Original Article

FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLET USING NATURAL TREE GUMS

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ABSTRACT

Objective: To develop a novel colon targeted tablet formulation using natural polysaccharides such as kondagogu gum and ghatti gum as carriers and diltiazem hydrochloride as a model drug.

Methods: The polymer-drug tablets were prepared by wet granulation technique, coated with two layers viz., inulin as an inner coat followed by shellac as outer coat and evaluated for properties such as average weight, hardness and coat thickness. *In vitro* release studies of prepared tablets were carried out for 2 h in pH 1.2 HCl buffer, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid (SCF) in order to mimic the conditions from mouth to colon.

Results: Percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) limits. Out of both the polymers, the tablets prepared with ghatti gum showed the maximum hardness of 7.1 kg/cm^2. The FTIR spectra of pure diltiazem HCl and the formulation KF3 were found to be identical. From the DSC, it was evident that the melting point peak of diltiazem HCl and formulation KF3 were observed at 217.16 and 218.34 °C respectively. *In vitro* studies revealed that the tablets coated with shellac (2.5% w/w), prevented the drug release in stomach environment and inulin coated tablets (4% w/w) have limited the drug release in the small intestinal environment. The data obtained from *in vitro* drug release studies were fit into Peppas model and in all the cases the value of A was found to be more than 2, i.e., drug release by a combination of both diffusion and erosion-controlled drug release.

Conclusion: The study revealed that polysaccharides as carriers and inulin and shellac as a coating material can be used effectively for colon targeting of drugs for treating local as well as systemic disorders.

Keywords: Colon targeted drug delivery system, Diltiazem HCl, Kondagogu gum, Ghatti gum, *In vitro* dissolution

INTRODUCTION

Oral administration of drugs is one of the most convenient routes and is associated with superior patient compliance compared to other routes of drug administration [1]. Targeting drug to a specific area not only increases the therapeutic efficacy of drugs but also it aims to decrease the toxicity associated with drugs to allow lower doses to be used in therapy [2]. In recent studies, colon targeted drug delivery systems are gaining importance to treat local pathologies of the colon and also for the systemic delivery of protein and peptide drugs [3].

Drug targeting to the colon is also useful when a delay in drug absorption is desired from a therapeutic point of view, such as treatment of diseases that have peak symptoms in the early morning like nocturnal asthma, angina or arthritis [4, 5]. CODES™ is a unique technology that was developed by utilizing a unique mechanism involving lactulose, which acts as a trigger form site-specific drug release in the colon [6, 7]. The system consists of a traditional tablet core containing lactulose, which is coated with and soluble acid material like Eudragit E [8, 9].

Kondagugu gum (KG) is the dried exudates obtained from tree *Cochlospermum gossypium* belonging to the family Bixaceae [10, 11]. It is used as a wound dressing sponge [12], food additive [13], buccal disc [14], the carrier in preparing floating drug delivery system [15] and a polyelectrolyte complex in combination with chitosan [16]. Gum ghatti is a complex non-starch polysaccharide obtained as amorphous translucent mucilage from wounds in the bark of *Anogeissus latifolia* [17]. Ghatti gum has also been used for preparing matrix tablets for domperidone [18], a floating drug delivery system [19] and also as an emulsifying agent [20].

Inulin is a polysaccharide obtained from plants such as onion, garlic, chicory, artichoke, etc. Only enzymes secreted by the microflora of colon degrade inulin [21]. Shellac is a resinous secretion of the insect *Laccifer lacca* and it is used as an enteric coat to prevent the drug release from the tablet in the stomach [22]. The drug selected for the present study is diltiazem hydrochloride, a calcium channel blocker, which is used in the treatment of early morning angina [23]. The present work aims to develop a novel colon targeted tablet formulation using kondagogu gum and ghatti gum as carriers and diltiazem hydrochloride as a model drug.

MATERIALS AND METHODS

Materials

Diltiazem HCl was obtained as a gift sample from M/s Divis Laboratories, Hyderabad, India. Diltiazem HCl is a white, odorless, crystalline powder freely soluble in water and methanol. Kondagogu gum and ghatti gum were purchased from the Girijan Co-operative Society, Govt. of Andhra Pradesh, Hyderabad. Inulin and shellac were procured from M/s Loba Chemie, Mumbai, India. All other ingredients used were of analytical grade.

