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Effect of Hydrophilic Polymers Properties in Controlling the Drug Release

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Abstract

Extended release matrix formulations are the most promising among the controlled release category. Various types of polymers available for formulation of extended release formulations, among them hydrophilic polymers are the most promising polymers. The release control mechanism of hydrophilic polymers following ingestion is complex, but is known to be based on diffusion of the drug through the hydrated portion of the matrix and erosion of the outer hydrated polymer on the surface of the matrix. For the selection of controlled release polymer in formulating the extended release formulations, one should expertise with the release behaviour of the selected polymer. In this study metoprolol succinate extended release matrix tablets were manufactured with various concentrations of controlled release hydrophilic polymers namely hypromellose (HPMC) K200M and polyethylene oxide (Polyox) WSR-303. The rate of swelling and erosion was different with two studied polymers. The effect of this swelling and erosion properties of the polymers on the drug release profile was studied. Dissolution studies were conducted using USP official methods. From the studies conducted, it was observed that a rate of swelling in initial time points and erosion in later time points were higher with Polyox WSR-303 than HPMC K200M. Comparatively, Polyox WSR-303 was able to greatly control the drug release in initial time points, and HPMC K200M was greatly control the drug release in later time points.

Keywords: Extended release, gelation index, hypromellose K200M, metoprolol succinate, POLYOX WSR-303, swelling index

Introduction

Controlled release (CR) tablet formulations are much desirable and preferred for hypertension therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high potency drugs (Vyas et al. 2002). Among the various controlled release formulations, extended release is more prominent and a lot of extended release formulations are currently available in the market with the potential business value.

Metoprolol succinate, β_1-selective adrenergic receptor blocking agent, was used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine.

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The half-life of drug is relatively short approximately 4–6 h, and in normal course of therapy drug administration is required every 4–6 h, thus warrants the use of sustained release formulation for prolonged action and to improve patient compliance (Deshmukh et al. 2009). The selected drug is a suitable candidature for formulating as an extended release formulation.

Hypromellose is a partly O-(methylated) and O-(2-hydroxypropylated) cellulose. It is available in several grades (from 3 to 200,000 cPs) that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity in cPs of a 2% w/w aqueous solution at 20 °C. High-viscosity grades may be used to retard the release of drugs at levels of 10–80% w/w from matrix tablets and capsules (Rowe et al. 2009). In this study, a high viscosity grade of HPMC K200M was selected, with the viscosity of 200,000 cPs.

Polyethylene oxide as a nonionic homopolymer of ethylene oxide belongs to water soluble resins, represented by the formula $(CH_2CH_2O)_n$, where '*n*' represents the average number of oxyethylene groups. Based on the molecular weight, it is also available in several grades (from 100,000 to 7,000,000 molecular weight). Based on an increase in the molecular weight, the viscosity also increases (from 10 to 10,000 cPs). The higher molecular weight grades provide extended drug release *via* the hydrophilic matrix approach (Rowe et al. 2009). In this study, the high viscosity grade of Polyox WSR-303 was selected, with the viscosity (1% solution) of 7500–10,000 cPs.

The most commonly used method of modulating the drug release is to include it in a matrix system. 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 *via* wet granulation or by direct compression (Salsa et al. 1997). In this study, the direct compression method was utilized for the manufacture of metoprolol succinate extended release formulations. The direct compression manufacturing process is a cost-effective and simple process bearing a high attractivity.

In this study, the influence of polymer concentration and its swelling and erosion properties on the drug release was evaluated by keeping the drug concentration constant and altering the controlled release polymer concentration.

Materials and Methods

Metoprolol succinate was obtained from Dr. Reddys Laboratories, Hyderabad. HPMC K200M was obtained from Ashland Incorporation and Polyox WSR-303 was obtained from Colorcon Asia Pvt Ltd. Talc was obtained from Luzenac Pharma and sodium stearyl fumarate was obtained from SPI Pharma. Solvents and all other reagents used were of analytical grade.

