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Research Article

Optimization of an Aqueous Tablet-Coating Process Containing Carboxymethylated *Cassia fistula* Gum

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Abstract. The present investigation was aimed at developing and optimizing a simple aqueous tablet-coating formulation and its process. 5-Fluorouracil (5-FU) was used to ascertain the relative lipophilic/hydrophilic behavior of the coating system. Optimization was performed by evaluating the adhesive force strength and cohesive force strength of the tablet coat using a texture analyzer. The *in vitro* release of 5-FU was found to decrease with an increase in (tablet surface-coat) adhesive force strength. The (tablet–tablet) cohesive force strength was reduced by the addition of magnesium silicate to the coating solution. The addition of magnesium silicate (0.2% *w*/*v*) to the carboxymethyl *Cassia fistula* gum–chitosan (CCG–CH) coating surface significantly inhibited the release of 5-FU possibly due to an increase in the hydrophobic character of the coated tablet surface. This was possible by coating cohesive force strength reduction coating compositions (CCG–CH (70:30) and 0.3% magnesium silicate). Further, the FTIR-ATR and DSC analyses suggested the pivotal role of magnesium silicate in modifying the release of 5-FU from CCG–CH-coated tablets due to hydrogen bonding of its Si–O–Si or Mg–O groups with –OH moieties of CCG–CH.

KEY WORDS: 5-fluorouracil; carboxymethyl *Cassia fistula* gum; chitosan; magnesium silicate adhesive force strength of tablets; texture analysis.

INTRODUCTION

Tablet coating is a popular method to improve tablet texture, mask taste, odor, enteric delivery, sustained delivery, and targeted delivery of drug(s). In a conventional aqueous sugar-coating process, natural gums are added to improve the texture of the coating surface as well as to enhance the binding of the coat with the uncoated tablet surface. This type of aqueous coating process suffers from the drawback of batch-to-batch variation in appearance as well as *in vitro* release. In addition, nonavailability of a simpler coating process, increased labor input, and availability of cheap synthetic non-aqueous coating processes using synthetic nonbiodegradable polymers seems to have contributed to the decrease in the usage of aqueous coating processes. Another drawback associated with unmodified natural gums is their susceptibility to solubility in acidic pH. Hence, when natural polysaccharides are used for colon delivery, they have to be employed in quantities as high as 75–80% *w*/*v* of the formulation (1, 2).

Natural or modified polysaccharides such as amylase (3), pectin (4), guar gum (5), and konjac glucomannan (6) have been widely investigated for the peroral delivery of drugs to the colon. Hence, the use of natural gum as a matrix system for sustained drug delivery or as tablet disintegrant is not new. The more important job is to develop and optimize an aqueous coating system and process that would be more acceptable as compared to an organic film-coating process as well as enable drug delivery to the colon. However, the major hurdle in aqueous coating process involving gums is their poor film-forming ability, acid solubility, and sticky coating surface that often necessitate optimization of the formulation as well as the process.

Gum obtained from the seeds of *Cassia fistula* comprises of β (1→4)-linked D-mannopyranose units with random distribution of α (1→6)-linked D-galactopyranose units as side chain having a mannose/galactose ratio of 3.0 (7) with high stickiness due to its viscosity. This gum is soluble in water and cannot be used in putative form for delivering drugs to the colon. Carboxymethylation of *Cassia tora* gum is reported to improve cold water solubility and viscosity (8). But the high acid solubility and poor film-forming ability of this modified gum do not make it suitable for use in colon release dosage forms. Therefore, chitosan (CH, a biodegradable polysaccharide with high film-forming ability) could be mixed with carboxymethylated *C. fistula* gum for developing the coating system. This combination can be envisaged to exhibit another advantage of being cross-linked owing to the high positive charge of CH due to the presence of $-NH_3^+$ groups (9, 10) and –COOH moieties of carboxymethylated *C. fistula* gum. The development of a technique involving coating of a polysaccharide or its combination with another polymer could be expected to offer a feasible method to reduce the contribution of polysaccharide

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to less than 20–30% *w*/*w*, which in turn would result in the decreased sticking of tablets among themselves or with the coating pan. Thus, the optimization of coating formulation and process seem to be essential.

Improper adhesion of the coating system with the tablet surface may produce a coated surface that can easily peel off (11, 12). Both interfacial interactions and internal stresses between the coat and tablet surface dictate adhesiveness of the coat. Internal stresses arise due to shrinkage of the film upon solvent evaporation, thermal stress due to the difference in thermal expansion of the tablet surface and film, and volumetric stress as the tablet surface swells during storage (13–17). Thus, evaluation of adhesive force strength is an indicator of tablet coat behavior. The cohesive force strength (coated tablet–coated tablet) estimation could provide additional information. Therefore, the aqueous tablet-coating process was evaluated using adhesive force strength as well as cohesive force strength by employing a texture analyzer.

