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Research Article

Development and evaluation of sustained release matrix tablet using hydrophilic gums as release modifier

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ABSTRACT

The objective of the present study was to design oral sustained drug delivery system for freely water-soluble drug, metoprolol succinate using hydrophilic gums. The gums selected were karaya gum and guar gum and their combination. To study the rheological synergism between karaya gum and guar gum in different ratio (0:10-10:0) was determined and the combination having highest viscosity (6:4) was used for matrix tablet formulation. Nine batches were prepared by using karaya gum and guar gum in 15%, 20% and 25% concentration of the total weight of tablet. Matrix tablets were prepared by wet granulation method and the prepared tablets were evaluated for weight variation, content uniformity, percentage friability, hardness, thickness, swelling index and *in vitro* dissolution studies. All the formulation showed compliance with pharmacopoeial standards. Formulation F1, F6 and F7 showed sustained release of drug for 12 hrs with 97.65%, 98.23% and 96.98% respectively. The optimized formulation was subjected to accelerated stability studies for one month at temperature of 40^0C and relative humidity of 75%. and showed physical stability and stability with respect to drug release pattern. The kinetic treatment showed that the formulations follow zero order with release exponent (n) was 0.8275, 0.9633 and 0.8079 for formulation F1, F6 and F7. So the combination of karaya gum and guar gum shows better prosperity for preparation of sustained release tablets as compare to individual gums.

Key words: Matrix tablet, Hydrophilic gum, Metoprolol succinate, Karaya gum, Guar gum.

INTRODUCTION

Many new drug delivery systems have been developed to deliver drugs with relatively short duration of action or narrow therapeutic indices at a controlled rate, which will maximize the pharmacological benefits and minimize the potential side effects. Considering all these aspects a distinct process and different materials, which can be easily employed at the production level, is an important aspect, which should be considered during developing good sustained release system. A properly designed matrix tablet as drug delivery system is a popular and expectable answer to all these problems.

During last two decades, swellable polymers are being used as controlled release polymeric devices[1]. The swellable matrices are monolithic systems prepared by compressing the drug along with the hydrophilic polymer. The matrices containing swellable release polymers are referred to as hydrogel matrices or swellable controlled release system[2].

Chief characteristics of hydrophilic gum is their ability to modify the properties of aqueous environment, i.e. their capacity to thicken, chelate, emulsify, stabilize, encapsulate, flocculate, swell and suspend or to form gels, films and membranes. The degree to which a hydrophilic gum hydrates governs the viscosity of the resulting solution/dispersion which in turn depends upon their degree of chemical uniformity, purity, molecular weight and ionic nature.

Industrially, there is a growing interest in the formulation of mixed hydrophilic gum systems. Blends of two or more hydrophilic gums exhibit complex and often spectacular properties, which depend not only on total polymer concentration, relative proportions of polymeric components, solvent medium characteristics and temperature, but also on the thermal and mechanical history experienced by the systems themselves. In other situations, the addition of small amount of a non-gelling polymer to a gelling one may induce a strengthening of the resulting gel or even, some polymers that are individually non-gelling can yield gels on mixing. Many such mixed-systems of hydrophilic gums show this additive behavior, which is currently termed synergism[3].

Karaya gum is a Galactomannan, obtained from the dry exudates of plant species sterculia. It has been investigated as sustained release carrier and regarded as non- toxic & non-

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irritant material. Guar gum is a galactomannan, obtained from the ground endosperm of guar seeds of plant *Cyamopsis tetragonolobus*. It has been investigated as controlled release carrier and regarded as a nontoxic and a nonirritant material[4, 5].

Metoprolol succinate is a ß$_1$-Adrenergic receptor blocking agent and use in the management of cardiovascular diseases. The elimination half life is 4 -6 hrs and require dosing every 6 hours in order to maintain optimal relief from cardiovascular disease. Consequently, once- daily sustained release tablets have been formulated.

The present study was designed to formulate matrix tablets using karaya gum and guar gum as hydrophilic matrix polymers in alone and in combination for controlling release of freely water soluble drug Metoprolol Succinate.

MATERIAL AND METHOD:

Metoprolol Succinate was obtained from Alkem pharmaceutical Ltd (Mumbai) as a gift sample. The karaya gum (KG) and guar gum (GG) were obtained from Krystal Colloids, Mumbai, all other reagents used were of analytical grade.

