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Formulation and Evaluation of Sustained Release Metoprolol Succinate Tablet using Hydrophilic gums as Release modifiers

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Abstract: The objective of this study was to design and evaluate oral sustained drug delivery system for Metoprolol succinate using natural hydrophilic gums such as karaya gum and xanthan gum as a release modifier. Nine batches were prepared by using karaya gum (KG) and xanthan gum (XG) in concentration of 15%, 20% and 25% alone and in combination of 2:8. Matrix tablets were prepared by wet granulation method and were evaluated for weight variation, content uniformity, friability, hardness, thickness, swelling index, *in vitro* dissolution, and stereo photography. Among the formulations studied, formulation F8 containing combination of KG and XG (2:8) having concentration of 20% showed sustained release of drug for 12hrs with cumulative percent release of 99.24%. The kinetic treatment showed that the optimized formulation follow zero order kinetic with release exponent (n) 0.7656 and having good stability as per ICH guidelines. No chemical interaction between drug and gums was seen as confirmed by IR studies. The matrix formulation F8 showed sustained release of Metotprolol succinate by the diffusion mechanism.
Key Words: Sustained release, Hydrophilic gums, Karaya gum, Xanthan gum, Metoprolol succinate.

Introduction and Experimental:

Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed[1]. 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[2]. 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[3]. 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[4]. 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.

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 4-6hrs and in normal

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

Materials:

Metoprolol succinate was obtained from Alkem pharmaceutical Ltd, Mumbai as a gift sample. The karaya gum (KG) and xanthan gum (XG) were obtained from Krystal colloids, Mumbai. Solvents and all other reagents used were of analytical grade. Double distilled water was used through out the study.

Preparation of Matrix Tablet:

ustained release matrix tablets were prepared by wet granulation method. All the ingredients was passes through sieve # 100, weight accurately, mixed and granulated using PVP K-30 in isopropyl alcohol as granulating aid. The granules obtained were dried in oven at 50^0C for 2 hours. After drying, granules passed through sieve # 16 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. Amount of drug in all formulation was kept constant, Formulation F1 to F6 contains single gum and formulation F7 to F9 contains combination of gums. The concentration of gum varies from 15%, 20% and 25% in different formulation.

The composition of various formulations is shown in Table 1.

Evaluation of Matrix Tablets:

All prepared matrix tablets were evaluated for weight variation, content uniformity. Friability testing was done by Roche friabilator. Hardness was measured by using Monsanto hardness tester. Thickness was measured by vernier caliper.[5]

The values of evaluation parameters is given in Table 2

Table 1: Composition of Metoprolol succinate matrix tablets.

Formulation/ ingredients (mg)	Drug	Xanthan gum	Karaya gum	Lactose	PVP-K30	Mg. stearate	Talc	Total weight
F1	47.5	36	-	142.1	7.2	2.4	4.8	240
F2	47.5	48	-	130.1	7.2	2.4	4.8	240
F3	47.5	60		118.1	7.2	2.4	4.8	240
F4	47.5	-	36	142.1	7.2	2.4	4.8	240
F5	47.5	-	48	130.1	7.2	2.4	4.8	240
F6	47.5	-	60	118.1	7.2	2.4	4.8	240
F7	47.5	28.8	7.2	142.1	7.2	2.4	4.8	240
F8	47.5	38.4	9.6	130.1	7.2	2.4	4.8	240
F9	47.5	48	12	118.1	7.2	2.4	4.8	240

Table 2: Evaluation parameters of different formulations

Formulation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity (%)	Weight Variation
F1	6.2±0.1528	0.68	5.01±0.010	99.58	240.66±1.3
F2	6.2±0.1528	0.67	5.03±0.015	100.02	239.96±1.1
F3	6±0.1732	0.57	50.1±0.026	95.89	240.26±0.3
F4	6.1±0.1627	0.62	50.1±0.016	100.62	240.1±1.15
F5	6.1±0.1627	0.69	5.01±0.016	95.62	240.53±0.40
F6	6.2±0.1529	0.59	5.03±0.019	99.92	239.36±0.37
F7	6.2±0.1529	0.65	5.01±0.010	99.96	240.3±1.5
F8	6±0.1429	0.62	5.02±0.013	100.03	241±0.88
F9	6±0.1429	0.51	5.01±0.010	102.1	240±00

In vitro Drug Release Study:

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. Temperature maintained at 37 ± 1^0C. 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[6]. All the release studies were conducted

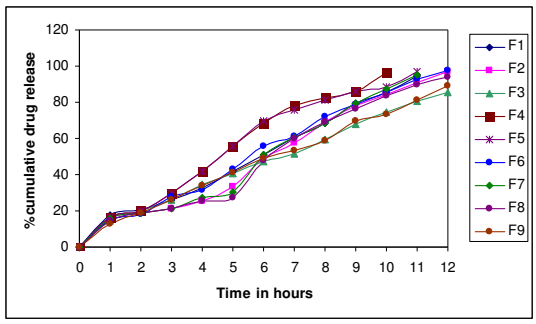
Table 3: Mathematical modeling and drug release kinetics of matrix tablets.

Formulation	Drug release kinetics, correlation coefficients (r^2)			Release exponent (n)
	Zero order	Matrix	First order	
F1	0.9913	0.9232	0.9557	0.7922
F2	0.9913	9232	0.9663	0.7922
F3	0.9779	0.9218	0.9663	0.8548
F4	0.9676	0.9429	0.9777	0.8688
F5	0.9601	0.9538	0.9874	0.8198
F6	0.9633	0.9721	0.9951	0.7381
F7	0.9852	0.9385	0.9670	0.7125
F8	0.9897	0.9356	0.9744	0.7656
F9	0.9785	0.9256	0.9707	0.8435

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.

