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EXTENDED RELEASE FORMULATION OF THEOPHYLLINE USING MODIFIED FENUGREEK GUM AS A HYDROPHILIC POLYMER

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ABSTRACT: The aim of current research work was to develop sustain release formulation of Theophylline. Modified plant derived Fenugreek gum (FG) polymer was synthesized and used as matrix forming agent. Matrix tablet formulations were prepare by wet granulation technique using modified fenugreek gum in different concentration. The prepared formulations were evaluated for physical properties such as tablet hardness, weight variation, drug content and *In vitro* drug release. Formulation prepared with drug: polymer weight ratio of 1:2 showed desired release profile as per USP specification. FTIR study showed absence of chemical interaction between drug and polymer. The optimized formulation was found to show stability for two month as per ICH guideline. Study suggested that modified fenugreek gum can be used as extended release polymer.

INTRODUCTION: Sustain release formulation generally preferred over conventional dosage form to achieve constant therapeutic response for extended period of time. The major advantages of such type of formulation is reduced frequency of administration, maintained plasma drug level, devoid of dose dumping effect and reduced side effects [1].

In oral drug delivery system hydrophilic matrices have been used since long time to control the drug release. A number of natural and modified polysaccharides have been used in controlled release formulation by various researcher, includes xanthan gum, guar gum, locust bean gum and khaya gum [2, 3, 4, 5].

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Hydrophilic and gelling properties of these natural polymers play the major role in controlling the drug release for the extended period of time. They are also associated with advantages such as biocompatible, inexpensive and easily availability.

Theophylline is a non-specific adenosine antagonist having methylxanthine as its back bone structure. Its bronchodilating property causes relaxation and opening of air passages to the lungs which makes breathing easy. Theophylline is mainly used in form of slow release solid oral dosage form and due to narrow therapeutic index it requires regular monitoring of serum Theophylline concentrations to avoid adverse effects [6, 7]. Generally hydrophilic polymer is always opted for preparation of controlled release formulation of poorly water soluble drug.

In this work fenugreek gum (*Trigonella Foenum-graceum)*, an herbaceous plant of the leguminous family was used as extended release polymer in modified release matrices.

It is one of the oldest cultivated plants and has wide range of applications as food additive and medicinal application [8, 9].

Pharmaceutically fenugreek gum has been explored as binder [10], disintegrant [11], solubility enhancer [12], emulsifier [13] and oral controlled release formulation [14].

Thus, the main of current work was to develop extended release formulation of Theophylline using modified fenugreek gum for better therapeutic response. Hydroxy propyl methyl cellulose (Methocel® K4M) was used as control polymer. Modified octenyl succinate derivative of fenugreek gum was synthesized and characterized as per our previous reported method and used as extended release polymer in Theophylline formulation.

MATERIALS AND METHODS: Fenugreek gum (Canafen®) was obtained as a gift sample from Emerald Seed Products Ltd., (Avonlea Saskatechewan, Canada). Sodium bicarbonate was purchased from S.D. fine Chem-limited (Mumbai, India), Mumbai, India. Theophyllinee IP was procured as gift sample from Bajaj Healthcare Ltd, Mumbai, India. Hydroxyl propyl methyl cellulose (Methocel® K4M) were procured from the Dow Chemical Co., USA. Other ingredients and excipients used were of analytical grade.

Synthesis of Modified Fenugreek gum: Modification was carried as per reported method [15]. In brief, fenugreek gum sample (1.5 g) and solid $NaHCO_3$ (3 g) was surface wetted with absolute ethanol (99 %, 2 ml) and mixed well. Reagent octenyl succinic anhydride (5 ml) was added drop wise and mixed well to give homogenous mixture. This reaction mixture was allowed to react for 2h at 98°C. After completion of reaction, pH of reaction mixture was adjusted to 7. Finally sample was washed with 75% ethanol followed by absolute ethanol and dried in oven at 60°C for 4h.

Characterization of Modified Fenugreek gum:

1. **Fourier transforms infrared spectroscopy (FTIR):** FTIR study was performed to investigate the change in chemical structure of Fenugreek. FTIR spectra were recorded for both native FG as well as modified FG. FTIR spectra of samples were recorded using PERKIN ELMER FTIR Spectrophotometer (Spectrum RX1, USA). A disk of sample and KBr was prepared under hydrostatic pressure and scanned between 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

2. **Differential scanning calorimetric (DSC):** DSC study was carried out to investigate change in thermal behavior of modfified gum with reference to plain FG. DSC instrument made from PERKIN ELMER DSC Pyris-6 (USA) was used for the study. Samples were heated in an open aluminum pan at a rate of 10 °C / min within a 30 to 350 °C temperature range under a nitrogen flow of 20 ml/min.

