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Controlled release floating multiparticulates of metoprolol succinate by hot melt extrusion

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Abstract

We present hot melt extrusion (HME) for the design of floating multiparticulates. Metoprolol succinate was selected as the model drug. Our foremost objective was to optimize the components Eudragit® RS PO, polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC) to balance both buoyancy and controlled release. Gas generated by sodium bicarbonate in acidic medium was trapped in the polymer matrix to enable floating. Eudragit® RS PO and PEO with sodium bicarbonate resulted in multiparticulates which exhibited rapid flotation within 3 minutes but inadequate total floating time (TFT) of 3 hours. Addition of

HPMC to the matrix did not affect floating lag time (FLT), moreover TFT increased to more than 12 hours with controlled release of metoprolol succinate. Floating multiparticulates exhibited $t_{50\%}$ of 5.24 hours and $t_{90\%}$ of 10.12 hours. XRD and DSC analysis revealed crystalline state of drug while FTIR suggested nonexistence of chemical interaction between the drug and the other excipients. The assay, FLT, TFT and the drug release of the multiparticulates were unchanged when stored at 40°C/75%RH for 3 months confirming stability. We present floating multiparticulates by HME which could be extrapolated to a range of other drugs. Our approach hence presents platform technology for floating multiparticulates.

Key words

Hot melt extrusion, Floating multiparticulates, Sodium bicarbonate, Metoprolol succinate, Polyethylene oxide, Eudragit® RS PO

Chemical compounds studied in this article

Metoprolol succinate (PubChem CID: 4171); Sodium bicarbonate (PubChem CID: 516892); Glyceryl monostearate (PubChem CID: 24699); Hydrochloric acid (PubChem CID: 313)

1. Introduction

Gastric residence time is an important factor affecting drug absorption and bioavailability (Desai and Bolton, 1993). Prolonging the gastric residence time of drug delivery systems is positively considered for design of controlled release formulations (Sauzet et al., 2009) of drugs having absorption window in the upper GIT and drugs exhibiting poor solubility in the basic pH of the intestinal milieu (Klausner et al., 2003, Singh and Kim, 2000; Jain et al., 2005). Floating systems provide a simple and sensible approach of gastroretention without adversely affecting the motility of the GIT (Tang et al., 2007). Monolithic (Qi et al., 2015) including layered tablets (Desai et al., 2014,) and multiparticulate floating systems may be

designed, nevertheless multiparticulates provide specific advantages for controlled drug delivery.

Ion exchange resins coated with a semipermeable membrane exhibited prolonged gastric retention and controlled release of theophylline (Atyabi et al., 1996). Drug loaded pellets of p-aminobenzoic acid (Ichigawa et al., 1991), zolpidem tartarate (Amrutkar et al., 2012) and theophylline (Sungthongjeen et al., 2006) coated with an inner effervescent layer and outer polymeric layer enabled prolonged floating with controlled drug release. Coated beads of calcium alginate prepared by ionotropic gelation exhibited immediate buoyancy and remained floating for prolonged periods (Iannuccelli et al., 1998). Floating microspheres of ranitidine hydrochloride (Saravanan and Anupama., 2011) verapamil hydrochloride (Streubel et al., 2002) and itopride hydrochloride (Bansal et al., 2014) were developed by solvent evaporation method, while the emulsion solvent diffusion method was effectively employed for preparation of floating microballoons which exhibited controlled release of riboflavin (Sato et al., 2003, 2004, Upadhyay et al., 2013), tranilast (Kawashima et al., 1992) and psoralen (Liu et al., 2011). Drug loaded porous calcium silicate microspheres coated with Eudragit® S also exhibited floating and controlled release (Jain et al., 2005). Multi-step processing and the need for organic solvents is a common feature of the above methods (Hamdani et al., 2006).

Hot melt extrusion (HME) is a recent versatile, green and scalable technology (Repka et al., 2007, Mooter 2012) amenable for continuous manufacturing and also process analytical technology (PAT) enabled (Islam et al., 2014). Matrix mini tablets of ibuprofen (De Brabander et al., 2003), lipid matrices of diclofenac sodium (Vithani et al., 2013) and extrudates of phenylpropanolamine hydrochloride (Sarraf et al., 2015) prepared by HME exhibited sustained release. In general HME may be considered a densification technique. Sustained release of paracetamol from pellets processed by HME was attributed to

densification of the pellets (Roblegg et al., 2011). Nevertheless a floating dosage form of nicardipine hydrochloride was successfully developed by HME using a twin-screw extruder with puff ability (Nakamichi et al., 2001). Fukuda et al. (2006) reported porous floating tablets (6 mm diameter) of chlorpheniramine maleate by generating effervescence during the HME process and trapping the released gas in the extrudates wherein extrudates were cut to obtain porous tablets. We present in this paper extruded floating multiparticulates by a standard HME process wherein in situ gas generation enabled buoyancy. Metoprolol succinate was selected as model drug for the feasibility study. The aim of the study was to exploit HME as a green and scalable process for the design of floating multiparticulates of metoprolol succinate. The specific objective of the study was to optimize the components of the floating multiparticulate system to balance both buoyancy and controlled release.

2. Materials and methods

2.1. Materials

Metoprolol succinate was kindly gifted by Phoenix Pharmaceuticals LLC, USA. Sodium bicarbonate was obtained from s. d. fine chemicals, Mumbai. Hydroxypropyl methylcellulose (HPMC; Methocel K100M) was supplied by Colorcon Asia Pvt. Ltd. Eudragit® RS PO was gifted by Evonik Degussa, Mumbai, glyceryl monostearate by Gattefosse India Pvt. Ltd. and polyethylene oxide (PEO; POLYOX™ WSR-303) by Colorcon Asia Pvt Ltd.