Methods

Preparation of matrix tablets

Extended release matrix tablets were formulated using the highest viscosity grades of hydrophilic polymers HPMC K200M or Polyox WSR-303 as a controlled release polymer in the ratio of 1–4 with respect to active substance concentration. Talc used as a glidant and sodium stearyl fumarate used as a lubricant at the concentration of near to 1% with respect to total tablet weight.

Tablets were prepared by a direct compression process. Metoprolol succinate and HPMC K200M or Polyox WSR-303 were sifted through the ASTM #40 mesh and blended for 15 min in a double cone blender. Then, talc and sodium stearyl fumarate were sifted through ASTM #60 mesh and transferred into the above blender and lubricated for 5 min.

Above lubricated blend was compressed in a single rotary tablet punching machine using appropriate size of standard concave punches.

In all the trials, drug concentration was kept constant (i.e. 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate) and controlled release polymer concentration (i.e. HPMC K200M or Polyox WSR-303) was varied from 1 to 4 times with respect to drug concentration. Glidant (i.e., talc) and lubricant (i.e., sodium stearyl fumarate) were kept near to 1% in all formulations. The composition of various formulations was shown in Table 1.

Table 1. Composition of metoprolol succinate extended release tablets

	HPMC K200M trials				Polyox WSR-303 trials			
Batch no →	**MH-1**	**MH-2**	**MH-3**	**MH-4**	**MP-1**	**MP-2**	**MP-3**	**MP-4**
Ingredients ↓	**Mg/tablet**							
Metoprolol succinate	95	95	95	95	95	95	95	95
HPMC K200M	95	190	285	380	–	–	–	–
Polyox WSR-303	–	–	–	–	95	190	285	380
Talc	2	3	4	5	2	3	4	5
Sodium stearyl fumarate	2	3	4	5	2	3	4	5
Total tablet weight	**194**	**291**	**388**	**485**	**194**	**291**	**388**	**485**

Evaluation of matrix tablets

The compressed tablets were characterized by their physical properties. The average tablet weight was determined from 20 tablets. Hardness of the tablets was tested using a Monsanto tablet hardness tester. Friability of the tablets was determined in a Roche friabilator (USP 2010). The observations for the same are provided in Table 2.

Table 2. Physical evaluation of metoprolol succinate extended release tablets

Batch no	**MH-1**	**MH-2**	**MH-3**	**MH-4**	**MP-1**	**MP-2**	**MP-3**	**MP-4**
Parameter	**Results**							
Average weight (mg)	194.6	292.1	389.5	386.2	194.6	291.7	387.6	487
Hardness (kg/cm^2)	2-6	2-6	2-5	3-6	2-6	3-7	3-6	3-6
Friability (%)	0.12	0.08	0.13	0.11	0.07	0.11	0.12	0.15

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of percentage weight gain by the tablets after imbibing in the dissolution medium. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 6.8. At the end of 2, 4, 8, and 24 h tablets were withdrawn, soaked on a tissue paper to drain the excess medium and weighed, and then percentage weight gain by the tablet was calculated using formula (Chowdary KPR et al. 2006).

$$SI = \frac{M_t - M_o}{M_o} \times 100 \qquad \ldots\ldots\ldots\ldots 1$$

where SI = swelling index, M_t = weight of tablet at time 't', and M_o = weight of tablet at time '0'.

Evaluation of tablet gelation

The gelation index is a useful tool to represent the portion of a tablet that has undergone gelation in time. Each tablet was inserted between two transparent polyacrylate plates (5 × 5 cm^2) and held tight with a rubber band. The tablet and polyacrylate plates were immersed in 900 ml of the dissolution medium (pH 6.8, 37 °C) and stirred with a magnetic bar (300 rpm/min). Test tablets were removed from the medium at predetermined time intervals (30, 60, 90, 120, 150, 180, 240, and 300 min), and the diameters of the gelated tablets were measured with a caliper (Sako et al. 1996). After the gel layer was carefully peeled off, the diameter of the non-gelated core was also measured (Dobs). The gelation index was calculated using equation (2). The gelation index also similar to swelling index, but it will give us the more precise observations of rate of hydration.

$$\text{Gelation Index } (G, \%) = \left\{1 - \frac{(D_{obs})^3}{(D_{ini})^3}\right\} \times 100 \quad \ldots\ldots\ldots\ldots (2)$$

where D_{obs} is the diameter of the portion not gelled after the test and D_{ini} is the diameter of the tablet before the test.

