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DESIGN, DEVELOPMENT AND *IN-VITRO* EVALUATION OF METOPROLOL TARTRATE TABLETS CONTAINING XANTHAN-TRAGACANTH

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Abstract: The present study was undertaken to develop oral sustained release tablets of metoprolol tartrate using natural hydrophilic matrix formers (xanthan gum and tragacanth). Sustained release matrix tablets of metoprolol tartrate were prepared by using different ratios of drug, xanthan gum and tragacanth. Microcrystalline cellulose (MCC) was used as diluent. The polymer was incorporated into a matrix system using direct compression technique. All the lubricated formulations were compressed using concave punches in compression machine. Compressed tablets were evaluated for diameter, hardness, friability, weight variation and *in vitro* dissolution using USP dissolution apparatus-II. Different formulations were evaluated with respect to dissolution profile in 900 mL phosphate buffer (pH 6.8), 0.1 M HCl solution and distilled water for 12 h at 37°C. Increasing the amount of polymer (xanthan gum) in the formulation led to slow release of drug and decreasing the amount of polymer gave enhanced release of metoprolol tartrate. The kinetic treatment showed the best fitted different mathematical models (Zero order, First order, Higuchi's and Hixson-Crowell). Most of the solid matrix formulations followed Higuchi or zero order kinetics. The formulations F1, F2, F3 and F7, F8, F9 showed maximum linearity while the formulations F4, F5, F6 were not of linear behavior. The results showed that the formulation F9 containing 30% xanthan gum and 10% gum tragacanth is the most similar to that of the reference marketed preparation.

Keywords: xanthan gum; gum tragacanth; metoprolol tartrate; sustained release

Formulation of oral sustained release dosage forms for highly water-soluble drugs has always been a difficult task because the highly water-soluble drugs, if not formulated properly and administered orally, are released at a high rate and cause problems due to toxic concentrations. Hence, it is a challenging task to formulate a suitable tablet dosage form for sustaining action of highly water-soluble drugs (1).

Hydrophilic polymers are widely used in the formulation of sustained release oral dosage forms. Various natural materials (xanthan, guar gum, and chitosan) have been tried by various researchers. It has been shown that in hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug release rate (2).

Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the Gram-negative bacterium *Xanthomonas campestris*. Xanthan gum offers potential utility as a drug carrier because of its inertness and biocompatibility. Xanthan gum not only retards *in vitro* drug release and provides time independent release kinetics, but also works effectively *in vivo* and establishes constant drug plasma levels (3). Dhopeshwarkar and Zatz evaluated xanthan gum as a matrix former for the preparation of sustained-release tablets. It was very effective in prolonging the release of soluble and sparingly soluble drugs (4).

Metoprolol is a cardioselective beta-blocker and it is used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure (5). The half-life of the metoprolol is stated to be 3–4 h. Metoprolol tartrate, with its incomplete oral bioavailability (due to extensive first-pass metabolism), short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day extended-release dosage form. Therefore, metoprolol tartrate is the ideal candidate

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for sustained release system because it is water-soluble and has a short half-life (6).

Tragacanth is a naturally occurring dried gum obtained from *Astragalus gummifer* Labillardiere and other species of *Astragalus*. The gum consists of a mixture of water-insoluble and water-soluble polysaccharides. Bassorin, which constitutes 60% to 70% of the gum, is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material, tragacanth. Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used (1).

The aim of this research work was to assess drug release from gum tragacanth and xanthan-based matrix tablet formulations of metoprolol tartrate and the ability of these natural gums in the production of sustained–release tablets.

MATERIALS AND METHODS

Materials

Metoprolol tartrate (Mass Pharmaceuticals, Pakistan), Mepressor SR (Novartis Pharma, Pakistan), xanthan Gum and tragacanth (Colorcon, India), microcrystalline cellulose (PH 101), Aerosil and magnesium stearate (Merck, Germany).

Preparation of matrix tablets using different proportions of xanthan gum and gum tragacanth

Solid matrix tablets of metoprolol tartrate were prepared using direct compression method. Metoprolol tartrate, various percentages of xanthan gum and gum tragacanth, Aerosil (colloidal silicon dioxide), microcrystalline cellulose (MCC) and magnesium stearate were used in preparing these matrix tablets. Formulae of these formulations are presented in Table 1. All the ingredients were weighed individually and sieved through mesh size no. 50 and were blended for 10 min in a blender. Magnesium stearate 1.0% w/w was added and blended for additional 5 min. Tablets were compressed by direct compaction using multi punch machine. The weight of tablets was adjusted to 600 mg and compressed.

