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HPMC-based Matrix Tablets of Atenolol and Cisapride: Effect of Viscosity of Polymer and Drug solubility on *In vitro* Release

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Matrix tablets of cisapride and atenolol were prepared with varying proportions of hydroxypropylmethylcellulose of different viscosity grades viz; E_{15}, E_4M, K_4M and $K_{15}M$ (15, 4000, 4000 and 15 000 cps at 2% aqueous solution, respectively), alone and in combinations by wet granulation technique. The prepared tablets were evaluated for uniformities of weight, thickness, drug content and diameter, hardness and tensile strength, friability and disintegration time. The *in vitro* release kinetics of the matrix tablets were studied using USP XXI apparatus with distilled water as the dissolution medium. The tablet properties complied with the official limits. The efficiency of viscosity grades of hydroxypropylmethylcellulose in sustaining the release was observed to be in the following order $E_{15}>E_4M>K_4M>K_{15}M$. As the solubility of drug increases from cisapride to atenolol, an increase in the release rate was observed. The release of cisapride and atenolol from their respective tablets followed predominantly diffusion controlled mechanism, based on Higuchi's model. The study also indicated that the amount of drug released decreased with an increase in the polymer concentration (from 10, 20 to 30%). The combination of the different viscosity grades did not provide any additional advantage.

The development of oral controlled release dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the most widely used of the numerous controlled release dosage forms currently available[1-4]. This is largely because they offer precise modulation of drug release through manipulation of a small number of formulation factors - this being true for drugs with widely differing physico-chemical characteristics[5]. Hydroxypropylmethylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems[6-7]. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. A number of varieties of HPMC alone and in combination with other polymers as controlled release agents in oral dosage forms have received wide acclaim. However, there have been few studies[8-9] examining the potential advantages of using mixtures of different grades of HPMC. Thus, an attempt has been made in the present study to formulate HPMC matrix tablets of cisapride, a prokinetic agent and atenolol, a β-blocker as a model insoluble and soluble drugs, respectively, using different viscosity grades of HPMC such as E_{15}, E_4M, K_4M and $K_{15}M$ and to evaluate their *in vitro* release.

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MATERIALS AND METHODS

The different viscosity grades of HPMC, atenolol and cisapride were generously gifted by Dow Chemical Co, Midland, USA, Biological (E) Ltd., Hyderabad and Unichem Laboratories Ltd, Mumbai, respectively. All other reagents used were of analytical grade.

Preparation of matrix tablets:

The drug:polymer ratios were 1:1, 1:2 or 1:3 for tablets prepared with each viscosity grade. The water soluble diluent used was lactose fast-flo® and magnesium sterate was used as lubricant at 1% w/w. The total tablet weight was kept at 100 mg, the batch size for each formulation was

100 tablets. For tablet prepared with mixtures of various grades of HPMC, the drug polymer ratio was kept constant at 1:3. The granules were prepared by wet granulation (with corresponding HPMC dissolved in distilled water acting as granulating agent) and the dried granules (40°, until a moisture content between 0.5 and 1% was achieved) were compressed on a Manesty E2 single punch machine fitted with 7mm round flat-face tooling. The desired tablet weight was 100 mg (± 5%) and the desired hardness was between 6 to 7 kg (Monsanto hardness tester).

Uniformity of thickness, weights and drug content:

The crown to crown thickness of 10 tablets from each batch was determined using a screw gauge. For uniformity of weight, 10 tablets from each batch were weighed individually and their average determined. For determination of uniformity of drug content at least 6 tablets from each batch were weighed individually, pulverized and dissolved in 100 ml of distilled water in case of atenolol and in 0.1 N HCl in case of cisapride and filtered. An aliquot of the filtrate was diluted and analyzed spectrophotometrically at 307.5 nm and 273.5 nm, respectively.

Hardness, friability and tensile strength:

The hardness and friability of the prepared tablets were determined using the Monsanto hardness tester and the Roche friabilator at 100 rpm. The tensile strength of the prepared tablets were determined using a method described by Summer *et al.*[10] The tensile strength was determined using the formula TS=2 CS/(πDE), where TS is tensile strength (N/mm^2), CS is crushing strength, D is the diameter of the tablet and E the thickness of the tablet.

