

A REVIEW ON: ORAL DISPERSIBLE TABLETS**Pawankumar Rai^{1*}, Kinjal Modi² and Alok Raghav³**¹CSIR- Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India.²Former Formulation & Development Executive, Cadila Pharmaceuticals Pvt. Ltd.,
Ahmedabad, Gujarat, India.³Project Scientist, IIT, Kanpur, Uttar Pradesh, India.Article Received on
26 October 2018,Revised on 16 Nov. 2018,
Accepted on 06 Dec. 2018

DOI: 10.20959/wjpr20191-13857

Corresponding Author*Pawankumar Rai**CSIR- Indian Institute of
Toxicology Research,
Lucknow, Uttar Pradesh,
India.**ABSTRACT**

The most preferred route for administration of various therapeutic agents is oral. Recent advances in technology prompted to develop oral disintegrating tablets with improved patient convenience/compliance. Oral disintegrating tablets are the solid unit dosage form which dissolve or disintegrate rapidly in the mouth without use of water or without chewing. The development of oral dispersible tablets has been formulated for pediatric, geriatric, and bed rest patients and for those people as well as patients who may not have access to water. Several formulation 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. The technologies used for manufacturing of oral disintegrating tablets are either conventional/patented technologies. This review describes various aspects of oral disintegrating tablet formulation, superdisintegrants and technologies developed for it, along with various drugs explored, evaluation tests and marketed formulations in this particular field.

KEYWORDS: ODT, Mechanism of action, Method of preparation, Selection of excipients, Evaluation parameters.

INTRODUCTION

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. But the most evident drawback of the commonly used oral

dosage forms like tablets and capsules is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.^[1,2]

Recently, the demand for development of orally disintegrating tablets has excessively increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications. Orally disintegrating tablets with good taste and flavor increase the acceptability of bitter drugs in various groups of population. This dosage form combines the advantages of both dry and liquid formulation. Some novel oral disintegrating tablet technology allow higher drug loading, have an acceptable taste, offer a pleasant mouth feeling and leaving minimal residue in the mouth after oral administration. ODT have been investigated for their potential in improving bioavailability of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs.^[1,2,3,4]

Characteristics of Oral Dispersible Delivery Systems

Easy of administration

Oral Dispersible Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Generally, elderly people experience difficulty in swallowing the conventional dosage forms i.e tablets, capsules, solutions and suspensions, because of tremors of extremities and dysphagia. Oral Dispersible tablets may offer a solution for these problems.^[4,5]

Taste of the medicament

As many of the drugs are unpalatable, mouth dissolving delivery systems usually contains the medicaments in taste masked form. This delivery systems dissolve/disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and therefore, taste masking of the drugs becomes critical to patient compliance.^[4,5,6]

Hygroscopicity

Several Oral Dispersible dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.^[4,7]

Friability

In order to allow oral disintegrating tablets to dissolve in the mouth, they are made of either very porous and soft- molded matrices or compressed into tablets with very low compression force, which makes the tablets friable or brittle which are difficult to handle and often require specialized peel-off blister packaging.^[5,6,7]

Mouth Feel

Mouth feel is essential and patients should receive a product that feels pleasant. If any large particle from the disintegrating tablet remain insoluble or slowly soluble in saliva, could lead to an unpleasant and gritty feeling. It can be overcome by keeping the majority of the particles below the detectable size limit range. In some cases, certain flavours can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavour. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.^[4,5]

Various technologies used in the manufacture of ODT

The performance of ODT depends on the technology used in their manufacturing process. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent & using highly water-soluble excipient in the formulation.^[8,9] Following technologies have been used by various researchers to prepare ODT

- ❖ Freeze-Drying or Lyophilization
- ❖ Tablet Molding
- ❖ Sublimation
- ❖ Direct Compression
- ❖ Cotton Candy Process
- ❖ Mass-Extrusion
- ❖ Wet granulation method

❖ Spray Drying.

Freeze-Drying or Lyophilization

It is the process in which water is sublimed from the product after it gets frozen. This technique creates an amorphous porous structure that get dissolve rapidly. A typical procedure involved in the manufacturing of oral disintegrating tablet using this technique is described here. The active drug is dissolved/dispersed in an aqueous solution of a carrier/polymer. The mixture is poured in the wells of the preformed blister packs. The trays which holds the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution/dispersion. After that 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. Finally the blisters are packaged and shipped.^[8]

The freeze-drying technique has shown improved absorption and increase in bioavailability. Remon and Corveleyn in one of their study found maltodextrins very useful in preparing oral dispersible tablets by lyophilization. The major disadvantages of lyophilisation technique are that it is expensive and time consuming; Fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.^[8,9]

