

## FORMULATION AND EVALUATION OF ORODISPERSIBLE FILM OF SILDENAFILCITRATE

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## ABSTRACT

Objective: Fast dissolving drug delivery systems (FDDDSs) have acquired an important position in the market by overcoming previously encountered administration problems. FDDDSs have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva. Therefore, these dosage forms have lured the market for a certain section of the patient population which include dysphagic, geriatric and patients [1].

In the present study was carried out to formulate and evaluate fast dissolving films of Sildenafil Citrate (SC) for an oral administration. The blank films were prepared from various grades and concentrations of Hydroxypropyl methyl cellulose polymer namely (HPMC K100, HPMC E4K and HPMC 100).

Methods: solvent casting method. Glycerin and propylene glycol were used as plasticizers. The blank films were evaluated in respect to their *in-vivo* & *In-vitro* disintegration and tensile strength. The blank film of optimum polymer and plasticizer had been chosen and then loaded with sildenafil citrate and the prepared sildenafil citrate oral films were studied the effect of incorporation of tween 80 (polysorbate 80) and of superdisintegrant polypl as done XL10 at (0, 2 and 5% w/w) of total dry weight in respect to their *in vitro* drug release by using USP dissolution apparatus. The time required for 80% of the drug to be released ( $T_{80\%}$ ) and percent drug dissolved in 2 minutes ( $D_{2 \text{ min}} (\%)$ ) were used for the comparison of the dissolution results.

Results: Disintegration time of 30 seconds. The result of  $D_{2 \text{ min}} (\%)$  and ( $T_{80\%}$ ) for LF4 was 75.56 % and 2.78 min. respectively.

Conclusion: LF4 is promising formulation suitable for the immediate release of Sildenafil citrate

**Keywords:** Orodispersible Film, Sildenafil Citrate, Fast Dissolving Films

## INTRODUCTION

Recent developments in the technology of pharmaceutical dosage forms have presented viable dosage alternatives from oral route for pediatric, geriatric, bedridden, nauseous or noncompliant patients [2].

A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists [3].

Fast dissolving dosage forms are useful in patients [4,5,6] such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy [7] with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style [8]. In disease conditions such as motion sickness, sudden episodes of attacks of coughing and repeated emesis and swallowing [9], conventional tablets become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva.

Thereafter, the drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form [10, 11].

Hence, orally disintegrating systems may be anticipated to result in achievement of the required peak plasma concentration rapidly for drugs stable in the gastric pH.

Oral films as dosage form are getting more attention for the delivery of active pharmaceutical ingredients (API). It offers distinct advantages like an easy application, no degradation of API by gastrointestinal fluids, bypassing the first-hepatic metabolism and

potentially improved bioavailability ensuring rapid invasion and fast onset. Many advantages of this route have been recently recognized

and various products are under development. There is no single definition of oral films so for practical purpose it is defined as "A thin flexible, non-friable polymeric film having dispersed active pharmaceutical ingredient which is intended to be placed on the tongue for rapid disintegration and dissolution in the saliva prior to swallowing for delivery into GIT [12].

Sildenafil Citrate (SC) is a selective inhibitor of phosphodiesterase type 5 enzyme (PDE5) extensively used for the treatment of erectile dysfunction (ED).

The main objectives of the present study were to prepare and evaluate the mouth melting thin film of SC and to study the various formulation variables that affect the drug release.

## MATERIALS AND METHODS

## Materials

Sildenafil Citrate (SC) was obtained as a gift sample from Assist. prof. Dr. Yehia I K, Hydroxypropyl methyl cellulose (HPMC K100, HPMC E4K and HPMC 100 LVEP) were purchased from CDH Ltd, New Delhi, India. Polyplasdone XL 10 purchased from Shanghai lite chemical technology co., China. Polysorbate 80 (tween 80) from Riedel-De-Haen, Germany. All chemicals used were of analytical grade and were used without further purification. Deionized distilled water was used throughout the study.

