INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

DEVELOPMENT AND EVALUATION OF MOUTH-DISSOLVING TABLET OF TASTE-MASKED AMLODIPINE BESYLATE FOR THE TREATMENT OF HYPERTENSION

Meghana S. Kamble*, Krunal K. Vaidya, Pravin P. Aute and Rohini P. Chavan

Department of Pharmaceutics, P. E. S. Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India.

ABSTRACT

The aim of the present study was to develop patient-friendly tablets of antihypertensive amlodipine besylate to increase patient's adherence to antihypertensive therapy. The patient might not strictly follow the dosage regimen and skip doses, reasons being trouble in swallowing tablets, unavailability of water during traveling to take the tablets. Mouth-dissolving tablets (MDT) provide excellent option to increase rate of persistence to therapeutic regimen. These tablets rapidly disintegrate in mouth in less than a minute, so no need to swallow whole tablet and no need of water to take it. In the present study bitterly tasting antihypertensive drug amlodipine besylate was successfully taste-masked by complexing with β – cyclodextrin (β-CD) and formulated as MDT. Six MDT formulations were prepared and evaluated for hardness, friability, in vitro disintegration time, wetting time, drug content and in vitro drug release. Formulation F5 was found to be optimum with 15.3 sec in vitro disintegration time, 2.83 kg/cm^2 hardness, 0.44% friability and 98.09% drug release in 30 minutes.

Keywords: Mouth dissolving, antihypertensive, amlodipine, β-cyclodextrin, taste masking.

INTRODUCTION

Hypertension is becoming an important public health challenge worldwide. Hypertension is one of the main risk factors for cardiovascular diseases, which is one of the leading causes of death in developed countries. The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1.56 billion[1].

The relationship between blood pressure and risk of cardiovascular disease is continuous, consistent and independent of other risks. The higher the blood pressure, the greater is the chance of ischemic heart disease, stroke, heart failure and kidney diseases. Therefore prevention, detection, treatment and control of hypertension should receive high priority[2].

In the treatment of hypertension, the patient's persistence to therapeutic regimen is very important. The patient should follow the regimen sincerely and should not skip the doses. The most common reasons for noncompliance or non-persistence to antihypertensive therapy are dysphagia (difficulty in swallowing seen in nearly 50% of general population) and during travelling due to non-availability of water to take medication[3].

To overcome these problems concept of a patient-friendly tablet i.e. mouth-dissolving tablet (MDT) has emerged. MDTs disintegrate or dissolve in mouth in less than a minute, so there is no need to swallow the tablet or no need of water to take it.

Amlodipine besylate a long-acting calcium channel blocker commonly used in the

treatment of hypertension was selected for present study. As amlodipine besylate bitterly tasting, its taste should be masked before formulating MDT. β-cyclodextrin (β-CD) was selected to mask the bitter taste of amlodipine besylate and taste was masked by complexing drug with β-CD. The taste-masked drug was then formulated as MDT for increasing patients' rate of persistence with the antihypertensive therapy.

MATERIALS

Amlodipine besylate was obtained as a gift sample from Perfect Consultants, Bhosari, Pune. Sodium Starch Glycolate was obtained as a gift sample from Maple Biotech Pvt. Ltd. Bhosari, Pune. Microcrystalline cellulose was obtained as gift sample from Cipla Ltd. Mumbai. β-cyclodextrin was obtained as a gift sample from Cadila Healthcare, Ahmedabad. Lactose Monohydrate and Mannitol were procured from Qualigens Fine Chemicals, Mumbai. Magnesium Stearate and Talc were procured from Loba Chemicals, Mumbai. All other solvents and chemicals used were of analytical grade.

METHODS

Amlodipine besylate β-CD complexation and compatibility testing

The complexation and compatibility between amlodipine besylate and β-CD were studied by Differential Scanning Calorimetry (Mettler) at temperature range of 30^{0}C to 280^{0}C in presence of reference material. Amlodipine besylate, β-CD and drug β-CD complex were subjected to Differential Scanning Calorimetry (DSC) study[4].

Taste masking by complex formation between amlodipine besylate and β-cyclodextrin

For taste masking, amlodipine besylate and β-cyclodextrin were mixed in 1:1 molar ratio and a paste was formed using water. It was dried at room temperature, washed with methanol to remove any free drug and dried[5].

