Research Article

Formulation Development and *In Vitro* Evaluation of Propranolol Hydrochloride Extended Release Matrix Tablets

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Abstract

The purpose of this investigation is to develop extended release matrix tablets of propranolol hydrochloride (PPH), which were designed to improve the patient compliance and prolong the drug release after oral administration. Different viscosity grades of hydroxypropyl methylcellulose (HPMC) polymers such as HPMC K4 M, HPMC K15 M and HPMC K100 M were used. The prepared formulations were characterized and all formulations exhibited satisfactory physical parameters such as thickness (mm), weight variation (mg), friability (%) and hardness (kg/cm^2). After evaluation of physical properties, the *in vitro* release study was performed in 0.1 N Hydrochloric Acid (HCl), pH 1.2 for 2 hours followed by release in phosphate buffer pH 6.8 up to 12 hours. The effects of polymer concentration and polymer blend concentration were studied. Among all the formulations, formulation F3 which contains 40% HPMC K4M followed zero order kinetics via, swelling, diffusion and erosion. This study gives the preliminary idea about the development of extended release drug delivery systems of PPH. The *in-vitro* drug release exponent of the peppas equation suggests the drug release mechanism was super case II transport mechanism. Based on compatibility studies such as differential scanning calorimetry (DSC) and fourier transform infrared spectrophotometry (FT-IR), there was no interaction between the drug and excipients.

Keywords differential scanning calorimetry, extended release tablets, fourier transforms infrared spectrophotometry, Propranolol, in vitro drug release

Introduction

Oral drug delivery is considered as the most common, most popular, convenient and safe [when compared to parenteral route] due to its ease of administration, patient acceptance, and cost effective manufacturing process [1]. In fact, the gastrointestinal physiology offers more flexibility in dosage form design than most other routes [2]. But the poor dissolution rate of water insoluble drugs is a major problem for pharmaceutical formulators to prepare them in the form of tablets [3]. The terms sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [4]. Instead of multiple or numerous doses, single dose having an advantage that the drug release was prolonged and it has been obvious to pharmaceutical industry [5].

Propranolol is a non-selective, β-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity [6-7].

Propranolol hydrochloride (PPH) is widely used in the treatment of hypertension, migraine, angina, cardiac arrhythmias and many other cardiovascular disorders [8-11]. It is highly lipophilic drug, having 15-23% oral bioavailability and it has 3-6 hours half-life. So, patients frequently take several times in a day.

The goal of drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. Considering all the delivery problems associated with the PPH, we plan to design a sustained release formulation of PPH for extended release profile that can reduce the frequency of administration.

Methodology

Pre Compression Studies

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped) and compressibility index [14-15]. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$Tan\ \theta = h/r$$

Here, 'θ' is angle of repose, 'h' is height of the cone and r is radius of the cone base. The carr's index (compressibility index) was determined from the bulk and tapped densities and was calculated using the following formula:

$$Carr's\ index = [\{(\rho tap-\rho bulk)/\ \rho tap\}/100]$$
$$Where\ '\rho tap'\ is\ tapped\ density\ and\ '\rho bulk'\ is\ bulk\ density$$

Drug-excipients compatibility studies

The DSC and FTIR studies were carried out to find the interaction among the drug and other excipients such as polymer, diluent, lubricant etc. [16].

Fourier Transforms Infrared Spectroscopy (FT-IR)

The FT-IR spectrum of pure drug and formulation were determined. A FT-IR (Bruker) was used for the analysis in the frequency range between 4000 - 400cm^{-1} and 4cm^{-1} resolution.

Differential Scanning Calorimetry (DSC)

Pure drug, 1:1 ratio of drug and polymer, and optimized formulation were subjected to the analysis. About 5-15 mg sample to be analyzed was taken in the pierced DSC aluminum pan and scanned in the temperature range of 50-300 °C.

Direct Compression

PPH and all other ingredients were accurately weighed and sifted through sieve # 40. Initially, PPH was well mixed with quantity of required polymer (HPMC K4 M, HPMC K15 M and HPMC K100 M), then mixed with the remaining ingredients in geometric proportions. Further, it was lubricated with the previously weighed and sieved magnesium stearate and talc to obtain the blend for compression. Finally, the lubricated blend was subjected to compression by required 7mm circular standard flat-faced punch on a sixteen station rotary tablet-punching machine [17-18].

