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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF PROPRANOLOL USING NATURAL AND SYNTHETIC POLYMER

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Abstract: The purpose of the work is to prepare Propranolol HCL sustained release matrix tablet, by using different combination of release retarding polymer and filler. Controlled release tablet by using natural polymer, guar gum and synthetic polymer, carbopol as a release retarding polymer. Propranolol HCL is a non-selective beta adrenergic blocker. It will maintain plasma concentration within therapeutic range for 12hrs having short half-life (3-5 hr) and first pass metabolism favors for sustained release dosage form. Matrix tablet were prepared by hydrophilic and hydrophobic polymer in combination. Matrix tablet were prepared by Ethyl cellulose (EC), and with different filler: microcrystalline cellulose and dibasic calcium phosphate, lactose. Extended release matrix tablet to reduce dosing frequency, and to improve patients compliance. Tablets were prepared by wet granulation technique. Prepared tablet were evaluated by various parameters: weight variation, thickness, hardness, friability, and % drug content and in-vitro drug release. In the present investigation natural polymer, guar gum and synthetic polymer, carbopol have been selected matrix forming material for the drug delivery.

KEYWORDS: Matrix tablet, sustained release, release retarding polymer, guar gum, carbopol, in-vitro dissolution.

I. INTRODUCTION

The most convenient and important method of administering drugs for systemic effect is the oral route. Over the past 30 years, as the expense and complication involved in marketing new drug entities have increased, with recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained release or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drug when administered or applied by conventional dosage form of tablet, capsules, injectables, ointments etc.

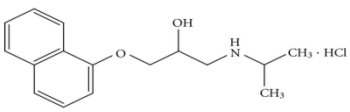
The goal in designing sustained or controlled delivery system is to reduce the frequency of the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Usually conventional dosage forms produce wide ranging fluctuation in the drug concentration in the blood stream and tissue with consequent undesirable toxicity and poor efficiency. This factor and factor such as repetitive dosing and unpredictable absorption led to concept of Contolled drug delivery system.

Controlled release dosage form provides a better control of plasma drug levels, less dosage frequency, less side effects, increased efficacy and constant delivery.

Drug profile

Propranolol hydrochloride is (RS)-1-(1-methylethylamino)-3-(1-naphthyloxy) propan-2-ol. Molecular formula is $C_{16}H_{22}ClNO_2$.

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol.



Propranolol is a beta-adrenergic receptor antagonist used to treat hypertension. Propranolol is non-selective beta adrenergic receptor antagonist.

MATERIALS AND METHOD

Materials:

Propranolol Hydrochloride was obtained as a gift sample from Renuka Raw Pharma (Mumbai), India. And other ingredients used were analytical grades**.**

Methods:

Preformulation Studies: The drug substance of Propranolol HCl was characterized for their identity and purity. The following studies were performed.

Determination of Absorption Maxima of Propranolol HCl: A solution of Propranolol HCl containing the concentration 10 µg/ ml was prepared in phosphate buffer 6.8PH respectively; UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm. Fig.1

Drug and Excipient Compatibility Studies:

The FTIR study was carried out on drug and excipients to find out compatibility in between drug-excipients, over the range of 4000-400 cm-1, on FTIR spectrometer.

Preparation of Propranolol tablet using guar gum by wet granulation method:

Different formulations were prepared by wet granulation method. The amount of drug 50mg/tablet is constant. The amount of polymer in these formulations varies from 25, 30, 35, 40, 45 & 50% w/w. the final tablet weight was adjusted to 350mg by adding MCC as filler. The different to the tablet formulation are given in **tablet: 1**

All the powders were first passed through sieve no.40. Required quantity of drug, polymer & MCC were mixed thoroughly and transferred into mortar and PVP K30 dissolved in isopropyl alcohol was added with constant mixing. The wet mass was passed through sieve n0.20 and the obtained granules dried for 1 hrs in an oven at 55℃. The dried granules were passed through a sieve no 20. Finally magnesium stearate and talc (1%w/w) was mixed for lubrication and Glidant for granules. The obtained granules were compressed with single punch tablet compression machine (Cadmach) using 11mm standard punch.