Preparation of Matrix Tablet: Sustained release (SR) matrix tablets were prepared by wet-granulation method. In all cases, the amount of active ingredient is 47.5mg. Karaya gum and guar gum was used as matrix forming material while lactose monohydrate used as diluent, Magnesium stearate and talc were used as lubricant and glidant. Drug, polymer and diluent were passed through 100 mesh sieve, weighed and were blended to obtain uniform mixing. After mixing the powder was granulated using PVP K-30 in isopropyl alcohol to form damp mass. The damp mass was passes through 12 No. mesh sieve and the granules obtained were dried in oven at temp 50^{0}C for 1 hour. After drying, granules passed through 16 No. mesh sieve to obtained uniform size granules. After sufficient lubrication matrix tablets were prepared using Cadmach single punch tablet machine (M/S. Cadmach Machinery Co. Pvt. Ltd, Ahmedabad) using 8mm deep concave punch. All the prepared Metoprolol succinate tablets were stored in airtight container at room temperature for further study. Formulation F1 to F6 contains single gum and formulation F7 to F9 contains combination of gums.

The composition of various formulations is shown in Table 1.

Evaluation of matrix tablets[6]:

All prepared matrix tablet were evaluated for Hardness (Monsanto hardness tester), weight variation, content uniformity, percentage friability (Roche friabilator), Thickness (vernier caliper).

The values of evaluation parameters are given in Table 2.

Swelling behavior of matrix tablets[7]:

The extent of swelling was measured in terms of percentage weight gain by the tablets. For determination of swelling index one tablet from each formulation was kept in the Petri dish containing phosphate buffer (pH 6.8). After every 2hrs tablet was withdrawn, soaked with tissue paper and weighed. The process is continued for 12hrs. Swelling index of formulation was calculated using following formula.

$$S.I.= \frac{M_t - M_o}{M_o} \times 100$$

Where, SI = Swelling index, M_t = Weight of tablet at time‘t’ and M_o = Weight of tablet at time ‘0’

***In vitro* drug release study[8]:**

The *in vitro* dissolution study was carried out using six station dissolution rate test apparatus USP at 50rpm. The dissolution medium consisted of 900ml simulated gastric fluid (pH 1.2) for first 2hrs followed by simulated intestinal fluid (pH 7.2) from 2 to 12hrs. Aliquots of 5ml were withdrawn every one hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 274.5nm spectrophotometrically. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of result.

The plot of percentage cumulative drug release against time (Hrs.) is shown in Figure 1.

Study of release kinetics[7]:

In order to investigate the mode of drug release from tablets, the release data was analyzed with the following mathematical models:

Zero order equation ($Q = K_o t$),

First order equation $\{\ln (100-Q) = \ln Q - K_1 t\}$,

Higuchi equation ($Q = kt^{1/2}$),

Korsmeyer and peppas equation ($Q = k_p t^n$),

Where Q is the percent of the drug release at time t and k_o and k_t are the coefficients of equation. K_p is constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of mechanism of release.

The values of mathematical modeling and drug release kinetics are given in Table 3.

Stability Studies of Matrix Tablets[9]:

The stability study was carried out on optimized formulation F1, F6 and F7. The tablets were wrapped in aluminium foil, and then placed in umber coloured bottle and was stored at temperature 40^{0}C ± 2^{0}C and RH 75% ± 6% for six month. The tablets were evaluated for any changes in physical ap-

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Table 1: Formulation table of Metoprolol Succinate tablets

Formulation (mg)	Drug	Guar gum	Karaya gum	Lactose	PVP-K30	Magnesium stearate	Talc	Total weight
F1	47.5	36	—	154.1	7.2	2.4	4.8	240
F2	47.5	48	—	142.1	7.2	2.4	4.8	240
F3	47.5	60	—	130.1	7.2	2.4	4.8	240
F4	47.5	—	36	154.1	7.2	2.4	4.8	240
F5	47.5	—	48	142.1	7.2	2.4	4.8	240
F6	47.5	—	60	130.1	7.2	2.4	4.8	240
F7	47.5	28.8	7.2	154.1	7.2	2.4	4.8	240
F8	47.5	38.4	9.6	142.1	7.2	2.4	4.8	240
F9	47.5	48	12	130.1	7.2	2.4	4.8	240

