Research Article

Development and Evaluation of Extended Release Matrix Tablet of Metoprolol Succinate

Gaurav Bhardwaj*[1], Kapil Tak[1], Y.S. Tanwar[1], R.P.S. Rathore[2], Kuldeep Choudhary[2]

[1]Department of Pharmaceutics, Bhupal Nobles' College of Pharmacy, Udaipur-313002, Rajasthan, India.
[2]Department of Quality Assurance, Bhupal Nobles' College of Pharmacy, Udaipur-313002, Rajasthan, India.

Abstract The objective of this study was to design and evaluate oral sustained drug delivery system for metoprolol succinate using hydrophilic polymers such as HPMC K4M and HPMC K100M batches. Four batches were prepared by using HPMC K4M in drug: polymer ratio of 1:1, 1:1.5, 1:2, 1:3 and five batches using HPMC K100M in ratios of 1:1, 1:1.25, 1:1.5, 1:1.75, 1:2. Further formulation F9 was modified by varying the ratios of diluents i.e. F10, F11, F12, F13 to check the effect of diluents on drug release. Matrix tablets were prepared by wet granulation method and were evaluated for weight variation, content uniformity, friability, hardness, thickness and in vitro dissolution. Among the formulations studied, formulation F9 containing HPMC K100M (1:2) showed sustained release of drug for 20 h with cumulative percent release of 88% similar to that of the research listed drug. The kinetic treatment showed that the optimized formulation follow first order kinetic with release exponent (n) 0.579 and having good stability as per ICH guidelines. No chemical interaction between drug and gums was seen as confirmed by DSC studies. The matrix formulation F9 showed sustained release of metoprolol succinate by the diffusion mechanism.

Keywords Sustained release, Hydrophilic gums, HPMC K4M, HPMC K100M, Metoprolol succinate.

Introduction

Among various dosage forms, matrix tablets are widely accepted for oral sustained release 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. In fact, matrix is defined as a well composite of one or more drugs with a gelling agent i.e. hydrophilic polymer. Past research therefore acknowledged various hydrophilic natural gums like agar, konjac, guar gum, chitosan, sodium alginate and locust bean gum in alone or in combination. Hydrophilic natural gums are high molecular weight substances, usually insoluble in alcohol, but can be made to dissolve, swell or disperse in water to give viscous or mucilaginous solutions. The varied structure and chemistry of polymers provide ample opportunity for complexes to form in solution. When solutions of polysaccharides (hydrophilic gums) are mixed, they interact with each other; this can result in an increase in viscosity, which becomes greater than the viscosity of each solution individually. Under certain conditions, they may even form a gel. Such a phenomena is often called as rheology synergism. A classical example of this phenomenon is one that, observed between the karaya gum and the xanthan gum. Such macromolecular reactions are highly selective and strongly dependent upon molecular size and conformation. Such synergistic interactions that often lead to gelling of even those gums which otherwise are non-gelling, can be put to varied uses, more specifically in the design of controlled drug delivery systems while employing a significantly low gum concentration (in combination) as compared to when the gums are used alone. This permits flexibility in dosage form design i.e. reduces the final size of dosage form and incorporate more amounts of active agent(s) having larger oral doses. Xanthan gum is a high molecular weight hydrophilic polymer obtained as a result of microbial fermentation of glucose by bacterium Xanthomonas campestris, which not only

retards the drug release but also provides the time dependent release kinetics with advantages of biocompatibity & inertness. Karaya gum is a galactomannan obtained from the stems of Sterculia urens, has been investigated as sustained release carrier & regarded as a non- toxic & a non- irritant material. These two hydrophilic polymers were used for present study [1].
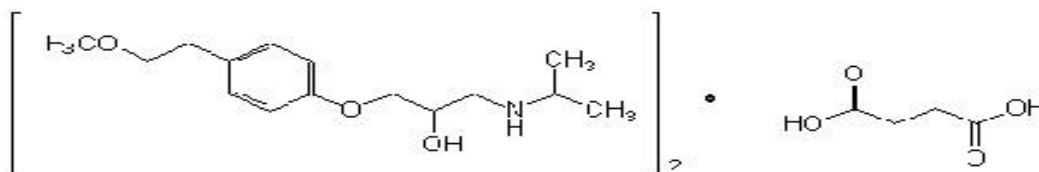

Figure 1: Structure of Metoprolol Succinate

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 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs, thus warrants the use of sustained release formulation for prolong action and to improve patient compliance [2].

