ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

Formulation and Evaluation of Solid Dispersion Technique of Poorly Water Soluble Drug Atenolol

Patil J.S[1], Prof. Patil S.T[2], Prof. Rane B.R[3], Prof. Ahirrao R.A[4], Prof. Pawar S.P[5]
PG Scholar, Dept. of QA, P.S.G.V.P.M's College of Pharmacy, Shahada, Maharashtra,India[1]
Professor, P.S.G.V.P.M's College of Pharmacy, Shahada, Maharashtra,India[2,3,4]
Principal, P.S.G.V.P.M's College of Pharmacy, Shahada, Maharashtra,India[5]

ABSTRACT- The objective of present study was to improve the aqueous solubility and dissolution rate of poorly water-soluble drug Atenolol by solid dispersion technique. The method of preparation used was Hot Melt Method and Kneading Method using a carrier polyethylene glycol 6000 (PEG 6000), and hydroxyl propyl methyl cellulose (HPMC E4). The study was further aimed to characterize prepared solid dispersions in the solid state by Fourier Transform Infrared Spectroscopy (FTIR). Dissolution studies were carried out to find out percentage released content of drug as a function of time; UV-visible spectroscopy method was used to find out drug contents in all the samples.

KEYWORDS- Solid dispersion, Atenolol, PEG 6000, HPMC (E4), Dissolution, Solubility.

I. INTRODUCTION

The major problem in oral administration of bitter drugs are unacceptability by the patients mainly pediatric and geriatrics [1] and this can be overcome by masking the bitterness of drug either by decreasing its oral solubility on ingestion or decreasing interaction of drug particles to taste buds [2].There are various techniques available which are used for masking the taste of bitter drugs including coating, solid dispersion, ion exchange resin, entrapment method and masking of taste buds etc. Coating avoids the contact of drug particles with taste buds and taste is not apparent to the users [3]. Dispersion of one or more active ingredients in an inert carrier or matrix in solid state is mainly utilizes in solid dispersion form asking the bitter taste of drug [4] which can be done either Melting method, Solvent method or melting solvent method [5]. Atenolol belongs to a group of beta blocker (selective β1antagonist) used as antihypertensive, antianginal and antiarrythmic [6]. Due to its bitter taste, slightly solubility in water, low bioavailability (50%) makes it suitable candidate for masking the bitterness and increase its solubility. atenolol is found to have adverse side effects resulting from accumulation of drug and erratic absorption patterns from the GIT. Its low solubility in water, low bioavailability (50%), variation in release patterns and use in cardiac diseases make it suitable candidates for a suitable formulation strategy to increase of its release from solid dosage forms. To overcome this problem, one technique could be enhancement of solubility and dissolution rate of Atenolol by preparing its solid dispersion by using carrier PEG 6000 and HPMC (E4) [7].

II. LITERATURE REVIEW

Ms. Trusha Y. Puttewar *et al*., (2015), prepared a solid dispersion of Aspirin using fusion (melt) method and PEG 6000 were used as carrier [8].

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

Anu Mahajan *et al.*, (2013), prepared was to improve the aqueous solubility and dissolution rate of poorly water soluble drug Atenolol by solid dispersion technique were prepare on solvent evaporation method using a hydrophilic carrier PEG 6000 [9].

Harish Gopinath *et al.*, (2012), enhanced the solubility and dissolution properties of SDs of Atenolol, prepared with PEG 6000, PEG 4000 and PVP as carriers were prepared solvent evaporation method [10].

Nidhi Jain *et al.*, (2012), the formulation of gastroretentive floating tablet of cefpodoxime proxetilc (CP) using SDs method increased dissolution rate and solubility of CP by preparing it's SDs with skimmed milk powder as carrier using solvent dispersion method [11].

Mukhija Umesh *et al.*, (2012), prepared to enhanced the solubility of meloxicam by various SDs using poloxamer 188 and to investigated the effect of different technique of preparation of solid dispersion on in-vitro dissolution of meloxicam [12].