3. **Scanning electron microscopy (SEM):** Morphological evaluation of gum and modified gum was performed by using JSM-6380 LA scanning electron microscope (ZEOL Ltd., Tokyo, Japan).

Drug-Excipients Interaction:

1. **FTIR spectroscopy:** To investigate the drug and excipients interaction, FTIR study was performed. FTIR spectra for drug and drug excipients mixture was recorded by following same method as described in earlier section.

2. **Preparation of extended release Theophylline matrix tablet:** Extended release matrix tablets, each containing 200mg drug was prepared by wet granulation technique as Theophylline has poor flow and compressibility problem. The compositions for different formulation batches are given in **Table 1**. Polymer concentration was selected in with respect drug in weight ratio.

   All the ingredients weighed accurately, passed through 40 mesh and mixed in geometric order. Mixing was continued for 10 min to achieve uniform mixing. Then the mixture was granulated with PVP K90 as granulating agent and isopropyl alcohol as a granulating vehicle. The obtained wet mass was sieved through 60 mesh and dried at 60°C for 4h. Dried granules was mixed with lubricant in a blender for 5 min and subjected

for compression into a tablet. Tablet was prepared on single punch tableting machine (Cadmach machinery Co. Pvt. Ahmedabad, India) using standard die and punches depending upon total weight of tablet. All the tablet formulations were stored in air tight container till further use.

TABLE 1: THEOPHYLLINE FORMULATION COMPOSITIONS

Ingredients	F1	F2	F3	F4	F5	F6	F7
Theophylline	200	200	200	200	200	200	200
Modified FG	100	200	400	-	-	-	
HPMC K4M	-	-	-	50	100	150	200
PVP-K90	20	20	20	20	20	20	20
Avicel (PH 101)	26	26	26	26	26	26	26
Magnesium stearate	4	4	4	4	4	4	4
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s
Total weight (mg)	350	450	650	300	350	400	450

Physical characteristics:

1. **Evaluation of powder blends:** The powder blends were evaluated for physical properties like flow in terms of angle of repose, bulk density, tapped bulk density, compressibility [16]. Angle of repose was determined by fixed funnel method. Bulk and tapped density was determined by cylinder method (Veego, India) and for Carr's Index (CI) value following equation was used:

Carr's Index = tapped bulk density-loose bulk densityx100/tapped bulk density

2. **Evaluation of Tablets:** The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation, friability and drug content. For hardness testing, Monsanto hardness tester and for friability, Roche friabilator (Campbell Electronics, Mumbai, India) was used to determine the value. Vernier calliper was used to measure the thickness of the tablets. Weight variation was performed as per official method [17].

3. ***In vitro* drug release:** *In vitro* drug release of Theophyllinee anhydrous was performed using a USP dissolution test apparatus II (paddles) with stirring speed of 100 rpm using 1000 ml pH 6.6 Phosphate buffer as dissolution medium. Temperature was maintained at 37±0.5°C. At time interval of 1, 2, 4, 5 and 8h an aliquot of 10 ml was withdrawn and replaced with same amount of fresh media. withdrawn sample was filtered through 0.45 µm filter paper and analysed for drug release using UV-Visible spectrophotometer 1600 (Shimadzu) at 273 nm respectively.

4. **Kinetic analysis of release data:** To analyze the mechanism of drug release from different batches, the obtained dissolution data was fitted to various release kinetic model such as Zero order, First order, Higuchi, Hixon-Crowell and Korsemeyer-Peppas equations. Drug release mechanism was predicted based on the correlation coefficients (r^2) values calculated form best suited for a particular model [18].

5. **Stability study:** The optimized formulation (F3 and F7) was packed in high density polyethylene bottle and subjected to stability studies at 40 °C± 2 °C/75±5% RH. Sample was withdrawn at predetermined time intervals of 0, 30 and 60 days and evaluated for the different physicochemical parameters i.e. appearance, average weight, thickness, hardness, friability, drug content and in vitro release.

