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Synthesis and Characterization of Carboxymethylated Locust Bean Gum for Developing Compression Coated Mucoadhesive Tablets of Cinnarizine

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Carboxymethylated locust bean gum (CLBG) was synthesized by carboxymethylation of locust bean gum (LBG) using monochloroacetic acid followed by characterization involving SEM, XRD and FTIR techniques. The CLBG exhibited changes in the surface morphology along with relative amorphous nature as indicated in SEM and XRD analysis, respectively. In SEM images, locust bean gum (LBG) exhibited irregular particle with smooth surface morphologies whereas CLBG depicted surface roughness with relatively irregular edges. XRD study indicated relative amorphous nature of CLBG. The modified gum was employed for developing compression coated tablets of cinnarizine. The core tablets coated with CLBG exhibited mucoadhesive detachment force of 11.44 ± 2.09 to 16.07 ± 1.88 N compared to 4.10 ± 0.95 to 5.52 ± 1.13 N of locust bean gum coated tablets. The CLBG depicted better sustained drug release behaviour when compared with the pure gum. In conclusion CLBG is a suitable polymer candidate for developing mucoadhesive drug delivery systems with controlled release property.

Keywords: Carboxymethylated locust bean gum, Compression coating, Cinnarizine, Mucoadhesive tablets.

INTRODUCTION

Mucoadhesion is the phenomenon of adhesion of a polymer to the mucosal surface lining the gastrointestinal, nasal, rectal, vaginal, ocular or buccal tracts. It offers various advantages including increased residence time, drug protection, enhanced drug permeation and bioavailability [1]. Mucoadhesive tablets contain suitable mucoadhesive polymer responsible for producing significant mucoadhesion via wetting, swelling, interpenetration, diffusion and/or electrostatic interactions [2].

Compression coating (press coating or dry coating) of tablets is a solvent free coating method in which the core tablets (containing active pharmaceutical ingredient) are coated with the polymer *via* direct compression. Polymers may be used for stability enhancement, controlled/sustained drug release, taste making, enhancement of mechanical strength and/or for developing gastroretentive drug delivery systems [3]. Composition of core, type and concentration of compression coating polymer are important parameters to be monitored for tailoring the drug release from the formulation. Various natural, synthetic and semi-synthetic polymers have been employed for the compression coating technology.

Locust bean gum (LBG) is a natural derived polysaccharide obtained from the fruits of *Ceretonia siliqua* (Carob tree) of family Fabaceae and is composed of D-mannopyranosyl chain units linked *via* β-(1→4) bonds with the units of D-galacto-pyranosyl. LBG is biocompatible/biodegradable natural polymer and generally recognized as safe by USFDA. Moreover, it is used as an emulsifying, stabilizing, thickening and gelling agent in pharmaceutical formulations [4,5]. Carboxymethylation is a process of chemical modification of polymers for decreasing the viscosity, enhancing solubility and increasing adhesive strength [6].

Kaity & Ghosh [7] performed the carboxymethylation of locust bean gum by Williamson synthesis method employing monochloro acetic acid as etherifying agent. Microspheres developed using carboxymethylated locust bean gum depicted controlled/sustained drug release behaviour. Singh *et al.* [8] developed and optimized the synthesis process of carboxymethylation of locust bean gum by Plackett-Burman design. Carboxymethylated locust bean gum with improved physical and rheological properties was developed. Carboxymethylated locust bean gum films with good tensile strength and low water vapor permeability were developed as drug delivery carrier .

Chakravorty *et al*. [9] studied the effect of carboxymethylation on drug release and rheological properties of matrix tablets of locust bean gum. Maiti *et al*. [10] performed the preparation and characterization of carboxymethyl derivatives of locust bean gum for developing hydrogel beads for controlled oral delivery of glipizide. John *et al*. [11] performed the synthesis and characterization of carboxymethyl locust bean gum for developing microspheres of disopyramide phosphate. The prepared microspheres were found to be bioequivalent in terms of rate and extent of drug absorption when compared with the marketed formulation of the selected drugs.

Cinnarizine (1-benzylhydryl-4[(*E*)-3-phenylprop-2-enyl]-piperazine) is a calcium channel blocker generally prescribed for nausea, motion sickness, vomiting and cerebrovascular vertigo. Cinnarizine being weakly basic in nature exhibits higher absorption in stomach as compared to small intestine. Cinnarizine is an ideal candidate for being incorporated into gastro-retentive drug delivery system as enhanced stomach retention of the drug will significantly enhance its bioavailability. Gastro-retentive microspheres, beads, tablets and other formulations of cinnarizine are well reported in literature [12].