Post Compression Studies

The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity [19]. In order to estimate weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, and Japan) and the strength of the physical properties of tablets was expressed by calculating hardness (kg/cm^2) and friability (%).

Table 1. Composition of PPH matrix tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
PPH	40	40	40	40	40	40	40	40	40
HPMC K4 M	26	39	52	-	-	-	-	-	-
HPMC K15 M	-	-	-	26	39	52	-	-	-
HPMC K100 M	-	-	-	-	-	-	26	39	52
MCC - PH 200	54	41	28	54	41	28	54	41	28
Aerosil	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	130	130	130	130	130	130	130	130	130

Drug content estimation

For estimation of drug content, from each batch ten tablets were randomly selected, crushed and the aliquot of powder equivalent to 100 mg of drug was dissolved in suitable quantity of methanol or 6.8 pH phosphate buffer solution. Solution was filtered, diluted and drug content was determined by double beam UV-Visible spectrophotometer (Elico, SL210, and Hyderabad, India) at 290 nm. The drug concentration was calculated from the calibration curve [20].

In vitro dissolution study

The USP dissolution apparatus II (Lab India, India) was used for all the *in vitro* dissolution studies. In this method, HCl and phosphate buffer having the pH of 6.8 was used as dissolution media. The rate of stirring was 100±2 rpm. The amount of PPH was 40 mg in all formulations. The dosage forms were placed in 900 ml of 0.1N HCl that was further replaced by phosphate buffer medium with pH 6.8 after 2 hours for remaining study and maintained at 37±0.5 °C. At appropriate time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 hours), 5 ml of samples were taken and filtered through a 0.45μm Millipore filter (membrane filter). Five ml of fresh dissolution medium was replaced to maintain a constant volume and samples were analyzed by double beam UV visible spectrophotometer (Elico, SL210, and Hyderabad, India) at 290 nm [21-26].

Mechanism of drug release

The drug release kinetics was explained by various kinetic models and to analyze the mechanism of drug release, the data of dissolution was fitted into zero-order, first-order, higuchi and korsmeyer-peppas release models [27-31].

Table 2. Pre-compression evolution parameters of all formulations

Formulation	Angele of repose (^{0}C)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)
F1	22.37±1.1	0.214	0.389	18.23
F2	36.42±1.8	0.202	0.392	19.96
F3	28.36±1.0	0.208	0.367	18.49
F4	28.82±1.9	0.201	0.402	17.36
F5	20.90±1.6	0.201	0.392	18.89
F6	34.57±0.8	0.204	0.402	16.32
F7	27.12±1.3	0.226	0.400	10.89
F8	28.88±0.5	0.199	0.381	12.54
F9	20.90±1.6	0.223	0.396	16.32
F10	32.57±0.8	0.227	0.395	18.86
F11	26.7± 0.5	0.282	0.410	19.43
F12	28.68±1.4	0.224	0.391	11.81

Table 3. Post-compression evolution parameters of all formulations

Character	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diameter (mm)	7	7	7	7	7	7	7	7	7
Thickness (mm)	3.28 ±0.23	3.26 ±0.82	3.18 ±0.62	3.24 ±0.34	3.27 ±0.45	3.28 ±0.20	3.26 ±0.59	3.32 ±0.25	3.31 ±0.25
Weight variation (mg)	129.6 ±0.56	130.4 ±0.48	128.9 ±1.4	129.4 ±0.56	130.3 ±0.68	128.2 ±0.12	129.8 ±1.72	128.0 ±1.18	130.6 ±0.4
Friability (%)	0.36	0.60	0.52	0.39	0.39	0.46	0.42	0.53	0.49
Hardness (kg/cm^2)	6.5 ±0.44	6.5 ±0.38	6.5 ±0.4	6.6 ±0.55	6.1 ±0.57	6.1 ±0.72	6.0 ±0.30	6.0 ±0.71	6.5 ±0.52
Drug content (%)	98.52 ±1.26	97.22 ±1.28	98.58 ±0.59	97.26 ±0.82	100.6 ±0.59	100.4 ±0.92	98.31 ±1.24	99.69 ±0.88	98.31 ±1.24

