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In Vitro Evaluation of Oral Extended Release Drug Delivery System for Metoprolol Succinate Using Kollidon SR

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ABSTRACT

The objective of this study was to develop a sustained release matrix tablet Metoprolol Succinate by cost saving and production efficient process. Among various tablet manufacturing process, direct compression is the simplest and cost saving process. Different trials were formulated and evaluated using different concentrations of directly compressible grade Kollidon SR as release retardant. The formulated tablets were evaluated for physical and dissolution study using buffer medium. The most outstanding aspect of this study is to monitor the influence of different percentage of Kollidon SR on release rate from the matrix tablet. In this study, influence of different ratio of polymer concentration on drug release was evaluated. The release pattern of different batches were evaluated for Zero order, Higuchi, First order, Krosmeyer-Peppas and Hixson-Crowell kinetics and showed that all the batches followed best the Higuchi kinetics. The drug release kinetics was found to be governed by the amount of the polymer in the matrix system. The higher polymeric content in the matrix decrease the release rate of the drug. The nature of the drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomales release. The studies indicated that the drug release can be modulated by varying the concentration of the polymer. Among the four formulations, formulation 1 is the best formulation as it controls the release best and best linearity for zero order plots.

Keywords: Metoprolol Succinate, Kollidon SR, Matrix Tablet

INTRODUCTION

Metoprolol succinate is a beta-selective adrenoreceptor bloking agent used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half life of this drug is relatively short approximately 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs (Gothi GD, 2010). When dose is missing it may causes nocturnal attack, so attention was made to develop the extended release tablets of Metoprolol Succinate by utilizing Kollidon SR. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Metoprolol Succinate is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug (Tiwari *et al*., 2003).

The most commonly used method of modulating the drug release is to include it in a matrix system (Mahesh *et al*., 2007 and Salsa *et al*., 1997). Matrix based controlled release tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. The matrix tablets can be prepared by wet granulation or direct compression method. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. In the present study direct compression method was selected using direct compressible grade controlled release polymer of Kollidon SR. Kollidon SR is a relatively new matrix retarding agent consisting of 80% polyvinyl acetate and 20% polyvinylpyrrolidone. With its excellent flowability, this formulated combination allows sustained release dosage forms to be manufacturing by the simple direct compression method.

Hence, the aim of the present study is to design sustained release matrix tablets of Metoprolol Succinate in Kollidon SR as the rate retarding substance and elucidate the release behaviors.

MATERIAL AND METHODS

Materials

Metoprolol Succinate was obtained as a gift sample from Drug International Ltd, Bangladesh. Polymer Kollidon SR was obtained as a gift sample from BASF Bangladesh Limited, The Chemical Company. Magnesium stearate and Lactose were obtained also as a gift sample from Novo Pharmaceuticals Ltd. All other chemicals used were of analytical reagent grade and distilled water was used throughout the experiments.

Preparation of Matrix Tablets

Matrix tablets, each containing 95 mg Metoprolol Succinate were prepared by direct compression method. The composition of various formulations was shown in Table no. 1.The active ingredient and other excipients were weighed accurately for thirty tablets according to the formulations and collected in mortar pastel. After proper mixing (5 min) passed through the sieve no. 40 and collected in polyethylene bag. Individually weighed the amount of granules for each tablet (323mg) and compressed the tablet by using a Perkin-Elmer laboratory hydraulic press equipped with a 13 mm flat faced punch and die set. The compression force and compression time were 4 tons and 1 min respectively. Before compression, the surface of the die and punch were lubricated with magnesium stearate. All preparations were stored in airtight photo film containers at room temperature for further study. This method of tablet production has previously been described by several authors(Shato *et al*., 1997 and Ritger *et al*., 1987) that provided reproducible experimental results in terms of in - vitro release.

Evaluation of Matrix Tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. The hardness of the tablets was determined by using a hand operated hardness tester apparatus (Electrolab EH-01P). Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. Friability of the tablets was determined by using Electrolab EF-2 friability test apparatus. The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm). Weight variation test was performed by taking 10 tablets using an electronic balance (Adventurer TM electronic balance, Model AR2140, Capacity (Max) - 210 gm, Readability- 0.0001 gm). The average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated.

Drug Content Assay

Standard solution was prepared by dissolving 20mg of Metoprolol Succinate in 100ml distilled water. Then, five tablets from each formulation were weighed accurately and grinded properly and an amount of finely powdered equivalent to 20 mg of Metoprolol Succinate (68mg of powder) was taken in 100 mL volumetric flask and dissolved in distilled water and make the volume up to 100 mL. The mixture was then filtered to remove the un-dissolve particle. Absorbance of both the standard solution and the filtrate was measured at 274 nm using double beam UV/Visible spectrophotometer (UV-1800-Shimadzu Japan).