***In vitro* drug release studies:**

Drug release kinetics of the prepared tablets was determined using USP XXI apparatus (paddle type) with 900 ml of distilled water as the dissolution medium. The paddle was rotated at 50 rpm and 5 ml aliquots were withdrawn at pre-determined time intervals and an equal amount of the medium was replaced to maintain sink conditions. The aliquots were diluted suitably and the amount of drug(s) released was determined spectrophotometrically as described earlier. The studies were conducted up to 8 h.

Statistical analysis:

Analysis of variance (ANOVA) was performed to find out significant difference among HPMC viscosity grades and drug: HPMC ratio on drug release from formulated tablets.

RESULTS AND DISCUSSION

The various formulation compositions of prepared tablets are shown in Table 1. The variation in weight, thickness, hardness and tensile strength, friability and content uniformity of the prepared tablets were studied in order to examine their influence on drug release from matrices. The prepared tablets had an average diameter of 7.09±0.06 mm. All the other tablet properties compiled with the official limits (Table 2).

Several authors[11,12] have stated that although compression force is a significant factor in tablet hardness, its effect on drug release from HPMC tablets was minimal. Thus it could be assumed that variation in compression force is closely related to a change in porosity of tablet[13,14]. However, the porosity of hydrated matrix is independent of the initial porosity, the compression force seemed to have little influence on drug release.

The effect of different viscosity grades of HPMC on cisapride and atenolol release are shown in figs.1 and 2. In both cases drug release from tablets based on E_{15} having the least viscosity showed the highest release compared to other higher viscosity grade (E_4M, K_4M and $K_{15}M$). The results obtained are in accordance with the data reported in the literature[14-19]. The efficiency of viscosity grades in sustaining the release was observed to be in the following order $E_{15}>E_4M>K_4M>K_15M$.

Further, the effect of three different concentrations of various viscosity grades of HPMC were also studied (figs.1 and 2). The results indicate that the amount of drug released decreased with an increase in the polymer concentration from 10 to 30%. An increase in polymer concentration causes an increase in the viscosity of the gel as well as the formation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of the drug and therefore a reduction in the drug release rate. Release of both cisapride and atenolol from their respective formulations predominantly followed matrix diffusion kinetics with n-values ranging from 0.5 to 0.7 for cisapride and from 0.5 to 0.62 for atenolol.

The combination of low and high viscosity grades (E_{15} and $K_{15}M$) and moderate viscosity (E4M and K4M) were studied at 30% level (figs. 3 and 4). However, the cumulative percent drug released from these formulations was intermediate between the 30% of individual viscosity grades. Hence mixing of these polymers in different combinations with different ratios was not considered.

TABLE 1: COMPOSITION OF THE PREPARED TABLETS

Drug	Batch Code	HPMC viscosity grade	Drug:HPMC ratio	Lactose (%w/w)	Magnesium stearate (%w/w)
	AE1	E_{15}	1:1	79	1
	AE2		1:2	69	1
	AE3		1:3	59	1
	AE4	E_4M	1:1	79	1
	AE5		1:2	69	1
	AE6		1:3	59	1
Atenolol	AK1	K_4M	1:1	79	1
	AK2		1:2	69	1
	AK3		1:3	59	1
	AK4	$K_{15}M$	1:1	79	1
	AK5		1:2	69	1
	AK6		1:3	59	1
	AEK1	E_{15}:$K_{15}M$	1:3	59	1
	AEK2	E_4M:K_4M	1:3	59	1
Cisapride	CE1	E_{15}	1:1	79	1
	CE2		1:2	69	1
	CE3		1:3	59	1
	CE4	E_4M	1:1	79	1
	CE5		1:2	69	1
	CE6		1:3	59	1
	CK1	K_4M	1:1	79	1
	CK2		1:2	69	1
	CK3		1:3	59	1
	CK4	$K_{15}M$	1:1	79	1
	CK5		1:2	69	1
	CK6		1:3	59	1
	CEK1	E_{15}:$K_{15}M$	1:3	59	1
	CEK2	E_4M:K_4M	1:3	59	1

