WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Volume 1, Issue 2,340-352. Research Article ISSN 2277 – 7105

FORMULATION DESIGN AND OPTIMIZATION OF TASTE MASKED RAPID DISINTEGRATING TABLETS USING FREEZE DRYING METHOD

Pravin K. Bhoyar*[1], Jagdish R. Baheti [2], Prabhat A. Naranje [3], Sharad Bhandarkar[4], Rengini Muraleedharan[4], Bhalchandra M. Deotale [3]

1. Department Of Pharmaceutical Sciences, NIMS University, Jaipur, Rajasthan, India
2. Shriman Suresh Dada Jain College of Pharmacy, Chandwad, Nasik, Maharashtra, India.
3. Department of Pharmacy, Agnihotri College of Pharmacy, Wardha, Maharashtra, India.
4. Department of Pharmacy, GIKIST College of pharmacy, Dist: Jabalpur, Madhya Pradesh, India

Article Received on
10 March 2012,

Revised on 27 March 2012,
Accepted on 14 April 2012

***Correspondence for Author:**

*** Pravin K. Bhoyar**
Department of Pharmaceutical Sciences, NIMS University, Jaipur, Rajastan, INDIA
pravinbhoyar007@rediffmail.com

ABSTRACT

Trimetazidine HCl is used in angina pectoris and in ischaemia of neurosensoral tissue as in manieres disease. It will be much advantageous to present such drug in Rapid Disintegrating dosage form,as their administration is easier for the patient of angina attack. Bitter taste of the drug pose a main problem in patient compliance. Hence Eudragit EPO polymer was used for complexation with drug for overcoming taste problem . The Lyophilization method was used to form the drug polymer complex in a tablet. 1:3 ratio of the drug to polymer was effectively masked the bitter taste of drug. Hydolysed Gelatin were used in different ratios. 2% Gelatin forms the optimized tablet. FTIR studies were done to study the drug polymer interaction. Rapid Disintegrating Tablet was formulated in the blister packs using Freeze Drying Method. The tablets were evaluated for different evaluation parameters. The tablet batch TEG3 having 1:3 ratio of Drug:Eudragit EPO and 0.5% Hydrolysed Gelatin were selected as the optimized batches. The marketed formulation showed much longer disintegration time (205±0.04) as compared to the presented formulations. Also the dissolution of marketed tablet is more (t_{90} around 13 min) as compared to the prepared tablet (t_{90} for TEP3 and TEG3 around 2.5 min).Thus prepared tablet is superior to marketed formulation in term

of disintegration time and dissolution behavior. Accelerated stability studies for 3 months shows no appreciable change in tablet properties and dissolution characteristics.

Key words: Trimetazidine Hcl, Taste masking, Eudragit EPO, Hydrolysed Gelatin, Rapid disintegrating tablets. Freeze Drying Method

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of an organoleptically elegant and patientfriendly drug delivery system for pediatric and geriatric patients.[1-2] More than 50% of the pharmaceutical products are orally administered for several reasons, and undesirable taste is one of the important formulation problems encountered with such oral products. Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment, especially in pediatrics. Therefore, formulation of taste-masked products is a challenge to the pharmacists. [3-4]

Trimetazidine HCl is used in angina pectoris and in ischaemia of neurosensoral tissue as in manieres disease .[5] It has clinical application in coronary insufficiency, angina pectoris, myocardial infarction and other old, right with severe cardiac dysfunction, and can be used with digitalis. Trimetazidine is a clinically effective antianginal agent that has no negative inotropic or vasodilator properties. It will be much advantageous to present such drug in rapid disintegrating dosage form, as their administration is easier for the patient of angina attack. Therefore, considering above factors, an attempthas has been made to mask the taste of Trimetazidine HCl and to formulate rapid disintegrating tablet with pleasant taste and better mouth feel.