In present work, carboxymethylation of locust bean gum was performed followed by characterization of the modified gum by FTIR, SEM and XRD techniques. The core tablets of cinnarizine were employed for being compression coated with pure locust bean gum and the carboxymethylated locust bean gum. The formulated compression coated tablets were quality checked for various parametric tests (*e.g*. weight variation, drug content, thickness, hardness, friability) of tablets, *ex vivo* muco-adhesion strength and *in vitro* drug release studies. Stability studies were also performed on optimized compression coated tablets of cinnarizine formulated using locust bean and carboxymethylated locust bean gum.

EXPERIMENTAL

Cinnarizine was kindly gifted by Ind-Swift Pharmaceuticals, Baddi, India. Locust bean gum was gifted by Hydrocolloid Plantations, New Delhi, India. MCC (Avicel-112), HPMC, sodium hydroxide, methanol, monochloro-acetic acid, glacial acetic acid, PVP K30, talc, magnesium stearate were purchased from Loba Chemicals, India. All the chemicals and reagents (analytical grade) used in the present work without further purification.

Synthesis of carboxymethylated locust bean gum: The reaction of for the synthesis of carboxymethylated locust bean gum was performed as per the method described by Kaity & Ghosh [7]. Firstly, the powdered locust bean gum (10 g) was completely dissolved in distilled water. The sodium hydroxide solution was then added dropwise with continuous stirring for 1 h. Monochloro acetic acid was the added slowly with continuous stirring. Temperature of the reaction mixture was increased to 50 ºC and was stirred for 4 h. The reaction was ceased with the addition of methanol, which precipitated out carboxymethylated locust bean gum from the reaction mixture (**Scheme-I**). The modified gum was washed with distilled water followed by drying in hot air oven and stored in desiccator till further use [6].

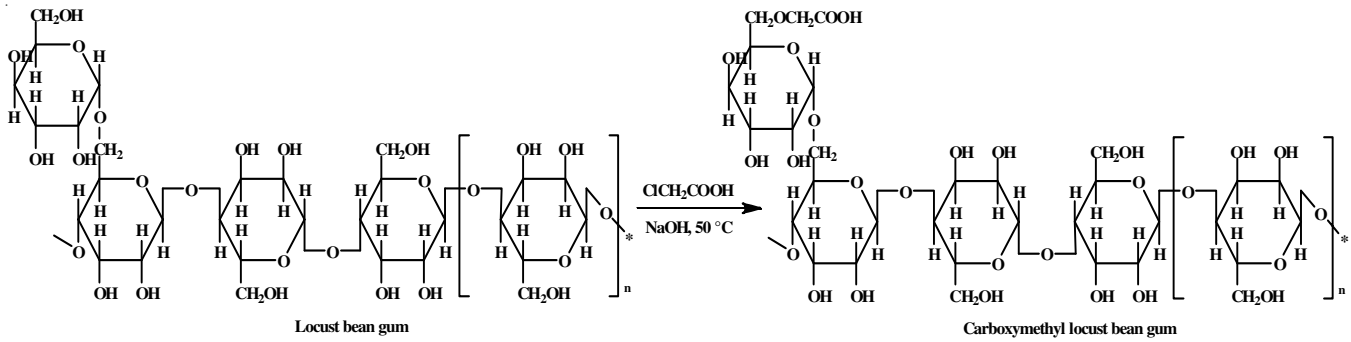
Fourier transform infrared (FTIR) spectroscopy: Spectral attributes the LBG and CLBG confirmed and compared using FTIR spectrometer (ALPHA-e, Bruker IR, Germany) in the spectral region 4000-500 cm^{-1}. The samples of the polymeric materials were blended with KBr powder for preparing the KBr pellet, which was subjected to FTIR spectrophotometry.

X-ray diffraction (XRD) analysis: The nature of LBG and CLBG were examined by X-ray powder diffractometer of Xpert PRO, Panalytical, Germany. The samples were at 2θ = 0-100º, 45 kV voltage and 40 mA current employing copper as anode material.

Scanning electron microscopy (SEM) analysis: For surface morphological analysis of LBG and CLBG, a scanning electron microscope (JSM-6510 LV, Jeol Ltd., Tokyo, Japan) with a tungsten filament operated in electron mode with an acceleration voltage at 15 kV was used. Double sided adhesive tape is used to adhere the gold palladium alloy (150-200 Å) coated samples onto the stubs of microscope.

Powder micromeritic studies: Pure locust bean gum and carboxymethylated locust bean gum powders were evaluated for micromeritic studies, which are indicators of the powder flow properties. The parameters *viz*. poured density (Dp), tapped density (Dt), angle of repose (θ), Carr's compressibility index (CI) and Hausner' s ratio were calculated.

Preparation of core tablets of cinnarizine: Core tablet of 80 mg net weight were prepared using cinnarizine (15 mg), Avicel 112 (58 mg) as diluent, PVP K30 (5 mg) as binder, talc (1 mg) and magnesium stearate (1 mg) as lubricant. All the ingredients were screened through sieve (60 mesh) and uniformly mixed by tumbling in a polybag for 30 min. Tablets were



Scheme-I: Synthesis reaction of carboxymethyl locust bean gum

formulated using single stroke punching machine equipped with round concave (6 mm) die-punch tooling.