5-Fluorouracil (5-FU) is one of the most widely used agents in the first-line chemotherapy of colorectal cancer (18). In addition, because of the short plasma half-life of 10–20 min, high doses have to be administered repeatedly by IV route to reach therapeutic drug levels (19). The oral bioavailability in humans is reported to be only 28% (20). The reported severe systemic toxic effects and very short plasma half-life make this drug particularly suitable for local delivery at the site by a suitable drug delivery system, thus exposing the diseased tissues in a continuous and sustained manner (21). However, its hydrophilic character makes it susceptible to easily get leached from the hydrophilic polymeric system. Hence, a need was felt to nullify the effect of GIT pH on coated tablets by employing a combination of hydrophilic and lipophilic polymeric systems for preventing the release in the upper GIT and deliver 5-FU slowly during transit through the colon.

In light of the above, it was envisaged to develop a coating composition containing carboxymethyl *C. fistula* gum (CCG) and CH. A hydrophilic drug 5-FU was selected for evaluating the hydrophilic/hydrophobic nature of the coating formulation for colon delivery. Further, the coating surface obtained by intercalating carboxymethylated CCG with CH to form CCG–CH films was characterized by Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR) and differential scanning calorimetry (DSC) and evaluated for modifying the release of 5-FU from tablets.

MATERIALS AND METHODS

Materials

5-FU was received as a gift sample from Dabur Research Foundation, Sahibabad, India. CH was purchased from Indian Sea Foods Ltd., Cochin, India. Ammonium acetate and acetic acid were of analytical grade and were purchased from Qualigens Fine Chemicals, India. Potassium dihydrogen orthophosphate of high-performance liquid chromatography grade was purchased from Merck India, Ltd. All reagents and chemicals were of analytical grade and used as received.

Methods

Extraction and Purification of Cassia fistula Gum

Cassia fistula seeds were size reduced to fine powder. One-hundred grams of this fine powder was soaked in 500 ml of 2% *v*/*v* acetic acid and stored at 45°C in a shaking incubator overnight. The jelly mass was diluted with lukewarm water to 1,000 ml and filtered using a muslin cloth to obtain a gum mucilage. This mucilage was added drop wise to 500 ml of acetone. The gum precipitates were filtered. These precipitates were again dissolved in water, filtered to remove any debris, and recrystallized using acetone. The precipitates obtained after filtration were dried in an oven at 45°C for 12 h and size reduced to get powdered gum of #80 sieve fraction. The gum was analyzed by FTIR-ATR and NMR.

Carboxymethylation of Cassia fistula Gum

Carboxymethylated CCG was prepared by modifying the method reported by Goyel *et al.* (22). In brief, *Cassia* gum (5 g) was dispersed in 16 ml of 45% *w*/*v* ice-cold sodium hydroxide solution. After stirring, 7 ml of 75% *w*/*v* monochloroacetic acid was added with constant stirring for 1 h. The temperature of the mixture was then raised to 75°C, and stirring was continued for a further 30 min. Separately, 80% *v*/*v* methanol solution in water was prepared and neutralized to pH 7.0 by adding glacial acetic acid. The reaction mixture in the gelled condition was cooled to room temperature, subdivided, and suspended in this methanolic solution. The suspended precipitates were filtered through a muslin cloth and washed three times with 80% *v*/*v* methanol (pH 7.0). The washed product was dried at 50°C for 4 h. The lumps were size reduced to #80 sieve size. The powder obtained was stored in a vacuum desiccator, sealed in a double-lined polyethylene bag till further use.

The degree of substitution of CCG was determined by a method reported earlier (23). The degree of substitution was found to be 0.5. The CCG was analyzed by FTIR-ATR and NMR analyses.

Preparation of 5-FU Tablets

Preparation of Binder Solution And Coating Solution. Chitosan (0.3–1.5% *w*/*v*) was dissolved in 2% *w*/*v* acetic acid solution. Separately, CCG (0.7–3.5% *w*/*v*) was dissolved in water. Ammonium acetate (5 M, 5 ml) was dissolved in a minimum quantity of water and equally distributed in both the solutions. Chitosan solution was added drop wise to gum solution. This clear solution was used as binder. The total concentration of the binder solution was varied from 1% *w*/*v* to 5% *w*/*v*. The same solution was used for coating the tablets (2% *w*/*v*).