III. MATERIALS AND METHODS

Materials

Atenolol was a gift sample from a Indo Gluf Ltd. Mumbai, India, PEG 6000 and HPMC (E4) from a FDC (Goa). All other reagents and solvents were of AR grade

Method

HOT MELT METHOD

In the Hot Melt Method, carriers are melted at a particular temperature in a china dish and the drug is then dispersed into the molten mixture with a constant stirring. The molten mixture is then poured and cooled immediately to obtain the formed dispersion [13-14].

KNEADING METHOD

A mixture of Drug and Polymers (1:1 to 1:4 by weight) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried in hot air oven at 50 ^{0}C for 24 hours. Dried powder was passed through sieve no. 40 and stored in a desicators until further evaluation [15-16].

Physical mixture-Physical mixtures (PM) were obtained by pulverizing in a glass mortar and carefully mixing accurately weighed (1:1 to 1:4 by weight) amounts of atenolol with Polyethylene glycol 6000 and Hydroxypropyl methyl cellulose (E4) [17].

Estimation of Atenolol-Atenolol was estimated at 272 nm using double bean UV-Visible spectrophotometer (Systronics 2201). Standard calibration curve of Atenolol was plotted in pH 7.4 phosphate buffer in concentration range 2-10 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R) - 0.994. The graph obeyed Beer-Lambert's law in the concentration range [18].

Phase Solubility Studies-The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of atenolol was added to the screw capped vials containing 10 ml of aqueous carrier solution (PEG 6000 and HPMC (E4) at various concentrations and placed on a roatatory shaker and agitated at room temperature

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No.41 filter paper and after appropriate dilution, solutions were analyzed at 272 nm by using UV- Visible spectrophotometry [19].

Analysis of Drug Content in Solid dispersions- The content of Atenolol in each physical mixture and solid dispersions was determined using by UV-visible spectroscopy in each medium. Accurately weighed solid dispersion or physical mixture equivalent to 10 mg of atenolol was transferred to 100 ml volumetric flask and diluted with distilled water and sonicated for 30 min. for complete solubilization of drug. Solution was filtered with Whatman filter paper no. 41 and absorbance was taken at 272 nm. Concentration of atenolol was determined using calibration curve of atenolol in pH 7.4 buffer and distilled water respectively [20].

Saturation Solubility Studies-The saturation solubility study was carried out to determine increase in the solubility of pure atenolol as compared with the physical mixture (PM) and solid dispersions (SDs). Weighed amount of solid dispersions were added to the glass vial containing 10 ml of solution. The sealed flasks were shaken for 24 hours at room temperature followed by equilibrium for three days. Then the aliquots were withdrawn and filtered through Whatman filter paper No.41. The concentration of atenolol was determined by UV-visible spectrophotometer at 272 nm. The saturation solubiliies of drug, physical mixtures and solid dispersions were in 7.4 buffer solution [21-22].

Characterization of solid dispersion

1) Fourier transforms infrared spectroscopy

Fourier transforms infrared spectroscopy (FTIR) spectra of the atenolol, PEG 6000 and HPMC (E4) their physical mixtures and solid dispersion was recorded using a Fourier Transform Infrared spectrophotometer (Schimadzu, Japan). Samples were prepared using KBr (Spectroscopic grade) disks by means of hydraulic pellet press at a pressure of 5 tons. The samples were scanned from 4000 to 400 cm^{-1} [23].

***In-vitro* drug release**

The *in-vitro* drug release of atenolol, its physical mixture and solid dispersions were studied in pH 7.4 phosphate buffer upto 2 hrs using USP I apparatus (Electrolab 8 station) at the speed of 100 rpm in 900 ml medium at 37±0.5oC. The samples of drug, physical mixtures and solid dispersions were taken in muslin cloth and tied to the backet. Aliquots of 10 ml, was withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The 1 ml of solution was taken and diluted upto 10 ml with phosphate buffer (pH 7.4) and filtered using Whatman filter paper No.41. The filtered samples were analyzed UV-visible spectrophotometric ally at 272 nm [5- 24].