Physical tests of tablets

In order to determine the uniformity in weight of tablets, 20 tablets of each formulation were randomly collected and weighed using class A weight balance and their percentage variation was determined. The weight variation of all tablets was well within the acceptable limits of BP 2002, indicating that the filling of die cavity for tablets was uniform. All the formulations were tested and the deviation was not greater than 7%. The result of tablets weight variation is presented in Table 1. Hardness of tablets was also determined using Erweka Hardness Tester. Ten tablets of each formulation were used and the average hardness value was determined. The tablets of each formulation were also subjected to friability testing employing Pharma Test Friabilator. Ten tablets were placed in tumbling chamber and rotated precisely for 4 min at a speed of 25 rpm. The weight of 20 tablets prior to their placement in the chamber and at the end of the test was recorded. The percent-

Table 1. Formulations of solid matrix tablets containing different proportions of xanthan gum and gum tragacanth.

Formulation	Metoprolol tartrate (%)	Xanthan gum (%)	Gum tragacanth (%)	MCC (%)	Aerosil (%)	Mg stearate (%)	Weight variation (mg)	Diameter (mm)	Friability (%)	Hardness (kg/cm^2)
F1	33.33	20	-	44.67	1	1	470 ± 6	7.35 ± 0.05	0.43	8
F2	33.33	30	-	34.67	1	1	600 ± 5	12.8 ± 0.04	0.55	6
F3	33.33	40	-	24.67	1	1	600 ± 4	12.8 ± 0.08	0.60	5
F4	33.33	-	20	44.67	1	1	600 ± 6	12.8 ± 0.11	0.58	7
F5	33.33	-	30	34.67	1	1	600 ± 3	12.8 ± 0.10	0.95	5
F6	33.33	-	40	24.67	1	1	600 ± 1	12.8 ± 0.05	0.85	6
F7	33.33	10	30	24.67	1	1	600 ± 2	12.8 ± 0.04	0.88	5
F8	33.33	20	20	24.67	1	1	600 ± 7	12.8 ± 0.20	0.67	6
F9	33.33	30	10	24.67	1	1	600 ± 5	12.8 ± 0.07	0.52	5

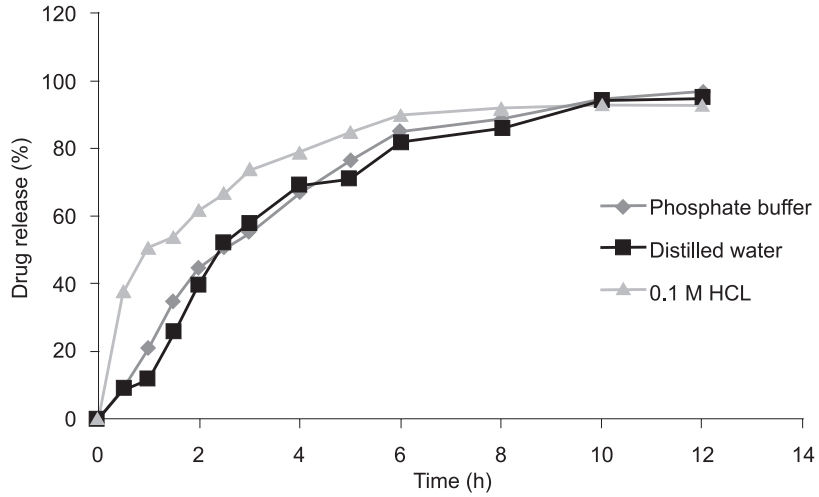

Figure 1. *In vitro* drug release behavior of formulations F1 in different dissolution mediums (Each data point is the mean of three values)

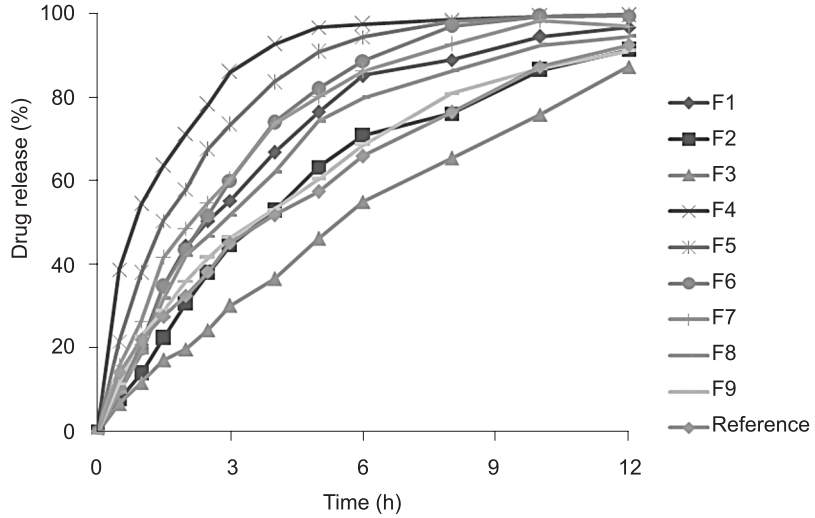

Figure 2. Drug release (%) study of metoprolol tartrate matrix tablets from batches F1–F9 and reference formulation in phosphate buffer medium (pH 6.8)

age weight loss was then calculated. Triplicate measurements were conducted for each formulation. The acceptable limit of weight loss was not more than 1.00%.