Dissolution studies

In vitro drug release studies from prepared matrix tablets were conducted as per the official monograph method of United States Pharmacopoeia. *In vitro* drug release studies for metoprolol succinate extended release tablets were conducted for a period of 20 h using a six stations USP type 2 apparatus at 37 ± 0.5 °C, with a paddle speed at 50 rpm and 500 ml of the dissolution medium using pH 6.8 phosphate buffer. Samples of 10 ml were taken from the dissolution medium at appropriate intervals of 1, 4, 8, and 20 h after filtration and appropriate dilution. The absorbance was measured by a UV spectrophotometer at 274 nm. The amounts of the drug present in the samples were calculated with the help of appropriate calibration curves constructed from standard solution (the amount of drug released was plotted against time).

Drug release kinetics

The *in vitro* release kinetics data were evaluated by using various kinetic models to describe the release kinetics. The zero-order rate equation (3) describes that the systems drug release rate was independent of its concentration (Hadjiioannou et al. 1993). The first-order equation (4) describes that the systems drug release rate was concentration-dependent (Bourne DW, 2002). Higuchi described the release of drugs from insoluble matrix as a square root of time-dependent process based on Fickian diffusion equation (5) (Higuchi et al. 1963). The Hixson–Crowell cube root law equation (6) describes the release from systems where there is a change in the surface area and diameter of particles or tablets (Hixson et al. 1931).

$C = k_0 t$ ..... (3)

where k_0 is the zero-order rate constant expressed in units of concentration/time and t is the time.

$\text{Log } C = \text{Log } C_0 - kt/2.303$ ..... (4)

where C_0 is the initial concentration of drug and K is first-order constant.

$Q = Kt^{1/2}$ ..... (5)

where K is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$ ..... (6)

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson–Crowell rate equation.

The following plots were made from the above data: *cumulative % drug release vs. time* (zero-order kinetic model); *log cumulative of % drug remaining vs. time* (first-order kinetic model); cumulative %

drug release vs. square root of time (Higuchi model) and *cube root of drug % remaining in matrix vs. time* (Hixson–Crowell cube root law).

Results and Discussion

The physical parameters of the compressed tablets (Table 2) from all the trials were satisfactory. There was no significant change in the physical parameters of the compressed tablets which was observed by changing the polymer concentration for all the trials.

Swelling index observations were presented in Figure 1 for all the trials. Batches manufactured with a 1:2 of drug:polymer ratio were shown for physical observation purpose in Figure 2. The photographs were taken after incubating the tablets for 1, 4, 8 and 20 h in the dissolution medium. It was observed that the rate of swelling was rapid with Polyox-WSR-303 than HPMC K200M, during initial time points and also in later time points.

