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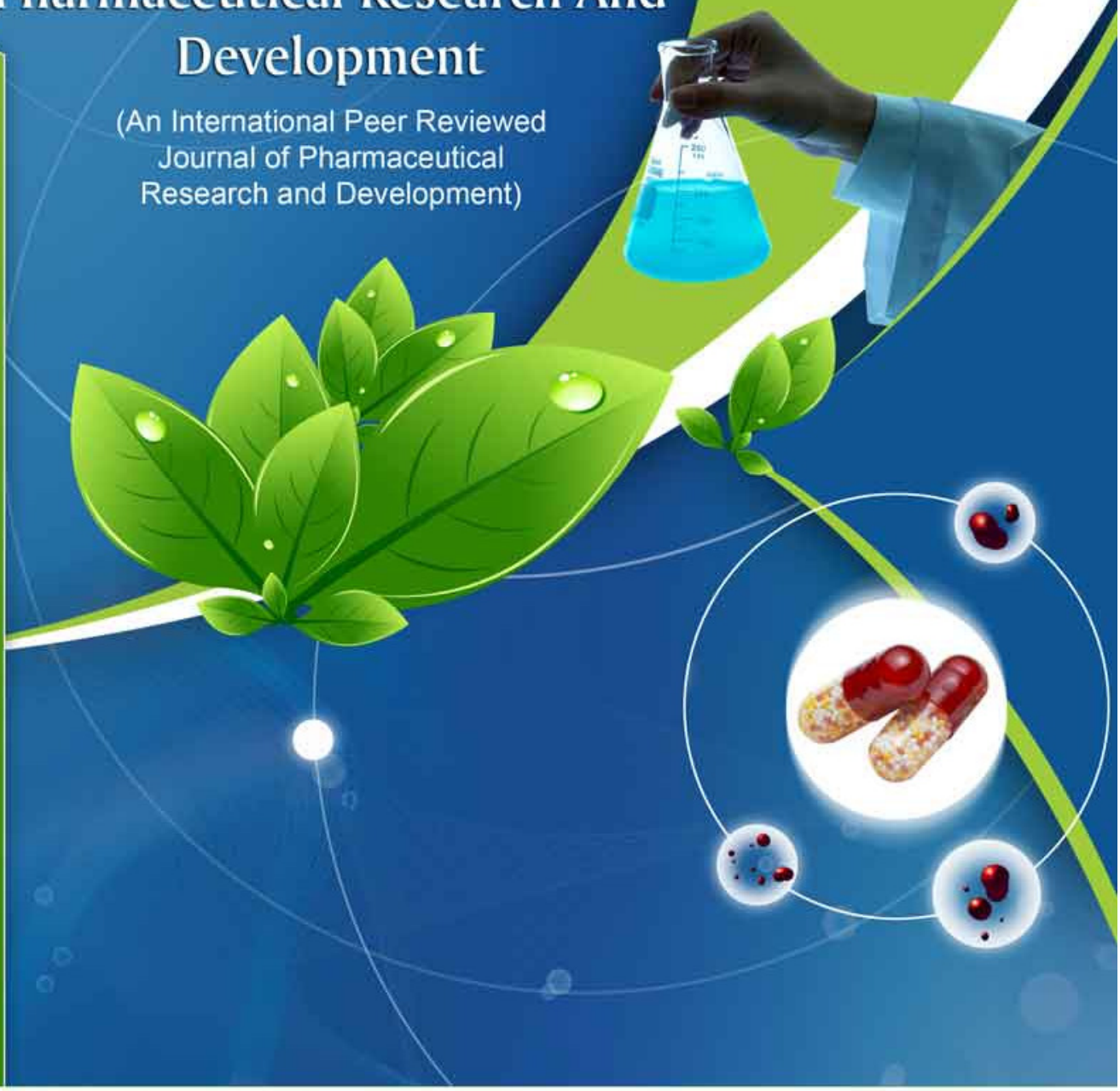

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Research Article

DESIGN AND EVALUATION OF SUSTAINED RELEASE FORMULATIONS OF THEOPHYLLINE USING NATURAL POLYMERS

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ABSTRACT

Theophylline has high oral bioavailability and narrow therapeutic index with a biological half-life of 3-4 hrs. Prolonged release dosage forms are designed to complement the pharmacological activity of the medicament in order to achieve the longer duration of action with decreased number of doses administered per day. Matrix tablets were designed using Karaya gum, Guargum and kondagogu gum as sustained release polymers. Wet granulation was employed with 1:1 drug, polymer ratio. The tablets were evaluated for uniformity of weight, hardness friability, swelling index, % drug content, drug dissolution, drug release kinetics and compared. F-2 was found to be better in terms of prolonging the drug release and all the other formulations met the pharmacopoeial requirements for physical tests.