Preparation of CCG–CH Films. The CCG–CH films were prepared by spraying 2% *w*/*v* solution employing a spray gun (5 ml/min, with the help of a peristaltic pump using a spray gun of 1-mm nozzle; Electrolab, PP201V, Mumbai, India) on the nonsticky surface of a rotating drum with hot air blown at 50°C for solvent evaporation. The dried film was recovered from the nonsticky surface and subjected to microwave

treatment (85 W, 15 s (each), five cycles in total) to remove bound water from the films. The films were stored in sealed packs till further use.

Preparation of 5-FU Tablets. Three milligrams of 5-FU per tablet was mixed with spray dried lactose (q.s. to 40 mg/tablet) in a dry state. Five milliliters of binder solution (1–5% *w*/*v*) containing chitosan/CCG (30:70) was used to prepare a wet mass. The granules were prepared by passing the mass through a #22 sieve and retaining on a #44 sieve. These granules were dried at 50°C for 30 min and then mixed with colloidal silica (0.5% *w*/*w*). This solid mixture was finally compressed using concave, round punches in a rotary tablet compression machine (A K industries, Nakodar, Punjab, India). The weight of the compressed tablets was 40±0.1 mg and their diameter was 4±0.1 mm.

Dummy Tablets. Dummy tablets (2.5 mm in diameter) were compressed (D tooling) using a six-punch rotary compression machine (Clit, CPM, Ahmedabad, India).

Coating of 5-FU Tablets

The CCG–CH solution (2% *w*/*v*) was prepared freshly for coating 5-FU tablets. These solutions were coated on a batch comprising of dummy tablets and tablets containing 5-FU. Dummy tablets were used along with 5-FU-loaded tablets (total tablet load, 200 g) for optimizing the tablet load charge in the coating pan. The coating solution was sprayed at a rate of 5 ml/min with the help of a peristaltic pump using a spray gun of 1-mm nozzle (Electrolab, PP201V, Mumbai, India) in a coating pan (12-in. diameter) being rotated at 18 rpm (A K Industries, M 1107, Nakodar, India). Compressed air was introduced at a pressure of 1.5 kg/cm^2. The inlet air temperature was maintained at 60–75°C.

The following steps were involved in optimizing the coating process:

1. Preparation and optimization of adhesive surface: This process was developed for coating tablets with surface films that would exhibit high adhesive force strength. The tablet load was preheated to 50–60°C before spraying the coating solution. The spray solution containing CCG–CH (2% *w*/*v*) solution was sprayed at the rate of 1 ml/min with the help of a peristaltic pump. After 30 min, the tablets with a smooth surface were developed. A sample of 20 tablets was withdrawn from the coating pan and subjected to adhesive force estimation using a texture analyzer. Further, 3^2 full factorial design was used for optimizing the surface film that could attain high adhesive force strength. During preliminary investigations, the compositions of coating solution ($X1$) and contact time ($X2$) were identified as the possible variables influencing adhesive force strength.
2. Preparation of coated tablets exhibiting minimum cohesive force strength: The coated 5-FU tablets prepared in step 1 were found to have high cohesive force strength. This may be due to high stickiness of CCG. Hence, 0.05–0.5% *w*/*v* magnesium silicate was added to the coating solution. The spray rate was enhanced to 3 ml/min with the help of a peristaltic pump, and the inlet air temperature was raised to 75°C. After ensuring a tablet weight gain of 10% *w*/*w*, spraying was stopped, and heating was continued for another 30 min. The inlet temperature was slowly decreased to room temperature, and tablets were stored in polypropylene bags till further use. The tablets were evaluated for cohesive force strength by employing a texture analyzer.

Evaluation

Testing of Uncoated Tablets. The axial and radial diameters of ten compressed tablets of each batch were determined by using electronic digital vernier calipers. The friability test, weight variation test, and disintegration test were performed in accordance with the methods prescribed in USP XXX, NF XXV.

Tablet-Crushing Strength. A texture analyzer (TAXT plus, Stable Microsystems, UK) was used for evaluating the hardness of the tablets. Tablet-crushing strength (T) was calculated using the formula: $T=2F/\pi dt$. Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively. The data reported are the means of six individual determinations.

Testing of Coated Tablets. The coated tablets were evaluated for weight variation and disintegration time. Further, the axial and radial diameters were measured as described above.

Tablet-Coating Strength. Tablet-coating strength was estimated by employing a texture analyzer (TAXT plus, Stable Microsystems, UK) using tablet-coating strength probe attachment. For the estimation of adhesive force, a coated 5-FU tablet was fixed at the lower station with the help of double adhesive tape, whereas, the upper station containing double adhesive tape only. However, for the estimation of cohesive force, CCG–CH films were fixed at the upper station with the help of double adhesive tape. The parameters set for the analysis were: pretest speed, 1 mm/s; test speed, 0.50 mm/s; posttest speed, 10 mm/s; applied force, 800 g; return distance, 10 mm; and contact time, 10–60 s.