Tablet Molding

The preparation of oral disintegrating tablet using molding technology invokes water-soluble ingredients so that the tablet dissolves completely and rapidly. Mainly the active ingredients are absorbed through the mucosal lining of the mouth. Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening of the powder blend with a hydro alcoholic solvent followed by a compression at low pressures in molded plates to form/make a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets prepared in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process incorporates preparation of a suspension that contains a drug, agar and sugar for e.g. Mannitol or lactose and pouring the suspension in blister packaging wells, solidifying agar at the room temperature to form a jelly and drying at 30° under vacuum. The mechanical strength of molded tablets is a matter of great concern. Incorporation of binding agents for increasing the mechanical strength of the tablets should be done. Taste masking is an added problem to this particular technology. To overcome this, 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. Tablets produced by the molding technique are easier to scale up for industrial manufacture, compared to that of lyophilization process. Agar solution can also be used as a binding agent and in blister packaging as well as a mold to prepare an intrabuccally fast disintegrating tablet.^[8,10]

Sublimation

The key to rapid disintegration of oral disintegrating tablet is preparation of a porous structure in the tablet matrix. Volatile ingredients are incorporated in the formulation to generate porous matrix so that it can be later subjected to a process of sublimation. Extremely volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride can be compressed along with other excipients into a tablet. These volatile materials afterwards removed by sublimation, which leaves behind a highly porous matrix. Tablets prepared by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents. Vacuum drying technique has been very often used by researchers to sublimate the volatile ingredients and thus maximize the porous structure in the tablet matrix. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.^[8,10,11]

Direct Compression

It represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied in the preparation of ODT because of the availability of improved excipients especially Superdisintegrants and sugar based excipients.^[9, 12]

Superdisintegrants

In many ODT technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and therefore the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the disintegration process. Microcrystalline cellulose (MCC) and low substituted hydroxyl propyl cellulose (HPC) can be used to manufacture ODT. Use of agar powder as a disintegrant can be done, because the powder absorbs water and swells without forming gel at physiological temperature. Ethylpharm (France) has introduced a Flash- dose technology, which contains coated crystals and micro granules along with the disintegrant. This

technology involves two types of granules i.e a disintegrating agent which has a high swelling force and a swelling agent which has a low swelling force.^[8, 10, 12, 13]

Sugar based excipients

It incorporates another approach to manufacture oral disintegrating tablet by direct compression. Sugar based excipient especially bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, incorporates taste masking property and a pleasing mouth feel. Oral disintegrating tablet formulators prefer to use a directly compressible Mannitol, which enables the preparation of robust tablets that can withstand processing and transportation. Specially textured directly compressible, spray-dried, or granulated Mannitol excipient has been designed to meet these needs. These excipients under given manufacturing conditions gives a highly porous structure and friable exterior structure which accelerates disintegration of ODT. This also provides a satisfactory mouth feel and is suitable for use in preparation of harder ODT by direct compression at low pressure.^[8,11,12]

Cotton candy process

The cotton candy process is also known as the “candy floss” process and forms the basis of the technologies such as Flash Dose® (Fuisz Technology). An Oral disintegrating tablet is formed using a candyfloss or shear form matrix; the matrix formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active ingredients and other excipient and subsequently compressed into ODT. However the high processing temperature limits the use of this technology to thermo stable compounds only.^[8, 12, 13]

Mass-Extrusion

Mass extrusion 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 segmented cylinder of product using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.^[8,13,14]

Wet Granulation Method

This technology involves the binding of the mixture of drug and suitable filler with the binder, like starch paste or PVP. After binding of the mass, it is dried until little moisture remains in the mass. Then for production of the suitable size granules, the mass is passed through the sieve. After that the size reduction, superdisintegrant is added and other remaining materials, like talc or magnesium stearate are added and mixed. This mixture is then compressed to form tablets. Addition of the superdisintegrant can be done either during granulation, intra granulation or extra granulation. Sometimes superdisintegrant is added partly in the formulation i.e. 50% amount is added during granulation and remaining amount is added after granulation.^[8, 13]