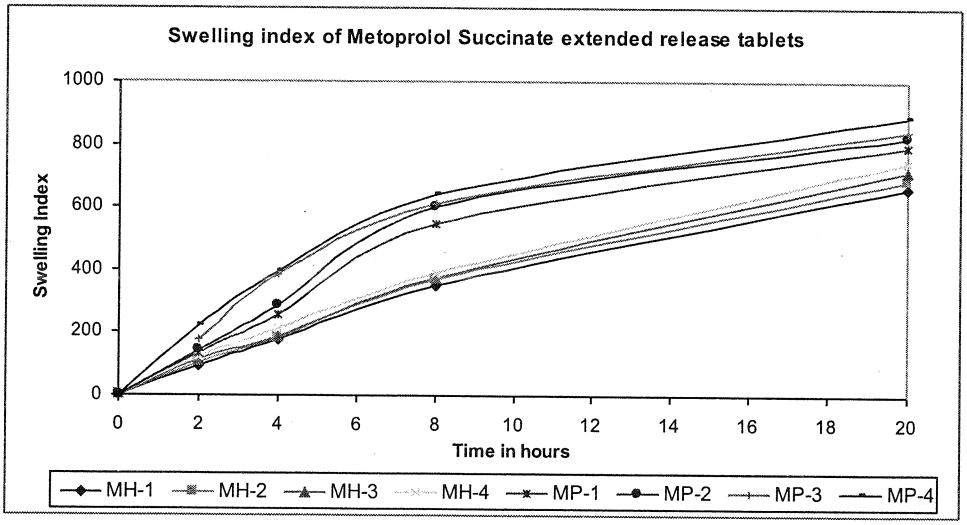

Figure 1. Swelling index of metoprolol succinate extended release tablets.

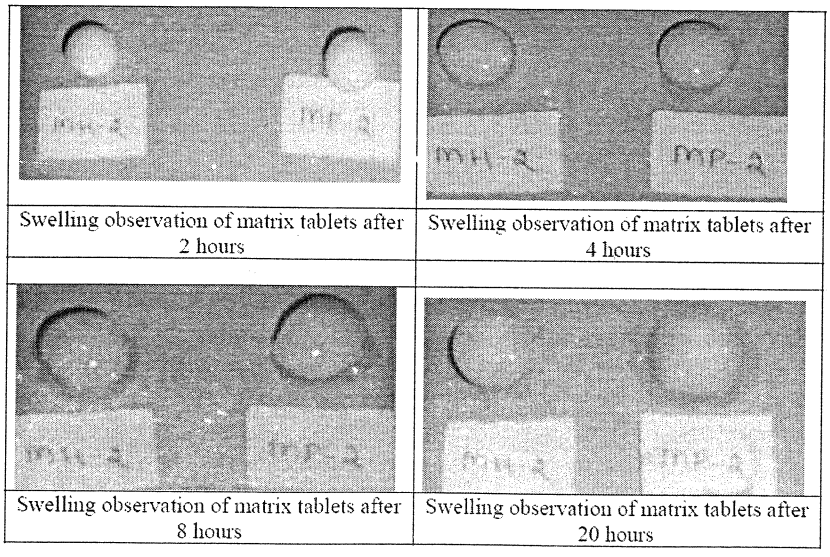

Figure 2. Swelling observation of matrix tablets.

Gelation index observations were presented in Figure 3 for all the trials. It was observed that the rate of hydration (gelation) was rapid with Polyox WSR-303 than HPMC K200M. The common observation from the swelling index and gelation index, Polyox WSR-303 hydration was rapid and also the rate and extent of swelling was more compared with the HPMC 200M.

