RESEARCH PAPER

Accepted 26 August 2004
Revised 30 April 2004
Received 21 July 2003
Indian J. Pharm. Sci., 2004, 66(5): 636-641

Influence of some Cellulose Ethers on the Release of Propranolol Hydrochloride from Guar Gum Matrix Tablets

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In the present research, an attempt has been made to develop controlled-release formulations of propranolol hydrochloride using guar gum as a carrier and also to study the influence of some cellulose ethers like sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and ethylcellulose on the *in vitro* release of propranolol hydrochloride from guar gum matrix tablets. *In vitro* release studies indicated that 30 % of guar gum was the minimum concentration of guar gum that can be used to sustain the release for 12 h. Combination of guar gum and cellulose ethers were found to be effective in retarding the release of propranolol hydrochloride. The ratios of guar gum:cellulose ethers which showed better retarding of drug release were, 1:1 2:1, 2:1 and 5:1 for guar gum:sodium carboxymethylcellulose, guar gum:hydroxypropylmethylcellulose, guar gum:hydroxypropylcellulose and guar gum:ethylcellulose, respectively. *In vitro* dissolution kinetics followed a first order release via Fickian diffusion controlled mechanism. IR spectroscopy revealed that there was no interaction between the drug and the polymers used in the investigation.

Propranolol hydrochloride, a non-selective beta-adrenergic blocker, has been widely used in the treatment of hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmias[1]. Because of its relatively short plasma half-life, patients are routinely asked to take propranolol HCl in divided daily doses once every 6 to 8 h. Such frequent drug administration may reduce patient compliance and therapeutic efficacy[2]. In recent years slow or sustained release formulations of propranolol HCl has become available with claims that these formulations maintain beta adrenoreceptor blockade throughout a 24 h period and enable the drug to be given once daily[3].

The present investigation is aimed at using the inexpensive, naturally and abundantly available guar gum for oral controlled delivery of propranolol HCl. Guar gum can be used as a carrier for controlled delivery[4-6]. In the present investigation matrix tablets of propranolol HCl were prepared using guar gum and the influence of some cellulose ethers like sodium carboxymethylcellulose (NaCMC), hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC) and ethylcellulose (EC) on the release pattern of propranolol HCl from guar gum matrix tablets was studied.

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MATERIALS AND METHODS

Propranolol HCl, IP was obtained as a gift sample from Cipla Laboratories Ltd, Mumbai. Guar gum (3500 cps) was obtained from Roland Pharmaceuticals Limited, Berhampur. NaCMC, HPMC, HPC and EC were purchased from S. D. Fine Chemicals Ltd., Mumbai. Microcrystalline cellulose (MCC), starch, magnesium stearate and talc were obtained from Atlas chemical company, Mumbai. Methanol was obtained from E. Merck, Mumbai.

Preparation of matrix tablets:

All the formulations were prepared by wet granulation

TABLE 1 : COMPOSITION OF PROPRANOLOL HCL MATRIX TABLETS

Formulations	Guargum: cellulose ethers	Ingredients (mg/tablet)						MCC
		Propranolol HCl	Guar gum	Cellulose ethers				
				NaCMC	HPMC	HPC	EC	
F1	-	80	60	-	-	-	-	136
F2	-	80	90	-	-	-	-	106
F3	-	80	120	-	-	-	-	76
F4	5:1	80	75	15	-	-	-	106
F5	2:1	80	60	30	-	-	-	106
F6	1:1	80	45	45	-	-	-	106
F7	5:1	80	75	-	15	-	-	106
F8	2:1	80	60	-	30	-	-	106
F9	1:1	80	45	-	45	-	-	106
F10	5:1	80	75	-	-	15	-	106
F11	2:1	80	60	-	-	30	-	106
F12	1:1	80	45	-	-	45	-	106
F13	5:1	80	75	-	-	-	15	106
F14	2:1	80	60	-	-	-	30	106
F15	1:1	80	45	-	-	-	45	106

The quantities in mg of ingredients and ratio of Guar gum: Cellulose ethers (NaCMC, HPMC, HPC, EC) that were used in the preparation of Propranolol HCl matrix tablets

method. Propranolol HCl and different proportions of additives used in the preparation of matrix tablets were listed in Table 1. The batch size for each formulation was 50 tablets. Total tablet weight was kept 300 mg. In all formulations, propranolol HCl was passed through mesh No. 100 and all other ingredients were passed through mesh No. 60. The ingredients were mixed thoroughly to ensure complete mixing. Microcrystalline cellulose (MCC) was used as diluent in all the formulations. The blend was than granulated using starch paste (15 %). The wet mass was then passed through mesh No. 14 and the granules were dried at 50 ° for 45 min in a tray drier. The dried granules were passed through mesh No. 16. The lubricants, talc (2%) and magnesium stearate (1%) were passed through mesh No. 60 and mixed with dried granules. The granules were compressed using 9 mm round, flat and plain punches on a single-station tabletting machine (Cadmach® Machinery Co. pvt. Ltd., Ahmedabad.)