Results and Discussion

Initially, the pure propranolol was scanned under UV-range between 200-400 nm for absorption spectrum. The maximum absorbance for propranolol was found at 290 nm. A standard concentration of propranolol in the range of 10-50 μg/ml was prepared in 6.8 pH phosphate buffer and the absorbance were measured at 290 nm. Propranolol showed good linearity between 10-50 μg/ml with a correlation coefficient of 0.999. Propranolol matrix tablets were prepared using different viscosity grades of HPMC such as HPMC K4 M, HPMC K15 M and HPMC K100 M (Table 1). The drug and polymer including all other excipients were mixed uniformly. The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped) and compressibility index. The results of angle of repose (<40) and Carr's index (<22) indicated fair to passable flow properties of the powder mixture and their values are shown in Table 2. After pre-compression evaluation, blend was compressed into tablet form using 7.0 mm punch. After preparation of tablets, various physicochemical properties were studied such as diameter, weight variation, hardness, thickness, friability and drug content. The physical properties are shown in Table 3 and based on the results; all the formulations were obtained within pharmacopoeial limits.

The USP dissolution apparatus –II (Lab India, India) was used for all the in vitro dissolution studies. In this method, the tablet was placed inside the dissolution vessel containing 900ml of HCl and after 2 hours the medium was replaced by 6.8 phosphate buffer. Five ml of samples were withdrawn at time intervals of 1hr, 2hr and 3hr, 4hr, 5hr, 6hr, 8hr, 10 hr and 12hr. The volume of dissolution fluid was adjusted to 900 ml by replacing fresh 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets (n=3), and the mean values were plotted versus time. F-1 formulation containing 20% of HPMC K4 M retarded the drug only for 7 hours, whereas F-2 and F-3 containing 30% and 40% of HPMC K4 M retarded the drug for 8 hours and 12 hours respectively. F-4 formulation containing 20% of HPMC K15 M retarded the drug only for 8 hours. F-5 formulations containing 30% and retards the drug for 11 hours. The F6 formulation containing 40% of the HPMC K15 M retarded the drug more than 12 hours.

Table 4. Compilation of the results from all the mathematical models applied to the optimized formulation (F3)

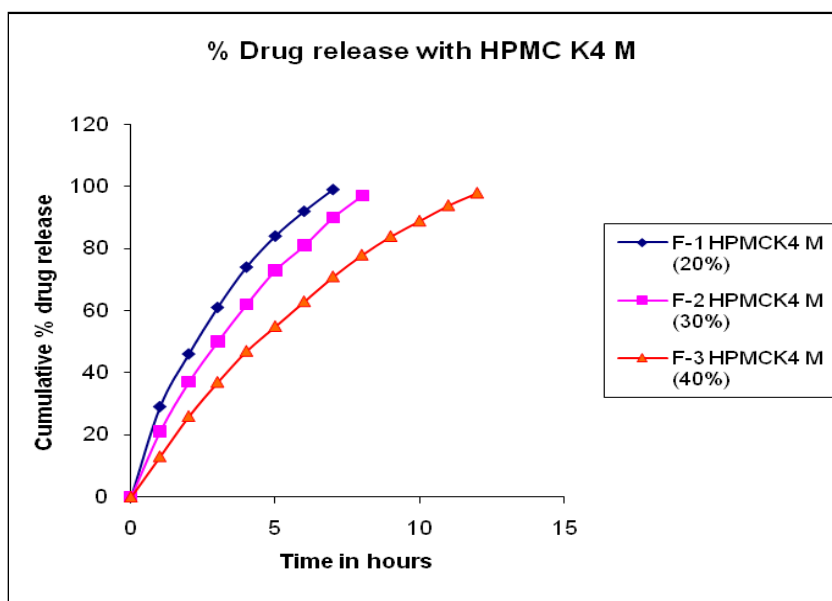| Type of Plot	Regression Coefficient R^2
Zero order	0.972
First Order	0.897
Higuchi Square Root Law	0.976
Hixon Crowell Cube Root Law	0.898
Korsemeyer – Peppas Plot, (n)	0.749; (1.265)

