Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol. 4, Suppl 1, 2011 ISSN - 0974-2441

Research Article

FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF METOPROLOL SUCCINATE

JAGADEESH NADIGOTI[1], SATHISH DHARANI[1], SHAYEDA[2*], MADHUSUDAN RAO YAMSANI[2]

1Vaagdevi College of Pharmacy, Warangal (A.P), India, 2 Centre for Biopharmaceutics and Pharmacokinetics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal (A.P), India. Email: shayeda_ucpsc@yahoo.com

ABSTRACT

Site and time specific oral drug delivery have recently been of great interest in the field of pharmaceutical formulation development to achieve improved therapeutic efficacy. Oral sustained release gastro-retentive dosage forms (GRDF) is such an approach which offers many advantages for drugs with absorption from upper parts of gastrointestinal tract (GIT), drugs required to exert local therapeutic action in the stomach, drugs unstable, insoluble in the lower parts of GIT. A multiple-unit floating drug delivery system for Metoprolol succinate, based on low density polymeric system was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form.

The system consists of a narrow absorption window drug – Metoprolol succinate containing microparticles prepared from polymethacrylate polymers (Eudragit S100, RSPO, RLPO) by non-aqueous emulsion solvent evaporation method. The drug-excipient compatibility studied using FTIR revealed no interaction of drug and polymers used in formulation development. Increasing the drug to polymer concentration of Eudragit RSPO increased the entrapment efficiency (93.27 %), buoyancy (80.6 %). In vitro release studies performed in 0.1 N HCl revealed that the optimized formulation could prolong the release for 8 hours in a sustained fashion following zero order kinetics. The SEM studies showed that the floating microparticles were nearly spherical and rough textured. Both floating and sustained release properties were achieved in multiunit floating drug delivery system developed in this present study.

Keywords: Multiple-unit floating drug delivery, Non-aqueous emulsion solvent evaporation, Low density polymeric system, Metoprolol succinate.

INTRODUCTION

Site and time specific oral drug delivery have recently been of great interest in the field of pharmaceutical formulation development to achieve improved therapeutic efficacy. Oral sustained release gastro-retentive dosage forms (GRDF) is such an approach which offers many advantages for drugs with absorption from upper parts of gastrointestinal tract (GIT), drugs required to exert local therapeutic action in the stomach, drugs unstable, insoluble in the lower parts of GIT[1]. Methods or forms for prolonging the gastric retention have been attempted based on different mechanisms such as floating[2-5], expansion/ plug type [6,7], swellable and bioadhesive [8]. The floating systems in particular have been extensively researched, mainly because it does not adversely affect the motility of GIT [9]. Multiple unit dosage forms, include hollow microspheres (microballoons)[10], granules[11], mini-tablets and pellets. These multiunit dosage forms are more reliable because they reduce the inter-subject variability in absorption, lower the probability of dose dumping[12], more uniform distribution, providing a possibility of achieving a long-lasting and more reliable release of drugs[13]. Floating microspheres of Cimetidine[14], Lansoprazole[15], Metformin HCl[16] were formulated using different polymers.

Metoprolol succinate which is used in the treatment of hypertension, angina and arrhythmia has an absorption window and is mainly absorbed from the upper parts of GIT, and good stability in the acidic environment of the stomach makes it a suitable candidate to formulate in a GRDF. Moreover it has a half-life of 3-7 hours[17], making repetitive dosing necessary. Therefore a sustained drug delivery system that spends most of its time in acidic environment of stomach i.e., floating dosage form which improves the bioavailability of the drug was opted-for.

Eudragits are group of polymers belonging to polymethacrylates family some having pH dependent solubility (Eudragit S100) and others with sustained release properties (Eudragit RSPO, RLPO) were exploited here in formulating GRDF.

MATERIALS AND METHODS

Metoprolol succinate, [1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol] was a gift sample from Dr. Reddy's Laboratories (Hyderabad, India), Eudragit RSPO, Eudragit RLPO, and Eudragit S100 were gift samples from AET laboratories (Hyderabad, India). Light liquid paraffin, n-Hexane, petroleum ether, methanol were purchased from Finar chemicals Ltd, Ahmedabad, India. Acetone was purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals used were of analytical grade and purchased from Merk Co., Germany.