## Method

## Screening of the components for formulation of blank fast dissolving films

Fast dissolving films were prepared by solvent casting method [13] in which aqueous solution I was prepared by dissolving (in 20 mL hot water 80°C with stirring) polymer and plasticizer, then remaining ingredients tween 80, sodium saccharine and citric acid were added in the proportions as given in (Table 1) to produce a

clear viscous solution and kept for 1 h to remove all the air bubbles[14].

The solutions were cast on to 9.9 cm diameter petri dish and were dried in the oven at 45°C for 24 h. The films was carefully removed

from the petri dish and checked for any imperfection and cut according to size required for testing (square film 3 cm length, 2.5 cm width). The samples were stored in a glass container maintained at temperature 30 °C and relative humidity 60% ± 5% until further analysis.

#### Preparation of the Sildenafil citrate containing fast dissolving films

The prepared sildenafil citrate oral films were fabricated as per the method described for the fabrication of blank fast dissolving films. Briefly, SC and tween 80, citric acid were dispersed in specific proportion, in distilled water, and form an aqueous solution II. The aqueous solutions I and II were mixed and stirred for 1 h. and the

rest of the procedure was same as that for the fabrication of blank fast dissolving films[15], as shown in Table 2.

The optimum blank fast dissolving film had been selected in respect to an *In-vivo* and *In-vitro* disintegration time and mechanical properties.

Hydroxypropyl methyl cellulose (HPMC) is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely *HPMC K100M*, *HPMC E4M* and *HPMC K100 LVEP* were studied to select a primary film former[16, 17].

For the fabrication of films, glycerin and propylene glycol were investigated to choose the best plasticizer at three different concentrations and tween 80 used as surfactant and Sodium saccharin was used as a sweetener. The prepared films were evaluated for surface perfection, smoothness, ease of separation from petri dish without cracking (peel-ability) and also were evaluated for imperfections and cuts and surface roughness.

Table 1: Composition of the blank fast dissolving films\*

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
HPMC K100M	57.1	60	62.25	-	-	-	-	-	-	-	-	-	-	-
HPMC E4M	-	-	-	57.14	60	62.25	-	-	-	-	-	-	-	-
HPMC K100LVEP	-	-	-	-	-	-	57.14	60	62.25	57.14	57.14	57.14	57.14	57.14
Glycine	21.4	20	18.22	21.42	20	18.22	21.42	20	18.22	14.28	28.93	-	-	-
Propylene Glycol	-	-	-	-	-	-	-	-	-	-	-	14.28	21.42	28.93
Tween 80	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.07	7.14	6.6	6.07
Citric acid	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.07	7.14	6.6	6.07
Na. Saccharine	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.6	6.07	7.14	6.07	7.14	6.6	6.07

\*Quantities are expressed in terms of % w/w

Table 2: Composition of drug loaded films

	LF1	LF2	LF3	LF4
Sildenafil Citrate	25	25	25	25
HPMC K100LVEP	45	45	43	40
Glycine	15	15	15	15
PolyplasdoneXL 10	-	-	2	5
Tween 80	-	5	5	5
Citric acid	7.5	5	5	5
Sod. Saccharine	7.5	5	5	5
Total weight ( mg )	100	100	100	100

#### Evaluation of Oral Films

##### Thickness Measurements

Determination of thickness and area weight are routine tests[18], all the batches were evaluated for thickness at five different locations (center and four corners) by using calibrated digital vernier calipers micrometer (Shanghai, China). Five samples from all the batches was withdrawn and evaluated for thickness[19]. Samples with air bubbles, nicks, or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Data are represented as a mean ± SD of three replicate determinations.

##### Surface pH Study

The surface pH of oral strip was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose.

Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and average values were reported[20].