Figure 1. Cumulative percentage drug release profiles of formulations of PPH matrix tablets with HPMC K4 M

The formulation F-7 containing 20% of HPMC K100 M retarded 86% of drug in 12 hours and the release was retarded more in the concentration of 30%. Only 60% of drug was released in 12 hours for F-9 formulation contain 40% of the HPMC K100 M. The results of in vitro dissolution studies are summarized in the Figure 1, Figure 2 and Figure 3. The dissolution studies indicated that as the polymer concentration of HPMC increased, the drug release rate was retarded. The release kinetics of optimized formula is shown in Table 4. DSC and FT IR studies showed that there was no interaction between the drug and excipients (Figure 4 to Figure 7). The thermograms of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in the drug in the tablet dosage form.
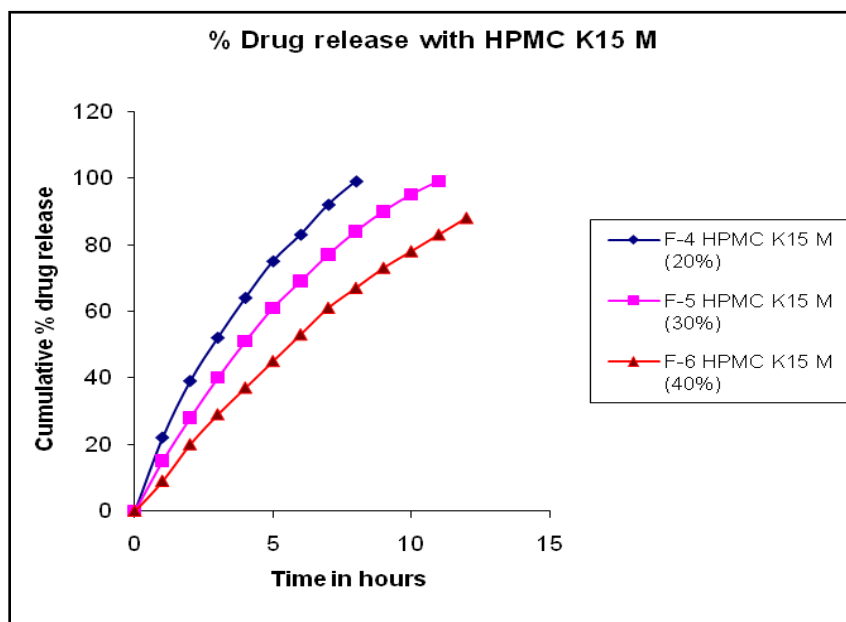

