*Available online at* www.scholarsresearchlibrary.com

Scholars Research Library

**Der Pharmacia Lettre, 2010, 2(2): 350-361**
*(http://scholarsresearchlibrary.com/archive.html)*

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

# Fast Drug Delivery Systems: A Review

**Arya Arun* and Chandra Amrish**

*Department of Pharmacy, Institute of Biomedical Education and Research, Mangalayatan University, Beswan- Aligarh, U.P., India*

---

## Abstract

*Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Fast-dissolving drug-delivery systems (FDDS) were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid dosage forms. Over the past three decades, fast disintegrating tablets (FDTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. FDTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Products of FDTs technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding. New FDDS technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. Mouth dissolving films (MDFs) are another FDDS evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to MDFs formats. Today, FDDS are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications.*

**Key Words:** Fast disintegrating tablets, Fast-dissolving drug-delivery systems, API, FDDS.

---

## INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes [1]**.**

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected [2-4].

The concept of (fast drug delivery system) FDDDS emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients [5].

***Criteria for Fast dissolving Drug Delivery System*** **[**6]**:**

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

***Salient Feature of Fast Dissolving Drug Delivery System*:**

- 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.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

***Selection of drugs*:**
The ideal characteristics of a drug to be selected [7]

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

***Excipients***
***Super disintegrants*:** Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

***Flavours*:** Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets include, vanilla, citus oils, fruit essences

***Sweetners*:** Aspartame, Sugars derivatives

***Fillers*:** Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

***Surface active agents*:** sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.

***Lubircants*:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

**Various Approaches for Fast Dissolving Tablets**

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation [8-10].

Various methods used in the manufacture of Fast dissolving tablets include:

- Freeze –drying or lyophilization
- Tablet Molding
- Direct compression technologies
- Spray drying
- Sublimation
- Taste masking
- Mass extrusion

Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies regarding the following [11]:

- Mechanical strength of final product.
- Drug and dosage form stability.
- Mouth feel.
- Taste.
- Rate of dissolution of drug formulation in saliva.
- Swallowability.
- Rate of absorption from the saliva solution.
- Overall bioavailability.

***1) Sublimation***

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose [12]. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Makino et al., [13] reported a method using water as a pore-forming material.

***2) Mass-Extrusion***

This technology involves softening of the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste [14].

***3) Nanonization***

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique [15]. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

***4) Direct Compression (DC)***

DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tabletting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugarbased excipients.

***Disintegrants***

In many MDT products based on DC process, the disintegrants mainly affect the rate of disintegration and hence dissolution which is further enhanced in the presence of water soluble excipients and effervescent agents.

The introduction of superdisintegrants has increased the popularity of this technology [16]. Tablet disintegration time can be optimized by focusing on the disintegrants concentration. Below a critical disintegrant concentration, tablet disintegration time becomes inversely proportional to disintegrant concentration. However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant [17].

***5)Freeze drying or Lyophilization***

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation [18]. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolve rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin[19]

***Evaluation of Mouth Dissolving Tablets***

***1) Measurement of Tablet Tensile Strength***

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation[20]:

$$T = 2F / \pi dt$$

*Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.*

***2) Friability***

Tablet friability [21] was measured using a ROCHE friabilator (USP) at 25 rpm for 4 min. The weight of twenty tablets before and after completion of the test was recorded and friability was calculated by the following formula:

$$\text{Percentage friability} = (\text{initial weight-final weight/initial weight}) \times 100$$

***3) Wetting time and water absorption ratio***

The wetting time of the tablet was measured by placing five circular tissue papers (10 cm in diameter) in a Petri dish of 10 cm diameter. Water (10 ml) containing methylene blue (0.1% w/v) was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper and the time required for the dye to reach the upper surface of the tablet was recorded as wetting time. The measurements were carried out in triplicate. Water absorption ratio can be calculated using [22]:

$$\text{Water absorption ratio} = (Wa - Wb) / Wb$$

*Where Wb = weight of tablet before absorption of water and Wa = weight of tablet after absorption of water.*

***4) In Vitro Dispersion Test*** **[**23]

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a fast dissolving tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8.