Formulation of compression coated tablets: Compression coating of cinnarizine tablets (inner core tablets) was performed with the ingredients as mentioned in Table-1. All ingredients were sieved (through 60 mesh) and mixed thoroughly in a polybag before proceeding for compression coating. The coating (approximately half quantity) was placed followed by the placement of core tablet and then the remaining coating material was added over the core tablet. Compression coating was performed using multipunch tableting machine fitted with 8.5 mm concave punches at an applied force of 5000 kg [13].

TABLE-1
COMPRESSION COATING COMPOSITION

Components	F1LBG	F2LBG	F1CLBG	F2CLBG
LBG (mg)	250	500	–	–
CLBG (mg)	–	–	250	500
HPMC (mg)	200	200	200	200
Avicel 112 (mg)	90	40	90	40
PVP K 30 (mg)	50	50	50	50
Talc (mg)	5	5	5	5
Magnesium stearate (mg)	5	5	5	5
Total weight (mg)	600	800	600	600

Evaluation of core and compression coated tablets

Weight variation: Randomly selected 20 tablets of each batch and weighed individual tablet to determine for weight variation.

Drug content: Ten tablets were weighed and then powdered in a pestle and mortar. The drug was extracted using 0.1N HCl and after suitable dilution, the drug content was determined at 254 nm using double beam UV-Vis spectrophotometer (AU 2701 model, Systronics, India).

Thickness: Digital vernier caliper of Mitutoyo, Japan was used for determining the thickness of the tablets. Ten tablets from each batch of core tablets and compression coated tablets were selected for the thickness determination.

Hardness and friability: Hardness and friability of 20 tablets were measured using the Monsanto hardness tester (Model VMT- 1, VinSyst Technologies, India) and the Roche friabilator (Campbell Electronics, India), respectively. Pre-weighed tablets were placed in the friabilator. The friability test machine (Roche friabilator) was rotated at the rate of 25 rpm (100 revolutions). Afterwards, tablets were again weighed and the values were calculated using eqn. 1:

$$F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (1)$$

Determination of mucoadhesion strength: Mucoadhesion testing of the compressed coated tablets of cinnarizine was performed using texture analyzer (TA.XT plus, Stable Micro-Systems, UK). Compression coated tablet was attached to tje cylindrical probe by a double side adhesive tape. The porcine stomach tissue was equilibrated at 37 ± 0.5 ºC before placing onto the holder stage. The probe attached with tablet was allowed to make contact with the animal tissue for a specified period of time. The probe was then uplifted at predetermined test speed for determining maximum detaching force (F_{max}). The settings of the instrument for computing F_{max} are: test speed (0.5 mm s^{-1}), contact time (60 s), contact force (1.0 N) and distance (15 mm).

***in vitro* drug release:** *in vitro* drug release study of compressed coated tablets of cinnarizine was performed using USP-II Paddle type dissolution apparatus (DS 8000, LabIndia, India) with a rotating speed of 50 rpm and at 37 ± 0.5 ºC employing 0.1 N HCl (pH 1.2) as the dissolution medium. At fixed time intervals, samples (5 mL) were taken out and filtered through membrane filter (0.45 µm) and were analyzed at 254 nm using UV double beam spectrophotometer (AU 2701, Systronics, India) following suitable dilution. *in vitro* drug release data was fitted into various kinetic models *viz*. zero order, First order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas model for understanding the mechanism of drug release from the formulation.

Stability study: Stability study was performed on the core tablets of cinnarizine compression coated with locust bean gum (F2LBG) and carboxymethyl locust bean gum (F2CLBG). The formulated tablets were packed in sealed container and stored in stability chamber at 40 ºC and 75% relative humidity for three months.

A graph was plotted in between percentage drug remaining *versus* time and this plotted graph depicts the degradation rate constant (K). First order equation was utilized to determine the shelf life of compressed tablets at specified temperature.

RESULTS AND DISCUSSION

Carboxymethylation is a well reported method for altering the physico-chemical attributes of the natural material including gums. The rheological properties, drug release ability and mucoadhesive potential of natural gum has been significantly enhanced by carboxymethylation process. The synthesized carboxy-methylated gum was used for developing compression coated tablets of cinnarizine. The compression coated tablets were further evaluated for various tablet parametric tests.

FTIR studies: In the FTIR spectra of LBG, a broad peak at 3227.05 cm^{-1} could be attributed to O-H stretching vibrations. The peaks at 1067.77, 1258.2 and 1400.89 cm^{-1} were attributed to the C-O-H stretching, C-O ether stretching and CH_2 bending vibrations (Fig. 1a).

