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FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ANTI ANGINAL DRUG USING NATURAL EXCIPIENTS

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ABSTRACT

The aim of the present investigation is to, formulate and develop a novel oral monolithic, controlled release tablet dosage form for Propranolol hydrochloride to provide steady state drug release over an extended period of time. The drug candidate selected Propranolol hydrochloride was formulated as controlled release matrix tablets which consisted of locast bean gum as polymer, electrolytes and other diluents by wet granulation technique. Electrolytes such as sodium carbonate, magnesium carbonate and calcium carbonate were added at various concentrations in various formulations, while the drug to polymer concentrations was maintained at different ratios respectively. The tablets were analyzed to determine their hardness, friability, dug content and *in vitro* release profile. The influence of the proportion of the gum and electrolytes on the release rate of the drug from the tablets was evaluated. The drug release rate was influenced by diffusion and swelling mechanisms exhibiting non-Fickian transport. The findings indicated that the swelling and gel formation in the presence of electrolytes within the hydrophilic matrices provided controlled drug delivery of drug from a simple monolithic system. The DSC and FTIR studies indicated that there was no chemical interaction between drug and excipients. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Propranolol hydrochloride was stable in the matrix tablets.

Keywords: Propranolol HCl, Locust Bean Gum, Electrolytes and Controlled release

INTRODUCTION

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range over prolonged period of time **[1]**. Matrix system is one of the methods used in the development of controlled release oral formulations. Matrix is defined as a well-mixed composite of one or more drugs with a gelling agent i.e. hydrophilic polymer **[2]**. In fact, matrix system has proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale up and process validation **[3-5]**. Development of oral controlled release tablets for water-soluble drugs with constant release rate has always been a challenge in pharmaceutical product development. Most of these water-soluble drugs if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of the drug up on oral administration. In recent years, considerable attention has been focused on natural excipients in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance **[6]** and non toxicity.

Propranolol Hydrochloride (PPN), a non- selective beta adrenergic blocking agent, widely used in the treatment of hypertension, angina pectoris, and in many other cardiovascular disorders **[7]**. It is highly lipophilic and is almost completely absorbed after oral administration. However, its bioavailability is limited to (30%) due to the hepatic first pass effect. Its elimination half-life is also relatively short (about 2–6 h) **[8-9]**. Therefore, it was chosen as a model drug for the preparation of an oral controlled delivery system.

Locust Bean Gum used in tablet formulations and obtained from *sterculia urens*. It is a partially acetylated polymer of glactose, rhamnose and glucoronic acid. Locust Bean Gum is used as rate controlling in producing directly compressible matrix. It shows lower hydration capacity and high rate of erosion **[10]**. The aim of the present investigation was to design and develop a novel oral monolithic, controlled release tablet dosage form of propranolol HCl with Locust Bean Gum as natural polymer along with pharmaceutically acceptable electrolytes which can induce in situ reactions between drug and electrolyte that alters drug release mechanism by matrix stiffening and changes in the gel would lead to extended drug release at a steady state manner has been elucidated.

Materials

Propranolol HCl was obtained as a gift sample from Mylon labs, Hyd. Locust Bean Gum purchased from Girijan co-operation society, Visakhapatnam. Micro Crystalline Cellulose from yarrow Chem Pharma Limited, Mumbai. Magnesium carbonate, Calcium carbonate, Sodium carbonate, Magnesium stearate, Talc and Isopropyl alcohol were procured from S.D Fine Chem. Ltd., Mumbai.

Methods

Estimation of Propranolol HCl

In the present investigation, a simple, sensitive more accurate UV Spectrophotometric method was used for the estimation of Propranolol HCl. The absorbance values of Propranolol HCl were measured at a λ_{max} of 320 nm by using phosphate buffer pH 6.8 in the concentration range of 2, 4, 6, 8 & 10 µg/ml using UV Spectrophotometric model.