2.2. Preparation of floating multiparticulates

A mixture of metoprolol succinate, sodium bicarbonate, glyceryl monostearate and the polymers was sifted through sieve no. 40 and hand blended in a polyethylene bag for 15 min. The mixture was extruded on a HME (Thermo Scientific™ Pharma 11 twin-screw extruder) using a die of 2mm diameter. The hopper screw speed was set at 4 rpm. The screw rotation

speed was set at 15 rpm to obtain a residence time of approximately 9 min. The temperature settings of the extruder zones were as follows: zone 2 (40°C), zone 3 (100°C), zone 4 (100°C), zone 5 (120°C), zone 6 (120°C), zone 7 (125°C), zone 8 (125°C) and die (128°C). The torque limit was set at 90 Nm. The extrudates were allowed to attain room temperature (28°C) and cut in to segments of 5 mm length using a cutting blade. The polymers evaluated were PEO from 30 to 65% (w/w), Eudragit® RS PO from 10 to 75% (w/w) and HPMC from 10 to 20% (w/w) in combination. Sodium bicarbonate selected as effervescent agent was varied from 5 to 15% (w/w). The concentration of the drug metoprolol succinate and glyceryl monostearate which was included as a thermal lubricant was maintained constant at 10% (w/w) and 5% (w/w) respectively.

2.3. Evaluation of floating multiparticulates

2.3.1. Drug content

Extrudates were crushed using a mortar and pestle, and an amount equivalent to 50 mg of metoprolol succinate was accurately weighed and transferred to a 200 mL volumetric flask and distilled water was added. The flask was sonicated in a bath sonicator for 1 h with intermittent shaking, the volume made up with distilled water and an aliquot (10mL) centrifuged at 5000 rpm for 5 min. The supernatant (2mL) was diluted to 10mL with distilled water and analysed spectrophotometrically (UV1650PC, Schimadzu Corporation USA) at λ max of 274nm.

2.3.2. In-vitro buoyancy studies

In-vitro buoyancy was assessed by monitoring two parameters, namely floating lag time (FLT) and total floating time (TFT) in 900 mL of 0.1N HCl maintained at 37°C, using USP type II dissolution apparatus (Electrolab TDT- 08L) at a paddle speed of 50 rpm. The

extrudates were dropped in to the medium and the FLT was calculated as the time taken for 100% extrudates to exhibit floating. The TFT was the time at which a single extrudate sank in the medium.

2.3.3. In-vitro drug release study

Extrudates equivalent to 50 mg metoprolol succinate were filled in off white coloured hard gelatin capsules of size 00. Dissolution (n=6) was performed in 500mL of 0.1N HCl maintained at 37°C using USP type II dissolution apparatus (Electrolab TDT- 08L) at a paddle speed at 50 rpm. At predetermined time intervals, 5mL sample was withdrawn and replaced with fresh medium (37°C). Samples were analysed spectrophotometrically (UV1650PC, Schimadzu Corporation USA) at λ max of 274nm. The similarity factor (f_2) and difference factor (f_1) implemented by the U.S. FDA was employed to compare dissolution profiles between the formulations (U.S. FDA, 1997, Pillay and Fassihi, 1998, Shah et al., 1998). The f_2 is a logarithmic transformation of the sum squared error of differences between the test and reference product, and was calculated using equation 1.

$$f_2 = 50\, log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-(1/2)} \times 100\right\} \quad (1)$$

where R_t is cumulative release rate of the reference product, T_t is cumulative release rates of test product at the predetermined time period and n is the number of the time points. The f_2 value $\geq$ 50 indicates similarity between two dissolution profiles. The f_1 value is the function of the average absolute difference between the two dissolution profiles and was calculated by the equation 2.

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n}R_t}\right\} \times 100 \quad (2)$$

where R_t and T_t are the cumulative release rates of the reference and test product at the determined time period respectively, and n is the number of the time points. The f_1 calculates the percent difference between the two dissolution profiles at each time point and is a

measurement of the relative error between the two curves. The f_1 values up to 15 ensure sameness or equivalence of the test (post change) and reference (prechange) products.

2.3.4. Drug release kinetics

The in-vitro drug release data of the optimized formulation was subjected to different mathematical models, i.e. zero order, first order, Hixson–Crowell model, Higuchi, and Korsmeyer–Peppas models (Higuchi, 1963, Korsmeyer et al., 1983, Costa and Sousa Lobo, 2001) as follows.

Zero-order model: $Q = kt + Q_0$

Where Q is the amount of drug released in time t, Q_0 indicates the initial drug amount (generally $Q_0 = 0$) and k represents the rate constant.

First-order model: $Q = Q_0 e^{kt}$

Where Q is the amount of drug released in time t, Q_0 indicates the initial drug amount and k represents the rate constant.

Hixson–Crowell model: $Q^{1/3} = kt + Q_0^{1/3}$

Where Q is the amount of drug released in time t, Q_0 indicates the initial drug amount and k represents the rate constant.

Higuchi model: $Q = kt^{1/2}$

Where Q is the amount of drug released in time t, and k represents the rate constant.

Korsmeyer–Peppas model: $Q = kt^n$

where Q is the amount of drug released in time t, k represents the rate constant and n is the diffusion exponent which indicates the mechanism of drug release.