MATERIALS AND METHODS

Materials

Trimetazidine HCl was procured as a gift sample from Ipca labs Ltd, Ratlam, India; Aminoalkylmethacrylate Copolymer was obtained as a gift sample from Degussa India Private Ltd., Mumbai, India under trade name of Eudragit EPO. Hydrolysed Gelatin was purchased from HiMedia India Pvt.Ltd. All other chemicals used in the study were of analytical grade.

Drug-Polymer interaction study

Pure Drug, polymer Eudragit EPO, physical mixture of Drug+Eudragit EPO and Drug+Eudragit EPO+Gelatin were analyzed for interaction by Fourier Transform Infrared Spectroscopy (FTIR) using KBr disk method.

Preparation of tablets

Table 1: Formulation design.

Sr. No.	Batch	Drug: Eudragit EPO	Hydolysed Gelatin (%w/v)	Glycine (%w/v)
1	TEH1	1:1	0.5%	0.8%
2	TEH2	1:2	0.5%	0.8%
3	TEH3	1:3	0.5%	0.8%
4	TEH4	1:4	0.5%	0.8%
5	TEK1	1:1	1%	0.8%
6	TEK2	1:2	1%	0.8%
7	TEK3	1:3	1%	0.8%
8	TEK4	1:4	1%	0.8%
9	TEG1	1:1	2%	0.8%
10	TEG2	1:2	2%	0.8%
11	TEG3	1:3	2%	0.8%
12	TEG4	1:4	2%	0.8%

A 0.5,1 and 2% w/v solution of Gelatin in water was prepared by first soaking the Gelatin in water until complete hydration. The Hydrated Gelatin was stirred using a magnetic stirrer until a clear solution was obtained. Equal weights of Glycine (0.886% w/v) and Mannitol (0.886% w/v) were added to the gelatin solution while stirring until completely dissolved. An accurately weighed amount of Trimetazidine HCl and Eudragit EPO in different ratios was then dispersed in the aqueous solution of Gelatin, Glycine, and Mannitol. 0.2 ml of the resulting suspension was poured into each of the pockets of a tablet blister pack to result in a Trimetazidine HCl dose of 20 mg in each tablet as shown in figure 1.

Fig. 1: Tablet with Gelatin

The tablet blister packs as shown in figure 2, each containing 10 tablets, were then transferred to a freezer at −22°C and kept in the freezer for 24 h. The frozen tablets were placed in a lyophilizer for 24 h using a Freeze Dryer (LARK, Penguin Classic Plus, Chennai.) with a condenser temperature of −45°C and a pressure of 7 × 10−2 mbar. [6] The Lyophilized Rapid Disintegrating Tablets were kept in a desiccators over calcium chloride (0% relative humidity) at room temperature until further use. Six blister packs containing a total of 60 tablets were produced in each run. The formula of the tablets is as shown in Table 1.

Evaluation of Tablets

Rapid disintegrating tablets were evaluated for following parameters.

Drug Content, Hardness, Friability Weight variation and Weight variation

Ten tablets were taken and triturated in a glass mortar. The powdered tablet equivalent to 20 mg of drug was dissolved in a 500ml of simulated gastric fluid and the drug content was determined spectrophotometrically at 269.4 nm. Hardness was measured using Monsanto hardness tester. [7] Friability was evaluated as the weight loss of tablets equivalent to 625 mg, tumbled in a friabilator for 4 min at 25 rpm. The tablets then were dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability. For weight variation, 20 tablets were weighed individually. Average weight was calculated and individual tablet weights were compared to the average.

Wetting time and Water absorption ratio

A piece of tissue paper folded twice was kept in a culture dish (i.d. 5.5 cm) containing about 6ml of purified water. A tablet having small amount of amaranth powder on the upper surface

was placed on the tissue paper.[8-10] Time required to develop red color on the upper surface of the tablet was recorded as a wetting time.

The same procedure was repeated for determining water absorption ratio without using amaranth. The wetted tablet was then weighed and water absorption ratio, R, was determined according to following equation:

$R= \{(W_a-W_b)/ W_b\}* 100$

Where,

W_b = weight of tablet before study

W_a = weight of tablet after study.