Materials
Metoprolol succinate was donated by Aarti drug Laboratories Ltd Thane, India. HPMCK4M, HPMCK100M, MCC101, MCC102, Lactose monohydrate, PovidoneK25, PovidoneK30 and Sodium Stearyl Fumarate were donated by MSN Laboratories Ltd India.

Methods

Preparation of hydrophilic tablets
Thirteen different hydrophilic formulations were prepared by wet granulation procedure having Metoprolol succinate 95 mg, Hydroxy propyl methyl Cellulose K4M or Hydroxy propyl methyl Cellulose K100M (42-46%), Lactose monohydrate (11%), MCC102 (21%), were accurately weighed. The dry components were mixed together which were then wet massed with PVP K-30 (4%), the granules were dried in an oven which were mixed with extragranular ingredients then lubricated with Sodium stearyl fumerate (0.5%). At the end, tablets were compressed with multiple punch tablet machine as shown in Table 1 (a), 1 (b) and 1 (c) respectively.

Table 1 (a): Formulations Containing Drug & HPMCK4M

INGREDIENTS	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)
Metoprolol succinate	95	95	95	95
HPMCK4M	95	142.5	190	285
HPMCK100M	-	-	-	-
Lactose monohydrate	150	103	55	20
MCC102	100	100	100	25
PVPK30	20	20	20	20
Sodium stearyl fumerate	2.5	2.5	2.5	2.5
Total	462.5	463	462.5	447.5

Table 1 (b): Formulations containing drug & HPMC K100M

INGREDIENTS	F5 (mg/tab)	F6 (mg/tab)	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)
Metoprolol succinate	95	95	95	95	95
HPMCK4M	-	-	-	-	-
HPMCK100M	95	118.7	142.5	166.2	190
Lactose monohydrate	150	126.2	107.5	79.2	55
MCC102	100	100	100	100	100
PVPK30	20	20	20	20	20
Sodium stearyl fumerate	2.5	2.5	2.5	2.5	2.5
Total	462.5	462.4	467.5	462.9	462.5

Table 1 (c): Formulations containing drug, HPMCK100M & various concentrations of excipients.

INGREDIENTS	F10 (mg/tab)	F11 (mg/tab)	F12 (mg/tab)	F13 (mg/tab)
Metoprolol succinate	95	95	95	95
HPMCK100M	190	190	190	190
HPMCK4M	-	-	-	-
Lactose monohydrate	65.35	44.5	24.7	74.25
MCC102	100	100	128.7	79.2
PVPK30	10	29.7	20	20
Sodium stearyl fumerate	2.5	2.5	2.5	2.5
Total	462.85	461.7	460.9	460.95

Evaluation of granules and powder blends
Carr's Index and Hausner's ratio
In order to assess the flow characteristics of powder blends, ratio of tapped and bulk density can be explained in the two ways as followed:

Hausner's ratio = Tapped Density/Bulk Density …(1)

CI % = (Tapped Density − Bulk Density) 100 / Bulk Density …(2)

Where,

Bulk density = Weight of the powder / Bulk volume …(3)

Tapped density = Weight of the powder / Tapped volume …(4)

Bulk and tapped densities were analyzed by pouring 50 gm of powder into the 100 mL cylinder and assessing bulk volume and then the final volume after 100 times tapping [3].

Angle of repose
The angle of repose was estimated by fixed base technique. By assessing the powder heap and its radius, angle of repose was estimated as follows:

$$\theta = \tan^{-1} h/r \qquad …(5)$$

Evaluation of trial batches
All the formulations were evaluated by various physical parameters such as thickness (by vernier caliper), weight variation analysis was done by using electronic balance, hardness was determined by hardness tester and friability assessment was done by friability tester [4].

Evaluation of content uniformity test

Five tablets were weighed and triturate, from that transfer an accurately weighed portion of the powder equivalent to about 95 mg of metoprolol succinate to a 100 ml volumetric flask containing buffer solution and then concentration is measured at λ_{max} i.e. 274 nm [5].

Dissolution test
The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8, maintained at 37±0.50C. An aliquot (5 ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer (DU640B, Backman, Fullerton, CA) at 274 nm [6].

