



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1174319>Available online at: <http://www.iajps.com>

Research Article

**DESIGN AND DEVELOPMENT OF MATRIX TABLET OF LABETALOL
HCL BY USING TAMARIND SEED POLYSACCHARIDE AS POLYMER****Vijay R. Chakote*, Mrunal K. Shirsat, Deepak A. Joshi, Mayuri M. Ban, Gunesh N.
Dhembre**Dept. of Pharmaceutics, S.V.P College of Pharmacy Hatta, Hingoli – 431705
Maharashtra, India**Abstract:**

The objective of present work was to design and develop sustained release matrix tablets of anti-hypertensive drug Labetalol hydrochloride. Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide used as a rate retarding polymer. Whereas Polyvinyl Pyrrolidone and Microcrystalline cellulose are used as granulating agent and diluent. The influence of variable concentration of polymers on the release rate of drug was investigated. The results of the present work point out that the rate of Labetalol hydrochloride release from polymers like Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide are mainly controlled by the drug-polymer ratio. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content and in vitro drug release studies.

Keywords: *Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, Sustained-release, Labetalol hydrochloride Formulation.*

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Please cite this article in press as Vijay R. Chakote et al., *Design and Development of Matrix Tablet of Labetalol Hcl by Using Tamarind Seed Polysaccharide as Polymer*, Indo Am. J. P. Sci, 2018; 05(02).

INTRODUCTION:

Sustained release system includes any drug delivery system that “achieves slow release of drug over an extended period of time.” The term sustained release has become associated with those systems from which therapeutic agent may be automatically delivered over a long period of time. A simple dosing scheme with a once or twice daily administration of the antihypertensive agent is known to increase patient compliance. For this reason, the pharmaceutical industry is intensively searching for longer-acting antihypertensive drugs, either by the development of novel agents with a longer elimination half life, or by the improvement of the dosage form of existing shorter acting compounds, so that plasma concentrations compatible with a blood pressure lowering activity are maintained during the whole day. Sustained drug delivery has been introduced to overcome the drawback of fluctuating drug level associated with conventional dosage form [1-3].

The goal in designing oral sustained or controlled delivery is to reduce the frequency of the dosing or to increase effectiveness of the drug by localizing at the site of action, reducing the dose required or provide uniform drug delivery, thereby also improving patient compliance. Controlled or sustained release dosage forms provide a better control drug levels, less dosage frequency, less than effects, increased efficiency and constant delivery [4].

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of sustained release drug delivery system like application of different polymers to achieve sustained delivery that could revolutionize method of medication and provide a number of therapeutic benefits. To fabricate matrix tablet of Labetalol HCl using polymers like Hydroxypropylmethylcellulose (HPMC), Sodium CMC, Xanthan gum and Tamarind seed polysaccharide (carried out the Isolation and Extraction of Tamarind seeds polysaccharide from tamarind husk kernels).

MATERIALS & METHODS:

Labetalol hydrochloride was obtained as a gift sample from Yarrow chem. distributor, Mumbai and ingredients like HPMC K 15, Sodium CMC,

Microcrystalline Cellulose, and Talc, obtained from loba chemicals Mumbai. Tamarind seed polysaccharide is used.

PREPARATION OF MATRIX TABLETS OF LABETALOL HYDROCHLORIDE:

In the present work, wet granulation method has been used to prepare matrix tablets of Labetalol hydrochloride and the polymer used is: Hydrophilic swellable polymer i.e., hydroxypropyl methyl cellulose with grade K15. Sodium CMC
Xanthan gum
TSP (Starch)

Diluents (bulking agent or compression vehicles) used are

Microcrystalline cellulose
Binder: Polyvinyl pyrrolidone K30 (PVPK30) in water.
Lubricant: Magnesium stearate
Glidant: Talc

Method:

In the present work, drug with different polymer in their variable concentration is used to give a drug-polymer proportion of 1:0.5, 1:0.75 and 1:1 for the preparation of matrix tablet. Among the three drug polymer ratios studied drug-polymer ratio 1:1 released approximately 90% of the drug in 11.5 hours.

Procedure for Preparation of Matrix Tablets:

Matrix tablets were prepared by wet granulation method. The composition with respect to drug-polymer ratio 1:0.5, 1:0.75 and 1:1 was selected. Weighed all the ingredients accurately. Drug, Polymer and diluents were mixed in a poly bag and the mixture was passed through a mesh No. 44. Granulation was done with a solution of PVP K30 in sufficient quantity of distilled water. The wet mass was passed through mesh No. 22 to get granule of desired size. The wet granules were dried at 50°C for about 2 hours. The dried granules were sieved by a mesh No. 20 and mixed with magnesium stearate and talc. Granules thus obtained weighing equivalent to required weight were compressed into tablets by using 8mm flat round punches on a single punch sixteen station Cadmach tablet machine.