Taste evaluation of lyophilized tablets

In-vitro taste evaluation of lyophilized tablets

Lyophilized tablet containing 20 mg of Trimetazidine HCL was taken in a 25ml volumetric flask. To this, 10ml of simulated salivary fluid (SSF) was added and was shaken for 60 seconds on mechanical shaker [9]. The amount of drug released was analyzed spectrophotometrically at 269.8 nm.

Disintegration Time

***In Vitro* Disintegration Study**

The disintegration test apparatus used in the study was same as described by Khan S.A.et al. [9] The apparatus consist of a glass beaker of capacity 1000 mL. This beaker is placed on magnetic stirrer (E) provided with a thermostat. The wire basket (B) has been positioned in a beaker with the help of support (D). It is positioned in an assembly in such a way that when beaker contains 900 mL of disintegrating medium, the basket will have only 6 mL of this medium. The assembly is provided with magnetic bead (C) which is rotating with speed 25 rpm.

Test Method

The disintegration test for Rapid Disintegrating Tablet was performed by using modified disintegration apparatus as shown in figure 2. In this modified disintegration apparatus, first 900 ml of simulated salivary fluid was taken in a beaker. Basket was positioned in a beaker. The beaker was placed at 25 rpm and 37.5˚c. temperature. Then the tablet was dropped in the basket and the time required for complete disintegration of tablet was recorded using a stopwatch.

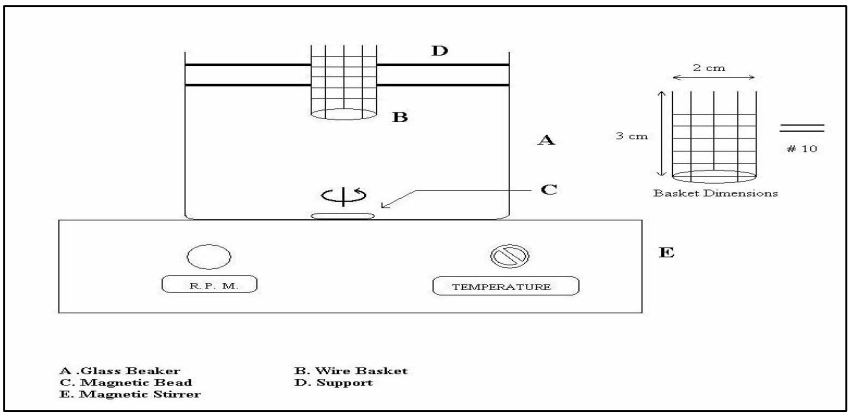

Fig. 2: Schematic representation of disintegration test apparatus.

In Vivo Disintegration Time

This study was performed with six healthy volunteers, from whom informed consent was first obtained. After the mouth was rinsed with purified water, one tablet was held in the mouth and the time required for complete disintegration of tablet was recorded. [8] The same disintegrated material was held in the mouth for up to 60 sec. then spat out. Mouth was again rinsed with water without swallowing the disintegrated materials. Finally the roughness level were recorded on numerical scale ranging from 0 to 3; 0- no roughness. 1- Slight roughness. 2- Moderate roughness and 3-Highly rough.

Dissolution study of tablets

In vitro dissolution studies for lyophilized rapid disintegrating tablets of different batches and marketed tablet were carried out in 500 ml simulated gastric fluid without enzymes (SGF) pH 1.2 using USP type II (paddle) apparatus at 50 rpm and 37± 0.5°C temperature. Dissolution study of marketed tablet of Trimetazidine HCL was done in a same way as that of the formulated tablet.

Stability studies of tablet formulations

The tablets were studied for stability at 40°C and 75% RH conditions for the period of three months. Each tablet was individually weighed and wrapped in an aluminium foil and packed in black PVC bottle and put at above specified conditioned in a heating humidity chamber for 3 months. [11-12] After each month tablet samples were analyzed for the weight gain, drug content, disintegration time and in vitro drug release study.

