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Formulation and Evaluation of Sustained Release Matrix Tablet of Atenolol Based on Natural Polymer

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ABSTRACT

The purpose of the present investigation was to develop sustained release matrix tablets of Atenolol (ATL) using Xanthan gum (XG) and Guar gum (GG) as matrix former. Different ratios of XG and GG were selected and their suitability was tested as drug carrier. A natural gum Jeol (JG) was used as binder and its effect on hardness and drug release profile of prepared tablets were examined. The *in-vitro* drug release studies were performed in 0.1N HCl for 2 h followed by phosphate buffer at pH 6.8. The drug release profiles reveal that the release is dependent upon the nature and concentration of the polymer. The matrix tablets composed of XG showed 20.64% drug release during 2h in the acid stage, whereas for XG-GG mixture tablets, it was 27.96% to 39.26%. The addition of JG was found to increase the hardness of the tablets. The dissolution data demonstrated that JG has significant influence on drug release from XG matrix whereas insignificant effect was observed in XG-GG mixture. Statistical analysis of the drug release data at 2h indicated that the drug release is significantly ($^{***}p<0.0001$) affected by the nature and concentration of the polymers as compared to marketed product Aten®.

Keywords: Atenolol, Xanthan gum, Guar gum, Jeol gum, Sustained release matrix tablet.

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INTRODUCTION

Atenolol is a β-blocker, prescribed widely in hypertension, angina pectoris, arrhythmias, and myocardial infarction [1]. It has been reported that Atenolol undergoes extensive hepatic first-pass metabolism following oral administration and has a short biological half-life [2]. Administration of conventional tablets of Atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects like nausea, diarrhea, ischemic colitis, and mesenteric arterial thrombosis or reduction in drug concentration at the receptor site [2-4]. The development of sustained release matrix tablets containing Atenolol that would maintain proper blood level for a long time without fluctuation is of paramount importance [2, 5, 6]. Various research studies have been reported on controlling the drug release by sustained release systems such as osmotic pumps [7-9], matrix tablets [10-13, and transdermal drug delivery systems [5, 14].

Hydrophilic matrix tablets have been used as drug delivery systems due to their simplicity, cost-effectiveness, reduced risk of systemic toxicity and minimal chance of dose dumping [15]. Hydrophilic matrix materials such as hydroxypropyl methylcellulose [16], sodium carboxy-methylcellulose [17], sodium alginate [18] and carbopol [19] have been successfully utilized as retardant for controlling drug release. Recently, naturally occurring polymers have gained considerable attention amongst formulation scientists due to their advantages like natural abundance, biocompatibility, biodegradability, and non-immunogenicity over synthetic polymers [20, 21]. Natural gums popularly used as matrix former are Gum karaya [22], okra gum [23] locust bean gum, xanthan gum and guar gum [24].

XG is a naturally occurring polysaccharide produced by the fermentation of gram-negative bacterium, *Xanthomonas campestris*. It has been reported by many researchers that XG can be used as an effective excipient for developing sustained release and colon targeted formulations [2, 25, 26]. GG is a natural nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (L.). When XG is mixed with GG, optimum synergistic effects are obtained [27]. The JG was obtained as an exudate from the plant commonly known in West Bengal, India as "Jeol trees" (*Odinawodier, Roxb*) [28]. In the present investigation, the influence of XG-GG mixture and JG on Atenolol release from matrix tablets was statistically evaluated using one way ANOVA in comparison with Aten®.

MATERIALS AND METHODS

Materials

Atenolol was obtained from Yarrow Chem Products Mumbai, India. Aten® (Batch no. ZHL 3754, Zydus Cadila, Sikkim, India) was purchased from medical shop. XG, GG, Talc, Magnesium stearate and other chemicals were obtained commercially from S.D. Fine Chemicals, Mumbai, India and used without further purification. JG was extracted and purified according to the procedure described by Bhattacharyya *et al*., 1964 [28].

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Preparation of matrix tablets

Drug (Atenolol), XG, GG, and JG were separately passed through sieve no. 80. The drug was then mixed with the polymer(s) and other ingredients in the weight proportion mentioned in Table 1. Magnesium stearate and talc were uniformly mixed with the above mixture, and compressed on a 10 station tablet punching machine equipped with a 7 mm flat-faced punch and die set (Rimek, Karnavati, India).

Table 1: The composition of the developed matrix tablets (mg).