Table 1: Formulation chart of Labetalol HCL Matrix tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Labetalol HCl	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K 15	50	75	100	-	-	-	-	-	-	-	-	-
Sodium CMC	-	-	-	50	75	100	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-	50	75	100	-	-	-
TSP(Starch)	-	-	-	-	-	-	-	-	-	50	75	100
Microcrystalline cellulose	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight (mg)	300	300	300	300	300	300	300	300	300	300	300	300

RESULT AND DISCUSSION:**Preformulation study of Labetalol HCl:-****1. Description**

Test	Specification	Result
Description	White crystalline powder	White crystalline powder.

2. Solubility

Parameter	1 Trial	2 Trial	3 Trial	Mean
Solubility* (mg/ml)	20	19.5	20.5	20

*Solubility in water at 25°C

3. Melting point: Melting point of Labetalol HCl was found to be 195°C**Evaluation of Formulation Parameters:**

Evaluation was divided in mainly

- Pre-compression Parameters.
- Post-compression Parameters.

PRECOMPRESSION STUDY**Table 2: Results of flow properties:**

BATCH	ANGLE OF REPOSE(°)	BULK DENSITY (gm/ml)	TAPPED DENSITY(gm/)	COMPRESSIBILITY INDEX	HAUSNER'S RATIO
F1	24.6	0.537	0.610	12.23	1.13
F2	23.7	0.524	0.601	12.83	1.14
F3	24.7	0.541	0.626	13.55	1.15
F4	24.8	0.560	0.630	11.55	1.12
F5	23.5	0.580	0.658	11.85	1.13
F6	24.0	0.579	0.670	12.18	1.15
F7	23.5	0.565	0.637	12.80	1.12
F8	22.5	0.540	0.626	11.95	1.15
F9	23.6	0.559	0.631	12.63	1.12
F10	22.4	0.584	0.659	12.45	1.12
F11	25.2	0.545	0.625	11.82	1.14
F12	24.2	0.572	0.664	13.15	1.16

The formulated granules were characterized with respect to angle of repose, bulk density and tapped density. All granules from all formulation show excellent flow property.