RESULTS AND DISCUSSION

Trimetazidine HCl is used in angina pectoris and in ischaemia of neurosensoral tissue as in manieres disease. It has clinical application in coronary insufficiency, angina pectoris, myocardial infarction and other old, right with severe cardiac dysfunction, and can be used with digitalis. Trimetazidine is a clinically effective antianginal agent that has no negative inotropic or vasodilator properties.

Drug-polymer Interaction Study

FTIR spectrum of the physical mixture of the drug and Eudragit EPO shows no significant shifts or reduction of intensity of FTIR bands of Trimetazidine HCl. The fig 3 shows Principal peaks of Trimetazidine HCl found at wavenumbers 1730, 1802, 1098, 1200, 770, 1295 cm^{-1} which matches with reference peaks.[13] In case of Eudragit EPO, The figure 4 shows the characteristic bands of the ester groups at 1,150 - 1,190, 1,240 and 1,270 cm-1, as well as the C=O ester vibration at 1,730 cm-1. In addition, CHX vibrations can be discerned at 1,385, 1,450 - 1,490 and 2,950 cm-1. The absorptions at 2,770 and 2,820 cm-1 can be assigned to the dimethylamino groups. Also the combination of Drug, Eudragit EPO, and gelatin shows no change in the peaks.

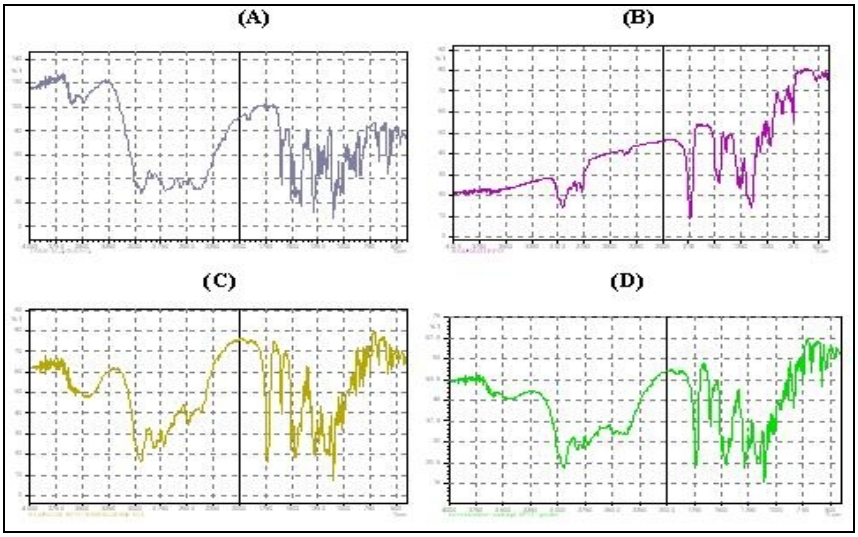

Fig. 3: FTIR Spectrum of (A) Trimetazidine HCl, (B) Eudragit EPO, (C) Trimetazidine HCl + Eudragit EPO, (D) Trimetazidine HCl + Eudragit EPO+ Gelatin.

Formulation of Rapid Disintegrating Tablet

It is well known fact that gelatin is the main constituents in the preparation of lyophilized Rapid Disintegrating Tablet.[14] Hence gelatin was used in different ratios. Glycin was also

used in all 24 batches in the concentration range of 0.8% w/v as it prevents shrinkage of the tablet during manufacturing.

Evaluation of lyophilized tablets

All Rapid Disintegrating Tablets from batches TEP1 to TEG4 were evaluated for tablet properties like friability, weight variation, drug content. Tablets passed all the tests. Friability, Weight variation and Content uniformity of all formulations were within acceptable limits as shown in Table 2.

Table 2: Evaluation of Tablets.

