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FORMULATION AND EVALUATION OF *CORDIA DICHOTOMA* FRUIT MUCILAGE AS MATRIX FORMING AGENT FOR SUSTAINED RELEASE OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

The objective of the present study was to design sustained release tablets of Propranolol HCl by direct compression using HPMC K 100 M and *Cordia dichotoma* fruit mucilage. Tablets were prepared by direct compression method and prepared tablets were subjected to physicochemical studies, *in vitro* drug release kinetic studies and stability studies. FTIR studies were shown that, there was no interaction between drug and polymer. The physicochemical properties of tablets were found within the limits. The optimized formulation (F6) was subjected to stability studies for three months at 40 ˚C, RH 75 ± 5 % and showed there were no significant changes in drug content, physicochemical parameters and release pattern. The kinetic treatment of selected formulation (F6) showed that the release of drug follows Higuchi models. The obtained results of the present study indicated that *Cordia dichotoma* fruit mucilage as matrix former in sustained release formulation of Propranolol HCl.

Keywords: Propranolol HCl, Sustained release, HPMC K -100 M, *Cordia dichotoma* fruit mucilage.

INTRODUCTION

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in development a sustained release system [1]. For sustained release systems, the oral route of drug administration has received the most interest as it is natural, uncomplicated, convenient and safer route [2]. Matrix tablets were prepared by direct compression method. The aim of the present work was to prepare sustained release matrix tablets of propranolol hydrochloride and to study the effect of *in vitro* release characteristics, kinetics of the prepared formulations and stability studies. Polysaccharide mucilage derived from the seeds of *Plantago major* L. (family *Plantaginaceae*) was investigated for use in matrix formulations containing propranolol hydrochloride [3]. *Cordia dichotoma* G. Forst fruit mucilage used as a matrix forming agent in design of sustained release matrix tablets of glimepiride [4]. Propranolol Hcl is a sympatholytic non-selective beta blocker. Propranolol is highly lipophilic and almost completely absorbed after oral administration. Peak plasma concentrations occur about 1 to 4 h after an oral dose [5]. Propranolol hydrochloride is a nonselective beta adrenergic blocking agent, used in the treatment of angina pectoris, hypertension and many other cardiovascular disorders [6, 7]. Propranolol has a short half life (3-4 h) and variable bioavailability due to first pass metabolism [8, 9]. Mucilages are composed of heterogenous polysaccharide complexes formed from

the sugars, arabinose, galactose, glucose, mannose, xylose and uronic acid units. Mucilages possess a variety of pharmaceutical properties, which make them useful as additives in pharmaceutical preparations and in present investigations, mucilages plays important role in design of formulations [10, 11]. In this present study, *cordia dichotoma* fruit mucilage as matrix forming agent for sustained release of propranolol hydrochloride and also compared with HPMC K 100 M. Thus, the present study aims to design the sustained release matrix tablets using *Cordia dichotoma* fruit mucilage and HPMC K 100 M along with drug in varying proportions (1:1, 1:2 and 1:3).

MATERIALS AND METHODS

Materials: Propranolol HCl was provided by Dr. Reddy's Laboratories Ltd. (Hyderabad, India). Magnesium stearate was obtained as gift samples from Unichem Laboratories Ltd. (Goa, India). All other reagents and chemicals were of analytical grade.

METHODS

Extraction of mucilage: The plant fruits of *Cordia dichotoma* were collected from surrounding area of Srikakulam, Andhra Pradesh, India. Fresh *Cordia dichotoma* fruits were collected and the seeds were removed prior to extraction process. The fruits were sliced, crushed, homogenized with 5-10 times its weight of water and the clear, viscous solution decanted. The fruit mucilage was precipitated with 3-4 volumes of ethanol and washed with more ethanol followed by acetone. The fruit mucilage so obtained was dried under vacuum. The precipitate was washed 2-3 times with 95% ethanol. After complete washing filtered, dried and powdered, passed through a sieve no.80 and stored in a desiccator till use.