In FTIR spectra of carboxymethylated locust bean gum (Fig. 1b), the shifting of spectral band were observed at 3189.31 cm^{-1} indicates the involvement of hydroxyl groups of the LBG in the process of carboxymethylation. The CH_2 stret-ching was observed with the appearance of perk at 2935.96 cm^{-1}. Additionally, the sharp peaks at 1450.77 and 1592.83 cm^{-1} were attributed to symmetrical and asymmetrical vibrations of C=O group. Appearance of other peaks at 1063.02, 1255.68 and 1409.15 cm^{-1} indicates the basic structural resemblance of CMLG with LBG.

SEM studies: Pure LBG exhibited irregular particle with smooth surface morphologies (Fig. 2). However, carboxy-

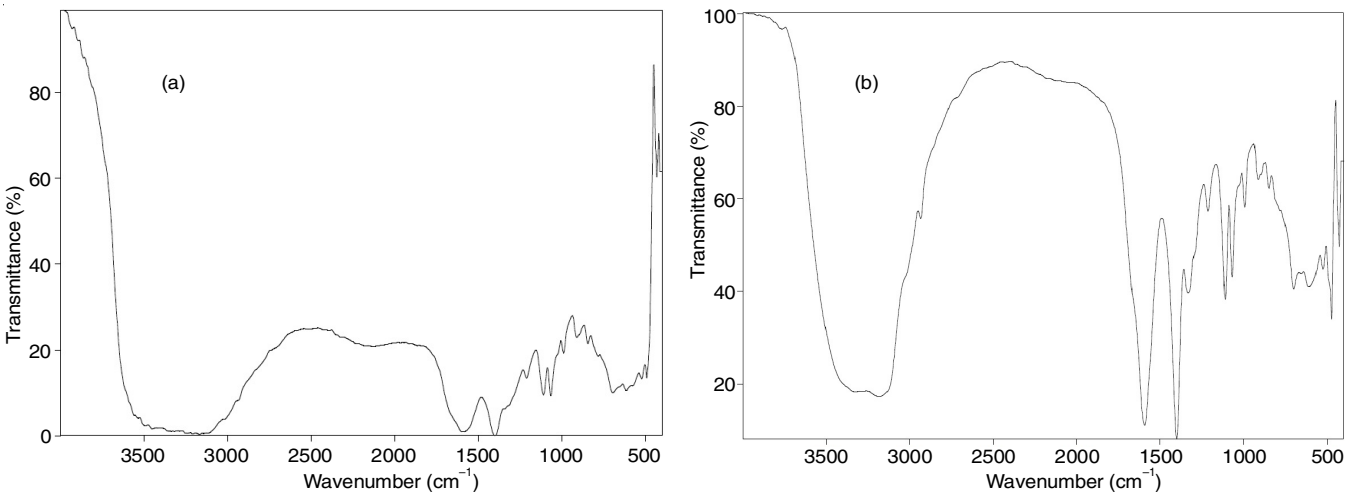


Fig. 1. FTIR spectra of (a) locust bean gum; (b) carboxymethylated locust bean gum

methylated LBG depicted surface roughness with relatively irregular edges. The surface roughness could be attributed to uneven distribution of groups added after carboxymethylation onto the structure of LBG (Fig. 3).

XRD studies: Interaction of natural gums with water is largely based on their amorphous and crystalline nature. XRD study helps is evaluating the crystalline and amorphous properties of the material. LBG exhibits peak at 18.90º with *d*-spacing and area of 4.69 Å, however, CLBG exhibits broad diffraction peak at 19.92º with *d*-spacing and area of 4.45 Å, indicating a relative increase in the amorphous nature of CLBG compared to LBG (Fig. 4).

The powders of pure locust bean gum and carboxymethylated locust bean gum were investigated for the micrometric studies and the results are presented in Table-2. The studies primarily included evaluation of bulk density, tapped density,