FTIR-ATR Analysis

The coated tablet surface was subjected to spectral analysis using Bruker FTIR-ATR (ZnSc crystal, Alpha T, Bruker Optik GmbH, Rudolf-Plank-Str, 27-76275 Ettlingen, Germany).

DSC Analysis

CCG, CH, chitosan acetate films, and different CCG–CH films were subjected to DSC analysis (Mettler Toledo Star System, Switzerland) at a heating rate of 10°C/min from 20°C to 300°C.

Preparation of EDTA-Treated Magnesium Silicate

One percent *w/v* EDTA disodium salt was dissolved in water, and 1 g magnesium silicate was suspended in this EDTA solution. After storing this reaction mixture for 1 h at 40°C in a closed vessel, the suspended powder was washed thrice with water and dried in an oven for 24 h at 50°C. The dried EDTA-treated magnesium silicate (0.05–0.5% *w/v*) was then used in the coating process instead of magnesium silicate.

SEM Analysis of Coated Tablets

The outer macroscopic structure of coated tablets after sequential pH environmental treatments was analyzed by S-3400N scanning electron microscope (Hitachi, Japan). The tablet coat was peeled off with the help of a sharp knife and fixed on a brass stub. The samples were made electrically conductive by coating in vacuum (10 Pa) with gold using Hitachi Ion splitter (E-1010). The photographs of all the samples were taken at ×500 magnification.

In Vitro Release of 5-FU in Presence or Absence of Rat Cecal Content

Preparation of Rat Cecal Content Medium. Sprague Dawley rats having weights in the range of 200 to 300 g and maintained on normal diet were used for the study. CH and CCG aqueous solutions were administered orally for inducing the enzymes specifically acting on these polymers. The procedure involved oral administration of 1 ml of 1% *w/v* solution of CH and 1 ml of 1% *w/v* solution of CCG for 5 days. Cecal contents were extracted as detailed by Rubinstein *et al.* (24).

Drug Release Investigations. In vitro drug release studies were carried out using USP XXX-NF XXV (Apparatus 1–basket method) dissolution apparatus utilizing temperature of 37± 0.5°C with a constant stirring rate of 50 rpm. The uncoated as well as coated tablets prepared using different types of binders and coatings were evaluated for drug release by sequential exposure to buffer I.P pH 1.2 (500 ml) for 2 h, buffer I.P pH 7.4 (500 ml) for 3 h, and finally, in the presence of rat cecal content (5% *w/v*) in buffer pH 6.8 under a CO_2 environment (24). A sample of 5 ml was withdrawn from each dissolution vessel at regular intervals and replaced with an equal volume of respective fresh dissolution medium. The sample was filtered through a G3 filter, and 1 ml of filtered sample was diluted suitably whenever required with the respective dissolution medium. At the end of the study, the tablets were crushed with a pestle and mortar to determine the residual content of 5-FU in the tablet. The amount of drug released was determined spectrophotometrically employing a wavelength of 266 nm for acidic conditions and in basic conditions.

RESULTS AND DISCUSSION

In a traditional sugar-coating technique, a dispersion of gum is added to increase the viscosity of coating solution that can easily adhere to the uncoated tablet surface. However, natural gums possess a poor film-forming property and exhibit high acid solubility. It is possibly due to these reasons that gums in their putative form did not become popular for use in film-coating formulations for colon release dosage forms. Therefore, physicochemical modifications of gums could be a feasible way to make them suitable for use in formulating colon release dosage forms.

Preparation and Evaluation of Uncoated 5-FU Tablets

5-FU was granular powder. A 3-mg dose for the rat was found to be nonuniformly distributed in 35-mg spray dried lactose or microcrystalline cellulose (MCC). Hence, 5-FU was solubilized in a minimum quantity of water, and one portion of binder solution was added. The remaining binder solution was added to this portion, and the whole solution was used to form a wet mass. The dried mass was regranulated, mixed with colloidal silica, and compressed to form tablets. Interestingly, the yield of the batch prepared with MCC was found to be 50% as compared to 95% with spray dried lactose (Table I). It was observed that a film-like structure was formed by the movement of the upper punch into the die cavity when MCC was used as diluent. This film formation could have contributed to a decrease in yield of the batch when MCC was used as diluent. Hence, tablets were prepared using spray dried lactose as diluent for further investigations. The results of the evaluation of these uncoated 5-FU tablets are summarized in Table I.