Figure 2. Cumulative percentage drug release profiles of formulations of PPH matrix tablets with HPMC K15 M
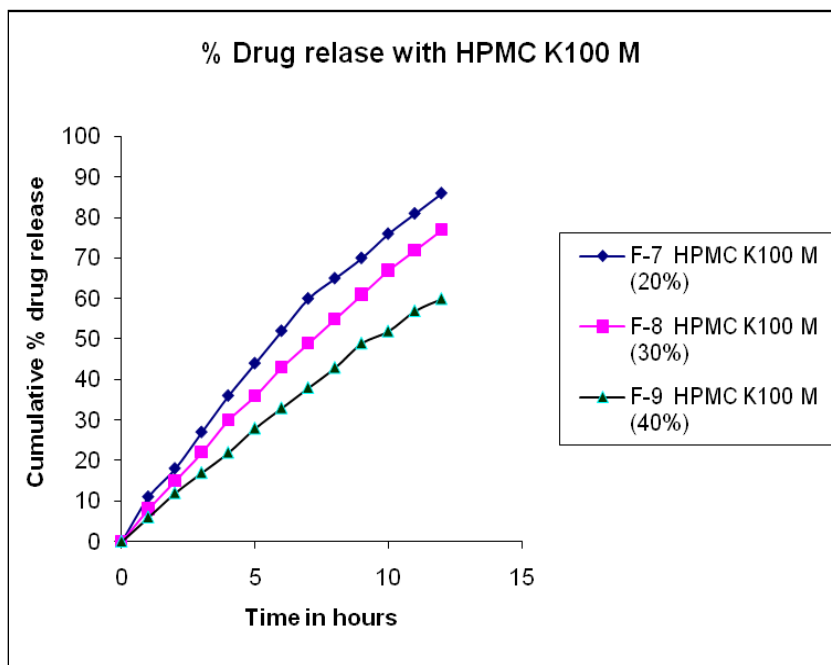
Figure 3. Cumulative percentage drug release profiles of formulations of PPH matrix tablets with HPMC K100 M
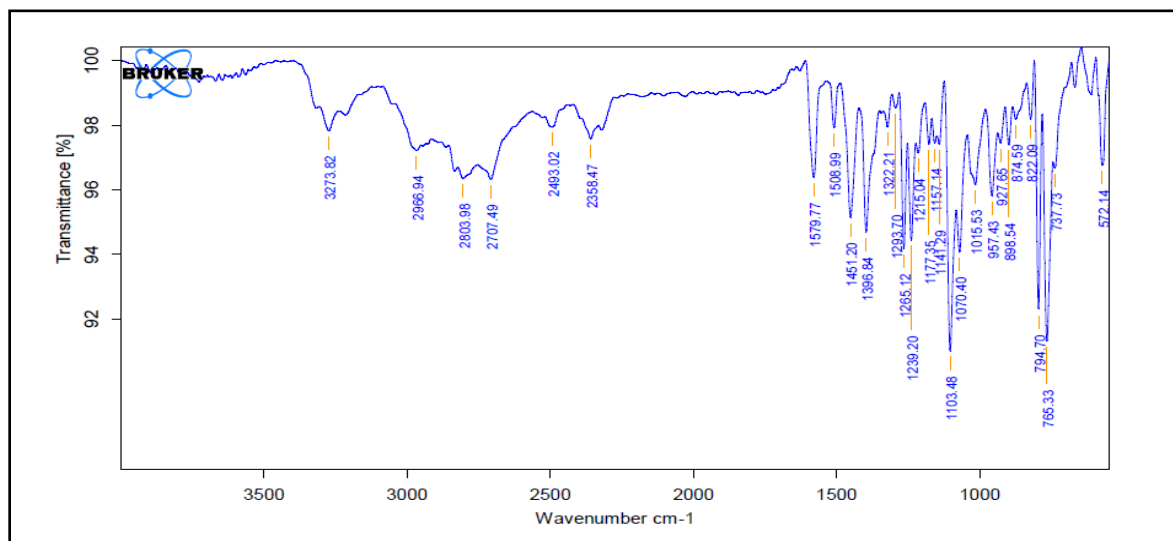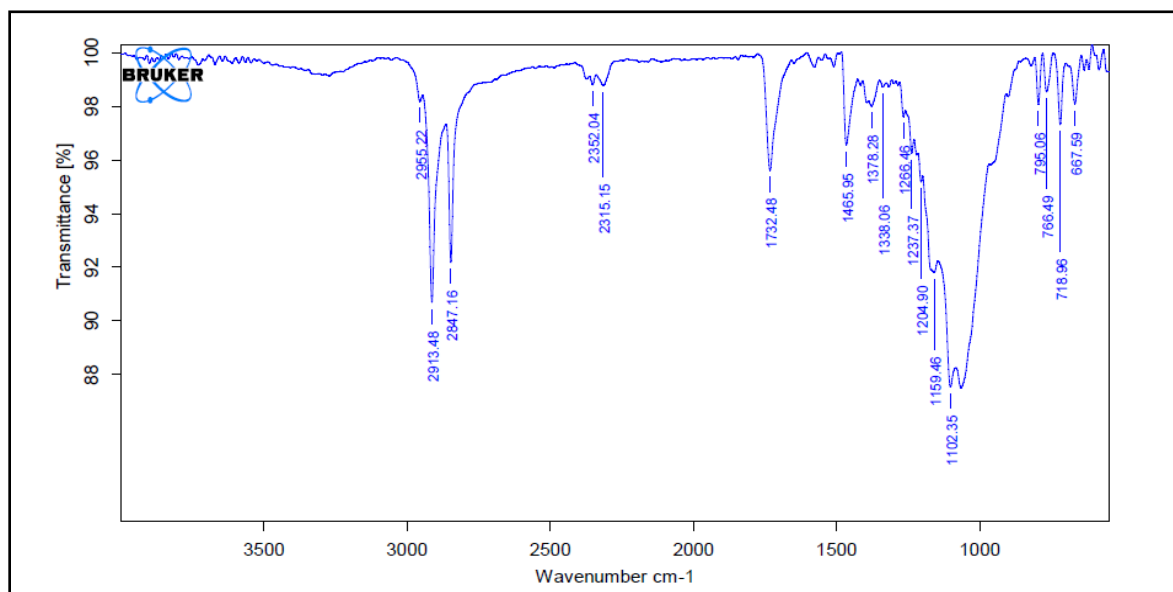