Sr. No.	Parameters / Formulation	Drug content (%)	Hardness ($kg/cm^{2)}$	Friability (%)	Wetting time (sec)	Water absorption ratio (%)
1	TEH1	97.22±0.04	0.72±0.03	0.17±0.08	9±0.04	159.53±0.04
2	TEH2	101.38±0.05	0.67±0.00	0.19±0.09	13.23±0.02	170.8±0.011
3	TEH3	98.6±0.05	0.69±0.00	0.18±0.04	13.2±0.03	167.26±0.004
4	TEH4	100.69±0.04	0.70±0.03	0.14±0.02	14.9±0.13	166.13±0.11
5	TEK1	92.38±0.04	0.75±0.05	0.15±0.02	14.95±0.02	165.8±0.003
6	TEK2	90.27±0.044	0.77±0.00	0.15±0.02	16.23±0.04	166.83±0.11
7	TEK3	90.96±0.05	0.74±0.00	0.13±0.03	17.9±0.11	169.57±0.03
8	TEK4	86.87±0.056	0.78±0.00	0.14±0.04	14.95±0.03	166.78±0.02
9	TEG1	98.6±0.054	0.82±0.00	0.17±0.04	13..20±0.01	167.25±0.009
10	TEG2	99.3±0.003	0.81±0.05	0.15±0.05	17.3±0.05	168.12±0.1
11	TEG3	99.3±0.004	0.82±0.00	0.17±0.04	13.9±0.001	170.18±0.02
12	TEG4	99.99±0.003	0.86±0.00	0.13±0.03	15.2±0.011	167.81±0.11

* Average of three determinations

Wetting and Disintegration time of tablets

There was not much difference in the wetting time of tablets containing Gelatin is hydrophilic and form open-network type matrix on lyophilization which get wet rapidly in the presence of aqueous medium. Wetting time for TEG3 was lowest 13.9±0.001 sec. From the results shown

in Table 2, it can be observed that in batch 1, tablets containing 2% hydrolysed gelatin and ratio1:3 (Drug: Eudragit EPO) disintegrate quickly. With respect to batches containing hydrolysed geletin it was observed that as concentration increases disintegration time was not much affected but hardness increases. 2% concentration of hydrolysed geletin forms optimised tablet having sufficient hardness and disintegrate quickly to dissolve rapidly or disintegrate when they come in contact with water or any aqueous fluids. The batch TEG3 with disintegration time (12.32±1.14 sec.) was much less, ($p<0.02$) as compared to the marketed tablet (205±0.04 sec) The batches from TEH1 to TEK4 were having disintegration time not so much different but hardness of the tablets were so poor that the intact tablet was not coming out of the blister, hence batch TEG3 were decided as optimized batch amongst all 12 batches of Gelatin as shown in Table 3. These dosage forms include of an open matrix network of water-soluble or water dispersible carrier material, which is impregnated with a unit dose of the pharmaceutical active agent. [15-16]

Table 3: Comparative Study of Disintegration Time with Different Methods.

Sr. no.	Batch	*In vitro* disinter-	*In vivo* disinte-
0	0	0	0
1	TEH1	13.15±1.65	15.15±0.98
2	TEH2	11.33±1.01	14.55±1.7
3	TEH3	16±0.22	18.14±1.73
4	TEH4	14.2±0.59	16.7±1.64
5	TEK1	12.92±1.09	15.84±0.82
6	TEK2	14.17±1.12	17.23±1.02
7	TEK3	14.9±1.07	16.8±1.29
8	TEK4	18.9±0.92	19.5±1.22
9	TEG1	18.7±1.67	20.24±0.023
10	TEG2	17±1.92	19.5±1.35
11	TEG3	12.32±1.14	12.5±1.8
12	TEG4	14±0.09	16.1±1.39
13	M	205±0.04	190±0.06

M-Marketed Tablet

***In vitro* taste evaluation**

In vitro taste evaluation study of the lyophilized Rapid Disintegrating Tablet was done in the simulated salivary fluid for approximate estimation of drug release in human saliva before doing actual volunteer study. [15] This study shows that batch TEG3 having 1:3 (drug: Eudragit EPO) ratio and 2% gelatin shows 0.2±0.033% of the drug release from the tablet in simulated

salivary fluid. The amount released was less than the amount that can induce bitterness. The low amount of drug was released in Simulated Salivary Fluid because Eudragit EPO is insoluble above pH 5. Sensory evaluation of optimized tablet proves better palatability.

