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Physicochemical Characterization and Dissolution Study of Ibuprofen Compression-Coated Tablets Using Locust Bean Gum

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ABSTRACT

The aim of the present study was to minimize drug release in the upper gastro intestinal tract and target the colon using the principles of compression coating. Compression-coated tablets of ibuprofen were prepared by a direct compression method using locust bean gum (LBG) at 300, 250, 200, and 175 mg. Tablets were evaluated for their physicochemical properties and in vitro drug release. In vitro drug release studies were performed with and without rat caecal contents. In rat caecal contents, tablets showed enhanced drug release due to degradation of the LBG coating by colonic enzymes. The in vitro release studies in pH 6.8 phosphate buffer containing 2% w/v rat caecal contents showed the cumulative percentage release of ibuprofen after 26 h as 39.91 ± 0.05%, 53.21 ± 0.37%, 69.17 ± 0.19%, and 94.46 % ± 0.92%. Coating thickness and the amount of chitosan control the release rate. Formulations were best fitted with Korsmeyer–Peppas kinetics, and the mechanism of drug release was non-Fickian super case II transport. FTIR studies reveal there is no drug–polysaccharide interaction. The F_1 formulation is a promising system for drug targeting to the colon.

INTRODUCTION

Colonic delivery refers to targeting drugs to the colon for treatment of its local diseases. It is also considered as an oral delivery method for drugs that are unstable, unabsorbed in the upper GI tract, or both. Additionally, the other category of drugs targeted to this site includes drugs that need delayed absorption from a therapeutic point of view. This site of the GI tract presents a nearly neutral pH, longer residence time, and less enzymatic activity, which makes it less hostile compared with the proximal part of the GIT (*1*).

There are several pharmaceutical approaches to prepare colon-targeted drug delivery systems. These approaches could be categorized in two main classes (*2*). The first is covalent linkage of the drug with a carrier to make conjugates, and the second approach is delivering intact molecules to the colon. The second approach itself is subdivided into seven subclasses. These include systems developed using polymer coatings (pH-sensitive, biodegradable polymers), systems embedded in matrices (biodegradable matrices, hydrogels, pH-sensitive matrices), time-released systems, systems with redox-sensitive polymers, bioadhesive systems, microparticle-coated systems, and osmotic controlled-delivery systems (*2*, *3*).

Locust bean gum (LBG), also known as carob gum, is a galactomannan vegetable gum derived from the seeds of the leguminous plant *Ceratonia siliqua* Linn belonging to the family Fabaceae (*4*). It consists chiefly of high molecular weight hydrocolloidal polysaccharides composed of galactose and mannose units (1:4) combined through glycosidic linkages. This natural, non-starch polysaccharide forms water-insoluble films that degrade in colonic microflora, making it useful in a colon-targeting strategy (*5*). On the other hand, LBG has various properties that make it a good choice in drug delivery: (1) it is biocompatible, biosorbable, biodegradable, cheap, and abundant; (2) it is nonteratogenic and nonmutagenic according to Joint FAO/WHO Expert Committee on Food Additives held in Geneva, April 1975; (3) it has acceptable shelf-life; and (4) its degradation products are excreted readily (*4*).

The aim of the present study was to develop a new colon-specific, compression-coated formulation for ibuprofen using LBG as coating material. Ibuprofen, a non-steroidal anti-inflammatory agent, was selected for formulation because of its most common adverse effect, gastrointestinal discomfort. Moreover, it is well absorbed throughout the colon and also reported to decrease both tumor growth and metastatic potential in mice (*6*, *7*).

MATERIALS AND METHODS

Ibuprofen was obtained from Strides Acro Labs, Bangalore, India. Locust bean gum was purchased from Alembic Pharma, Baroda, India. Sodium hydroxide pellets were received from SD Fine-Chem. Ltd., Mumbai, India.