Figure 4. FTIR spectra of pure drug (PPH)

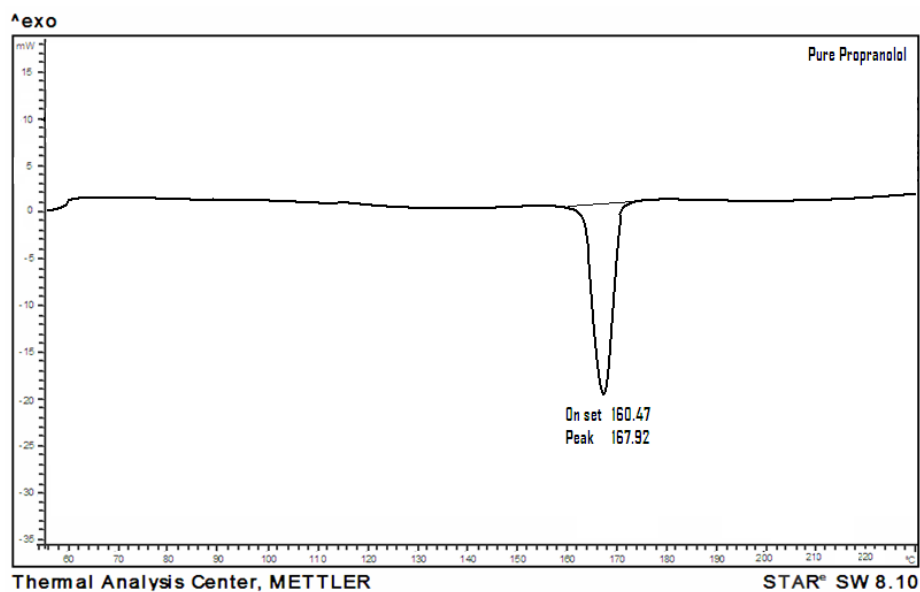**Figure 5. FTIR spectra of optimized formulation (F3)**

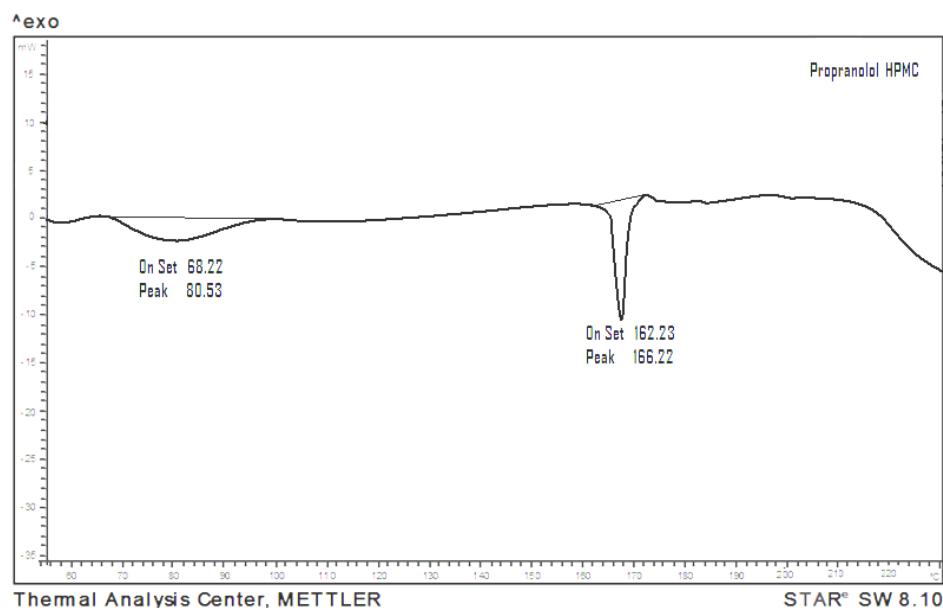**Figure 6. DSC thermogram of pure drug (PPH)**