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Atenolol	100	100	100	100	100	100	100	100
Xanthan gum	164.6	82.3	115.22	148.14	159.2	79.6	111.44	143.28
Guar gum	0	82.3	49.38	16.46	0	79.6	47.76	15.92
Jeol gum	0	0	0	0	5.4	5.4	5.4	5.4
Magnesium Stearate	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Talc	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total Weight	270	270	270	270	270	270	270	270

Physicochemical characteristics of matrix tablets

Tablets were evaluated for hardness by using a monsanto type hardness tester. Friability of the tablets was evaluated by a Roche Friabilator (Mumbai, India). Thickness of the tablets was measured using vernier caliper. Weight variation of tablets was determined, taking twenty tablets randomly and accurately weighed. Results are expressed as mean ± standard error (S.E).

Drug content uniformity

Ten tablets were randomly taken from each batch. The tablets were weighed and powdered. The powdered material equivalent to the average weight of the tablets was dissolved in 0.1N HCl and the volume was made upto 100 ml. The samples were filtered and analyzed by UV spectrophotometry (UV-1800 pharma spectroscopy, Shimadzu, Japan) at 224 nm [10].

Swelling study

The swelling behaviour of the tablets was determined according to the method described by Khamanga *et al.,* 2006. The tablets were subjected to dissolution testing using USP apparatus II (Electrolab TDT-08L, Mumbai, India) filled with 900 ml 0.1 N HCl for 2h followed by phosphate buffer of pH 6.8, maintained at 37±0.5°C at a speed of 50 rpm. Tablets were removed at 1h interval and excess surface water was carefully removed using filter. The wet tablets were weighed. The increase in weight of the wet tablet mass represented the water uptake and used for the determination of percentage swelling. The percentage swelling (S) was calculated using the following formula:

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$$S = (W2-W1) \times 100/W1$$

W1 = mass of tablet before placing in dissolution media,
W2 = wet mass of tablet after placing in dissolution media.

In-vitro drug release study and data analysis

The U.S.P. dissolution apparatus II was used for all the *in-vitro* dissolution studies of all the developed tablets and Aten®. The dissolution medium was 0.1 N HCl for 2h followed by phosphate buffer of pH 6.8. The tablet was placed in 900 ml of dissolution medium maintained at 37±0.5°C and the stirring rate was 50 rpm. The sample was collected at one hour interval and was analyzed using UV spectrophotometer (UV-1800 pharma spectroscopy, Shimadzu, Japan) at 224 nm.

All the dissolution data were analyzed by various pharmacokinetic models. The correlation coefficient of zero order, Higuchi and first order kinetics were calculated by relevant software. All data were further analyzed by Korsmeyer-Peppas equation for determination of release mechanism. The Korsmeyer–Peppas model was employed for describing drug release from polymeric systems. The Korsmeyer–Peppas model takes into account that the drug release mechanism often deviates from Fick's law and follows an anomalous behavior described by the following equation: $M_t / M\infty = Kt^n$, where M_t is the drug released at time t, $M\infty$ is the quantity of drug released at infinite time, *k* is the kinetic constant and *n* is the release exponent. The value of *n* is related to the geometrical shape of the delivery systems and determines the release mechanism. The statistical analysis of the release data were performed in comparison to Aten® as positive control by one way ANOVA followed by Dunnett's *post hoc* test of significance where $P < 0.05$ and $P < 0.01$ were considered to be significant and highly significant respectively (Graph Pad Prism Software, Version 4.03,Graph Pad Software Inc, San Diego, CA).

RESULTS AND DISCUSSIONS

Physicochemical characteristics of matrix tablets

Sustained release matrix tablets of Atenolol were developed using natural polymer(s) like XG and/or GG as retardant and JG as binder. The incorporation of JG in matrix tablets was found to enhance tablet hardness in direct compression. From the results, it was observed that tablet hardness had some effect on the drug release profile depending on tablet composition. Increasing the hardness would possibly reduce the drug release significantly for tablets containing XG alone as retardant. But gradual increase in concentration of GG as alternative to XG in the formulated tablets showed decreasing effects of hardness on drug release profile. The physicochemical properties of the matrix tablets are summarized in Table 2. The thickness of all tablets ranged within 4.91 ± 0.01 to 5.42 ± 0.24 mm. The weight of the tablets ranged from 269±1.41 to 270.8±1.37 mg. All the developed matrix tablets met the USP requirements for weight variation tolerance. Drug content uniformity results were found to be good among

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different tablet batches (98.94±0.41 to 100.1±0.79 %). The percentage friability for all tablets was less than 0.67±0.01%., indicating good mechanical resistance.