IV. RESULT AND DISCUSSION

Phase solubility studies

Solubility of atenolol in distilled water at room temperature was 10. 11 µg/ml at the highest polymer concentration (4% w/v), the solubility increased approximately 6.7 fold and 5.7 fold for HPMC (E4) and PEG 6000 at room temperature respectively. The influenced of HPMC (E4) and PEG 6000 on solubility of atenolol is as shown in Figure No.1. The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

polymer solution. Both the type show AL type of plot i.e. the solubility of atenolol increased with increasing carrier concentration.

Drug content

The percentage drug content of physical mixture and solid dispersions prepared with HPMC (E4) and PEG 6000 are shown in Table No.1

Table No. 1: Percentage Drug Content of Physical Mixtures and Solid Dispersions

Method	Ratio	Percentage Drug Content in pH 7.4 Phosphate Buffer	
		HPMC (E4)	PEG (6000)
Physical Mixture	1:1 1.2 1:3 1:4	92.54 ±0.08 93.21± 0.42 94.5± 0.43 95.28 0.43	92.55 ±0.76 93.43±0.56 93.34 ±2.06 93.64 ±0.2
Kneading Method	1:1 1:2 1:3 1:4	97.16± 1.00 100.8± 0.35 99.59 ±0.57 99.51 ±1.26	98.79 ±1.11 100.48 ±1.02 98.73 ±2.73 99.51 ±1.26

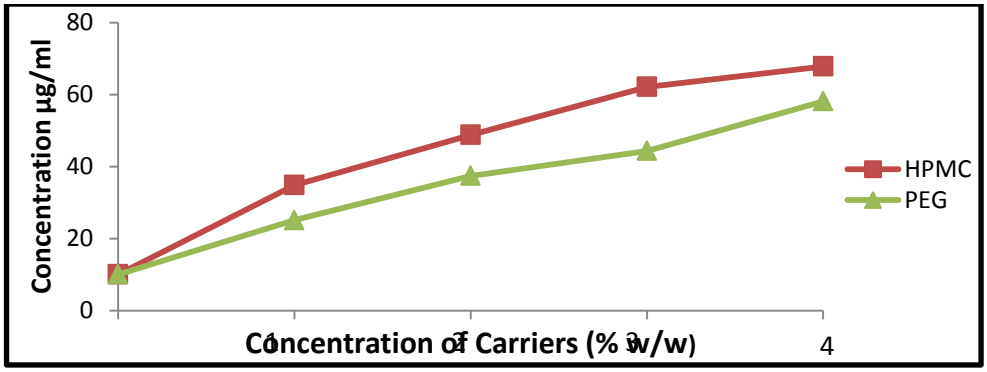

Fig.1 Results of Concentration of Carriers on Solubility of Atenolol

Saturation Solubility Studies-In order to study the saturation solubility of all solid dispersions prepared by HPMC (E4) and PEG 6000 are given in Figure No. 2 and Figure No. 3 respectively. The solubility study will be carried out in pH 7.4.

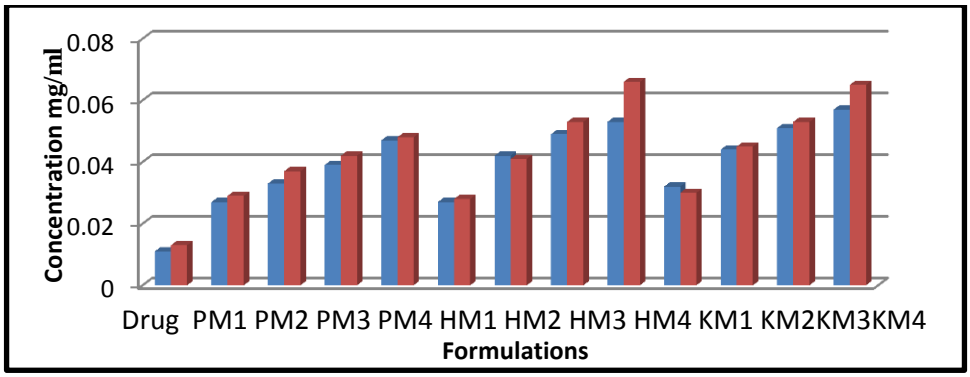

Fig. 2 Results of Solubility of Atenolol, PMs and SDs with HPMC (E4)