RESULTS AND DISCUSSION:

Characterizations of synthesized modified fenugreek gum:

1. **FTIR:** An FTIR spectrum is better tool to indentify the modification in chemical structure. The absorption band at 1734 cm^{-1} (1730–1750 cm-1) for –C=O functional

group indicates the esterification of native fenugreek gum. A peak at 1568 cm^{-1} ascribing the asymmetry stretching of $RCOO^-$ indicates that derivative product was present as fenugreek sodium octenyl succinate (fig.1). Absence of peaks in the region 1850–1750 cm^{-1} indicated that the product is free of unreacted anhydrides and their byproducts.

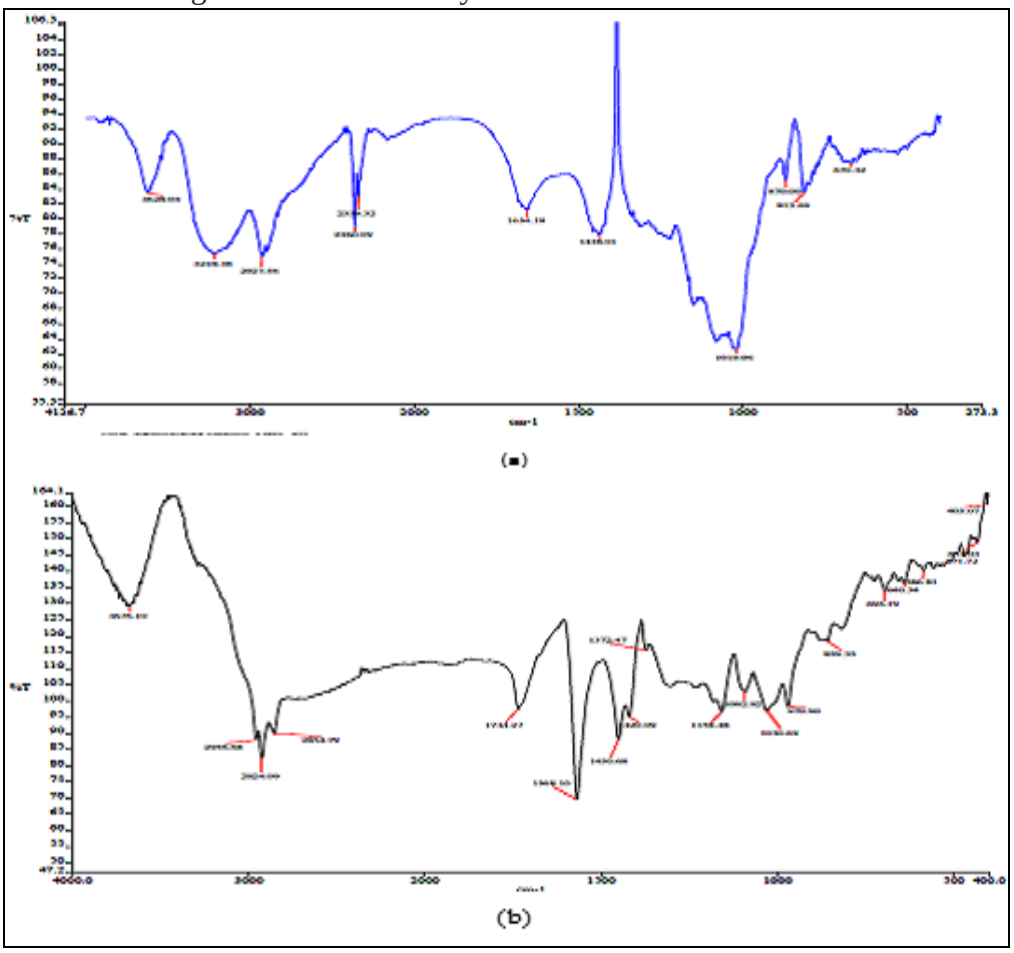
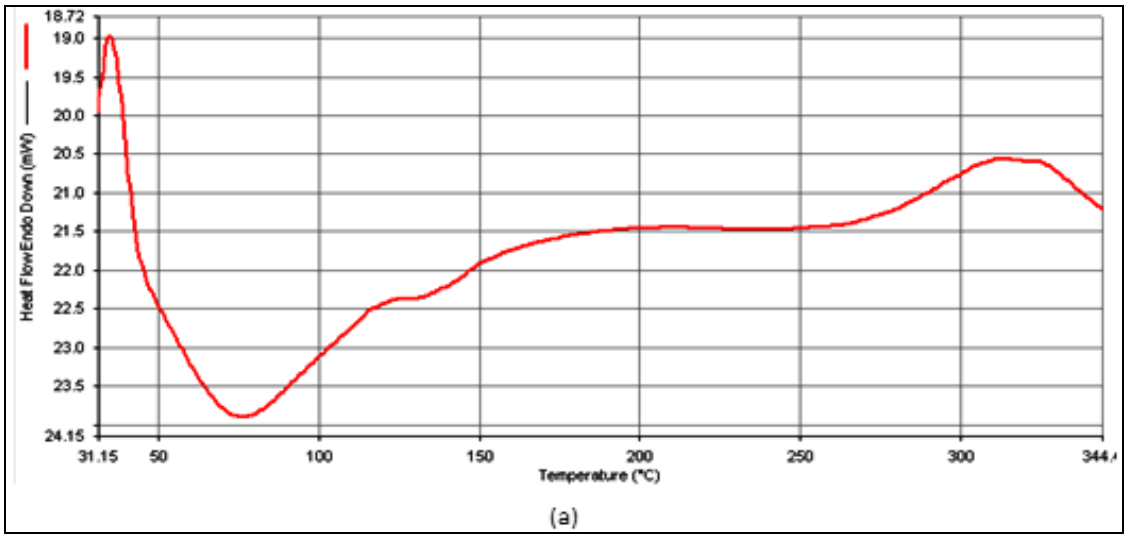