##### Measurement of mechanical properties

Mechanical properties of film were evaluated using Z wick Testing Instrument (Model D-89079 Ulm, Germany) equipment with a 5-kilogram load cell. Film strips in dimensions of 4 cm x 2 cm and free from air bubbles or physical imperfections were held between two

clamps positioned at a distance of 2 cm during measurement. The strips were pulled by the top clamp at a rate of 10 cm/min. The force and elongation were measured when the film broke[21].

Results from film samples, which broke at and not between the clamps, were not included in calculations. Measurements were run in triplicate for each film.

Three mechanical properties, namely, tensile strength (*TS*), elastic modulus (*EM*), and percent elongation (*%E*) were computed for the evaluation of the film. It is suggested that a suitable film should have a relatively high *TS*, *E* and *Strain* but a low *EM*[22, 23]. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the following equation:

$$\text{Tensile strength (N/cm}^2\text{)} = \frac{\text{Force at break (N)}}{\text{Initial cross-sectional area of the sample (cm}^2\text{)}}$$

The percent elongation (*%E*) was calculated using the following equation:

$$\text{The percent elongation (\%E)} = \left[ \frac{L_s - L_0}{L_0} \right] * 100$$

Where *L0* is the original length and *Ls* is the length of the film after elongation.

The modulus of elasticity of films was calculated from the following equation:

$$F/A = EM \left[ \frac{L_s - L_0}{L_0} \right]$$

Where  $F$  = breaking load ( $N$ ),  $A$  = cross-sectional area of the sample, and Modulus of Elasticity ( $EM$ ) is the modulus of elasticity.

#### Uniformity of dosage units of the oral films

The content uniformity of prepared sildenafil citrate oral films were tested for SC using UV spectroscopy. The results were expressed as mean of three determinations. Sildenafil showed the absorption maxima at 291 nm in 0.1N HCl (pH 1.2) and the absorption was linear through 5µg/ml to 30µg/ml. This method was found to be accurate, precise and specific for sildenafil citrate.

#### In-vitro disintegration time

Different methods have been described in the literature, but a standard method does not exist. Previous disintegration and dissolution tests were performed with large amounts of media (Ali et al. 2002 [24], Desai and Kumar 2004[25]), which are physiologically not present in the oral cavity. Furthermore, a disintegration measurement setup for fast-dissolving oral dosage forms, in this case orodispersible tablets ODTs, has been described using a texture analyzer as well (Abdelbary et al. 2005) [26], Dor. and Fix 2000 [27]), but this setup cannot be transferred to oral wafers. In the present work consideration was given to developing a simple test with a few milliliters of medium. For the assessment of disintegration behavior, an independent method will be introduced in this study. For this method only a small amount of medium was needed, so natural conditions could be simulated in which 2 mL of distilled water was placed in a petri dish and one film as per the dimensions (2.5 x 3 cm<sup>2</sup>) was added on the surface of the water and the time measured until the oral film was dissolved completely [28, 29].

#### In-vitro dissolution study [30, 31]

The dissolution test was performed according to the USP type I paddle apparatus (Campbell Electronics, Mumbai). Test solution was 900 mL of 0.1 Hydrochloric acid (pH 1.2) at 37°C with rotation rate of 50 rpm. Weight used to settle the film sample [32]. Ten ml aliquots of samples were taken at time intervals from 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 30 min and 45 min and the same volume of fresh of 0.1 N HCl, at 37 ± 0.5°C was replenished. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved sildenafil citrate was determined using spectrophotometric technique at 291 nm. (PerkinElmer Lambda 25, USA). And then the % release of sildenafil citrate from film was measured, the results were expressed as mean of three determinations [33, 34].

## RESULT AND DISCUSSION

#### Thickness measurements

The strip thickness was measured by using vernier calipers. As all the formulations contained different amounts of polymer, hence the thickness was varied in the range of 0.068–0.19 mm. With increase in

HPMC concentration from 57.14 to 62.25 mg, increase in thickness of the strip was observed (Table 3). The thickness of the prepared sildenafil citrate oral films were measured and showed in (table 4).

