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FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF DOXOFYLLINE

M. Maheshwar*

Assistant Professor, Department of Pharmaceutics, Marri Laxman Reddy Institute of Pharmacy, Dundigal, Medchal, Hyderabad, Telangana-500043.

***Corresponding Author: M. Maheshwar**
Assistant Professor, Department of Pharmaceutics, Marri Laxman Reddy Institute of Pharmacy, Dundigal, Medchal, Hyderabad, Telangana-500043.

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ABSTRACT

Asthma is the most common life-threatening pulmonary disease that requires constant monitoring. Doxofylline is a new generation xanthine derivative that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is highly metabolised by liver to an extent of 80-90%. Present work studies were carried on the formulation of sublingual tablets of Doxofylline using super disintegrant like sodium starch glycolate and croscarmellose with a view to obtain rapid disintegration when held beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa and it also avoids the fast pass metabolism and improve the bioavailability. In-vitro release studies were carried out for different formulations. FTIR studies were carried out for pure drug Doxofylline and for optimised formulation to confirm that there is no interaction between drug and different excipients used in the formulation.

KEYWORDS: Doxofylline, croscarmellose, sodium starch glycolate, Asthma, rapid disintegration.

INTRODUCTION

Sublingual tablets are the types of solid dosage form that to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein that are usually metabolized by liver called as first pass metabolism. But the drugs whose absorption takes place through oral cavity avoids first-pass metabolism because in oral cavity the highly vascularized mucosal lining followed by jugular veins and superior vena cava directly links to arterial circulations. The tablets are usually small and flat, compressed lightly to keep them soft and they must dissolve quickly allowing the API to be absorbed quickly. It's designed to dissolve in small quantity of saliva. After the tablet is placed in the mouth below the tongue. Different formulations such as tablets, films and spray are useful for sublingual administration of drug. The task of formulation of sublingual dosage form is very challenging. The challenges are mechanical strength, disintegration time, taste masking, mouth feel, sensitivity to the environmental condition and cost etc. The sublingual tablets are usually prepared by using various super disintegrant like sodium starch glycolate, different grades of croscarmellose and different grade of cross povidone for quick and easy disintegration of tablets.[1,2]

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life-threatening pulmonary disease that requires constant monitoring. Xanthine derivatives are used since a long period of time for treatment of Asthma and COPD. Doxofylline is a new generation xanthine derivative that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is extensively metabolized in liver by demethylation and oxidation to an extent of 80-90% and 50% plasma protein bound Elimination half-life ($t_{½}$) is around 6-7 hour and daily dose is 200-400 mg two to three times in a day. It is having solubility of 12 mg/ml in water and having P^{Ka} of 9.87.[3]

The present studies were carried on the formulation and evaluation of sublingual tablets of Doxofylline using super disintegrant like sodium starch glycolate and croscarmellose with a view to obtain rapid disintegration

when held beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa and it also by passes fast pass metabolism and improve the bioavailability by reducing the overall daily dose.[4]

MATERIALS AND METHODS

Materials

Doxofylline was procured as a gift sample from Dr. Reddy's Laboratories Hyderabad, India. The super disintegrant Sodium Starch Glycolate (SSG) and croscarmellose sodium were obtained SD fine chemicals Pvt. Ltd. The diluent Micro crystalline cellulose and mannitol were purchased from Otto Manufacturers. PVP K30, Talc and magnesium Stearate were purchased from SD fine chemicals Pvt. Ltd' Mumbai, India.

Methods

Preparation of calibration curve of Doxofylline:

Primary stock solution of Doxofylline having concentration of 1000µg/ml was prepared using phosphate buffer P^H 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10µg/ml was prepared using same phosphate buffer P^H 6.8. The prepared secondary stock solution was then scanned by a UV spectrophotometer at 274 nm. The secondary stock solution was then diluted using same phosphate buffer P^H 6.8 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at 274nm.

Table 1: Standard Curve of Doxofylline.