Purification of gums

First the extraneous foreign matter like bark etc was separated from both kondagogu gum and ghatti gum, and then powdered using a mixer grinder and passed through sieve #80. The powdered gum was dispersed in distilled water to get a 1% solution, kept in a sonicator for 10 min until it was clear and then added to an equimolar mixture of acetone and ethanol (2:1 v/v) to give precipitation of gum. The precipitated polymer was kept in an oven at 40 °C for drying, powdered and evaluated for general characteristic properties [18].

Preparation of diltiazem HCl-polymer matrix tablets

Preliminary studies had demonstrated that directly compressed kondagogu gum and ghatti gum formulations lacked the required mechanical strength. Hence all the core tablets were prepared by wet granulation technique. Accurately weighed quantities of the drug, polymer (kondagogu gum/ghatti gum) and binder (PVP K-30, 3% w/w) were physically blended in a mortar and pestle. The required quantity of the ethanol (solvent) was added and the resultant mixture was mixed thoroughly to form a dough mass suitable for the preparation of granules. The dough mass was then passed through sieve # 22 to form granules which were dried in an oven at 60 °C. The granules were mixed

with required quantities of lactose (diluent) and lubricant (magnesium stearate, 2% w/w) and were compressed to form tablets in a 10-station rotary tablet machine (Rimek, Mumbai, India) at 10 RPM and using 9 mm round concave punches at optimum pressure [4, 15]. Three formulations of 300 tablets each were prepared with different amount of kondagogu gum viz., 25, 50 and 75% w/w of the tablet (KF1, KF2 and KF3) and ghatti gum-based matrix tablets (GF1, GF2 and GF3 code for 25, 50 and 75% w/w of ghatti gum respectively) as shown in table 1. The prepared core tablets were evaluated for tablet properties such as hardness, thickness, weight variation, percent friability and drug content. Drug content studies were carried out to evaluate the amount of drug present in the prepared tablet.

Table 1: Composition of diltiazem HCl colon targeted tablets

Ingredients	Formulation code and weight in mg					
	KF1	KF2	KF3	GF1	GF2	GF3
Diltiazem HCl	60	60	60	60	60	60
Kondagogu gum	75	150	225	--	--	--
Ghatti gum	--	--	--	75	150	225
PVP K-30	9	9	9	9	9	9
Magnesium Stearate	6	6	6	6	6	6
Directly compressible lactose	150	75	--	150	75	--
Total weight of tablet (mg)	300	300	300	300	300	300

Coating of the prepared tablets

For the primary coat, a solution of inulin (10% w/v) in hot water (80 °C) was used to get the desired weight gain (4% w/w) on the tablets. Triethyl citrate (1.5% w/w of inulin) and polyethylene glycol (PEG 6,000, 4% w/w of inulin) were used as plasticizers and magnesium stearate (12% w/w of inulin) was added to reduce the tackiness of the tablets. For the secondary coat, which is enteric in nature, a solution of shellac (20% w/v) in ethanol was used to get the desired weight gain (2.5% w/w) over the tablets. PEG 6000 (4% w/w of shellac) was used as a plasticizer. Both the coating solutions were passed through a 0.3 mm sieve prior to coating. The prepared matrix tablets were coated with the inulin solution by spray coating. Coating of the tablets has been carried out in a conventional coating pan (Ram Scientific Suppliers, Bangalore, India) at an inlet temperature of 55 °C, pan rotation speed of 15 RPM, spray pressure of 4 kg/cm^2 and a spray rate of 10 ml/min. A pilot type spray gun (Bullows 630) fitted with a 1 mm atomizing nozzle was used to spray the solution [4, 8, 9]. The coated tablets were subsequently evaluated for hardness and drug content.

UV/Visible spectroscopy

The wavelength of maximum absorbance (λ_{max}) of diltiazem hydrochloride drug was determined by scanning a known concentration of sample solution in the wavelength region 200–400 nm by using Shimadzu 1601 UV/Visible spectrophotometer [24]. The λ_{max} was found to be 237 nm and this wavelength was used for further studies.

FTIR Spectrophotometry

In order to evaluate the integrity and compatibility of diltiazem with the carrier polymers in the polymer-drug matrix formulations, IR spectra of the drug and its optimized formulation were obtained by FTIR spectrophotometer (Perkin Elmer-1000, Japan), using a potassium bromide pellet method [25].