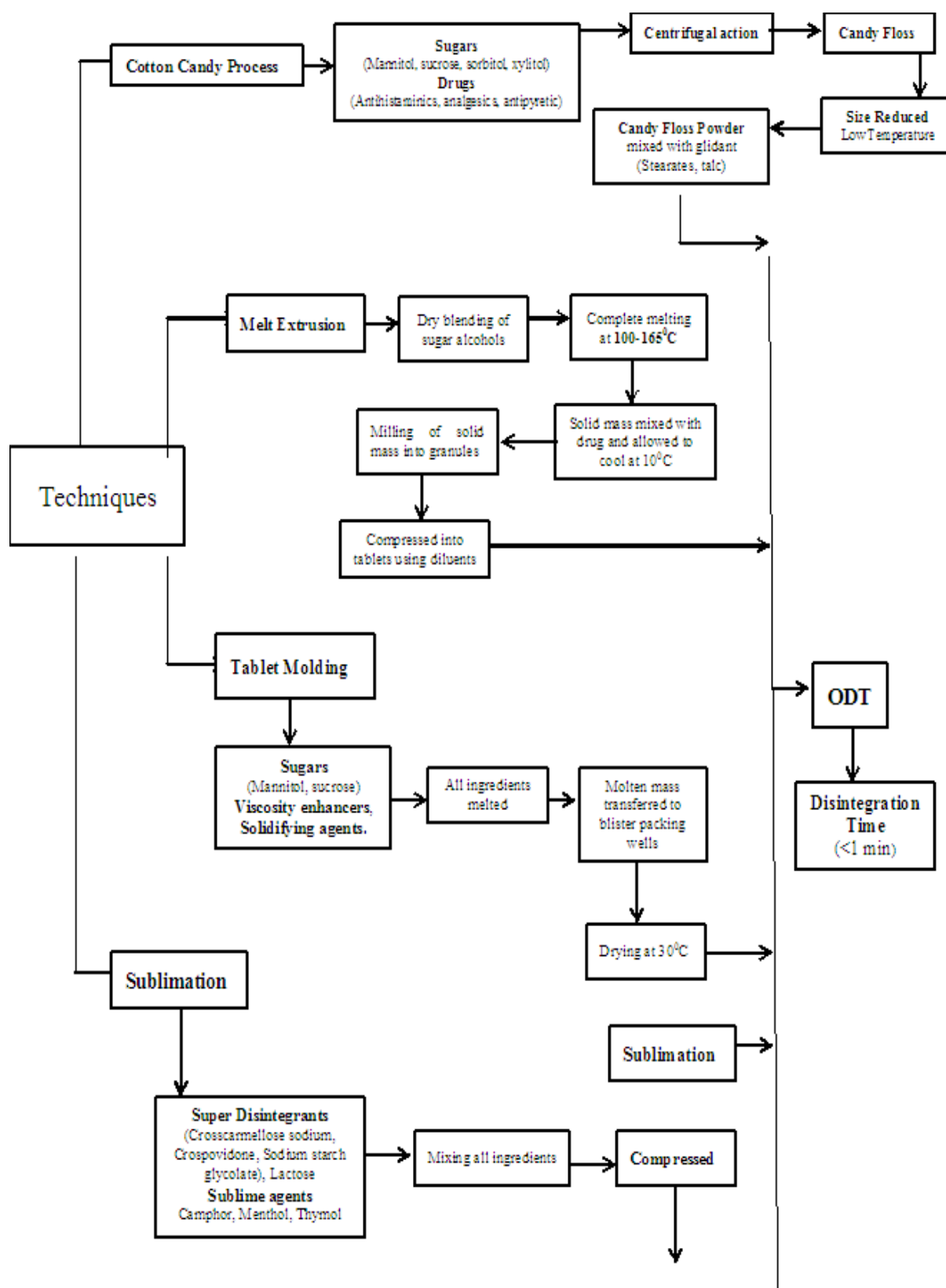


Figure 1: Schematic representation of the processes involved in the preparation of ODTs by employing heat based technology.