FIGURE 1: FTIR SPECTRA OF (A) NATIVE FG AND (B) MODIFIED FG

DSC: A sharp endothermic peak was found at 182 $^{\circ}C$ for modified fenugreek gum which was absent in native fenugreek (**fig. 2**). This endothermic peak was due to melting of succinic acid anhydride group which indicates substitution of hydrophobic group on native fenugreek gum.



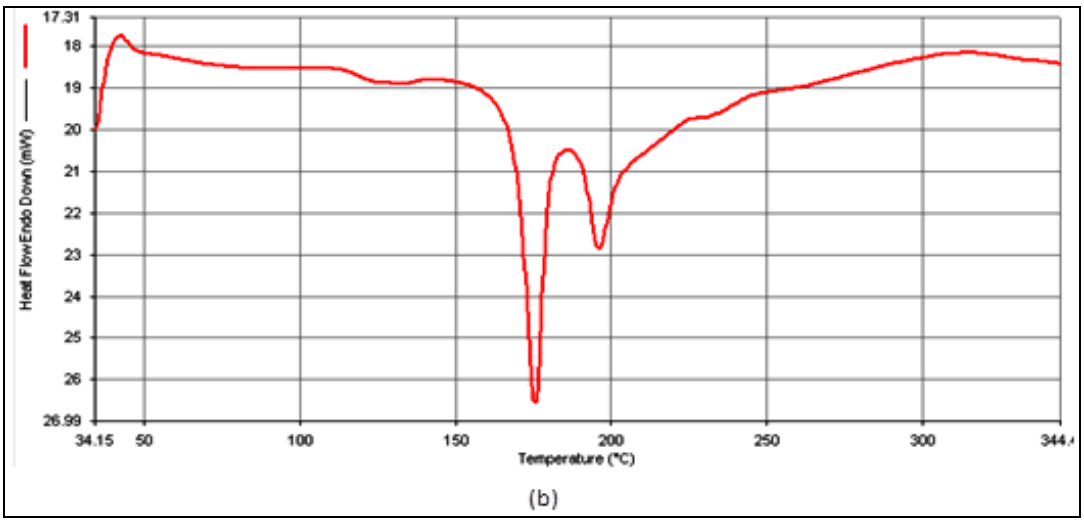
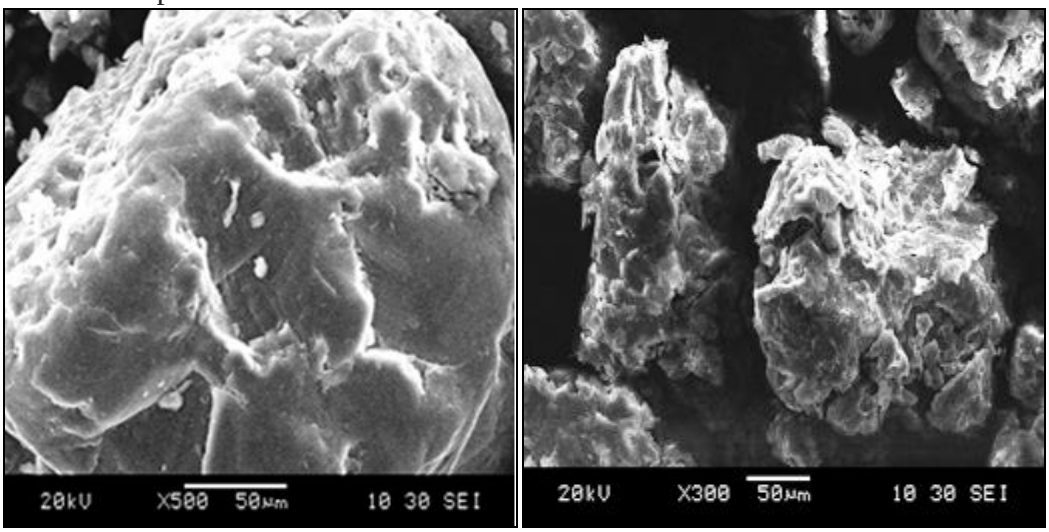