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

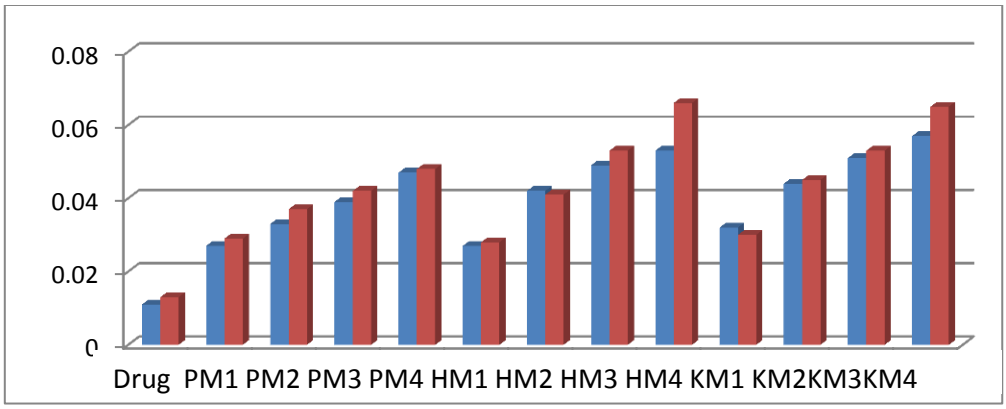

Fig.3 Results of Solubility of Atenolol, PMs and SDs with PEG 6000

Characterization of solid dispersion

1) Fourier transforms infra red spectroscopy

FTIR studies carried out to detect the possible interactions between atenolol, PEG 6000 and HPMC (E4) in solid dispersion. The characteristics peak of Atenolol, HPMC, PEG 6000, their physical mixture and solid dispersion are shown in Figure No.4,5,6,7,8 and 9. Comparing the spectra of physical mixture and solid dispersion prepared by Hot melt and Kneading method revealed that there were no differences in the position of absorption bands, hence providing no evidence for the absence of hydrogen bonding interactions in the solid state between atenolol, HPMC (E4) and PEG 6000.