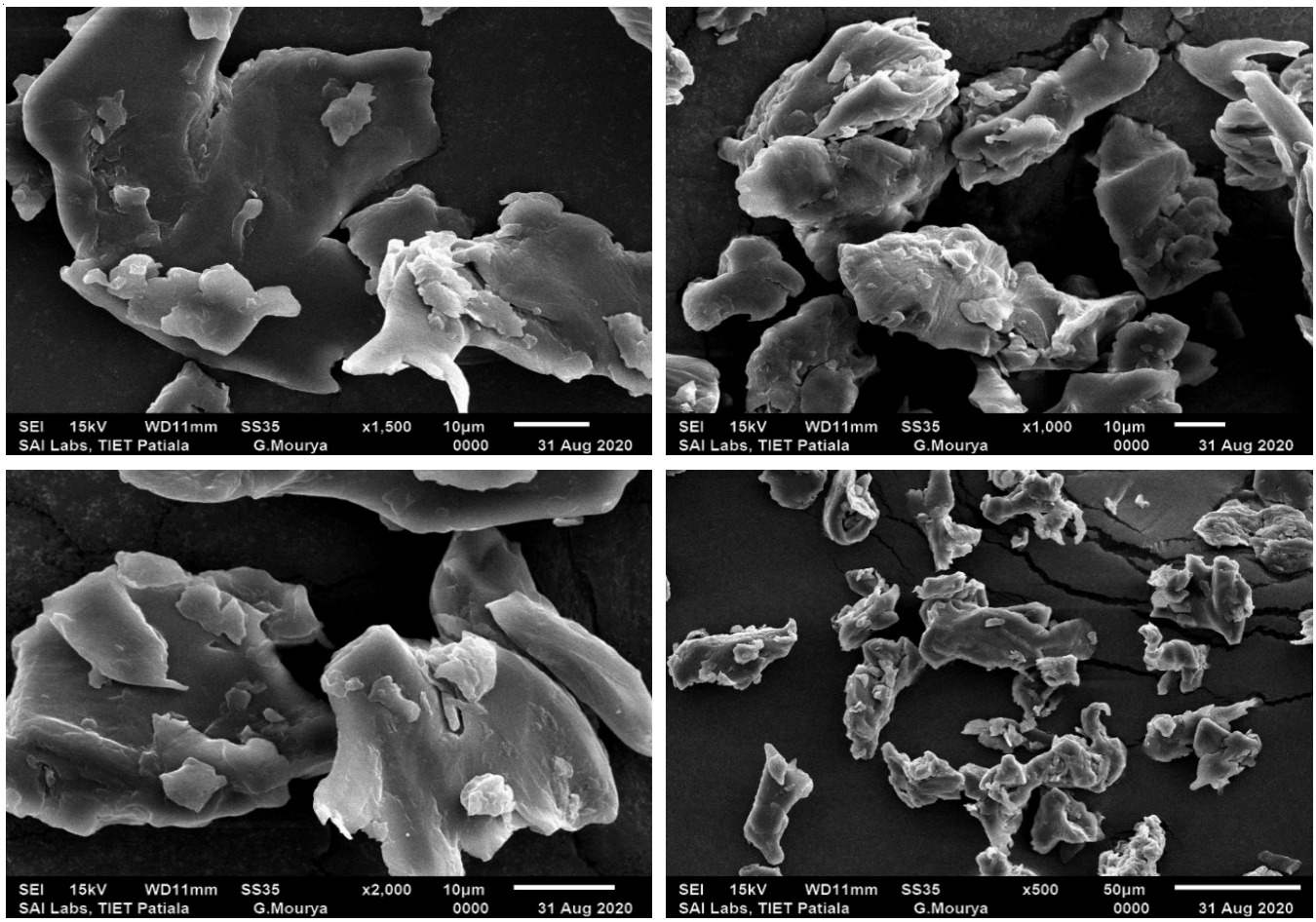


Fig. 2. SEM micrographs of locust bean gum at different magnifications

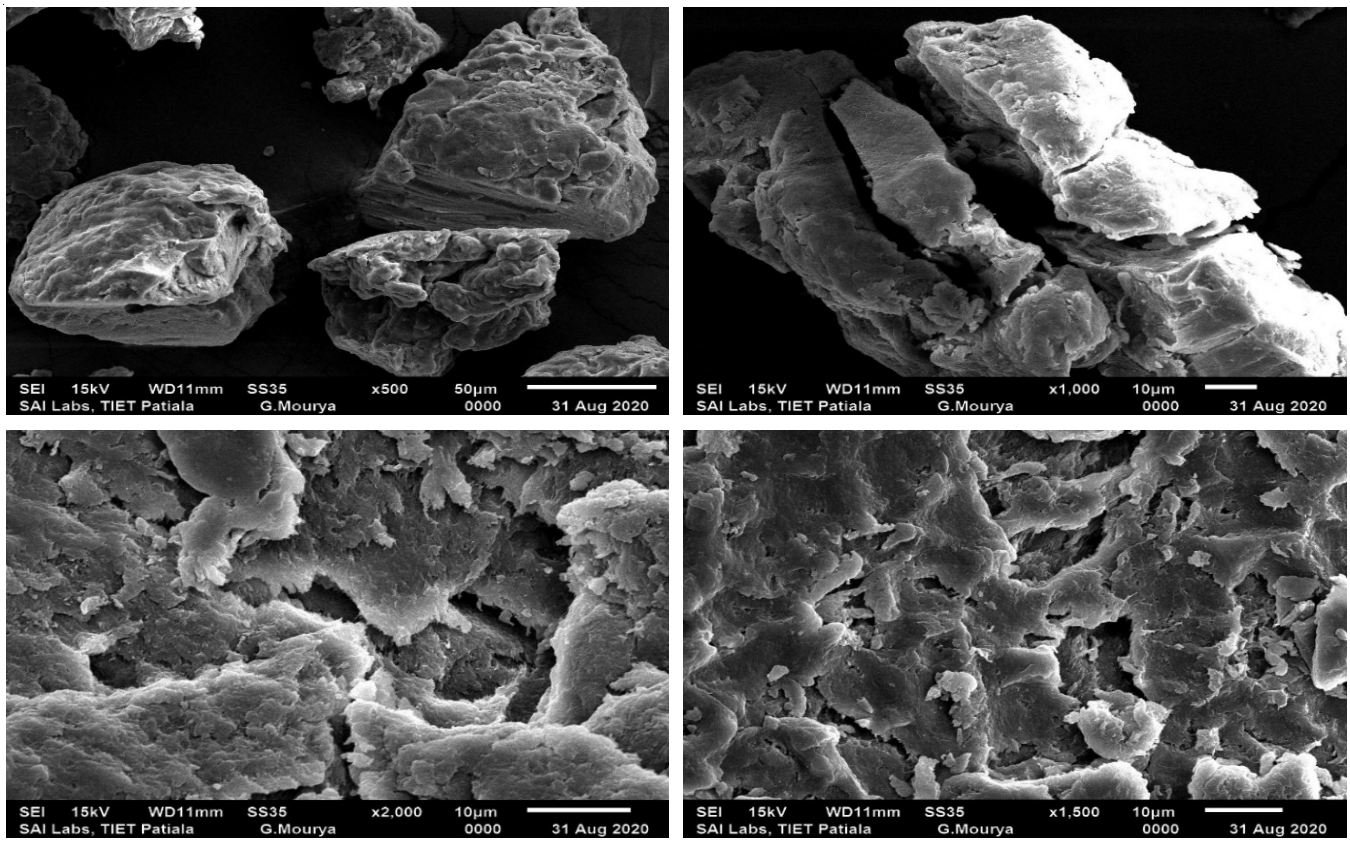


Fig. 3. SEM micrographs of carboxymethylated locust bean gum at different magnifications

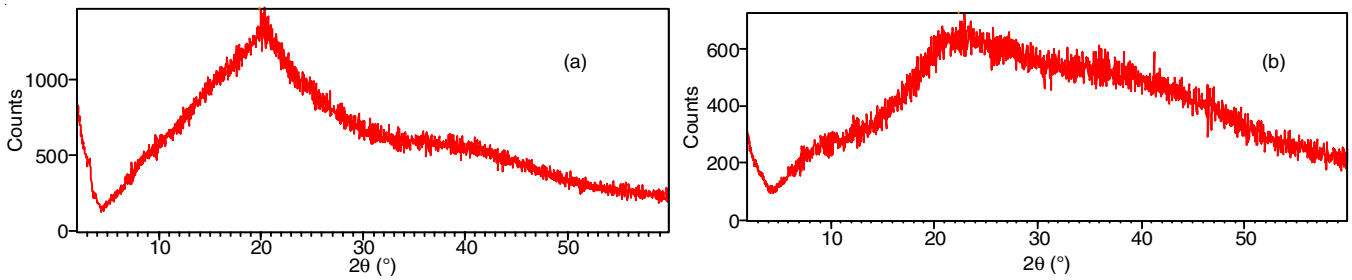


Fig. 4. X-ray diffractogram of (a) LBG; (b) CLBG

TABLE-2
VALUES DEPICTING THE DIFFERENT MICROMERITIC STUDY PARAMETERS

Parameter	LBG	CLBG
Bulk density (g/cm^3)	0.512	0.485
Tapped density (g/cm^3)	0.594	0.555
Carr's index (%)	13.81	12.61
Hausner ratio	1.16	1.14
Angle of repose (°)	33.55	30.06

Carr's compressibility index, Hausner's ratio and angle of repose. The bulk density and tapped density were found to be 0.512 and 0.485 g/cm^3, respectively for locust bean gum and carboxymethylated locust bean gum. The Carr's index, Hausner ratio and angle of repose were reported to be 13.81 and 12.61%; 1.16 and 1.14; 33.5º and 30.06º, respectively for locust bean gum and carboxymethylated locust bean gum. Different micromeritic parameters evaluated in the present study indicated good powder flow characteristic of pure as well as modified gum. Good powder flow properties are essential during tablet compression process. Moreover, as per the objective of the study for performing compression coating using natural and modified gum, powder flow properties are vital for uniform and smooth compression coat by the natural polymer.

Evaluation core and compression coated tablets: The core tablets were evaluated for various quality control tests. The weight of the inner core tablets of cinnarizine was 80 ± 7 mg. Hardness and friability of tablets were 3.8 ± 0.12 kg/cm^2 and 0.8 ± 0.07%, respectively. The thickness of the core tablets was 1.52 ± 0.04 mm.

