ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 7, Issue 3, 2014

ISSN - 0974-2441

Original Article

FORMULATION AND EVALUATION OF CONTROLLED RELEASE OSMOTIC TABLET OF METOPROLOL SUCCINATE

FALGUNI SHARMA[1*], HITESH JAIN[1], VIRAL KANZARIYA[1], UMESH UPADHYAY[1]

[1]Sigma Institute of Pharmacy, Vadodara-390019
Email: falguni.sharma@chemist.com;

Received: 10 May 2014, Revised and Accepted: 5 June 2014

ABSTRACT

Objective: Metoprolol Succinate has a short elimination half- life (3-7 hours) and rapidly absorbed in GIT If it is formulated by conventional tablets requires multiple daily administration with resulting inconvenience to the hypertensive patient and the possibility of reduced compliance with prescribed therapy.

Methods: Core tablets were prepared by direct compression technique using fructose and KCl as osmogens and Avicel PH101 as filler. The core tablets were coated by spray gun in coating pan and used a coating agent cellulose acetate (2%w/v) with PEG 400 and PEG 6000 as water soluble pore former and dibutyl-pthalate as plasticizer. The optimized formulation was evaluated for Compatibility Study by FTIR, *InVitro* drug release study by USP-II dissolution apparatus and, accelerated stability study.

Results: Optimized batch FaC3 was formulated using ratio 3:2 (Fructose : KCl) of osmogent mixture, (20% w/w) of pore former (PEG 6000) and 4% weight gain It gave about 97.59 % drug release for 12 hours. The highest r^2 value (0.979) through zero order drug release and n≈0.982 indicates case-II transport or typical zero-order. Optimized formulation had no significant effect on pH, agitational intensity and found to be compatible with the excipients and stable. Before contact with the dissolution medium, SEM images revealed that no pores were observed before dissolution and after dissolution had shown the porous nature of the membrane.

Conclusion: The present study confirmed that the drug release inversely proportional to membrane weight gain and release increases with mixture of osmogens and system provides a controlled release.

Keywords: Semi Permeable Membrane, Antihypertensive, Osmotic, Controlled, PEG 6000, Scanning Electron Microscope.

INTRODUCTION

Oral controlled release systems continue to be the most popular amongst all the drug delivery systems because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices over the past 2 decades. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, gastric pH, motility, presence or absence of food and hydrodynamic condition. They typically give a zero order release profile after an initial lag. Deliveries may be delayed or pulsed if desired Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. This route offers the advantage of reduced dose, targeting of site and avoiding GI stability, hepatic by-pass of drug molecule. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane [1-5]. Metoprolol Succinte {2-hydroxy-3-[4-(2-methoxyethyl) phenoxy]propyl} (propan-2-yl) amine Metoprolol is a cardioselective β1-adrenergic blocking agent used for acute myocardial infarction and mild to moderate hypertension. Metoprolol Succinate is a white crystalline solid with a molecular weight of 267.363. Metoprolol Succinate is having high solubility and high permeability (BCS Class-I). Metoprolol Succinate has short elimination half life (3-7 hours) and a potent drug. Drugs utilized for long duration of action in hypertension. The rationale for this approach is that the presence of water in gastro intestinal tract is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.

MATERIALS AND METHODS

Metoprolol Succinate was provided as a gift sample from (Ranbaxy Lab Ltd, Gurgaon, India); Potassium chloride and Fructose as a gift sample from (SD Fine Chemicals, Mumbai, India); Talc and Magnesium stearate as a gift sample from (Elegant Drugs Pvt Ltd) Following chemicals were purchased from commercial sources and used as such: Poly Ethylene Glycol 400 and Poly Ethylene Glycol 6000 from (Ranbaxy Lab Ltd, Gurgaon, India); Avicel PH101, Cellulose Acetate, Dibutyl Pthalate (Thomas Baker Chemicals Pvt Ltd, Mumbai, India) All other reagents and solvents used were of analytical grade.

