to environment due to its significant hardness than Zydis or Orasolv. WOWTAB product is suitable both for conventional bottle and blister packaging.

FlashDose Technology

(Fuisz Technologies, Ltd.)

Fuisz has patented the FlashDose technology. The FlashDose technology utilizes a unique spinning mechanism to produce floss like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. FlashDose tablet consists of self-binding sheaform matrix termed “floss”. The procedure has been patented by Fuisz and known as “Shearform”. Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of floss- like material, small spheres of saccharide can be produced to carry the drug. The procedure of making microspheres has been patented by Fuisz and known as “Ceform”.

a. Shearform Technology™

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

b. Ceform technology™

In ceform technology microspheres containing active ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly spinning machine. The centrifugal force of the rotating head of the ceform machine throws the dry drug blend at high speed through small heated openings. The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance.

Flashtab Technology

This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like microencapsulation, coacervation and extrusion-spheronization. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

Table 1: Examples of Some Patented Technologies

Patented Technologies	Method of Manufacturing	Manufacturer
Zydis	Freeze drying	R.P.Scherer, Inc.
Quicksolv	Freeze drying	Janseen Pharmaceutics
Lyoc	Freeze drying	Farmalyoc
Flashtab	Direct Compression	Ethypharm
Orasolve	Direct Compression	Cima Labs, Inc.
Durasolv	Direct Compression	Cima Labs, Inc
WOWTAB	Direct Compression	Yamnanouchi Pharma Tech. Inc.
Ziplets	Direct Compression	Eurand
Flash Dose	Moulding	Fuisz Technology, Ltd.
Efvdas	Moulding	Elan Corp
Oraquick	Micromask Technique	K.V. Pharmaceutical Co. Inc.

Oraquick Technology

The oraquick fast dissolving tablet formulation utilizes a patented taste masking technology by K. V. Pharmaceutical Company, who claim that its taste masking technology i.e. microsphere technology (micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression.

FastWrap system

BioProgress had developed novel tablet cores with a high disintegration profile that were easily coated using the TabWrap finishing process. The FastWrap system combines the TabWrap process with the company's patented novel tablet core technology to create coated tablets that can rapidly disintegrate and dissolve, allowing for a faster onset of action. The FastWrap technology can also be used to manufacture film-flavoured orally disintegrating tablets. As standard coating techniques tend to involve spraying on a coating that has been dissolved in liquid, they have run into problems with tablets hat incorporate highly moisture sensitive super-disintegrants or excipients. The TabWrap system, on the other hand, is a completely dry coating process.

NanoCrystal Technology

RDT, 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 nanometers (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.
- 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.

Conventional Techniques[5,7,13]

Direct compression

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. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary**.** 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 solubilization are strongly affected by tablet size and hardness. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially superdisintegrants like cross carmellose sodium, microcrystalline cellulose, crosspovidone, sodium starch glucolate and partially substituted hydroxypropyl cellulose, effervescent agents (citric acid, sodium bicarbonate) and sugar-based excipients (dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol)

Tablet moulding

In this technology, water soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air drying. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidine can increase the mechanical strength of the tablet.

Spray drying

Spray drying produces highly porous and fine powder as the processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolysed an non hydrolysed gelatin and other components like mannitol as bulking agent, sodium starch glycolate, cross carmelose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution.

Taste masking

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethylcellulose) masked the bitter taste of sparfloxacin. The addition of low substituted

hydroxypropyl cellulose as disintegrant to the drug in cores, resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets.

Freeze drying

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly disperses when placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colours and flavours. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Lyophilization is relatively expensive and time consuming manufacturing process. Other drawbacks include fragility, which make the use of conventional packing difficult and poor stability during storage and stressful condition.