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Talc was obtained from Leo Chem., Bangalore, India. Potassium chloride and potassium bromide (IR grade) were from Thomas Baker, Mumbai, India and Merck specialities Pvt. Ltd., Germany, respectively. Microcrystalline cellulose, sodium starch glycolate, potassium dihydrogen phosphate, and magnesium stearate were obtained from Spectrochem Pvt. Ltd., Mumbai. Hydrochloric acid (HCl) was provided by Swastik Pharmaceuticals, Mumbai, India. The instruments used were as follows: FTIR spectrometer (FTIR-8400S, Shimadzu, Japan), UV-vis spectrophotometer (UV-1800, Shimadzu, Japan), Disso DS 14000 dissolution test apparatus (LabIndia, India), C-DS 3 disintegration test apparatus (Serwell Instruments Inc., Bangalore, India), 12-station tablet compression machine (*IP*/*BP*/*USP* standard, Karnavati Engineering, Ahmedabad, India), hot-air oven (Serwell Instruments Inc., Bangalore, India), ATL-224-I digital balance (Acculab Sartorius Group, Bangalore, India), Shore Hardness Tester model HT-6510A (Scientific Engineering Corp., Delhi, India), hydraulic pellet press model KP-974 (S. V. Scientific), pH meter (Serwell Instrument Inc., Bangalore, India), FT-20 friability tester (Dutta Scientific Works., Madras, India), and CHM-6 Plus humidity cabinet (Remi Laboratories Ltd., India).

Preparation of Optimized Core Tablets of Ibuprofen

Each core tablet for in vitro studies consisted of ibuprofen (100 mg), dried starch (4 mg), and microcrystalline cellulose (MCC, 46 mg). Starch was added to obtain quickly disintegrating tablets. All materials were weighed, mixed, and passed through a 250-µm mesh to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 7-mm round, flat, plain punches on a single-station tablet machine (Cadmach, India). The thickness of the core tablets was 0.2 mm, and their crushing strength was about 3 kg/cm^2.

Compression Coating of Ibuprofen Core Tablets

The coating material, consisting of different amounts of LBG (270, 220, 170, 145, and 120 mg), was compressed on the previously prepared core tablet, which was carefully placed in the center of the die cavity (Table1). The compression pressure was 5000 kg, and the strength of the compression-coated tablets was 5 kg/cm^2. The resulting coating had adequate hardness due to the use of microcrystalline cellulose in the coating formulation.

Table 1. Composition of Locust Bean Gum Coats Used to Cover Ibuprofen Core Tablets

Batch code	Coat Weight (mg)	Composition (mg)			
		LBG	MCC	Mg Stearate	Talc
F_1	300	270	25	2	3
F_2	250	220	25	2	3
F_3	200	170	25	2	3
F_4	175	145	25	2	3
F_5	150	120	25	2	3

Characterization of Compression-Coated Tablets

Prepared tablets were subjected to quality control tests including hardness, friability, weight variation, and uniformity of drug content tests. These studies were carried out according to *USP* methods (*8*).

Drug Release Studies in the Presence and Absence of Rat Caecal Contents

In the first step, drug release from tablets was characterized using the USP basket dissolution apparatus and 900 mL of acidic buffer (0.1 N HCl, pH 1.2) and pH 7.4 phosphate buffer as test media for 2 h and 3 h, respectively. A stirring speed of 100 rpm was used. Two samples of 1 mL were withdrawn and immediately filtered. Drug concentration was measured spectrophotometrically.