KEY WORDS: *Theophylline, Sustained release, Guar gum, Kondagogu gum, Karaya gum.*

INTRODUCTION

Oral slow and sustained release drug delivery system can release their drug content with a controlled manner producing a desirable blood serum level, reducing drug toxicity and improving patient compliance by prolonging dosing interval [1, 2]. The oral route is the most common route of drug administration because of its advantages in terms of convenient administration, thus leading to increased patient compliance. Extended release formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration [3]. Matrix systems composed of polymers and other excipients as vehicles for drug delivery are extremely popular in sustaining release rate [4]. Hydrophobic materials for an insoluble matrix carrier and water-soluble hydrophilic materials have been reported as the most commonly used matrix carriers [5]. These are prepared by either wet granulation or direct compression method. Theophylline is a methylxanthine derivative and it is very effective in the chronic treatment of bronchial asthma and bronchospastic reaction. It has a biological half life of 3-4 hrs and its therapeutic concentration range is narrow (from 10 to 20 µg/mL) while toxicity usually appear at concentration above 20 µg/mL and the fluctuations of its serum concentrations can result in variability in clinical response.

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Therefore, there is an obvious need for sustained release dosage form which will be able to maintain therapeutic serum levels of theophylline throughout 24h using once or twice administered dose daily [6, 7]. The main aim of the study was to formulate therapeutic sustained release matrix tablets using natural polymer like guar gum, kondagogu gum and karaya gum.

EXPERIMENTAL MATERIALS

Theophylline and guar gum were procured from (NATCO Pharma Pvt. Ltd, Kothur). Karaya gum and kondagogu gum from Girijan co-operative corporation Ltd, Visakhapatnam. Isoprophyl alcohol, talc and magnesium stearate were obtained from (S.d.fine-chem.Pvt; Ltd, Mumbai). All other chemicals used were of analytical grade.

METHOD OF PREPARATION OF THEOPHYLLINE TABLETS

All the formulations were prepared according to the composition showed in Table-1. Theophylline and polymer were triturated well and moistened with Isopropyl alcohol and water mixture in the ratio of 1:1 to form a damp mass. The damp mass is passed through sieve no # 12 to obtain granules. The granules thus obtained were dried at 40^{O} C. The dried granules were sieved through sieve no # 16 and lubricated with talc and magnesium stearate. The granules were compressed by employing 12 mm round shaped die with Cadmach CMS 25 tabletting machine to get tablets of average weight 848 mg.

Table-1: Formulation design of sustained release Theophylline matrix tablets

S. No.	*Ingredients*	*F-1 (mg)*	*F-2 (mg)*	*F-3 (mg)*
1.	Theophylline	400	400	400
2.	Karaya gum	400	-	-
3.	Guar gum	-	400	-
4.	Kondagogu gum	-	-	400
5.	PVP	40	40	40
6.	Talc	4	4	4
7.	Magnesium stearate	4	4	4
Total Weight		848	848	848

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical characteristics.

***General Appearance*:**

The formulated tablets and sintered tablets were assessed for its general appearance. [8]

Weight Variation:

Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

% Weight variation= (Average weight-intial weight/average weight) x 100

Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed 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. [9]

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} X100$$

***Drug Content for Theophylline*:**

Twenty tablets of each formulation were collected and powdered. Powder equivalent to 0.25 g of Theophylline was weighed. 50 ml of water was added and gently warmed the mixture on a water-bath until complete solution is affected. Diluted a suitable volume with sufficient 0.1 M sodium hydroxide and the absorbance was measured by using Shimadzu Double Beam Spectrophotometer (UV - 1700) at 272 nm.