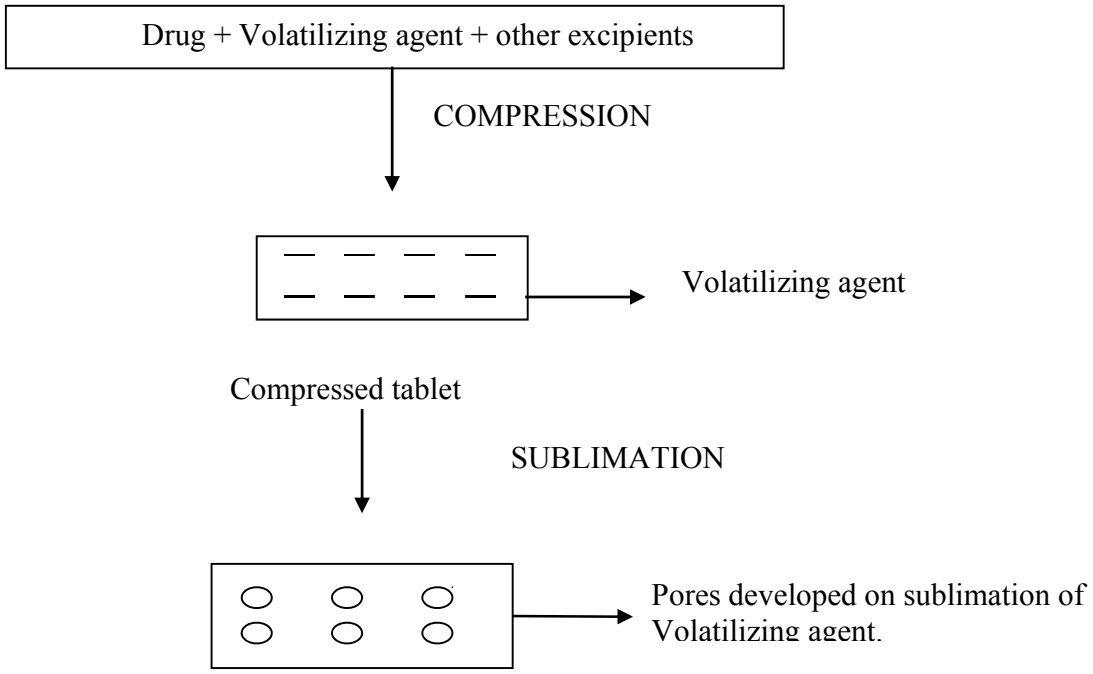
Mass Extrusion

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

Sublimation

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile salt to the tabletting component, mixing the components to obtain a substantially homogenous mixture and volatizing salt. The removal of volatizing salt creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. The tablets were then subjected to vacuum at 80º C for 30 minutes to eliminate volatile components and thus create pores in the tablet. Volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea, etc., were also used as sublimable components to prepare porous tablets of good mechanical strength. (Figure 3)

Figure 3: Sublimation Technique



Drugs to be Promising to Incorporate[5,18]

Analgesics and Anti-inflammatory Agents: Aloxiprin, Diflunisal, Fenbufen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Nabumetone, Naproxen, Oxaprozin

Anthelmintics: Albendazole, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.

Anti-Arrhythmic Agents: Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate,

Anti-Bacterial Agents: Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Cloxacillin, Doxycycline, Erythromycin, Imipenem, Nitrofurantoin, Rifampicin, Sulphabenzamide

Anti-Coagulants: Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

Anti-Depressants: Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide.

Anti-Epileptics: Beclamide, Carbamazepine, Clonazepam, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Valproic acid

Anti-Fungal Agents: Amphotericin, Butoconazole Nitrate, Clotrimazole, Fluconazole, Fiucytosine, Griseofulvin, Ketoconazole, Miconazole, Nystatin, Terbinafine, Terconazole, Tioconazole.

Anti-Hypertensive Agents: Amlodipine, Carvedilol, Benidipine, Dilitazem, Diazoxide, Felodipine, Indoramin, Isradipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine.

Anti-Malarials: Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.

Anti-Migraine Agents: Dihydroergotamine Mesyiate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate.

Anti-Muscarinic Agents: Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide.

Anti-Neoplastic Agents and Immunosuppressants: Aminoglutethimide, Amsacrine, Azathiopnne, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Methotrexate, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics: Alprazolam, Barbitone, Bentazeparn, Bromperidol, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Diazepam, Flunanisone, Fluopromazine, Lorazepam, Nitrazepam, Oxazepam, Pentobarbitone, Prochlorperazine.

β-Blockers: Acebutolol, Alprenolol, Atenolol, Labetalol, Metoptolol, Oxprenolol, Propranolol.

Cardiac Inotropic Agents: Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.

Corticosteroids: Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Fluticasone Propionatu, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.

Diuretics: Acetazolarnide, Amilo , Metolazone, Spironolactone, Triamterene.

Anti-Parkinsonian Agents: Bromocriptine Mesylate, Lysuride Maleate.