Figure 7. DSC thermogram of optimized formulation (F3)

Conclusion

Present research study provided useful information for scientists on formulation and characterization during the development of controlled drug delivery systems of propranolol using the hydrophilic polymers. All formulations can be successfully employed in the preparation of controlled release matrix tablets of propranolol. The prepared formulations can be successfully commercialized after establishing their safety measures and efficacy. This dosage form holds promise for further studies, which can be extrapolated for the development of other delivery systems.

Acknowledgements

References

[1] L. Lachman, H. A. Lieberman and L. J. Kanig **(2013)**. The theory and practice of industrial pharmacy, 4th ed. Edited by R.K. Khar, S.P. Vyas, F.J. Ahmad and G.K. Jain. CBS publishers and distributors.

[2] S. P. Vyas and R. K. Khar **(2002)**. Targeted and controlled drug delivery. Novel carrier systems, JCBS Publications.

[3] P. Madhusudhan and S. Nazeer **(2010)**. Extended release formulation. Int. J. Pharm. Tech., **2:** 625-684.

[4] M. H. Ehab Ahmed (2002). Application and evaluation of extended release technology to loop diuretics (Ph.D, thesis). University of cincinnati. http://rave.ohiolink.edu/etdc/view?acc_num=ucin1037205224

[5] D. M. Brahmankar and S. B. Jaiswal **(2015)**. Biopharmaceutics and pharmacokinetics; a treatise. 3rd ed. New delhi, Vallabh prakashan.

[6] C. McKee, J. Soeda, E. Asilmaz, B. Sigalla, M. Morgan, N. Sinelli, and T. Roskams et al., **(2013)**. Propranolol, a β-adrenoceptor antagonist, worsens liver injury in a model of non-alcoholic steatohepatitis. Biochem. Biophys. Res. Commun., **437:** 597-602.

[7] K. F. Morris, E. J. Billiot, F. H. Billiot, C. B. Hoffman, A. A. Gladis, K. B. Lipkowitz and W. M. Southerland et al., **(2015)**. Molecular dynamics simulation and NMR investigation of the association of the β-blockers atenolol and propranolol with a chiral molecular micelle. Chem. Phys., **457:** 133-146

[8] K. D. Tripathi **(2003)**. Eessentials of medical pharmacology. 5th ed. New delhi: Jaypee brothers.

[9] D. A. Williams and T. L. Temke **(2002)**. Foye's principles of medicinal chemistry. International student ed. Philadelphia: Lippincott williams and wilkins.

[10] L. M. Friedman, R. P. Byington, R. J. Capone, C. D. Furberg, S. Goldstein, E. Lichstein **(1986)**. Effect of propranolol in patients with myocardial infarction and ventricular arrhythmia. J. Am. Coll Cardiol., **7:** 1-8.

[11] A. H. El-Sabbagh **(2015)**. Oral propranolol: A useful treatment for infantile hemangioma. Journal of biomedical science and engineering, 8: 441-450. doi: 10.4236/jbise.2015.87041.

[12]. S. Vidydydhara, P. Rama Rao and J. A. Prasad **(2004)**. Formulation and evaluation of propranolol hydrochloride oral controlled release matrix tablets. Indian J. Pharm. Sci., **66:** 188-192.