Differential scanning calorimetry (DSC)

DSC thermograms were recorded for pure diltiazem HCl drug and the optimized formulation. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids and heated at a constant rate of 5 °/min over a temperature range of 0–400 °C [15]. All dynamic DSC studies were carried out using a DuPont thermal analyzer with 2010 DSC module.

Scanning electron microscopy (SEM)

To evaluate the uniformity of coat on the polymer-drug blend (core) tablet and to examine the coat morphology, scanning electron microscopy (Joel-LV-5600, USA) studies were performed [26].

In vitro dissolution studies

Dissolution testing of colon delivery systems with the conventional basket method has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the colon-specific delivery systems might encounter in vivo. Dissolution studies were carried out using USP XXII dissolution apparatus, basket type at 100 RPM and 37±1 °C. In vitro drug delivery studies were carried out for 2 h in 900 ml of 1.2 pH (HCl buffer), 3 h in 900 ml of 7.4 pH (phosphate buffer) and for 6 h in 100 ml of SCF [27, 28]. The samples were withdrawn at regular intervals and analysed spectrophotometrically at 237 nm for drug release.

Preparation of simulated colonic fluid (SCF)

To evaluate the performance of colon-specific delivery systems triggered by colon specific bacteria, animal cecal contents of rats have been utilized as an alternative dissolution medium. Because of the similarity of human and rodent colonic microflora, predominantly comprising *Bifidobacteria, Bacteroides* and *Lactobacillus*, rat cecal contents were used for dissolution studies. 4% w/v of rat cecal contents in pH 7 saline phosphate buffer, incubated for 24 h was used as SCF [4, 29]. Incubation of the prepared solution was carried out in order to increase the enzyme concentration. This is done in order to simulate the conditions of human colon wherein a large amount of cecal contents would be present. As the bacteria present in cecal contents are predominantly anaerobic, all the processes were done by keeping the solution bubbled with carbon dioxide. Dissolution studies were carried out in both incubated and unincubated SCF to check the effect of the enzyme's action over drug release.

Peppas model fitting

Koresmeyer-Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery [30]. The Koresmeyer-Peppas equation is as follows;

$$Mt/M\infty = 1-A\ (exp\text{-}kt) \dots (1)$$

$$\log (1\text{-}Mt/M\infty) = \log A\text{-}kt/2.303 \dots (2)$$

Where, M_t/M_∞ is the fractional amount of drug released and t is the time in h. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In (1-M_t/M_∞) versus time t respectively where, Mt is the amount of drug release at time t; M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet, and A is the diffusional exponent indicative of the mechanism of drug release.

Stability studies

Stability studies for the optimized formulation of matrix tablets was carried out to determine the effect of formulation additives on the stability of the drug in the final formulation and also to determine the physical stability. The optimized formulation was subjected to stability studies according to ICH guidelines by storing at 25±2 °C/60±5 % RH and 30±2 °C/65±5 % RH for 12 mo, and 40±2 °C/75±5 % RH for 6 mo (Thermolab, Mumbai, India). The samples were analyzed and checked for changes in physical appearance and drug content at regular intervals [15, 17].

RESULTS AND DISCUSSION

The prepared core tablets were showing an average diameter of 9 mm. Percentage weight variation, percent friability, and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) limits. The polymer coated tablets were evaluated for hardness and drug content. The prepared tablets were evaluated for properties such as hardness (Inweka hardness tester, Ahmedabad, India), thickness (Mitotoya screw gauge, Japan), weight variation (Shimadzu AW 120, Japan), percent friability (Electrolab EF-2 friabilator, Mumbai, India) and drug content (Shimadzu 1702 UV/Visible spectrophotometer, Japan). The data obtained for coated and uncoated tablets is given in table 2.