Table I. Formulation and Evaluation of Uncoated 5-FU Tablets

Batch code	Composition of uncoated 5-FU tablets				
	Drug/tablet	Binder/tablet	Diluent/tablet		
	5-FU	CH, CCG (30:70, 1.5% *w/v*)	Spray dried lactose	Microcrystalline cellulose (MCC)	
SDL	3 mg	5 ml	35 mg	–	
MCC	3 mg	5 ml	–	35 mg	
	Evaluation of uncoated 5-FU tablets				
	Percentage yield	Maximum tablet-crushing strength (kg/cm^2)	Weight variation (%)	Drug content (%)	Friability (%)
SDL	95±1.5	6.5±0.5	0.39±0.12	99.6±1.25	0.07±0.01
MCC	50±2.5	5.5±0.5	0.44±0.14	99.3±0.25	0.10±0.02

5-FU 5-Fluorouracil, *SDL* spray dried lactose

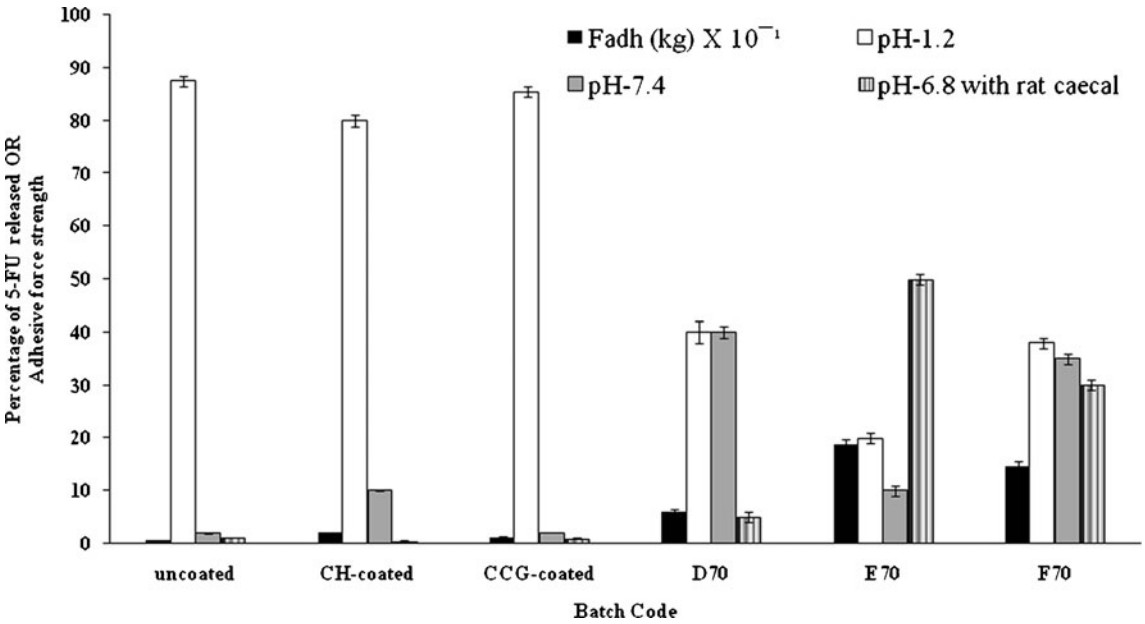


Fig. 1. Effect of adhesive force strength (Fadh using 25 s of contact time) of CH–CCG-coated tablets on *in vitro* release of 5-FU in pH 1.2, 7.4, and 6.8 with rat cecal content

Optimization of Tablet-Coating Process by Employing Texture Analyzer

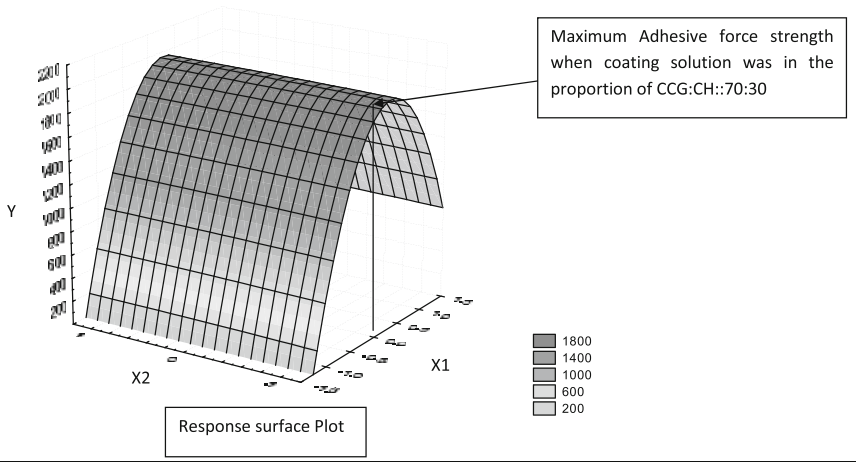
The ideal coating material is one that displays the highest binding of coating material with the tablet surface. Secondly, after drying, the coat of the coated tablet should exhibit negligible stickiness. Hence, an attempt was made to optimize these two essential properties using a texture analyzer by determining the adhesive force strength and cohesive force strength of the tablet coating. Adhesive force strength depicts the force required to separate the film coating from the coated tablets. Cohesive force strength is the estimation of stickiness among the coated tablets.