Preparation of MDT of taste-masked amlodipine besylate

The tablets were prepared by wet granulation method using 60% v/v ethanol to form a damp mass which was passed through mesh #18 to obtain granules. The granules were dried at room temperature. Individual doses were weighed and placed in the die cavity (6 mm) and compressed using round flat punch on 8-Station Rotary Tablet Compression Machine (CIP, D8 Lab Press, Ahmadabad)[6]. Table 1 shows composition of MDTs.

EVALUATION

Preparation of standard curve of amlodipine besylate

A 0.1% w/v stock of amlodipine besylate was prepared in methanol. From the stock solution aliquots were withdrawn and diluted suitably to prepare 10, 20, 30, 40 and 50 µg/ml solutions and absorbance was recorded at 238 nm on UV-visible spectrophotometer (Jasco, V-530). Standard curve was plotted. Regression coefficient was determined.

Evaluation of drug and β-CD complex

Particle size distribution study

The particles of the complex were observed under the optical microscope. 100 particles were determined for particle size and their distribution[7].

Drug loading efficiency

Accurately weighed 10 mg of complex were transferred to 50 ml volumetric flask. The volume was made up with methanol. The solution was suitably diluted and absorbance was recorded at 238 nm using UV-visible spectrophotometer (Jasco, V-530)[8].

In vitro evaluation of Taste masking of the drug- β-CD complex:

Accurately weighed quantity of drug β-CD complex equivalent to drug 5 mg was added to 50ml water in a beaker. The release of the drug was determined at time intervals of 15, 30, 45, 60 sec. The samples were filtered, diluted with methanol and absorbance was recorded at 238 nm using UV-visible spectrophotometer (Jasco, V-530)[9].

Pre-compression evaluation
Evaluation of the granules
The granules prepared were evaluated for bulk and tapped densities[10], Carr's compressibility[11] and angle of repose[12].

Post-compression evaluation
Evaluation of MDT
The tablets were evaluated for diameter and thickness [13], hardness [13], friability [13], weight variation[14], drug content, wetting time, in-vitro disintegration time, in-vitro drug release, accelerated stability testing.

Drug content
Three tablets were powdered and weight of powder equivalent to 1 mg of amlodipine besylate was dissolved in sufficient quantity of methanol, shaken and volume was made up to 25 ml using methanol. The solution was filtered and 1 ml of filtrate was diluted suitably with methanol and absorbance was determined at 238 nm using UV-visible spectrophotometer (Jasco, V-530).

Disintegration time
The tablet was placed in a glass petridish of 10 cm diameter containing 20 ml of distilled water. The time taken for total disintegration of the tablet in to particles was noted down. The test was repeated for total of 3 tablets[15].

Wetting time
5 circular tissue papers of 10 cm diameter were placed in the 10 cm diameter glass petridish. 10 ml of distilled water containing water soluble dye (eosin) were added to the petridish. The tablet was placed in the petridish on the tissue papers and the time taken by the dye solution to reach to upper surface of the tablet was noted down. This was repeated for total of 3 tablets[16].

In-vitro drug release
USP Dissolution Apparatus Type -II was used for determination of dissolution of MDT of amlodipine besylate. The speed of the paddles was kept at 50 rpm. The dissolution medium selected was 900ml of 0.1 M HCl. The temperature was maintained at 37± 0.5^0 C. The samples were withdrawn at time intervals of 5, 15, and 30 min and replaced with equal quantity of fresh dissolution medium maintained at same temperature. The samples were filtered, 1 ml was suitably diluted with methanol and absorbance was recorded at 238 nm using UV-visible spectrophotometer (Jasco, V-530)[17].

Accelerated stability testing
The promising formulation F5 was subjected to short term stability testing by storing the tablets at 40± 2^{0}C and 75± 5% RH over a 2-month period. The formulation was evaluated for any physical changes, changes in drug content and drug release[18].