2.3.5. Length, diameter and density evaluation

The length and diameter of extrudates was measured with the help of a vernier calliper. The density (D) of extrudates was calculated from weight, length and diameter of extrudates using the following equation commonly used for density measurements of cylinders.

$$D(g/cm^2) = \frac{w}{\pi \times (d/2)^2 \times h} \quad (3)$$

Where w is the weight, d is the diameter, π is the circular constant and h is the length of the extrudate. All measurements were performed in six replicates and the averages and standard deviations were calculated.

2.3.6. X-ray diffraction (XRD) analysis

XRD analysis was carried out on a Panalytical Xpert PRO MPD diffractometer equiped with xcelerator with diffracted beam monochromator detector, variable slits and a 0.050 step size, operated at a voltage of 45KV and 40mA current, 2θ/min scanning speed and wavelength of 1.5405 Angstorm.

2.3.7. Differential scanning calorimetry (DSC) analysis

DSC analysis was carried out using Perkin Elmer, Pyris 6 DSC (Perkin Elmer life & Analytical Sciences Inc., USA) system in the temperature range 30 -300°C at a heating rate of 10°C /min in a dynamic nitrogen atmosphere (17 ml/min). Approximately 5 mg of sample was sealed in an aluminium DSC pan and an empty sealed aluminium pan was used as the reference.

2.3.8. Fourier transform infrared (FTIR) analysis

FTIR spectra were determined on a Shimadzu MIRACLE IR Affinity-1 FTIR spectrophotometer. The samples were premixed with KBr using a mortar and pestle and discs were prepared by means of a hydraulic press. The scanning range was 4000 to 400 cm^{-1}.

2.4. Stability studies

The extrudates equivalent to 50 mg metoprolol succinate was filled in off white coloured hard gelatin capsules (size 00). The capsules placed in high density polyethylene (HDPE) bottles sealed with induction sealing of aluminium were stored at 40°C and 75% relative humidity for 3 months. The appearance, drug release profiles, buoyancy and drug content of stability samples were compared with the initial samples.

3. Results and Discussion

HME is a widely used technique for the development of several types of drug delivery systems. Extrudates obtained by HME generally exhibit enhanced density, a property not ideal for floating. Design of floating multiparticulates by HME is therefore challenging. Further as not all polymers are amenable for HME, formulation design is limited by the polymer selection afforded. Polymers extensively explored for HME include Eudragits, PEO and selected cellulose based polymers like HPMC, hydroxypropyl methylcellulose phthalate, and hydroxypropyl methylcellulose acetate succinate. Among these Eudragits and PEO which are low melting polymers are the most widely explored. In the present study Eudragit® RS PO a pH independent polymer was selected as it exhibits low T_g and low torque during extrusion (Wu and McGinity, 2003, Dierickx et al., 2012) while PEO was employed due to its swelling and gelling property (Lei Li, et al., 2006) which proposed its application as a controlled release polymer. Glyceryl monostearate served as a lipophilic thermal lubricant (Zhu, et al., 2004).

Incorporation of sodium bicarbonate in matrix tablets is a proven strategy for flotation of tablets in acidic media. Floating tablets of cephalexin are reported using HPMC as matrix and sodium bicarbonate as a gas forming agent (Yin et al., 2013). Tablets of valacyclovir hydrochloride containing PEO and sodium bicarbonate exhibited prolonged buoyancy due to

entrapment of carbon dioxide (CO_2) in the polymer gel matrix (Upadhyay et al., 2014). Matrix tablets of ciprofloxacin comprising HPMC and sodium alginate as gelling agent and sodium bicarbonate or calcium carbonate as effervescent agent enabled floating with controlled release up to 12 hours (Tadros, 2010). Bilayered tablets comprising HPMC as release modifier and sodium bicarbonate as effervescent agent exhibited immediate release of pioglitazone hydrochloride and prolonged floating with controlled release of metformin hydrochloride up to 12 hours (Wei et al., 2014). We extrapolated this concept of entrapping gas in polymer matrices to design floating multiparticulate drug delivery system by including sodium bicarbonate in the formulation (Table 1).

A maximum screw speed of 15 rpm was considered optimum as at higher speeds the torque increased, probably due to the narrow die of 2mm used in the study. Further continuous increase in the temperature of the extruder zones facilitated ease of extrusion. Conventionally the temperature of the final zone and the die are maintained the same. In our study the die temperature was increased marginally to 128°C compared to 125°C maintained in zone 8 to enable smoother extrusion.

Eudragit® RS PO alone exhibited low torque and ease of processing but no flotation was observed even after addition of sodium bicarbonate (FM1). Furthermore the resulting extrudates revealed a rough and porous surface implying that although CO_2 was generated in situ the same had escaped. Replacing Eudragit® RS PO partially with PEO revealed a gradual increase in torque, nevertheless even at 60% (w/w) PEO the torque was significantly low and the mass was easily extrudable (Table 1).

All extrudates were cut in to 5 mm length and had average diameter of 2 mm. Eudragit® RS PO and PEO with sodium bicarbonate (FM2) exhibited rapid flotation confirming the feasibility of this strategy. Although rapid FLT of 3 minutes was observed, the TFT of less than 1.5 hour was grossly inadequate. Increase in PEO concentration enabled decrease in

FLT with a marginal enhancement in TFT to about 3 hours (Fig.1). However in-vitro release rate increased probably due to corresponding decrease in Eudragit® RS PO concentration (Fig.2). A maximum $t_{50\%}$ of 4.06 hours and $t_{90\%}$ of 8.22 hours was achievable.