Table 2: Physicochemical properties of the developed matrix tablets (n=3)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	4.91±0.01	5.12±0.07	5.22±0.18	5.11±0.10	5.2±0.17	5.23±0.14	5.09±0.13	5.42±0.24
Hardness (Kg/cm^2)	2.92±0.22	3.08±0.07	3.2±0.09	3.34±0.14	3.6±0.14	4.18±0.13	4.67±0.16	4.7±0.17
Friability (%)	0.67±0.01	0.65±0.02	0.62±0.04	0.61±0.00	0.51±0.01	0.55±0.04	0.54±0.02	0.52±0.02
Weight Variation (mg)	269.8±1.52	270.8±1.37	269±1.41	270.7±1.07	269.5±1.43	270.6±1.10	269.8±1.37	270.4±1.24
Content Uniformity (%)	99.33±0.51	99.75±0.40	100.1±0.69	98.94±0.41	99.13±0.47	99.82±0.39	100±0.69	100.1±0.79
#Swelling at 5 hrs (%).	782.70±8.19	634.3±6.69***	574.00±7.51***	495.3±5.49***	626.00±5.77***	544.00±6.66***	505.30±6.89***	460.7±2.33***

All values were expressed as mean±SE. # Values differs significantly from F1 (*** p<0.0001).

Swelling study

The hydration ability of the matrix tablet is important because it influences drug release profiles. It may possibly be concluded that the dissolution medium uptake by the developed matrix tablet depends on the type of polymer used and the composition of the tablets (Table 2). F1 showed the highest percentage swelling throughout the study period of 5h. This might be due to the less hardness and less viscous gel formation around the surface of the tablet in contact with the dissolution medium through which the rate of penetration of dissolution medium could have been faster. On the other hand, significant reductions ($p < 0.0001$) in the percentage of swelling were observed with the tablets F2 to F4 containing increasing amount of GG. In the study, a gradual decrease in the percentage swelling was observed with tablet F1 to F4 and F5 to F8. This could have relevance to the increasing viscosity and lower solvent penetration in to the tablets. It is already reported that, addition of GG in XG solution, leads to attainment of synergistic viscosity [27]. In addition, JG also reduces the percentage swelling by increasing hardness of the tablets. It is assumed that tablet swelling starts with water penetration into the glassy polymer matrix and a pseudo gel is formed around the tablet surface with dry core material. At the surface of the pseudo gel layer the polymer concentration is assumed to be the critical polymer concentration for gel and the percentage swelling is influenced by the gel viscosity and if viscosity of the pseudo gel is more, then the water penetration is less leading to less percentage swelling and vice-versa.

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In-vitro drug release study and data analysis

The drug release profiles of developed matrix tablets formulated with XG and GG are represented in Figure 1 and Figure 2. Formulation containing XG alone as retardant showed the highest drug release compared to other formulations. Among other formulations, GG containing tablets showed slower release rates. It was found that the nature and concentration of natural gum used in the matrix tablet, was responsible for gel strength and resulted in the observed drug release profile of the tablets. When GG concentration was 50% with XG, the drug release was significantly decreased. The drug release was further decreased with incremental concentration of XG in presence of GG. This was attributed to synergistic increase in viscosity of XG in presence of GG. When JG was used as binder, the drug release was significantly reduced for tablet composed of XG alone as retardant due to decrease in percentage swelling in presence of JG. But diminution of drug release in presence of JG declined with decreasing concentration of GG, because of simultaneous reduction in percentage swelling differences between the tablets containing same retardant components.

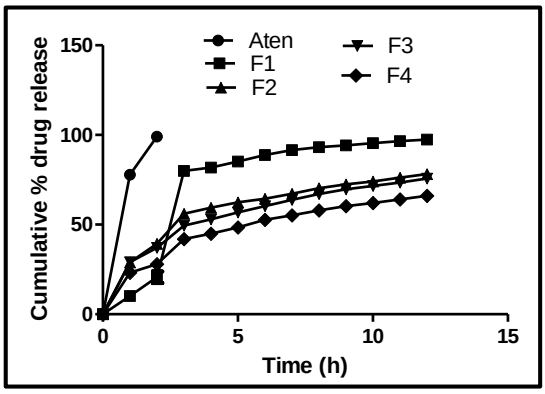

Figure 1: Cumulative percent drug release vs. time graph of F1- F4 and Aten® (Values were expressed as mean±SE for three replications).