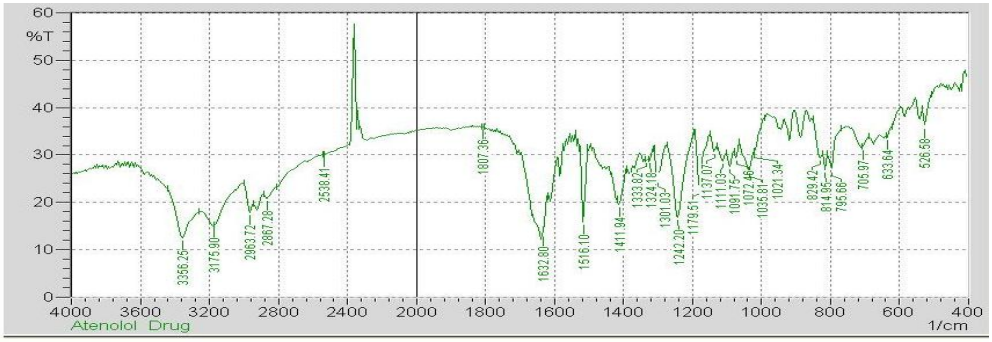

Fig. 4 FTIR Spectrum of Atenolol

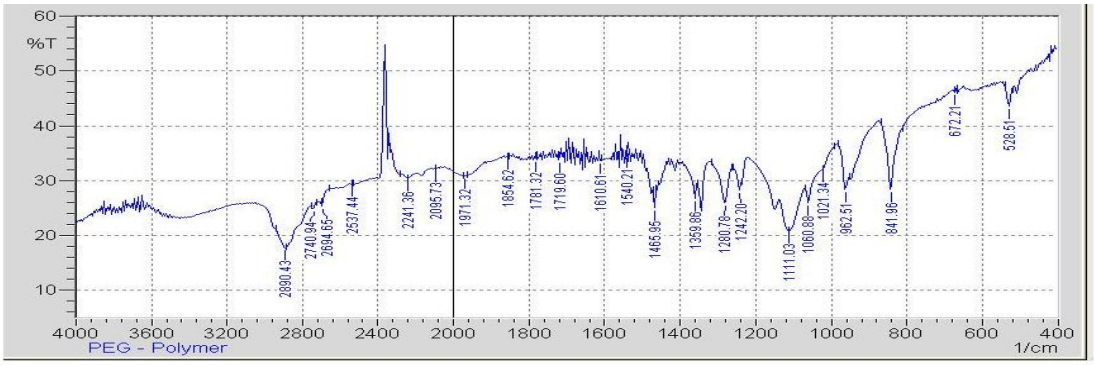

Fig. 5 FTIR Spectrum of PEG 6000

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

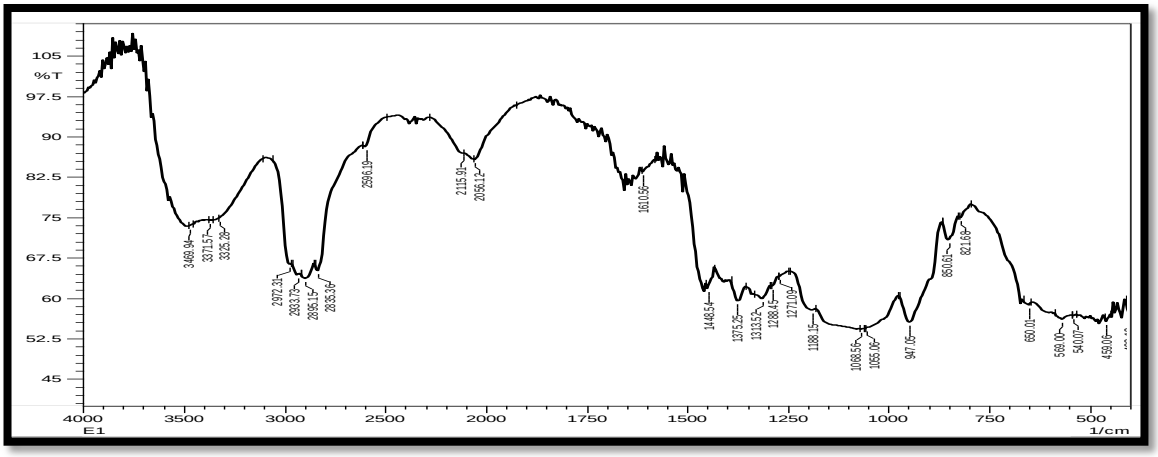

Fig.6 FTIR Spectrum of HPMC (E4)

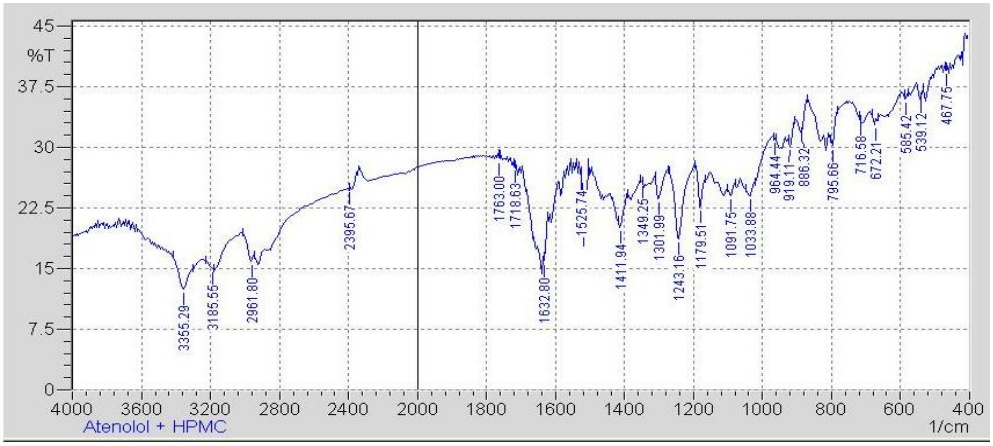

Fig. 7 FTIR Spectrum of Physical Mixture of Atenolol with HPMC (E4)