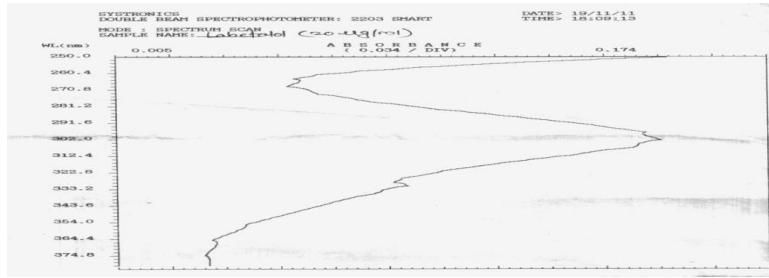


Fig. 1: UV spectra of Labetalol HCl

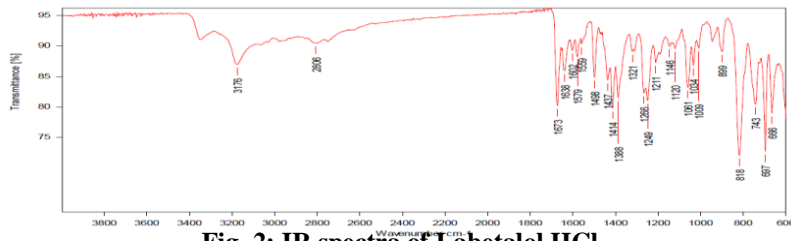


Fig. 2: IR spectra of Labetalol HCl

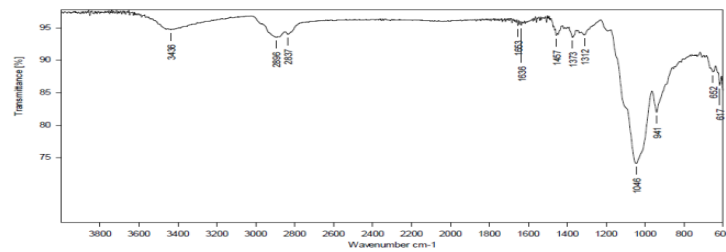


Fig. 3: IR spectra of HPMC K 15

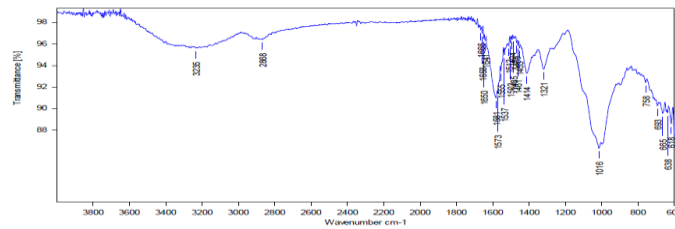


Fig. 4: IR spectra of Sodium CMC

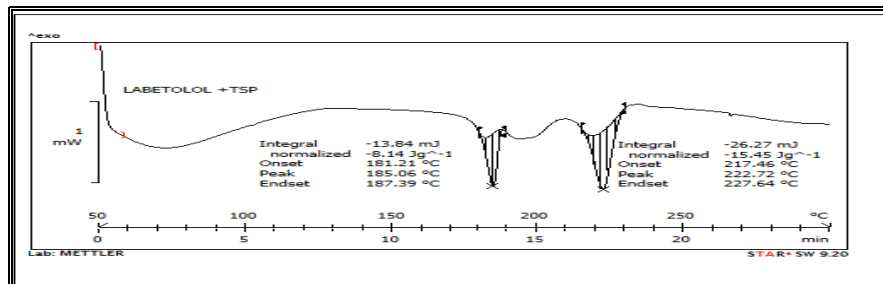


Fig. 5: DSC spectra of Labetalol + Tamarind seed polysaccharide

Table 3: Evaluation parameters of formulations

Formulation code	Evaluation parameter				
	Thickness \pm S.D. (mm) (n = 5)	Hardness \pm S.D. (kg/cm ²) (n = 5)	Friability (%)	Average weight variation (n=20)	Drug content (%)
F1	4.64 \pm 0.13	5.86 \pm 0.21	0.03	310 \pm 1.153	99.24
F2	4.55 \pm 0.11	5.74 \pm 0.41	0.07	295 \pm 2.111	95.41
F3	4.62 \pm 0.23	5.72 \pm 0.25	0.11	305 \pm 2.172	99.5
F4	4.52 \pm 0.15	5.82 \pm 0.25	0.63	310 \pm 1.183	96.87
F5	4.53 \pm 0.27	5.68 \pm 0.13	0.18	310 \pm 2.211	97.71
F6	4.44 \pm 0.19	5.66 \pm 0.23	0.21	290 \pm 1.121	98.47
F7	4.52 \pm 0.16	5.96 \pm 0.28	0.29	310 \pm 3.189	96.45
F8	4.53 \pm 0.19	5.44 \pm 0.23	0.17	290 \pm 1.198	98.98
F9	4.56 \pm 0.22	5.74 \pm 0.11	0.29	295 \pm 1.143	95.87
F10	4.65 \pm 0.21	5.62 \pm 0.19	0.27	290 \pm 0.102	97.33
F11	4.53 \pm 0.23	5.70 \pm 0.15	0.25	310 \pm 3.172	98.41
F12	4.43 \pm 0.21	5.72 \pm 0.23	0.67	290 \pm 2.173	97.07

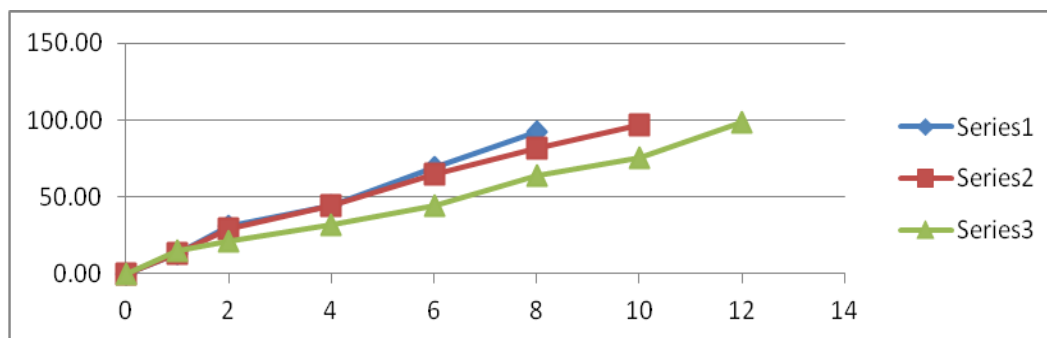
In vitro drug release of Labetalol HCl through HPMC K 15