The batch size of the prepared tablets is 100 and the target tablet weight is 100 mg. 'A' and 'C' indicates atenolol and cisapride, respectively. Similarly E_1, E_2, E_3 and E_4, E_5, E_6 indicates E_{15} and E_4M viscosity grades of HPMC; K_1, K_2, K_3 and K_4, K_5, K_6 indicates K_4M and $K_{15}M$ viscosity grades of HPMC. Further, EK_1 and EK_2 indicates mixture of HPMC viscosity grades of E_{15}:$K_{15}M$ and E_4M:K_4M, respectively at 1:3 ratio.

Many reports[15,20,21] have illustrated that the solubility of drug affects the release mechanism from HPMC based matrices. Further drug release from these matrices is affected by three different fronts viz., erosion, swelling and diffusion[22]. In this study out of the two drug candidates used cisapride is an insoluble drug while atenolol is a moderately soluble drug.

Fig. 5 depicts the drug release of cisapride and atenolol from E_4M based tablets containing drug to polymer ratio of 1:3. As the solubility of drug increases from cisapride to atenolol, an increase in the release rate is observed. Further the percentage of linearity for cisapride is longer than that of atenolol. This could be attributed to the fact that the release of more soluble drug like atenolol from HPMC tab-

TABLE 2: PHYSICO-CHEMICALCHARACTERISTICS OF PREPARED TABLETS

Batch Code*	Weight variation (mg)	Thickness variation (mm)	Hardness (kg)	Tensile Strength (N/cm^2)	Drug content uniformity (%)	Friability (%)
AE_1	99.9±3.4	2.9±0.2	5.9±.0.9	154.2	98.6±1.2	
AE_2	103±1.4	2.9±0.1	5.5±0.9	173.0	100±1.5	0.61
AE_3	100±2.1	2.8±0.3	5.7±0.6	179.3	101±0.5	0.34
AE_4	101±2.3	2.9±0.1	5.6±1.0	176.2	101±0.9	0.02
AE_5	100±1.2	2.9±0.1	5.9±3.2	125.8	98.1±1.2	0.22
AE_6	99.5±1.8	2.9±0.1	6.0±0.3	188.8	97.6±1.6	0.32
AK_1	99.2±4.3	2.9±0.1	6.4±0.8	201.3	98.4±2.1	0.09
AK_2	101±1.2	2.9±0.1	5.9±2.1	191.9	100±1.5	0.00
AK_3	99.9±1.2	2.9±0.1	6.9±1.1	217.1	99.6±0.6	0.00
AK_4	101±1.0	3.0±0.1	5.5±2.1	173.0	98.2±0.7	0.00
AK_5	98.2±3.1	2.8±0.1	6.7±1.1	210.8	98.3±0.5	0.00
AK_6	99.9±1.2	2.9±0.1	5.5±1.1	173.0	99.6±1.6	0.00
AEK_1	99.8±2.1	2.9±0.1	5.7±1.4	179.3	97.9±1.8	0.00
AEK_2	99.5±2.3	2.9±0.1	7.0±0.1	218.1	98.1±0.8	0.00
CE_1	101±2.3	2.9±0.1	5.5±0.9	173.0	98.5±0.7	0.59
CE_2	100±1.2	2.9±0.1	5.9±0.8	180.6	99.5±1.6	0.10
CE_3	99.5±2.3	2.8±0.1	6.7±0.6	179.3	99.8±2.1	0.01
CE_4	99.9±3.4	2.9±0.0	5.6±1.0	176.2	99.6±2.3	0.42
CE_5	102±1.4	2.8±0.2	5.8±3.2	125.8	99.1±0.8	0.02
CE_6	100±2.1	2.9±0.1	6.4±0.8	210.3	101±0.4	0.00
CK_1	99.5±1.8	2.8±0.2	6.1±0.8	191.9	100±0.6	0.00
CK_2	99.2±4.3	2.9±0.0	6.8±0.7	182.5	97.4±2.5	0.00
CK_3	101±2.1	3.0±0.1	6.8±2.5	151.0	99.6±1.2	0.00
CK_4	99.9±1.2	2.8±0.1	6.4±0.5	210.3	98.4±0.6	0.00
CK_5	105±1.0	2.8±0.2	6.2±0.4	195.0	100	0.00
CK_6	98.2±3.1	2.7±0.2	6.7±0.4	179.3	98.5±2.1	0.00
CEK_1	99.9±1.2	2.9±0.1	7.0±0.1	218.1	101±1.4	0.00
CEK_2	102±2.3	2.9±0.0	6.0±2.4	217.1	101±0.2	0.00