Preparation of Matrix Tablets

Matrix tablets were prepared by wet granulation method as reported by Bettini R **[11]**. The ratio of drug and polymer were maintained constant while electrolyte concentration was varied. They were placed in motor and triturated well and added isopropyl alcohol (granulating fluids) to prepare a dough mass. Then dough mass was passed through sieve no. 18 for obtaining wet granules. Then these wet granules were dried and they were passed through sieve no. 40. To dried granules added magnesium stearate & talc and mixed well before punching. Tablets were prepared by using 10 station tablet punching machine for obtaining 300 mg of tablet weight. To minimize the processing variables, all batches of tablets were compressed under identical conditions. Compositions of various formulations are given in **Table 1**.

The granules were evaluated for flow properties such as angle of repose, compressibility index and Hauser's ratio. The compressed tablets were further evaluated for their physical parameters such as weight uniformity, hardness, friability, drug content; swelling index and *in vitro* dissolution studies was given in **Table 2**.

***In vitro* drug release studies**

Drug release studies for the prepared tablets were performed using USP dissolution test apparatus (Apparatus 2, 50 rpm, 37 ± 0.5°C) employing phosphate buffer pH 6.8 (900 ml) and tested for drug release for 12hrs. Thus; the dissolution testing conditions were representing same as that of simulated gastric and intestinal juices without enzymes. At Predetermined interval, samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the

amount of drug present in each Sample was determined spectrophotometrically at 320 nm. Drug release profiles were shown in **Figure 2 & 3**.

Kinetic analysis of dissolution data

To study the mechanism of drug release from the matrix tablets the release data were fitted to zero-order, first-order, and Higuchi equation. The dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation) 1, which is often used to describe the drug release behaviour from polymeric systems.

$$\text{Log } (Mt / Mf) = \text{Log } k + n \text{ Log } t \text{ -------- (1)}$$

Where, Mt is the amount of drug release at time t,

Mf is the amount of drug release after infinite time,

k is a release rate constant incorporating structural and geometric characteristics of the tablet and 'n' is the diffusional exponent indicative of the mechanism of drug release.

To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. Dissolution parameters was shown in **Table 3**.

Water uptake and erosion studies

Erosion and water uptake of the tableted formulations were determined under conditions identical to those described for dissolution testing using SGF as the medium. Three tablets were used at each time interval. At the predetermined times, the tablets were lightly patted with tissue paper to remove excess surface water. The swollen weight of the tablets was determined (Ts), The tablets were then dried in a vacuum oven at 40 °C for 48 h and their dry weight (Tf) was determined. The study was carried out in triplicate. Swelling (%) and erosion (%) was calculated using Eqs 2 and 3, respectively **[12]**.

$$\text{Swelling (\%)} = (Ts - T)/T \times 100 \text{ …….. (2)}$$

Where Ts is the weight of the swollen tablet

T is the initial weight of the tablet, i.e., prior to the test.

$$\text{Erosion (\%)} = (T - Tf)/Tf \times 100 \text{ …… (3)}$$

Where T is the initial weight of the tablet and Tf is the weight of the tablet after the erosion test.

Based on the dissolution studies, the optimized formulation was selected and Fourier Transfer Infrared (FTIR) and Differential Scanning Calorimeter (DSC) studies were performed to observe the drug

and excipient interactions. The detailed spectral elucidations and DSC thermogram interpretations were shown in **Figure 4 and 5**.

Scanning electron microscopy (SEM)

The surface morphology of the matrix tablets was analyzed with a scanning electron microscope (JEOL-JSM-840A, Japan) and results were shown in **Figure 6**.

Comparison of dissolution profiles

Model independent approach was applied for comparison of dissolution profiles. The dissolution profiles comparison was done using difference factor (*f*1) and similarity factor (*f2)* to compare the dissolution profile of prepared Propronolol HCl formulations with marketed tablet formulation with all time points included in the *in vitro* dissolution studies. Dissimilarity and similarity factor was calculated using Equation 4 & 5.

$$f_1 = \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} 100 \quad \text{- Equation 4}$$

The percent error is zero when the test formulation and reference formulation drug release profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. Similarity factor, (*f2) is* a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves of marketed and test formulations. The equation for calculating similarity factor is

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} 100 \right\} \quad \text{---}$$

-------- Equation 5

Where 'n' is the number of dissolution time and R_t and T_t are the reference (theoretical) and test dissolution values at time't'. Dissolution profile was considered satisfactory if (*f*1) values lies below ≤ 15 (nearing zero) and (*f2)* value lays more than 50. Two dissolution profiles are considered similar when the *f*2 value is 50 to 100 **[13]**.