Drug-Excipeint Interactions

The physicochemical compatibilities of the drug and the used excipients were tested by measuringthe UV-spectra of metoprolol succinate and formulated tablets blends. At first 1mg/ml solution of metoprolol succinate and formulated tablets blends are prepared. Then UV spectra are measured by photometric method within a range 200-400 nm. Standard solution was prepared by dissolving 5mg of metoprolol succinate in 5ml of distilled water. Sample solution of formulations (F1, F2, F3, F4) was prepared by dissolving 17mg (equivalent weight of 5mg standard) of mixed powder from each formulation in 17 ml of water.

Table. 1: Formulation of Metoprolol Succinate (MS) loaded Kollidon SR Based Matrix Tablet.

Formulation code	Wt. of MS/ Tablet (mg)	Wt. of Kollidon SR/ Tablet (mg)	Wt. of Lactose/ Tablet (mg)	Wt. of Mg-stearate/ Tablet (mg)	Total Weight (mg)
F-1	95	200	25	3	323
F-2	95	175	50	3	323
F-3	95	150	75	3	323
F-4	95	125	100	3	323

In-Vitro Dissolution Study

The in vitro release of Metroprolol Succinate from the formulated tablets was carried out in USP type II test apparatus (rotating paddle method) using 900 mL of dissolution medium maintained at 37.0±0.5˚C and a stirring rate of 50 rpm. Three tablets from each formulation were tested individually in 900 mL phosphate buffer (pH 7.4) for the following 7 hours. At specific time interval 5 mL of medium was withdrawn for measuring the drug release and in every case 5 mL of fresh buffer was substituted to maintain the volume constant. After filtration, the amount of Metroprolol Succinate in each sample was determined spectrophotometrically at 274 nm.

Analysis of Release Data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time (hr)), first order (log cumulative percentage of drug remaining versus time (hr)), Higuchi (cumulative percentage of drug release versus square root of time (hr)), Korsmeyer-Peppas (log cumulative percentage of drug release versus log time (hr)) and Hixson-Crowell (cubic root of percentage drug release versus time (hr)) equation models. Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer-Peppas *et. al.,* (Korsmeyer *et al.,* 1983).

$$M_t / M_\infty = k\, t^n$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. A value of n = 0.45 indicates Fickian (case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Shato *et al.,* 1997).

RESULTS AND DISCUSSION

Physical Parameters

The prepared tablets were subjected to preliminary characterization such as physical parameters (thickness, diameter, hardness and friability) and weight uniformity of all the fabricated tablets. The values are presented in Table no. 2. Physical parameters of the tablets were observed by increasing the polymer concentration. Improvement in the physical parameters of the compressed tablets was observed by increasing in the polymer concentration. Low hardness was observed with trials formulated with low concentration of polymer. This is due to low bulk density and low compressibility nature of Metoprolol Succinate drug substance. A linear relationship was found between amount of kollidon SR and hardness of the tablets (R^2=0.996).

The thickness of tablets ranged from 2.3±0.02 to 2.4±0.02. The hardness of the tablets of all the formulation ranged from 5.87±0.25 to 10.61±0.75 kgf. Drug content among different batches of tablets ranged from 97.40% to 99.65%. According to BP, the pharmacopoeial limit for the percentage deviation for tablets within the range 130-324mg is ±7.5%. Weight variation of the tablets was not more than 7.5%. Good uniformity in drug content was found among different batches of tablets and percent of drug content was not less than 97% (Table 2). All the tablet formulation showed acceptable pharmacotechnical properties and complied with the in-house specification of weight variation, drug content and hardness.

Table. 2: Tablet properties of the different formulations of Metoprolol Succinate sustained release matrix tablets.

	Parameters					
Formulation Code	**Thickness (mm) (n=3)**	**Diameter (mm) (n=3)**	**Hardness (kgf) (n=3)**	**Friability (%)**	**Average weight (mg) (n=10)**	**Drug content (%)**
F-1	2.3± 0.05	13	10.61± 0.75	0.15	322.9± 1.22	98.45%
F-2	2.4± 0.02	13	9.78± 0.42	0.18	327.3± 0.64	99.21%
F-3	2.3± 0.05	13	5.92± 0.50	0.22	326± 0.360	99.65%
F-4	2.3± 0.02	13	5.87± 0.25	0.25	325.1± 0.34	97.40%

The values are expressed as mean ± SEM, n is specified in each column head

Drug-Excipient Interactions

The UV- spectra of frormulated tablets were compared with the standard spectrum of Metoprolol Succinate. UV-spectrum of Metoprolol Succinate is characterized by the absorption UV-light within the range of wavelength 200-400nm. In spectra of formulated tablets, this range shows same absorption pattern as that of pure drug (Data shown). Mentioned evidences thus lead to the conclusion that changes are not seen as there is no physical interaction between the drug and polymer (Fig. 1).