In the next step, release profiles were examined using the rat caecal contents as dissolution medium (*9*) to check whether tablet cores might be affected as the dosage form passes through the GI tract. Drug release studies in the presence of caecal contents were carried out using USP Apparatus 1 with a slight modification in procedure. The experiments were carried out in 200-mL beakers immersed in water contained in the 1000-mL vessel that was maintained in the water bath of the dissolution test apparatus. Initial studies were carried out in 200 mL of 0.1 N HCl (pH 1.2) for 2 h. After this, the dissolution medium was replaced with 200 mL of pH 7.4 phosphate buffered saline (PBS), and the dissolution continued for another 3 h. Then a drug release study was carried out in pH 6.8 buffer medium containing 2% w/v rat caecal contents for 21 h (100 rpm, 37 °C). As the caecum is naturally anaerobic, all experiments in caecal content media were conducted under a continuous supply of nitrogen. At different time intervals, 1-mL samples were withdrawn from the dissolution medium and replenished with 1 mL of 2% w/v caecal contents maintained under anaerobic conditions to maintain a constant volume. The samples were diluted and analyzed spectrophotometrically. The Institutional Animal Ethics Committee approved the experimental protocol for preparation of rat caecal contents. Briefly, five Wister rats weighing between 200 and 300 g were kept on a normal diet and administered 1 mL of 2% w/v solution of LBG in water through Teflon tubing placed directly into stomach region via the oral cavity. After pretreatment for 7 days with locust bean gum dispersion, the rats were sacrificed by spinal traction thirty minutes before the release studies. Then the caecal

contents were collected and transferred into pH 6.8 PBS solution previously bubbled with CO_2 to make a final caecal dilution of 2% w/v (*6*, *9*).

FTIR Studies

An FTIR study was performed to determine the compatibility of drug and excipients. Briefly, 10 mg of sample and 400 mg of KBr were placed in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and compressed at 10 kg/cm^2 using a hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in a Shimadzu FTIR spectrophotometer. Samples of ibuprofen, LBG, and a physical mixture of drug and polymer were prepared. The spectra obtained were compared and interpreted for the functional group peaks.

Evaluation of Release-Rate Kinetics

To investigate the mode of release from tablets, the release data were analyzed using the following mathematical models:

Zero-order kinetics	$Q = Q_0 - K_0 t$
First-order kinetics	$\ln Q = \ln Q_0 - K_1 t$
Higuchi equation (square root of time equation)	$Q = K_2 t^{1/2}$
Hixson–Crowell cube-root law	$Q_0^{1/3} - Q_t^{1/3} = K_3 t$
Peppas equation	$Q/Q_0 = K t_n$

where K_0, K_1, K_2, and K_3 are release rate constants, Q/Q_0 is the fraction of drug released at time t, Q_0 is the initial amount of drug, Q_t is the amount of drug released at time t, K is a constant, and n is a diffusion constant that indicates general operating release mechanism. The exponent n is calculated through the slope of the straight line (Table 2), which indicates the mechanism of drug release (*10–12*).

RESULTS AND DISCUSSION

Fourier-transform infrared (FTIR) spectra were scanned over the wavenumber range of 3600–400 cm^{-1}. They showed characteristic peaks of ibuprofen at 1716 cm^{-1} and 2943 cm^{-1} due to carbonyl and hydroxyl stretching, respectively. For pure locust bean gum, the band at 3427 cm^{-1} is due to O–H stretching. The band at 2926 cm^{-1} represents C–H stretching of the –CH_2 groups. The bands due to ring stretching of galactose and mannose appear at 1657 cm^{-1}. Moreover, the bands in the region of 1350–1450 cm^{-1} show the symmetrical deformations of the CH_2 and COH groups. The bands representing the primary alcoholic –CH_2OH stretching mode and CH_2 twisting vibrations appear at 1078 and 1024 cm^{-1}, respectively (*13*). The peaks of the spectra for ibuprofen, the polysaccharide (LBG), and their physical mixture were the same, so no drug–polysaccharide interaction was observed (Figure 1).

Table 3 shows the physicochemical parameters evaluated for ibuprofen compression-coated and core tablets.