Formulation of floating microparticles

Floating microparticles containing Metoprolol succinate as a core material were prepared by "Non-aqueous Emulsion Solvent Evaporation" method. Briefly, the drug was dissolved in 10 ml of methanol and polymer was dissolved in 10 ml of acetone. Magnesium stearate (17.54 % w/w of total drug and polymer) was added to methanolic solution of drug. The methanolic solution of drug and magnesium stearate was poured dropwise into polymer solution under vigorous mixing conditions. The above slurry was slowly introduced into 300 ml of light liquid paraffin while being stirred at 1000 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature. The stirring was continued for three-and-a half (3 ½) hours to allow the solvents (acetone, methanol) to evaporate completely and the formed microparticles were collected by filtration. The microparticles were washed repeatedly with n-Hexane and petroleum ether until free from oil. The collected microparticles were dried at room temperature for 24 hours. Different formulations were prepared using polymers like Eudragit S100, RSPO, and RLPO in varying ratios of drug to polymer as shown in Table 1.

Evaluation of floating microparticles

The prepared floating microparticles were evaluated for various parameters such as yield, particle size, drug entrapment efficiency, in vitro evaluation of floating ability (Buoyancy %), in vitro drug release studies.

Yield of floating microparticles

The yield of microparticles was calculated from the amount of microparticles obtained divided by the total amount of all non-volatile components.

$$\% \text{ Yield} = \frac{\text{Actual weight of the microparticles}}{\text{Total weight of the drug and excipients}} \times 100$$

Particle size and shape

The particle size of the microparticles was measured by optical microscopy. The shape of the microparticles was visualized and the photographs were taken with the aid of a binocular microscope (Quasmo, India, model PZRM 700).

Table1: Compositions of Floating Microparticles containing Metoprolol succinate

Formulation code	Metoprolol succinate (mg)	Eudragit RLPO (mg)	Eudragit RSPO (mg)	Eudragit-S 100 (mg)	Magnesium stearate (mg)
F1	47.5	47.5	---	-	16.63
F2	47.5	95	---	-	24.99
F3	47.5	142.5	---	-	33.32
F4	47.5	190	---	-	41.65
F5	47.5	---	47.5	-	16.63
F6	47.5	---	95	-	24.99
F7	47.5	---	142.5	-	33.32
F8	47.5	---	190	-	41.65
F9	47.5	---	285	-	58.32
F10	47.5	23.75	23.75	-	16.63
F11	47.5	---	---	47.5	16.63
F12	47.5	---	---	71.25	20.28
F13	47.5	---	---	95	24.99

Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing 20 mg of microparticles using mortar and pestle, and extracting drug with aliquots of 0.1 N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1 N HCl. The solution was taken in a beaker and sonicated in a bath sonicator (PCi, Mumbai, India) for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically using double beam UV Visible spectrophotometer (SL 164, Elico India Ltd, Mumbai, India) at 274 nm against an appropriate blank. The amount of drug entrapped in the microparticles was calculated using the following formula.

$$DEE = \frac{\text{Amount of drug actually present}}{\text{Theoritcal drug load expected}} \times 100$$

In vitro evaluation of floating ability (Buoyancy %)

Seventy five milligrams of floating microparticles were spread over the surface of a type II USP dissolution apparatus (TDT 06P, Electro lab, Mumbai, India) filled with 900 ml of 0.1 N HCl containing 0.02 % v/v Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 8 hours. After 8 hours, the layer of buoyant microparticles were pipetted and separated by filtration. The particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in dessicator and weighed. The buoyancy % was calculated from the weight of floating particles to the sum of floating and sinking particles.

$$\text{Buoyancy \%} = Wf / (Wf + Ws) \times 100$$

Where, Wf and Ws are weights of the floating and settled microparticles respectively.

In vitro drug release study

In vitro drug release studies were carried out for all formulations in USP type II dissolution test apparatus containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.2^{0}C at a rotation speed of 100 rpm. Samples were withdrawn at predetermined intervals and analysed for the drug content by UV-Visible spectrophotometer at 274 nm.

