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PREPARATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

The present study in the development of sustained release matrix tablets of anti-hypertensive drug propranolol hydrochloride. Hydroxypropyl methyl cellulose K100M used as a rate retarding polymer where as lactose and dibasic calcium phosphate are used as diluent. The effects of the proportion of the polymer and the influence of co-excipients like lactose and dibasic calcium phosphate on the release rate of drug was investigated. The results of the present study point out that the rate of propranolol hydrochloride release from HPMC K100M matrices are mainly controlled by the drug – HPMC ratio. When the influence of excipients on the release of drug was examined, the excipients lactose enhanced the release rate of propranolol hydrochloride, however the dibasic calcium phosphate (DCP) demonstrated slower release rate. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, *invitro* drug release and short term stability studies. The dissolution $t_{50\%}$ and $t_{90\%}$ values for the co-excipients were in the order of lactose>dibasic calcium phosphate.

KEYWORDS

Hydrophilic matrix tablet, HPMC, Sustained-release, propranolol hydrochloride, Formulation

INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be

automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities[1].

Controlled release also denotes systems which can provide some control whether this be of a temporal or spatial nature or both for drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time[2].

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.

The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug[4].

One approach to the manufacture of sustained release dosage forms is the direct compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternatively, retardant drug blends may be granulated prior to compression. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug[5].

MATERIALS AND METHODS

Propranolol Hydrochloride was obtained as gift sample from Cipla Pharmaceuticals, Mumbai. Hydroxy propyl methyl cellulose K100M was obtained from colorcon asia Ltd, Goa. Di-basic calcium phosphate was obtained as Gift sample from Pharmed Medicare, Bangalore. lactose, talc, magnesium stearate were procured from SD Fine chemical, Mumbai.

EVALUATION OF MATRIX TABLETS OF PROPRANOLOL HYDROCHLORIDE

All the formulations of propranolol hydrochloride matrix tablets prepared were evaluated for the following parameters

a) ***Friability test***: Previously weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rpm for 4 minutes. Then the tablets were dusted and reweighed and the percentage of powder eroded during 4 minutes was recorded. The resulting tablets were weighed and the percentage loss was calculated using the formula. The results are given in table-2.

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Table–2
Physical properties of formulations F1 to F8

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight variation*(mg)	Percent drug content* ± SD
F1	5.82	0.63	132.50	99.82±1.15
F2	5.91	0.63	172.45	98.81±0.80
F3	5.81	0.58	212.70	98.68±0.90
F4	5.73	0.64	192.85	99.43±1.10
F5	5.62	0.64	212.80	98.18±1.41
F6	5.92	0.59	232.80	98.43±1.29
F7	5.82	0.64	193.10	97.70±0.62
F8	5.53	0.53	212.95	100.21±0.99

b) ***Hardness test*:** Hardness of the tablets was tested using "Monsanto" hardness tester. In all the cases, means of six replicate determinations were taken. The physical properties of the tablets are shown in table-2.

c) ***Uniformity of weight***: Average weight of the tablet was calculated by weighing 20 tablets individually and all together. The percent weight deviation of each tablet was computed as per official method. The results are given in table-2.

d) ***Drug content uniformity of the tablets***: Five tablets were powdered in a mortar. From this, powder equivalent to 50 mg of drug was taken in a 100 ml round bottom flask. It is extracted with 20 ml of 1.2 buffer for ½ hour, filtered in a volumetric flask and the filtrate was made up to the mark with 1.2 buffer. Further appropriate dilutions were made and the absorbance was measured at 289 nm against blank. The results are given in table-2.

IN VITRO DISSOLUTION STUDIES[6-7]

In vitro dissolution studies of propranolol hydrochloride tablets were studied using USP XXIII tablet dissolution test apparatus-I (Electrolab) employing a basket stirrer, 900 ml of 1.2 pH buffer was used as a dissolution medium for first one hour and replaced with 7.5 phosphate buffer for specified time. The temperature of the dissolution medium was previously warmed to 37±0.5ºC and was maintained throughout the experiment. One tablet was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of syringe fitted with a pre filter at known intervals of time (1 hour). The sample was analyzed for drug release by measuring the absorbance at 289 nm and 288.5 nm using UV-visible spectrophotometer shimadzu -1700 after suitable dilutions. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium.