Preparation of Propranolol tablet using Carbopol-934 by wet granulation method:

The same procedure was followed for formulation batch B1-B6 using carbopol 934 instead of guar gum

Table: 1Formulation of tablet

Ingredients	**Formulation code**											
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Propranolol HCL	50	50	50	50	50	50	50	50	50	50	50	50
Guar gum	25	30	35	40	45	50	-	-	-	-	-	
Carbopol-934	-	-	-	-	-	-	5	10	15	20	25	30
Microcrystalline cellulose	q.s.	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
PVP K30	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
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	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Totalweight (mg)	350	350	350	350	350	350	350	350	350	350	350	350

Evaluation of granules

Angle of repose: The angle of repose of granules was determined by the fixed funnel method. The accurately weighed granules were taken into a funnel. The height of the funnel was adjusted in such a way that the tip of funnel just touches the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the following equation

$$\text{Tan } \theta = h/r$$

Where h= height, r = radius of the powder cone.

Bulk density: Both bulk density (BD) and tapped density (TD) were determined. A quantity of powder from each formulation into a 100ml graduated cylinder. After the initial volume was observed, the cylinder tapped and measured the final volume after tapping. The BD &TD were calculated using the following formula:

BD = weight of the powder/ bulk volume of the powder

TD = weight of the powder/ tapped volume of powder

Compressibility index:

In theory, less compressible a material the more flowable it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$\text{Carr's index} = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$$

Table: 2 Evaluation of granules

Formulation code	Angle of repose	BD	TD	Compressibility index	Hausner's ratio
A1	24.699±0.013	0.597±0.011	0.531±0.010	6.304±0.032	1.086±0.014
A2	25.139±0.022	0.577±0.021	0.508±0.021	5.137±0.041	1.016±0.021
A3	25.546±0.011	0.558±0.042	0.486±0.022	5.617±0.040	1.016±0.011
A4	26.371±0.023	0.564±0.043	0.494±0.031	5.866±0.056	1.006±0.031
A5	27.613±0.034	0.549±0.040	0.471±0.021	5.703±0.027	1.065±0.084
A6	28.613±0.030	0.642±0.013	0.497±0.036	5.363±0.017	1.095±0.045
B1	20.093±0.020	0.498±0.011	0.485±0.064	5.884±0.010	1.095±0.045
B2	24.734±0.014	0.469±0.026	0.492±0.054	5.789±0.023	1.085±0.015
B3	25.552±0.010	0.499±0.012	0.467±0.028	5.420±0.025	1.065±0.043
B4	27.463±0.013	0.546±0.023	0.458±0.018	5.092±0.029	1.055±0.014
B5	28.234±0.011	0.429±0.041	0.451±0.041	5.034±0.031	1.045±0.010
B6	30.234±0.014	0.432±0.019	0.479±0.029	6.812±0.046	1.081±0.061

Evaluation of tablet

Thickness: The thickness of the tablets was determined by using vernier calipers. Five tablets from each batch were used, and average values were calculated. Results were shown in table: 3

Hardness: hardness of the tablet was determined using the monsanto hardness tester. The lower plunger was placed in constant with the tablet and zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet is fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The result were showed in the table: 3

Weight variation test: formulated matrix tablet were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated by using the following formula.

$$\%\text{weight variation} = \frac{average\ weight - individual\ weight}{average\ weight} \times 100$$

The results were shown in table: 3

Friability: the Roche friability test apparatus was used to determine the friability of the tablets. 20 reweighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\text{Friability (\%)} = (1+x)^n = \frac{initial\ wt\ of\ tablet - final\ wt\ of\ tablet}{initial\ wt\ of\ tablet} \times 100$$