#### Surface pH Study

The surface pH of the drug loaded and drug free oral films were ranging from 6.5±0.12 and 6.9±0.2 as reported in table (3 and 4).

Since surface pH of films was found to be around neutral pH, there will not be any kind irritation to the mucosal lining of the oral cavity. This result is in a consistent with the pH of oral mucosa of the oral cavity[35].

#### In-vivo and In-vitro disintegration study

All the batches of drug free fast dissolving strips (F1– F14) were found to be disintegrate in less than 60 sec[36].

*In-vivo* and *In vitro* disintegration time were found to increase with increase in the amount of HPMC used in the formulations (table 3).

Formula 7 found to gave fastest *In-vivo* and *In vitro* disintegration time (10.43 and 14.41) respectively as compared to other formulas.

Formulas of F2 and F3 were gave the slowest *In-vivo* and *In vitro* disintegration time of (37.82 sec, 38.5sec) and (54.19 sec, 50.22 sec) respectively.

This may be due to that F2 and F3 were harder compared with other fast dissolving films as evident by higher elastic modulus [22].

#### Mechanical properties

Fast dissolving film should possess moderate tensile strength, high percent elongation(% E), low EM and shorter time for disintegration with respect to their high percent of drug release[37, 38].

The results revealed that all the blank oral films showed moderate tensile strength values, films of F7, F8 and F9 showed significantly higher %E as compared with other formulas.

Formula 7 and 8 showed significantly lowest EM. Table (3).

On the other hand the mechanical properties showed that addition of plasticizers (PG and glycerin) decreased the tensile strength, increased % elongation and decreased elastic modulus[39].

Tensile strength measurements of formula 7 revealed that higher % E and lowest EM (table 3).

Based on above results the drug free formula of F7 showing the fastest time of *In-vivo* and *In vitro* disintegration and more satisfactory mechanical properties so, was chosen as best formula to be loaded with sildenafil citrate and subsequent more comparative study like physical characterization, content uniformity and dissolution pattern were achieved and showed in ( table 5).

Table 3: Evaluation of blank films

Formulation code	Film thickness (mm)	tensile strength (N/cm <sup>2</sup> )	% of elongation (cm <sup>2</sup> %)	Elastic Modulus (EM)	In vivo DT(sec)	In vitro DT(sec)	Surface pH
F1	0.068	4.08	55	7.42	19.03	18.9	6.9±0.2
F2	0.146	8.4	50	16.80	37.82	38.5	6.7±0.21
F3	0.184	14.2	47	30.21	54.19	50.22	6.9±0.11
F4	0.108	6.33	53	11.94	22	23.09	6.8±0.1
F5	0.123	7.43	50	14.86	24.1	25.9	6.8±0.07
F6	0.19	8.9	55	16.18	27	26	6.7±0.08
F7	0.075	4.5	86	5.23	10.43	14.41	6.6±0.09
F8	0.1	5.01	91	5.51	14.32	17.02	6.6±0.10
F9	0.18	6.65	89	7.47	24.34	18.4	6.7±0.11
F10	0.064	8.09	34	23.79	11.6	14.3	6.5±0.12
Same of F7	0.075	4.5	86	5.23	10.43	14.41	6.6±0.09
F11	0.09	2.5	41	6.10	10.99	15.3	6.8±0.14
F12	0.09	5	36	13.89	16	16	6.7±0.15
F13	0.11	4.7	38	12.37	16	19	6.5±0.16
F14	0.11	2.5	44	5.68	29	22	6.6±0.17

### Dissolution study

The time required for 80% of the drug to be released ( $T_{80\%}$ ) from the prepared sildenafil citrate oral film and percent drug dissolved in 2 minutes ( $D_{2 \text{ min}} (\%)$ ) were considered for the comparison of the dissolution results in 0.1N HCl as shown in table(4). The prepared sildenafil citrate oral films were studied the effect of presence of tween 80 at (0 and 5% w/w of total dry weight of film) on the rate of release of drug for batches LF1 and LF2. The results revealed that the release rates of drug from these films in 0.1 N HCl (at 37°C) temp

were found to increase with the addition of surfactant (tween 80) at 5% w/w[40].