Statistical analysis

Comparison among the developed formulations and the reference formulation (Propranolol HCl) were made by Student t-test at 95 % level of confidence was applied for the comparison of the samples (optimized formulations) having difference variance levels.

Accelerated stability studies

Stability Studies on the optimized matrix tablets (F12) were carried out as per ICH guidelines at 25°C ±20°C/60% ± 5% RH and 40°C ±2°C/75% ± 5% RH for by storing the samples in stability chamber. Further, the matrix tablets were evaluated for appearance, weight variation, hardness, drug content and for *in vitro* drug release profiles over a period and graph was shown in **Figure 7**.

RESULTS

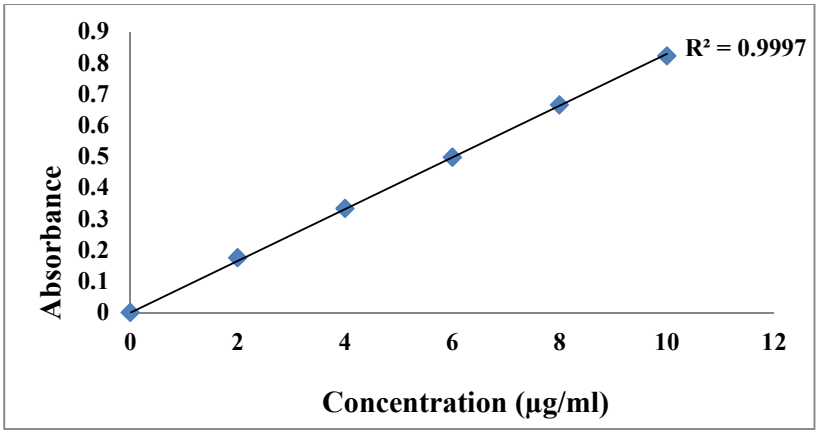


Figure 1: Calibration Curve for Propranolol HCl by Using Phosphate Buffer pH 6.8

Table 1: Composition of Propranolol HCl Matrix Tablets by Wet Granulation Method

Ingredients (mg/tab)	Tablet formulation											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Propranolol HCl	80	80	80	80	80	80	80	80	80	80	80	80
Locust Bean Gum	40	80	120	120	120	120	120	120	120	120	120	120
Calcium carbonate	-	-	-	10	20	30	--	-	-	-	-	-
Magnesium carbonate	-	-	-	-	-	---	10	20	30	-	-	-
Sodium carbonate	-	-	-	-	-	-	-	-	-	10	20	30
Isopropanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC	176	136	96	86	76	66	86	76	66	86	76	66
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total tablet weight(mg)	300	300	300	300	300	300	300	300	300	300	300	300

Table 2: Physical evaluation parameters of Propranolol HCl matrix tablets with electrolytes

Formulation code	Weight Variation (%)	Friability (%)	Hardness (Kg/cm2)	Drug content (mg)
F1	299±1	0.48	4.2±0.1	290±0.3
F2	300±3	0.64	4.8±0.3	298±0.2
F3	299±1	0.68	4.6±0.3	297±0.1
F4	300±2	0.78	4.5±0.2	299±0.2
F5	295±3	0.54	4.4±0.1	290 ±0.2
F6	299±1	0.52	4.4±0.1	292±0.1
F7	289±1	0.48	4.2±0.1	280±0.3
F8	300±3	0.64	4.8±0.3	298±0.2
F9	299±1	0.68	4.6±0.3	295±0.1
F10	300±2	0.78	4.5±0.2	299±0.2
F11	300±3	0.54	4.4±0.1	300 ±0.2
F12	299±1	0.52	4.4±0.1	298±0.1

Table 3: *In- vitro* Dissolution Parameters of Propranolol HCl matrix tablets with electrolytes