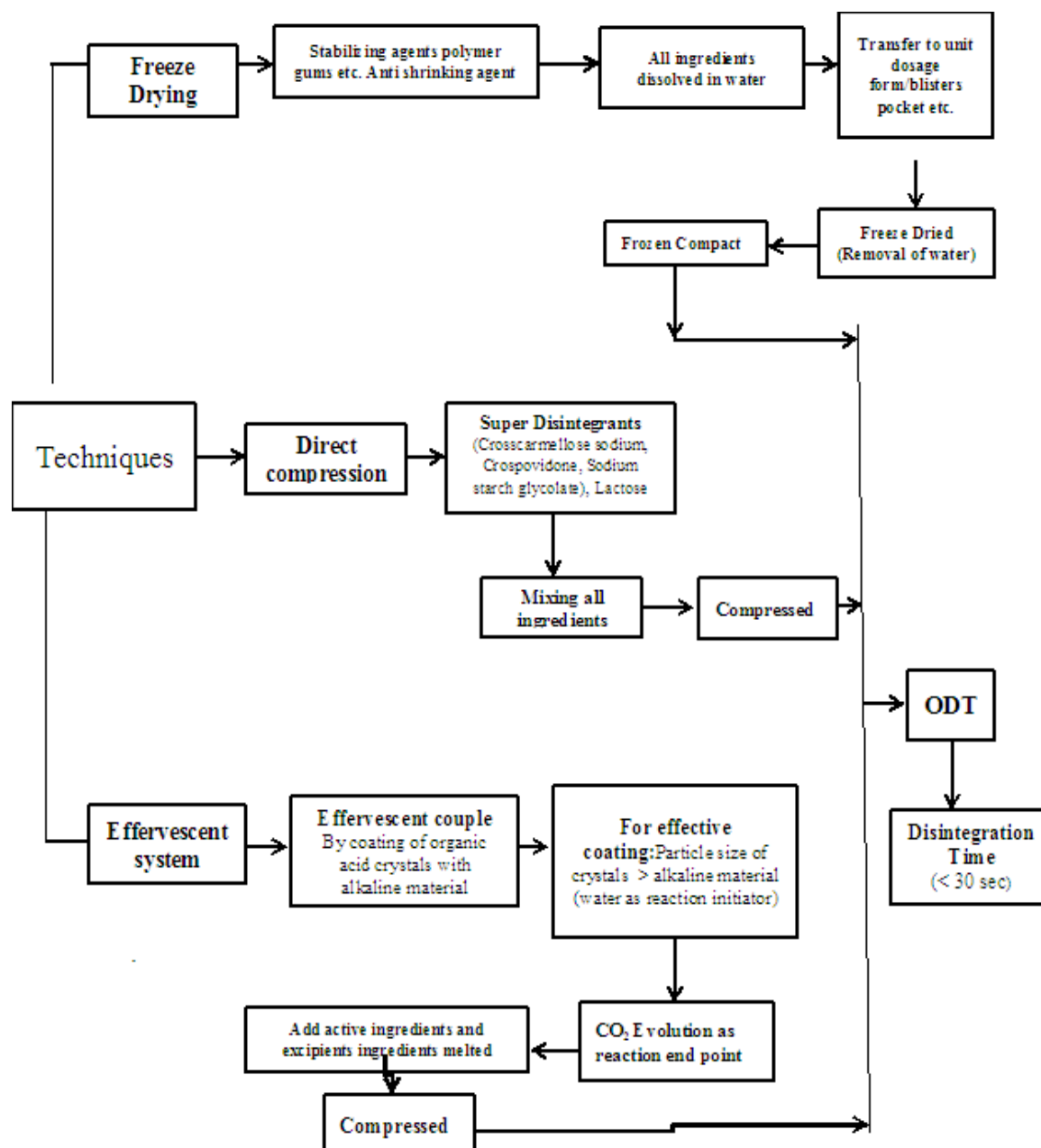


Figure 2: Schematic representation of the process involved in the different methods for preparation of ODTs without using heating process.

Table 1: Flow properties corresponding to Angle of repose.

Angle of repose (θ)	Predicted flow property
25-30	Excellent
31-35	Good
36-40	Fair (Aid not needed)
41-45	Passable (May hang up)
46-55	Poor (Must agitate or vibrate)
56-65	Very poor
>66	Very poor

Table 2: Flow Properties Corresponding to Compressibility Index.

Compressibility Index (%)	Flow Character
< 10	Excellent
11–15	Good
16–20	Fair
21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very poor

Table 3: Flow Properties Corresponding to Hausner's Ratio.

Hausner's Ratio	Flow Character
1.00–1.11	Excellent
1.12–1.18	Good
1.19–1.25	Fair
1.26–1.34	Passable
1.35–1.45	Poor
1.46–1.59	Very poor
>1.60	Very poor

Table 4: The Similarity factor f2 and its significances.

Similarity factor (f2)	Significance
< 50	Test and reference profiles are dissimilar.
50 – 100	Test and reference release profiles are similar.
100	Test and reference release profiles are identical.
> 100	The equation yields a negative value.

Spray Drying

It is used in pharma industries to produce highly porous powders. The processing solvent is evaporated rapidly by the spray drying technique, which renders the product highly porous and therefore can be used in manufacturing ODT. In this technique, 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 superdisintegrant. The tablets which are manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. This technique can be used for preparing fast dissolving tablets also having bulking agent like Mannitol and lactose, a superdisintegrant 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.^[8,14,15]

Selection of Excipients^[8,15,16,17,21]

Following excipients were selected to fulfill the criteria of fast disintegrating tablet.

(a) PVP k-30

Povidone solutions are incorporated as binders in wet granulation processes. It is also used as an aid in disintegration and dissolution. It is used as a solubilizer in oral and parenteral formulations and used to enhance dissolution of poorly soluble drugs from solid-dosage forms.