The prepared formula LF2 (with tween 80) showed a significant improvement ( $p < 0.05$ ) in the dissolution rate (pH1.2) ( $D_{2 \text{ min}} (\%)$  was 11.7%) compared with prepared formula LF1 (contain no tween 80) due to the effect of surfactant (tween 80) that which improved wettability and solubilized the non-molecularly dispersed and then, provided the fastest rate of dissolution for sildenafil citrate from oral film[41].

These results are represented in figure 3.

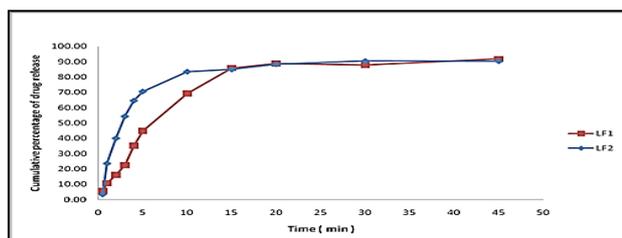
**Table 4: In vitro Dissolution Parameters in 0.1N HCl (pH 1.2)**

Formula no.	$T_{80\%}$ (min)	$D_{2 \text{ min}} (\%)$
LF1	13.55	12.54
LF2	8.7	41.3
LF3	4.65	53.57
LF4	2.78	75.56
Samagra®	29.1	27.68
Viagra®	19.26	21.42

**Table 5: Evaluation of Sildenafil Citrate Oral Films**

Formulation code	Drug content (%)	Film thickness (mm)	tensile strength ( $N/cm^2$ )	% of elongation ( $cm^2\%$ )	Elastic Modulus (EM)	In vivo DT(sec)	In vitro DT(sec)	Surface pH
LF1	93.78± 1.1	0.094	6.8	64	10.63	38	41	5.7±0.1
LF2	90.04±2.5	0.11	7.1	53	13.40	31	36	6.01±0.21
LF3	92.4± 7.17	0.08	6.8	47	14.47	34	38	5.9±0.3
LF4	94.12±4.3	0.12	5.1	53	9.62	30.09	33.3	6.01±0.41

### In-vitro dissolution profile of LF1 and LF2



**Fig. 1: Cumulative drug release profile of the prepared sildenafil citrate oral film LF1 and LF2, in 0.1 N HCl (pH 1.2) at 37°C temp. (results are expressed as mean ± SEM, n=3).**

The prepared sildenafil citrate oral films which contained a tween 80 as surfactant (LF2) was also, studied the effect of incorporation of superdisintegrant Polypl as done XL 10 at (0, 2 and 5% w/w) of total dry weight for formula LF2, LF3 and LF4 respectively, on the *In-vitro* dissolution performance in 0.1 N HCl (at 37°C) temp and the results revealed that drug release rate of formula LF2 was lower in an absent of Polyplasdone XL 10 when compared with other formulas and the formula LF4 (5% of Polyplasdone XL 10) showed higher release of drug than formula LF 3, owned to higher amount of superdisintegrant which produced the fastest rate of drug dissolution. When working with cationic drugs[42, 43]. Results of dissolution profiles represented in figure 4 and physical-mechanical characterizations were represented in (table 5). After 2 minutes time interval, 75.56% of drug was released from LF4 formula and 53.57% of drug released from formula LF3 and the LF2 released 41.3%. The LF4 formula gave a highly enhancement in the solubility and dissolution of sildenafil citrate in 0.1 N HCl (at 37°C) temp as compared with others LF2, LF3.