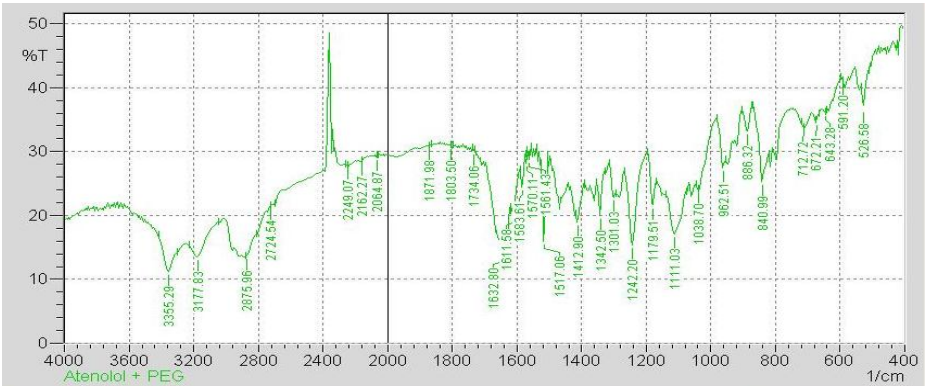

Fig. 8 FTIR Spectrum of Atenolol with PEG 6000

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

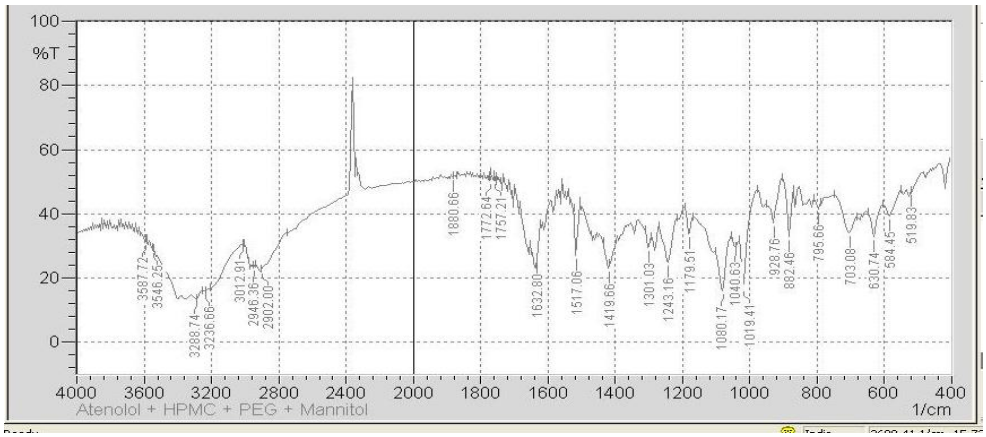

Fig. 9 FTIR Spectrum of Kneading Method of Atenolol with HPMC (E4) and PEG 6000

In-vitro drug release

Atenolol release from physical mixtures and solid dispersions alone were studied in pH 7.4 phosphate buffer over the period of 2 hrs. The average percentage release of pure drug was 63.48% and in solid dispersion prepared with HPMC (E4) and those prepared with PEG 6000 were shown in Figure No. 10 and Figure No. 11 respectively. The percentage drug release increase with increased in the amount of polymer. The best results were among solid dispersion were obtained with HPMC (E4) at 1:4 i.e. 101.22 % in 70 min. as compared to those prepared to PEG 6000 (1:4) i.e. 91.38 % in 70 min and this is due to higher solubility of HPMC (E4) in dissolution medium as compared to PEG 6000.