Table 2: Evaluation data obtained for prepared tablets

Formulation code	Uncoated tablets					Coated tablets	
	Weight variation* (mg)	Thickness* (mm)	Hardness* (kg/cm^2)	Friability* (%)	% Drug content*	Hardness* (kg/cm^2)	% Drug content
KF1	301±3.2	5.02±0.11	5.7±0.52	0.42±0.12	100.2±2.4	5.8±0.41	99.8±1.8
KF2	302±2.9	5.01±0.10	6.3±0.38	0.38±0.11	101.8±2.6	6.5±0.51	101.1±2.5
KF3	299±3.1	4.99±0.12	6.6±0.45	0.31±0.11	100.3±3.1	6.8±0.39	99.5±2.3
GF1	299±2.4	5.01±0.11	5.9±0.73	0.39±0.13	98.7±1.8	6.2±0.46	98.2±2.6
GF2	301±3.1	4.99±0.12	6.9±0.82	0.34±0.11	100.5±2.2	7.1±0.54	99.7±1.4
GF3	301±2.9	4.98±0.13	7.1±0.46	0.28±0.12	101.4±3.2	7.4±0.84	100.1±2.9

*mean±SD, n = 3

From the table, it is clear that the hardness of the core tablets increased as the amount of polymer concentration in the tablet increased. Formulations containing 75% w/w of the gums (KF3 and GF3) showed the maximum hardness among the three ratios selected (25%, 50% and 75%). Out of both the polymers, the tablets prepared with ghatti gum showed the maximum hardness of 7.1 kg/cm^2. The estimated drug content before and after the coating of the tablets is given in table 2. From the table it was noticed that, the percentage of drug content lies in the range 98.7–101.4 and 98.2–101.1 for before and after coating operation of the tablets

respectively. This result clearly indicates that a slight reduction in drug content occurred during the coating operation and this is expected.

The FTIR spectra of pure diltiazem HCl and the formulation KF3 were found to be identical as shown in fig. 1. The characteristic IR absorption peaks of diltiazem at 2966 (aliphatic C–H stretch), 2837 (O–CH$_3$ stretch), 2393 (amine HCl), 1679 (lactam C=O stretch), 839 (o-substituted aromatic C–H out of plane deformation) and 781 cm^{-1} (p-substituted aromatic C–H out of plane deformation) were obtained.
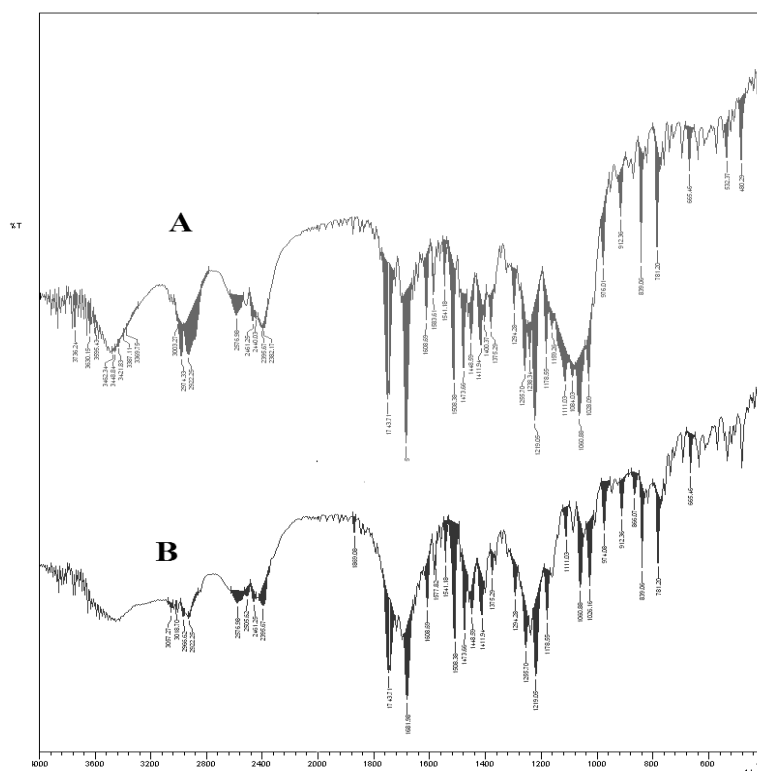

Fig. 1: FTIR chromatogram for pure diltiazem (peak A) and formulation KF3 (peak B)

The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, diltiazem, polymers and the excipients used in formulating the tablet. But, a slight shift in absorption peak position was noticed which indicated that physical interaction might have occurred between the drug and the polymer/excipients used.