RESULTS AND DISCUSSION
Amlodipine besylate bitterly tasting drug so it needs taste masking before formulating into MDT. For this purpose β-CD was selected for taste masking and the complex was prepared by kneading method. The drug, β-CD and their complex were subjected to DSC studies; the spectra are shown in fig 1. Drug alone shows sharp endothermic peak near 205^{0}C. β-CD alone shows endothermic peak near 120^{0}C. In the spectra of the complex both these peaks are widened and slightly shifted indicating complex formation, drug in amorphous form and compatibility with each other.
The prepared drug -β-CD complex was further evaluated for particle size analysis, drug loading efficiency and in vitro evaluation of taste masking. About 62%of the particles were found to be in size range of 10-40µm. The results of the particle size distribution are shown in table 2. The standard curve of amlodipine besylate was prepared and is shown in fig.2. The drug loading efficiency was found to be 35.08%. The in vitro evaluation of taste masking revealed that in one minute period only a negligible amount of drug (about 12.5%) was released. This indicates that the bitter taste would not be experienced when tablet is in the oral cavity.
The MDTs of taste-masked drug-β-CD complex were prepared by using sodium starch glycolate (SSG), crospovidone, microcrystalline cellulose (MCC) as superdisintegrants by wet granulation.

Lactose was added to increase wettability of tablet which was thought to aid disintegration. Mannitol was added to give pleasant cooling effect when tablet is in oral cavity and it might show additional taste masking effect. The concentration of the tablet ingredients was varied and six formulations were prepared. The MDTs were prepared by using 4.98-5.24% w/w of SSG, 31.44 - 36.72 % w/w of lactose, 26.95 – 31.47% w/w of mannitol, 4.98-18.13% w/w of crospovidone. The formulation were evaluated for pre-compression parameters (results shown in table 3) and post compression parameters (results shown in table 4).

The hardness of all the formulations was found to be above 2.5kg/cm^2. Drug content and weight variation were found to be within acceptable limits. The friability of all the formulations was found to be well below 1% indicating good mechanical strength to packaging operations and transportation.

The drug content of all the formulation was found to be between 97.76 - 102.2% and was within acceptable limits. Wetting time of the MDT formulation was found to be between 18-31s. The in-vitro disintegration time was in the desirable range of 15-22 s for F1, F2, F5and F6, while for F3and F4 it was 95 and 41 s respectively. Aim of our project was to develop a MDT formulation which will give disintegration time less than 30 s. Considering all these parameters F5 was found to be optimum with in vitro disintegration time 15.33 s and wetting time 27 s, friability 0.44% and drug release 98.09 % within 30 minutes. Table 5 and fig 3 show the results of in vitro drug release. In fig 4, a and b show disintegration time and wetting time studies of taste-masked MDT, respectively. The optimum formulation F5 was subjected to accelerated stability testing for a period of two months and did not show any significant changes in drug content and drug release indicating formulation was stable.

CONCLUSION

The use of superdisintegrants crospovidone and SSG in preparation of MDT by wet granulation process is highly effective and industrially acceptable. The fast disintegration of tablets might have effect on enhancing dissolution characteristic of drug. In our formulation the use of sweetening agent is avoided, also flavoring agent is not added, as we thought that mannitol addition would be sufficient to give pleasant mouth feel. However, flavor and sweetening agent may be added but compatibility testing must be done. The use of β-CD as taste masking agent also might be increasing dissolution rate of poorly water soluble drug amlodipine besylate. The prepared MDT is expected to disintegrate rapidly in mouth and release drug fast when administered in vivo. Taste masking with β-CD would provide best option for preparing MDT of bitter tasting poorly water soluble drugs.

ACKNOWLEDGEMENT

The authors are thankful to BCUD, University of Pune for providing grant for this project. The authors are thankful to Dr. G. R. Ekbote, Chairman, Business Council, Progressive Education Society, Pune and Dr. P. D. Chaudhari, Principal, PES's Modern College of Pharmacy, Nigdi and Dean, Faculty of Pharmaceutical Sciences, University of Pune, for providing excellent research facilities to carry out this project work. The authors owe their thanks to Perfect Consultants (Bhosari), Maple Biotech (Bhosari), Cadila Healthcare (Ahmedabad), Cipla Ltd. (Mumbai) for their kind donations of drug and excipients.

