

FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METOPROLOL SUCCINATE USING HYDROPHILIC POLYMERS

Antesh K Jha,^{1*} Bhattacharya A² and Pankaj Verma¹

¹Anand College of Pharmacy, AEC Campus, Keetham, Agra, India, PIN-282007

²Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India. PIN-786004

*Corres author: jha_antesh@rediffmail.com,
Mob No-09368002909

ABSTRACT: The objective of the present study was to develop sustained-release matrix tablets of metoprolol succinate, β_1 -selective adrenergic receptor blocking agent. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC) and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC) and guar gum. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties. The results of dissolution studies indicated that formulation F1 (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 12 hours. In the further formulation development process, F5 (drug-to-HPMC, 1:4; EC 4% wt/vol as granulating agent), the most successful formulation of the study, exhibited satisfactory drug release. All the formulations exhibited diffusion-dominated drug release.

KEYWORDS: Metoprolol succinate, hydroxypropyl methylcellulose, wet granulation, matrix tablets.

INTRODUCTION AND EXPERIMENTAL

Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience. However, developing oral controlled release tablets for water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of the drug on oral administration.¹

Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed.² Metoprolol succinate, β_1 -selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs, thus warrants the use of sustained release formulation for

prolong action and to improve patient compliance.³ In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivative such as hydroxypropyl methylcellulose (HPMC) is generally considered to be stable and safe as release retardant excipient in the development of oral controlled release dosage forms. This semisynthetic polymer is quite expensive when compared with natural polymers such as guar gum, alginates, and so forth.¹ The objective of the present investigation was to develop oral controlled release tablets for freely water soluble metoprolol succinate using HPMC.

Materials

HPMC and Guar gum were purchased from BDH Chemicals (Mumbai, India). Ethyl cellulose was purchased from SD Fine Chemicals Ltd (Mumbai India). PVP was procured from Loba Chemie (Mumbai, India). Metoprolol succinate was obtained as a gift sample from

Alkem Pharmaceutical Ltd (Mumbai, India). All the other chemicals used were of high analytical grade. Magnesium stearate, and talc used were of USP/NF quality.

Methods

Preparation of Tablets

Different tablet formulations were prepared by wet granulation technique (Table 1). All the powders were passed through 80 mesh. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent (ethanolic solution of EC and PVP) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Talc and magnesium stearate were finally added as glidant and lubricant. The practical weight of tablets was calculated based on the drug content of the granulations, and the tablets were compressed using a single-punch tablet compression machine (Cadmach, Ahmedabad, India). Each tablet contained 40 mg of Metoprolol succinate and other pharmaceutical ingredients as listed in Table 1. Prior to the compression, the granules were evaluated for several tests.

Evaluation of Granules

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = \frac{h}{r} \quad (1)$$

where h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas:

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}} \quad (2)$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}} \quad (3)$$

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index:

$$\text{Carr's index (\%)} = \frac{[(\text{TBD} - \text{LBD}) \times 100]}{\text{TBD}} \quad (4)$$

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V):

$$\text{Porosity (\%)} = \frac{V_{\text{bulk}} - V}{V_{\text{bulk}}} \times 100 \quad (5)$$

Drug Content

An accurately weighed amount of powdered metoprolol succinate granules (100 mg) was extracted with water and the solution was filtered. The absorbance was measured at 222 nm after suitable dilution.⁸

Evaluation of Tablets

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver TP-214), and the test was performed according to the official method⁹.

Drug Content

Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described above.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Hardness tester (Toshiba India, New Delhi) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

In Vitro Release Studies

The in vitro dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 7.4 from 3 to 16 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu, UV-1800) at 222 nm.⁸ The release studies were conducted in triplicate (6 tablets in each set), and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results.