(b) Microcrystalline Cellulose (Avicel 102)

It is widely used as a diluent in tablets/capsules. It is used in both wet granulation and direct compression processes also used as tablet disintegrant. It has both binding and disintegrant action.

(c) Crosscarmellose Sodium: It swells 4-8 folds in 10 seconds. The cellulose derivative swells in two dimensions radially. In formulation of tablets it may be used in both direct compression and wet granulation processes. When used in wet granulation croscarmellose sodium is added to in both the wet and dry stages of the process so that wicking and swelling ability can both be utilized.

(d) Sodium Starch Glycolate: Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in tablet and capsule formulations. It is generally used in tablets prepared by either direct compression or wet granulation process. The usual concentration employed in a formulation is between 2-8%. The disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

(e) Sodium Bicarbonate (NaHCO_3): Carbon dioxide generating agents like sodium hydrogen carbonate (NaHCO_3), it swells in the gastric fluid as it gets contact with the aqueous medium. Formation of carbon di oxide and entrapment of that gas into the polymeric gel causes swelling of the dosage form, resulting a bulk density less than 1. Then after, it then remains buoyant and floats in the gastric fluid resulting a prolonged gastric residence time.

(f) Mannitol: As a Diluent in tablets (10-90% w/w). It is not hygroscopic and used with moisture sensitive active ingredients. Mannitol is commonly use as an excipient in the manufacture of chewable tablet and mouth dissolving formulation because of its negative heat of solution, sweetness and mouth feel.

(g) **Talc:** Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. However, it is widely used as a dissolution retardant in the development of controlled-release products.

(h) **Lactose:** Lactose is widely used as filler or diluents in tablets and capsules, and to a more limited extent in lyophilized products and infant formula.

(i) **Magnesium stearate:** Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% to 5.0% w/w.

Pre Compression Evaluation Parameters

Bulk Density

Bulk density is a ratio of mass of powder to the bulk volume. Bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed powder was carefully poured in to graduate measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by the formula.^[16,17,18]

$$\text{Bulk density} = M/V_o$$

Where, M = mass of the powder

V_o = bulk volume of the powder

Tapped density

10gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by.^[16, 18-22]

$$\text{Tapped density} = M/V_t$$

M = mass of the powder

V_t = final tapping volume of the powder

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the powder and the horizontal plane. Fixed funnel method was used and then funnel was fixed with its tip at a given height 'h', above a flat horizontal surface to which a graph paper was placed. Powder

was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was calculated using following equation.^[16, 20-26]

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

Where, h = height of the pile

r = radius of the pile

Compressibility index (Carr's index)

Carr's index is used as an important parameter to determine the flow behavior of powder. It's indirectly related to a relative flow property rate, cohesiveness and particle size. It's simple, fast and well known method for predicting flow characteristics. Carr's index can be represented by equation.^[16,18, 24-30]

$$\text{Carr's Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is used to predict the flow ability of the powders. This method is similar to compressibility index. Hausner's ratio can be represented by equation.^[16,19,27,29]

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Post Compression Evaluation Parameters

Hardness

The tablet should be stable to the mechanical stress during handling and transportation. The hardness was tested using Monsanto hardness tester.^[20, 23-25]

Thickness and Diameter

Tablets of each batch were selected and measured for thickness and diameter using verniour caliper.^[20, 24-36]

Friability Test

The friability of tablets can be determined by using Roche Friabilator. It's expressed in percentage (%). Five tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions.^[20,21,32] The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

Weight Variation

Randomly selected twenty tablets were weighed individually and all together, the average weight and the percentage deviation were calculated. The % difference in the weight variation should be within the permissible limits ($\pm 7.5\%$). The % deviation is then calculated using the following formula,

$$\text{Percentage Deviation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Individual Weight}}$$

As per Indian Pharmacopoeia (IP), permissible limit of weight variation is 7.5% for tablet weight of 200 mg.^[21,22,29-38]

Drug Content

The drug content can be carried out by weighing ten tablets from each batch and average weight is calculated. Then the tablets triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to specified weight of drug and dissolved in 100 ml volumetric flask containing 100 ml of respective buffer and volume was made to 100 ml with respective buffer. The volumetric flask was shaken using sonicator and after suitable dilution with respective buffer, the drug content was determined using UV-Visible Spectrophotometer at respective wavelength.^[22,23, 36-45]

Disintegration Time

Place one tablet in each of the six tubes of the basket, insert disc and operate the apparatus for the specified time, using distilled water and maintain it at $37 \pm 2^\circ\text{C}$ as the immersion fluid. Note down the time in sec when tablets disintegrate completely. The tablet fulfills the test if all six get disintegrated. If one or two tablet fails to disintegrate completely then repeat the test on another twelve tablets. From the total of eighteen tested tablets, sixteen tablets should comply the test i.e. should disintegrate completely.^[21,27,32, 42-49]