Drug- Excipients compatibility studies [6]

The technique employed in this study is Fourier transform Infrared spectroscopy using FTIR (IR Affinity-1, Shimadzu, Japan). Fourier Transform Infrared spectroscopy is one of the most powerful analytical techniques which offer the possibility of identifying chemical interaction between drug and excipients. The diffusion reflectance spectroscopy technique was utilized in the mid-IR (400–4000 cm^{-1}) spectral region. Powder mixture of drug and excipients in the ratio of 1:1 were prepared in KBr discs. The samples were placed in the light path and the spectra were obtained Infrared was performed in duplicate for each of the samples.

Preparation of Core tablets

The core osmotic tablets were prepared by direct compression technique [7] and preparation of osmotically controlled tablets, drug was mixed with KCl and Fructose, as an osmotic agent in different concentration and Avicel PH 101 were sifted together through 40# sieve and blended for 15 minutes. The blend was again passed through 40 # sieve and lubricated with Talc and Magnesium stearate (previously Sifted through 60 # sieve) for 5 minute. The blend was compressed into tablets using multi station rotary tablet punching machine (Cadmach, Ahmedabad, India) of keeping round standard concave punch of 9.5 mm Formulation composition are shown in Table 1.

Table 1: It Shows Formulation of Core Tablets of Metoprolol Succinate and Composition of Coating Solution.

Ingredients (mg)	FC1	FC2	FC3	FC4
Metoprolol Succinte	100	100	100	100
Fructose	50	50	50	50
Potassium Chloride	75	75	75	75
Avicel PH 101	170	170	170	170
Mg Stearate	3	3	3	3
Talc	2	2	2	2
		Composition of Coating Solution		
Cellulose Acetate	2g	2g	2g	2g
PEG 400	20%(w/w)	20%(w/w)	-	-
PEG 6000	-	-	20%(w/w)	20%(w/w)
Di butyl Pthalate	10%(w/w)	10%(w/w)	10%(w/w)	10%(w/w)
Weight Gain	4%	8%	4%	8%
		Coating Solvent : (Acetone : Methanol) in ratio 9 : 1		

Preparation of Coating Solution

A coating of Cellulose Acetate as an Semi permeable membrane was done around the tablets in which PEG 400 and PEG 6000 are added in 20 %(w/w) Concentration of Cellulose Acetate as pore forming agent & Dibutyl Pthalate was added at 10%(w/w) concentration of cellulose acetate to achieve proper plasticity. Then required Quantity of acetone and methanol was gradually mixed with the resultant polymeric solution for 80-100 RPM using Remi magnetic stirrer Coating was performed by Painter Spray Gun PS-3(Sheffield, United kingdom) in a Manesty 354255 Coating pan (Bosch, Germany). Coating process was started with rotation speed of 4 to 5 rpm. The spray rate and atomizing air pressure were 4 to 6 ml/min and 17.5 kg/cm^2, respectively Inlet and outlet air temperatures were 60°C±10°C and 45°C, respectively. Coated tablets were dried at 50°C for 12 hours and the percentage weight gain of the coating membrane was measured The detailed composition is mentioned in Coating Solution Composition Table 1.

Table 2: It Shows Formulation Composition of Core Tablets of Optimized Batch.

Ingredients (mg)	FaC3	FbC3	FcC3
Metoprolol Succinte	100	100	100
Fructose	75	100	25
Potassium Chloride	50	25	100
Avicel PH 101	170	170	170
Mg St	3	3	3
Talc	2	2	2

The tablets so prepared by different ratio of osmogen mixture of fructose and KCl from optimized batch FC3. The detailed composition is mentioned in formulation and composition of core tablets of optimized batch in Table 2.

Evaluation of Osmotic Tablets:

Post- compression parameters: [8-14]

Hardness

To perform this test, a tablet was placed between two anvils, force was applied to the anvils & the crushing strength that just caused the tablet to break was recorded. The hardness was measured using Pfizer tester. It is expressed in Kg/cm^2.

Friability Test

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Approximately 6.5 gm (Wo) of dedusted tablets were subjected to rotate at 25 rpm for 4 minutes in a rotating drum of 6 inches & are then reweighed (W). The friability is given by following formula; $F= (1 – Wo/W) \times 100$.