The tablets were evaluated for weight variation, hardness, and friability. The hardness was from 4.5 ± 0.42 to 5.0 ± 0.24 kg/cm^2, and in all cases the friability was less than 1%. The drug content for core ibuprofen tablets was 97.84 ± 0.15%. The results showed that the percent weight variation of formulations ranged from 0.48 ± 0.023% to 1.40 ± 0.012%. This indicates that there was no significant weight variation in all prepared formulations. Therefore, the compression-coated tablets complied with

Table 2. Mechanism of Drug Release and the Relevant n Value in Peppas Equation

Type of Mechanism	*n* value
Fickian diffusion	<0.5
Supercase II transport	>1
Non-Fickian diffusion	0.5–1

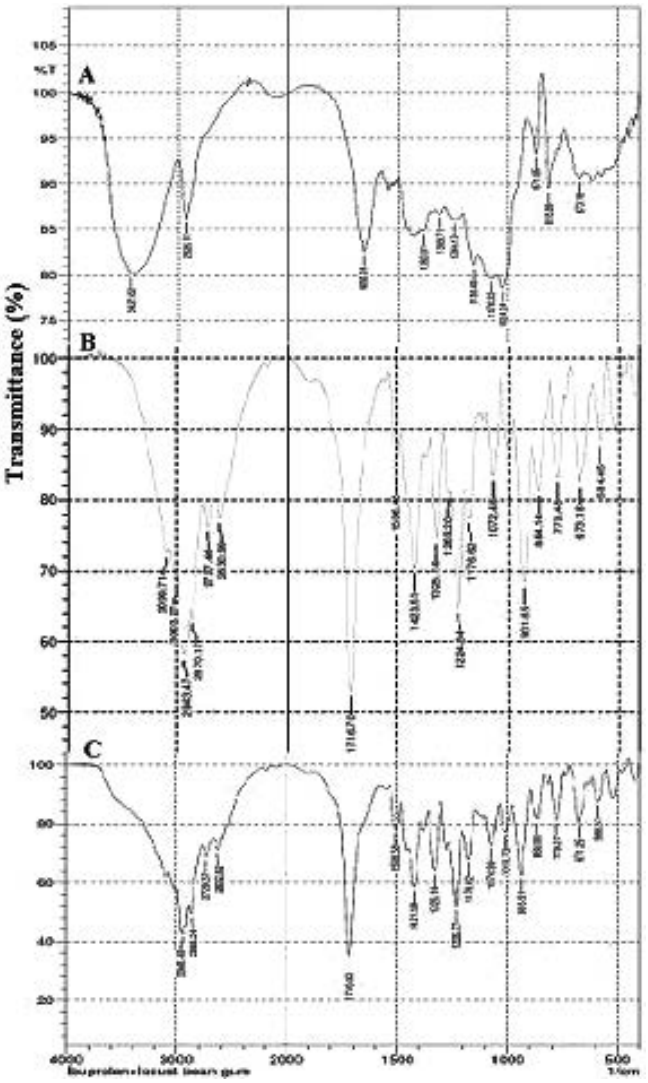

Figure 1. IR spectra of (A) locust bean gum, (B) ibuprofen, and (C) their physical mixture.

Table 3. Physicochemical Evaluations of Compression-Coated and Core Ibuprofen Tablets

Formulation	Hardness (kg/cm² ± SD)	Friability (% ± SD)	Weight variation (% ± SD)
Core tablet	4.6 ± 0.42	0.20 ± 0.021	1.40 ± 0.012
F_1	5.0 ± 0.24	0.06 ± 0.021	0.68 ± 0.034
F_2	4.9 ± 0.13	0.08 ± 0.015	0.63 ± 0.052
F_3	4.7 ± 0.42	0.07 ± 0.016	0.54 ± 0.074
F_4	4.7 ± 0.18	0.06 ± 0.014	0.48 ± 0.023
F_5	4.5 ± 0.42	0.07 ± 0.021	0.37 ± 0.048