The uncoated tablets were observed to exhibit negligible adhesive force strength, while CH-coated and CCG-coated tablets exhibited very low adhesive strength (Fig. 1). However,

Table II. 3^2 Full Factorial Design for Optimizing Coating Solution that Provides Maximum Adhesive Force Strength

Factors	Formulation code								
	A80	**B80**	**C80**	**D70**	**E70**	**F70**	**G60**	**H60**	**I60**
X1	-1	-1	-1	0	0	0	1	1	1
X2	-1	0	1	-1	0	1	-1	0	1
Y[Adhesive Force strength (gms)]	597.2±5.6	600.6±6.2	608.4±6.4	1990.2±14.3	1997.7±17.1	1997.4±14.8	1879.3±47.3	1889.0±45.1	1889.5±47.1

Factors ↓	LEVELS →	-1	0	1	Coefficients ↓
Composition of CCG:CH	**X1 (CCG:CH)**	80:20	70:30	60:40	641.9(P=0.011)
Contact Time	**X2 (Sec)**	10	25	60	4.76 (p=0.979)



all these tablets released approximately 80% 5-FU in pH 1.2. According to USP30NF25; less than 10% of drug should be released in acidic conditions to satisfy delayed-release criteria. Hence, these tablets did not fulfill the delayed-released criteria. Therefore, tablets coated with solutions containing different proportions of CCG and CH were subjected to optimization through measurement of adhesive force strength. The selected compositions of CCG/CH ($X1$) and contact time ($X2$) of the upper probe with the coated/uncoated tablet surface for estimating adhesive force strength were identified as variables. The 3^2 full factorial design was used to explore a level that could provide maximum adhesive force strength. The results are shown in Table II. The multiple regression suggested compositions of CCG/CH mixture to significantly influence adhesive force strength ($p<0.05$) as compared to contact time of the upper probe with the coated tablet surface ($p>0.05$) (Table II). This behavior was evident in response surface plot too and suggested 70:30 ratio of CCG/CH to exhibit the highest adhesive force strength. Therefore, batch D70, E70, and F70 were selected for further studies. However, contact time of 10, 25, or 60 s did not show any significant effect at the significant level of 0.05. Hence, batch E70 evaluated by employing the midpoint of the contact time (25 s) was selected for modification of the coated surface. Interestingly, an increase in adhesive force strength of batch E70 tablets decreased the *in vitro* release of 5-FU. Hence, a crucial role of adhesive force strength on the release of 5-FU from CCG–CH-coated tablets could be suggested.

Magnesium silicate is widely accepted for use in various applications like paint, paper, and plastic industries. The morphology of magnesium silicate in sheets confers interesting lubricant properties due to its hydrophobic nature (25). In addition, the interaction of guar gum and dextrin with magnesium silicate studied through adsorption, floating, and electrokinetic measurements revealed adsorption densities to be independent of pH and the isotherms exhibited Langmuirian behavior (26). In another investigation, Wang and Somasundaran (27) studied the adsorption of locust bean gum (LBG) and guar gum (GG) at the solid–liquid interface using adsorption tests, electrophoretic mobility measurement, FTIR, and fluorescence spectroscopy (27). The results suggested the possibility of hydrogen bonding between LBG or GG with magnesium silicate. Hence, these findings reflected the role of magnesium silicate in reducing cohesiveness (stickiness that may arise over the coating surface) of coated tablets among themselves.

The results revealed tablets of batch E70 to exhibit high cohesive force strength. To decrease the cohesive force strength (i.e., reduce stickiness), magnesium silicate (0.05–0.5% *w*/*v*) was added at the final stage of the coating process. The effect of concentration of magnesium silicate on cohesive force strength is summarized in Table III. Further, the addition of 0.2% *w*/*v* magnesium silicate in the coating solution after preliminary coating was found to result in negligible cohesive force strength in batch E70.