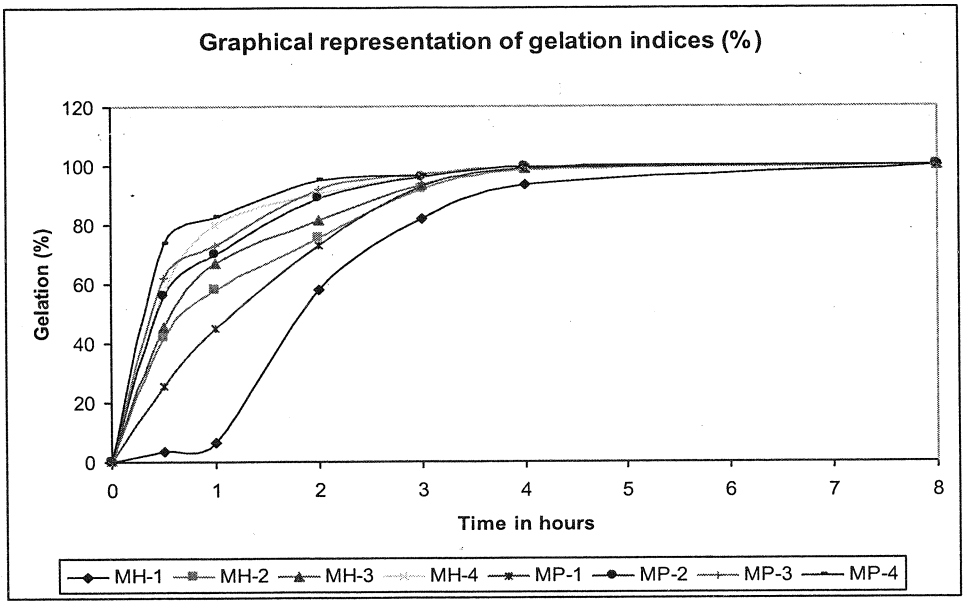

Figure 3. Gelation index of metoprolol succinate extended release tablets.

Drug release results from the prepared extended release tablets are tabulated in Table 3. The effect of different controlled release polymer and its concentration on the release profile of metoprolol succinate extended release tablets are presented in Figure 4.

Table 3. Dissolution profile of metoprolol succinate extended release tablets

Batch no →	**USP limits**	**MH-1**	**MH-2**	**MH-3**	**MH-4**	**MP-1**	**MP-2**	**MP-3**	**MP-4**
Time points ↓		**Cumulative % drug release**							
1 h	Not more than 25%	36	31	23	21	24	19	20	19
4 h	Between 20% and 40%	67	60	39	35	63	56	35	33
8 h	Between 40% and 60%	79	68	53	51	85	73	58	55
20 h	Not less than 80%	99	94	88	86	101	95	90	88

The effect of different concentration of Hypromellose K200M on the release profile of metoprolol succinate extended release tablets were presented in Figure 5. The effect of different concentration of Polyox WSR-303 on the release profile of metoprolol succinate extended release tablets are presented in Figure 6.

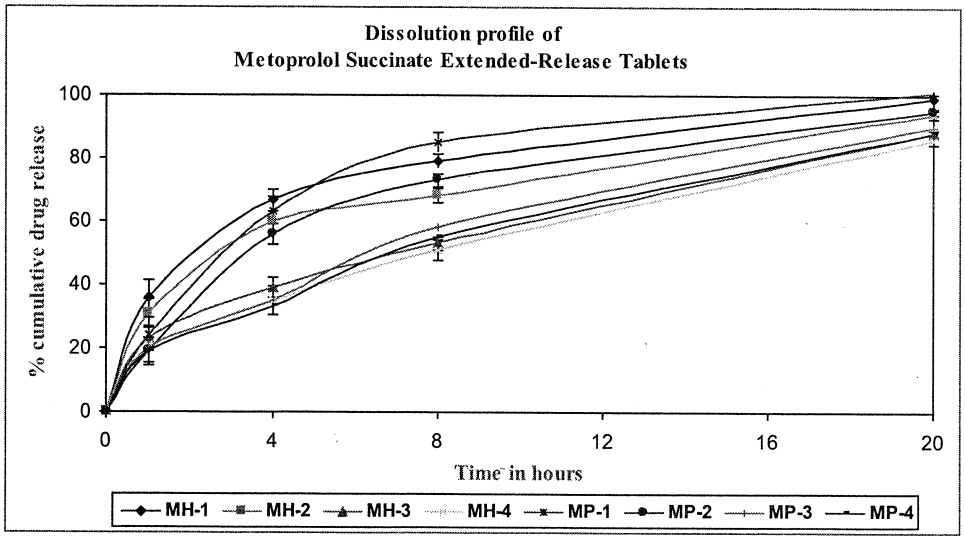

Figure 4. Dissolution profile of metoprolol succinate extended release tablets.