RESULTS AND DISCUSSION

Results

The granules of different formulations were evaluated for angle of repose, compressibility index, total porosity, and drug content (Table 2). The results of angle of repose and compressibility index (%) ranged from 21.20 ± 0.02 to 26.07 ± 0.03, and 10.78 ± 0.09 to 12.33 ± 0.02, respectively. The results of percentage porosity of the granules ranged from 24.23 ± 0.03 to 34.27 ± 0.02. The drug content in a weighed amount of granules of all formulations ranged from 96.53 ± 0.03 to 98.55 ± 0.03%. The average percentage deviation of 20 tablets of each

formula was less than $\pm 5\%$. Drug content was found to be uniform among different batches of the tablets and ranged from 96.34 ± 0.03 to 98.89 ± 0.01 . The hardness and percentage friability of the tablets of all batches ranged from 4.3 ± 0.13 to 4.9 ± 0.33 kg/cm² and 0.70 ± 0.06 to $0.87 \pm 0.09\%$, respectively (Table 3). The results of dissolution studies of all the formulations (drug-to-polymer ratio, 1:4), are shown in **Figure 1**. Tablets F1 and F2 released 35.23% and 55.43% of drug at the end of 2 hours; 82.24% and 99.29% of drug at the end of 8 hours, respectively. Tablets F1 released 99.67% of drugs at the end of 12 hours. The formulation F1 was further modified by incorporating different granulating agents, such as PVP (10% wt/vol, F3), EC (2% wt/vol, F4) and EC (4% wt/vol, F5). The results of dissolution studies of these tablets indicate that F3, F4 and F5 released 30.37%, 24.37% and 21.29% of drug at the end of 2 hours and 99.17%, 94.69% and 92.67% at the end of 16 hours, respectively. Incorporation of EC (4% wt/vol, granulating agent) along with HPMC (drug-to-HPMC, 1:4) better retarded the release rate of drug compared to other granulating agents.

Discussion

The granules for tablet preparation were prepared according to the formula given in Table 1. Granulation is the key process in the production of many dosage forms involving the controlled release of a drug from coated or matrix-type particles. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of different formulations were evaluated for angle of repose, compressibility index, total porosity, and drug content (Table 2). The results of angle of repose ($<30^\circ$) indicate good flow properties of the granules. This was further supported by lower compressibility index values (Table 2). Generally, compressibility index values up to 15% result in good to excellent flow properties.⁶ The percentage porosity values of the granules ranged from 24.23% to 34.27%, indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates. The drug content in the weighed amount of granules of all formulations was found to be uniform. All these results indicate that the granules possessed satisfactory flow properties, compressibility, and drug content.

The tablets of different formulations were subjected to various evaluation tests, such as uniformity of weight, drug content, hardness, friability, and in vitro dissolution.

In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is $\pm 5\%$. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 96%. The formulation F5 showed a comparatively high hardness value of 4.9 kg/cm². This could be due to the presence of more EC, which is generally responsible for more hardness of the tablet. The low hardness value observed with formulation F2 may be due to the presence of guar gum, which generally decreases the hardness of tablets. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

The in vitro drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 16 hours using USP XXIII dissolution apparatus 2. Among the polymers tested, HPMC could retard the release only up to 12 hours, and hence it was selected for further formulation development. Formulations F1 and F2 showed burst release of drug in the initial hours, which is probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules. A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release. The formulation F1, which exhibited the slowest dissolution profile of the initial series, was modified using different granulating agents, such as PVP (10% wt/vol, F3), EC (2% wt/vol, F4) and EC (4% wt/vol, F5), to control the drug release in the initial hours, besides making the formulation release a high cumulative amount of drug at the end of 16 hours. Among the formulations F3, F4, and F5, the release rate was increased in the following order: PVP (10%) > EC (2%) > EC (4%), indicating that as the hydrophilicity of the polymer was reduced, the release rate was also reduced. These formulations also showed a high release in the initial hours. To know the mechanism of drug release from these formulations, the data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer et al's (log cumulative percentage of drug released vs log time) equations along with zero order (cumulative amount of drug released vs time) pattern. As

clearly indicated in Figure 1, the formulations did not follow a zero-order release pattern. The release rate kinetic data for all the other equations can be seen in Table 4. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.8889 and 0.921. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics.¹² In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity

(R^2 : 0.9692 to 0.9852). To confirm the diffusion mechanism, the data were fit into Korsmeyer et al's equation. The formulations F1 to F5 showed good linearity (R^2 : 0.9969 to 0.9989), with slope (n) values ranging from 0.4225 to 0.7309, indicating that diffusion is the dominant mechanism of drug release with these formulations.