Controlled release formulations dictate a TFT of at least 10 hours and the desirable $t_{50\%}$ and $t_{90\%}$ values for our study were >5 and >10 hours respectively. HPMC K100M a swelling gelling polymer is extensively reported for controlled release (Li et al., 2005) and could also enable flotation (Baumgartner et al., 2000, Yin et al., 2013). Inclusion of HPMC in the extrudates influenced both process and product parameters. Increase in HPMC concentration resulted in increase in torque (Table 1), with a very high torque seen at 20% (w/w) HPMC concentration (FM8), thereby limiting the HPMC concentration in the extrudates to 15%, w/w (FM7). Increase in the concentration of HPMC revealed an increase in both FLT and TFT (Fig.3). At HPMC 15%, w/w (FM7) extrudates revealed $t_{50\%}$ of 5.24 hours and $t_{90\%}$ of 10.12 hours (Fig. 4), which was significantly greater than ($P<0.05$) the values seen without HPMC (FM5) with f_2 value of 23.68 for in vitro release. Although the f_2 value for compositions with 10% (w/w) HPMC (FM6) and 15% (w/w) HPMC (FM7) was 62.64, the $t_{50\%}$ for FM6 was significantly lower. Hence FM7 was modified further.

Maintaining HPMC concentration at 15% (w/w), increase in sodium bicarbonate revealed decrease in FLT with no effect on TFT, while increase in Eudragit® RS PO concentration revealed increase in FLT (Fig.5). Nevertheless these changes revealed no significant effect on drug release (Fig.6) as confirmed by similarity factor (f_2 >50). The formulations revealed diameter between 1.98 to 2.09 mm, length 4.92 to 5.11mm, density of 1.018 to 1.203 g/cm^3, and drug content between 98.54 to 100.02%. The optimized formulation (FM7) exhibited FLT of 3 minutes with TFT greater than 12 hours and $t_{50\%}$ and $t_{90\%}$ values of 5.24 and 10.12 hours respectively.

To evaluate the kinetics and mechanism of drug release, the in-vitro dissolution data of FM7 was subjected to different mathematical models, such as zero order, first order, Hixson–Crowell model, Higuchi, and Korsmeyer-Peppas model.

The result of the curve fitting into these mathematical models above is given in Table 2. It was found that the in-vitro dissolution data was well fitted to the zero order mathematical model (R^2= 0.9955) which indicated that the optimized formulation exhibits zero order drug release kinetics wherein concentration independent and constant rate drug release is observed (Acharya et al., 2014). The value of diffusional exponent n in the Korsemeyer-Peppas model was found to be 0.74. This suggested the possibility of anomalous transport due to contribution of both swelling and diffusion. (Desai et al., 2014, Korsmeyer et al., 1983, Qi et al., 2015). Hence swelling coupled with effervescence induced porosity in the matrices could have enabled zero order release as seen (Table 2).

3.1. X-ray diffraction analysis

Crystalline nature of pure Metoprolol succinate is shown in the x-ray diffraction profile (Fig. 7). The XRD of metoprolol succinate showed sharp peaks at an angle of 14.42, 20.08 and 23.62 (2θ). XRD pattern of FM7 exhibited corresponding peaks with decrease in intensity of the peaks indicating a decrease in the crystallinity of the drug. The peak at 30.44 (2θ) of sodium bicarbonate was also observed in the XRD pattern of suggesting crystalline nature.

3.2. Differential scanning calorimetry analysis

The DSC thermogram of metoprolol succinate revealed a sharp endothermic peak at 136.4 °C which corresponds to the melting point of metoprolol succinate (Fig. 8). The thermogram of FM7 also exhibited the characteristic endotherm of metoprolol succinate, indicating crystalline state of the drug and no interaction with other excipients. In the thermogram of

FM7 the endotherm observed at 69.9°C corresponds to melting of PEO, while the endotherm at 159.6°C is attributed to degradation of sodium bicarbonate.

3.3. Fourier transform infrared analysis

Infrared spectrum of metoprolol succinate revealed –NH symmetric stretching at 3147 cm^{-1} due to secondary amine, –C=O stretching at 1620 cm^{-1} due to succinic acid, –C=C– ring stretching at 1481 cm^{-1}, and –C–O–C– asymmetric stretching at 1242 cm^{-1}. Infrared spectrum of FM7 revealed all the characteristic peaks of metoprolol succinate, –NH stretching of secondary amine at 3153 cm^{-1}, –C=O stretching of succinic acid at 1620 cm^{-1}, and –C=C– ring stretching of metoprolol succinate at 1473 cm^{-1} and –C–O–C– asymmetric stretching at 1242 cm^{-1} which clearly shows the nonexistence of any chemical interaction between the drug and the other excipients even at elevated operating temperatures during HME process (Fig. 9).

3.4. Stability studies

Formulation FM7 was evaluated for stability. In-vitro buoyancy study of extrudates revealed FLT and TFT comparable to the zero time samples. No significant difference in drug release profile was observed during three months stability as indicated by $t_{50\%}$ and $t_{90\%}$ values and f_2 values >50 as well as f_1 value <15 (Table 3) confirming stability of the floating multiparticulates of metoprolol succinate.

4. Conclusion

We present HME for design of floating multiparticulate drug delivery systems. The successful design of floating controlled release multiparticulates of a water soluble drug

metoprolol succinate proposes this approach as platform technology which could be extrapolated to a range of other drugs with varying solubility.