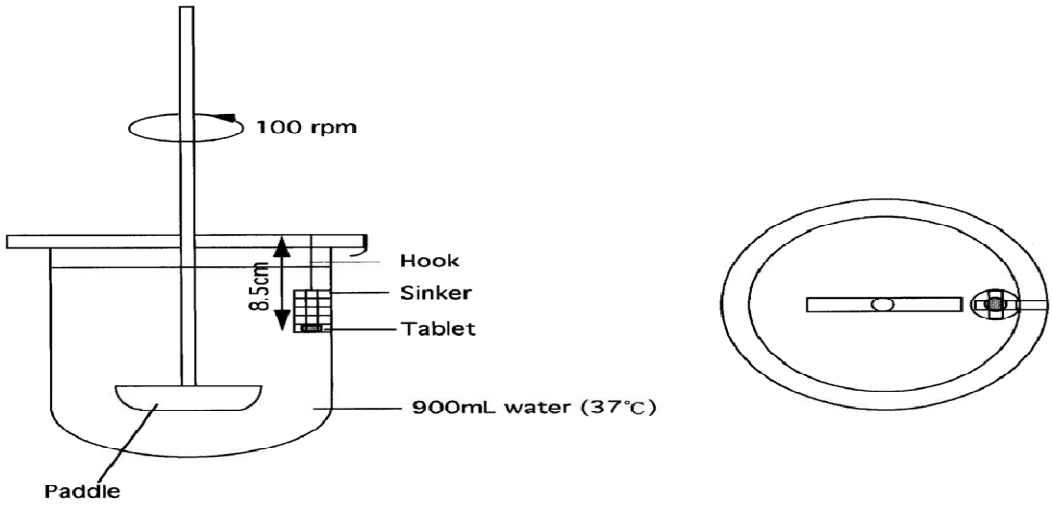

**Fig.1. Schematic view of modified dissolution apparatus for disintegration test**

***5) In vitro disintegration test* (*Modified Dissolution Apparatus*)**

Bi et al., [24] suggested the use of a modified dissolution apparatus, instead of the disintegration apparatus as shown in Fig.1. In this experiment, 900 ml of water maintained at 37 °C as the disintegration fluid and a paddle at 100 rpm as stirring element were used. Disintegration time was noted when the tablet disintegrated and passed completely through the screen of the sinker (3–3.5 mm in height and 3.5–4 mm in width, immersed at a depth of 8.5 cm from the top with the help of a hook). This method was useful in providing discrimination among batches which was not possible with the conventional disintegration apparatus.

***6) In vitro dissolution test***

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used [25].

***7) Stability Studies* [**26- 27]

The tablets were studied for stability at 40$^{o}$C and 75% RH condition for period of three months. Each tablet was individually weighed and wrapped in aluminum foil and packed in black PVC bottle and put at above specified condition in a heating humidity chamber for 3 months. After each month tablet samples was analyzed for the hardness, disintegration time and in vitro drug release study.

**Mouth dissolving films**

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets [28].

The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption, or, with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed [29].

***Special features of mouth dissolving films***

- Thin elegant film and available in various size and shapes

- Unobstructive, excellent mucoadhesion
- Fast disintegration and rapid release
- Convenient dosing no risk of chocking
- Enhanced stability
- Improved patient compliance

The mouth dissolving films has also a clear advantage over the Oral dissolving tablets (ODTs):

- ODTs are sometimes difficult to carry, store and handle (fragility and friability).
- Many ODTs are prepared by using the expensive lyophilization process [27].

***Manufacturing Methods***

One or combination of the following process can be used to manufacture the mouth dissolving films [29].

***1) Solvent casting method***

In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the petri plate dried and cut in to uniform dimensions [28].

***2) Semisolid casting***

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

***3) Hot melt extrusion***

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion [30].

-Fewer operation units
-Better content uniformity
-An anhydrous process

***4) Solid dispersion extrusion***

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

***5) Rolling Method***

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes [27].

**Evaluating parameters**

***1) Mechanical properties***

Mechanical properties of films are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Films are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks.

Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated [31].

***a) Tensile strength***

Tensile strength is calculated by formula:

force at break/ initial cross sectional area of film in $mm^2$

***b) Elastic modulus***

Elastic modulus is calculated by formula:

$$\text{Elastic modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area } (mm^2)} \times \frac{1}{\text{Corresponding strain}}$$

***c) % Elongation***

It is calculated as:

$$\frac{\text{Increase in length}}{\text{Original length}} * 100$$

***d) Folding endurance***

Folding endurance is determined by folding the films of uniform cross sectional area and thickness until it breaks [32].

***2) Morphology study***

The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magnification[33].

***3) Swelling property***

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed [31].