Wetting Time

The wetting time of the tablets can be measured by using a simple procedure i.e five circular tissue papers of 10 cm diameter are then placed in a Petri dish with a 10 cm diameter. 10 ml of respective buffer was poured into the tissue paper placed in the Petri dish. A tablet is then

carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.^[21, 25, 27, 43]

***In vitro* Dissolution Study**

The developed formulations subjected to release studies using dissolution apparatus at 50 RPM. Dissolution medium to be used should be maintained at $37 \pm 0.5^\circ\text{C}$, which is found to provide sink conditions. The samples are withdrawn at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-mm nylon membrane filters, were analyzed using a validated UV spectroscopic method at respective wavelength.^[49,52]

Comparison of Dissolution Profiles by Similarity and Dissimilarity Study^[50,51,52]

Comparison between innovators product and test batches was done using two statistical factors called difference factor (f_1) & similarity factor (f_2).

The similarity factor (f_2) is defined by CDER, FDA and EMEA as the “logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products”. Moore and Flanner give the model independent mathematical approach for calculating a similarity factor f_2 for comparison between dissolution profiles of different samples. The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form is used as a basis for the comparison of dissolution profile. The dissolution profiles of products can be compared using f_2 . The similarity factor is calculated by following formula.

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n = No. of time points

R_t = Reference profile at the time point t

T_t = Test profile at the same point

The difference factor (f_1) calculate the percentage difference between two profiles i.e. innovator dissolution profile & test sample dissolution profile at each sampling points and corresponds to a relative error measure between the two profiles.

$$f1 = (\sum |R-T| / \sum R) * 100$$

Where,

|R-T|- Defined as absolute difference of % drug released at each time points between innovator or reference product & test product

R- Defined as % drug released of reference product at each time points

f1 value should be less than 15 ideally it should be as close as possible to 0.

Accelerated Stability Studies

Stability of medicinal products is defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specifications, i.e. the stability of drug is its ability to resist the deterioration. Ninety percent of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of drug may infuse several forms arising from changes in physical, chemical and microbiological properties. The changes can affect the therapeutic value of preparation or increase its toxicity. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$ for time period of 1 Months. Tablets were evaluated for general appearance, wetting time, disintegration time, drug content and for *in-vitro* dissolution study and were compared with initial tablets results.^[53]

CONCLUSION

In recent scenario these tablets are gaining more importance in industry targeting pediatrics, geriatrics and all age groups. The orally disintegrating tablets have the 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. Though considerable research has been done in the formulation development and technologies for fast dissolving tablets, more intensive investigations are to be carried out in this promising area to result for new cost effective technologies and better products. The basic approach followed by all the available orally disintegrating tablet technologies is to maximize the porous structure of tablet matrix so that rapid tablet disintegration can be achieved in the oral cavity along with excellent mechanical strength and good taste-masking properties

REFERENCES

1. Shukla D, Chakraborty S, Singh S, Mishra B., "Mouth Dissolving Tablets: An Overview of Formulation Technology", *Sci Pharm*, 2009; 77: 309–326.
2. Prajapati BG and Ratnakar N. "A Review on Recent patents on Fast Dissolving Drug Delivery Systems", *Inter. J. Pharm. Tech. Res.*, 2009; 1(3): 790-798.
3. Bharadwaj S, Jain V, Sharma S, Jat RC, and Jain S., "Orally Disintegrating Tablets: A Review." *Drug Invention Today*, 2012; 2(1): 81-88.
4. Gavaskar B, Kumar SV, Sharan G, Nagaraju M and Rao YM. "Present investigation and future prospect of oral disintegrating tablets: a review." *Int. J. Pharm. Sci. & Research*, 2010; 1(8): 87-96.
5. Mehta K, Garala K, Basu, Bhalodia R, Joshi B, Charyulu RN. "An emerging trends in oral drug delivery technology: Rapid disintegrating tablet". *J. Pharm. Sci. & Tech.*, 2010; 2(10): 318-329.
6. Gill B, Kumar S, Kaur T, "Mouth dissolving tablet: a novel approach to the drug delivery system", *Int. J. Curr. Pharm Res.*, 2011; 3(1): 1-7.
7. Harsoliya MS, "A review formulation of mouth dissolving tablet", *Int. J. Pharma Clinical Sci*, 2011; 1(1): 1-8.
8. Patel VN, Gupta MM, "Emerging trends in oral dispersible tablet", *J. drug del. & therap.*, 2013; 3(2): 199-206.
9. Biradar S, Bhagavati S, "fast dissolving drug delivery system a brief overview" *Int. J. Pharmacol*, 2005; (4): 1-3.
10. Shrivastava S, Bala R, Joshi B, "Mouth Dissolving Tablets: A Future Compaction", *Int. Res. J. Pharm*, 2012; 3(8): 98-109.
11. Dali S, Chakra S, "Mouth Dissolution Tablets an Overview of Formulation Technology", *Sci. Pharm.*, 2009; 309-326.
12. Shaikh J, .Khirsagar RV, "fast disintegrating tablets: an overview of formulation and technology", *Int. J. Pharma. Pharm Sci*, 2010; 2(3): 9-15.
13. Reddy B, Sai Ram S, "Rapimelts A Review", *J. Pharma Biomed. Sci*, 2011; 6(10): 1-8.
14. Piplani M, Pahwa R, "Orally disintegrating tablet: friendly to pediatrics and geriatrics". *Arch. Appl. Sci. Res.*, 2010; 2(2): 35-48.
15. Debjit CB, "Emerging trends of disintegrants used in formulation of solid dosage form", *Der pharmacialettere*, 2010; 2(1): 495-504.
16. Kuchekar BS, Badhan AC, Mahajan HS. "Formulation development of oral dispersible tablets of cinnarizine". *Pharma Times*, 2003; 35: 7-9.