Formulation	Zero order constant		First order constant		Higuchi's constant		Peppas's constant	
	K(mg)	R^2	K(hr^{-1})	R^2	K($mg^{1/2}$)	R^2	n (value)	R^2
F1	24.51	0.925	2.01	0.979	57.75	0.953	0.513	0.953
F2	30.97	0.970	1.637	0.973	75.53	0.980	0.530	0.990
F3	34.02	0.935	0.991	0.978	60.28	0.970	0.675	0.958
F4	33.02	0.959	0.727	0.976	66.04	0.973	0.543	0.953
F5	27.64	0.981	0.438	0.992	52.65	0.998	0.616	0.990
F6	6.52	0.702	0.298	0.969	22.63	0.974	0.531	0.99
F7	8.31	0.804	0.384	0.967	23.62	0.983	0.501	0.984
F8	8.65	0.842	0.224	0.971	21.39	0.974	0.703	0.965
F9	6.22	0.913	0.231	0.982	23.26	0.993	0.640	0.987
F10	6.66	0.946	0.280	0.982	35.00	0.997	0.573	0.993
F11	6.02	0.996	0.280	0.882	17.00	0.997	0.956	0.993
F12	6.66	0.993	0.280	0.816	15.00	0.991	0.901	0.993

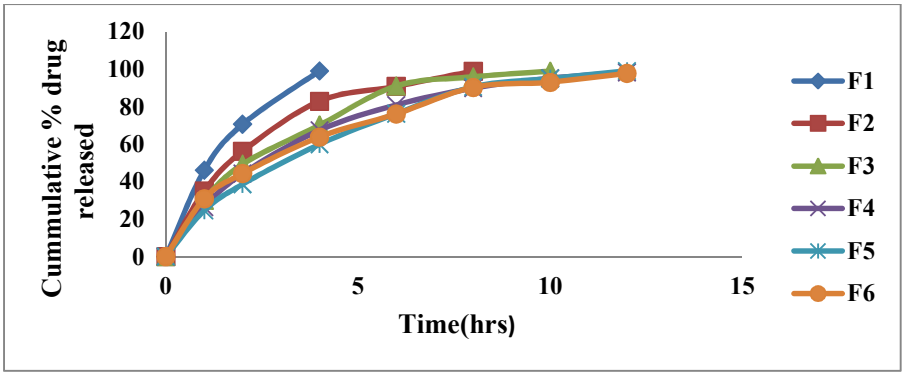


Figure 2: Drug Release Profiles of Propranolol HCl matrix tablets with electrolytes

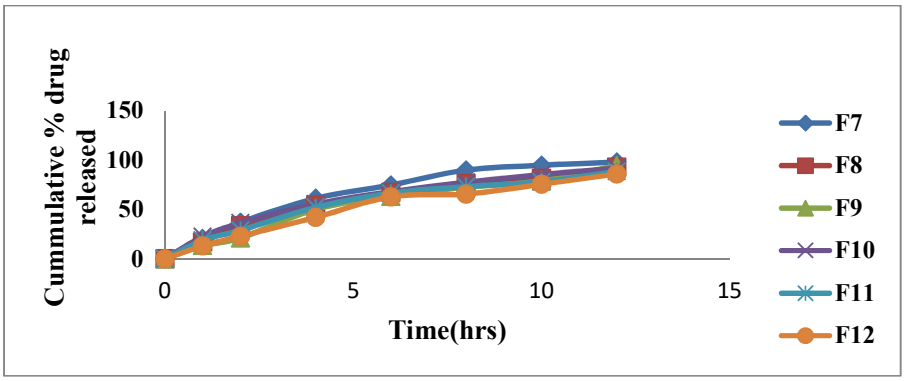


Figure 3: Drug Release Profiles of Propranolol HCl matrix tablets with electrolytes

Table 4: Swelling characteristics of selected matrix tablet formulations

Time (hrs)	Percentage Swelling Index		
	F1	F2	F3
1	64.89	59.96	60.67
2	85.94	80.77	79.96
4	15.67	113.46	112.46
6	133.65	128.46	127.78
8	157.95	156.25	157.79
10	165.32	162.48	161.64
12	168.23	169.62	168.31