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Conflict of interest

None to declare

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Table 1: Composition of hot melt extruded multiparticulate formulations (%, w/w) and resulting torque

Formulation Code	Metoprolol Succinate	Sodium Bicarbonate	HPMC	Eudragit® RS PO	Glyceryl Mono Stearate	PEO	Torque (Nm)
FM1	10	10	-	75	5	-	30-32
FM2	10	10	-	45	5	30	33-35
FM3	10	10	-	30	5	45	36-39
FM4	10	10	-	15	5	60	44-47
FM5	10	5	-	15	5	65	42-46
FM6	10	5	10	15	5	55	56-59
FM7	10	5	15	15	5	50	65-71
FM8	10	5	20	15	5	45	>90
FM9	10	5	15	10	5	55	82-86
FM10	10	5	15	20	5	45	53-58
FM11	10	5	15	25	5	40	48-51
FM12	10	10	15	15	5	45	67-70
FM13	10	15	15	15	5	40	69-73

Table 2: Results of mathematical models after curve fitting of *in-vitro* drug release data of FM7

Models	Slope	Intercept	R-square
Zero order	8.2004	7.0069	0.9955
First order	0.1863	2.2814	0.8126
Hixon-Crowell	3.2807	0.9282	0.9493
Higuchi	29.4812	10.4340	0.9816
Korsmeyer-Peppas	1.1858	2.4361	0.8301

Table 3: Stability data for floating multiparticulates of metoprolol succinate (FM7)

Parameters	Initial	One month	Two months	Three months

Floating lag time (sec)	176 ± 3.60	174 ± 1.53	171 ± 2.08	167 ± 1.53
Total floating time (h)	>12	>12	>12	>12
Assay (%)	99.85 ± 0.11	99.71 ± 0.20	99.04 ± 0.16	99.53 ± 0.25
t_{50} (h)	5.24	5.07	4.9	4.76
t_{90} (h)	10.12	9.92	9.72	9.57
f_2 value	reference	84.69	72.84	64.69
f_1 value	reference	3.36	6.6	9.25

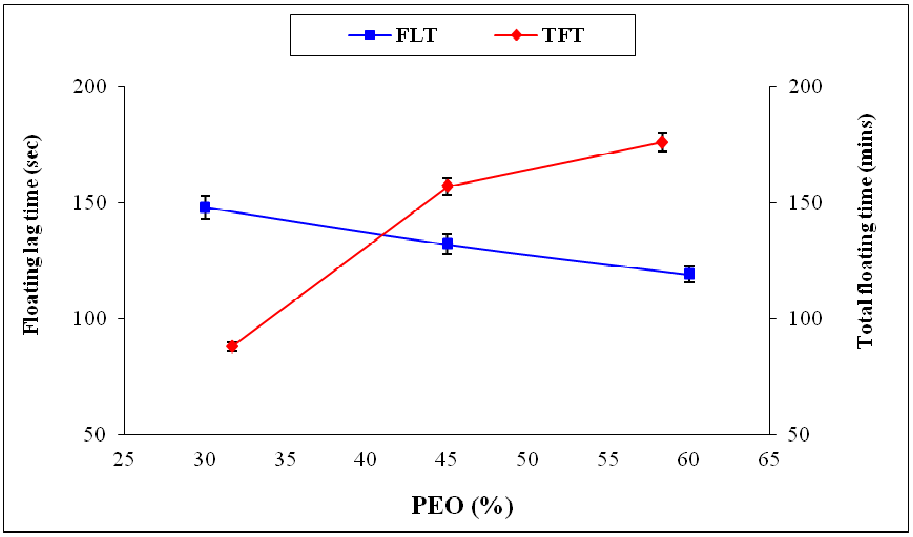

Fig.1. Effect of concentration of PEO on floating lag time and total floating time of floating multiparticulates

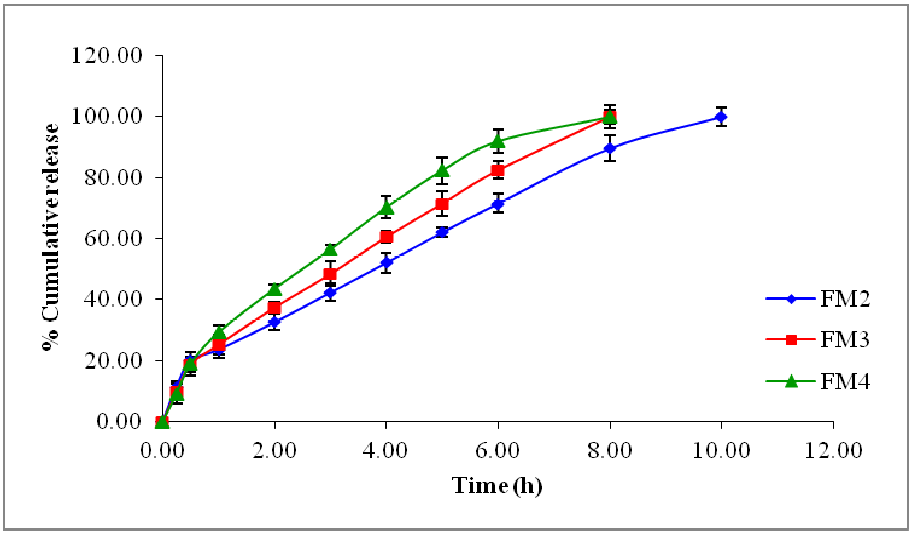

Fig.2. Effect of concentration of PEO on in-vitro release of metoprolol succinate