Analysis of Data
Model-dependent Methods
Data obtained from drug release were built-in into four kinetic models which were: Zero-Order (Eq.6), First Order (Eq.7), Higuchi model (Eq.8) and Korsmeyer-peppas (Eq.9)

$$F = K.t \qquad \qquad \dots (6)$$

Where K is the zero-order rate constant expressed in units of concentration/time, *t* is the time in hours and F is the concentration of drug release in time t.

$$Log\ C = log\ C_o - (K.t / 2.303) \qquad \dots (7)$$

Where C_0 is the original amount of drug, K is the first order rate constant and t is the time.

$$F = K.t^{1/2} \qquad \qquad \dots (8)$$

Where K is the Higuchi release rate constant and t is the time (hr).

$$M_t/M_\infty = K.t \qquad \qquad \dots (9)$$

Where M_t is the absolute cumulative concentration of drug release at time t and M_∞ is the absolute cumulative concentration of drug release at infinite time, K is the kinetic constant property of the compound/polymer system and *n* was measured through the slope of the straight line which explains the drug release mechanism [7]. Kinetic models explained above were estimated by DD-Solver an aid in program for Microsoft Excel TM 2007 (Microsoft Corporation, USA).

Stability Studies
The optimized formulation was subjected for two month stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at 40ºC / 75% RH for 2 months and evaluated for their drug release study [8].

Results and Discussion
One of the basic objectives of dosage form design is to maintain the release rate in *in-vivo* environment. Sustained release formulations are designed to attain extended therapeutic response over an extended period of time after the administration of the single dose. Thus, at a specific site maximum drug concentration will be ensured without much difficulty, which is often seen in conventional dosage form [9].

Table 2: Parameters of Reference Formulation

Parameters	Reference Formulation
Thickness (mm)	5.34 ±0.10
Hardness (kg/cm^2)	12.00 ±0.89
Weight (mg)	495.00 ±1.30
Friability (%)	0.06
Content Uniformity (%)	100.10

Evaluation of reference formulation

In the present study the physical attributes of the reference formulation were assessed by different physico-chemical tests and the results were found within the adequate limits as presented in Table No. 2.

The *in-vitro* drug release profile was performed using phosphate buffer pH 6.8. The amount of drug release at 1 hr, 4 hr, 8 hrs and 20 hr were found to be 13.30%, 33.80%, 51.50% and 88.00% respectively as shown in Figure No. 2 and Table No. 4.

Figure 2: Cumulative % Drug release of reference formulation

Evaluation of powder blend and tablets

As preformulation assessment, the flow features of powders were estimated by various flow parameters such as carr's index, hausner's ratio and angle of repose. Results indicated that powders showed satisfactory flow properties and compressibility during tablet manufacturing. Powder flow establishes tablet weight, hardness and content uniformity. It is important to evaluate the flow properties of powders prior to tablet compression [10].

Table 3: Preformulation studies of powder blends

Formulation	Bulk Density* G/CC	Tapped Density* G/CC	Hausner Ratio	Compressibility Index %	Angle Of Repose*(Θ)
F1	0.427±0.003	0.577±0.004	1.35	30.7	31.2±1.001
F2	0.43±0.036	0.663±0.003	1.54	35.6	31.6±0.5
F3	0.412±0.003	0.646±0.005	1.56	32.75	35.8±0.95
F4	0.423±0.006	0.623±0.002	1.47	33.8	32.6±0.5
F5	0.435±0.001	0.634±0.004	1.45	32.4	33.4±0.4
F6	0.421±0.001	0.652±0.004	1.54	33.4	35.9±0.458
F7	0.423±0.003	0.632±0.005	1.49	33.9	32.3±0.3
F8	0.462±0.004	0.648±0.002	1.40	34.7	34.2±0.34
F9	0.453±0.003	0.655±0.001	1.44	29.4	32.5±0.5
F10	0.441±0.002	0.648±0.003	1.46	21.4	36.8±0.529
F11	0.437±0.002	0.638±0.003	1.45	32.1	33.1±0.624
F12	0.455±0.001	0.654±0.004	1.43	31.7	36.7±0.208
F13	0.422±0.004	0.647±0.003	1.53	33.2	35.6±0.5