From the DSC data obtained (fig. 2), it was evident that the melting point of diltiazem HCl has not changed after placing the tablets for stability studies (peaks at 217.16 and 218.34 °C for pure drug and formulation KF3 respectively). Hence, it may be inferred that there was no interaction between diltiazem and polymers used.
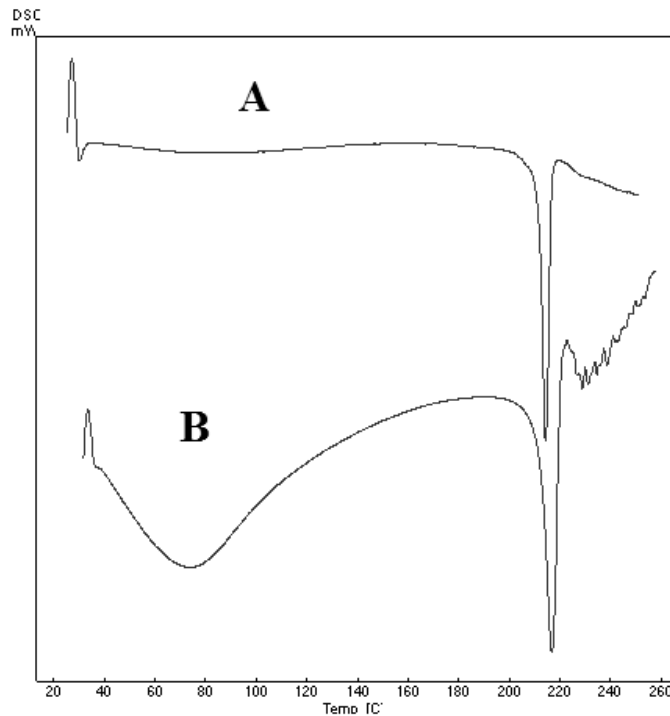

Fig. 2: DSC chromatogram for pure diltiazem HCl (peak A) and formulation KF3 (peak B)

From DSC results it can be concluded that the drug maintained its chemical identity throughout the process. The obtained SEM microphotographs of inulin and shellac coated tablets is shown in fig. 3.
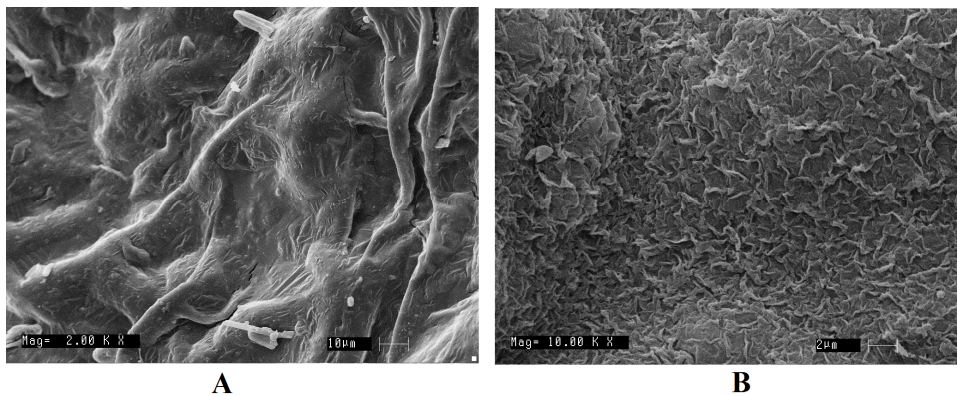

Fig. 3: SEM microphotograph of tablet surface after inulin (A) and shellac (B) coating

From the fig. it is evident that the shellac coating was smooth when compared to inulin coat. This can be attributed to the high molecular weight and complex structure of inulin.

The plot of cumulative drug release as a function of time is shown in fig. 4 and from the fig. it is clear that all the formulations did not show any drug release in pH 1.2 buffer indicating that shellac has prevented the drug release in stomach environment. *In vitro* studies revealed that the formulations containing 25 % of kondagogu gum and ghatti gum (KF1 and GF1