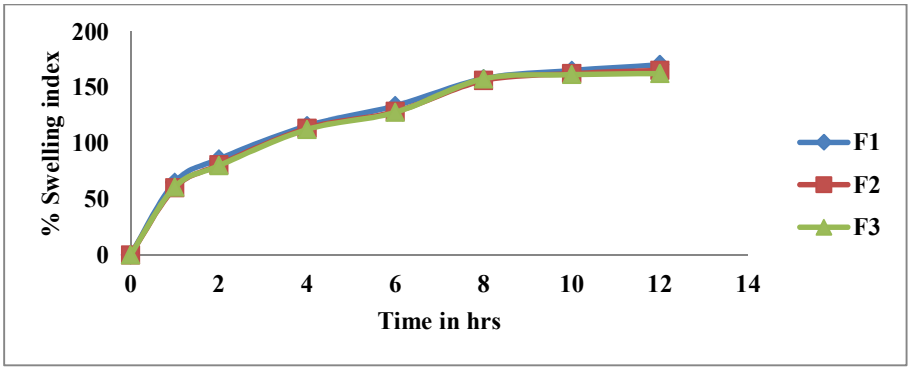


Figure 4: Percentage swelling profiles of sustained release formulations of Propranolol hydrochloride

Table 5: Swelling characteristics of selected matrix tablet formulations with electrolytes

Time (hrs)	Percentage Swelling Index		
	F10	F11	F12
1	50.89	59.96	60.67
2	75.94	73.77	74.96
4	105. 67	101.46	112.46
6	125.65	123.46	121.78
8	141.95	132.25	147.79
10	152.32	154.48	159.64
12	151.23	154.32	160.64

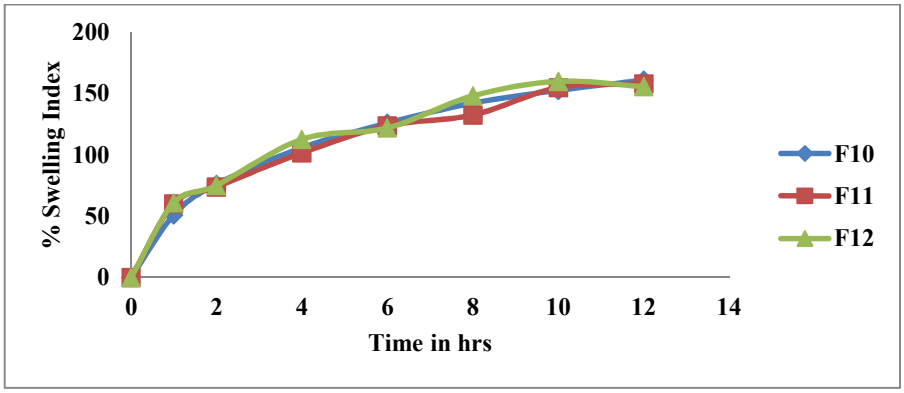
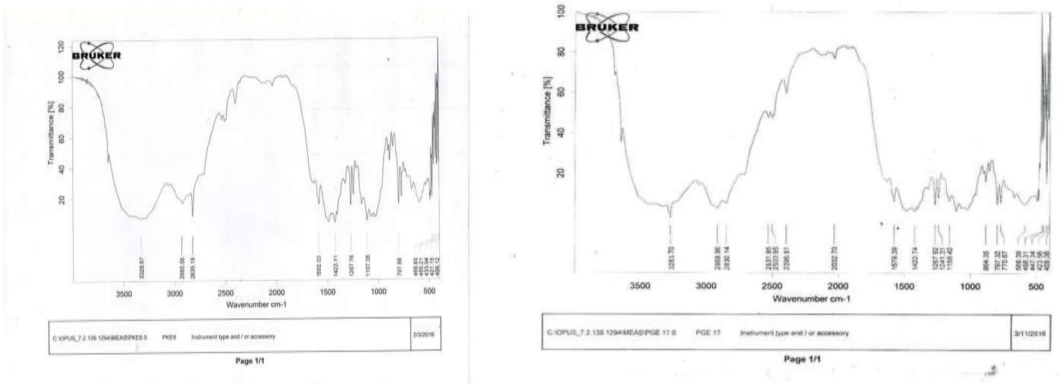


Figure 5: Percentage swelling profiles of sustained release formulations of Propranolol hydrochloride with electrolytes