Weight Variation Test

Twenty tablets were weighed individually on weighing balance (Shimadzu, Japan), average weight was calculated & individual tablet weights were compared to the average weight. The tablets met the USP test if no more than 2 tablets are outside the percentage limit & if no tablet differs by more than two times the percentage limit.

Drug Content

10 tablets were randomly selected and average weight was calculated and powdered in a glass mortar Powder equivalent to 100 mg of drug was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer using magnetic stirrer (Ricon, Hyderabad, India) then filtered using Whatman filter paper no.1 and diluted suitably and drug content analyzed spectrophotometrically at 274 nm wavelength.

Thickness

Thickness of the coated tablets is measured by using digital vernier caliper (Absolute Digimatic, Mitutoyo Corp, Japan). Ten tablets from each formulation selected randomly and used to measure in the screw gauze. Thickness of the tablet was measured by screw guaze in millimeters. Thickness of each tablet was deviated from ±5% of mean value.

***InVitro* Drug release studies [15-16]**

Dissolution test was performed using a USP type-2 paddle apparatus (Veego, Mumbai, India) at 37 ± 0.5° C in 900 ml of 1.2 pH buffer with a speed of 100 rpm. After 2 hrs of release buffer medium changed to 6.8 phosphate buffer for next 10 hrs through maintaining sink condition. Samples (5ml) were withdrawn at 1 hour time intervals over a period of 12 hour and medium was replenished with fresh dissolution fluid and samples were measured using a UV spectrophotometer at a 274nm wavelength.

Drug Release Kinetics [17-19]

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time, and Higuchi's model a drug released vs. square root of time, Krosmeyer equation as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

Effect of pH of media on drug release [20-21]

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the Standard (changed pH) formulations were carried out at pH 1.2 in simulated gastric fluid (SGF) and pH 6.8 in simulated intestinal fluid (SIF).

Effect of agitational intensity of media on drug release [22-23]

To study the effect of agitation intensity (rpm) of the dissolution medium, the release study was carried out using USP-type II dissolution apparatus (paddle type) at rotational speeds of 50, 100, and 150 using the dissolution medium (900 ml) of SGF of pH 1.2 for the first 2 hours and SIF of pH 6.8 thereafter.

Statistical Data Analysis [24-25]

Release profiles of optimized batch were compared using a model independent pairwise approach, which includes calculation of the 'difference factor' *f1* and 'similarity factor' *f2.* The two release profiles were considered to be similar if *f1* value was lower than 15 (between 0 and 15) and *f2* value was more than 50 (between 50 and 100).

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

$$f_1 \frac{\sum_{j=1}^{n}|R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100$$

Surface morphology study [26-27]

Scanning electron microscope

Scanning electron microscopy (SEM) micrographs of the coating membrane are taken, before and after conducting the dissolution studies, in order to examine the effect of optimized batch FaC3 containing PEG 6000 as pore forming agent. Briefly, a piece of the coating membrane would be removed from the tablet core, fixed on an sample holder with double sided adhesive tape, and coated with layer of gold and 24nm palladium coating at 4^{0}C using a sputter coater. The sample was examined using a scanning electron microscope (Zeiss EVO MA10, Germany).

Accelerated Stability Study [28]

The optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH). The tablets were packed in high density polyethylene (HDPE) container and were stored in ICH certified stability chamber for 3 months (zone III conditions as per ICH Q1guidelines). The samples were withdrawn at the end of 3 months and evaluated for *in vitro* drug release.

RESULTS

FTIR Compatability Study

The possible interaction between the pure drug Metoprolol Succinate and the polymer such as KCl, Fructose, Avicel PH101 and PEG 6000 and pure drug physical mixture was studied by IR spectroscopy. The IR spectra for Metoprolol Succinate and its physical mixtures are shown in Figure 1 & 2.

Post compression parameters evaluation of Metoprolol Succinate tablets

All prepared tablets were evaluated for weight variation and drug content, Thickness, Hardness and Friability as shown in Table 3.

Table 3: It Shows Evaluation of Post Compression Parameters.