***In vitro* dissolution studies of solid matrix system**

In vitro dissolution of all the tablets was determined using the USP apparatus II, Pharma Test, China. The apparatus was validated by counting the revolutions of the paddle per minute. The test was performed in 900 mL of phosphate buffer (pH 6.8) with the temperature maintained at 37.0 ± 0.5°C, while the stirring speed was maintained at 50 rpm. Samples of about 10 mL each were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours with the help of pipette. All the samples were analyzed directly at 275 nm using a UV-Vis 2020 spectrophotometer (Irmeco, Germany). Dissolution study was also carried out in 0.1 M HCl and distilled water (pH 6.5). All the tests were run in triplicate and the average of three values were taken.

Statistical analysis

The dissolutions release profiles were analyzed using various models dependent kinetic approaches i.e., zero order, 1st order, Higuchi and Hixson-Crowell models. Moreover, dissolution data of various formulations was also compared by similarity factor (f2).

RESULTS AND DISCUSSION

Figure 1 shows dissolution behavior of metoprolol formulation F1 in phosphate buffer (pH 6.8), 0.1 M HCl and distilled water (pH 6.5) for 10 h. An initial burst release of metoprolol was observed in 0.1 M HCl whereas a slow release behavior (no burst effect) was seen in phosphate buffer (pH 6.8) and distilled water (pH 6.5). Due to these results, phosphate buffer (pH 6.8) was used in all the study. This observation also elaborates that a basic drug undergoes better solubility/ionization in an acidic medium than a basic medium.

Figure 2 elaborates a decrease in the rate of drug release from hydrophilic matrix tablets with an increase in xanthan gum concentration indicating that the polymer content is important for achieving sustained drug delivery. An increase of xanthan gum concentration from 20% to 40% resulted in low swelling characteristic of matrix tablets and slows down drug release profile. Figure 2 shows that as the amount of tragacanth increased from 20–40% in formulations F4, F5 and F6, there was a slow release of the drug from the matrices. Formulation F7 containing 10% xanthan gum and 30% gum tragacanth released more than 80% of the drug in six hours while formulations F8 and F9 released the drug at a slower rate releasing 80% of the drug in almost 8 and 10 h, respectively (Fig. 2).

Influence of increasing amount of xanthan gum on drug release from hydrophilic matrices

Figure 2 shows drug release profiles of various tablet formulations containing increasing amounts of xanthan gum. It is apparent that drug release from hydrophilic matrix tablet decreased as the amount of xanthan increased indicating that the polymer content is important for achieving sustained drug delivery. As the concentration of xanthan gum increased from 20 to 40% in tablet formulations (F1, F2 and F3) a corresponding decrease in the release rate of metoprolol tartrate was observed. This is evident from the literature that the diffusion is related to transport of drug from the tablet matrix into the dissolution media, depending upon the concentration of polymer used in formulation. As the concentration of hydrophilic polymer, xanthan gum was increased in the tablet formulation, an increase in diffusion path length and ultimately slower drug release resulted. Similarly, swelling of polymer was also dependent upon polymer concentration (7). An increase of the concentration from 20% to 40% resulted in low swelling characteristic of matrix tablets and slows down drug release profile.

Influence of increasing amount of gum tragacanth on drug release from hydrophilic matrices

Figure 2 shows that as the amount of tragacanth increased from 20-40 % in formulations F4, F5 and F6,

Table 2: Regression analysis (R^2) of release data based on best curve-fitting method for Mepressor SR and different formulations of metoprolol matrix tablets based on natural gums.