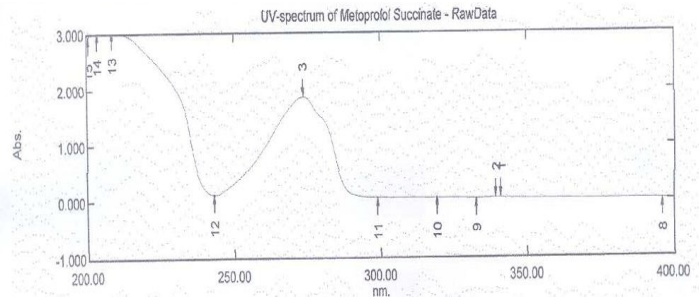

Fig. 1: UV Spectra of Metoprolol Succinate.

Release Kinetics Studies

The condition of matrix tablets after swelling during 8 hour dissolution was observed (Fig 2). Comparing all the formulation, it was obvious that the thickness and diameter of formulation-4(F4) is the smallest. This observation also indicates that among four formulations F4 releases the highest amount of drug. The diameter and thickness of tablets from each batch were measured after dissolution. The percent of change in thickness and diameter was calculated (Table 3). The rate of swelling is high in formulation-1 as this formulation contains highest amount of

Kollidon SR. After 8 hour dissolution study diameter change is 15.3% and thickness chance is 26%.

Table. 3: Change in the thickness and diameter of Metoprolol Succinate matrix tablets after dissolution.

Formulation	Diameter(mm)		Thickness(mm)		% of change	
	Initial	After dissolution	Initial	After dissolution	Diameter	Thickness
F1	13	15.0	2.3	2.9	15.3%	26.0%
F2	13	14.8	2.4	2.8	13.8%	16.6%
F3	13	14.8	2.3	2.7	13.8%	17.3%
F4	13	14.0	2.3	2.4	7.6%	4.3%

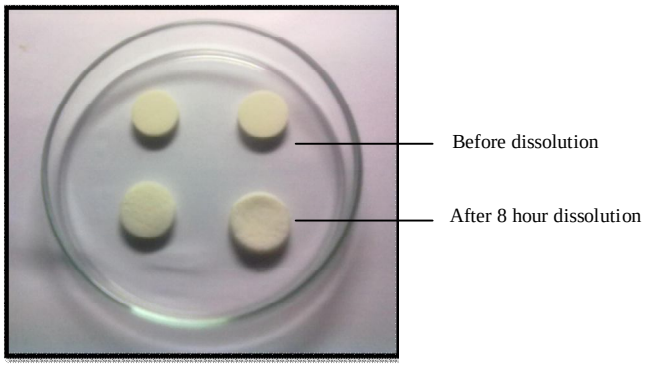

Fig. 2: Images of Metoprolol Succinate matrix tablets

The dissolution data (from the values of 0 to 8 hours drug release) of all formulations were fitted into various mathematical models (zero-order, first-order, Higuchi, Kroysmeyer-Peppas model, Hixson-Crowell plot) to know which mathematical model will best fit the obtained release profile. The plotted figures of zero-order and Higuchi are presented in fig. 3(a) and 3(b). The release kinetic parameters of all formulations are presented in Table No. 4. Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. When the data plotted according to a Higuchi equation, the formulations F-1, F-2, F-3 and F-4 showed a fair linearity, with regression values 0.99, 0.99, 0.98 and 0.96 respectively. Release of the drug from a matrix tablet containing hydrophobic 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 (Higuchi T., 1961). To confirm the diffusion mechanism, the data were fitted into Korsmeyer *et al*'s equation (Korsmeyer *et al*., 1983). Based on the 'n' values ranging from $0.45 < n < 0.89$ the drug release was found to follow anomalous or non-Fickian release. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled by more than one process. This finding was in accordance with other reported works (Goodhart *et al*., 1974 and Peterlin et. al., 1980).

From this study also observed how the polymeric concentration controls the release rate. A negative correlation was observed between the percent of Kollidon SR and release rate (R^2=0.880) and also between hardness of tablets and release rate constant (R^2=0.898). From these two correlations, it was found that as the amount of polymer increases the release rate is decreased.