*The composition of batches is shown in Table 1.

lets is predominantly controlled by the diffusion of the drug in tablet while that of the insoluble cisapride is controlled by erosion of matrix. Similar results have been reported by Cheng *et al.*[23] for theophylline and diltiazem HCl. Similarly, Rao *et al.*[20] had proposed that for highly water soluble drugs, the diffusion and swelling fronts are similar and the rate of drug release is determined by diffusion of the drug from the gel which in turn is dependant on gel thickness and for poorly water soluble drugs it is dependant on the erosion of the matrix, predominantly.

The dissolution data were examined for models of zero

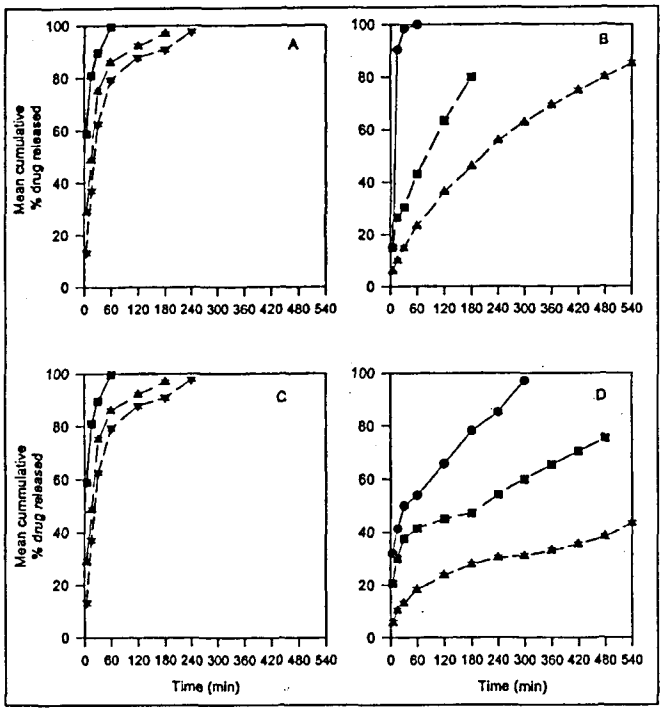

Fig. 1: Effect of viscosity grade of HPMC on cisapride release

The *in vitro* release profiles of (-▫-) CE_1, (-▲-) CE_2, (-▼-) CE_3 [A]; (-▫-) CE_4, (-▲-) CE_5, (-▼-) CE_6 [B]; (-▫-) CK_1, (-▲-) CK_2, (-▼-) CK_3 [C]; (-▫-) CK_4, (-▲-) CK_5, (-▼-) CK_6 [D] in 900 ml of distilled water are shown. The studies were conducted in triplicate (n=3). The compositions of these systems are shown in Table 1.