Table 2: Evaluation parameters of different formulations

Batch code	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Content uniformity(%)	Weight Variation
F1	6.3	0.71	5.01	99.58	Passes
F2	6.2	0.68	5.02	100.02	Passes
F3	6	0.60	5.03	95.89	Passes
F4	6.1	0.62	5.01	100.62	Passes
F5	6.1	0.69	5.01	95.62	Passes
F6	6.2	0.58	5.02	99.92	Passes
F7	6.4	0.62	5.00	100.03	Passes
F8	6.4	0.54	5.00	102.1	Passes

Table 3: Mathematical modeling and drug release kinetics of sustained release tablets of Metoprolol Succinate

Batch code	n	k	r²	Model Fitting
F1	0.8275	12.8738	0.9929	Zero order
F2	0.8345	12.3110	0.9879	Zero order
F3	0.8310	11.3374	0.9898	Hixson-Crowell
F4	0.9676	11.6529	0.9958	Zero order
F5	0.9601	13.5946	0.9894	Zero order
F6	0.9633	13.9065	0.9832	Korsmeyer-Peppas
F7	0.8079	14.1882	0.9925	Zero order
F8	0.8285	12.8728	0.9939	Zero order
F9	0.8335	12.3100	0.9899	Zero order

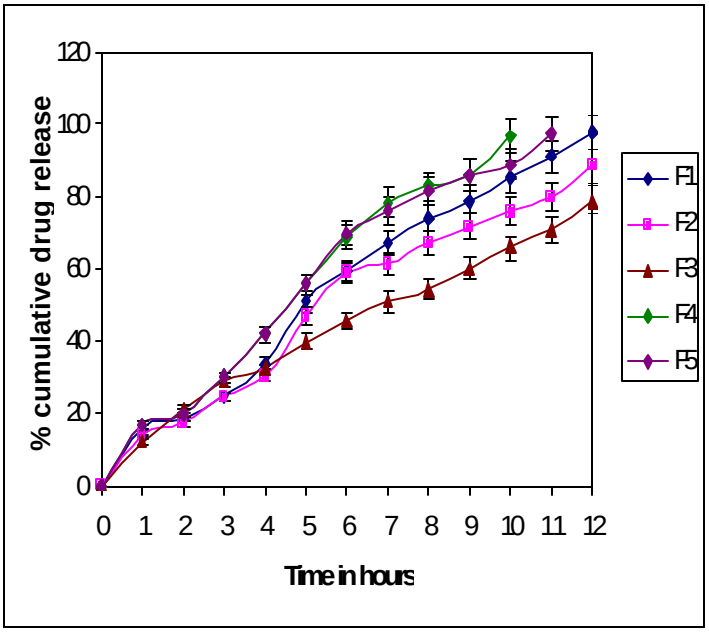

Figure 1. Percentage cumulative drug release of batches F1 to F5

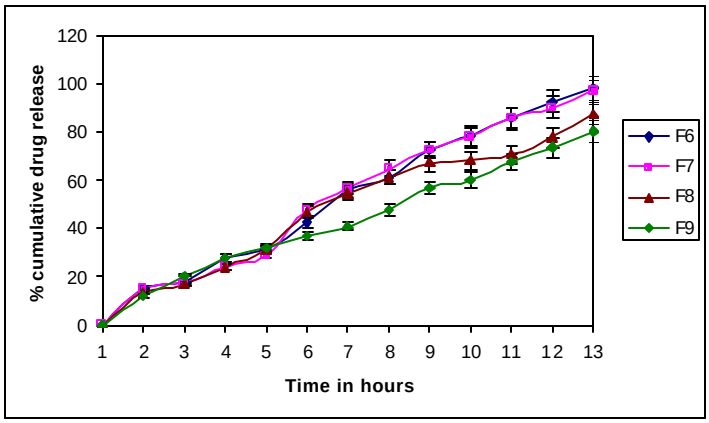

Figure2. Percentage cumulative drug release of batches F6 to F9

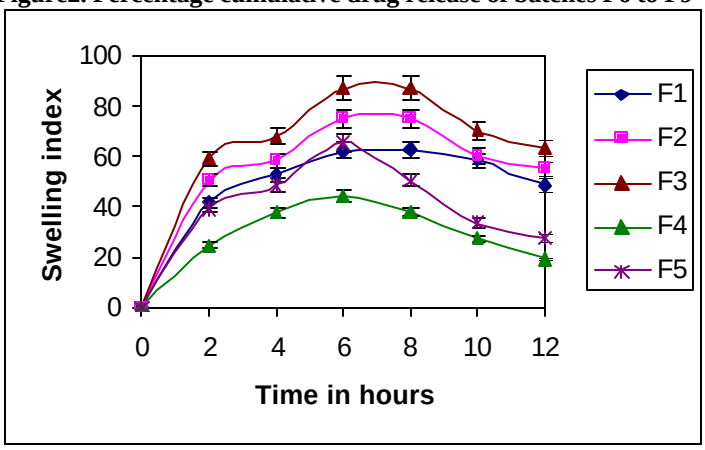

Figure 3. Swelling index of batches F1 to F5

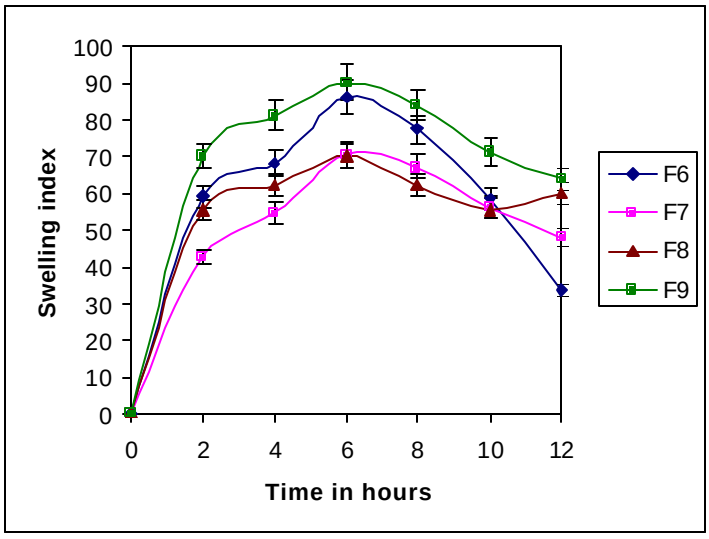

Figure 4. Swelling index of batches F6 to F9

pearance and percent cumulative drug release after two, four and six month.

Result obtained was compared with data obtained for Zero time and room temperature ($28^0C \pm 2^0C$) and relative humidity (42% ± 2%).

RESULTS AND DISCUSSION:

All the batches were evaluated for the Physical properties, Hardness of the tablet in the range of 6-6.4 kg/cm^2, thickness 5 to 5.03 mm Percentage weight loss in the Friability test was less than 0.7% in all batches and all the batches contained Metoprolol succinate within 100 ± 5% of the labeled content. Overall the prepared tablet batches of good quality with regard to hardness, friability and drug content.

The swelling index of the formulations are directly proportional to the concentration of the gum, as the gum concentration increases there is increase in swelling index as the gum absorbs water and swell but after 6-8Hrs there is decrease in swelling index due the erosion of surface layer of matrix tablet.

The dissolution study shows that the Metoprolol succinate release from all tablets but the F1, F6 and F7 was found to be slow and extended over longer period of time. Rate of drug release from the matrix tablets was found to decrease with increase in polymer ratio.

The direct relationship was observed between swelling index and gum concentration, as gum concentration increase swelling index was increase and the percent cumulative drug release was decrease, as in formulation F4, F5 and F6. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of gums.

The release kinetics shows that the formulation F1, F6 and F7 shows zero order models fitting with release exponent 0.8275, 0.9633 and 0.8079 respectively.

The stability studies show that there was no significant change in hardness, percentage friability, content uniformity and percent cumulative drug release of the selected formulation.

The present study shows that the single hydrophilic gum like karaya gum and guar gum showed the sustained release profile for short time where as the combination of these two hydrophilic gums in proportion of 6:4 gives sustained drug release for 12 hours.

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