Figure 1: Percentage cumulative drug release of matrix tablets.



Study of Release Kinetics:

In order to investigate the mode of release from tablets, the release data was analyzed with the following mathematical models[2]:

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

First order equation {In (100-Q) =In Q-K1t},

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 indicate the release mechanism.

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

Swelling Behavior of Matrix Tablets[7]:

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in Petri dish containing

Figure 2: Swelling index of formulation F1 to F5.

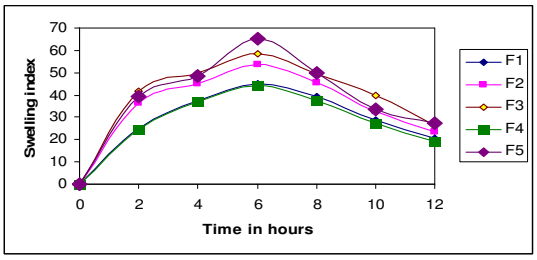
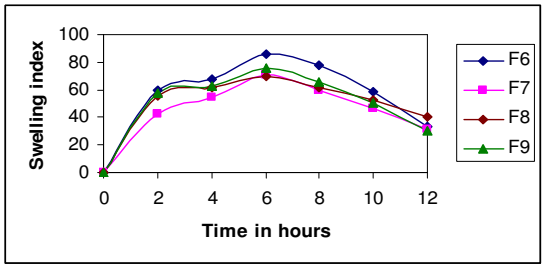


Figure 3: Swelling index of formulation F6 to F9



phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10 and 12hrs tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.

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

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

The swelling index of the different batches is given in Figure 2 and 3.

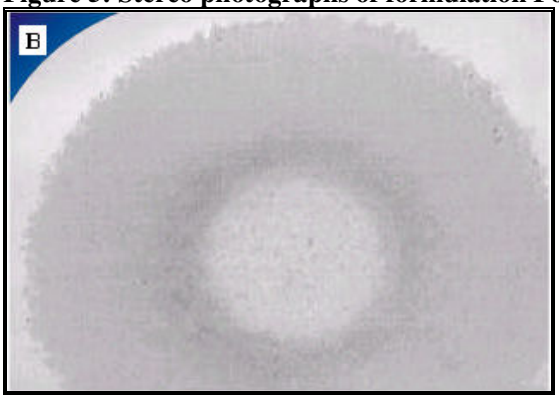
Stereo Photography:

The front movement of swellable matrices was determined by clamping two glass discs onto the two faces of the sustained-release matrix tablet and performing the dissolution according to the procedure described in *vitro* dissolution studies. Water penetration, matrix expansion and drug release occurred through the lateral side of the matrix. Magnified stereo photographs of tablets (Batch F2, F6 & F8) were taken after 4 hours of dissolution using Interplay microscope QX3 attached to a computer. The photographs were used to analyses the various front positions and degree of swelling of each formulation.

The stereo photographs of matrix tablets is shown in Figure 4, 5 and 6.

Figure 4: Stereo photographs of formulation F2

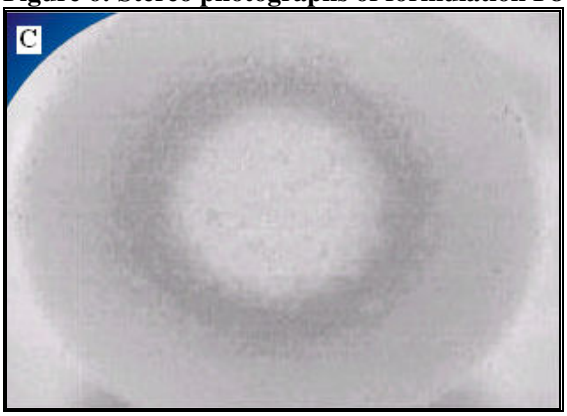
Figure 5: Stereo photographs of formulation F6



Stability Studies of Matrix Tablets[8,9]:

The stability study was carried out on optimized formulation F8. The tablets were wrapped in aluminium foil, and then placed in umber coloured bottle and was stored at temperature $40^0C \pm 2^0C$ and RH 75% ± 6% for six month. The tablets were evaluated for any changes in physical appearance 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%).

Figure 6: Stereo photographs of formulation F8



Results and Discussion:

The formulated matrix tablets have content uniformity 99.58% to 100.2%, hardness 6 kg/cm^2 to 6.2 kg/cm^2, thickness 5.01mm to 5.03mm. Percentage friability and weight variation passes the test as per standard pharmacopoeial limit.

As the time increase, swelling index was increased, because weight gain by tablet was proportional to rate of hydration up to 6hrs, later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, as gum concentration increase swelling index increased. It was observed that the cumulative percent drug release decrease with increasing concentration of gum and swelling index.

Stereo photography studies showed the different front position like swelling, diffusion and erosion front. The front position showed that the drug release from matrix by swelling and diffusion process.

Among the formulation studied, formulation F8 showed 99.24% release of drug for 12hrs. The release kinetics revealed that all the formulation follows zero order drug release with release exponent value (n) 0.7656

Stability studies revealed that there were no significant changes in hardness, friability, drug content and dissolution profile of formulation F8. Thus formulation was stable at accelerated condition. So it could be concluded that karaya gum & xanthan gum can be used as an effective matrix former to retard the release of metoprolol succinate for extended period of time.

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