Table 1: Composition of mouth-dissolving tablets of amlodipine besylate

Ingredients	Formulations					
	F1 (mg /tab)	F2 (mg /tab)	F3 (mg /tab)	F4 (mg /tab)	F5 (mg /tab)	F6 (mg /tab)
Drug- β-CD complex equivalent to drug	5	5	5	5	5	5
Sodium Starch Glycolate	--	5	5	--	--	--
Lactose	35	35	35	35	35	35
Mannitol	30	30	30	30	30	30
Crospovidone	5	5	--	10	20	20
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Microcrystalline cellulose	--	--	--	--	5	--
Total	95.3	100.3	95.3	100.3	111.3	110.3

Table 2: Particle size analysis of drug-βCD complex

Particle size range (in µm)	(%) of Particles
10 – 20	36
20 – 40	26
40 – 60	12
60 – 80	03
80 – 100	14
100 – 120	06
120 – 140	03

Table 3: Pre-Compression evaluation

Parameters	F1	F2	F3	F4	F5	F6
Bulk density (g/cc) (±SD)(n=3)	0.292 ±0.002	0.344 ±0.006	0.346 ±0.003	0.384 ±0.005	0.348 ±0.18	0.335 ±0.06
Tapped density (g/cc) (±SD)(n=3)	0.424 ±0.003	0.423 ±0.006	0.465 ±0.006	0.426 ±0.004	0.435 ±0.063	0.413 ±0.004
Angle of repose (^{0})	21^0 7'	25^0 17'	26^0 10'	27^0 37'	26^0 56'	28^0 48'
Carr's index	31.13	18.67	25.59	9.85	20	18.88

Table 4: Post-Compression Evaluation

Parameters	F1	F2	F3	F4	F5	F6
Diameter* (mm)	6.01 ±0.006	6.01 ±0.006	6.0 ±0.006	6.0 ±0.006	6.02 ±0.006	6.0 ±0.003
Thickness* (mm)	2.53 ±0.01	2.61 ±0.05	2.52 ±0.01	2.7 ±0.02	3.19 ±0.01	3.13 ±0.01
Hardness* (kg/cm^2)	2.91 ±0.028	3.0 ±0.0	2.66 ±0.43	2.5 ±0.0	2.83 ±0.22	3.0 ±0.0
Weight variation	Within acceptable limits					
In vitro Disintegration time*	20.33 ±1.11	22.66 ±1.78	95.33 ±3.55	41 ±2.66	15.33 ±0.89	20.0 ±1.33
Wetting time* (seconds)	20 ±1.33	22 ±1.33	22.66 ±1.55	18.33 ±1.11	27 ±0.66	30.66 ±1.11
Friability (%)*	0.7 ±0.02	0.64 ±0.03	0.53 ±0.01	0.58 ±0.01	0.44 ±0.03	0.33 ±0.02
Drug content*	99.9 %	97.76 %	97.76 %	99.99 %	102.2 %	99.9 %

* Values indicate average ± S.D. (n = 3)

Table 5: In vitro drug release of MDT of taste-masked amlodipine besylate

Time (min)	In-vitro drug release (%)					
	F1	F2	F3	F4	F5	F6
5	80.5	61.9	74.9	76.7	67.4	54.4
15	86.5	67.8	82.7	86.5	82.7	62.2
30	92.5	79.3	92.5	96.2	98.08	69.9