Table 6: Similarity Factor for Optimized Matrix Tablet Formulation in Comparison With Marketed Formulation

	F10	F11	F12
Similarity factor f2	58	75	57
Difference factor f1	9	4	9



(a) **(b)**

Figure 4: FT-IR interpretation image of Propranolol hydrochloride and optimized formulation F12

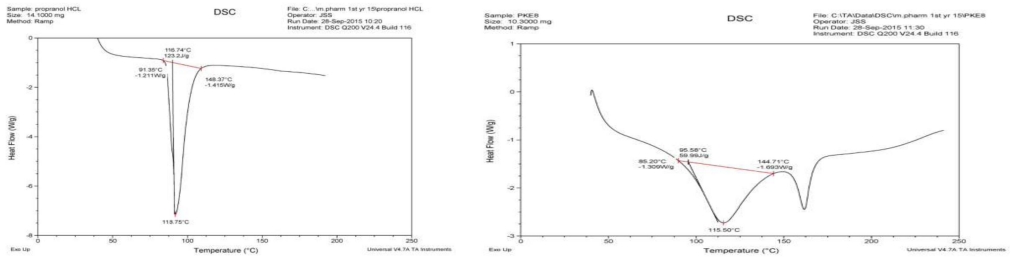


Figure 5: DSC image of Propranolol hydrochloride and optimized formulation F12

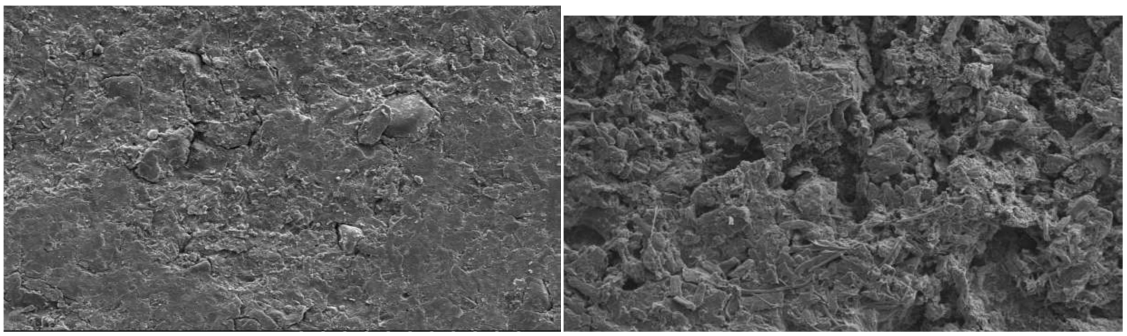


Figure 6: SEM image of Propranolol hydrochloride optimized formulation before and after dissolution

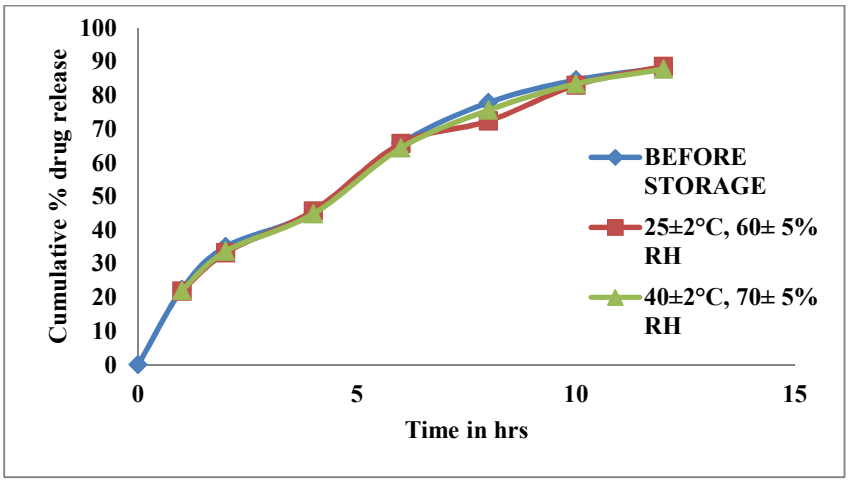


Figure 7: Drug Release Profile of Propranolol hydrochloride optimized formulation (before and after storage at different condition