STABILITY STUDIES

Short-term stability studies were performed at temperature 40±2^{0}C over a period of three months on the matrix tablet formulation F_4. Sufficient number of tablets (10) were packed in amber colored screw capped bottles and kept in stability chamber maintained at 40±2^{0}C . Samples were taken at one month intervals for drug content estimation shown in table-7. At the end of three months period, dissolution test was performed to determine the drug release profiles. The data of dissolution after stability studies are shown in table-8.

Table-7
Stability studies of F_4 Formulations

Sl. No.	Time in Days	Physical Changes	40 ± 2^{0}C Mean% drug content ±S.D. F_4
1.	01	--	99.13±1.53
2.	30	No Change	98.26±0.91
3.	60	No Change	97.91±0.82
4.	90	No Change	97.39±1.70

Table-8
Stability studies for formulations F_4 at 40 ± 2^{0}C

Sl. No.	Time (Hrs.)	Cumulative percent drug released* ± SD **F_4**	
		1st Day	90th Day
1.	1.00	20.05±0.70	19.15±0.53
2.	2.00	36.83±0.90	35.99±0.89
3.	3.00	39.85±0.35	39.15±0.65
4.	4.00	42.43±0.58	41.93±0.98
5.	5.00	46.36±0.91	45.86±0.66
6.	6.00	61.31±0.85	61.01±0.83
7.	7.00	61.22±0.94	60.99±0.57
8.	8.00	70.91±0.66	70.00±0.96
9.	9.00	75.48±0.81	74.98±0.68
10.	10.00	80.86±0.71	80.16±0.23
11.	11.00	85.71±0.12	84.93±0.52
12.	12.00	90.56±0.96	88.99±0.76

*Average of three determinations.

RESULTS AND DISCUSSION

In the present work, an attempt has been made to prepare sustained release matrix tablets of propranolol hydrochloride, a beta-adrenoreceptor blocking agent using HPMC K100M with two different diluents namely lactose, DCP by wet granulation method with PVP K30 as binder. The prepared tablets were tested for physical parameters like hardness, weight variation, friability, drug content uniformity, *in vitro* drug release studies and short-term stability studies. The results of all these evaluations are given in table-2 to 8.

Table–3
In vitro release data of propranolol hydrochloride matrix tablets of formulations F1 to F4

Sl. No.	Time (Hrs)	F1	F2	F3	F4
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	01	25.5±0.94	19.08±0.52	18.23±0.91	20.05±0.70
2.	02	34.16±0.69	28.01±0.72	29.42±0.21	36.83±0.90
3.	03	38.08±0.81	33.12±0.56	32.17±0.86	39.85±0.35
4.	04	43.2±0.51	41.31±0.47	33.90±0.96	42.43±0.58
5.	05	49.45±0.30	47.01±0.67	37.17±0.91	46.36±0.91
6.	06	53.81±0.54	52.51±0.69	43.05±0.99	61.31±0.85
7.	07	60.47±0.65	58.37±0.58	44.98±0.37	61.22±0.94
8.	08	72.32±0.81	63.76±0.53	49.50±0.56	70.91±0.66
9.	09	78.25±0.97	73.17±0.73	58.06±0.54	75.48±0.81
10.	10	85.51±0.73	80.98±1.10	62.63±0.82	80.86±0.71
11	11	90.35±0.89	83.40±0.81	69.10±0.57	85.71±0.12
12	12	92.23±1.02	88.51±0.76	77.71±0.30	90.56±0.96

*Average of three determinations

Table–4

In vitro release data of propranolol hydrochloride matrix tablets of formulations F5 to F8

Sl. No.	Time (Hrs)	F5	F6	F7	F8
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	01	24.08±0.64	26.12±0.43	21.01±0.63	21.52±0.54
2.	02	35.27±0.66	41.13±0.48	32.47±0.65	32.45±0.74
3.	03	39.10±0.21	46.78±0.14	36.67±0.28	37.56±0.35
4.	04	44.37±0.75	50.17±0.92	41.08±0.73	39.66±1.09
5.	05	49.32±0.61	54.27±1.02	44.63±0.91	45.47±0.65
6.	06	54.17±1.13	58.08±0.97	49.70±1.10	49.51±0.60
7.	07	60.41±0.88	64.33±0.94	53.46±0.50	54.30±0.26
8.	08	66.33±0.11	71.87±0.79	61.65±0.61	61.35±0.61
9.	09	77.37±0.84	76.17±0.46	71.06±0.38	67.53±0.77
10.	10	85.17±1.04	80.48±0.73	74.56±0.86	79.92±0.66
11	11	90.82±0.91	87.75±0.87	78.33±0.55	83.68±0.57
12	12	93.25±0.71	93.13±0.56	82.63±0.49	88.26±0.30