respectively) could not show sustained release whereas, the formulations KF2 and GF2 (50% w/w of kondagogu gum and ghatti gum) showed sustained drug release from the coated tablets over a period of time. Kondagogu and ghatti gum formulations containing 25 % w/w of the tablet (KF1 and GF1) released entire drug within 8 h of dissolution period. On the other hand, tablets containing 50% w/w of Kondagogu gum and ghatti gum (KF2 and GF2) showed about 47 and 51% of drug release at the end of 6 h indicating that the formulation did not with hold the drug before it reached the target site.
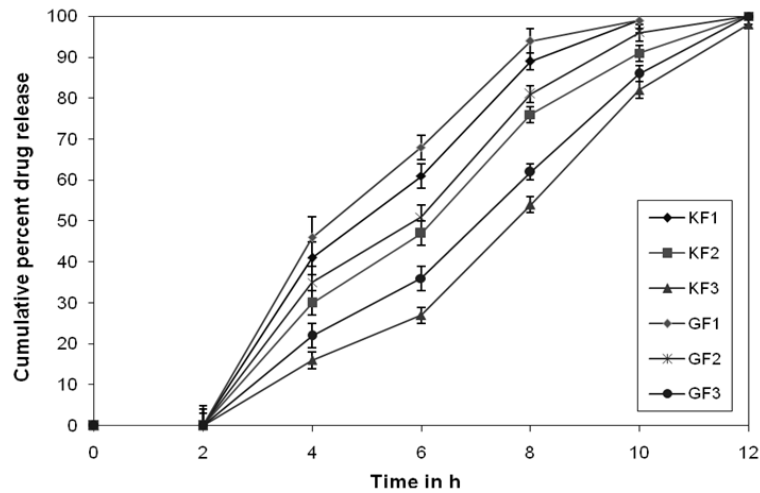
Fig. 4: *In vitro* drug release profile for the prepared tablet formulations (Data represents mean±SEM (n=3)

The formulations KF3 and GF3 were found to show a low amount of about 19 and 22% of the drug in pH 7.4 phosphate buffer (small intestinal environment) and released the remaining amount of drug in the colonic environment. Drug delivery studies revealed that the tablets coated with shellac (2.5% w/w), prevented the drug release in stomach environment and inulin coated tablets (4% w/w) have limited the drug release in the small intestinal environment. On reaching the colonic environment, the inulin coat gets biodegraded in the bacteriological media and the drug present in the core gets exposed to the bacteriological solution. The bacteria present in the solution breakdown the polysaccharide units and the drug gets released.

At the end of 11 h of dissolution, 80% of the drug was released from the polymer-drug blend tablet. This is because of the multiplication of bacteria present in the cecal content, which got multiplied during the incubation period and the enzymes secreted by the bacteria have enhanced the rate of biodegradation of the coated and matrix polysaccharides used. Hence, for all the drug release studies incubated SCF was used.

The data obtained from *in vitro* drug release studies were fit into the Peppas model. From the plot of log $Mt/M\infty$ versus t, the parameters such as release constant (k), constant (A) and the regression coefficient (R^2) were calculated and the obtained values are shown in table 3.

In all the cases the value of A was found to be more than 2. This result indicates that the release of drug from the polymer matrix formulations was found to be super case-II transport, i.e., drug release by a combination of both diffusion and erosion-controlled drug release. From the table it was concluded that formulation KF3 with R^2 value of 0.9941 is the optimized formulation for colon targeted delivery.

The optimized formulation KF3 was subjected for stability studies. Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any degradation during its shelf life. The data obtained from the stability studies are tabulated in table 4.

Table 3: Data obtained from Peppas model fitting for the formulations

Parameters	KF1	KF2	KF3	GF1	GF2	GF3
Constant (A)	2.324	2.257	2.362	2.214	2.278	2.307
Regression coefficient (R^2)	0.9867	0.9836	0.9941	0.9721	0.9875	0.9896

Table 4: Stability study data of optimized formulation KF3

Stability condition	Sampling interval (Months)	Formulation KF3	
		Physical appearance	% Drug content
	0	No change	99.5±2.3
25±2 ˚C/	3	No change	99.2±2.8
60±5 % RH	6	No change	98.8±2.7
	12	No change	98.5±2.6
30±2 ˚C/	0	No change	99.5±2.9
65±5 % RH	3	No change	99.4±2.3
	6	No change	98.9±2.6
	12	No change	98.7±2.8
	0	No change	99.5±2.4
40±2 ˚C/	3	No change	99.3±2.1
75±5 % RH	6	No change	98.6±2.5

*Standard deviation n=3, from the stability study data, it was clear that the drug was stable in the optimized formulation for the study period.

CONCLUSION

From the present study, it can be concluded that kondagogu gum and ghatti gum, which are natural and biodegradable polymers can be employed for use as carriers in developing colon targeted drug delivery systems. However, kondagogu gum was found to be superior to ghatti gum as a carrier for colon targeting.

ACKNOWLEDGMENT

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare

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