Drug excipient compatibility studies: Infrared (IR) spectroscopy was conducted using a FTIR Spectrophotometer (Perkin-Elmer 841, Model Spectrum One) and the spectrum was recorded in the wavelength region of 4000 to 500 cm^{-1}. The procedure consisted of dispersing a powder (drug alone or mixture of drug and excipients) in KBr and compressed into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Preparation of matrix tablets: The formulations containing propranolol hydrochloride (80 mg), and *Cordia dichotoma* fruit mucilage powder (drug to mucilage ratios 1:1, 1:2 and 1:3) or HPMC K 100 M (drug to polymer ratios 1:1, 1:2,1:3) were thoroughly blended for 15 min. Magnesium stearate (1 %, *m/m*) was then added, followed by further mixing for 5 min. The resultant powder mixture was compressed into tablets using a single punch tableting machine (Korsch, Germany), with a 8 mm diameter flat punch according to the formula given in the **(Table 1).**

Table 1: Various formulations of Propranolol Hcl sustained release tablets

	Formulation ingredients				
Formulation code	**Propranolol Hcl (mg)**	***Cordia dichotoma* fruit mucilage powder**	**HPMC K 100 M**	**Mg-stearate**	**Total weight(mg/tablet)**
F1	80	80	-	1.61	160.50
F2	80	160	-	2.40	242.40
F3	80	240	-	3.21	323.20
F4	80	-	80	1.60	161.60
F5	80	-	160	2.42	242.40
F6	80	-	120	2.00	202.00

Evaluation of tablets

Pre-compression parameters

Angle of repose: The mixture of powder was allowed to flow through the funnel fixed in definite height (h). The angle of repose was then calculated by measuring the height and radius of the pile of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel [12].

θ = tan-1 (h/r),

Where , θ = Angle of repose, h = Height of the pile, r = Radius of the pile

Bulk density: Bulk density (ρb) was determined by pouring pre-sieved bulk powder blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula [13].

ρb= M/Vb

Tapped density: The tapped density was determined by placing a graduated cylinder containing a known mass of powder on mechanical tapping apparatus, which was operated for a fixed number of taps (around 100) until the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was calculated by the formula [14]. **ρt= M/Vt** ,
Where, ρt = Tapped density, M = Weight of powder, Vt= Volume of powder

Hausner's ratio: The Hausner's ratio is an index of ease of powder flow. Lower the value (< 1.25) indicates better flow properties. It was determined by using formula [15].
Hausner's ratio=ρb/ρt,
Where, ρb = Bulk density, ρt = Tapped density

Compressibility index: The compressibility index is a measurement of free property of powder, an indication of the ease with which a material can be induced to flow is given by % compressibility that was calculated as follows [16].
C = (ρt – ρb)/ρt x 100,
Where, ρt = Tapped density, ρb = Bulk density

Post Compression parameters
Weight variation test: Twenty tablets were randomly selected, weighed and from that the average weight was determined by using a weighing balance. Then individual tablets weight was compared with the average weight. As per specifications, not more than two of the individual weights deviate from the average weight by more than the 7.5%.

Hardness: Six tablets were randomly selected from each batch and the hardness of prepared tablets was determined by using the Monsanto Hardness Tester. The mean and standard deviation values for each batch were calculated. The hardness was measured in kg/cm^2.

Friability test: Six tablets from each batch were subjected for friability using Roche fribilator and the fribilator was rotating for 4 min at 25 rpm. The tablets were taken out, de-dusted, reweighed and % friability was calculated by using following formulae:
% Friability = (loss in weight/initial weight) x 100

Content uniformity: The prepared tablet was randomly selected from each batch, weighed individually and powdered. The powder equivalent to 80 mg of Propranolol Hydrochloride was weighed and dissolved in 100 ml phosphate buffer solutions (pH 6.8), to obtain the stock solution. From this stock solution, suitable dilution was prepared and analyzed using previously validated UV method at 290 nm.

***In vitro* dissolution studies:** *In vitro* dissolution studies of Propranolol Hydrochloride was determined using USP (XXI) six stage dissolution rate test apparatus I (Labindia) at 50 rpm. The dissolution rate was studied using 900 ml of pH 6.8 phosphate buffer. The temperature was maintained at 37± 0.2 ˚C. Samples of 5 ml each were withdrawn at different time intervals, filtered through whatman filter paper and replaced with an equal amount of fresh dissolution medium. Samples were diluted and analyzed for propranolol hydrochloride content using double beam UV/Visible spectrophotometer (UV-2450-Shimadzu Japan) at 290 nm. The release studies were conducted in triplicate.

Kinetic treatment of dissolution data: The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem .The dissolution data obtained was fitted to zero order, first order, Higuchi, erosion and exponential equation to understand the order and mechanism of drug release from the beads.

Zero order release kinetics: It defines a linear relationship between the fraction of drug released versus time.
$\mathbf{Q = k_o t}$
where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics: Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is
$\mathbf{\ln (1-Q) = -k_1 t}$
where, Q is the fraction of drug released at time, (t) and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.
$\mathbf{Q = k_2 t^{1/2}}$
where, k_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.