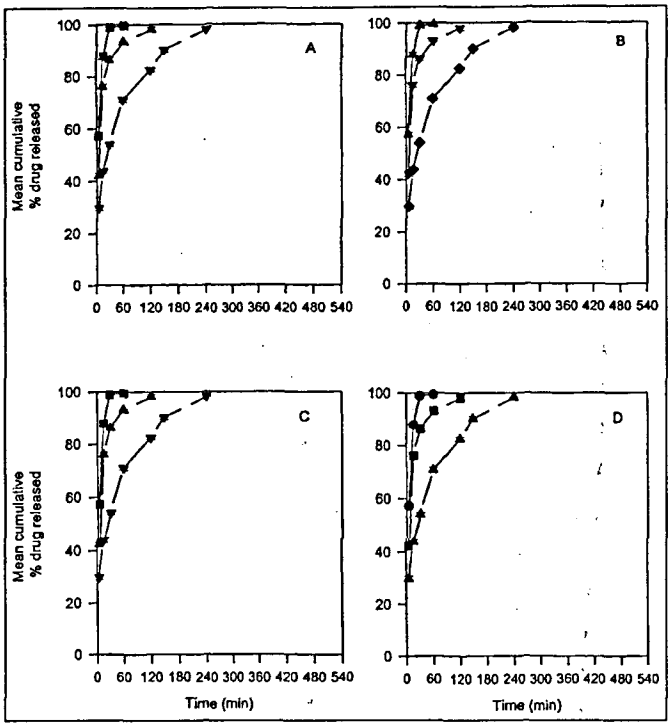

Fig. 2: Effect of viscosity grade of HPMC on atenolol release

The *in vitro* release profiles of (-▫-) AE_1, (-▲-) AE_2, (-▼-) AE_3 [A]; (-▫-) AE_4, (-▲-) AE_5, (-▼-) AE_6 [B]; (-▫-) AK_1, (-▲-) AK_2, (-▼-) AK_3 [C]; (-▫-) AK_4, (-▲-) AK_5, (-▼-) AK_6 [D] in 900 ml of distilled water are shown. The studies were conducted in triplicate (n=3). The compositions of these systems are shown in Table 1.

order, first order and Higuchi model (Table 3), the derived correlation co-efficient (r^2) indicating good fit of Higuchi model suggests that diffusion is the predominant mechanism limiting drug release. Although, some minor deviations from Higuchi kinetics were observed (particularly for tablets made with low proportions of HPMC or with HPMC of low viscosity), the fit was in all cases good. The "n" values for tablets containing cisapride was found to be in the range of 0.5 to 0.7 and for atenolol, it was 0.5 to 0.6. These values are closely approximate with n= 0.5, indicating Fickian diffusion. This was also further confirmed with the good correlation co-efficient found in all formulations (Table 2) with Higuchi kinetics. The small deviation of "n" values from its actual value may be because of association of diffusion and erosion of polymer simultaneously. However, the higher values of "n" (n=0.7 and n=0.64) as seen in case of cisapride tablets of batch code C_E u2 (containing HPMC E_{15} –20%) and CK_1 (containing K_4M–10%), respectively, indicate anomalous (non-Fickian) behavior of drug release, may be because of high fragmentation observed in HPMC E_{15} containing formulations or lower content of HPMC content of HPMC K_4M containing formulations.

Analysis of variance (ANOVA) was applied to identify the significance of factors, which influence drug release. The ANOVA analysis showed a significant difference among HPMC viscosity grades and drug:HPMC ratio of formulations containing cisapride (Table 4). However, in case of formulation containing atenolol, although release rate was varied among HPMC viscosity grades as well as drug:HPMC ratio, the results are not significant (Table 4). This may be attributed to higher atenolol solubility in water. Since for controlling the release of water soluble drugs, higher amounts of polymer will be required.