Table III. Evaluation of CCG–CH-coated 5-FU Tablets (Batch E70)

Batch code	Concentration of magnesium silicate (% *w*/*v*)	Evaluation						
		Coating surface	Cohesive force strength (g) at contact time of					
			10 s	20 s	30 s	40 s	50 s	60 s
E70/0	Control	Smooth and uniform	893.2±4.29	894.8±4.09	899.3±4.44	899.8±3.98	899.7±3.87	899.8±3.90
E70/0.05	0.05	Smooth and uniform	493.3±3.01	497.8±3.40	501.2±3.11	501.8±2.97	501.2±3.52	501.7±4.45
E70/0.1	0.1	Smooth and uniform	94.8±1.49	96.2±1.33	98.3±1.74	98.4±1.74	98.2±2.01	98.1±2.14
E70/0.2	0.2	Smooth and uniform	0.82±0.21	0.04±0.01	0.0	0.0	0.0	0.0
E70/0.3	0.3	Rough and nonuniform	0.0	0.0	0.0	0.0	0.0	0.0
E70/0.4	0.4	Rough and nonuniform	0.0	0.0	0.0	0.0	0.0	0.0
E70/0.5	0.5	Rough and nonuniform	0.0	0.0	0.0	0.0	0.0	0.0

Effect of Magnesium Silicate on Cohesive Force Strength and In Vitro 5-FU Release

The results indicated a decrease in the release of 5-FU with an increase in concentration of magnesium silicate.

Further, increasing the concentration of magnesium silicate resulted in a negligible increase in cohesive force strength. It is interesting to note here that 5-FU is a polar drug. It was expected to dissolve and release faster in an acidic dissolution medium of pH 1.2 (Fig. 2). However, the addition of magnesium silicate to the intercalated CCG–CH coating surface significantly inhibited the release of 5-FU from coated tablets to such an extent that the release of 5-FU decreased to less than 6% as compared to 15% from formulations prepared without magnesium silicate. The criteria for the delayed-release dosage form according to USP30NF25 reveal that not more than 10% of the drug should be released from individual dosage form in acidic medium. Thus, the addition of magnesium silicate to the CCG–CH coating solution made the coating system lipophilic that prevented the release of 5-FU in an acidic environment. Further, the increase in concentration of magnesium silicate from 0.2% to 0.5% *w/v* did not significantly affect the 5-FU release, indicating 0.2% *w/v* concentration of magnesium silicate to be optimum for preventing 5-FU release. These findings suggested possibilities of intercalation of magnesium silicate in CH and/or CCG.

Exploring the Paradoxical Effect of Magnesium Silicate

Magnesium silicate is structurally endowed with two distinct features. The basal sheets are hydrophobic and are formed as a result of the rupture of van der Waals bonds. However, the edges contain broken Si–O and Mg–O bonds which, being charged species, contribute to the hydrophilic character (28). Therefore, due to these features, the possibility of interaction of Mg^+ ions with polysaccharides cannot be ruled out. The chance of Mg^+ ions to interact with polysaccharides could be explored by removing Mg^+ ions by pretreatment with EDTA and then coating the tablets with this magnesium silicate-treated EDTA. The 5-FU tablets