17. Swamy NGN, Kumar S.S, "Formulation and Evaluation of Fast Dissolving Oral Films of Palonosetron Hydrochloride Using HPMC-E5", *Int. J. Pharm. Chem. Sci*, 2014; 3(1): 145-150.
18. Yang X, Jun L, "Phase II Study on EANI Combined with Hydrochloride Palonosetron for Prevention of Chemotherapy-induced Nausea and Vomiting Following Highly Emetogenic Chemotherapy", *Asian Pacific J. Cancer Prev.*, 2014; 15: 3952-3954.
19. Pathi PJ, N. Appala R, "The Estimation of Palonosetron Hydrochloride in Parenterals by RPHPLC", *Asian J. Pharm. Tech*, 2012; 2(2): 77-79.
20. Dangi AA, Zalodiya PB, "Formulation and Evaluation of carvedilol Melt in mouth tablet using mucoadhesive polymer and PEG-6-stearate as hydrophilic waxy binder", *Int. J. Pharma investigation*, 2012; 2(4): 183-188.
21. Mishra SK, Varma R, "Formulation and Evaluation of Mouth Dissolving Tablets of Carvedilol", *Int. J. Pharma Bio Sci*, 2011; 2(1): 232-239.
22. Lakshmi CSR, Akul SP, "Development and Characterization of Melt-in-mouth Tablets of Atenolol by sublimation technique", *Int. J. Pharma. Res. Dev.*, 2011; 3(3): 27 - 36.
23. Kakade SM, Mannur VS, "Formulation and Evaluation of mouth dissolving tablets of losartan potassium by direct compression techniques", *Int. J. Res. Pharm. Sci*, 2010; 1(3): 290-295.
24. Jain SP, Mehta DC, "Melt-in-Mouth Pellets of Fexofenadine Hydrochloride Using Crospovidone as an Extrusion-Spheronisation Aid", *AAPS Pharm Sci Tech*, 2010; 11(2): 918-923.
25. Kumar R, Patil MB, "Development and characterization of melt-in-mouth tablets of haloperidol by sublimation technique", *Int. J. Pharma Pharm Sci*, 2009; 1(1): 65-73.
26. Dhiman S, Verma S, "Optimization Of Melt-In-Mouth Tablets Of Levocetirizine Dihydrochloride Using Response Surface Methodology", *Int. J. Pharma Pharm Sci*, 2012; 4(1): 176-184.
27. Bhanja S, Hardel D, "Mouth Dissolving Tablets of Losartan potassium: formulation and evaluation", *Int. J. Pharma Sci Res*, 2012; 3(9): 3444-3453.
28. Gaur K, Tyagi LK, "Formulation and Characterization of Fast Disintegrating Tablet of Aceclofenac by using Sublimation Method", *Int. J. Pharma Sci Drug Res*, 2011; 3(1): 19-22.
29. Bhardwaj S, Jain V, "Formulation and evaluation of fast dissolving tablet of aceclofenac", *Int. J. Drug Del*, 2010; 93-97.