S. No	Conc. (µg /mL)	Absorbance at 274nm
1	0	0
2	2	0.135
3	4	0.248
4	6	0.352
5	8	0.433
6	10	0.535

Preparation of Doxofylline sublingual tablets

The tablets of Doxofylline were prepared by wet granulation method. Accurate quantities of all ingredients were weighed and passed through sieve no #80 before their use in formulations. For each formulation specific and accurate quintile of powder like Doxofylline, MCC, SSG, Cross carmellose, and PVP K30 were blended uniformly and passed through sieve no #20. PVP K30 was used as binder. The aggregates formed after addition of binder were initially dried for 5-10 minutes to reduce moisture level and to prevent sticking with sieve. The aggregates were passed through sieve # 44 to get wet granules. The granules are dried at 40^o C for 20 minutes. Magnesium stearate and talc were used as lubricants and the required quantities are mixed with dried granules for 2-3 minutes [5,6]. After lubrication the formulations were evaluated for angle of repose, bulk density, compressibility; and flow properties of granules were predicted prior to compression. The evaluated granules were compressed into tablets on a ten-station rotary punching machine using 8mm concave punches.

Table 2: Compositions of Doxofylline tablet formulations.

Code	Doxofylline (mg)	MCC (mg)	Mannitol (mg)	SSG (mg)	Cross carmellose (mg)	PVP (mg)	Magnesium stearate (mg)	Talc (mg)	Total wt. (mg)
F1	100	50	20	2	2	20	4	2	200
F2	100	48	20	3	3	20	4	2	200
F3	100	46	20	4	4	20	4	2	200
F4	100	48	20	4	2	20	4	2	200
F5	100	48	20	2	4	20	4	2	200

Drug-Excipient compatibility

The FTIR spectra of Doxofylline and optimized formulation (F4), the sharp peaks that appear in spectra of Doxofylline at~ 3110 cm^{-1} also appears in physical mixture (drug and excipients) at~ 2916 cm^{-1}. The characteristic IR absorption peaks of Doxofylline at ~ 1700 cm^{-1} (C=O stretch), at ~1656 cm^{-1} (C=C stretch), at ~1547 cm^{-1} (C=N stretch), at ~1477 cm^{-1} (C-H bend) and at ~ 1190 cm^{-1} (C-N vibration) were also present in the physical mixture (drug and excipients) with no shifting in the major peaks and there was no additional peaks formed in the physical mixture that indicate there were no interaction occurred between the Doxofylline and excipients used in the preparation of different formulations.

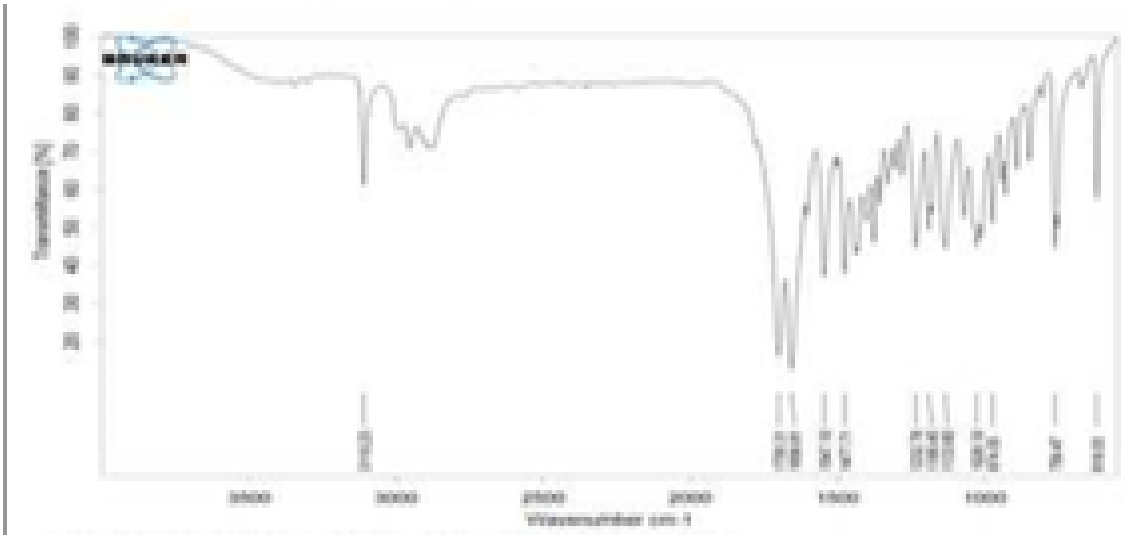

Figure 1: FTIR spectrum of Doxofylline.