Results were shown in table: 3

Drug content: 20 tablet of each formulation were collected and powdered. Powder equivalent to100mg of Propanolol was weighed and added to 5ml methanol and diluted with 6.8 phosphate buffer make up the volume to 100ml it will allowed to sonicate 15min. the solution was filtered and the absorbance was measured with suitable dilution by using shimadzu UV spectrophotometer at 225nm. Results were shown in table 1.3

Table: 3 Evaluation of tablet

Formulation code	Thickness	Hardness	Friability	Weight variation	Drug content
A1	4.91±0.01	4.5±0.172	0.77±0.011	4.151±0.035	98.14±0.219
A2	4.79±0.01	4.3±0.451	0.76±0.021	3.199±0.064	98.87±0.229
A3	4.78±0.01	4.2±0.129	0.81±0.032	2.585±0.053	98.67±0.069
A4	4.72±0.01	4.9±0.278	0.55±0.031	3.095±0.071	96.97±0.052
A5	4.70±0.02	5.0±0.289	0.68±0.015	2.494±0.066	98.95±0.0117
A6	4.91±0.02	4.8±0.324	0.71±0.014	2.469±0.027	97.87±0.137
B1	4.87±0.02	4.7±0.167	0.72±0.045	4.159±0.057	98.27±0.086
B2	4.78±0.03	4.0±0.198	0.76±0.033	2.758±0.092	98.84±0.069
B3	4.96±0.03	4.3±0.189	0.85±0.034	3.367±0.167	98.32±0.034
B4	4.88±0.03	4.1±0.246	0.82±0.041	3.527±0.079	98.54±0.051
B5	4.77±0.01	4.6±0.122	0.88±0.011	2.951±O.116	98.08±0.056
B6	4.69±0.02	4.4±0.132	0.75±0.012	2.161±0.048	98.83±0.068

In-vitro dissolution study: the in-vitro dissolution study was carried out using USP type II dissolution apparatus. The study was carried out in 900ml of phosphate buffer for 12 hrs. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5℃. the paddle was lowered so that the lower end of the stirrer was 25mm above from the base of the beaker. The tablet was then introduced into the dissolution jar and the paddle was rotated at 50rpm. At different time intervals, 5ml sample was withdrawn and analyzed by using spectrophotometrically at 225nm, and using pH 6.8 phosphate buffer as a blank for the drug release. At each time of withdrawal, 5ml of fresh dissolution medium was replaced into the dissolution flask.