Standard physical tests for the matrix tablets:

The physical tests for the matrix tablets of all the formulations were performed and average values were calculated. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a Stokes-Monsanto® hardness tester and the average of applied pressure (kg/cm^2) for crushing the tablet was determined. Friability was determined by first weighing 10 tablets after dusting and placing them in a Roche®friability tester, which was rotated for 4 min at 25 rpm. After dusting, the total remaining weight of the tablets recorded and percent friability was calculated.

Drug content uniformity:

Three tablets were finely powdered and an amount equivalent to 50 mg of propranolol HCl tablet powder was accurately weighed and transferred to a 100 ml volumetric flask. Initially about 20 ml of distilled water was added to the volumetric flask and the flask was shaken for 10 min. Then 50 ml of methanol was added to the volumetric flask

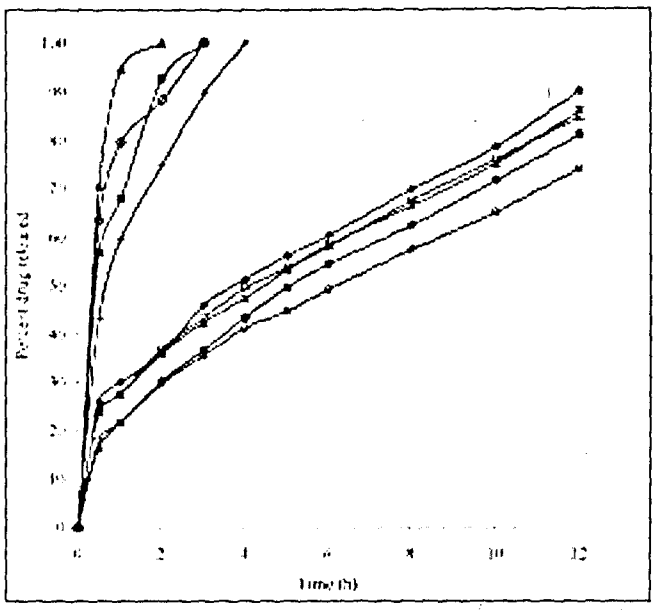

Fig. 1: Dissolution profile of propranolol HCl from matrix tablets

Dissolution profile of propranolol HCl from matrix tablets of formulations F1 (-■-), F2 (-□-), F3 (-▲-), F4 (-♦-), F5 (-●-) and F6 (-o-). Each point is an average of three determinations (n=3).

and the flask was shaken for an additional 10 min. Finally the volume was made up to 100 ml with methanol. The mixture was then filtered and 1 ml of the filtrate was suitably diluted and analyzed for propranolol HCl content at 290 nm using an UV/Vis spectrophotometer.

In vitro dissolution studies:

Dissolution studies were carried out using USP XXI six stage dissolution rate test apparatus (Tab-machines®). Stirring rate was maintained at 100 rpm. Distilled water was used as dissolution medium (900 ml) and was maintained at 37°±1. Aliquots of 5 ml were withdrawn at different time intervals i,e 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 h. At every interval, 5 ml of fresh medium was added to replace the sample that was withdrawn. The samples were analyzed spectrophotometrically at 290 nm to assay the amount of propranolol HCl released at each interval. Dissolution studies were performed three times and the mean values were taken.

Statistical analysis:

Area under the curve (AUC) summarized release of propranolol HCl from matrix tablets of different formulations. AUC values were determined by using the trapezoid rule. The AUC of different formulations were subjected to one-way ANOVA followed by multiple comparison test using least square difference (LSD). Statistical analysis was done by using Microsoft Excel® software.

FT-IR spectroscopy:

Infrared spectrum was taken for the matrix tablets of formulations F2 and F5 using a Jasco® FT-IR by scanning the sample in potassium bromide discs for 16 times continuously. The spectra of matrix tablets were compared with those of propranolol HCl, guar gum and NaCMC.