In vitro Dissolution Studies for Theophylline Tablets:

The *in vitro* dissolution rate studies were conducted for all the Theophylline tablets formulations using USP dissolution apparatus 2 (basket TDT - 08L, Electrolab, Mumbai). Dissolution test was carried out for a period of 24 hrs using 0.1N HCl (900 ml) as dissolution media for the first 1 hr and pH 6.8 phosphate buffer for the rest of the period. At appropriate time intervals 5 ml samples were withdrawn and replaced with the same volume of dissolution medium. The absorbances of these samples were measured at 272 nm against blank using Shimadzu (UV - 1700) double beam spectrophotometer to determine the amount of the drug released from the tablets.

RESULTS AND DISCUSSIONS

Polymers like Gum karaya, Gum kondagogu, Guar gum were used. The tablets were subjected to various quality control tests and the results are expressed in Table-2. All the formulated tablets were complained Pharmacopeial standards. Dissolution studies on these tablets were conducted by using 0.1N HCl for first hour, followed by 6.8 P^H phosphate buffer for subsequent time. The dissolution data was shown in Table-3. The graphs drawn between the amount of drug released versus time were found to be linear for F-1 and F-3, hence it was concluded that the formulation followed zero order kinetics as shown in Fig-2. However the formulation prepared with Guar gum follows first order kinetics as shown in Fig-3. The mechanism of drug release was found to be Non-Fickian diffusion as exponential coefficient value was found to be in between 0.5 - 1. Various in-vitro release parameters were computed from the dissolution data and depicted in Table 4.

Table-2: Physical Properties of the Theophylline Tablets Formulated With Various natural Polymers

Formula	*Avg. weight*	*% Drug content*	*Hardness kg/cm*	*% Friability*	*Swelling index*
F-1	845.7±0.89	100.89±0.98	4.02±0.98	0.37±0.062	62.88±0.032
F-2	840.2±0.93	101.26±0.94	4.20±0.96	0.38±0.021	73.19±0.045
F-3	846.32±0.56	99.43±0.65	4.42±0.21	0.66±0.033	65.48±0.09

Table-3: Dissolution data of Theophylline sustained release tablets formulated with various polymers

S. No	Time (in hrs.)	F-1	F-2	F-3
1.	1	23.78±0.59	12.67±0.26	20.87±0.45
2.	2	47.98±0.28	28.76±0.37	41.54±0.83
3.	3	67.98±0.17	42.64±0.56	60.54±0.74
4.	4	86.76±0.67	55.83±0.89	82.76±0.43
5.	5	100.80±0.73	66.59±0.73	98.98±0.31
6.	6	-	75.76±0.38	-
7.	8	-	86.45±0.63	-
8.	10	-	95.54±0.28	-
9.	12	-	99.76±0.69	-