FIGURE 2: DSC THERMOGRAM OF (A) NATIVE FG AND (B) MODIFIED FG

SEM: The morphological change in modified Fenugreek gum was compared with native FG and shown in **fig. 3**. Native FG particles present as irregular size and shape with smooth surface whereas surface of modified fenugreek was found to be rough as compared to native FG indicate that surface modification after derivatization process.



A **B**

FIGURE 3: DSC THERMOGRAM OF (A) NATIVE FG AND (B) MODIFIED FG

Drug excipient interactions: FTIR study of drug and formulation mixture indicated absence of chemical interaction between drug and excipients. Study revealed presence all the major functional group of Theophylline.

Evaluation of Powder blends and Tablet formulations: Theophylline is associated with poor flow and compressibility property. All the formulation mixture showed improvement in flow property as the angle of repose values was found to be less than 30^{θ} (**Table 2**). Compressibility was also improved as Carr's index values were found between 5-15% which indicates excellent compressibility. The prepared tablet has good mechanical property in terms of hardness and friability (**Table 3**).

***In vitro* drug release:** Matrix tablets were prepared in different drug and polymer weight ratio (1:0.5-1:2) to achieve the desire drug release profile. Matrix tablet prepared from modified fenugreek gum level at 1:0.5 (F1) and 1:1 (F2) showed 30-40% drug release in first hour and more than 90% drug released in 5h. Polymer level was further increased to double the amount of drug (F3) and dissolution study was carried out. In this case also drug release was faster but the release pattern followed the upper limit release profile as specified in USP pharmacopoeia (**fig. 4**).

TABLE 2: PHYSICAL CHARACTERISTICS OF THEOPHYLLINE FORMULATIONS POWDER MIXTURE

Batch code	Bulk density (gm/cc)	Tap density (gm/cc)	Carr's index (%)	Angle of repose (θ)
F1	0.435	0.465	6.45	15.55
F2	0.423	0.454	6.82	17.23
F3	0.510	0.54	6.29	16.45
F4	0.523	0.553	5.42	15.54
F5	0.55	0.585	5.98	11.34
F6	0.540	0.576	6.25	14.34
F7	0.512	0.545	6.05	12.42

TABLE 3: PHYSICAL CHARACTERISTICS OF THEOPHYLLINE TABLET FORMULATIONS

Batch code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability
F1	350±2.5	3.03±0.05	5-6	0.54
F2	449±2.8	3.13±0.03	6-7	0.46
F3	652±2.3	3.23±0.05	7-8	0.34
F4	298±2.4	2.98±0.032	5-6	0.45
F5	347±2.4	3.1±0.05	7-8	0.34
F6	401±2.5	3.1±0.1	7-8	0.32
F7	450±1.5	3.21±0.25	7-8	0.31