Analysis of in vitro release data

The obtained dissolution data was fitted into various kinetic models (zero order, first order, Higuchi and Koresmeyer-Peppas) to understand the kinetics of the drug release from floating microparticles.

Surface morphology of the floating microparticles

The surface morphology of the floating microparticles was studied with the aid of a Scanning Electron Microscope (SEM).

Drug - Excipient compatibility

Drug - Excipient compatibility was studied by FTIR (Perkin-Elmer) spectra of physical mixtures and formulation using KBr pellet method.

RESULTS AND DISCUSSION

Floating Microparticles containing Metoprolol succinate was successfully prepared by "Non-aqueous Emulsion Solvent Evaporation" method. The yields of the obtained formulations were shown in Table 2**.** The yield was high for the formulation F10 (Drug: RSPO: RLPO: at a ratio of (1: 0.5: 0.5) amounting to 86.56 % and the yield of the formulation F11 (Drug: Eudragit S 100 at a ratio of 1:1) was low among all the formulations.

The average particle size (Table 2) of the prepared microparticles was lowest for the F 10 formulation (16.25 µm) and was highest for F 9 formulation (41.09 µm). The minimum and maximum size ranges were 6.66-26.6 µm for F 1 formulation and 16.65- 86.58 µm for F13 formulation respectively. From the results of the particle size measurement it was concluded that as the core to coat ratio (drug to polymer ratio) increased there was an increase of the particle size. This may be attributed to the increase in the viscosity of the solution containing drug and polymer mixture, as constant amounts of the solvents were used for their solubilization.

The drug entrapment efficiency (Table 2) was higher for F 9 formulation (93.3 %) and it was low for F 10 formulation (75.3%). The results obtained clearly indicated that the drug entrapment efficiency increased as the drug to polymer (core to coat) ratio increased. This may be attributed to the availability of more coat material per core molecule. The entrapment efficiency was also higher because the drug was present in a non-aqueous media (light liquid paraffin) in which the solubility of the drug is very low, thereby preventing the loss of the drug into the dispersion medium during the formulation of microparticles.

Table 2: % Yield, Particle size, Entrapment efficiency and Buoyancy % of prepared formulations

Code	Parameter*			
	% Yield	Particle size	Entrapment Efficiency	Buoyancy %
F1	72.9± 2.21	16.31 ±5.5	77.64 ± 1.0	69.69 ± 0.7
F2	75.6± 2.86	18.51 ±4.2	78.77 ± 2.0	73.95 ± 4.1
F3	81.3± 2.49	25.84 ± 5.1	83.13 ± 2.7	75 ± 1.7
F4	76.4± 2.65	27.30 ± 8.6	90.19 ± 3.3	76.1 ± 1.9
F5	73.4± 3.43	20. 97 ± 5.3	79.21 ± 1.3	73.8 ± 2.8
F6	85.8± 2.04	24.57 ± 5.5	79.94 ±2.0	74.38 ± 2.6
F7	82.1± 3.12	28.30 ± 5.8	90.97 ± 2.7	79 ± 3.0
F8	82.1± 2.54	35.29 ± 7.9	92.15 ± 3.3	78.02 ± 1.7
F9	77.0± 2.65	41.09 ± 10.6	93.27 ± 2.3	80.6 ± 1.8
F10	86.6± 1.96	16.25 ± 4.0	75.29 ± 0.1	71.55 ± 1.6
F11	71.2±2.87	40.09 ± 12.2	81.56 ± 1.3	61.58 ± 5.2
F12	77.3± 2.32	41.22 ± 14.3	79.41 ± 0.4	67.81 ± 3.0
F13	76.4± 2.76	42.02 ± 14.6	83.47 ± 2.0	69.52 ± 1.3