Formulation Code	Weight Variation n=20(±SD)	% Friability	Hardness (kg/cm^2) n=3(±SD)	Thickness (mm) n=10(±SD)	Drug Content (%) n=10(±SD)
FC1	400±0.12	0.14	6.8±0.13	4.62±0024	98.10±0.12
FC2	400±0.16	0.23	7.0±0.16	4.73±0023	97.89±0.19
FC3	399±1.21	0.17	6.6±0.11	4.69±0041	99.12±0.33
FC4	398±1.09	0.12	6.5±0.16	4.66±0011	98.45±0.67
FaC3	400±1.04	0.15	7.0±0.18	4.52±0042	99.23±0.58
FbC3	399±1.31	0.16	6.8±0.22	4.74±0014	99.37±0.97
FcC3	400±0.73	0.12	6.8±0.17	4.81±0024	98.56±0.35

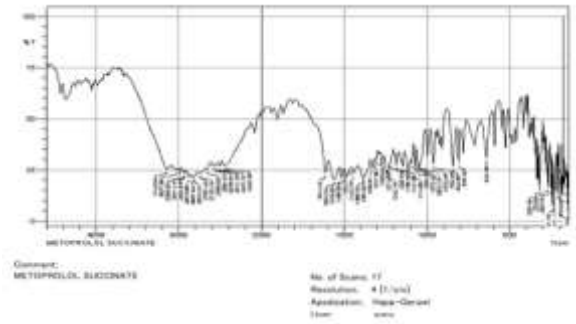


Fig. 1: It Shows FTIR spectra of Metoprolol Succinate.

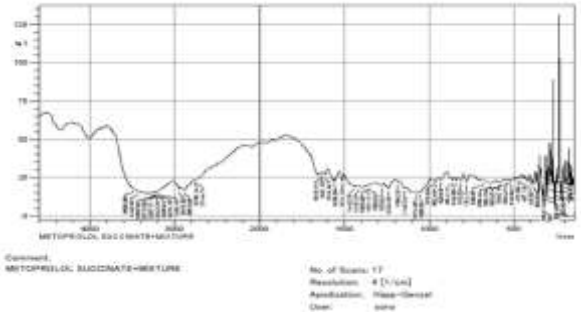


Fig. 2: It Shows FTIR spectra of Metoprolol Succinate + Mixture.

***In Vitro* Drug release study of Metoprolol Succinate Tablets**

FC1, FC2, FC3 and FC4 formulations exhibited 81.38%, 75.12%, 92.65% and 85.00% drug release, FaC3 and FcC3 formulations exhibited 97.59%, 84.19% drug release at 12 hours while FbC3 formulation exhibited 87.69% in 10 hours respectively (Figure 3-4). *In Vitro* dissolution studies revealed that drug release rate increases as equal amount ratio of osmogent mixture increases because of increased water uptake due to osmosis mechanism, and hence increased driving force for drug release Drug release was inversely proportional to membrane weight gain.

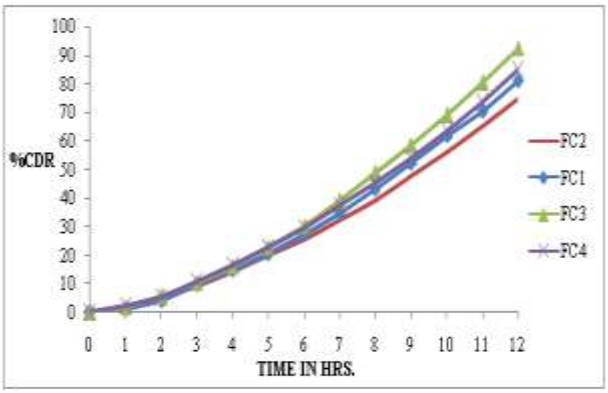


Fig. 3: It Shows % *InVitro* Drug release of Formulation FC1-FC4 in 12 hours.

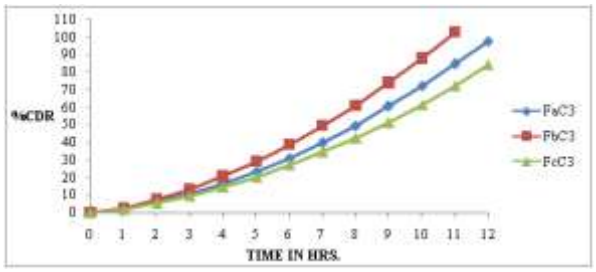


Fig. 4: It Shows % *InVitro* Drug release of Formulation FaC3-FcC3 in 12 hours.