The degree of swelling was calculated using parameters $w_t$-$w_0/w_o$, $w_t$ is weight of film at time t, and $w_o$ is weight of film at time zero.

***4) Contact angle***

Contact angle measurements is performed at room temperature with a goniometer (AB Lorentzen and Wettre, Germany). A drop of double distilled water was placed on the surface of the dry film. Images of the water droplet were recorded within 10 seconds of deposition by means of digital camera. Digital pictures were analyzed by imageJ 1.28v software (NIH, USA) for angle determination. A minimum of five measurements, taken at different positions of the film, was carried out. The contact angle was measured on both sides of the drop and averaged [34].

***5) In vitro disintegration time***

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates [35].

***6) In vitro dissolution studies***

The *in vitro* dissolution study is carried out in simulated saliva solution pH 6.4 phosphate buffer using USP paddle apparatus at 37±0.5°C. samples are withdrawn at regular time interval and analyzed by UV-Visible spectrophotometer [33].

**7*) Surface pH of film***

Surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the colour of pH paper was observed and reported [36].

**Table 1: List of commercially Available Fast dissolving tablets**

| **Trade Name Active Drug Manufacturer** | **Trade Name Active Drug Manufacturer** | **Trade Name Active Drug Manufacturer** |
|---|---|---|
| Felden fast melt | Piroxicam | Pfizer Inc., NY, USA |
| Claritin redi Tab | Loratidine | Schering plough Corp., USA |
| Maxalt MLT | Rizatriptan | Merck and Co., NJ, USA |
| Zyprexia | Olanzapine | Eli lilly, Indianapolis, USA |
| Pepcid RPD | Famotidine | Merck and Co., NJ, USA |
| Zofran ODT | Ondansetron | Glaxo Wellcome, Middlesex, UK |
| Zoming-ZMT | Zolmitriptan | AstraZeneca, Wilmington, USA |
| Zeplar TM | Selegilline | Amarin Corp., London, UK |
| Tempra Quiclets | Acetaminophen | Bristol myers Squibb, NY, USA |
| Febrectol | Paracetamol | Prographarm, Chateauneuf, France |
| Nimulid MDT | Nimesulide | Panacea Biotech, New delhi , India |
| Torrox MT | Rofecoxib | Torrent pharmaceuticals , India |
| Olanex instab | Olanzapine | Ranbaxy lab. Ltd. New-delhi, India |
| Romilast | Montelukast | Ranbaxy lab. Ltd. New-delhi, India |
| Benadryl Fastmelt | Diphenhydramine and pseudoephedrine | Warner Lambert, NY, USA |

**Table 2. List of marketed fast dissolving films**

| S. No. | Product | Mfg. By |
|---|---|---|
| 1. | Dextromethorphan HBr (cough suppressant), Diphenhydramine Citrate (cough and cold), Breath Strips | MonoSolRx |
| 2. | Doneprezil rapid dissolving films, Ondansatron rapid dissolving films | Labtec Pharma |
| 3. | Life-saving rotavirus vaccine to infants | Johns Hopkins |
| 4. | Methylcobalamin fast dissolving films, Diphemhydramine HCl fast dissolving films, Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films | Hughes medical corporation |

## CONCLUSION

The popularity of FDDS has increased tremendously over the last decade. There are many drugs that have been formulated into marketed FDDs using various technologies. The key to FDT formulations is fast disintegration, dissolution,or melting in the mouth. FDDS have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Today, FDDS are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms.
The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand.