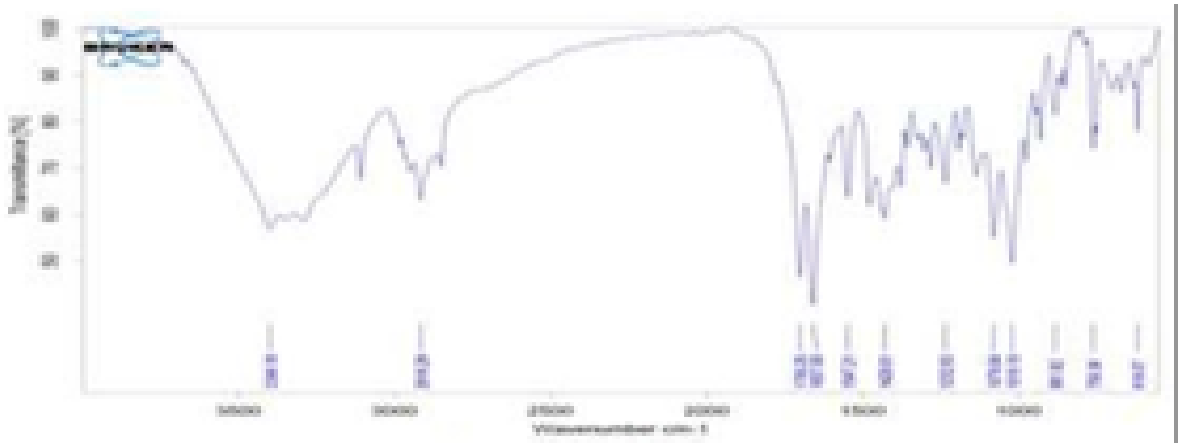

Figure 2: FTIR Spectrum of optimized formulation(F4).

Evaluation of pre-compression parameters of Doxofylline

1. Angle of Repose (θ)

This is the maximum angle possible between the surface of a pile of granules and the horizontal plane.[7] The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

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

Where, θ = angle of repose, h = height of the heap, r = radius of the heap.

2. Carr's Index: The Carr's index or compressibility index was calculated from the bulk and tapped density value by following equation.[8]

$$\text{Carrs index} = \frac{\text{Tapped density- bulk density}}{\text{Tapped density}} \times 100$$

3. Hausner's Ratio: It is measurement of frictional resistance of tablet blend. The ideal range should be 1.2-1.3. It was determined by the ratio of tapped density and bulk density.[9]

Hausner′s ratio=Tapped density/Bulk density

4. Bulk Density: Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.[10,11] Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25ml measuring cylinder and the initial volume was observed. It is given by the equation as

Bulk density=Mass of the powder/ bulk volume of the powder

5. Tapped density: Weighed quantity of tablet blend was introduced into a graduated cylinder. Volume occupied by the drug was noted down. Then cylinder was subjected to 100, 200 and 300 taps in tap density apparatus.[12,13] According to USP, tapped density was given by

Tapped density=Mass of the powder/Tapped volume of the powder

Table 3: Specifications for flow properties.

Flow Character	Carr's index (%)	Hausner's ratio	Angle of repose
Excellent	< 10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very very poor	>38	>1.60	>66

Evaluation of post compression parameters of Doxofylline tablets

1. Weight variation

All formulated Doxofylline sublingual tablets were evaluated for weight variation test. Twenty tablets were weighed collectively and individually using an electronic balance.[14] The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.

Table 4: Specifications for weight variation test of un coated tablets.