Dissolution studies

Dissolution studies of the optimized tablet of batch TEG3 reveled rapid release of drug (t_{90} for batch TEG3 is 150 sec.) as compared to marketed tablet wherein t_{90} around 780 sec. ($p<0.03$) as shown in Table 4.

Table 4: Cumulative % drug released from lyophilized rapid disintegrating tablet at different time interval.

Sr. No.	Time (sec)	Cumulative % drug released			
		TEG1	TEG2	TEG3	TEG4
1	0	0	0	0	0
2	30	22.9±1.02	4.1±1.33	20.8±2.31	4.1±2.34
3	60	25±0.99	10.4±0.34	35.5±3.03	8.3±1.24
4	90	33.4±1.23	16.7±2.33	52.3±2.87	20.9±3.11
5	120	44±2.15	39.7±2.53	73.2±3.42	33.4±0.1
6	150	58.7±1.67	50.2±1.67	85.9±2.1	43.9±0.93
7	180	71.3±3.01	60.7±2.67	100.7±1.44	58.6±1.21
8	210	88.1±1.22	73.4±1.67	100.9±2.9	71.3±2.45
9	240	92.5±3.11	88.1±2.11	99.0±2.31	86±2.56
10	270	96.8±1.34	90.4±2.34	99.2±3.41	98.7±1.54
11	300	99.1±1.09	96.8±3.03	97.3±2.77	98.9±3.01

* Average of three determinations

Stability study

Stability study was performed on optimized formulations TEG3 results for weight gain, drug content, disintegration time and dissolution shows no appreciable change upto 3 months of accelerated stability studies.

Table 5: Parameters of Formulations at Time 0, 1, 2 and 3 Months of Stability Testing under 40°C and 75% RH.

Batch	Parameter	Months			
		0	1	2	3
TEG3	Weight gain (%)	0	0.042	0.046	0.051
	Disint. time (sec)	12.3±1.1	12.2±0.9	12.1±1.1	12.0±1.6
	Drug content (%)	99.3±0.4	99.3±0.6	99.3±0.3	99.1±0.3

* Average of three determination

Table 6: Stability Study of TEG3 Tablet for Dissolution Pattern.

Time	Cumulative % drug release			
(sec)	0 month	1 month	2 month	3 month
00	0	0	0	0
30	20.8±0.1	22.4±0.1	22.5±0.2	23.3±0.102
60	35.5±0.024	33.6±0.01	35.5±0.01	33.3±0.1
90	52.3±0.045	55.5±0.022	56.5±0.012	60.4±0.011
120	73.2±0.023	72.7±0.025	72.8±0.011	75.2±0.02
150	85.9±0.1	88.9±0.03	88.5±0.1	89.2±0.002
180	100.7±0.11	100.5±0.02	100.2±0.1	100.3±0.105
210	100.9±0.01	100.9±0.03	100.4±0.12	100.8±0.104
240	99.0±0.02	99.3±0.03	99.2±0.02	100.2±0.019
270	99.2±0.04	99.3±0.02	99.2±0.1	99.5±0.013
300	97.3±0.03	97.4±0.1	97.2±0.21	98.4±0.023

* Average of three determinations

The results for weight gain, drug content and disintegration time are shown in table 5 and those for dissolution profiles of optimized lyophilized rapid disintegrating tablets are shown in table 6 and figure 4.