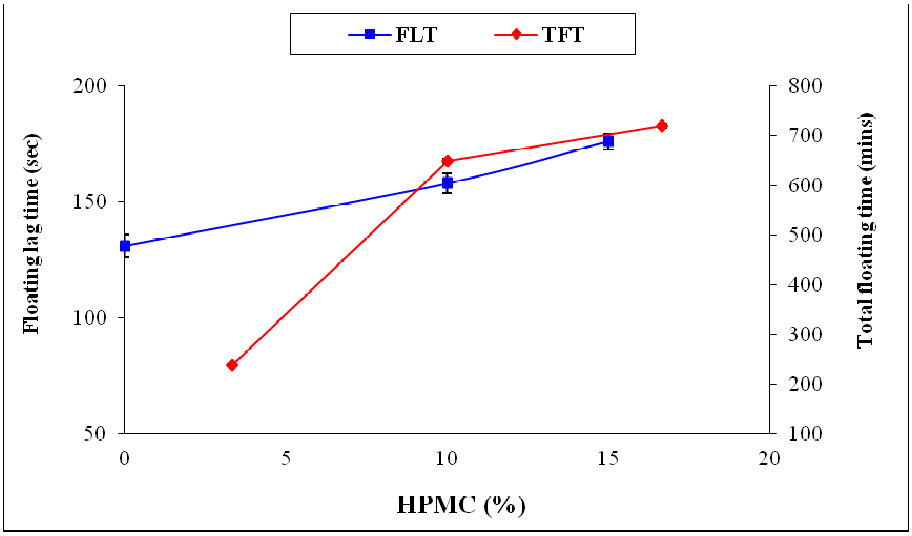

Fig.3. Effect of concentration of HPMC on floating lag time and total floating time of floating multiparticulates

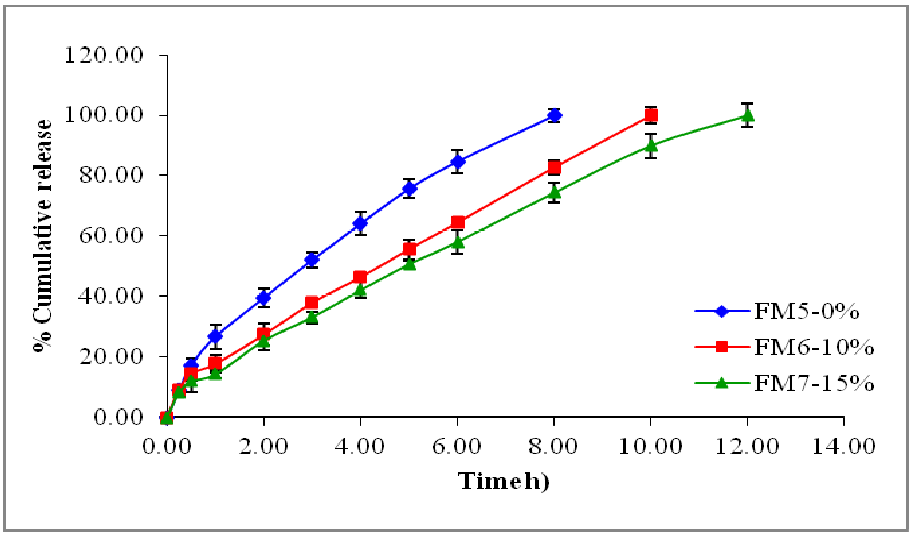

Fig.4. Effect of concentration of HPMC on in-vitro release of metoprolol succinate

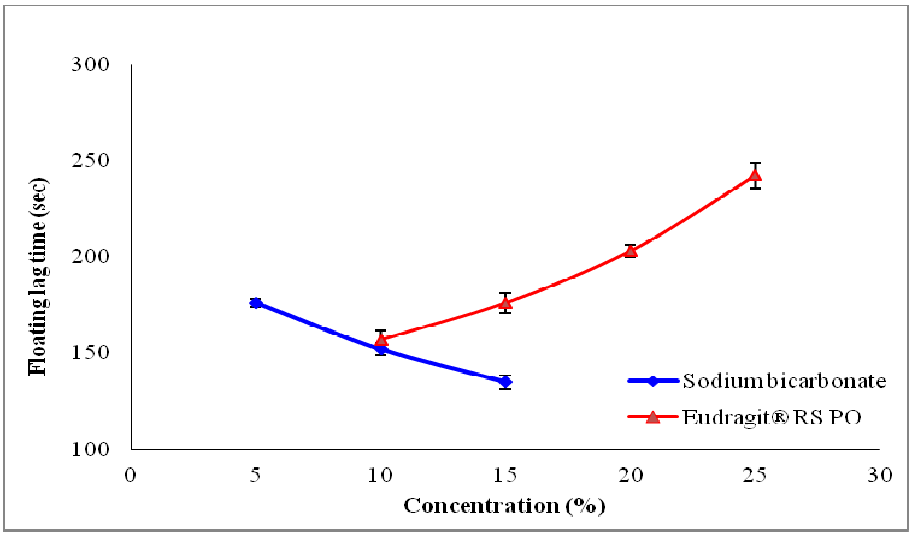

Fig.5. Effect of concentration of sodium bicarbonate and Eudragit® RS PO on floating lag time of floating multiparticulates