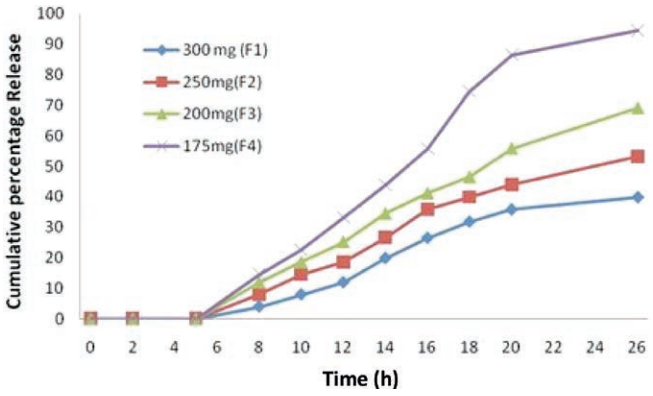

Figure 2. Cumulative percent release profile of ibuprofen in formulations F_1 to F_4 using rat caecal content.

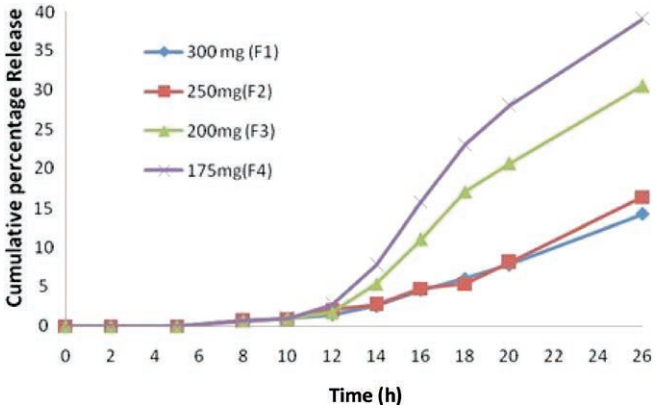

Figure 3. Cumulative percent release profile of ibuprofen in formulations F_1 to F_4 without rat caecal content.

pharmaceutical quality control standards. The in vitro release profiles of drug from tablets in the presence and absence of rat caecal contents are shown in Figures 2 and 3, respectively. Generally, drug release from LBG-coated tablets in the medium containing rat caecal contents was higher than that in pH 6.8 phosphate buffer. This result is due to the enzymatic degradation of coating material by colonic bacteria. It is also noted that drug release from tablets decreases with increased LBG levels (i.e., formulations with highest amount of polysaccharide in the coat, F_1) represented only 39.9 ± 0.05% drug released in the presence of caecal contents in which 94.46 ± 0.92% drug release was observed for F_4 with lowest level of LBG. The same trend was observed in the drug release experiments in the absence of caecal contents. This is confirmed by the findings of a study by Chithaluru et al. (*10*) in which ketorolac tromethiamine compression-coated tablets were prepared using guar gum/metalose 90 SH. Based on their results, a smaller amount of guar gum as a microbially triggered coating leads to a thinner coating and a higher drug release rate. The percent drug released from tablets coated with coating formulation F_3 increased from 18 h onward, indicating the commencement of the breaking of gum coats. F_4 follows this same trend. The percent drug released after 26 h of testing was 69.17%, and the tablet coating was broken at one point making way for the release of the drug. Moreover, the drug in tablets was not released until 5 h, which indicates that ibuprofen was not released in 0.1 N HCl and pH 7.4 phosphate buffer. This observation confirms the protective effect of LBG for drug to be intact in stomach and upper intestine during its GI transit time.

In earlier studies (*14*), a polymer blend consisting of HPMC K4M as a drug-release retarding agent in combination with colon degradable polysaccharide guar gum was successfully used to protect ibuprofen from release under conditions mimicking mouth-to-colon transit. In our previous study (*15*), almost the same result was observed for ibuprofen compression-coated tablets using chitosan.