*All values are given as Mean ± SD; n= 3

The floating ability (Table 2) of F 11 formulation was lower, amounting to 61.58 % and it was highest for F 9 formulation (80.6 %). The formulations prepared from RSPO polymer were found to have good floating ability than those formulated from RLPO and Eudragit S 100. The lower floating ability of the prepared microparticles may be ascribed to their small size. As the size was small, the mass / volume ratio (density) may be more, leading to an early settling of the microparticles. The drug release from the 1: 1 of Drug: RLPO showed a burst effect, releasing 46.73 % of the drug within 0.5 hour and overall the release could be sustained only for 2 hours. This might be due to the more effective surface area of the microparticles owing to their small size and the volume of the dissolution media (900 ml) to which the microparticles were exposed. More- over the inherent hydrophilicity of the drug may be one of the parameters for its faster release. Therefore 1: 1 core to

coat ratio was not sufficient to retard the drug release for a prolonged period of time.

On increasing the drug to polymer ratio, the drug release could be prolonged. The 1:4 ratio of drug to RLPO could sustain the release for 5 hours releasing about 91% of the drug (Figure 1). The drug release from RSPO polymer was slower and the cumulative % drug release was less when compared to the same ratio of drug: RLPO. The difference in the release from the polymers may be attributed to their permeability characteristics. As the quaternary ammonium groups in RLPO are more than those in RSPO, the drug release was faster from microparticles formulated from RLPO. The available literature (Rowe, 2006) suggests that the quaternary ammonium groups in RLPO and RSPO are 10 % and 5 % respectively, have a profound influence on the permeability of the polymer. The formulation F 9 (drug to RSPO 1:6, Figure 2) could prolong the release for a longer time, releasing 91 % at the end of 8th hour. The drug release from Eudragits S 100 was much slower than the release from the RLPO and RSPO polymers. This may be attributed to the acid resistant film forming ability of Eudragit S 100 (Figure 3) compared to the inherent permeability characteristics of RLPO and RSPO. Therefore, a high core to coat was essential to prolong the release of the drug from microparticles and this could be achieved by using 1: 6 ratio of drug to RSPO. The drug release data was fitted in to various kinetic models and the R^2 values were obtained to know the pattern of release and the results are given in the table below. The obtained R^2 values suggested that the drug release from RLPO and RSPO polymers followed Higuchi model and release from Eudragit S 100 followed zero order pattern. The drug release from the optimized formulation F 9 followed more of a zero order release (R^2 = 0.9831) than a Higuchi model (R^2 = 0.9652). The R^2 values and n value of all the formulations obtained after fitting the data into various kinetic models was given in the Table 3. The "n" of most of the formulations fit in a range of 0.43- 0.85, indicating an anomalous (non- fickian) transport drug release mechanism. The binocular microscopic (Figure 4) and SEM studies (Figure 5) showed that the floating microparticles were nearly spherical and rough textured. There is no interaction between the drug and excipient was observed from the FTIR spectras.