In order to assess the *in-vitro* drug release profile, dissolution test was performed, It was found that the *in-vitro* dissolution profile of metoprolol succinate from Batch F9 containing HPMC K100M (1:2) is almost similar with that of RLD (Figure No. 3 and Table No. 4). Hence, Formulation F9 was selected as a best formulation.
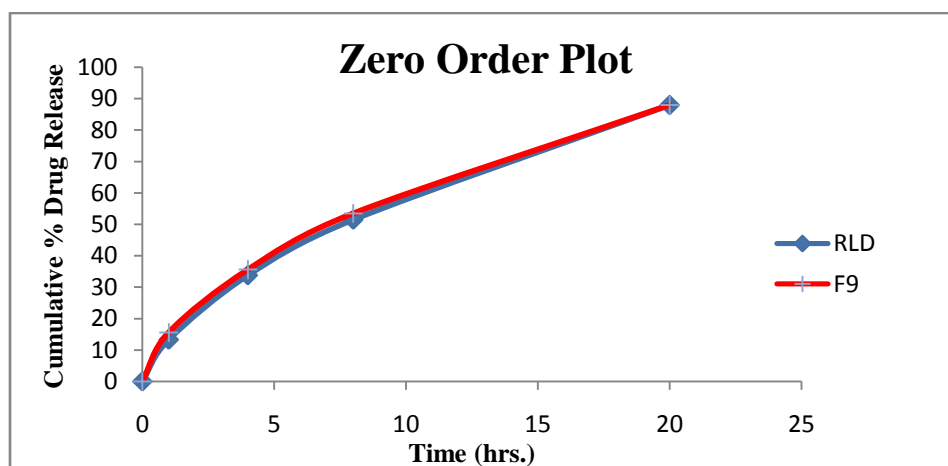
Figure 3: *Comparison of drug release profiles*

Table 4: Comparison of drug release profiles

Time (hrs.)	Cumulative % Drug Release	
	RLD	**F9**
0	0	0
1	13.30	15.60
4	33.80	35.60
8	51.5	53.5
20	88.00	88

Drug release kinetics

The *in-vitro* drug release profiles of Batch F9 and reference formulation expressed cumulative % drug release at time point 1, 4, 8 and 20 hrs.

Dissolution profiles were then analyzed by model-dependent method. In the present study the drug release kinetics were described by various kinetic models and equations (Table No. 5) i.e., Zero-order, First-order, Higuchi and Korsmeyer-peppas were applied to reference formulation, Batch F9.

Table 5: Mathematical Modeling and Drug Release kinetics

Formulation	Drug Release Kinetics (R^2)				Release exponential (n)
	Zero-order	**First-order**	**Higuchi**	**Korsmeyer**	
RLD	0.948	0.995	0.992	0.998	0.632
F9	0.934	0.995	0.996	0.999	0.579

In this experiment, the *in-vitro* release profiles of the drug from these formulations can be best expressed by Higuchi's equation as the plots showed the highest linearity (R^2 0.950 to 0.990). To confirm the diffusion mechanism of metformin hydrochloride from matrix tablets, the dissolution data were subjected to the Korsmeyer-peppas diffusion model. The 'n' values for all formulations ranged from 0.50 to 0.70, indicating that the release mechanism was non-fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation.

Stability Studies:

The formulation subjected for stability studies was found to have no change in the physical appearance and drug content.

Conclusion

In the present study, metoprolol succinate extended release tablet were formulated and evaluated. These formulations showed excellent drug release profiles. Results showed that First-order kinetics was fitted to all formulations.

References

1. Shah Mitul, Controlled Release Drug Delivery System (CDDS), 29-Jun-2010.
2. Kamboj Sunil et al., Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms, Pharmainfo.net, 2009, 7(6).
3. Rajput G.C. et al., Stomach Specific Mucoadhesive Tablets As Controlled Drug Delivery System, International Journal on Pharmaceutical and Biological Research, 2010, Vol. 1(1), 30-41.
4. Brannon PL, Med. Plast L, & Biomater, Med. Plast. & Biomater. 1998; 199(6); 34-46.
5. Robinson JR., Lee LH, Controlled Drug Delivery: Fundamentals and Applications, 2nd ed., 1987, pg 29:312-319.
6. M Flu Lu et al., Drug Development and Industrial Pharmacy, 1991, 17(4):1987-2004.
7. Nicholson SJ et al., Journal of pharmacy and Pharmacology, 1990, 42; 21-26.
8. Nigayale A. G. et al., Drug Development and Industrial Pharmacy, 1990, 16:2-8.
9. Singh P, Desai SJ, Simonelli AP, Higuchi WI, Role of Wetting on the Rate of Drug Release from Inert Matrices, Journal of Pharmaceutical Science, 1968, 57(2):217-226.
10. Serota DG, Meyer MC, Autian J, The Effects of Structure on the Permeability of Substituted Anilines from Aqueous Solutions Through Polythene, Journal of Pharmaceutical Science, Drug Cosmet. Ind., 1970, 107(3):416-419.