The stability of three formulations having 175 mg LBG in the coating material was studied under the accelerated conditions at 40 °C and 75% relative humidity in a humidity cabinet. During the stability test, the characteristics of the compression-coated tablets and percent cumulative drug release (CDR) were evaluated on days 10, 20, and 30. Table 4 shows the tablet characteristics during the storage time in the stability chamber versus those of formulations kept in ambient conditions as a control group. There were no significant changes in drug content from the control tablets, and average drug content in samples was greater than 99% of label claim. In vitro drug release studies also showed no noteworthy alteration in percent CDR during the stability test. In other words, at the end of test period more than 93.53% drug was released from tablets compared with 94.46% and 94.36% for the initial value and tablets at ambient conditions, respectively. All other evaluated characteristics including physical appearance, average weight, and hardness of tablets were also unchanged during the period.

The results of various kinetics models and the mechanism of drug release from ibuprofen compression-coated tablets are shown in Table 5. To determine the mechanism

Table 4. Stability Data of Compression-Coated Ibuprofen Tablets with 175 mg Locust Bean Gum in Coating (F_4)

	Observation in Day						
		Room temperature			45 °C / 75% RH		
Evaluation parameter	**Initial**	**10**	**20**	**30**	**10**	**20**	**30**
Physical appearance	Coated tablets	No change	No change	No change	No change	No change	No change
Average weight (mg)	177	179	182	178	177	179	180
Hardness (kg/cm²)	4.7	4.7	4.8	4.8	4.6	4.6	4.5
Drug content[a] (% w/w ± SD)	100	98.54 ± 0.12	99.51 ± 0.08	99.42 ± 0.09	99.84 ± 0.13	99.47 ± 0.14	99.56 ± 0.10
% CDR[a]	94.46 ± 0.92	94.36 ± 0.08	94.57 ± 0.15	94.08 ± 0.23	94.64 ± 0.35	93.72 ± 0.19	93.53 ± 0.45

[a] *initial drug content as 100% w/w (n = 3)*

Table 5. Release Kinetics of Ibuprofen from Compression-Coated Tablets with Locust Bean Gum Coating

	First-order			Zero-order			Higuchi			Peppas				Hixon–Crowel	
Formulation	R^2	k_1	**MPE**	R^2	k_0	**MPE**	R^2	k_H	**MPE**	R^2	k_p	n	**MPE**	R^2	**MPE**
F_1	0.949	0.0291	12.81	0.931	0.0222	17.86	0.959	0.1785	11.44	0.931	0.0007	2.06	16.99	0.943	14.63
F_2	0.984	0.0395	5.33	0.962	0.264	10.32	0.982	0.2115	5.30	0.953	0.0031	1.64	10.90	0.978	7.06
F_3	0.991	0.0594	7.65	0.988	0.0329	5.23	0.995	0.2615	3.88	0.992	0.0039	1.67	3.98	0.996	3.86
F_4	0.947	0.161	39.4	0.945	0.049	9.12	0.961	0.3957	10.26	0.999	0.0026	1.94	1.10	0.965	17.37

of drug release, the in vitro results were fitted to the Korsmeyer–Peppas equation. All formulations showed values of $n > 1$, indicating that the drug release mechanism was non-Fickian super case II transport. Therefore it seems that drug release depends upon swelling, relaxation, and polymer erosion (*12*, *16*, *17*).

CONCLUSION

The results of this study demonstrate that LBG, in the form of a compression coating, is a potential carrier for colonic-specific drug delivery systems that possess acceptable physical characteristics. This polysaccharide is capable of retarding the release of core materials until they reach the colon, an environment rich in bacterial enzymes that degrade the LBG allowing drug release. Stability studies indicated no significant change in physical appearance, drug content, and in vitro release pattern. Moreover, no physical or chemical interaction was evident from FTIR studies, indicating stability of ibuprofen in the prepared tablets.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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