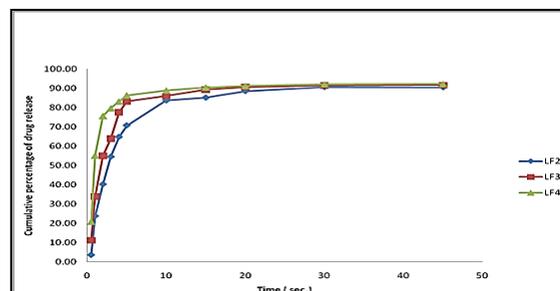
### Comparison of best formulated film with marketed tablet

The best formulated sildenafil citrate oral film LF4 was then compared with marketed tablet Samagra® and Viagra® 25mg (results obtained from a reference [45] for drug release profile. Formulas LF4 gave a significant enhancement ( $p < 0.05$ ) in the solubility and dissolution of sildenafil citrate in 0.1 N HCl (pH 1.2) at 37°C compared with conventional sildenafil citrate tablets. The result of  $D_{2 \text{ min}} (\%)$  for LF4 was 75.56% compared with 27.68 and 21.42% for Samagra®, and Viagra® respectively. These results are represented in figure 5.

### Uniformity of dosage units of the oral strips

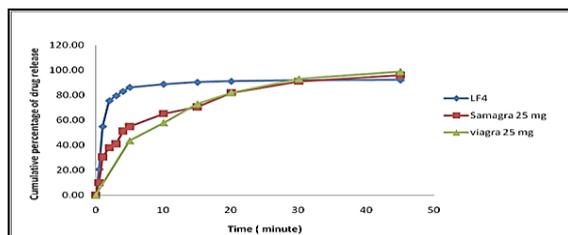
The content uniformity of dosage units of the oral film preparation LF1, LF2, LF2 and LF4 were tested for sildenafil citrate using UV spectroscopy, and the results were listed in table 5.

### In-vitro dissolution profile of batches LF2, LF3 and LF4



**Fig. 2: Cumulative drug release profile of the prepared sildenafil citrate oral film LF2, LF3 and LF4 in 0.1 N HCl (pH 1.2) at 37°C temp. (Results are expressed as mean ± SEM, n=3)**

### In-vitro dissolution profile of LF4 with marketed tablets



**Fig. 3: Cumulative drug release profile of the prepared sildenafil citrate oral film LF4 and the conventional sildenafil citrate tablets (Samagra® and Viagra®[44]) in 0.1 N HCl (pH 1.2) at 37°C temp. (Results are expressed as mean  $\pm$  SEM, n=3).**

## CONCLUSION

On the basis of obtained results, one can conclude that HPMC K100LVEP and Glycerin are better for formulation of oral strips of Sildenafil citrate. Overall result suggests that 5% (w/w) of Superdisintegrant (Polyplasdone XL-10) is suitable for the preparation of Sildenafil citrate, and LF4 formula release higher percentage of drug, Show of *In-vivo* disintegration time of 30 seconds.

On the basis of data obtained from *in vitro* dissolution that LF4 is promising formulation suitable for the immediate release of Sildenafil citrate for systemic use since they exhibited maximum drug release.