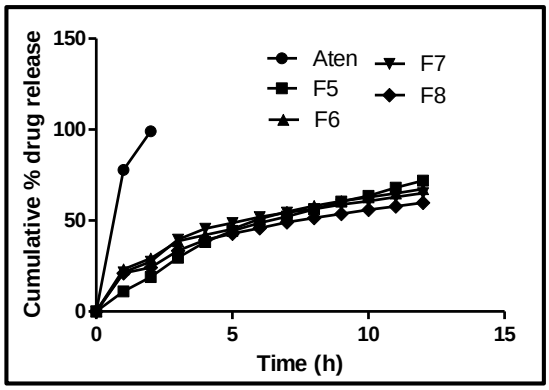

Figure 2: Cumulative percent drug release vs. time graph of F5- F8 and Aten® (Values were expressed as mean±SE for three replications).

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All the release data were analyzed by Zero order, First order and Higuchi kinetics. From table 4 it was observed that the drug release was best explained by Higuchi's kinetics for most of the formulations (r^2>0.943±0.01) followed by first order and zero order kinetics. The drug release data of formulation F1 was best fitted to first order kinetics followed by Higuchi and zero order kinetics as correlation coefficient (r^2) was 0.942±0.007. The data were subjected to Korsmeyer-Peppas equation to determine the drug release mechanism. The acceptable linearity was observed (r^2>0.943±0.02) for developed formulations (F2 to F8) and for F1 it was 0.773±0.001. For a matrix tablet, when n=0.45, it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport). Anomalous transport indicated that diffusion as well as erosion was responsible for drug release. The values of n with the corresponding correlation coefficients for all the formulations are shown in Table 4. For F2 to F8, "n" varies between 0.382±0.007 and 0.449±0.005, indicating that, only diffusion mechanism was responsible for drug release. But for F1, n value was 0.857±0.035 indicating the anomalous drug diffusion.

Table 3: Comparison of drug release profile of developed formulation (F1-F8) with Aten® (n=3)

Time (h)	% Drug release								
	Aten®	F1	F2	F3	F4	F5	F6	F7	F8
#2	99.12 ± 0.95	20.64 ± 3.21***	39.26 ± 1.13***	37.09± 0.36***	27.96± 1.45***	18.93± 0.35***	29.2 ± 0.65***	27.44 ± 0.63***	24.23 ± 1.08***
12	-	97.42 ± 0.65	78.22 ± 0.98	75.63±0 .37	66.03 ± 1.98	71.89± 0.47	67.3± 0.3	65.04 ±1.32	59.42 ±1.27

Values were expressed as mean±SE. #Values differs significantly from Aten® (*** p<0.0001).

Table 4: Mathematical modeling and drug release kinetics of developed matrix tablets (mean±SE, n=3).

Formulations	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	n
F1	0.686±0.002	0.942±0.007	0.829±0.003	0.773±0.001	0.857±0.035
F2	0.751±0.014	0.895±0.019	0.943±0.010	0.943±0.021	0.382±0.007
F3	0.86±0.013	0.946±0.009	0.972±0.007	0.982±0.007	0.384±0.003
F4	0.832±0.004	0.923±0.005	0.972±0.001	0.959±0.002	0.426±0.007
F5	0.952±0.002	0.995±0.001	0.982±0.001	0.983±0.001	0.743±0.016
F6	0.882±0.006	0.965±0.003	0.993±0.001	0.992±0.000	0.441±0.004
F7	0.838±0.004	0.930±0.000	0.976±0.001	0.969±0.002	0.449±0.005
F8	0.871±0.010	0.944±0.006	0.986±0.003	0.976±0.003	0.446±0.001

All the release data at 2h were analyzed by one way ANOVA followed by Dunnett's *post hoc* test of significance at 95% fiducial limit as compared with Aten® as positive control. Table 3 depicted that the percentage drug release of the developed formulations were significantly different from Aten® (p<0.0001).

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CONCLUSIONS

The effects of XG, GG and JG on Atenolol release profile of the formulated sustained release matrix tablets were evaluated. Tablets composed of XG alone exhibited 97.42±0.65% drug release at 12h. To reduce the rate of drug release, GG was successfully used in addition to XG. It was observed that the drug release was reduced by more than 19% with the addition of GG at a concentration of 50% or below the total amount of retardant used. The extent of reduction in drug release was dependent on the nature and concentration of the polymer used. The tablet hardness was successfully augmented using 5% JG. Addition of JG also reduced the drug release by about 7 to 21%. It was concluded that Atenolol was successfully formulated as sustained release matrix tablet using XG and GG as retardant and JG as binder. Hence the developed formulations may possibly be a better alternative to efficiently control the Atenolol release, leading to consistent maintenance of steady state blood level ensuring a safer and effective option.

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