The compression coated tablets with batch number F1LBG, F2LBG, F1CLBG, F2CLBG were also evaluated for various tablet parametric tests indicator of quality and reproducibility. The weight variation, hardness, drug content, friability and thickness were found to be well within the prescribed limits (Table-3). The mucoadhesive detachment force (F_{max}) was found to be between 4.10 ± 0.95, 5.52 ± 1.13, 11.44 ± 2.09 and 16.07

TABLE-3
EVALUATION PARAMETERS OF COMPRESSION COATED TALETS PREPARED WITH PURE LOCUST BEAN GUM AND CARBOXYMETHYLATED LOCUST BEAN GUM

Batch code	Weight variation (mg) (n = 20)	Hardness (kg/cm²) (n = 5)	Drug content (%) (n = 5)	Friability (%) (n = 10)	Thickness (mm) (n = 20)	F_{max} (N) (n = 3)
F1LBG	601.16 ± 7.46	4.4 ± 0.12	96.40 ± 0.15	0.42 ± 0.04	4.11 ± 0.062	4.10 ± 0.95
F2LBG	804.53 ± 5.70	4.1 ± 0.13	97.63 ± 0.17	0.48 ± 0.07	4.41 ± 0.074	5.52 ± 1.13
F1CLBG	605.37 ± 6.20	4.3 ± 0.19	97.25 ± 0.16	0.51 ± 0.09	4.51 ± 0.053	11.44 ± 2.09
F2CLBG	807.40 ± 9.52	4.9 ± 0.18	99.50 ± 0.18	0.54 ± 0.05	4.60 ± 0.083	16.07 ± 1.88

± 1.88 N for compression coated batches F1LBG, F2LBG, F1CLBG and F2CLBG respectively. The CLBG exhibited good mucoadhesive properties compared to LBG [14]. The mucoadhesive detachment force was found to increase with increase in the concentration of the polymer.

***in vitro* drug release:** *in vitro* drug release profiles of core tablet and batches of compression coated mucoadhesive tablets prepared with locust bean gum and carboxymethyl locust bean gum are shown in Fig. 5. Carboxymethylated locust bean gum was found to be suitable candidate for compression coating and sustained release polymer for developing mucoadhesive tablets. *in vitro* release of cinnarizine was found to be in the following order: core tablet > F1LBG > F1LBG > F1CLBG > F2CLBG. Core tablets exhibited more than 90% drug release in first hour of the study. The compression coating of the core tablet with LBG and CLBG sustained the released of drug from within the core tablet. CLBG exhibited better sustained drug release behaviour compared to LBG.

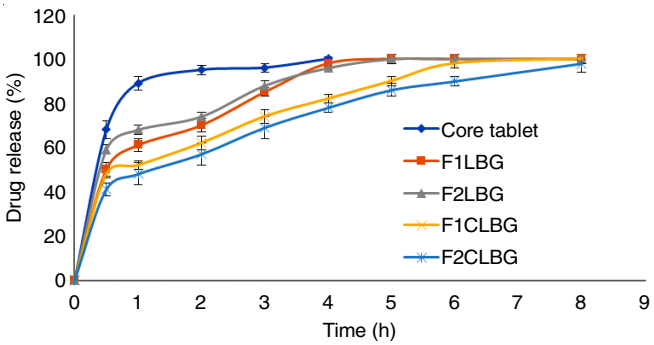


Fig. 5. *in vitro* release profiles of cinnarizine from the core tablet and different batches of compression coated tablets

in vitro drug release was fitted to various kinetic models (Table-4) for understanding the possible mechanism of drug release from the formulation. The value of release exponent (n) was found to be less than 0.5 depicting that diffusion to be responsible for the release of drug through the press coated polymer matrix. Swelling of the polymer, relaxation of polymeric chains and formation of swollen gelatinous barrier could be mainly responsible for the diffusional transport of drug. Subsequently, polymer erosion and dissolution may also contribute towards the release of drug from the carboxymethylated gum matrix [15-17].

Stability study: The percent cinnarizine remaining *versus* time plot for the elevated temperatures (20, 30 and 40 ºC) exhibited a straight line indicating that at these temperatures cinnarizine core tablets compression coated with locust bean gum and carboxymethylated locust bean gum ghatti followed first order kinetics as shown in Fig. 6.

Arrhenius plots for cinnarizine core tablets compression coated with locust bean gum and carboxymethylated locust bean gum were employed to calculate the log K values at 25 ºC. The K value (degradation rate constant) for cinnarizine core tablets compression coated with locust bean gum was found to be 1.66×10^{-4} day^{-1} at 25 ºC , whereas K value for cinnarizine core tablets compression coated with carboxymethylated locust bean gum was found to be 1.42×10^{-4} day^{-1} at 25 ºC. The predicted shelf life of domperidone in the formulated batches coated with locust bean gum and carboxymethylated locust bean gum was found to be 1 year 7 months and 2 year 1 month at room temperature, respectively. Furthermore, there was no change in colour, appearance was observed during accelerated stability study and suggesting it to be a robust formulation.