*Average of three determinations

Table-5

Dissolution $t_{50\%}$ and $t_{90\%}$ values of various formulations of matrix tablets

Sl. No.	Formulation	$t_{50\%}$ (hr)	$t_{90\%}$ (hr)
1.	F1	5.1	11
2.	F2	5.5	13.0
3.	F3	8.2	15.5
4.	F4	5.8	12.0
5.	F5	5.0	10.7
6.	F6	4.0	11.5
7.	F7	6.2	>12
8.	F8	6.3	>12

Table-6

Linear regression analysis data of Propranolol Hydrochloride Matrix Tablet

Batches		Zero Order	First Order	Higuchi's Equation	Peppas Equation
F1	r	0.987	0.974	0.984	0.983
	a	21.69	2.108	-9.339	1.352
	b	5.78	0.094	28.474	0.545
F2	r	0.987	0.983	0.992	0.995
	a	18.450	2.093	13.829	1.252
	b	5.565	0.081	28.470	0.624
F3	r	0.988	0.971	0.979	0.980
	a	16.320	2.100	-14.038	1.219
	b	4.644	-0.065	25.370	0.590
F4	r	0.990	0.959	0.981	0.981
	a	18.650	-0.079	-9.848	1.316
	b	6.123	2.052	28.020	0.576
F5	r	0.994	0.944	0.978	0.983
	a	18.935	2.093	-9.941	1.350
	b	6.313	-0.091	28.683	0.545
F6	r	0.992	0.948	0.988	0.989
	a	26.570	2.013	0.5117	1.427
	b	5.530	-0.079	25.440	0.476
F7	r	0.995	0.857	0.980	0.986
	a	17.650	2.156	-11.655	1.297
	b	5.624	-0.093	27.350	0.567
F8	r	0.991	0.948	0.973	0.981
	a	16.830	2.042	-9.895	1.308
	b	5.886	-0.069	26.660	0.551

r =correlation coefficient a=intercept b=slope

All the prepared tablets were evaluated for weight variation and the results are given in table-2. The percent deviation from the average weight was found to be within the prescribed official limits.

Hardness of tablets was found to be in the range of 5.53 to 5.92 Kg/cm^2 and is given in tables-2. The friability of all the prepared tablets was found to be in the range of 0.53 to 0.64, fulfilling the official requirements (not more than 1%).

Drug content estimation data for all batches are given in table-2. It was found to be in the range of 97.70 to 100.21% with low values of standard deviation indicates uniform drug content in the tablets prepared.

In vitro drug release studies were carried out using USP-XXIII tablet dissolution test apparatus by rotating basket method at 50 rpm (apparatus-I), 900 ml of pH 1.2 buffer solution was used as dissolution medium for the first two hour and phosphate buffer pH 7.5 for the next 10 hours, temperature of the dissolution medium was maintained at 37±0.5ºC. The drug release data given in table-3 to 4 and the drug release profiles are shown in figure-1 to 12. The t_{50} and t_{90} from all the formulation studied are shown in table-5. During the dissolution process a general trend was observed i.e., increase in the amount of HPMC in the tablets resulted in a reduction in drug release rate. Among the three drug polymer ratios studied, the formulation F2 containing drug-polymer ratio 1:1 released approximately 90% of the drug in 12.5 hours was chosen to study the influence of co-excipients like lactose, and DCP.

Release profile of propranolol hydrochloride from formulations F4, F5 and F6 prepared at drug-polymer ratio 1:1 containing lactose 20 mg, 40 mg and 60 mg respectively were shown in figure-5 to 8, which indicates that all the formulations containing lactose displayed higher release rates as compared to formulation without lactose.

Formulations F7 and F8 containing DCP as co-excipient exhibited slow release rates as compared to formulation F2 without DCP and formulations prepared with lactose .

The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order, kinetic equations, Higuchi and Peppas models in order to determine the mechanism of drug release. The results of linear regression analysis of data including regression coefficients are summarized in table-6.

The release of drug from the formulations containing lactose were found to be governed by diffusion controlled process, since the r-values for Huguchi's plot were found to be in the range of 0.98 and 0.99.