Gastro-Intestinal Agents: Bisacodyi, Cimetidine, Cisapride, Diphenoxylate, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Sulphasaiazine.

Histamine H,-Receptor Antagonists: Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Flunarizine, Loratadine, Meclozine, Oxatomide, Terfenadine, Triprolidine.

Lipid Regulating Agents: Bezafibrate, Clofibrate,Fenofibrate, Gemfibrozil, Probucol.

Nitrates and Other Anti-Anginal Agents: Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

Nutritional Agents: Betacarotene, Vitamin A, Vitamin B_2, Vitamin D, Vitamin E, Vitamin K.

Opioid Analgesics: Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.

Evaluation of Blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics-of blends produced.

The various characteristics of blends tested are as given below:

Angle of repose (θ)[20,21]

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powder is allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose is then calculated by measuring the height and radius of the heap of powder formed.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height, r = radius

Bulk Density (D_b)[20,21]

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may be therefore be more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (gm/ml) is determined by pouring bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can be calculated by the following formula,

$$\text{Bulk Density, } D_b = M / V_b$$

Where, M = mass of the powder

V_b = bulk volume of the powder

Tapped density (D_t)[20,21]

Tapped density is the bulk density of a powder which has been compacted by tapping or vibration. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density is computed by taking the weight of drug in cylinder and final volume.

$$\text{Tapped Density, } D_t = M / V_t$$

Where, M = mass of the powder

V_t = bulk volume of the powder

Compressibility Index (Carr's Consolidation Index)[20,21]

Another indirect method of measuring powder flow form bulk densities was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It is calculated according to the following equation,

$$\text{Carr's index (\%)} = (D_t - D_b / D_t) \times 100$$

Where, D_t = tapped density of the powder

D_b = bulk density of the powder

Hausner Ratio[19,21]

Hausner Ratio is an indirect index of ease of powder flow. If the hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the following formula

$$\text{Hausner Ratio} = D_b / D_t$$

Where, D_t = tapped density of the powder

D_b = bulk density of the powder

Void Volume[22]

The volume of the spaces is known as the void volume "v" and is given by the formula,

$$V = V_b - V_p$$

Where, V_b = Bulk volume (volnme_before tapping)

V = True volume (volume after tapping)

Porosity[22]

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by

$€= V_b - V_p / V_p = 1 - V_p / V_b$

Porosity is frequently expressed in percentage and is given as

$\%€ = (1 - V_p / V_b) \times 100$

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

Evaluation

Tablets from all the formulation were subjected to following quality control test.

General Appearance[23,24]

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape[23,24]

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness[23,24]

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight[23,24]

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The limit for weight variation is given in Table 2.

Table 2: I.P. Limit for Weight Variation

Average Weight of Tablets (mg)	Maximum percentage different allowed
80mg or less	10
60mg but < 250mg	7.5
250mg or more	5

Tablet hardness[21,25]

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability[21,25]

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the fribaiator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

%Friability = loss in weight / Initial weight x 100

Wetting time[26,27]

The method reported by yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

Surface pH[28]

The surface pH of the tablets was determined in order to investigate the possibility of any side effects due to change in pH *in vivo*, since an

acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1.0 ml of simulated saliva for 2 hours and pH was noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1.0 min.

***In-vitro* dispersion time[26,27]**

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

***In-vitro* Disintegration test[25,29]**

The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

***In vitro* Drug Release Studies[25]**

In-vitro drug release studies were carried out by using USP XXIII Dissolution Apparatus II (Paddle type) [Electrolab (TDT-06T) Tablet Dissolution Tester] at 50 rpm. The drug release profile was studied in 900 ml of hydrochloric acid buffer at pH 1.2 by maintaining at 37 ± 0.5º C. Aliquots of dissolution medium were withdrawn at specific time intervals, filtered and the amount of drug released was determined spectrophotometrically. Six trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

Stability testing of drug (temperature dependent stability studies)[23,24]

The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C
(ii) 50 ± 1 °C
(iii) 37 ±1 °C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 °C.

Packaging

Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Unlike these other quick-dispersing and/or dissolving oral delivery systems, the system can be packaged using various options, such as single pouch, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser, depending on the application and marketing objectives.

Conclusion

Rapid disintegrating tablets constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The paediatric and geriatric populations are the primary. The availability of the various technologies and manifold advantages of rapid disintegrating tablets will surely increase its popularity in the near future.

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