Erosion equation: This equation defines the drug release based on erosion alone.

$$Q = 1-(1-k_3t)^3$$

where, Q is the fraction of drug released at time t, k_3 is the release rate constant. Thus, a plot between $[1-(1-Q)^{1/3}]$ against time will be linear if the release obeys erosion equation.

Stability studies: Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F6), by keeping at 40°± 2 ˚C, in air tight high density polyethylene bottles for three months, at RH 75 ± 5 %. Physical evaluation and *in vitro* drug release was carried out in each month.

***In vitro* drug release study:** The release profile of Propranolol hydrochloride from different batches of formulated matrix tablets were plotted in **(Figure. 2)**. When increases drug to polymer ratio, the rate of drug release is slow.

RESULTS AND DISCUSSION

Pre formulation studies: The results of pre-compression studies were in the acceptable range as per the specification. The results of angle of repose, tapped density, bulk density, hausner's ratio and compressibility are shown in the **(Table 2)**, which indicates that the flow property of powder was good.

Table 2: Pre compression parameters results

Formulation	Bulk density	Tapped density	Hausner's ratio	Compressibility index	Angle of repose (θ)
F1	0.46±0.04	0.53±0.02	0.867±0.03	13.2±0.08	26±0.12
F2	0.48±0.04	0.51±0.04	0.941±0.02	5.88±0.09	29±0.42
F3	0.43±0.02	0.51±0.02	0.843±0.03	15.68±0.07	30±0.29
F4	0.42±0.03	0.52±0.03	0.807±0.04	19.23±0.03	27±0.11
F5	0.46±0.02	0.54±0.02	0.851±0.01	14.81±0.05	28±0.10
F6	0.47±0.01	0.52±0.05	0.903±0.02	9.61±0.03	27±0.32

Drug excipient compatibility studies

Drug excipient compatibility studies were carried out by IR spectrophotometer. The IR spectra of pure Propranolol Hydrochloride and its polymers were shown there was no interaction between drug and polymer. The spectra of prepared optimized tablet and the physical mixture were compared with the spectra of pure drug **(Figure 1)**.

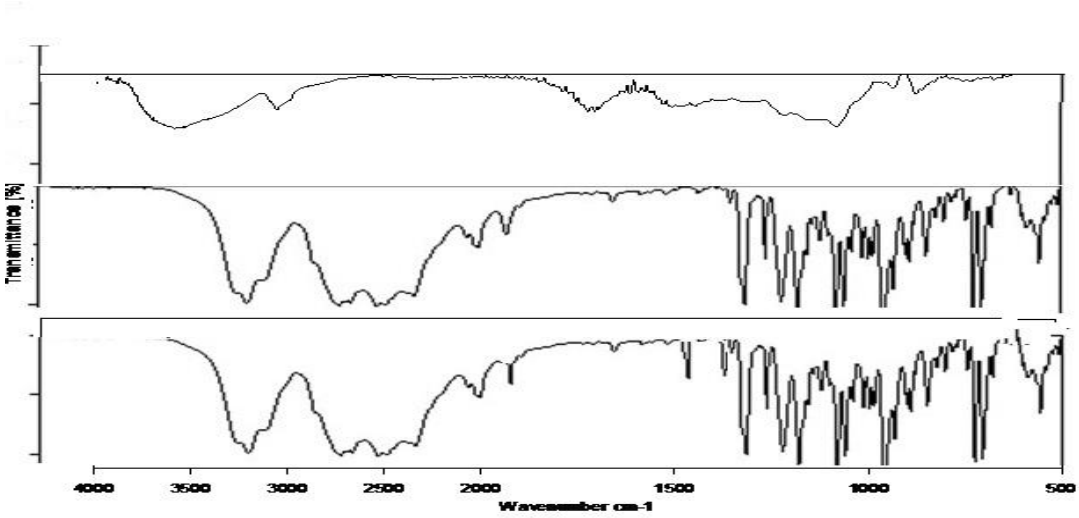

Figure 1: FT-IR studies of a) *Cordia dichotoma* fruit mucilage powder ; b) Propanolol HCl; c)F6 formulation.

Post compression evaluation study: The values of weight variation, friability, hardness and content uniformity are shown in the **(Table 3)**.The results of post-compression parameters were in the acceptable range as per pharmacopoeia specified.