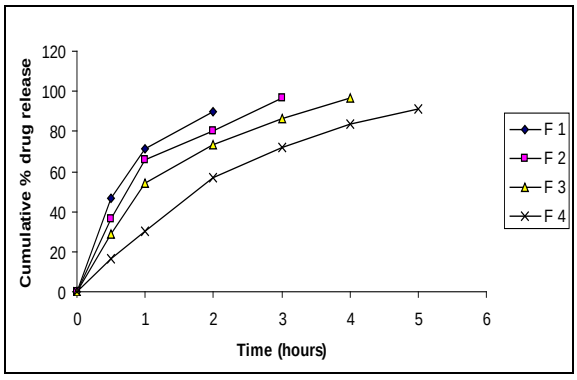


Fig. 1: *In vitro* drug release profiles of formulations F1-F4

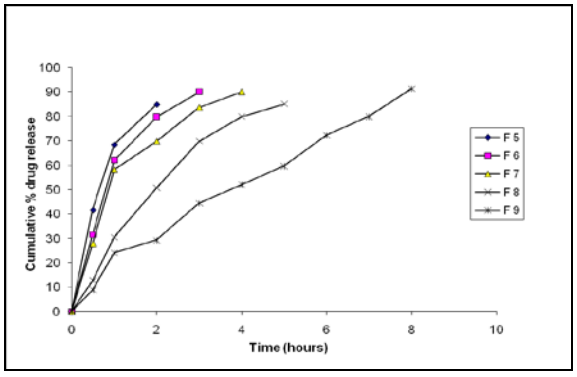


Fig. 2: *In vitro* drug release profiles of formulations F5-F9

Table 3: Drug release kinetics of prepared formulations

Formulation Code	R^2			Koresmeyer Peppas(n)
	Zero order	First order	Higuchi release	
F1	0.9343	0.8710	0.9925	0.473
F2	0.9046	0.8133	0.9834	0.516
F3	0.9186	0.8077	0.9882	0.558
F4	0.9480	0.8353	0.9767	0.759
F5	0.8683	0.8385	0.9873	0.513
F6	0.8637	0.7702	0.9758	0.593
F7	0.8450	0.7370	0.9706	0.534
F8	0.9462	0.7971	0.9703	0.823
F9	0.9831	0.8262	0.9652	0.774
F10	0.8783	0.5954	0.9904	0.523
F11	0.9826	0.6763	0.9489	0.991
F12	0.9909	0.6936	0.9416	0.911
F13	0.9666	0.7019	0.9370	0.996

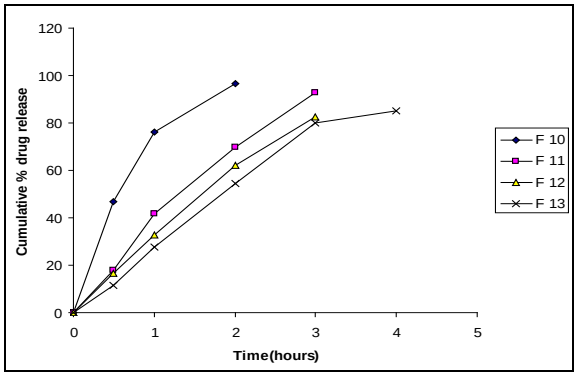


Fig. 3: *In vitro* drug release profiles of formulations F10-F13

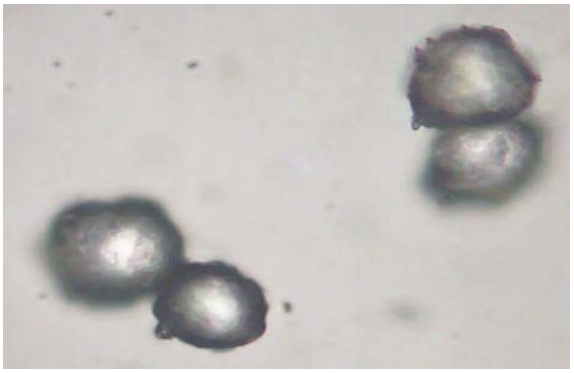
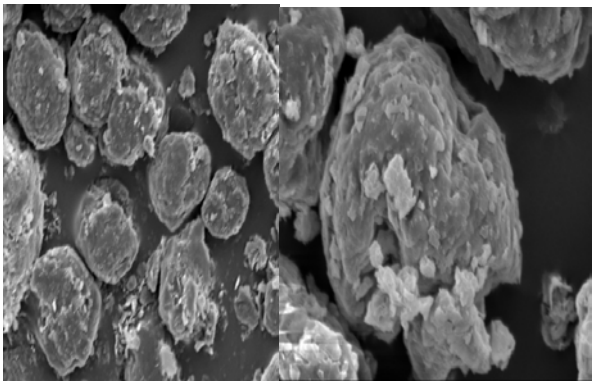


Fig. 4: Binocular microscopic photographs showing the morphology of the floating microparticles.



Magnification of 500 x **Magnification of 2000 x**

Fig. 5: SEM photographs showing the surface morphology of the floating microparticles.

CONCLUSION

Floating Multiunit Drug Delivery System was successfully prepared by non-aqueous emulsion solvent evaporation method for a freely water soluble drug, Metoprolol succinate by using Eudragit RLPO and RSPO, Eudragit S 100. The formulation containing drug to Eudragit RSPO in 1:6 ratio could sustain the release for 8 hours. However, further pharmacokinetic studies are needed to understand and confirm the effective absorption of Metoprolol succinate from floating microparticles. Further, the microspheres can also be compressed into tablets, filled into capsules, or formulated into oral suspension for reconstitution.