Result and discussion

Table 4: Calibration curve for the estimation of Propranolol HCl

Concentration	Absorbance
0	0.0000
2	0.1561
4	0.1906
6	0.4852
8	0.5874
10	0.7438

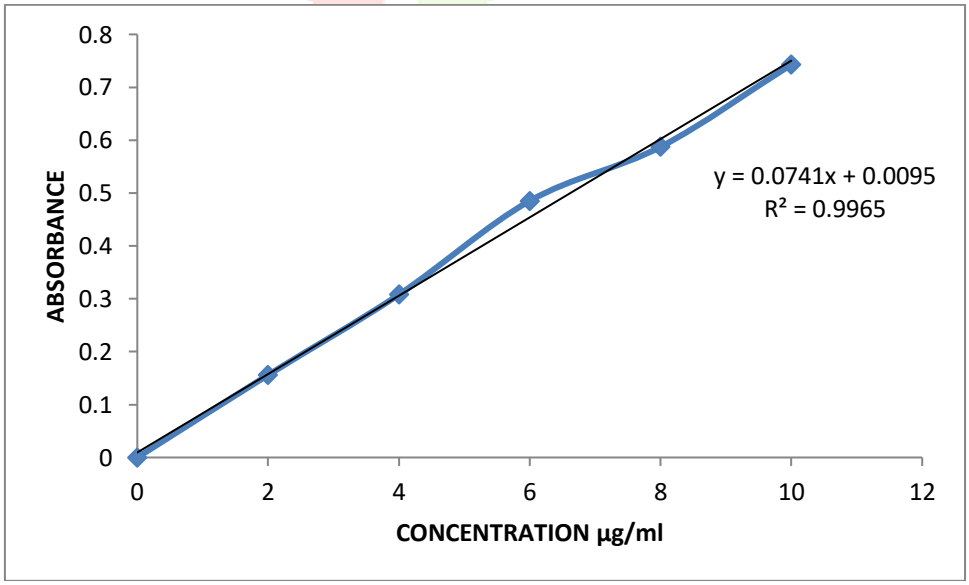


Fig. 1: Calibration curve for the estimation of Propranolol

Drug and Excipient Compatibility Studies: No significant changes were observed in the IR spectra as shown in **Figure No. 2.**

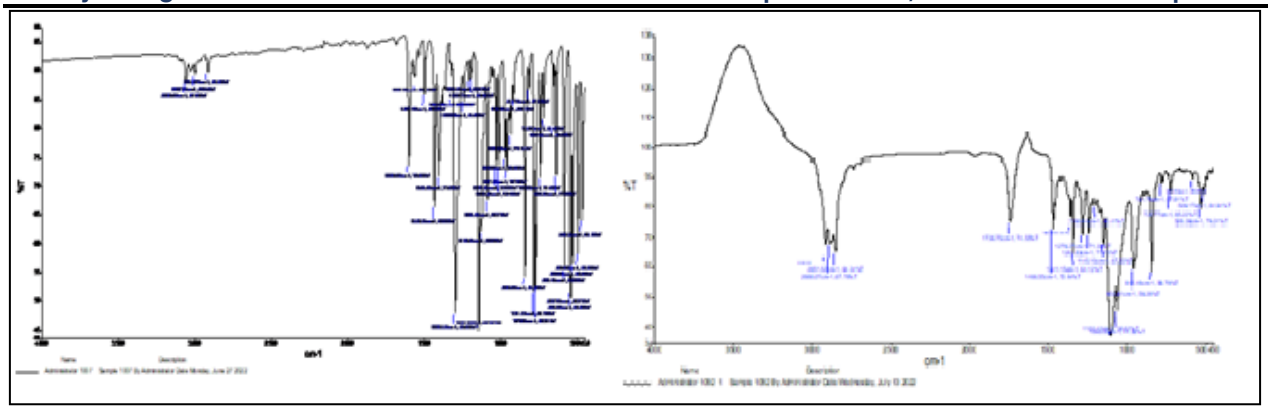


Fig 2: a) FTIR of pure drug & b) FTIR of drug and excipients

Evaluation of granules:

The granules of different formulation A1, A2, A3, A4, A5 and A6 were evaluated for angle of repose, LBD, TBD, compressibility index and Hausners ratio. The results were reported in table 2.

From the above studies, the results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by compressibility index (<15), also Hausner's ration (< 1.25). All these results indicate that the granules having free flowing nature.

The granules of different formulation B1, B2, B3, B4, B5 AND B6 were evaluated for angle of repose, LBD, TBD, compressibility index and Hausner's ratio. The results were reported in table: 2

From the above studies, the results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by compressibility index (<15), also Hausner's ratio (<1.25). All these results indicate that the granules having free flowing nature.

Evaluation of tablets:

The results of physicochemical evaluation of tablets for the formulation A1, A2, A3, A4, A5, & A6 are shown in table: 3

From the above results, all the formulations showed uniform thickness, hardness of the tablets was satisfactory and the percentage friability for all the formulations was below 1% indicating that friability is within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulation.

The results of physicochemical evaluation of tablets for the formulation B1, B2, B3, B4, B5, and B6 are shown in table: 3

From the above results, all the formulation showed uniform thickness, hardness of the tablet was satisfactory and the percentage friability for all the formulation was below 1% indicating that friability is within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulation.

In vitro dissolution

The results of in vitro release studies for the formulations A1, A2, A3, A4, A5, and A6 in 6.8 phosphate buffer. The data was depicted in table: 4.