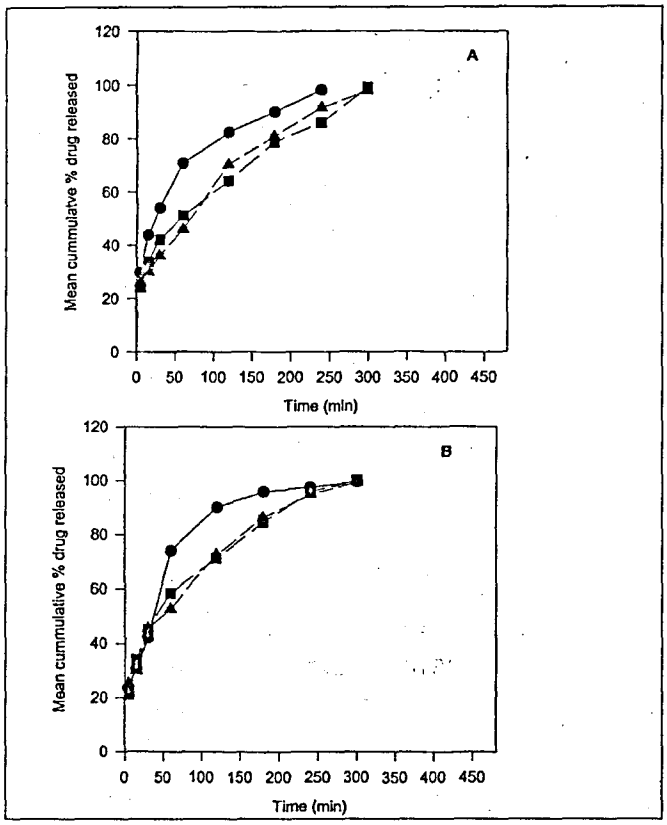

Fig. 3: Effect of mixture of HPMC viscosity grade on atenolol release

The *in vitro* release profiles of (-●-) AE_1, (-▫-) AEK_1, (-▲-) AK_6 [A]; (-●-) AE_6, (-▫-) AEK_2, (-▲-) AK_3 [B] in 900 ml of distilled water are shown. The studies were conducted in triplicate (n=3). The compositions of these systems are shown in Table 1.

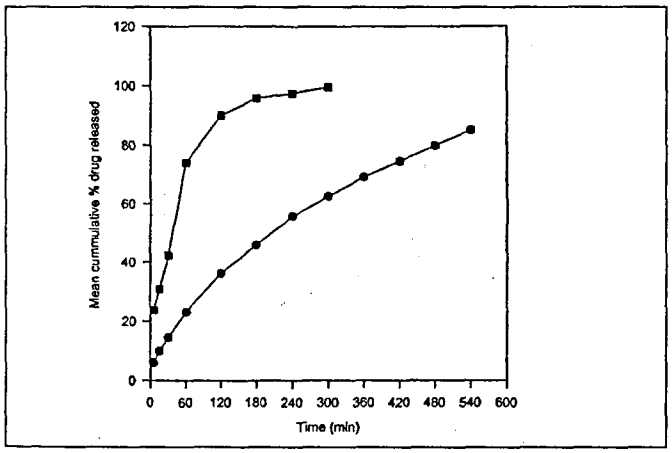

Fig. 5: Effect of drug solubility on atenolol and cisapride release from HPMC matrix tablets.

Cumulative percent of (-●-) cisapride and (-▫-) atenolol released in water as a function of time.