CONCLUSION

The hydrophilic matrix of HPMC alone could not control the metoprolol succinate release effectively for 16 hours. It is evident from the results that a matrix tablet prepared with HPMC and a granulating agent of a hydrophobic polymer (EC, 4% wt/vol) is a better system for once-daily sustained release of a highly water-soluble drug like metoprolol succinate. Formulations F1 to F5 exhibited diffusion-dominated drug release.

Table 1. Formulation table*

Ingredients(per tablet)/formulation	F1	F2	F3	F4	F5
Drug (mg)	40	40	40	40	40
HPMC (mg)	160	-	160	160	160
Guar gum (mg)	-	160	-	-	-
Ethanol (95%)	qs	qs	-	-	-
PVP (10%wt/vol)	-	-	qs(10 mg)	-	-
EC (2%wt/vol)	-	-	-	qs(2 mg)	
EC (4%wt/vol)					qs(4mg)
Magnesium stearate(%wt/wt)	3	3	3	3	3
Talc (%wt/wt)	2	2	2	2	2

*qs indicates quantity sufficient.

Table 2. Properties of the Granules*

Formulations	Angle of Repose	Compressibility Index (%)	Total Porosity (%)	Drug Content (%)
F1	23.03 ± 0.04	11.67 ± 0.06	26.92 ± 0.04	98.33 ± 0.08
F2	21.20 ± 0.02	10.78 ± 0.09	24.23 ± 0.03	96.53 ± 0.03
F3	26.07 ± 0.03	12.33 ± 0.02	34.27 ± 0.02	97.25 ± 0.02
F4	22.43 ± 0.01	11.45 ± 0.01	30.19 ± 0.05	97.96 ± 0.02
F5	23.49 ± 0.02	11.92 ± 0.07	32.96 ± 0.04	98.55 ± 0.03

*All values are expressed as mean ± SE, n=5

Table 3. Properties of the Compressed Tablets

Tablets	Deviation in Weight Variation Test *(%)	Drug Content** (%)	Hardness # (kg/cm ²)	Friability # (%)
F1	2.635 ± 0.004	97.58 ± 0.01	4.7 ± 0.24	0.79 ± 0.12
F2	3.812 ± 0.005	97.21 ± 0.05	4.3 ± 0.13	0.87 ± 0.09
F3	2.167 ± 0.001	98.89 ± 0.01	4.7 ± 0.16	0.82 ± 0.06
F4	2.891 ± 0.003	96.34 ± 0.03	4.6 ± 0.19	0.72 ± 0.04
F5	2.213 ± 0.002	97.67 ± 0.04	4.9 ± 0.33	0.70 ± 0.06