Kinetics and mechanism of drug release

In vitro dissolution data of the optimized formulation was fitted into various mathematical models (zero order, first order, and Higuchi) in order to describe the kinetics of drug release. Drug release from FC3 and FaC3 formulations fitted well into zero order kinetics as shown in Table 4, After applying different mathematical models to the release profile of FC3 and FaC3 regression co-efficient (R^2) for different models were estimated, and n is an exponent that characterizes the mechanism of release n≈0.982 indicates case-II transport (zero-order release) or typical zero-order for FaC3. From the regression co-efficient values of FaC3 showed best controlled release manner.

Table 4: It Shows Drug release kinetics of Osmotic Tablets.

Batch No.	Zero order	First order	Higuchi	Krosmeyer peppas	
	R^2	**R^2**	**R^2**	**N**	**R^2**
FC3	0.977	0.918	0.911	0.959	0.938
FaC3	0.979	0.916	0.901	0.982	0.930

Effect of pH of media on drug release

By performing the dissolution profile of optimize batch (FaC3) using a USP type-2 paddle apparatus were conducted through three method such as pH change method, media 1.2 pH HCl buffer and pH 6.8 phosphate buffer at 37 ± 0.5° C in 900 ml with a speed of 100 rpm, drug release rate was found to be independent of pH of media as shown in Figure 5. Drug release pattern from the optimize batch (FaC3) was found to be similar in all above three different pH medium. The similarity factor (F2) value for 1.2 pH was 62.16 and for 6.8 pH was 68.43 So there is no such significant difference in the release studies after effect of pH studies.

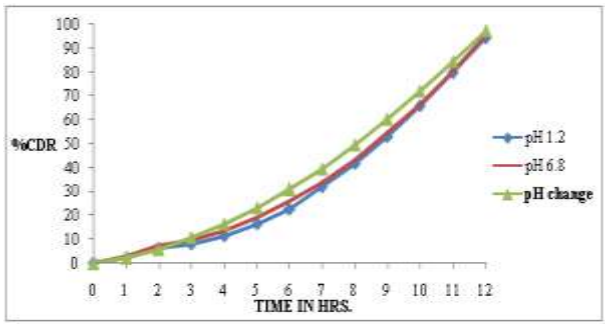


Fig. 5: It Shows Dissolution Profile Comparison through Change in pH of Media of FaC3.

Effect of agitation intensity in media on drug release

By performing the dissolution profile of optimize batch (FaC3) using a USP type-2 paddle apparatus at a speed of 50 rpm, 100 rpm and 150 rpm, drug release rate was found to be independent of agitation intensity as shown in Figure 6. Drug release pattern from the optimize batch (FaC3) was found to be similar in all three different agitational speed. The similarity factor (F2) value for 50 rpm was 72.14 and for 150 rpm were 92.98. So there is no such significant difference in the release studies after effect of change in agitation intensity studies.

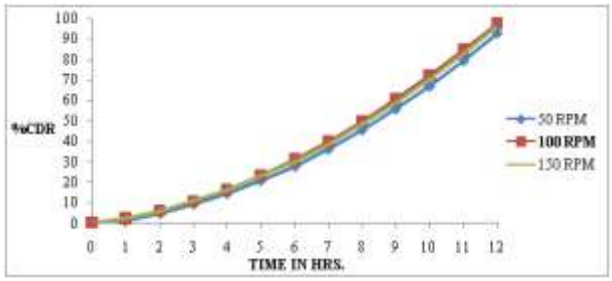


Fig. 6: It Shows Dissolution Profile Comparison through Change in Agitation Intensity of Media of FaC3.

Surface morphology study through Scanning electron microscope

Figures (7A-7B) compares SEM micrographs of the coating membrane of the formula (FaC3) before and after the dissolution studies. Before contact with the dissolution medium, SEM micrographs (417 X) revealed that the no pores were observed in membrane has a roughly spherical dispersion on surface (Figure 7A).