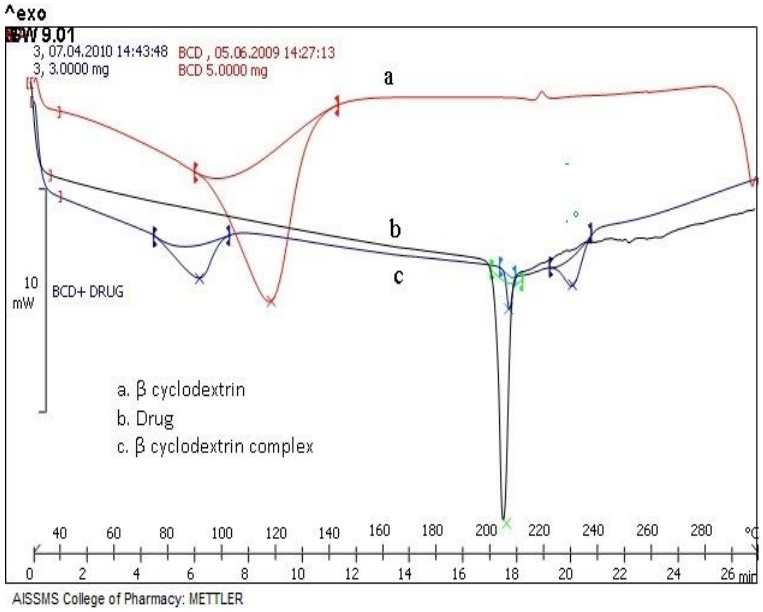

Fig. 1: Drug –βCD compatibility and complexation study

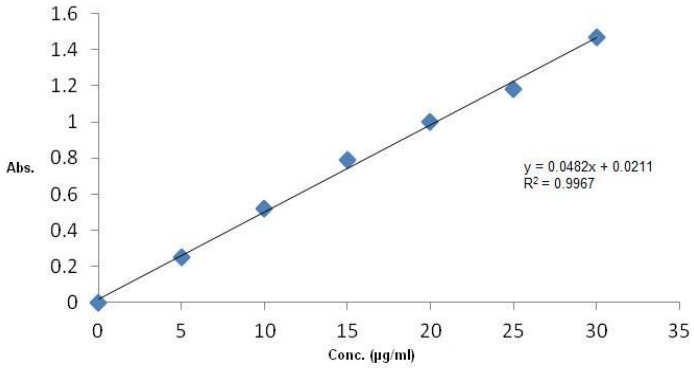

Fig. 2: Standard curve of amlodipine besylate

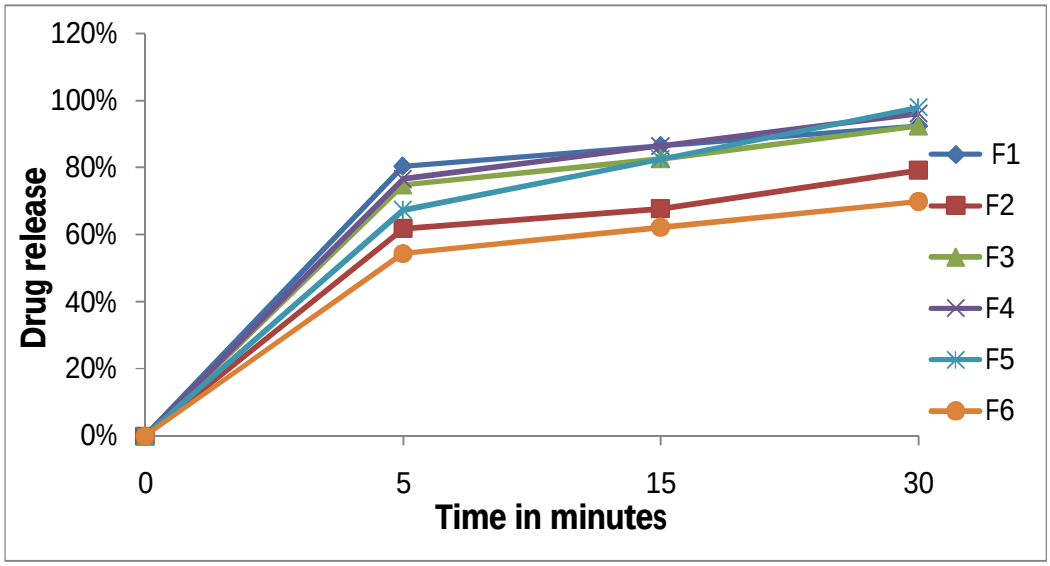

Fig. 3: *In-vitro* drug release profile of MDT of amlodipine besylate

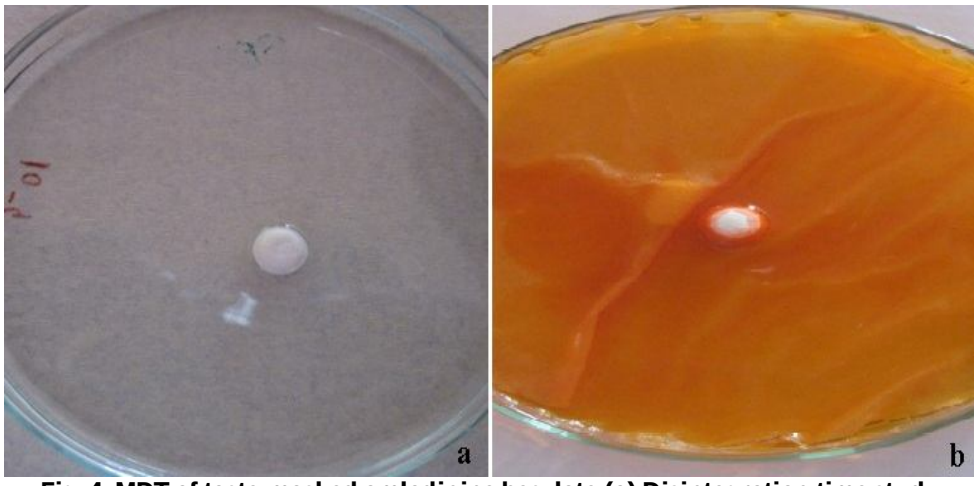

Fig. 4: MDT of taste-masked amlodipine besylate (a) Disintegration time study (b) Wetting time study