DISCUSSION OF RESULTS

The calibration curve for the estimation of propranolol HCl in phosphate buffer pH 6.8 was found to be linear and obeyed Beer's law in the concentration range of 2-10µg/ml and measured at 320nm using UV spectrophotometer. Matrix tablets were prepared by wet granulation method using drug, polymer and electrolytes. Flow properties such as angle of repose and Carr's index were evaluated for the prepared granules and were found to exhibit good flow properties were in the range of 21.32-25.85 and 11.14-15.77%. Tablet formulations were further evaluated for physical parameters. It was revealed that all the tablet formulations were found to be stable and meeting I.P. specified limits for weight uniformity, friability and drug content.

The hardness of all the tablet formulations was in the range of 4.0-4.5 kg/cm^2. Weight uniformity of all the tablet formulations were in the range of 299-300±3mg. Friability loss of the tablet formulations were found to be negligible and were in the range of 0.4-0.78% w/w. Drug content estimated for all the tablet formulations were highly uniform with less than 2.5% variation. The matrix tablet

formulations prepared with drug and polymer along with electrolytes in F9, F10, and F11 & F12 suitable for extending the drug release up to 12 hrs. The matrix tablet formulations (without electrolytes) showed drug release less than 6hrs. The first order R^2 values of tablet formulations were in the range of 0.971-0.998. Thus all the formulations were found to be linear with first order rate constant. The drug release from the tablets depends on the composition of electrolytes employed. Electrolyte such as sodium bicarbonate shows high influence on extending the drug release over a prolonged period of time while magnesium carbonate and calcium carbonate has mild influence on the drug release.

The release exponent "n" values for all the matrix tablet formulations were in the range of 0.45-0.8 indicating that the drug release is by non Fickian diffusion. Thus, the drug release from the matrix tablet formulations was by diffusion of the drug from the polymer matrix followed by polymer swelling.

Bioavailability and bioequivalence study guidance for oral dosage forms, describes the model independent mathematical approach proposed by Moore and Flanner (1996) for calculating a dissimilarity factor (*f*1) *and* a similarity factor (*f2)* of dissolution across a suitable time interval. The similarity factor (*f2)* (where $0 \leq f2 \leq 100$ and (*f2)* $\geq 50\%$ implies dissolution profiles are similar) is a function of mean differences and does not take into account the differences in dissolution within the test and reference batches. The significance of using similarity factor was to compare the solubility and release profile of the prepared tablets with that of the marketed tablets**.** The *f2* value was found to vary from 57 to 75. The *f1* value ranged from 4 to 9. **Table 6** represents the similarity and the dissimilarity factors for the various batches.

The similarity and the dissimilarity factors indicate that the sustained release formulations are quite different from the marketed tablet, and more sustained than the marketed tablet. It may thus be concluded that the sustained release formulation can be achieved using hydrophilic polymers, which can also maintain the sustained release profile over an extended period of time.

Swelling index characteristics were performed on optimized matrix tablet formulations. The matrix tablet formulation with Locust Bean Gum as polymer tends to swell at a rapid rate.

Based on the statistical analysis using student – *t,* the t value obtained was 0.599, 0.101, and 0.596. The tabulated t value obtained at 5% level of significance with 8 (n-1) 7 degrees of freedom

Based on the statistical analysis using Student *t* test, the calculated *t* value obtained was 0.108 - 0.598. The tabulated *t* value obtained at 5% level of significance with 8 degrees of freedom is 2.36. Hence, $t_{cal} < t_{tab}$ and thus indicated that there was no significant difference between formulation F10, F11& F12 (test) and marketed formulation (standard).

FTIR and DSC studies were performed for pure drug, F10, F11& F12 formulations. The results revealed that there were no major interaction between the drug, polymer and electrolytes**.**

The SEM photomicrograph of the tablets at 8 hr after hydration commenced showed a highly porous tablet surface which probably also reflects a porous tablet matrix structure. This would facilitate diffusion of drug from the tablet core to the surface. Since the gel layer undergoes surface erosion, it is possible that the inner porous network is exposed after the dissolution of the outer layer of the matrix. The formation of both pores and gel structure on the tablet surface indicates involvement of both erosion and diffusion mechanisms for sustained drug release.