Table 4: *In vitro* release profile of formulation F₁ & F₂

Time	F1					F2				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	Mg	Mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.07	13.32	0.00	13.32	13.32	0.07	13.20	0.00	13.20	13.20
2	0.17	31.44	0.07	31.51	31.51	0.16	29.64	0.07	29.71	29.71
4	0.25	44.46	0.25	44.71	44.71	0.25	44.46	0.24	44.70	44.70
6	0.38	68.52	0.50	69.02	69.02	0.36	64.26	0.49	64.75	64.75
8	0.51	91.08	0.88	91.96	91.96	0.45	81.12	0.84	81.96	81.96
10	-	-	-	-	-	0.53	95.52	1.29	96.81	96.81

Table 5: *In vitro* release profile of formulation F₃

Time	F3				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	Mg	%
0	0	0	0	0	0
1	0.09	15.54	0.00	15.54	15.54
2	0.12	21.48	0.09	21.57	21.57
4	0.18	31.98	0.21	32.19	32.19
6	0.24	43.86	0.38	44.24	44.24
8	0.35	63.36	0.63	63.99	63.99
10	0.42	74.88	0.98	75.86	75.86
12	0.54	96.78	1.40	98.18	98.18



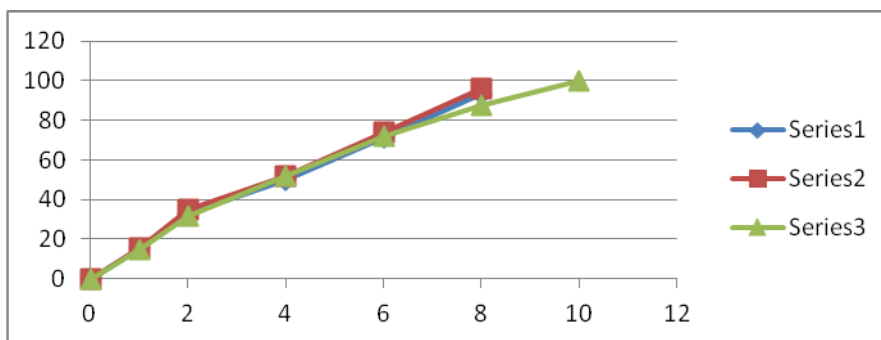
Graph 1: In vitro drug release of Labetalol HCl through HPMC K 15 (F1, F2, F3)

Table 6: *In Vitro* drug release of Labetalol HCl through Sodium CMC

Time	F4					F5				
	Concentration of Drug (mg)		Cumulative loss mg	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss mg	Cumulative drug release *	
	5ml	900ml		mg	%	5ml	900ml		mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	13.32	0.00	15.48	15.48	0.09	15.48	0.00	15.48	15.48
2	0.18	31.44	0.09	32.97	32.97	0.19	34.98	0.09	35.07	35.07
4	0.28	44.46	0.27	50.07	50.07	0.29	51.30	0.28	51.58	51.58
6	0.39	68.52	0.55	71.47	71.47	0.41	73.50	0.57	74.07	74.07
8	0.51	92.52	0.93	93.45	93.45	0.53	94.86	0.97	95.13	95.13

Table 7: *in vitro* release profile of formulation F6

Time	F6				
	concentration of Drug (mg)		cumulative loss mg	Cumulative drug release	
	5ml	900ml		mg	%
0	0	0	0	0	0
1	0.08	14.94	0.00	14.94	14.94
2	0.17	31.38	0.08	31.46	31.46
4	0.29	51.42	0.26	51.68	51.68
6	0.40	71.16	0.54	71.70	71.70
8	0.48	86.46	0.94	87.40	87.40
10	0.55	98.34	1.42	99.76	99.76

Graph No. 2 *In vitro* drug release of Labetalol through Sodium CMC (F4, F5, F6)