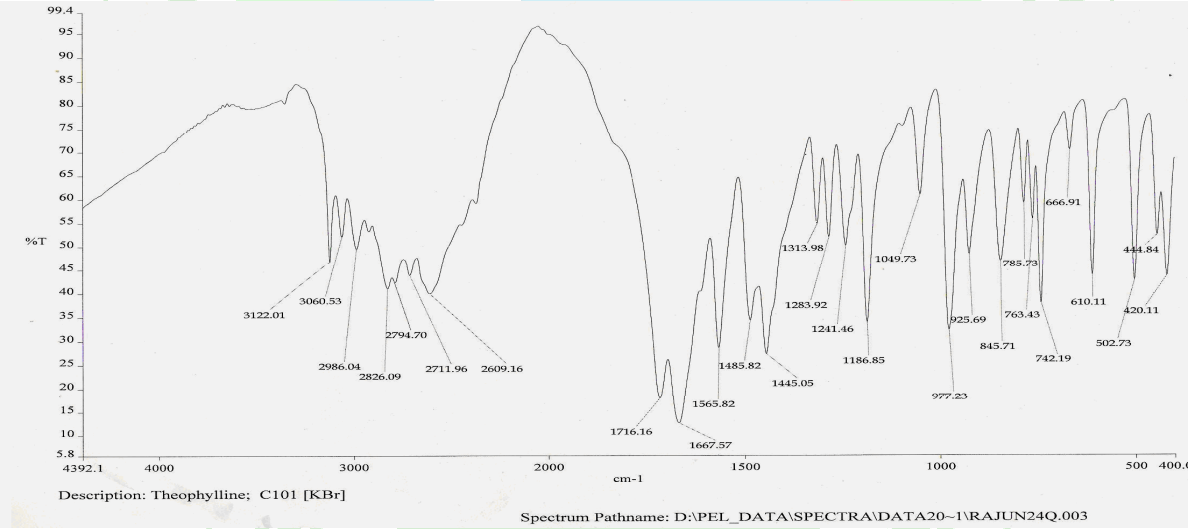

Figure-1: IR studies of Theophyllline

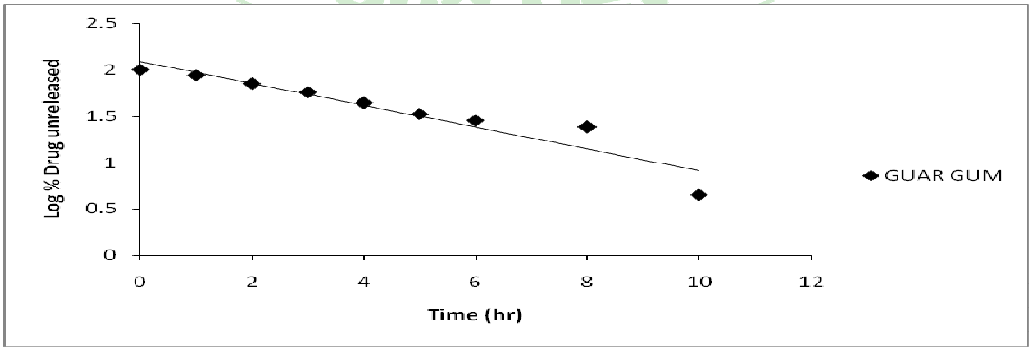

Figure-2: First order release plot of Theophylline sustained release tablet formulated with Guar gum

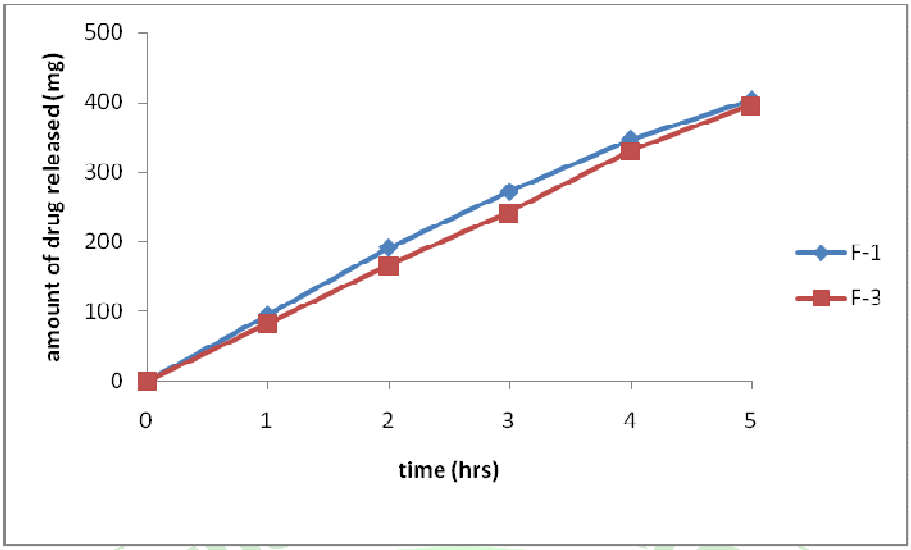

Figure-3: Comparative Zero order profiles of Theophylline sustained release tablets formulated with karaya gum (F-1) and kondagogu gum (F-3)

Table-4: In vitro release kinetics of Theophylline sustained release tablets formulated with various polymers

Formula	*Correlation coefficient*				*Release rate*			
	Zero order	*First order*	*Higguchi*	*Peppas*	*K mg/hr*	*T_{50} Hr*	*T_{90} hr*	*Exponential coefficient (n)*
F-1	0.9990	0.9562	0.9571	0.9993	86.39	2.31	4.16	0.9652
F-2	0.9840	0.9946	0.9565	0.9710	0.270	2.566	8.52	0.6956
F-3	0.9989	0.9044	0.9484	0.9995	79.95	2.50	4.50	0.9646

CONCLUSION

Sustained release Theophylline matrix tablets were prepared by employing three different natural polymers i. e Karaya gum, guar gum, kondagogu gum by wet granulation method and the release rate was found to be influenced by the nature of the polymer employed. Based on the release rate suitability of the polymer for extended release can be rated as follows Gum karaya < Gum kondagogu < Guar gum.

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