Stability studies:

Physical stability and effect of ageing on the drug release was studied for the matrix tablets of the formulations F2, F5, F8, F11 and F13. The tablets were strip packed using an Elmach® strip-packing machine and kept in a Thermolabâ humidifier maintained individually at temperatures 37° and 45° with relative humidities of 70 % and 80 %, respectively for 8 w. A control of strip packed tablets was kept at room temperature (22-31°). The tablets were observed every alternate week for changes in physical characteristics and *in vitro* drug release pattern.

RESULTS AND DISCUSSION

The physical parameters for the matrix tablets of all the formulations were within the specified limits. Hardness of the tablets ranged from 5 to 6 kg/cm². Average weight of the tablets varied from 391 to 407 mg. Tablets of all formulations passed the test for friability (<1 %)[7]. Drug content uniformity in the matrix tablets were within the range from 92.5 to 107.5 %[8].

Matrix tablets of all the formulations were subjected to study the *in vitro* drug release study for 12 h. Physical integrity of the matrix tablet was also taken into consideration. The dissolution profiles of propranolol HCl from the matrix tablets of various formulations were shown in figs. 1 and 2. Tablets of formulation F2 have shown better drug retarding ability up to 12 h which shows that 30 % of guar gum is the minimum quantity required to retard the release of propranolol HCl from matrix tablets (fig. 1). Therefore F2 was optimized for further evaluation to study the influence of various cellulose ethers like NaCMC, HPMC, HPC and EC on the release of propranolol HCl from guar gum matrix tablets. The dissolution profiles of matrix tablets of formulations F4, F5 and F6 have shown that release of propranolol HCl was inversely related to the concentration of NaCMC

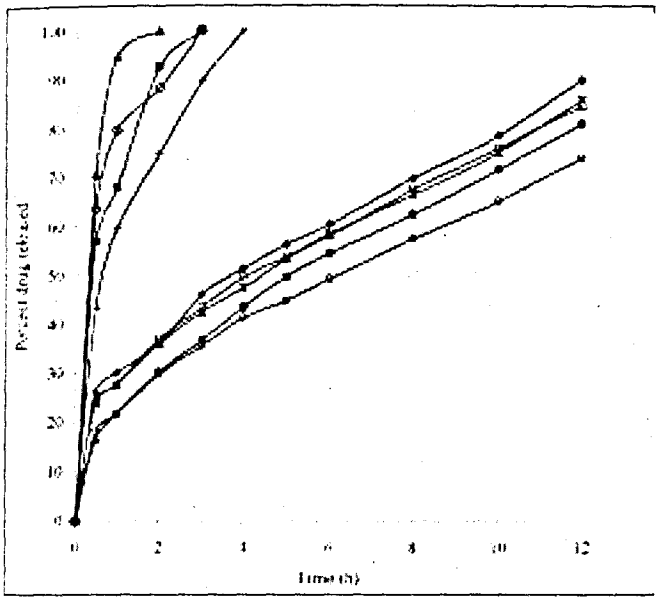

Fig. 2: Dissolution profile of propranolol HCl from matrix tablets

Dissolution profile of propranolol HCl from matrix tablets of formulations F7 (-♦-), F8 (-●-), F9 (-◘-) and F10 (-□-), F11 (-o-), F12 (-▲-) and F13 (-★-), F14 (-+-) and F15 (-♦-). Each point is an average of three determinations (n=3).

(fig. 1). Similarly the tablets of formulations F7, F8, F10, F11 and F13 have shown drug release retarding capacity, whereas the tablets of formulations F9, F12, F14 and F15 have disintegrated without retarding the release of propranolol HCl (fig. 2). Failure of the tablets to maintain the physical integrity may be due to poor binding of certain guar gum-polymer ratios. Therefore further study on these failured matrix tablets were not carried out. It was observed from the above study that the maximum possible guar gum-polymer ratio that can be used for retarding the release of propranolol HCl from various matrix tablets were 2:1, 2:1 and 5:1 for guar gum:HPMC, guar gum:HPC and guar gum: EC, respectively.

Drug release mechanism from the matrix tablets of formulations F1 to F8, F10, F11 and F13 were of similar nature. Matrix tablets exhibit best correlation by the Higuchi equation[9], followed by first order[10] and the mode of release approaches Fickian type[11] (Table 2). This may be attributed to an increase in diffusional path length for the drug because the polymer swells forming a gel around the matrix, retarding the release of propranolol HCl. So the results of the study indicated that the release of propranolol HCl from the matrix tablets followed first order kinetics via Fickian diffusion controlled mechanism.