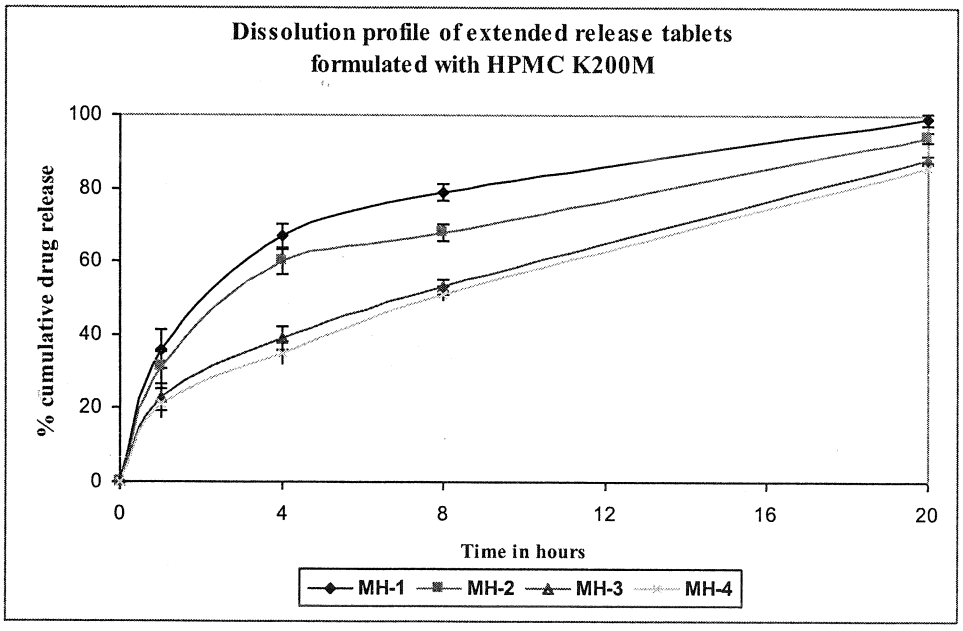

Figure 5. Dissolution profile of extended release tablets formulated with HPMC K200M.

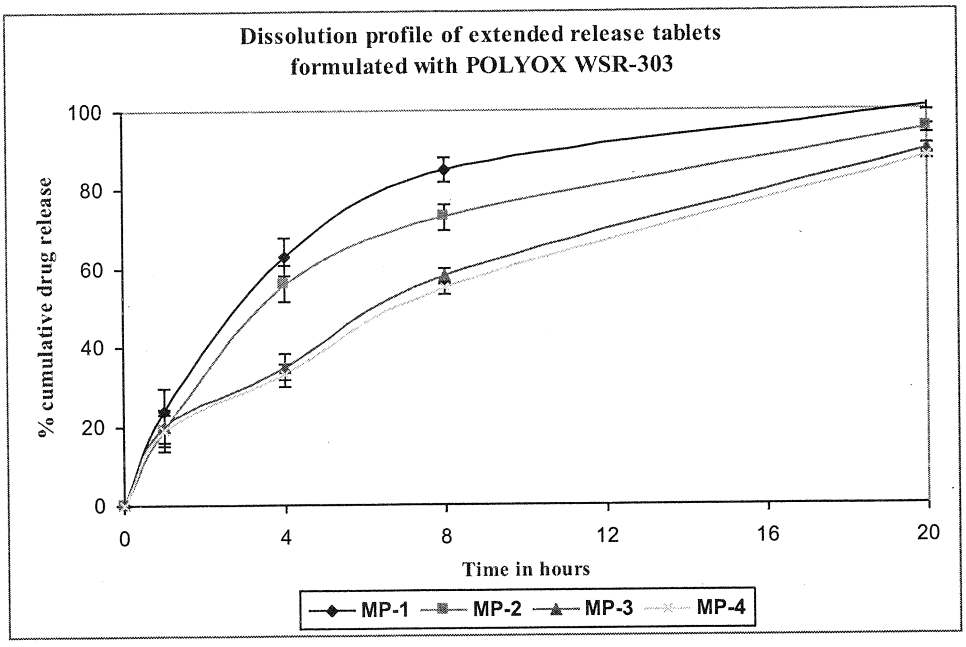

Figure 6. Dissolution profile of extended release tablets formulated with POLYOX WSR-303.