Accelerated stability studies were performed for optimized formulations. No significant change was observed in physical parameters such as weigh uniformity, hardness, friability and drug content. Drug release from the matrix tablets after storage at different conditions remained unaltered and found to be quite stable.

CONCLUSION

Propranolol HCl sustained release matrix tablets were successfully formulated using the combinations of natural gum such as Locust Bean Gum with electrolytes for delivery of drug over an extended period of time. Previous studies have shown that natural gums like xanthan gum, guar gum, Locust Bean Gum and sodium alginate alone in the tablets cannot efficiently control the drug release for prolonged period of time. This study demonstrates that the combination of hydrophilic natural gum and electrolytes with optimum concentrations led to prolonged release of the drug up to 12 hrs. An important feature of this system is the potential for generating constant drug release.

The physical parameters were satisfactory and obtained within IP specified limits. The FT-IR studies revealed the absence of drug-polymer interaction. The optimized formulation was able to control the drug release up to 12 hours. The formulated sustained release tablets can decrease, the frequency of drug administration and it can decrease the plasma drug fluctuation and it can improve the patient compliance. In this study it was also found that the concentration of polymer have also a tremendous effect on drug release rates, by increasing the amount of polymer, drug

release rate can be reduced to a high value. The tablets showed good stability and physicochemical characteristics.

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REFERENCE

[1] Pandit JK, Singh S, Muthu MS. Controlled release formulation in neurology practice. Ann Indian Acad. Neuro. l; 9: 207-16, 2006.

[2] Yeole PG, Galgatte UC, Babla IB, Nakhat PD. Design and evaluation of xanthan gum-based sustained release matrix tablets of diclofenac sodium. Indian Journal of Pharmaceutical Sciences; 68(2). 185-189, 2006.

[3] Varma MV, Kaushal AM, Garg A, Garg S. Factor's affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Drug Deliv; 2: 43-57, 2004.

[4] Selvendran M, Rathnam G. Formulation and evaluation of controlled release matrix tablets of ondansetron hydrochloride. Indian Pharm; 1: 56-9, 2002.

[5] Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech;4:1-6, 2003

[6] Formulation and Evaluation of Matrix Tablets of Propranolol Hydrochloride Having Natural Gums N L Prasanthi, S S Manikiran Martindale, The extra pharmacopoeia, 31st ed., the pharmaceutical press, London 1996, 936-937.

[7] Rekhi GS, Porter SC, Jambhekar SS. Factors affecting the release of propranolol hydrochloride from beads coated with aqueous polymeric dispersions. Drug development and industrial pharmacy. 1995 Jan 1; 21(6): 709-29.

[8] Serlin MJ, Orme ML, MacIver M, Green GJ, Sibeon RG, Breckenridge AM. The pharmacodynamics and pharmacokinetics of conventional and long-acting propranolol in patients with moderate hypertension. British journal of clinical pharmacology. 1983 May 1; 15(5): 519-527.

[9] Prasanthi NL, Manikiran SS. Formulation and Evaluation of Matrix Tablets of Propranolol Hydrochloride Having Natural Gums. Inventi Rapid: Pharm Tech. 2(1): 2011.

[10] Bettini R, Colombo P, Massimo G, Catellani PL, Vitali T. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. European Journal of Pharmaceutical Sciences. Oct 1; 2(3): 213-219; 1994

[11] Afrasim Moin and HG Shivakumar. Formulation of Sustained-Release Diltiazem Matrix Tablets Using Hydrophilic Gum Blends, Tropical Journal of Pharmaceutical Research June; 9 (3): 283-291; 2010.

[12] Zaki, Randa Mohamed, *et al*. "Effect of binary and ternary solid dispersions prepared by fusion method on the dissolution of poorly water soluble diacerein." *International Journal of Drug Delivery*; 5(1): 99-109, 2013.

[13] Saranadasa, H., and K. Krishnamoorthy. "A multivariate test for similarity of two dissolution profiles." *Journal of biopharma-ceutical statistics*; 15(2): 265-278, 2005.