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## REFERENCES

1. DebjitBhowmik, Fast Dissolving Tablet: A Review on Revolution of Novel Drug Delivery System and New Market Opportunities. Scholars Research Library; 2009; 1 (2):262-276.
2. Malke M, Shidhaye S, Kadam VJ. Formulation and evaluation of Oxacarbazine fast dissolve tablets. Ind. J. Pharm. Sci., 2007; 69: 211-14.
3. Biradar SS, Bhagavati S, Kuppasad J., Fast Dissolving Drug Delivery Systems: A Brief Overview. the Internet Journal of Pharmacology. 2006; 4:Bachynsky, M.O., Infeld, M.H., Rashed, M., Shah, N.H.: US20080085310 (2008).
4. M.D. Nehal Siddiqui, GarimaGarg; A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents"; Advances in Biological Research., 2011; 5 (6): 291-303.
5. Krause, Julia; Breitkreiyz, Improving Drug Delivery in Paediatric Medicine; Pharmaceutical Medicine. 2008; Volume 22 - Issue 1: 41-50.
6. Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. Can J Psychiatry. 2004; 49:701-703.
7. Seager H. Drug delivery products and the zydis fast dissolving dosage form. J. Pharm Pharmacology. 1998; 50:375-378.
8. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech. 2004 September; 5(3): 10-15.
9. Anderson, O.; Zweidorff, O.K.; Hjelde., Problems When Swallowing Tablets. A questionnaire study from general practice. TidsskrNorLaegeforen, 1995; 20, 947-9.
10. Ghosh TK, PfisterWR, Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceuticals perspective; In: Drug delivery to the oral cavity: Molecules to market. New York, CRC Press 2005; 337-356.
11. Dobbetti L. Fast melting tablets: Developments and technologies. Pharm Technology Drug Delivery(Suppl 2001); 44-50.
12. Giannola LI, Caro VD, Giandalia G, et al. Current Status in Buccal Drug Delivery, Pharm Tech Eur. 2008; 32-39.

13. Borsadia, S., O'Halloran, D., Osborne, J.L. Quick Dissolving Films-A Novel Approach to Drug Delivery. Drug Delivery Technol. 2003; 3(3); 63-66.
14. Nafee NA, Boraie NA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing Cetylpyridinium chloride. Acta Pharm. 2003; 53:199-212.
15. Barnhart S D, Rathbone M, Hadgraft J, Roberts M, Lane M. Thin film oral dosage forms. Modified release drug delivery technology Informa Healthcare. 2008;68(7):209-216.
16. MeenuDahiya, SumitSaha and Aliasgar F. Shahiwala, A Review on Mouth Dissolving Films; Current Drug Delivery, 2009; 6: 469-476.
17. Mishra, R.; Amin, A., Formulation Development of Taste-Masked Rapidly Dissolving Films of Cetirizine Hydrochloride. Pharm. Tech., 2009; 33(2), 48-56.
18. StradaVigevanese, localitàBarbattola, Gaggiano,Milano, , A Novel, Fast-Dissolving Dosage Form. Manuf. Chem.;1990;61:36-37.
19. Amnuaitkit C, Ikeuchi I, Ogawara K, Higaki K & Kimura T, Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use, Int. J. Pharm. 2005; 289:167-178.
20. S. Kunte, P. Tandale, Fast Dissolving Strips: A Novel Approach for the Delivery of Verapamil. Journal of Pharmacy and Bioallied Sciences October-December 2010; Vol 2 Issue 4.
21. VerenaGarsuch, JörgBreitkreutz, Novel Analytical Methods for the Characterization of Oral Wafers. European Journal of Pharmaceutics and Biopharmaceutics, (2009); 73 195-201.
22. El-Setouhy DA, El-MalakNS., Formulation of a Novel Tianeptine Sodium Orodispersible Film. AAPS PharmSciTech 2010; 11(3):1018-25.
23. KokKhangPeh, Choy Fun Wong, Polymeric Films As Vehicle For Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties. Pharm Pharmaceutical Sci.; 1999; 2 (2):53-61.
24. Gosai A.R., Patil S.B. and Sawant K.K., Formulation and Evaluation of Oro Dispersible Tablets of Ondansetron Hydrochloride by Direct Compression using Superdisintegrants. International Journal of Pharmaceutical Sciences and Nanotechnology. 2008; Volume 1. Issue 1.
25. Ali J, Khar R, Ahuja A., Buccoadhesive Erodible Disk for Treatment of Oro-Dental Infections: design and characterization. Int. J. Pharm, (2002); 23893-103.
26. Desai Kgh., Kumar TMP., Preparation and Evaluation of a Novel Buccal Adhesive System. aapsPhamscitech, 2004;5: Article 35.
27. Abdelbary G, Eouani C, Prinderre P, Joachin M. J., Determination of the In vitro Ddisintegration Profile of Rapidly Disintegrating Tablets and Correlation with Oral Disintegration. Int J Pharm, 2005;292:29-41.
28. DorPjm, FixJa., In Vitro Determination of Disintegration Time of Quick-Dissolve Tablets Using a New Method. Pharm Delivery Techno, 2000;5: 575-577.
29. Mishra, R., Amin, A. Quick API Delivery. Pharm Techno Eur. 2007; 9(10): 35-39.
30. Borsadia, S., O'Halloran, D., Osborne, J.L., Quick Dissolving Films-A Novel Approach to Drug Delivery. Drug Delivery Technol. 2003;3(3):63-66.
31. Mishra, R., Amin, A. Formulation Development of taste masked rapidly dissolving films of cetirizine hydrochloride. Pharm Technol. 2009; 33(2): 48-56.
32. Chen, M.J., Tirol, G., Bass, C., Corniello, C.M., Watson, G., Sanchez, I. Castable edible pharmaceutical films. Drug Delivery Technol. 2008; 8(6): 34-41.
33. Nishimura, M., K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, T. Sugiyama and Y. Itoh. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film, International J. Pharmaceutics. 2009; 368(1-2): 98-102.
34. Patel R, Naik S, Patel J, Baria A. Formulation development and evaluation of mouth melting film of ondansetron. Arch Pharm Sci Res 2009;1:212-7.
35. Siewert M, Dressman J, Brown CK, Shah VP; FIP; AAPS. FIP/AAPS guidelines for dissolution/in vitro release testing of novel/special dosage forms. AAPS PharmSciTech 2003;4(1):E7.
36. V. A. Perumal, D. Lutchman; Formulation of Monolayered Films with Drug and Polymers of Opposing Solubilities; international journal of pharmaceutics, (2008); 358: 184-191.