S. No	As per USP standards the Average weight of tablet(mg)	Maximum percentage difference allowed (%)	As per IP standards the Average weight of tablet(mg)
1	≤ 130	10	≤ 85
2	130-324	7.5	85-250
3	≥ 324	5	≥ 250

2. Hardness

All the formulations of Doxofylline sublingual tablets hardness were measured by using Monsanto hardness tester [15]. From each formulation the crushing strength of ten sublingual tablets were recorded in kg/cm^2 and average were calculated. According to specifications of USP hardness values of 3-3.5 Kg for sublingual tablet is considered as acceptable limit.

3. Friability

Ten sublingual tablets from each batch were taken in Roche friabilator. After100 revolutions of friabilator tablets were recovered.[16] The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\text{Percent Friability} = (W_0 - W_1)/ W_0 \times 100$$

Where W_0 and W_1 were the initial and final weight of the tablets before and after friability test. The maximum limit up to 1% of the tablet weight are consider acceptable for friability.

4. *In-vitro* drug release study

Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II. A total volume of 900 ml of phosphate buffer P^H 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium.[17] Samples were collected at 5 min interval and samples were analyzed spectrophotometrically at 274 nm.

5. Drug content

Twenty Doxofylline sublingual tablets were taken and triturated to form powder and dissolved in 100 ml of phosphate buffer P^H 6.8 and heated at 37 ^{0}C for 15-20 minutes with stirring.[18] The solution was filtered, suitably diluted and the drug content was measured by using UV Spectrophotometer at 274 nm.[19,20] Each measurement was carried out and the average drug content in the Doxofylline sublingual tablets was calculated.

RESULTS AND DISCUSSION

The characteristic IR absorption peaks of Doxofylline at ~1700 cm^{-1} (C=O stretch), at ~1656 cm^{-1} (C=C stretch), at ~1547 cm^{-1} (C=N stretch), at ~1477 cm^{-1} (C-H bend) and at ~1190 cm^{-1} (C-N vibration) were also present in the physical mixture (drug and excipients) with no shifting in the major peaks and there was no additional peaks formed in the physical mixture (drug and excipients), that indicate there were no interaction occurred between the Doxofylline and excipients used in the preparation of different sublingual formulations.

The result of angle of repose of granules after mixing with magnesium stearate and talc were less than 25^o for all formulations that indicates excellent flow properties of granules. Compressibility index is also good for most of the formulations which indicates excellent flow properties of granules. The Hausner's ratio values lie below 1.25 for all formulations which also satisfy with

good flow properties of granules according to standard specifications.

The thickness of the tablets was ranged between 4.79 to 4.85 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 199 to 200 mg. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Doxofylline sublingual tablets formulations were ranged from 1.02 to 2.32 kg/cm^2. The percentage friability of all the formulations were ranged from 0.59 % to 0.92 %. In the present study, the percentage friability for all for formulations was within the prescribed limits.

When both the super disintegrants were used in combination in total concentration of 3% it shows some better dissolution profile and release almost all the drug within 20 minutes. The Formulation F4 having super disintegrant concentration of 3% (2% cross carmellose and 1% SSG) release the drug within 20 minutes. Combination of MCC and mannitol worked good as diluents so it was used in all the formulations. Formulation F4 containing SSG and cross carmellose showed complete drug release within 20-minute emerging as optimized formulation and using both the super disintegrant in combination it gives better drug release profile.

Table 5: Evaluation of precompression parameters of Doxofylline sublingual tablet granules.

Code	Bulk density(gm/ml)	Tappeddensity (gm/ml)	Angle of repose (^{0})	Carr'sindex (%)	Hausner'sratio
F1	0.488	0.563	21.23	15.36	1.15
F2	0.439	0.531	20.19	20.95	1.21
F3	0.481	0.568	24.34	18.08	1.18
F4	0.465	0.549	22.32	18.06	1.18
F5	0.473	0.523	21.56	10.57	1.11

Table 6: Evaluation of post-compression parameters of Doxofylline sublingual tablets.