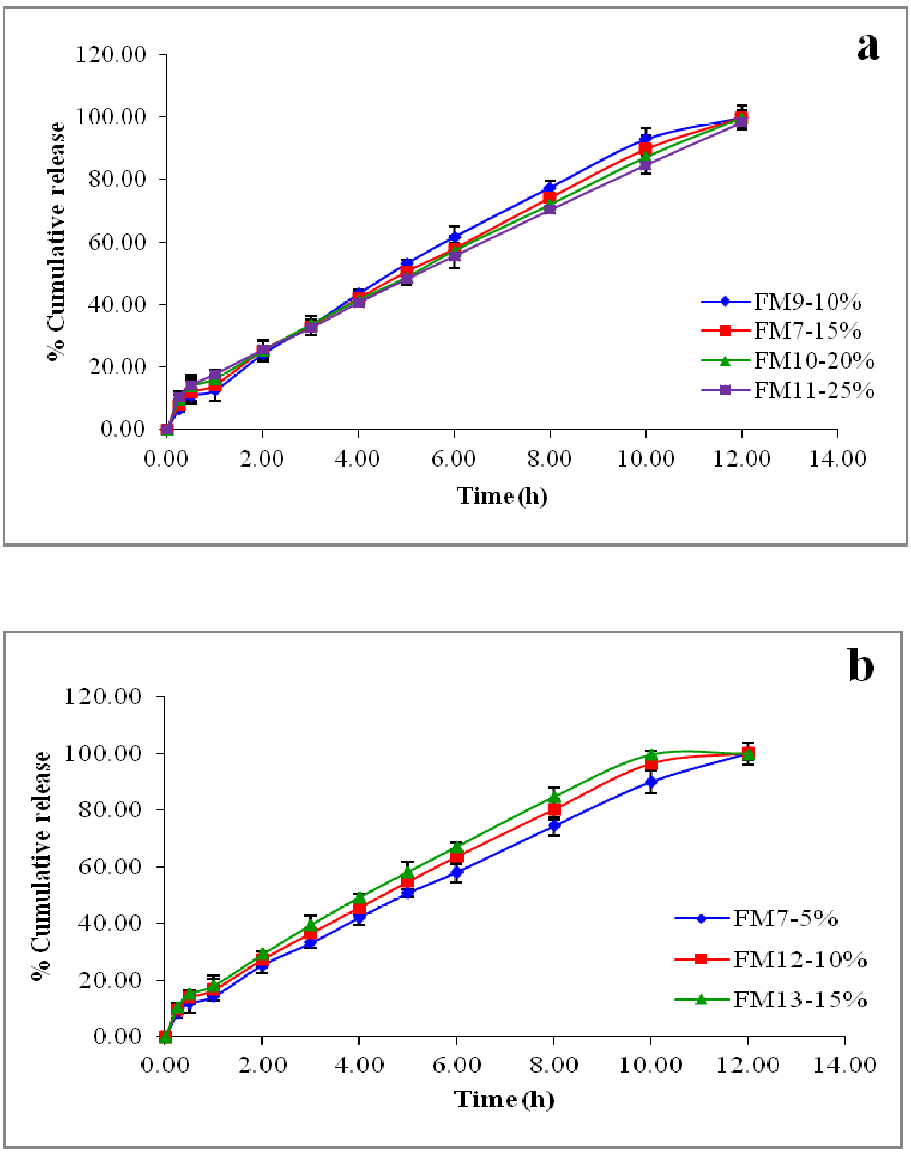

Fig.6. Effect of concentration of Eudragit® RS PO (a) and sodium bicarbonate (b) on in-vitro release of metoprolol succinate

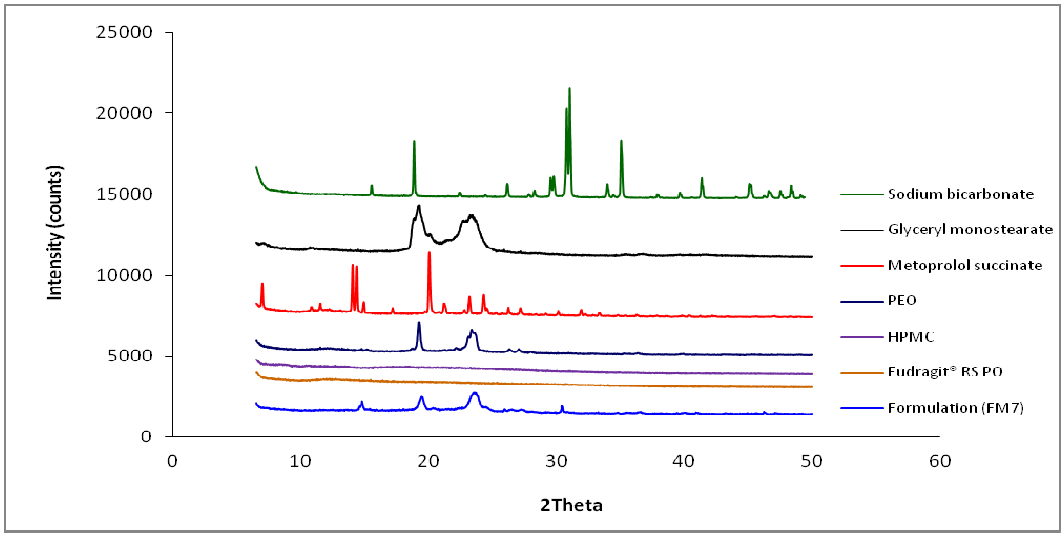

Fig.7. Powder X-ray diffraction patterns of sodium bicarbonate, glyceryl monostearate, metoprolol succinate, PEO, HPMC, Eudragit® RS PO, and FM7