37. Dixit R, Puthli S. Oral strip technology: Overview and future potential. *J Control Release* 2009;139:94-107.
38. Garsuch V. Preparation and characterization of fast-dissolving oral films for pediatric use [Doctoral thesis]: Heinrich Heine University, Dusseldorf;2009
39. Aulton, M.E.; Abdul-Razzak, M.H.; Hogan, J.E. The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems Part1: The influence of Plasticizers. *Drug Dev. Ind. Pharm.*, 1981; 7(6): 649-668.
40. RENUKA MISHRA\* & AVANI AMIN, Design and Developments of Rapidly Dissolving Films Using Ion Exchange Resin for Taste Masking, *International Journal of Drug Formulation & Research* Mar.-Apr. 2011; Vol. 2(2) 314.
41. Sarisuta N, Saowakontha R, Ruangsuksriwong C., Effects of surfactant on release characteristics of clonidine hydrochloride from ethylcellulose film. *Drug Dev Ind Pharm.* 1999 Mar;25(3):373-7.
42. Siriporn Okonogi and Satit Puttipatkhachorn ; Dissolution Improvement of High Drug-loaded Solid Dispersion; *AAPS PharmSciTech.* 2006; 7(2): Article 52.
43. J. Balasubramaniam, K. Bindu, V.U. Rao, D. Ray, R. Haldar, and A.W. Brzezczko, Effect of Superdisintegrants on Dissolution of Cationic Drugs, *Dissolution Technologies* 2008; 15 (2): 18-25.
44. Sivakranth. M, Abdoul S. Althaf, Rajasekhar .S; Formulation And Evaluation of Oral Fast Dissolving Tablets of Sildenafil Citrate; *International Journal of Pharmacy and Pharmaceutical Sciences.* 2011; Vol 3, (Suppl 2):112-121.