Code	Hardness (kg/cm^2)	Average Weight (mg)	Friability (%)	Thickness (mm)	Drug content (%)
F1	2.32	200	0.59	4.81	98.62
F2	2.11	202	0.62	4.79	98.22
F3	1.42	199	0.92	4.84	98.42
F4	2.13	200	0.82	4.85	99.19
F5	2.15	199	0.74	4.80	98.45

Table 7: Cumulative Percentage Drug Release of sublingual tablets of Doxofylline.

Time [min]	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	55.61	58.61	53.28	58.64	51.32
10	68.23	66.25	64.38	69.27	62.58
15	77.54	77.24	74.21	78.59	73.62
20	91.52	92.31	91.26	96.52	91.25

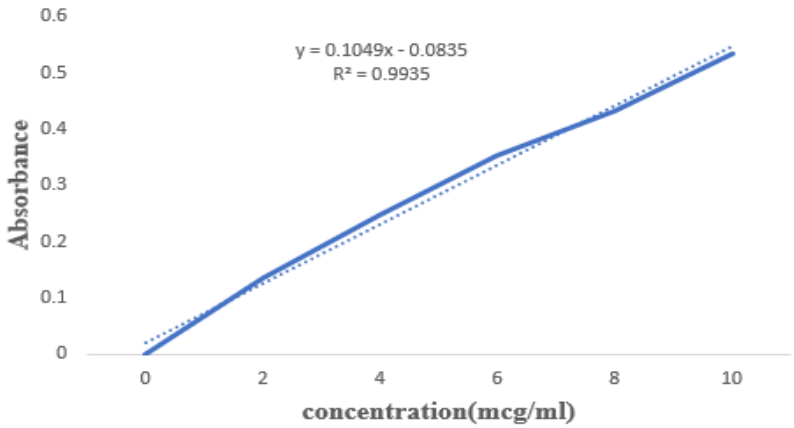

Figure 3: Standard graph of Doxofylline.

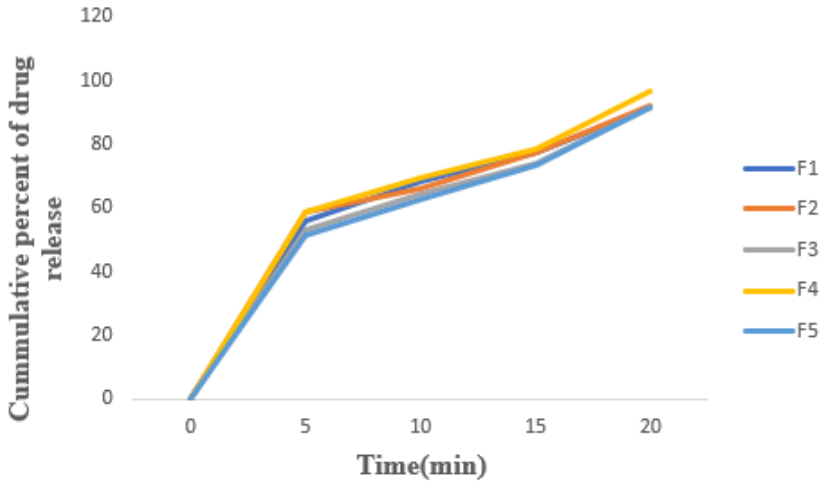

Figure 4: Cumulative drug release of Doxofylline tablets (F1 to F5).

CONCLUSION

In the present work Doxofylline sublingual tablets were successfully developed. The major challenge in this work was to study the effect of sodium starch glycolate and cross carmellose sodium on *in vitro* release rate of sublingual tablet of Doxofylline. FTIR studies revealed that there is no chemical interaction between drug and excipients. Wet granulation methods were adopted for the preparation of Doxofylline sublingual granules and the evaluation results of all the precompression parameters were satisfied the acceptance criteria. All the post compression parameters like average thickness, hardness, friability, weight variation also fall within acceptable limit. Mannitol and MCC were used both as diluents for all the formulations for better drug release. Formulation F4 containing 1% of SSG and 2% of cross carmellose showed complete drug release within 20 minutes emerging as optimized formulation and using both the super disintegrant in combination it gives better drug release profile. Thus, from the results of the current study clearly indicate, a promising potential of the Doxofylline sublingual system as an alternative to the conventional dosage form because it bypasses the first pass metabolism and improve the bioavailability of the drug and over all daily dose can be reduced.