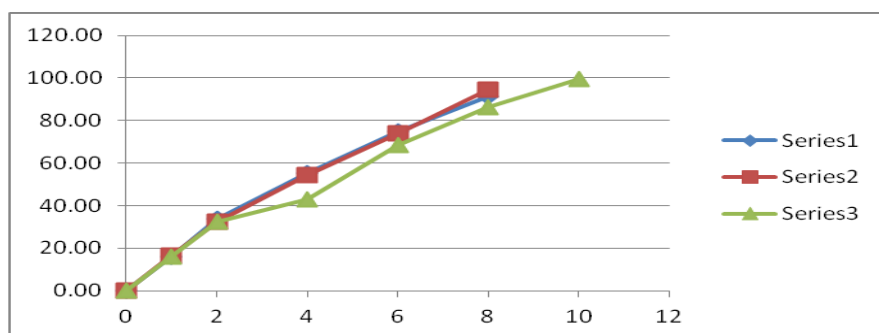
in vitro drug release of Labetalol through Xanthan gum

Table 8: *In vitro* release profile of formulation F7 & F8

Time	F7					F8				
	Concentration of Drug (mg)		Cumulative loss mg	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss mg	Cumulative drug release *	
	5ml	900ml		mg	%	5ml	900ml		mg	mg
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26	0.09	16.56	0.00	16.56	16.56
2	0.19	33.78	0.09	33.87	33.87	0.18	32.28	0.09	32.37	32.37
4	0.31	55.08	0.28	55.36	55.36	0.30	54.00	0.27	54.27	54.27
6	0.41	74.52	0.58	75.10	75.10	0.41	73.62	0.57	74.19	74.19
8	0.50	90.18	1.00	91.18	91.18	0.52	93.48	0.98	94.46	94.46

Table 9: *in vitro* release profile of formulation F9

Time	F9				
	concentration of Drug (mg)		cumulative loss Mg	Cumulative drug release	
	5ml	900ml		mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26
2	0.18	32.28	0.09	32.37	32.37
4	0.24	42.78	0.27	43.05	43.05
6	0.38	67.98	0.51	68.49	68.49
8	0.48	85.50	0.89	86.39	86.39
10	0.54	97.98	1.36	99.34	99.34



Graph No. 3: *In vitro* drug release of Labetalol through Xanthan gum (F7, F8, F9)

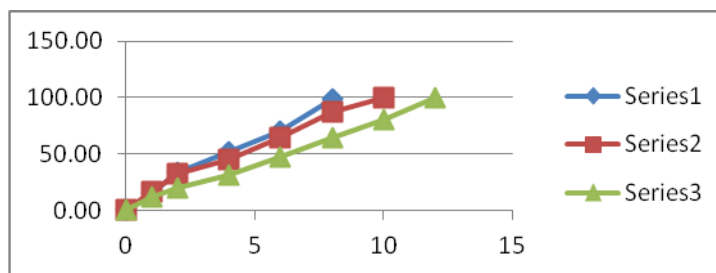
In vitro drug release of Labetalol HCl through the Tamarind seed polysaccharide.

Table 10: *in vitro* release profile of formulation F₁₀ & F₁₁

Time	F10					F11				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	15.30	0.00	15.30	15.30	0.09	16.02	0.00	16.02	16.02
2	0.19	33.30	0.09	33.39	33.39	0.18	32.76	0.09	32.85	32.85
4	0.29	52.08	0.27	52.35	52.35	0.25	44.28	0.27	44.55	44.55
6	0.39	69.66	0.56	70.22	70.22	0.36	64.32	0.52	64.84	64.84
8	0.55	98.10	0.95	99.05	99.05	0.48	86.76	0.87	87.63	87.63
10	-	-	-	-	-	0.54	97.98	1.36	99.34	99.31

Table 11: *In vitro* release profile of formulation F₁₂

Time	F12				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.07	12.12	0.00	12.12	12.12
2	0.11	19.62	0.07	19.69	19.69
4	0.17	30.72	0.18	30.90	30.90
6	0.26	46.80	0.35	47.15	47.15
8	0.36	64.20	0.61	64.81	64.81
10	0.44	79.44	0.96	80.40	80.40
12	0.55	98.22	1.41	99.63	99.63



Graph No. 4: in vitro drug release of Labetalol through Tamarind seed polysaccharide (F10, F11, F12)

CONCLUSION:

From the present study, The sustained release matrix tablet of Labetalol HCl using polymers such as HPMC K 15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, 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. IR and DSC studies indicated that the drug and polymers are in the pure form and compatible with each other. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer concentration is increased, the drug release rates were found to be decreased. Formulation F3 and F12 with drug-polymer ratio 1:1 containing PVP K 30 and MCC as binder and diluents respectively have shown promising results as per USP Test-I requirements. Sustained release matrix tablets of Labetalol hydrochloride can be prepared using HPMC K 15 and Tamarind seed polysaccharide 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, F3 and F12 appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

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