## REFERENCES

[1] M. Valleri, P. Mura, F. Maestrelli, M. Cirri, R.D. Ballerini, *Drug Dev. Ind. Pharm.*, **2004**, 525-34.
[2] T. Hanawa, A. Watanabe, T. Tsuchiya, R. Ikoma., M. Hidaka, M. Sugihara, *Chem. Pharm. Bull*., **1995**, 43(2), 284-288.
[3] L. Mallet, *J. Am. Pharm. Assoc*., **1996**, 36(11), 628-635.
[4] S.C. Porter, *Am.Pharm. Rev*., **2001**, 85, 28-35.
[5] S. Lindgren, L. Janzon, *Dysphagia*., **1991**, 6, 187–192.
[6] D. Bhowmik, B. Chiranjib, R.J. Margret Chandira, *Chem. Pharm. Res*., **2009**, 1(1), 163-177.
[7] R.P.William, T.K. Ghosh, *Pharmaceutical Technology*, Oct, **2005.**
[8] L.H. Reddy, B. Ghose, Rajneesh, *Ind. J. Pharm. Sci*., **2002**, 64(4), 331- 336.
[9] S.R. Parakh, A.V. Gothoskar, *Pharma. Tech*., November **2003**, 92- 100.
[10] B.S. Kuchekar, A.C. Badhan, H.S. Mahajan, *Pharma Times*, June **2003**, 35, 7-9.
[11] M. Slowson, S. Slowson, *Pharm. Times*, **1985**, 51, 90-96
[12] K.I. Koizumi, Y. Watanabe, K. Morita, N. Utoguchi, M. Matsumoto, *Int J Pharm*. **1997**, 152, 127–131.
[13] T. Makino, M. Yamada, J.I. Kikuta, "Fast-dissolving tablet and its production", US Patent 5,720, 974. **1998** Feb 24.
[14] S. Bhaskaran, G.V. Narmada, *Indian Pharmacist* **2002**, 1, 9–12.
[15] http://www.elan.com
[16] R. Shangraw, A. Mitrevej, M. Shah, *Pharm Technol*. **1980**, 4, 49–57.
[17] J. Ringard, A.M. Guyot-Hermann, *Drug. Dev. Ind. Pharm*. **1988**, 14, 2321-2339.

[18] S.L.Nail, L.A. Gatlin, Freeze drying: Principles and Practice, in Pharmaceutical Dosage Forms-Parenteral Medications, Marcel Dekker Inc., New York, **1993**,2nd Edn., Vol. 2,163.
[19] T.T. Jaccard, J.L. Leyder, *Ann. Pharm. Fr.*, **1985**, 43 (2), 123-131.
[20] Y.X. Bi, H. Sunada, Y. Yonezawa, K. Danjo, *Drug. Dev. Ind. Pharm*. **1999**; 25: 571-581.
[21] "Indian Pharmacopoeia", Controller of Publications, New Delhi, 4th edition, vol II, **1996**, 234-236.
[22] M.C. Gohel, N. Bhatt, *Pharm. Bio. World*. **2005**; 75-79.
[23] D.P. Venkatesh, C.G.G. Rao, *Asian. J. Pharm*., **2008**, 261-264.
[24] Y. Bi, H. Sunada, Y. Yonezawa, K. Danjo, A. Otsuka, K. Iida, *Chem. Pharm. Bull*., **1996**, 44, 2121–2127.
[25] J. Klancke, *Dissolution Technol*., **2003**, 10(2), 6-8.
[26] A.J. Seitz, P.S. Metha, L.J. Yeager, L. Lachman, H.A. Liberman, J.C. Kanig, The Theory and Practice of Industrial Pharmacy, Marcel Dekker, Bombay, **1996**, 3rd Edn., 364.
[27] R.W.Mendes, O.A. Aloysius, J.B. Daruwala, Chewable tablets, In, Pharmaceutical Dosage Forms: Tablets, Liberman, A.H., Lachman, L. and Schwartz, J.B. (Edis.), Vol. 1, Marcel Dekker,**1989**, 2nd Edn. 368-389.
[28] U. Vollmer, P. Galfetti, *Drug. Dev. Report*., **2006**, 64-67
[29] R. Mishra, A. Amin, *Pharm. Tech.* **2009**, 1-5.
[30] K. A. Coppens, M.J. Hall, S.A. Mitchell, M.D. Read, *Pharmaceutical Technology*, September **2005**,1-6.
[31] K.K Peh, C.F. Wong, *J. Pharm. Pharm. Sci.***1999**, 2,53-61.
[32] S.K. Mishra, N.M. Joseph. S. Palani, N. Garud, R. Irchhaiya, P. Bhardwaj, *The Indian Pharmacist*, **2007**, VI (66), 95-98.
[33] R.C. Mashru, B.C. Sutariya, PP. Parikh, *Drug. Dev. Ind. Pharm*. **2005**, 31, 25-34.
[34] R. Bettini, A. Antonello, M. Mariana, F. Borghetti, *Eu J Pharm and Biopharm*., **2008**, 68, 74-81.
[35] M. J. Chien, G. Tirol, C. Chien, R. Schmitt, Poster presented at the **2006** Annual Meeting and Exposition of the American Association of Pharmaceutical Scientist Oct. 29–Nov.2 AAPS. 2006, 1-5.
[36] M. Semaltym, A. Semalty, G. Kumar, *Indian. J. Pharm. Sci*. **2008**, 70(1), 43-48.