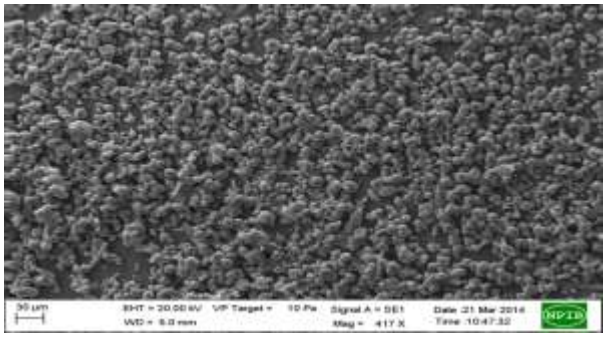


Fig. 7A: It Shows SEM Image of Membrane Containing PEG 6000 of Osmotic Tablet Before Dissolution Study of FaC3.

At the end of the dissolution studies, SEM micrographs (1.18 KX) revealed that the membrane became porous (Figure 7B), possibly, due to the dissolution of PEG 6000, a pore-forming agent, upon contact of the tablet with the dissolution medium.

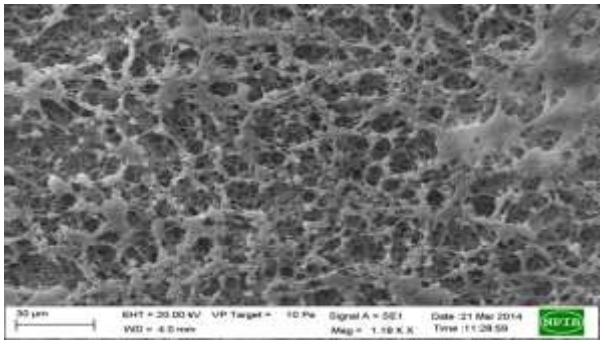


Fig. 7B: It Shows SEM Image of Membrane Containing PEG 6000 of Osmotic Tablet After Dissolution Study of FaC3.

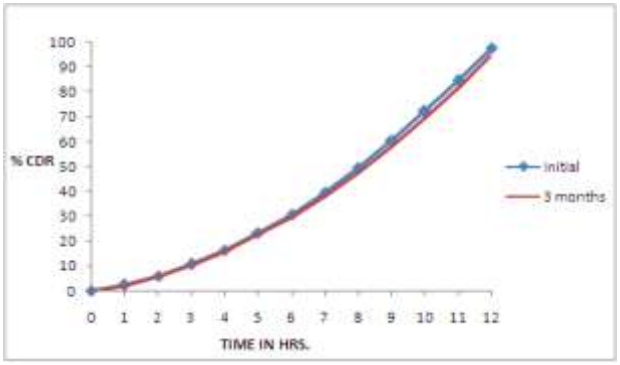
Based on these observations, it could be suggested that release of the drug from controlled release osmotic pump tablets passes through the following steps: (a) dissolution of PEG 6000 upon contact with the dissolution medium, (b) penetration of the tablet by the dissolution medium through the formed pores, (c) dissolution of the drug particles within the tablet, and (d) release of the drug through the pores. Examination of the coating membrane after dissolution studies was necessary to investigate the porous nature of

the membrane. The pores are characterized by inter-connecting channels that are formed from open surface pores that continued into the deeper layers.

Accelerated Stability Study

Accelerated stability study was carried out at 40±2°C/75±5% RH for 3 months on optimized formula (FaC3) and it was found that there was no statistically significant difference in in-vitro drug release before and after stability study. No fracture of coat from any tablet of optimized batch was noticed during and after stability study. The similarity factor (F2) value after 3 months was 84.95. So there is no significant difference in the release studies after stability studies which indicated that the formulation was stable. The formulation FaC3 was found to be stable in terms of *in vitro* release as shown in Figure 8.

Fig. 8: It Shows *InVitro* Drug Release of FaC3 After Accelerated Stability Study.