When the data was treated according to Peppas equation, the release exponents (n-values) for most of the formulations was found to be $0.45 < n < 0.89$ indicating non-Fickian release mechanism. Although the drug release data fitted better to anomalous (non-Fickian) diffusion mechanism, a model representing zero order was also very close (r=0.99 for formulations F4, F5, F6, F7 & F8).

When $t_{90\%}$ values were compared, the formulation containing lactose F4, F5, F6 was found to be in the range of 10 to 12 hours whereas formulation containing DCP F7 and F8 were more than 12 hours.

Short-term stability studies were performed for the best formulation F4 at 40±2ºC for three months (90 days). The samples were analyzed for percent drug content and *in vitro* drug release studies. The results are given in table-7 to 8. No appreciable difference was observed for the above parameters.

Table-1

Drug-polymer ratios for the preparation of matrix tablets of Propranolol Hydrochloride (for 1 tablet)

Formulation code	Drug (mg)	HPMCK 100M (mg)	Lactose (mg)	Dibasic calcium phosphate (mg)	PVP K30 (mg)	Talc (mg)	Magnesium stearate (mg)
F1	80	40	--	--	10	2	2
F2	80	80	--	--	10	2	2
F3	80	120	--	--	10	2	2
F4	80	80	20	--	10	2	2
F5	80	80	40	--	10	2	2
F6	80	80	60	--	10	2	2
F7	80	80	--	20	10	2	2
F8	80	80	--	40	10	2	2

Fig-1

Percent drug released versus time plots of formulations F1 to F3

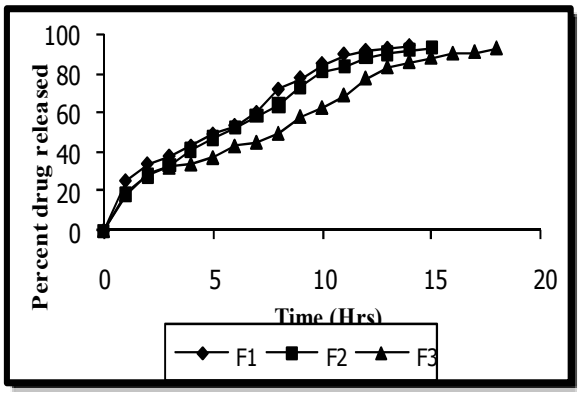


Fig-2Log cumulative percent drug remaining versus time plots of formulations F1 to F3

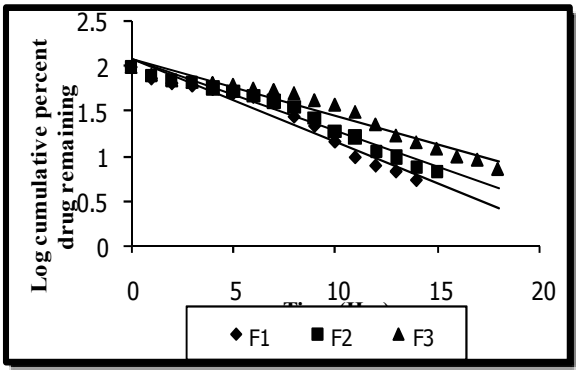
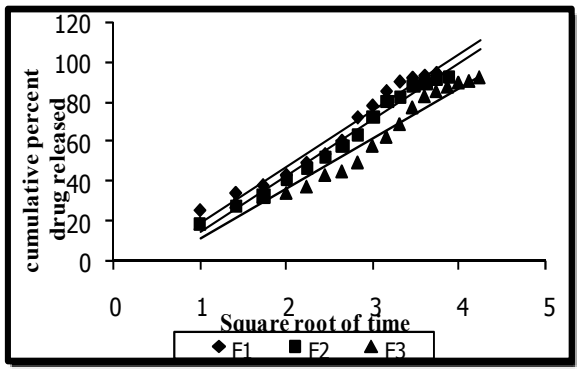


Fig-3

Cumulative percent drug released versus square root of time (Higuchi's) plots of formulations



F1 to F3

Fig-4

Log cumulative percent drug released versus log time (Peppa's plots) of formulations F1 to F3