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CONFLICT OF INTEREST: NIL.

REFERENCES

1. Rodden DM, Antiarrhythmic Drugs, In: Goodman and Gilman's Pharmacology Basis of Therapeutics, 10th ed., McGraw Hill Publishing Division, New York, 2006; 949-50.
2. Sahoo S., Mishra B., Biswas PK, Panda O., Mahapatra SK. Fast Dissolving Tablet: As A Potential Drug Delivery System, 2011; 2(1): 45- 50.
3. Naik PS., Kurup NS. Design and optimization of fast dissolving tablets containing metoprolol by sublimation method. IRJP, 2010; 1(1): 346- 357.
4. Giannola LI., De Caro V., Giandalia G., Siragusa MG., Tripodo C., Florena M., and Campisi G. Release of naltrexone on buccal mucosa: Permeation studies, histological aspects and matrix system design. Eur J.Pharm. Biopharm, 2007; 67: 425-433.
5. Kumar M., Visth S.,ali S.,Bhola A., Preparation and evaluation of fast dissolving drug delivery system Containing levocetrizine Hcl, Int J of Pharm and Pharm Sci, 2010; 2(3): 108-112.
6. Palkhede M., Amrutkar S., Erande K. Formulation, optimization and evaluation of fast disintegrating tablet of mebeverine HCl. Int J Pharm Pharm Sci. 2012; 4(4): 121-125.
7. Aulton`s Pharmaceutics, The design & manufacture of medicines, Biopharmaceutics and pharmacokinetics, A Treatise, second edition, Vallabh Prakashan, 315-84.
8. Leon Lachman, Herbert A, Liberman, Joseph L.Kaing , The theory and practice of Industrial Pharmacy:293-303.
9. Ansel`s Pharmaceutical dosage forms & drug delivery systems, 8th ed., 227-60.
10. Shirwaikar R., Shirwaikar A., Prabu L., Mahalaxmi R., Rajendran K.,Kumar C. Studies of super disintegrant properties of seed mucilage of Ocimum gratissimum. Indian J. of Pharmaceutical sciences, 2007; 69(6): 753-758.
11. Gohel MC., Bansal G., and Bhatt N. Formulation and evaluation of orodispersible taste masked tablets of famotidine. Pharma Bio World, 2005; 3: 75-80.
12. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: A brief overview. International J Pharm Sci, 2006; 4(2).
13. Kumar B Sutradhar, Dewan T Akhter, Riaz Uddin. Formulation and evaluation of taste masked oral dispersible tablets of Domperidone using

sublimation method. International J Pharm Sci., 2012; 4(2): 727-732.
14. Abhilash AS, Jayaprakash S, Nagarajan M, Dhachinamoorthi D. Design and evaluation of timolol maleate occuserts. Indian J Pharm Sci., 2005; 67(3): 311- 314.
15. Agarwal SP, Vasudha S, Anitha P. Spectrophotometric determination of atenolol and timolol dosage forms via charge-transfer complexation. Indian J Pharm Sci., 1998; 53-55.
16. Amelia A, Vikram K. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. AAPS PhramSciTech, 2007; 8(4): E88.
17. Atul K, Ashok KT, Narendra KJ, Subheet J. Formulation and in vitro in vivo evaluation of extended-release matrix tablet of zidovudine: Influence of combination of hydrophilic and hydrophobic matrix formers. AAPS Pharm Sci Tech, 2006; 7(1): E1.
18. Basak SC, Jayakumar Reddy BM, Lucas Mani KP. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. Indian J Pharm Sci., 2006; 594-597.
19. Bhalla HL, Handa AK. Development and evaluation of controlled release tablets of carbamazepine. Indian Drugs, 1999; 36(2): 100-105.
20. Bolton S, Bon C. Pharmaceutical Statistics: Practical and Clinical Applications. Marcel Dekker, New York, 2004.