ACKNOWLEDGEMENTS

The authors would like to thank All India Council for Technical Education (AICTE) for giving financial support and Dr.Reddy's Laboratories, AET laboratories for their gift samples. The authors also thank the management of Vaagdevi College of Pharmacy, Warangal, for providing necessary infrastructure to carry out this work.

REFERENCES

1. Brahma N. Singh Kwon H. Kim. Drug delivery-oral route. In: Swarbrrick J, ed. Encyclopedia of pharmaceutical technology. NewYork, Marcel Decker. 2002; 888-896.
2. Bhise SD, Aloorkar NH: Formulation and Invitro evaluation of floating capsules of Theophylline. Ind J Pharm Sci. 2008; 70(2): 88-93.
3. Ferdous K, Mohammed SMI, Razzak, Mohammed ZRK, Kazi RA, Sams MAS, Mohammed SR: Preparation and invitro evaluation of Theophylline loaded gastro retentive floating tablet of Methocel K4 M. J Pharm Sci. 2008; 7(1): 184-189.
4. Dumpeti J, Meka L, Chinnala KM, Vadlaboina V: Formulation and In vitro evaluation of gastro retentive drug delivery system for Ranitidine HCl. Int J Pharm Sci and Nanotech. 2008; 1(3): 227-232.
5. Lohray, Tiwari, Pai, Murthy, Mehta, Novel Floating dosage form (Bilayer tablet). European patent WO/2004/002445.
6. Eytan A. Klausner SE, Eran L, Michael F, Amnon H: Novel Levodopa Gastroretentie dosage from, in vivo evaluation in dogs. J Control Release. 2003; 88: 117-126.
7. Chen J, Blevins WE, Park H: Gastric retention properties of superporous hydrogel composites. J Control Release. 2000; 64: 235-259.
8. Mahesh D, Chavanpatil, Paras J, Sachin C, Rajesh S, Pradeep R: Novel sustained release, swellable and bioadhesive gastro retentive drug delivery system of Ofloxacin. Int J Pharm. 2006; 316: 86-92.
9. Yong-Dan T, Subbu S, Venkataraman, Freddy Y.C, Boey, Li-Wei Wang. Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form. Int J Pharm. 2007; 336: 159-165.
10. Jianhua Z, Chaowu L, Decai B, Yanjun Z, Xiaojun M: Preparation and evaluation of floating-bioadhesive microparticles containing Clarithromycin for the eradication of Helicobacter pylori. J Appl Polym Sci. 2006; 102: 2226-2232.
11. Dashrath MP, Natwarlal MP, Vival FP, Darshini AB: Floating Granules of Ranitidine Hydrochloride-Gelucire43/01: Formulation optimization using Factorial Design. AAPS Pharm Sci Tech. 2007; 8(2): E1-E7.
12. Shyam S, Bhaskar C, Mahadik K, Ananth P: Preparation and evaluation of Diltiazem Hydrochloride –Gelucire 43/01 floating granules prepared by melt granulation. AAPS Pharm Sci Tech. 2004; 5(3): 1-6.
13. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y: Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci. 1992; 81(2): 135-140.
14. Srivastava AK, Devendra N, Ridhurkar, Saurabh W: Floating Microspheres of Cimetidine:Formulation, characterization and invitro evaluation. Acta Pharm. 2005; **55**: 277-285.
15. Muthusamy K, Govindarazan G, Ravi TK: Preparation and Evaluation of Lansoprazole Floating Micropellets. Ind J Pharm Sci. 2005; 67(1): 75-79.
16. Asha P, Subhratha R, RamSharanagat T: Invitro evaluation and optimization of controlled release floating drug delivery system of Metformin Hydrochloride. DARU. 2006; 14(2): 57-64.
17. Wikstrand J, Andersson B, Kendal M, Stanbrook H, Klibaner M: Pharmacokinetic considerations of formulation: Extended release metoprolol succinate in the treatment of heart failure. J Cardiovasc Pharm. 2003; 41: 151-157.