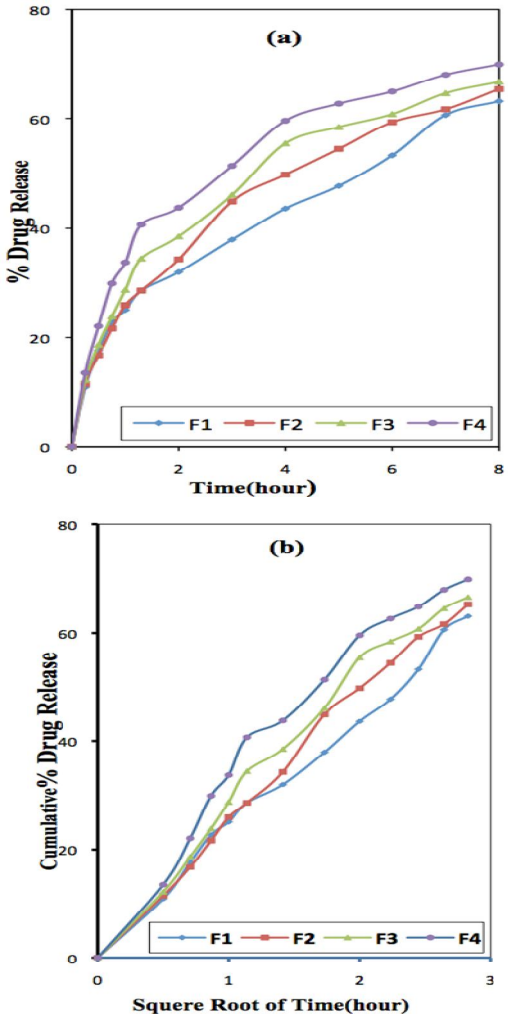

Fig. 3: Release model of Trimetazidine Dihydrochloride sustained release formulations (a) Zero-order release model and (b) Higuchi release model.

Among all formulation, the rate and extent of drug release was decreased with the increase in the amount of Kollidon SR. The designed formulation-4 (containing 125mg of Kollidon SR and 100mg of lactose) exhibited rapid drug release pattern than other formulations for 8 hour period. Among all the formulations only F1 (containing 200mg of Kollidon SR and 25mg of lactose) shows the best linearity in case of zero order curve(R^2=0.96). Considering the parameters like $T_{25\%}$, $T_{50\%}$ and $T_{75\%}$ for each formulation (Table 5), it is observed that formulation 1(F1) provides the best control over the release of drug from matrix tablet. F1 takes 12.73 hour for 75% drug release, while F2, F3, F4 releases 75% of drug within 9.83 hours, 8.9 hours and 7.8 hours respectively.

Table 4: Release kinetics parameters of designed sustained release matrix tablets of Metroprolol Succinate.

Code	Zero order		First order		Higuchi		Krosmeyer-Peppas		Hixson-Crowell	
	K_0	r^2	K_f	r^2	K_h	r^2	n	r^2	K_{HC}	r^2
F1	6.14	0.96	-0.048	0.97	22.52	0.99	0.46	0.98	-0.144	0.96
F2	6.68	0.93	-0.053	0.96	23.57	0.99	0.49	0.99	-0.163	0.94
F3	6.65	0.90	-0.056	0.94	24.10	0.98	0.47	0.98	-0.165	0.92
F4	6.53	0.87	-0.060	0.92	24.67	0.96	0.44	0.96	0.172	0.89

r^2 denote the regression coefficient and n denote the slope of Kosmeyer-Peppas plot.

Table. 5: Required time for 25, 50 and 75 percentage of drug release.

Formulation code	$T_{25\%}$ (h)	$T_{50\%}$ (h)	$T_{75\%}$ (h)
F1	1.165	5.025	12.73
F2	1.030	4.308	9.83
F3	0.839	3.816	8.90
F4	0.591	3.176	7.80

CONCLUSION

The present study showed that the hydrophobic polymer like kollodon SR could be used as a matrix material to design controlled release formulations of a water-soluble drug Metoprolol Succinate with desired quality and release characteristics. The tablet manufacturing method was relatively simple and can be easily adopted in conventional tablet manufacturing units in industries on a commercial scale. In the present investigation, it was concluded that the release rate of drug from the matrix tablets can be governed by the polymer and concentration of polymer employed in the preparation of tablet. Although, it seems that the drug is being loading for 12 hours from this matrix, in-vivo release study is also warranted.

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