Table 3: Evaluation of Propranolol sustained release matrix tablets

	Tableting Characteristics of propranolol HCl Sustained release tablets				
Formulation code	**Weight variation (mg)**	**Hardness (kg/cm^2)**	**Friability(%)**	**Tensile strength (N/m^2)**	**Content uniformity(%)**
F1	160±1.77	3.32 ± 0.24	0.95 ± 0.06	0.51 ± 0.06	101.09 ± 2.14
F2	242±1.43	4.78 ± 0.23	0.76 ± 0.05	0.58 ± 0.06	98.94 ± 3.17
F3	323±1.09	4.82 ± 0.31	0.52 ± 0.05	0.62 ± 0.07	99.34 ± 2.47
F4	161±1.52	5.19 ± 0.34	0.87 ± 0.07	0.67 ± 0.06	98.71 ± 3.04
F5	242±0.97	5.31 ± 0.34	0.75 ± 0.06	0.71 ± 0.05	100.78 ± 2.95
F6	202±0.57	5.34 ± 0.34	0.42 ± 0.05	0.67 ± 0.06	99.34 ± 2.47

Effect of hardness on dissolution rate: The rate of drug release in case of hardness 4-5 kg/cm^2 is slow, in comparison to that of 3-4 kg/cm^2 hardness.

Stability studies: The results of accelerated stability studies carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period.

Study of drug release kinetics mechanism of drug release: The *in vitro* drug release of F6 was best explained by Higuchi's equation, as the plots showed the highest linearity (r^2 =0.999). The drug release significantly follows Higuchi model for formulation F6. When comparison with HPMC K 100 M, the present study was an attempt to design of *Cordia dichotoma* fruit mucilage as matrix forming agent. The present work to be possessed that comparison of *Cordia dichotoma* fruit mucilage as matrix forming agent with HPMC K 100 M. Propanolol HCl used as a model drug for the design of sustained release matrix tablet, by using *Cordia dichotoma* fruit mucilage as matrix forming agent.

Table 3: r^2 values of various formulations

	R^2 values of various formulations (F1-F6)			
Formualtion code	**Zero-order model**	**First-order model**	**Higuchi model**	**Peppas model**
F1	0.925	0.967	0.979	0.988
F2	0.988	0.847	0.984	0.974
F3	0.989	0.853	0.991	0.981
F4	0.984	0.964	0.995	0.989
F5	0.974	0.988	0.996	0.991
F6	0.987	0.989	0.999	0.99

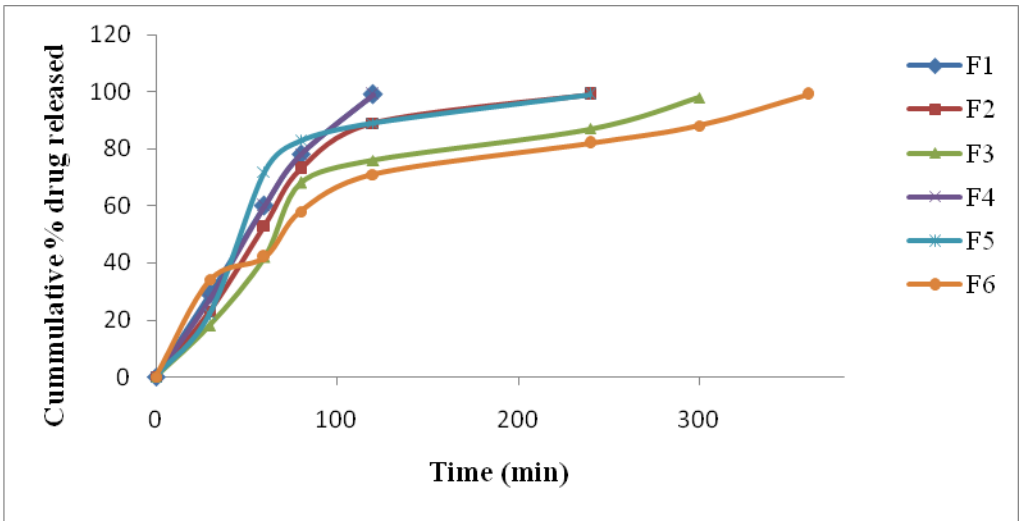

Figure 2: Comparative dissolution profiles for various formulations F1-F6

CONCLUSION

Thus, the present study can be concluded that undertaken with the aim to formulation and evaluation of Propranolol HCl sustained release tablet using HPMC grade of polymer as retarding agent. It is concluded that *Cordia dichotoma* fruit mucilage as matrix forming agent.

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