Modified fenugreek gum has both hydrophilic and hydrophobic property therefore it was able to control the release of poorly soluble drug by preventing its diffusion through hydrophilic gel barrier. Similarly, batches taken with Methocel® K4M in 1:0.25 (F4) and 1:0.5 (F5) drug: polymer ratio showed about 40% drug release in first hour and more than 80% drug released in 5h. Formulation F6 showed retarded drug release as compared to earlier Methocel® K4M batches but release was as not as per specification. Formulation F7 prepared with high amount of Methocel® K4M showed the desired release profile (**Fig. 5**). Methocel® K4M has higher gelling property as compared to modified fenugreek gum therefore it showed better control over drug release and required in low amount to sustain the drug release. Formulation batched F3 and F7 kept for stability study showed similar release profile as day one. Based on correlation coefficient values (r^2) as indicated in **Table 4**, optimized formulation showed zero order drug release suggesting that release was independent of drug concentration.

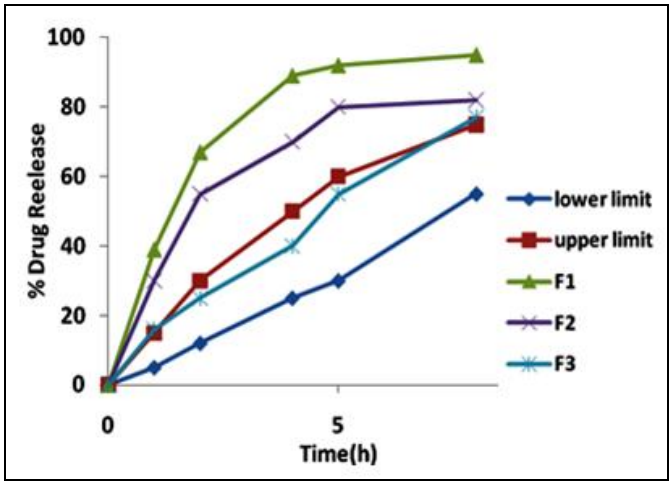


FIGURE 4: DISSOLUTION PROFILE OF THEOPHYLLINE FORMULATION PREPARED USING MODIFIED FENUGREEK GUM

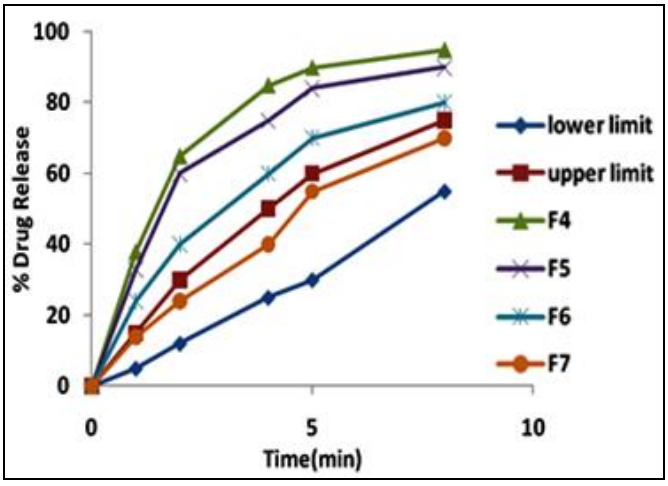


FIGURE 5: DISSOLUTION PROFILE OF THEOPHYLLINE FORMULATION PREPARED USING METHOCEL® K4M

TABLE 4: *IN VITRO* RELEASE KINETIC PARAMETERS

Formulation	Zero order		First order		Higuchi		Hixon-Crowell		Korsemeyer-Peppas	
	r^2	K	r^2	k	r^2	k	r^2	k	r^2	k
F1	0.942	15.51	0.997	1.993	0.967	6.23	0.988	1.83	0.990	0.650
F2	0.955	11.27	0.992	1.976	0.976	3.22	0.984	2.66	0.970	1.51
F3	0.990	10.15	0.986	2.00	0.972	7.13	0.989	4.88	0.938	2.21
F4	0.942	15.02	0.998	1.98	0.974	5.39	0.988	1.99	0.974	0.937
F5	0.946	12.97	0.992	1.97	0.980	3.57	0.983	2.33	0.986	0.606
F6	0.982	13.27	0.998	1.99	0.993	3.23	0.996	3.56	0.991	1.94
F7	0.994	10.33	0.987	2.02	0.976	6.47	0.991	4.41	0.976	3.32

CONCLUSION: Extended release formulation of Theophylline was successfully developed using modified fenugreek and Methocel® K4M. The modified fenugreek gum has potential to act as sustain release polymer.

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