Table 4: Dissolution data of Propranolol HCL tablets formulated with guar gum

Time	A1	A2	A3	A4	A5	A6
1	12.652±0.04	12.531±0.04	11.363±0.06	11.212±0.03	10.723±0.03	9.997±0.07
2	20.285±0.36	19.633±0.45	18.805±0.03	13.668±0.02	11.991±0.07	12.241±0.06
3	31.374±054	24.977±0.08	24.390±0.44	20.427±0.23	13.442±0.09	12.881±0.52
4	40.234±0.09	31.521±0.02	29.092±0.24	25.996±0.08	19.786±0.17	16.967±0.46
6	47.628±0.66	39.678±0.32	37.988±0.09	31.202±0.31	24.332±0.39	20.841±0.65
8	62.877±0.21	48.764±0.12	50.182±0.05	35.880±0.24	27.313±0.04	24.189±0.08
10	72.897±0.26	55.381±0.42	59.786±0.29	44.872±0.34	33.549±0.24	29.871±0.02
12	86.690±0.09	73.212±0.17	72.910±0.024	63.984±0.39	49.723±0.99	33.980±0.016

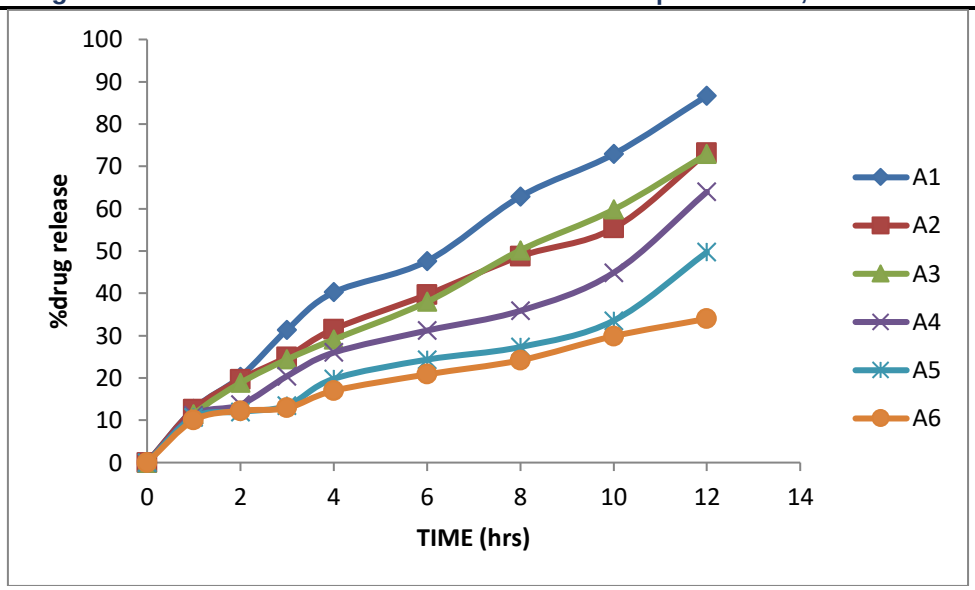


Fig 3: dissolution profile of Propranolol HCl tablet using guar gum

Table 5: dissolution data of Propanolol HCl tablets formulated with carbaopol-934

Time	B1	B2	B3	B4	B5	B6
1	12.547±0.02	12.491±0.42	11.760±0.02	11.093±0.06	10.633±0.21	10.164±0.01
2	19.936±0.56	18.585±0.63	13.986±0.06	12.603±0.04	12.629±0.05	11.648±0.26
3	23.713±0.81	21.225±0.05	18.227±0.52	13.834±0.055	16.781±0.02	13.639±0.16
4	31.251±0.23	26.381±0.54	24.705±0.08	24.822±0.24	21.198±0.21	14.810±0.27
6	44.537±0.41	37.981±0.23	33.691±0.12	26.601±0.36	22.467±0.42	20.933±0.23
8	61.260±0.23	51.459±0.36	48.395±0.54	35.001±0.23	27.566±0.48	24.671±0.40
10	78.836±720	64.916±0.23	60.312±0.18	45.463±0.50	34.669±0.26	29.149±0.16
12	89.905±0.34	77.874±0.12	71.152±0.22	53.760±0.33	49.275±0.45	36.192±0.17