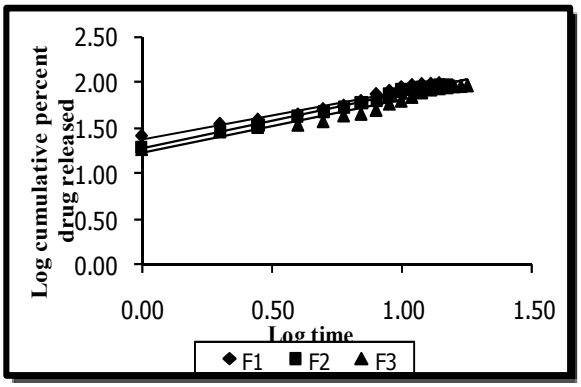


Fig -5

Percent drug released versus time plots of formulations F4 to F6

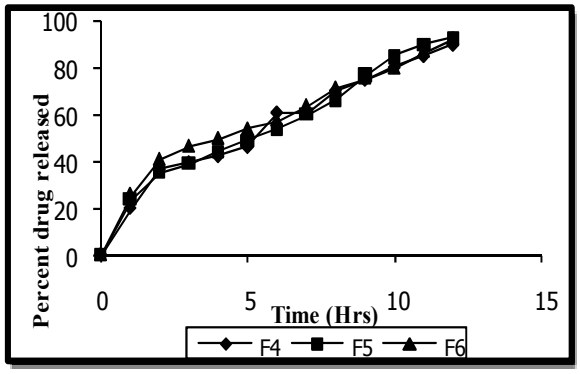


Fig- 6

Log cumulative percent drug remaining versus time plots of formulations F4 to F6

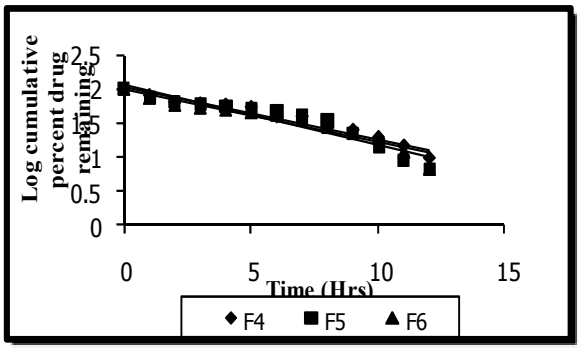


Fig-7:

Cumulative percent drug released versus square root of time (Higuchi's) plots of formulations F4 to F6

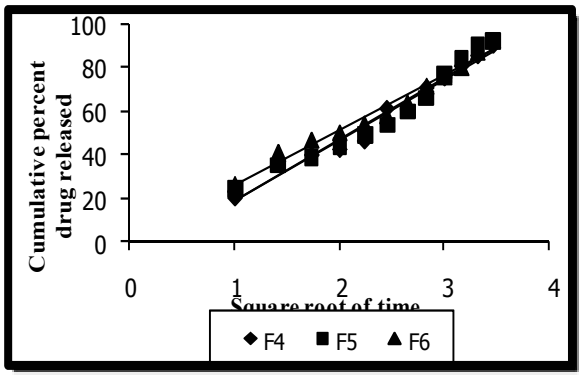


Fig-8

Log cumulative percent drug released versus log time (Peppa's plots) of formulations F4 to F6