* All values are expressed as mean ± SE, n=20

** All values are expressed as mean ± SE, n=5

All values are expressed as mean ± SE, n=6

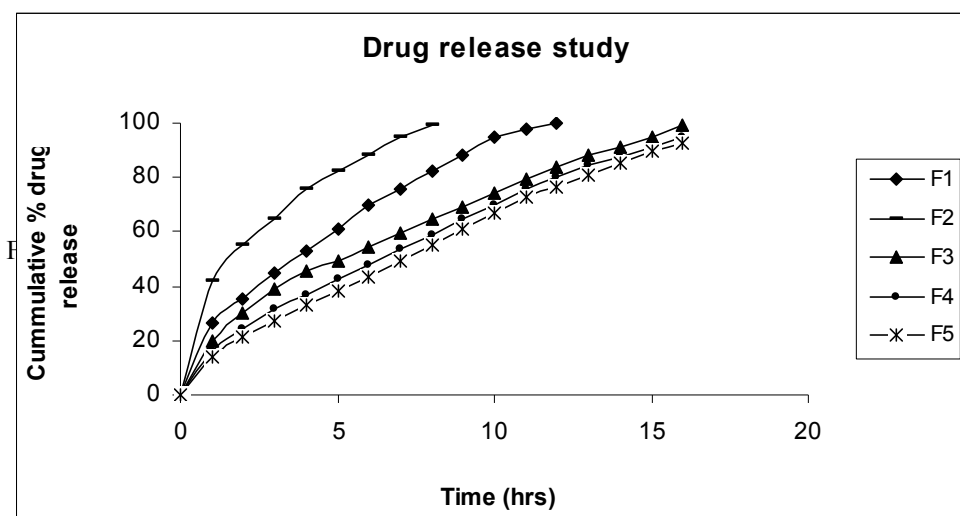
Table 4. Drug release kinetic values obtained from different plots of formulations

Formulations	First-Order Plot* (Regression coefficient, R ²)	Higuchi's Plot** (Regression coefficient, R ²)	Korsmeyer et al's Plot [#]	
			Slope (n)	Regression coefficient, R ²
F1	0.9089	0.9759	0.5801	0.9971
F2	0.921	0.9787	0.4225	0.9989
F3	0.8889	0.9692	0.5612	0.9975
F4	0.8972	0.9807	0.6678	0.9969
F5	0.9062	0.9852	0.7309	0.9974

* First-order equation, $\log C = \log C_0 - K_t/2.303$.

** Higuchi's equation, $Q = K_t^{1/2}$

Korsmeyer et al's equation, $M_t/M_\infty = K_t^n$

**Figure1. The in vitro release profile of metoprolol succinate, formulations F1 to F5****REFERENCES**

- 1) Sahel, M.A., Yellela, S. R. K., Srinivas S. P. and Vemulapalli, S. In Vitro and In Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-soluble Diltiazem Hydrochloride. *AAPS PharmSciTech* 2005; 6 (1) Article 5
- 2) Chien Y.W., Novel drug delivery system, Marcel Decker Inc., New York, 2005, 2nd edn, 1-3.
- 3) Deshmukh, V. N., Singh, S. P. & Sakarkar, D. M. Formulation and Evaluation of Sustained Release Metoprolol Succinate Tablet using Hydrophilic gums as Release modifiers. *International Journal of PharmTech Research*. ISSN : 0974-4304, Vol.1, No.2, pp 159-163.
- 4) Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. *Tutorial Pharmacy*. New Delhi, India: CBS Publishers and Distributors; 1986:211-233.
- 5) Shah D, Shah Y, Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross-linked poly (vinyl alcohol). *Drug Dev Ind Pharm*. 1997; 23(6):567-574.
- 6) Aulton ME, Wells TI. *Pharmaceutics: The Science of Dosage Form Design*. London, England: Churchill Livingstone; 1988.
- 7) Martin A. *Micromeritics*. In: Martin A, ed. *Physical Pharmacy*. Baltimore, MD: Lippincott Williams & Wilkins; 2001:423-454.
- 8) Cacovean Ioana, Ilie Mihaela, Bădulescu Magdalena, Bălălaşu Dan, Gubandru Miriana – UV-VIS Spectrophotometric Assay of Metoprolol. Note 1. Comparison Between the Direct and the Oxidative Methods – *Farmacia*, 2007, LV (5): 540-544
- 9) *Pharmacopoeia of India*. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications; 1996.
- 10) Banker GS, Anderson LR. Tablets. In: Lachman L, Liberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Mumbai, India: Varghese Publishing House; 1987:293-345.
- 11) Higuchi T. Mechanism of sustained action medication. *Theoretical analysis of rate*

release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-1149.
12) Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous

hydrophilic polymers. Int J Pharm. 1983;15:25-35.