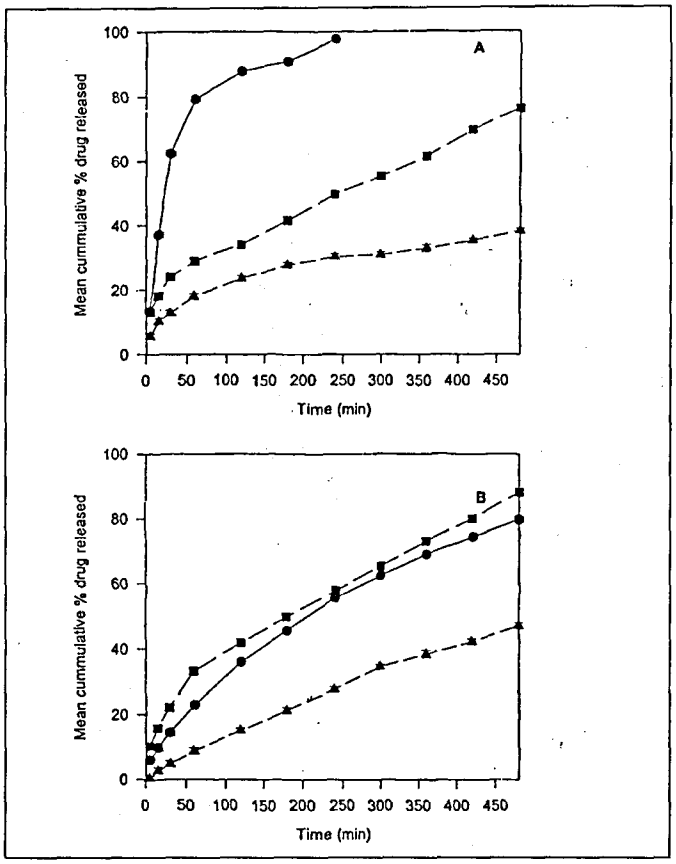

Fig. 4: Effect of mixture of HPMC viscosity grade on cisapride release

The *in vitro* release profiles of (-●-) CE_1, (-▫-) CEK_1, (-▲-) CK_6 [A]; (-●-) CE_6, (-▫-) CEK_2, (-▲-) CK_3 [B] in 900 ml of distilled water are shown. The studies were conducted in triplicate (n=3). The compositions of these systems are shown in Table 1.

This study provided an insight into the mechanism of drug release from HPMC matrices and also allowed for comparison of the efficacies of the various viscosity grades of HPMC in providing sustained release. However, mixing of the various viscosity grades of HPMC at the level studied did not prove to be beneficial in terms of sustaining the drug release further.

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TABLE 3: KINETIC ANALYSIS

Batch code*	Drug Release kinetics, Correlation coefficients (r^2)			Release Exponent (n)
	Zero order	First order	Higuchi	
AE_1	0.6062	0.5451	0.7640	0.5014
AE_2	0.6552	0.5521	0.8950	0.6012
AE_3	0.6852	0.5028	0.9421	0.5193
AE_4	0.4422	0.6692	0.7798	0.5124
AE_5	0.9862	0.8701	0.9894	0.5242
AE_6	0.9627	0.7871	0.9982	0.4924
AK_1	0.8681	0.7231	0.9541	0.5176
AK_2	0.9779	0.7583	0.9856	0.4961
AK_3	0.9056	0.6589	0.9727	0.4902
AK_4	0.9580	0.8880	0.9672	0.4974
AK_5	0.9678	0.9240	0.9693	0.4993
AK_6	0.9147	0.7383	0.9810	0.5121
AEK1	0.9664	0.8138	0.9957	0.4991
AEK_2	0.9201	0.7801	0.9899	0.4986
CE_1	0.7672	0.7440	0.9418	0.5426
CE_2	0.7803	0.6900	0.9001	0.7455
CE_3	0.9150	0.8693	0.9519	0.5999
CE_4	0.9164	0.7813	0.9409	0.5012
CE_5	0.9035	0.4610	0.9283	0.5102
CE_6	0.9044	0.3120	0.9147	0.5454
CK_1	0.8971	0.8182	0.8971	0.6406
CK_2	0.9813	0.8846	0.9906	0.5601
CK_3	0.8576	0.9120	0.9878	0.5101
CK_4	0.9385	0.9019	0.9686	0.5631
CK_5	0.9512	0.9118	0.9655	0.5769
CK_6	0.9179	0.9455	0.9789	0.5017
CEK_1	0.9860	0.8860	0.9905	0.4901
CEK_2	0.9412	0.8673	0.9945	0.4901

*The composition of batches is shown in Table 1.

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TABLE 4: STATISTICAL ANALYSIS (ANOVA) (COMPARISON AMONG RATIOS AND VISCOSITY GRADES).

Drug	HPMC viscosity grade/% of HPMC in tablet	Calculated F value	Table F value	Degree of significance (P<0.05)
	E_{15}	61.9	6.35	S
	E_4M	4.6	3.49	S
	K_4M	3.4	3.34	S
Cisapride	$K_{15}M$	14.6	0.01	NS
	10%	2.7	3.07	NS
	20%	1.8	2.92	NS
	30%	18.4	4.31	S
Atenolol	E_{15}	0.6	3.73	NS
	E_4M	0.3	3.80	NS
	K_4M	0.7	3.68	NS
	$K_{15}M$	0.03	3.68	NS
	10%	1.1	3.68	NS
	20%	1.8	3.59	NS
	30%	1.5	3.34	NS

S denotes statistical significance and NS indicates not significant.

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