30. Mohire NC, Yadav AV, "Novel Approaches in Development of Metronidazole Orodispersible Tablets", *Research J. Pharm. and Tech*, 2009; 2(2): 283-286.
31. Sekar S, Malarvizhi V, "formulation and optimization of fast dissolving tablets of olanzapine using vacuum drying technique by 22 factorial design", *Int. J. Pharma Sci Res*, 2011; 2(6): 1594-1599.
32. Patel B, Patel D, "Development and in vitro evaluation of fast dissolving tablets of glipizide", *Int. J. Pharm Pharma Sci*, 2009; 1(1): 145-150.
33. Kolhe SR, Chaudhari PD, "Development and Evaluation of melt-in-mouth tablets by sublimation technique", *Int. J. Pharma Stud Res*, 2011; 2(1): 65-76.
34. Kulkarni U, "Formulation and Development of lornoxicam fast dissolving tablets: influence of different excipients on property and performance of patient friendly dosage form", *Int. J. Pharma Chem. Sci*, 2012; 1(1): 67-74.
35. Nagar M, Nagar M, "Formulation and Evaluation of mouth dissolving film of antipsychotic drug aripiprazole", *Der Pharmacia Lettre*, 2012; 4(4): 1221-1227.
36. Ram DK, Patel VN, "A review article on mouth dissolving tablet techniques", *Int. J. Res Ayurveda Pharm*, 2011; 2(1): 66-74.
37. Bodar J, Yadav YC, "Development of the Chromatographic Method for The Estimation Of Palonosetron In Palonosetron Hydrochloride Injection", *Int J. Pharma Sci*, 2011; 2(3): 24-31.
38. Ellsworth, Allan J. Mosby's Medical Drug Reference, St. Louis: Mosby, 1999.
39. Martindale. The complete drug reference; 35th Edn; Pharmaceutical Press, London, 2007.
40. Parambi DGT, Mathewand SM, Ganesan V., "Estimation of Palonosetron Hydrochloride in Pharmaceutical Dosage form by U.V. Spectrophotometric method" *Int. J. Chem. Sci.*, 2011; 9(4): 1619-1624.
41. Singhvi G and Singh M, "Review: *In vitro* drug release characterization model" *Int. J. of Pharm. Studies and Res.*, 2011; 2(1): 77-84.
42. Rao NG, Reddy MS, "Development and Evaluation of Fast Dissolving Tablets of Fosinopril by Sublimation Method." *Int. J. Pharma. Sci. and Drug Res.*, 2012; 4(4): 230-235.
43. Lyer SR, Siva R, "Formulation and Evaluation of Fast Dissolving Tablets of Risperidone Solid Dispersion." *Int. J. Pharma. Chem. and Bio. Sci.*, 2013; 3(2): 388-397.
44. Patil SM, Ghatge GA, "Review on Taste Abatement Techniques" *Int. J. of Institutional Pharm Life Sci.*, 2013; 3(5): 43-67.

45. Thoke S, Gayke A, "Review On: Taste masking approaches and Evaluation of Taste Masking" *Int. J. Ph. Sci.*, 2012; 2(4): 1895-1907.
46. Sharma S, Gupta GD, "Formulation Design and Optimization of Mouth Dissolving Tablets of Domperidone Using Sublimation Technique." *Int. J. of Pharm. Sci.*, 2010; 1(1): 128-136.
47. Shaji J, Shinde A, "Formulation and Optimization of Pulsatile Aceclofenac Microspheres Using Response Surface Methodology." *Int. Res. J. of Phama*, 2012; 3(1): 166-169.
48. Shah TJ, Amin AF, "Process Optimization and Characterization of Poloxamer Solid Dispersions of a Poorly Water-soluble Drug" *AAPS Pharma. Sci. Tech.*, 2007; 8(2): E1-7.
49. Kattamuri SB, Mogili R, "Formulation and Evaluation of Zafirlukast Oral Disintegrating Tablets" *Int. J. of Uni. Pharm. and Bio Sci.*, 2013; 2(5): 87-101.
50. Solanki, Parikh JR. "Formulation and Optimization of Piroxicam Proniosome by 3-Factor, 3-level Box-Behnken Design." *AAPS Pharma. Sci. Tech.*, 2007; 8(4): 43-49.
51. Sumudeepthi B, Rao MP, "In Vitro Evaluation of Newly Formulated Metaxolone Tablets for immediate release by Wet Granulation Technique." *Int. J. Innovative Pharma. Sci. and Res.*, 2014; 2(10): 2425-2437.
52. Soni T, Nagda C, "Development of Discriminating Method for Dissolution of Aceclofenac Marketed Formulations." *Dissolution Tech.*, 2008: 31-35.
53. LadakeSH, Bhalekar MR., "Formulation and Evaluation of Sustained Release Matrix Tablet of Anti-Anginal Drug: Influence of Combination of Hydrophobic and Hydrophilic Matrix Former." *Pharma. and Tech*, 2008; 1(4): 410-413.