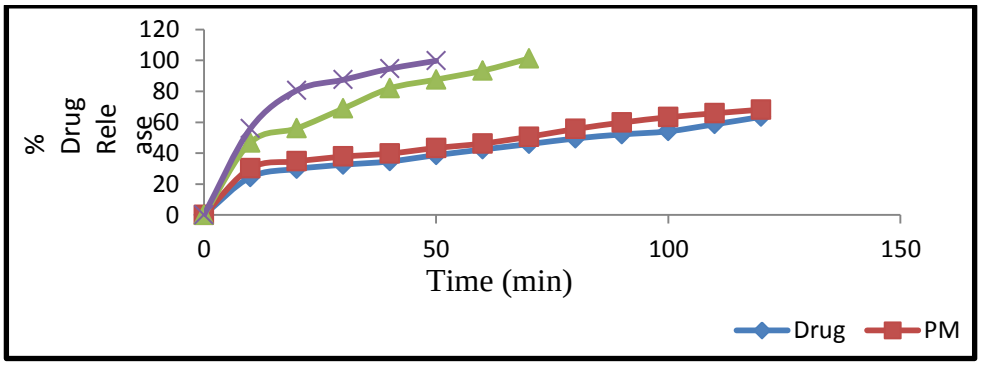

Fig.10 *In- vitro* Dissolution Profile of Atenolol, PM, HM and KM with HPMC (E4) (1:4) in pH 7.4

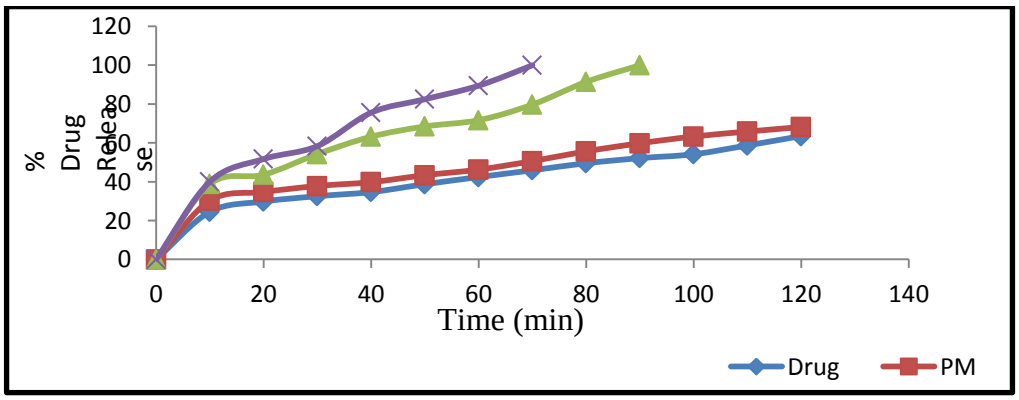

Fig.11 *In-vitro* Dissolution Profile of Atenolol, PM, HM and KM with PEG 6000 (1:4) in pH 7.4

V. CONCLUSION

From the results, it was observed that the solubility of Atenolol in presence of HPMC (E4) and PEG 6000 classified as AL type. The study shows that the dissolution rate of atenolol can be enhanced to a great extent by solid dispersion technique using Hot melt method and Kneading method due to wetting and solubilization phenomenon. The FTIR spectrum of pure drug, PEG 6000, HPMC (E4) and that of solid dispersion shows that there is no chemical interaction between drug and polymers. The solid dispersion prepared by HPMC (E4) shows higher dissolution rate as compared to PEG 6000. The higher drug release rate was found in 1:4 %w/w Atenolol: HPMC (E4) i.e. 101.22% in 70 min as compared to pure drug.

ACKNOWLEDGMENT

The author would like to express sincere thanks to Dr. S. P. Pawar, Principal P.S.G.V.P.M's, College of Pharmacy, Shahada for providing the facilities to carry out this research work. The author is also thankful to Dr. S. T .Patil, Department of Quality Assurance, P.S.G.V.P.M's, College of Pharmacy, Shahada, Indo Gluf Ltd. Mumbai, India for providing Atenolol as gift sample.