[13] B. Amulyaratna, B. Priyadarshini, P. Sachin Kumar, S. Chandra Sekhar, L. Pravin Kumar and S. S. Kumar **(2011)**. Formulation development and evaluation of propranolol hydrochloride sustained release tablet. Indian J. Pharmaceutics., **2:** 9-12.

[14] K. Sanka., R. R. Pragada and P. R. Veeraredy **(2015)**. pH dependent colon specific ketoprofen microspheres: screening of main effects of process and formulation variables using plackett-burman design. Lat. Am. J. Pharm., **34:** 1195-1204.

[15] S. K. Vemula and P. R. Veerareddy **(2011)**. Fast disintegrating tablets of flurbiprofen: formulation and characterization. Lat. Am. J. Pharm., **30:**1135-1141.

[16] K. Sanka., R. R. Pragada and P. R. Veeraredy **(2015)**. A pH-triggered delayed-release chronotherapeutic drug delivery system of aceclofenac for effective management of early morning symptoms of rheumatoid arthritis. J. Microencapsul., **32:** 794-803.

[17] R. K. Jadi, R. Bomma and V. Sellappan **(2016)**. Development of a new single unit dosage form of propranolol HCl extended release non-effervescent floating matrix tablets: In vitro and in vivo evaluation, J. App. Pharm. Sci., **6:** 112-118.

[18] J. Siepmann and N. A. Peppas **(2001)**. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev., **48:** 139-157.

[19] A. Martin **(2001)**. Micromeritics. In: Martin A, Physical pharmacy. Baltimore, MD: Lippincott williams and wilkins.

[20] Indian pharmacopoeia **(2014)**. Ministry of Health and Family welfare, Govt. of India. Indian pharmacopoeia company, Ghaziabad.

[21] Cheng Chinhwa, Wu Pao-Chu, Lee Hsin-Ya and Hsu Kuang-Yang (2014). Development and validation of an in vitro in vivo correlation (IVIVC) model for propranolol hydrochloride extended release matrix formulations. J. Food Drug Anal., **22:** 257-263.

[22] H. A. Alhmoud, E. I. EI-Hallous, N. E. Ibrahim, A. O. Attia and E. S. Dessoky **(2014)**. Formulation of propranolol hydrochloride controlled release tablets: Effect of surfactant charge and mechanism of drug release. Afr. J. Pharm. Pharmacol., **8:** 1110-1117.

[23] D. Jadhav, R. Kharat, S. Jadhav and M. Patil **(2015)**. Design and evaluation of sustained release matrix tablets of propranolol hydrochloride. Indo Am. J. Pharmaceutical Res., **5:** 1109-1117.

[24] T. Pongjanyakul and S. Rojtanatanya **(2012)**. Use of propranolol magnesium aluminium silicate intercalated complexes as drug reservoirs in polymeric matrix tablets. Indian J. Pharm. Sci., **74:** 292-301.

[25] J. C. O. Villanova and V. O. Consiglieri **(2011)**. Development and in vitro evaluation of propranolol hydrochloride controlled release tablets using HPMC as matrix former. Lat. Am. J. Pharm., **30:** 729-736.

[26] M. Khandai, S. Chakraborty, A. Sharma, D. Panda, N. Khanam and S. K. Panda **(2010)**. Development of propranolol hydrochloride matrix tablets: An investigation on effects of combination of hydrophilic and hydrophobic matrix formers using multiple comparison analysis. Int. J. Pharm. Sci. Rev. Res., **1:** 1-7.

[27] M. Rosa, H. Zia and T. Rhodes (1994). Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm., **105:** 65-70.

[28] S. Dash, P. N. Murthy, L. Nath and P. Chowdhury **(2010)**. Kinetic modeling on drug release from controlled drug delivery systems, Acta Pol. Pharm., **67:** 217-223.

[29] T. Higuchi (1963). Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci., **52:** 1145-1149.

[30] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri and N.A. Peppas **(1983)**. Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm., **15:** 25-35.

[31]. P. Costa and J. M. S. Lobo **(2001)**. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci., **13:**123-133.