Conclusion

The present study affirmed that carboxymethylation of locust bean gum is a suitable, sustainable and scalable method for developing modified gum with good mucoadhesive properties. The FTIR, SEM and XRD studies indicated successful carboxymethylation of locust bean gum (LBG). The carboxymethylated locust bean gum (CLBG) was employed for developing compression coated tablets in which core tablets of cinnarizine were coated with a solvent free method using LBG and CLBG as the mucoadhesive polymers. The CLBG coated tablets depicted better mucoadhesive and controlled drug release properties compared to LBG coated tablets. The CLBG could be used as a potential mucoadhesive and drug release retardant for developing different drug delivery systems *viz.* films, microspheres, nanoparticles. If regulatory and large-

TABLE-4
VARIOUS RELEASE MODELS AND THEIR RELEASE PARAMETERS

Batch no.	Zero order		First Order		Higuchi		Korsmeyer-Peppas			Hixon-Crowell	
	r^2	k_0	r^2	k_1	r^2	k_H	r^2	n	k_{KP}	r^2	k_{HC}
F1LBG	0.799	19.873	0.892	-0.834	0.943	9.241	0.971	0.310	5.948	0.940	0.155
F2LBG	0.696	18.505	0.942	-0.695	0.963	9.189	0.957	0.226	6.239	0.905	0.138
F1CLBG	0.811	12.791	0.896	-0.526	0.930	9.473	0.959	0.295	5.683	0.947	0.100
F2CLBG	0.816	10.195	0.952	-0.424	0.921	9.702	0.984	0.329	5.419	0.974	0.080

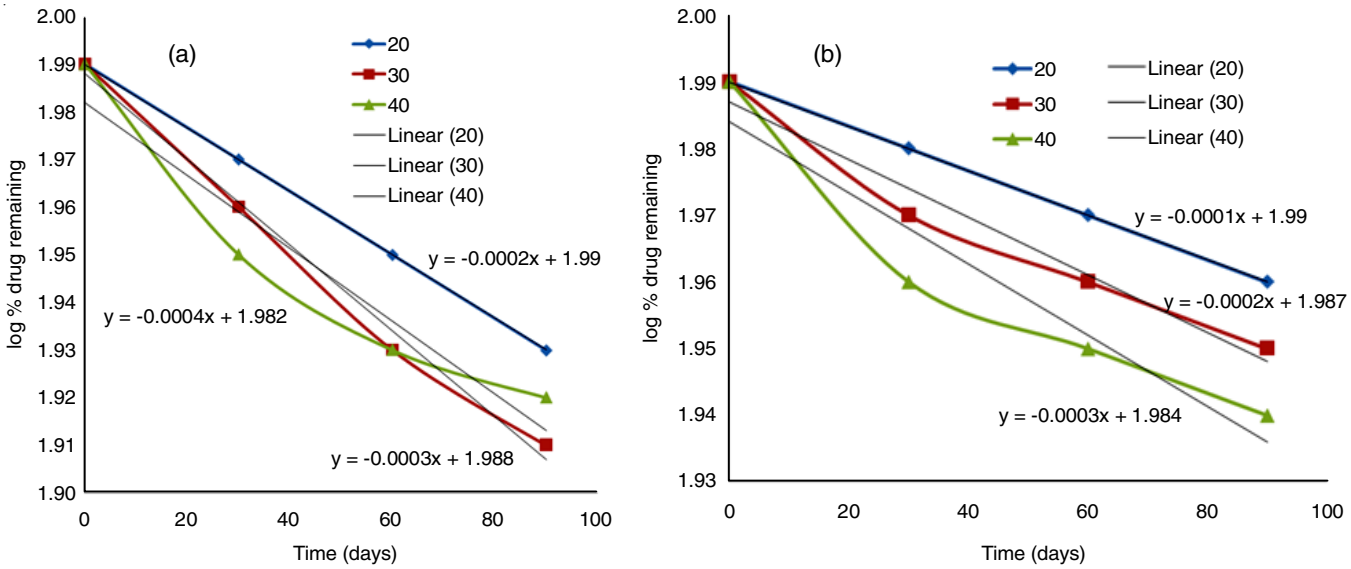


Fig. 6. Log % drug remaining *vs.* time (days) plot of cinnarizine core tablets compression coated with locust bean gum (a) and carboxymethylated locust bean gum (b)

scale production challenges are handled adequately, the carboxymethylated locust bean gum could be used as potential polymeric material for developing different mucoadhesive drug delivery systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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