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK and Jiang HE. Global burden of hypertension: analysis of worldwide data. The Lancet. 2005;365(9455):217–223.
2. Bosu WK. Epidemic of hypertension in Ghana: a systematic review. BMC Public Health. 2010;10:418.
3. Ambaw AD, Alemie GA, Solomon M, Yohannes W and Mengesha ZB. Adherence to antihypertensive treatment and associated factors among patients on follow up at University of Gondar Hospital, Northwest Ethiopia. BMC Public Health. 2012;12:282.
4. Malik K, Arora G and Singh I. Taste Masked Microspheres of Ofloxacin: Formulation and Evaluation of Orodispersible Tablets. Scientia Pharmaceutica. 2011;79(3):653-672.
5. Patel H. Preparation and characterization of etoricoxib β cyclodextrin complexes prepared by

the kneading method. Acta Pharma. 2007;57:351-359.
6. Suresh S, Pandit V and Joshi HP. Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Indian Journal of Pharmaceutical Sciences. 2007; 69(3):467-469.
7. Herman B and Lemasters JJ. Optical Microscopy: Emerging Methods and Applications. Academic Press, New York. 1993;441.
8. Madgulakr AR, Bhalekar MR, and Padalkar RR. Formulation Design and Optimization of Novel Taste Masked Mouth-Dissolving Tablets of Tramadol Having Adequate Mechanical Strength. AAPS Pharm Sci Tech. 2009;10(2):574-581.
9. SrinivasaRao Y, Doddayya H, Patil SS and Reddy VD. Design and evaluation of fast dissolving tablets of taste masked ondansetron hydrochloride. International Journal of Pharma Research and Development. 2011;3(2):008.
10. Mohsin AA, Nimbalakar NE, Sanaullah S and Aejaz A. Formulation and evalution of mouth dissolving tablets ofamitriptyline hydrochloride by direct compression technique. International Journal of Pharmacy and Pharmaceutical Sciences. 2010;2(1):204-210.
11. Chander H, Kumar S and Bhatt B. Formulation and evaluation of fast dissolving tablet of ramipril. Der Pharmacia Sinica. 2011;2(6):163-170.
12. Nigarish M and Sethi VA. Formultaion & evaluation of fast dissolving tablet of atenolol using superdisintegrant crosspovidone & sweetening agent sucralose. Asian Journal of Biochemical and Pharmaceutical Research. 2012;2(3):135-142.
13. Bhanja S, Hardel DK and Muvvala S. Formulation and evaluation of mouth dissolving tablets of losartanpotassium. International Journal of Current Pharmaceutical Research. 2012;4(4):15-23.
14. Shirsand SB, Suresh S, Jodhana LS, and Swamy PV. Formulation design and optimization of fast disintegrating lorazepam tablets by effervescent method. Indian Journal of Pharmaceutical Sciences. 2010;72(4):431–436.
15. Mangal M, Thakral S, Goswami M and Thakur N. Comparison study between various reported disintegrating methods for fast dissolving tablets. African Journal of Basic & Applied Sciences. 2012;4(4):106-109.
16. Ibrahim HK, Doa A and Setouhy EL. Valsartan orodispersible tablets: formulation, *Invitro*/*Invivo* Characterization. AAPS Pharm SciTech. 2010;11(1):189–196.
17. Tiwari V, Kinikar DJ, Pillai K and Gokulan PD. Preparation and Evaluation of fast dissolving tablets of celecoxib. Journal of Current Pharmaceutical Research. 2010;04:4-10.
18. Patidar K, Soni M, Saini V and Kshirsagar M. Mouth dissolving tablet: approaches, technology involved, marketed formulation & recent trend. International Journal of Pharmaceutical Science. 2012;1:1-10.