From the observed data, it was evident that there was a proportional decrease in the rate of drug release which was observed with an increase in the polymer concentration for tablets formulated with HPMC K200M and Polyox WSR-303. It was also observed that the rate of drug release was slow in initial time points (i.e. first hour and fourth hour time points) from the metoprolol succinate extended release tablets formulated with Polyox WSR-303 due to faster hydration and rapid swelling behaviour of the Polyox WSR-303. In the latter time points, the rate of drug release was faster with Polyox WSR-303, this was due to formation of more pore channels with an increase in swelling and erosion of hydrated gel layer.

The rate of drug release was slow in later time points (i.e. eighth hour and twentieth hour time points) from the metoprolol succinate extended release tablets formulated with HPMC K200M due to slower erosion and limited surface area for diffusion with the HPMC K200M compared with tablets of Polyox WSR-303 trials.

Drug release kinetics

The dissolution data were plotted according to various kinetic models and evaluated for a linear relationship. The release constant was calculated for all the trials from the slope of the appropriate plots, and the regression coefficient (r^2) is determined and presented in Table 4.

Table 4. Release kinetics of metoprolol succinate extended release tablets

Model →	Zero order	First order	Higuchi	Hixson–Crowell
Trial ↓	r^2	r^2	r^2	r^2
MH-1	0.7093	0.9892	0.9315	0.4058
MH-2	0.7651	0.9812	0.9567	0.4308
MH-3	0.9121	0.9895	0.9964	0.519
MH-4	0.9893	0.9916	0.9915	0.9425
MP-1	0.7414	0.9997	0.9402	0.4635
MP-2	0.7934	0.9944	0.9627	0.4947
MP-3	0.9214	0.9959	0.9949	0.5513
MP-4	0.9322	0.9956	0.9936	0.5612

For all the above trials from the observed data, it was found that the *in vitro* drug release was best explained by Higuchi's equation as the release was predominate by a diffusion process and release kinetics follows the first-order rate, since trials showed the highest linearity for first order.

For metoprolol succinate extended release tablets formulated with HPMC K200M, plots showed the highest linearity for first-order (r^2 = 0.9812–0.9916) followed by zero-order (r^2 = 0.7093–0.9893) and Hixson–Crowell (r^2 = 0.4058–0.9425).

For metoprolol succinate extended release tablets formulated with Polyox WSR-303, plots also showed the highest linearity for first order (r^2 = 0.9944–0.9997), followed by zero order (r^2 = 0.7414–0.9322), and Hixson–Crowell (r^2 = 0.4635–0.5612).

The above data explain that the rate of drug release was predominantly by a diffusion process with first-order release for all the batches. There was a good control in drug release with an increase in the polymer concentration and the release was very close to zero-order kinetics with highest polymer concentration.

The drug release data were also plotted in accordance with the Hixson–Crowell cube root law. It indicates that a change in the surface area and diameter of tablets with the progressive dissolution of matrix as a function of time for tablets formulated with highest concentration of HPMC K200M (r^2 = 0.9425). Tablets formulated with Polyox WSR-303 were not best fitted with Hixson–Crowell, this may attributed to faster erosion of the hydrated gel layer from the surface of the tablets.

Conclusion

The properties of swelling and erosion are important key parameters in selecting the hydrophilic polymers for controlling the drug release. The concentration of polymer also plays an important role in formulation of the extended release formulations. The evaluated polymers proved the feasibility for manufacturing of extended release table formulation by a direct compression process with acceptable tabletting quality attributes. Both polymers were controlled the release of drug from the prepared matrix tablets to a great extent. It was observed that a higher concentration level of controlled release polymer was required for the formulation of metoprolol succinate, for an extended period of release and it was evident from this study that comparatively Polyox WSR-303 was able to control the drug release during initial time points and HPMC K200M was able to control the drug release in later time points. Thus, a combination of these polymers can be utilized for designing the targeted release profile for controlling the release at all time points.

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