REFERENCE

[1] **Sohi H, Sultana Y, Khar KR. Taste Masking Technologies in oral pharmaceuticals: recent development and approaches. Drug Dev Ind Pharma. 2004 May; 30 (5): 429-48.**

[2] **Vijay D. Wagh. Taste masking methods and techniques in oral pharmaceuticals: Current Perspectives. J Pharm Res. 2009; 2(6): 1049-54.**

[3] **Pokharkar BV, Kshirsagar JS, Fatima L. Taste Masking of Pharmaceuticals Pharmainfo.net. 2005; 3(2): 1-14.**

[4] **Chiou LW, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971; 60(9):1281-1302.**

[5] **Craig MQD. The mechanism of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002; 231: 131-44.**

[6] **. Tripathi KD. Essential of Medical Pharmacology. 5th edn. Jaypee Brothers Medical Publishers Ltd., New Delhi 2003;129-130.**

[7] **Caplar V, Mihun MZ, Hofman H, Kuftinec J, Kajfez F. Atenolol. In: Klaus Florey (Ed.). Analytical Profiles of drug substances Acedmic press New York 1984; 1-25.**

[8] **Puttewar TY, Chaudhari FM, Patil Dr. RY. Solubility enhancement of Aspirin by solid dispersion method. Int J Pharm and Pharm Res. Human 2015; 5(1): 208-218**

[9] **Mahajan A, Singh S, Kuar S, Aggarwal A. Studies on solubility enhancement and in-vitro dissolution profile of poorly water soluble drug Atenolol using Solid dispersion technique. Int J Res Pharm Sci 2013; 4(3): 344-349**

[10] **Gopinath H, Suresh M, Bhowmik , Duraival. Studies on the enhancement of dissolution rate of Atenolol by solid dispersion technique. J Chem. and Pharm Sci 2012; 5(4): 185-188**

[11] **Jain N, Sharma N, Sudhaker CK, Jain S.Formulation and evaluation on of Gastro retentive floating tablets containg Cefpodoxime Proxetil Solid dispersions. Int. J current Pharm Res 2012; 4(4): 82-87**

[12] **Mukhija U, Soni N, Chawla A, Bhatt D.C. Physical properties and dissolution behavior of Meloxicam/ Poloxamer Solid dispersion prepared by Hot melt method and Microwave assisted method. Int J Res Pharm Sci 2012; 2(2): 64-74**

[13] **Ansari MT, Sunderland VB. Solid dispersions of Dihydroartemisinin in Polyvinylpyrrolidone. Arch Pharm Res. 2008; 31(3):390-8.**

[14] **Gohel MC, Patel LD. Improvement of Nimesulide dissolution from solid dispersions containing Croscarmellose sodium and Aerosil 200. Acta Pharm 2002; 52:227–41.**

[15] **Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS PharmSciTech 2006; 7 (3):E1-E6.**

[16] **Patel M, Tekade A, Gattani S, Surana S. Solubility enhancement of Lovastatin by modified Locust bean gum using solid dispersion techniques. AAPS PharmSciTech 2008; 9 (4):1262-69.**

[17] **Modi, A., Tayade, P., *AAPS PharmSciTech.* 2006, *7 (3)*, E1-E6.**

[18] **Kumar, N., Jain, A. K., Singh, C., Kumar, R., *Asian J Pharm.* 2008, 154-158.**

[19] **Indian Pharmacopoeia-1996, Government of India Ministry of Health and Family Welfare, volume II, Published by The Controller of Publications, Delhi, A_{80}-A_{84}.**

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

[20] Yadav AV, Yadav VB. Improvement of physicochemical properties of Mesalamine with hydrophilic carriers by solid dispersion (kneading) method. Research J Pharm and Tech 2008; 1(4):422-25.

[21] Sammour OA, Hammad MA, Megrab NA, and Zidan AS. Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion. AAPS PharmSciTech 2006; 7 (2): E1-E9.

[22] Murali GV, Mohan B, Kumar NR. In Vivo Evaluation of Modified Gum Karaya as a carrier for im-proving the oral bioavailability of a poorly water-soluble drug, Nimodipine. AAPS PharmSciTech. 2002; 3 (2):1-9.

[23] Chaulang, G., Patel, P., Hardikar, S., Kelkar, M., Bhosale, A., Bhise, S., *Trop J Pharm Res*. 2009, *8 (1)*, 43-51.

[24] Borgmann, S.H.M., Parcianello, L., Marcela, Z.A., Bajerski, L., Cardoso, S.G., *Sci Pharm*. 2008, 76, 541–554.