DISCUSSION

The core tablets were coated by coating agent cellulose acetate (2%w/v) with PEG 400 and PEG 6000 as water soluble pore former and dibutyl-pthalate as plasticizer. Optimized batch (Batch FC3) was further formulated batch (FaC3) using osmogent ratio 3:2 of mixture (fructose : KCl), 20% w/w of pore former (PEG 6000) and 4% weight gain FaC3 gave about 97.59 % drug release for 12 hours. From dissolution profile of different batches, we can say that increasing in % Wt gain % drug release was decreased. Hence we can select of % Wt gain like 4 % and 8 % and for Pore-former Concentration like 20 % of CA. The optimized batch (FaC3) the drug release was found to follow zero order kinetics with regression co-efficient of 0.979 and n value in Krosmeyer peppas release model was 0.982 indicates case-II transport (zero-order release) or typical zero-order. The similarity factor value for 1.2 pH was 62.16 and for 6.8 pH were 68.43. The similarity factor value for 50 rpm was 72.14 and for 150 rpm were 92.98. So, dosage form was independent of pH and agitational intensity. The accelerated stability study revealed that the optimized batch the similarity factor value after 3 months was 84.95 which indicated that the formulation was stable.

CONCLUSION

Formulation FaC3 shows highest amount of drug release (97.59%) in dissolution profile and releases the drug for longer period of time up to 12 hour. The evaluation study of coating solution, batch FC3 containing PEG 6000 had film lighter in weight than PEG 400 and also showed a better drug release in 12 hours than any other batches. Hence the batch FC3 was selected for further study. The obtained dissolution profile of different batches through which, we can say that increasing in % Wt gain, the % drug release was decreased. The drug release rate from dosage form was found no significant changes at different pH of dissolution media and agitational intensity Kinetics of drug release of optimized batch was studied and it showed that zero order was best fit for release of Metoprolol Succinate from dosage form. SEM micrographs of the coating membrane of the batch (FaC3) before and after the dissolution studies. Before contact with the dissolution medium no pores were observed in membrane, examination of the coating membrane after dissolution studies was necessary to investigate the porous nature of the membrane. The inter-connecting channels that are formed from open surface pores that continued into the deeper layers The accelerated stability study shows no significant changes and confirms the stability of formulations.