Formulation	Zero order kinetics	First order kinetics	Higuchi (square root) kinetics	Hixson-Crowell (cube root) kinetics
Reference	0.947 ± 0.025	0.904 ± 0.020	0.994 ± 0.004	0.957 ± 0.020
F1	0.958 ± 0.013	0.834 ± 0.006	0.989 ± 0.009	0.976 ± 0.030
F2	0.976 ± 0.008	0.912 ± 0.012	0.968 ± 0.016	0.940 ± 0.009
F3	0.963 ± 0.015	0.987 ± 0.009	0.898 ± 0.011	0.991 ± 0.007
F4	0.813 ± 0.007	0.767 ± 0.017	0.940 ± 0.020	0.865 ± 0.025
F5	0.861 ± 0.009	0.787 ± 0.006	0.966 ± 0.009	0.878 ± 0.032
F6	0.914 ± 0.011	0.795 ± 0.015	0.972 ± 0.016	0.892 ± 0.008
F7	0.935 ± 0.020	0.802 ± 0.027	0.985 ± 0.007	0.841 ± 0.023
F8	0.957 ± 0.013	0.852 ± 0.014	0.984 ± 0.008	0.889 ± 0.008
F9	0.992 ± 0.005	0.913 ± 0.009	0.997 ± 0.002	0.980 ± 0.009

there was a slow release of the drug from the matrices. It is apparent that drug release from hydrophilic matrix tablet decreased as the amount of tragacanth increased. But it is also evident that there was a faster release of drug from the tablets containing gum tragacanth as matrix former polymer as compared to the matrices containing xanthan gum as a matrix forming polymer, which is due to its low matrix forming ability as compared to xanthan gum (9).

Influence of different proportions of xanthan gum and gum tragacanth on drug release from hydrophilic matrices

Figure 2 shows drug release profiles of various tablet formulations containing different proportions of xanthan gum and tragacanth. Formulation F7 containing 10% of xanthan gum and 30% of gum tragacanth released more than 80% of the drug in 6 h, while formulations F8 and F9 released the drug at a slower rate releasing 80% of the drug in almost 8 and 10 h, respectively. This shows that increasing amount of xanthan gum with tragacanth slowed down the drug release.

Analysis of release data

The percentage release data (0–12 h) of tablet formulations was fitted to zero order, first order, Higuchi and Hixson-Crowell models. Regression analysis was performed to obtain the coefficient of regression (R^2) and the release constant was calculated from the slope of the appropriate plots as shown in Table 2. The release of the drug, as shown by various graphs, proves the existence of significant difference of drug release from each formulation by change in the concentration of polymer. The inverse relationship was noted between amount of polymer (xanthan gum and gum tragacanth) and release rate of metoprolol tartrate. Increasing the amount of xanthan gum in the formulation from F1, F2 and F3 and F7, F8, F9, resulted in slower rate and decreased amount of drug release from the tablet. The prolongation efficiency of tragacanth has also been demonstrated for other drugs. This slow release is due to the formulation of a thick gel structure that delays drug release from matrix tablet. As a result of rheology of hydrated product, the swollen particles coalesce (8, 11). This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet and retarding further penetration of the dissolution medium. There was the fast release of drug from the formulations F4, F5 and F6 containing only gum tragacanth as the matrix former polymer which is due to its low matrix forming ability. The release rate is the lowest in matrices containing the highest drug content (10). The *in vitro* drug released data were assessed using various kinetics models. Formulations containing xanthan gum were best fitted with a majority of the kinetic models and followed Higuchi or zero order kinetics (12). It was found that the *in vitro* drug release of metoprolol tartrate was best explained by Higuchi's equation, as the plots showed the highest linearity. This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics or Higuchi's kinetics (13, 14).

Comparison of the release data of prepared matrices with reference market formulation

The release data obtained from prepared matrices were compared with the marketed reference product by using similarity factor f_2, which was calculated for all the formulations containing natural polymers, xanthan gum and gum tragacanth (15).

$$f_2 = 50\mathrm{Log}\left\{\left[1 + 1/n\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Similarity factors were 47.17, 69.15, 46.86, 24.52, 31.47, 41.37, 40.84, 52.35 and 78.42 for the formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9, respectively. These results show that formulation F9 which contained 30% of xanthan gum and 10% of gum tragacanth is the most similar to that of the reference. Figure 2 shows a comparison of F9 and the reference Mepressor SR.

CONCLUSION

Various solid matrix formulations were prepared with natural gums (xanthan gum and gum tragacanth) in solid matrix using direct compression. Increasing the amount of xanthan gum and gum tragacanth in solid matrix tablet decreased the release rate of the drug. Moreover, the release data of various solid formulations were fitted to zero order, Higuchi, Hixson-Crowell and first order kinetic models. Most of the solid matrix formulations followed Higuchi or zero order kinetics. The formulations F1, F2, F3 and F7, F8, F9 showed maximum linearity while the formulations F4, F5, F6 have no linear behavior. Similarity factor f_2 was determined for all formulations and the results showed that the formulation F9 containing 30% xanthan gum and 10% gum tragacanth is the most similar to that of the marketed reference preparation. It is evident from

this study that xanthan gum, which is now gaining attention of researchers, gave good results alone and also in combination with gum tragacanth.

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