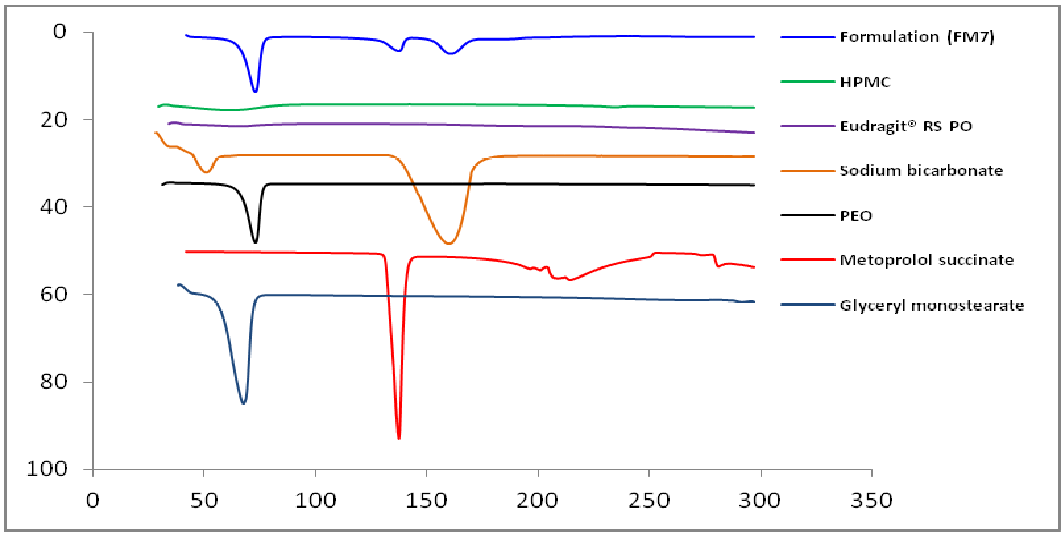

Fig.8. DSC thermograms of FM7, HPMC, Eudragit® RS PO, sodium bicarbonate, PEO, metoprolol succinate and glyceryl monostearate

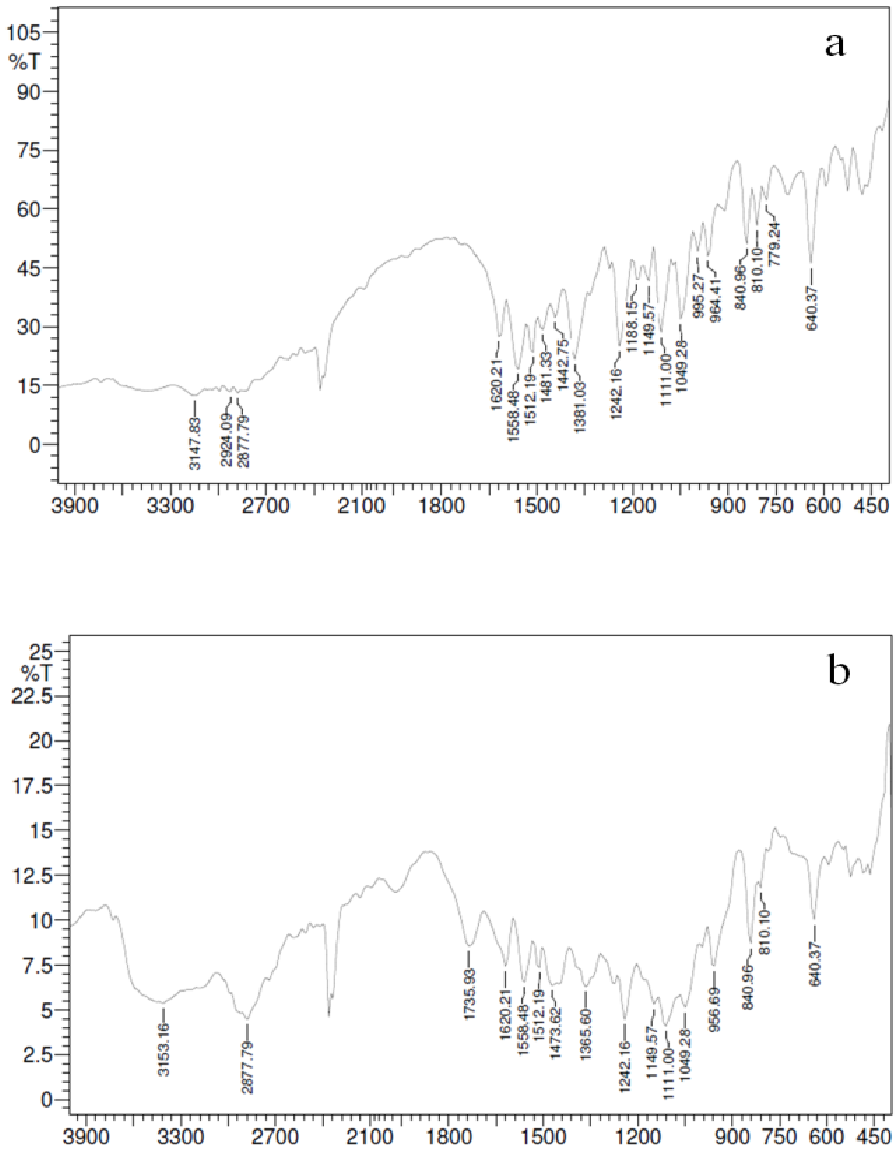

Fig.9. FTIR spectrum of metoprolol succcinate (a) and FM7 (b)