REFERENCES

1. Gupta PB, Thakur N, Jain PN, Banweer J and Jain S. Osmotically Controlled Drug Delivery System with Associated Drugs. J Pharm Pharmaceut Sci 2010; 13(3): 571-588.
2. Babu A, Rao PM and Vijaya RJ. Controlled Porosity Osmotic Pump Tablets. J Pharm Res H 2010; 2(1): 114-126.
3. Verma RK, Mishra B and Garg S. Osmotically Controlled Oral Drug Delivery. Drug Dev Ind Pharm 2000; 26(7): 695-708.
4. Malaterre V, Ogorka J, Loggia N and Gurny R. Oral Osmotically Driven Systems: 30 years of development and clinical use. Eur J Pharma Biopharm 2009; 73: 311-323.
5. Herrlich S, Speith S, Messner S and Zengerle R. Osmotic Micropumps for Drug Delivery. Adv Drug Deliv Rev 2012; 64: 1617-1627.
6. Wei L, Li J, Guo L, Nie S and Pan W. Investigations of a Novel Self-Emulsifying Osmotic Pump Tablet Containing Carvedilol. Drug Dev Ind Pharm 2007; 33:990-998.
7. Rani M and Mishra B. Comparative In Vitro and In Vivo Evaluation of Matrix, Osmotic Matrix, and Osmotic Pump Tablets for Controlled Delivery of Diclofenac Sodium. AAPS Pharm Sci Tech 2004; 5(4).
8. Sathyaraj A and Abhinav K. Formulation and Evaluation of Metoprolol Succinate Controlled Release Tablets Using Natural and Synthetic Polymer. Int J Pharm Sci Res 2012; 3(1): 247-256.
9. Kumar P, Singh S, Mishra B. Gastroretentive Drug Delivery System of Ranitidine Hydrochloride Based on Osmotic Technology: Development and Evaluation. Curr Drug Deliv 2008; 5: 332–342.
10. Diwedi R, Alexander S and Chandrashekar MJN. Preparation and *InVitro* Evaluation of Sustained Release TabletFormultions of Metformin HCl. Asian J Pharm Clin Res 2012; 5(1): 45-48.
11. Khan AZ, Tripathi R and Mishra B. Floating Elementary Osmotic Pump Tablet (FEOPT) for Controlled Delivery of Diethylcarbamazine Citrate: a Water-Soluble Drug. *AAPS* Pharm Sci Tech 2011; 12(4).
12. Khan HZ, Tripathi R and Mishra B. Design and Evaluation of Entric Coated Microporous Osmotic Pump Tablet of Quietiapine Fumarate for the Treatment of Psychosis. Acta Pol Pharmaceu-Dru Res 2012; 69(6): 1125-1136.
13. Bhoopathi GS, Jayanthi, Pramoda G and Srikanth S. Formulation and *InVitro* Evaluation of sustained release matrix tablets of furosemide. Wrd J Pharm Pharmceu Sci 2013; 2(6): 5052-5066.
14. Lachman L. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1987.
15. Dansankoppa FS, Ningangowder M and Sholapur S. Formulation and Evaluation of Controlled Porosity Osmotic Pump for Oral Delivery of Ketorolac. J Bas Clin Pharm 2013; 4(1).
16. Rao BP, Geetha M, Purushothama N and Sanki U. Optimization and Development of Swellable Controlled Porosity Osmotic Pump Tablet for Theophylline. Tro J Pharma Res 2009; 8(3): 247-255.
17. Sambath L, Kottai MA and Kumar AM. Soluplus Complexation Influence the Release of Lovastatin From Porous Osmotic Pump Tablet. Wrd J Pharm Pharmceu Sci 2013; 2(5).
18. Costa P, Lobo JMS. Modeling and Comparison of Dissolution Profiles. Eur J Pharm Sci 2001; 13: 123–133.
19. Goyal A, Shukla P and Srivastava AK. Factors Inflencing Drug Release Characteristics From Hydrophilic Polymer Matrix Tablet. Asian J Pharm Clin Res 2009; 2(1): 93-98.
20. Kumaravelrajan R, Narayanan N and Suba V. Development and Evaluation of Controlled Porosity Osmotic Pump for Nifedipine and Metoprolol Combination. Lipids Heal Dis 2011; 10(51).
21. Kumar P, Singh S and Mishra B. Development and Biopharmaceutical Evaluation of Extended Release Formulation of

Tramadol Hydrochloride Based on Osmotic Technology. Acta Pharma 2009; 59: 15-30.

22. Garg A, Gupta M and Bhargava NH. Effect of Formulation Parameters on the Release Characteristics of Propranolol from Asymmetric Membrane Coated Tablets. Eur J Pharma Biopharm 2007; 67: 725-731.
23. Mahalaxmi R, Sastri P, Atin K and Kanagale P. Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using A Wicking Agent and A Solubilizing Agent. Int J Pharm Tech Res 2009; 1(3): 705-711.
24. Prajapati ST, Patel AN and Patel CN. Formulation and Evaluation of Controlled-Release Tablet of Zolpidem Tartrate by Melt Granulation Technique. Int Sch Res Net Pharm 2011: 1-8.
25. Vranic E and Uzunovic A. Inflence of Splitting on Dissolution Properties of Metoprolol Tablets. Bosn J Bas Med Sci 2009; 9(3): 245-249.
26. Prabhakaran D, Singh P, Jaganathan KS and Vyas SP. Osmotically Regulated Symmetric Capsular Systems for Simultaneous Sustained Delivery of Anti-Tubercular Drugs. J Cont Rel 2004; 9: 239-248.
27. Liu L, Wang J and Zhu S. Delivery of Prazosin Hydrochloride from Osmotic Pump System Prepared by Coating the Core Tablet with an Indentation. Drug Deliv 2007; 14: 219-224.
28. Patel RB, Patel GN, Patel HR and Patel MM. Inlay Osmotic Pump Tablets Containing Metformin and Glipizide. Drug Dev Ind Pharm 2011; 37(10): 1244-1252.