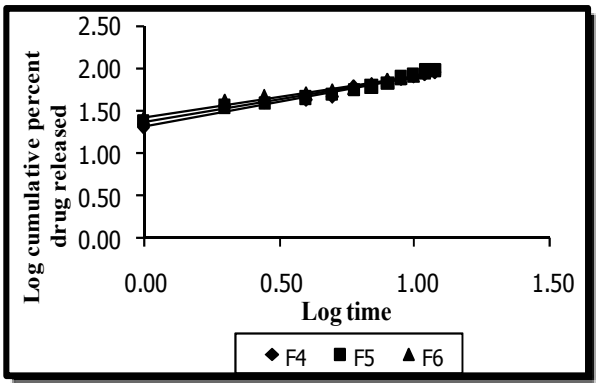


Fig-9

Percent drug released versus time plots of formulations F7 to F8

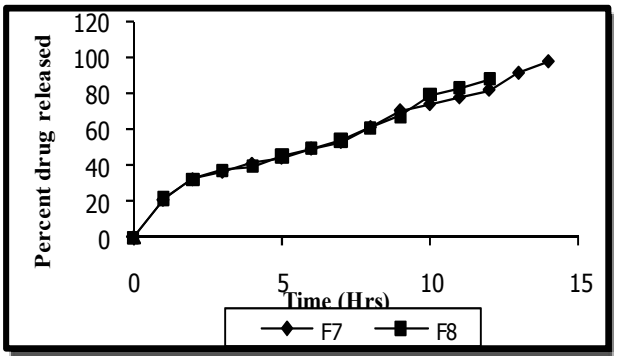


Fig-10

Log cumulative percent drug remaining versus time plots of formulations F7 to F8

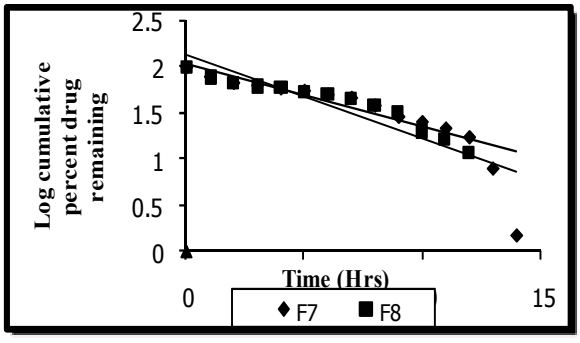
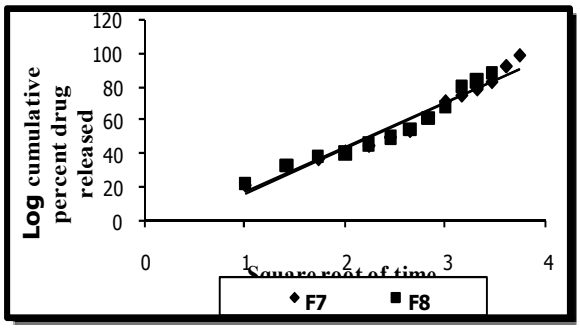


Fig-11



Log Cumulative percent drug released versus square root of time (Higuchi's) plots of formulations F7 to F8

Fig-12

Log cumulative percent drug released versus log time (Peppa's plots) of formulations F7 to F8

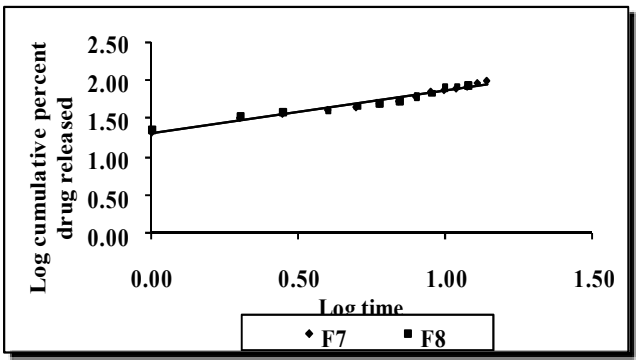
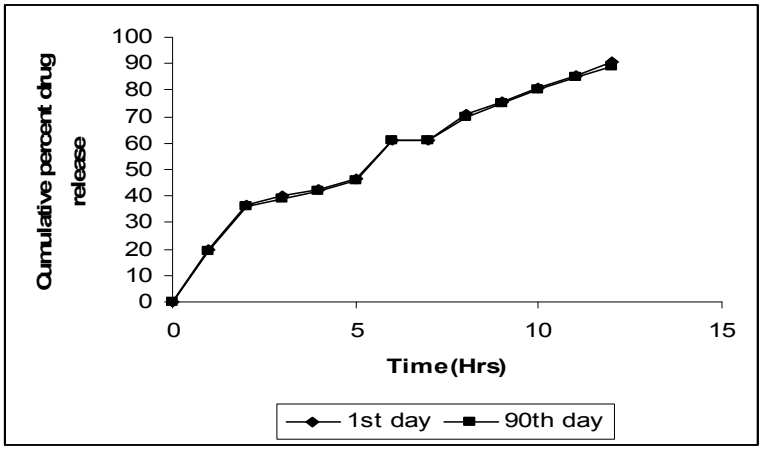


Fig-13

In vitro drug release profile for stability of formulation F4 at 40 ± 2^{0}C



CONCLUSION

From the present study, the following conclusions can be drawn:

- Matrix tablets of propranolol hydrochloride using HPMC K100M prepared by wet granulation method were found to be good without chipping, capping and sticking.
- The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug within the matrices.
- The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer level is increased, the drug release rates were found to be decreased.
- Addition of lactose resulted in the increase drug release rates but the addition of DCP was found to decrease the drug release rates.
- Formulation F4 with drug-polymer ratio 1:1 containing lactose (10%) have shown promising results as per USP Test-I requirements.
- Sustained release matrix tablets of propranolol hydrochloride can be prepared using HPMC K100M to achieve a desired drug release rates over a period of 12 hours, which can help to reduce the dose and frequency.
- Among the various formulations prepared, F4 appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

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