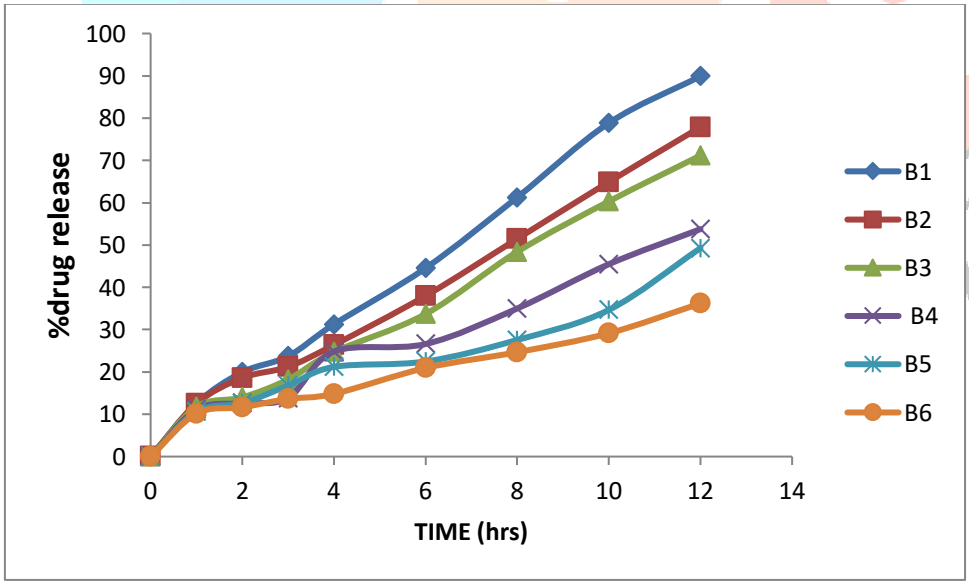


Fig 4 dissolution profile of Propranolol HCL tablet formulated with carbopol-934

The above results indicating, increasing concentration of Carbopol-934 content drug release was retarded.

CONCLUSION:

The objective of the present study to develop controlled release tablets of Propranolol HCL using Natural polymer, guar gum and synthetic polymer, Carbopol as a rate controlling polymers. The formulations were made by employing conventional wet granulation method. The granules for tablets prepared according to the formulas given, granulation is a key process in the production of dosage form involving the controlled release of a drug from matrix type particles. Micromeritic properties of granules such as angle of repose, LBD, TBD, and compressibility index for evaluated. The results were found to be within the specified limits of I.P. The tablets of different formulations made were subjected to evaluation test, such as thickness,

hardness, friability, weight variation, and drug content. The results obtained from the evaluation parameters found to be within the specified limits of I.P. The in vitro drug release characteristics were studied in phosphate buffer pH 6.8 for next 3-12hrs all the results were reported. The drug polymer compatibility studies were done by FTIR spectral analysis. All the tablets were found to be within the I.P limits.

The drug and polymers were found to be compatible, the formulation A1 containing 25% Guar gum released 85% of the drug in 12hrs, while the formulation A6 containing 50% Guar gum release 30% of the drug in 12hrs.

The formulation B1 containing 5% Carbopol-934 released 89% of the drug in 12hrs, while the formulation B6 containing 30% Carbopol-934 release 37% of the drug in 12hrs.

Though both the Natural and Synthetic polymer retards the drug release, the tablets prepared using Carbopol-934(5%) require lower amount and better release than the tablets prepared using Guar gum (25%).

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