TABLE 2: DISSOLUTION KINETICS OF PROPRANOLOL HCL MATRIX TABLETS

Formulations	Correlation coefficients (r)			Release exponent (n)	K (hr^{-1})
	Zero order	First order	Higuchi type		
F1	0.9642	0.9790	0.99457	0.50	0.3449
F2	0.9544	0.9750	0.9954	0.59	0.1913
F3	0.9639	0.9882	0.9974	0.56	0.1709
F4	0.9486	0.9868	0.9959	0.51	0.1104
F5	0.9719	0.9944	0.9959	0.52	0.0906
F6	0.9845	0.9948	0.9909	0.58	0.0734
F7	0.9531	0.9766	0.9946	0.52	0.1573
F8	0.9701	0.9936	0.9985	0.53	0.1228
F10	0.9634	0.9936	0.9977	0.52	0.0980
F11	0.9734	0.9942	0.9950	0.58	0.0813
F13	0.9563	0.9845	0.9958	0.57	0.1364

Correlation coefficients, Korsmeyers release exponent and first order rate constants of propranolol HCl release from matrix tablets.

TABLE 3: MULTIPLE COMPARISON TEST

Comparison Between	Mean AUC M1	Mean AUC M2	Group	d	LSD TEST		
					"t"	p	Sig
F1 and F2	12.82	8.38	2	4.43	8.793	<0.05	*
F1 and F3	12.82	8.68	2	4.14	8.362	<0.05	*
F2 and F3	8.38	8.68	2	0.29	2.236	<0.05	*
F1 and F5	12.82	6.60	2	6.21	11.236	<0.05	*
F1 and F8	12.82	7.51	2	5.31	10.178	<0.05	*
F1 and F11	12.82	6.68	2	6.14	11.194	<0.05	*
F4 and F5	6.96	6.60	2	0.35	2.684	<0.05	*
F4 and F6	6.96	6.12	2	0.83	3.773	<0.05	*
F5 and F6	6.60	6.12	2	0.48	3.139	<0.05	*
F7 and F8	7.84	7.51	2	0.33	2.517	<0.05	*
F10 and F11	7.45	7.51	2	0.06	0.431	>0.05	ns
F4 and F7	6.96	7.84	2	0.88	3.882	<0.05	*
F4 and F8	6.96	7.45	2	0.50	3.168	<0.05	*
F4 and F13	6.96	7.56	2	0.60	3.297	<0.05	*
F7 and F10	7.84	7.45	2	0.39	2.736	<0.05	*
F7 and F13	7.84	7.56	2	0.28	2.169	<0.05	*
F8 and F13	7.45	7.56	2	0.10	0.779	>0.05	ns

Random comparison test showing level of significance at P< 0.05 between formulations. * significant, ns: Not significant.

ANOVA was applied to identify significance of factors that influence drug release. The factors influencing the drug release were, the different polymers and drug to polymer ratios. ANOVA showed a highly significant difference among all drug to polymer ratios at p <0.05 levels. A highly significant difference was also observed among formulations F4, F7, F10 and F13 containing 5 % of NaCMC, HPMC, HPC and EC respectively. Similarly formulations F5, F8 and F11 containing 10 % of NaCMC, HPMC and HPC respectively have also shown significant difference at p<0.05 levels. For more substantial statistical analysis multiple comparison test was done using LSD. This test showed that there was no significant difference between the formulations in the groups, F10-F11 and F8-F13 (Table 3).

FT-IR study revealed that there was no shift in the peaks of propranolol HCl, guar gum and NaCMC in matrix tablets of F2 and F5 compared to pure ingredients indicating that there was no interaction between propranolol HCl and polymers. Stability studies for matrix tablets of formulations F2, F5, F8, F11 and F13 have shown that there was no appreciable change in the physical properties and release characteristics of the matrix tablets.

In conclusion, investigation has shown that the minimum possible quantity of guar gum required to prepare sustained release matrix tablets of propranolol HCl was 30 % to retard the drug release up to 12 h. The data presented in this work clearly demonstrates that combination of guar gum and cellulose ethers (NaCMC, HPMC, HPC, EC) up to certain ratios can be a useful controlled and sustained release matrix for formulating propranolol hydrochloride. The drug release follows first order kinetics via Fickian diffusion controlled mechanism.

ACKNOWLEDGEMENTS

The authors wish to thank Cipla laboratories Ltd., Mumbai for providing the gift sample of propranolol hydrochloride. The authors greatly acknowledge Roland Pharmaceuticals Ltd., Berhampur, for providing strip packing facility.

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