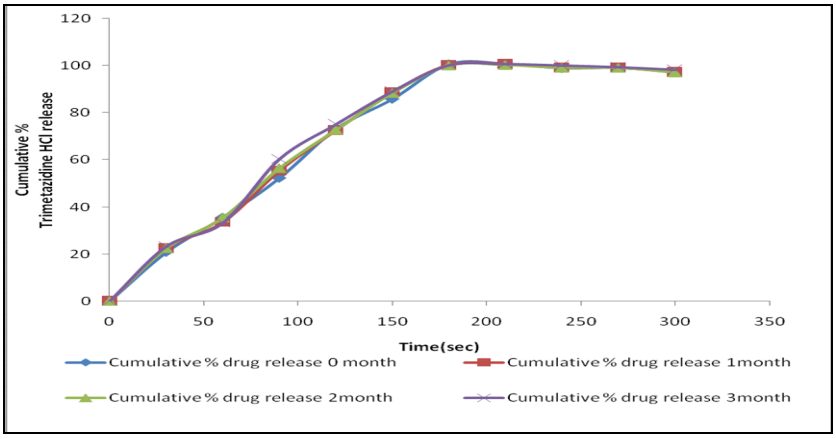

Fig. 4: Stability study of TEG3 tablet for dissolution pattern.

CONCLUSION

From present study it can be concluded that bitter taste of Trimetazidine HCl can be successfully with Eudragit EPO using lyophilization method. Well palatable and patient compliant Rapid Disintegrating Tablet can successfully prepared using lyophilization method. The prepared optimized tablet showed rapid disintegration as well as rapid dissolution as compared to marketed tablet. Thus, the Rapid Disintegrating Tablet of bitter drug having better taste and pleasant mouth feel can be successfully formulated.

REFERENCES

1. Shyamala B, Narmada GY. Rapid dissolving tablets: A novel dosage form. Indian Pharmac, 2002; 13: 9-12.
2. Wadhwani AR, Prabhu NB. Patient compliant dosage form for roxithromycin. Indian J Pharm Sci, 2004; 66: 670-73.
3. Khan S, Kataria P, Yeole P. Taste masking of ondansetron hydrochloride By polymer carrier system and formulation of rapid-disintegrating tablets. AAPS Pharm Sci Tech, 2007;8 : 1-6.
4. Nanda AR, Garg S. An update on Taste masking technologies for oral Pharmaceuticals. Indian J Pharm Sci, 2002;64 : 10-17.
5. McClellan KJ, Plosker GL. Trimetazidine-A review of its use in stable angina pectoris and other coronary conditions. Drugs, 1999; 58: 143-57.
6. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of a Fast-Dissolving Ketoprofen Tablet Using Freeze-Drying in Blisters Technique. Drug Dev Ind Pharm, 2008;5 : 20-6.
7. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed., Mumbai; Varghese Publishing House: 1987.

8. Schiermeier S, Schmidt PC. Fast Dispersible Ibuprofen Tablet. Eur J Pharm Sci, 2002;5: 295-305.
9. Khan SA, Kataria P, Nakhat P. Yeole P,Taste Masking of Ondansetron Hydrochloride by Polymer Carrier System and Formulation of Rapid-Disintegrating Tablets. AAPS Pharm Sci Tech, 2007;8: 34-8
10. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of Salbutamol Sulphate, A Novel Drug Delivery System. Ind Drug, 2004;41: 592-8.
11. Kulkarni GT, Gowthamarajan K, Suresh B. Stablity testing of pharmaceutical products: an overview. Ind J Pharm Edu, 2004; 38:194-203.
12. ICH harmonised tripartite guideline, stability testing of new drug substances and products, Q1A (R2).
13. Lachman L, Lieberman HA, Schwartz JB. Chewable tablets in pharmaceutical dosage form: Tablets. 2nd ed., New York; Marcel Dekker: 1989.
14. Winterborn KI. (1999), US Patent, US 5955488, 1999.
15. Masaki KB, Katsuhiro B. US Patent, US 5466464, 1995.
16. Shoukri RA, Ahmed IS, Shamma RN. *In-vitro* and *in-vivo* evaluation of nimesulide lyophilized orally disintegrating tablets. Eur J Pharm Biopharm, 2009; 18:1-42.

,