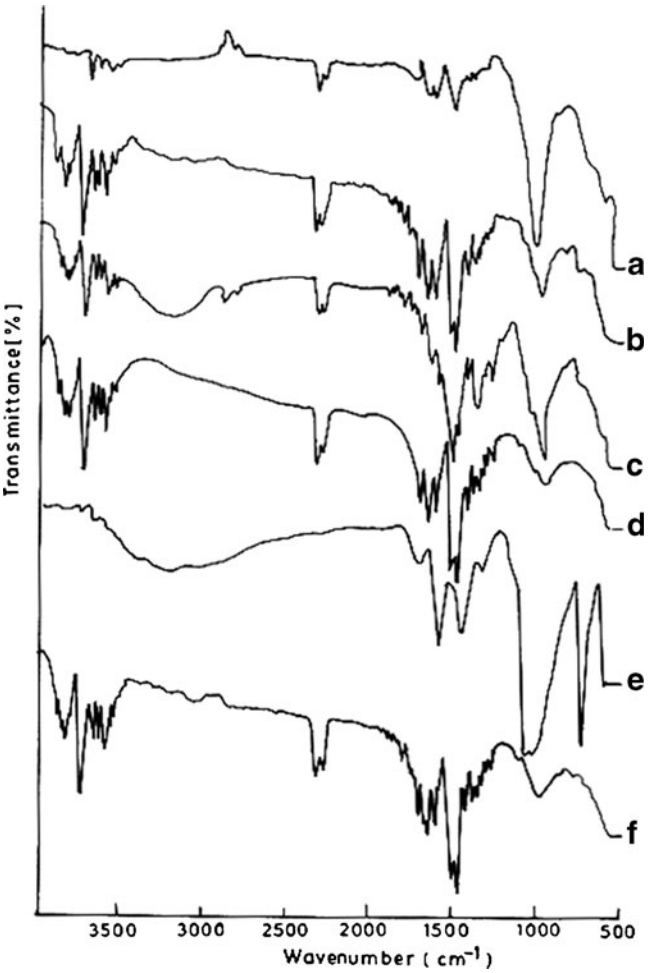


Fig. 3. FTIR-ATR spectra of **a** magnesium silicate, **b** pure *C. fistula* gum, **c** carboxymethylated *C. fistula* gum, **d** CCG–CH interacted, **e** CCG–CH (70:30) films processed with magnesium silicate as well as microwave treatment, and **f** CCG–CH (70:30) films processed with magnesium silicate pretreated with EDTA as well as microwave treatment

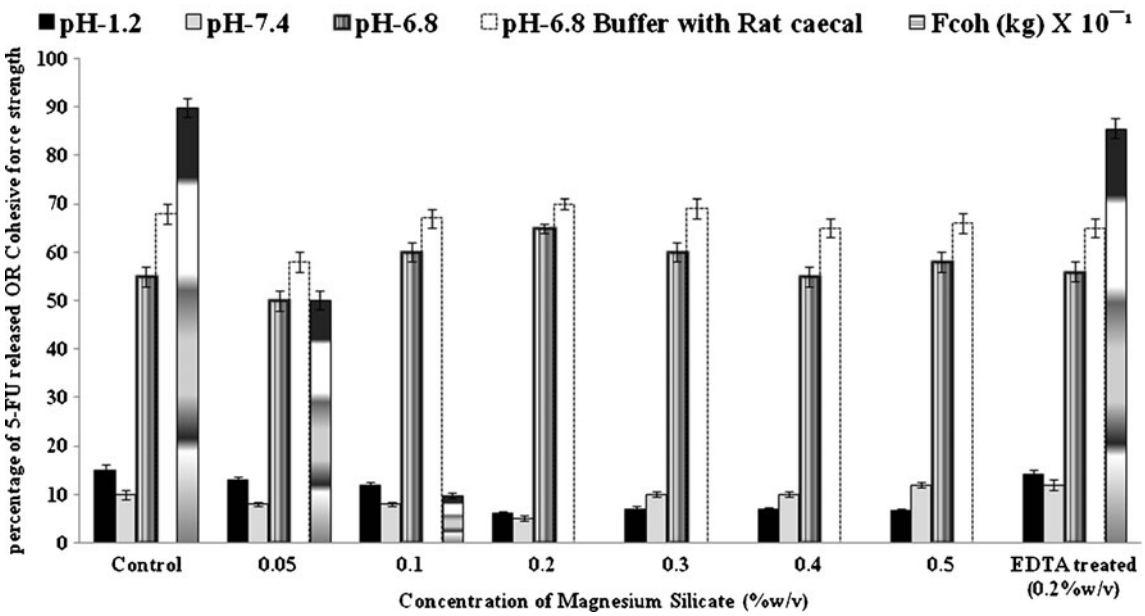


Fig. 2. Effect of cohesive force strength (Fcoh; 30 s of contact time) of CH–CCG-coated tablets (batch E70) prepared with various concentrations of magnesium silicate on *in vitro* release of 5-FU

coated with this magnesium silicate-treated EDTA showed a similar *in vitro* release profile as observed in 5-FU tablets prepared without magnesium silicate (Fig. 2). Thus, these findings point towards the interaction of Mg–O bonds with polysaccharide.

FTIR-ATR spectral analysis was conducted in order to evaluate the involvement of Si–O and/or Mg–O moieties of magnesium silicate. Figure 3 depicts the FTIR-ATR analysis of various combinations of CH, CCG, and magnesium silicate either alone or in combination. The FTIR-ATR spectra of pure magnesium silicate showed a band at 1,039 cm^{-1} characteristic of the out-of-plane symmetric Si–O–Si mode (Fig. 3a) as reported by Wang and Somasundaran (27). The bonds in the spectrum of around 870.7 and 568.32 cm^{-1} are probably associated with various Mg–OH modes. The band at 3,677 cm^{-1} of single Mg–OH stretching indicates a centrosymmetric relationship between the hydroxyl groups on both sides of the octahedral layers. The FTIR-ATR spectra of pure *C. fistula* gum (Fig. 3b) showed the band at 3,744 cm^{-1} representing O–H stretching vibration. The band at 2,360 and 2,322 cm^{-1} can be attributed to C–H stretching of CH_2 moieties. The bands due to ring stretching of galactose and mannose, respectively, were observed at 1,646 and 1,676.91 cm^{-1}. The bands in the region 1,500–1,450 cm^{-1} are

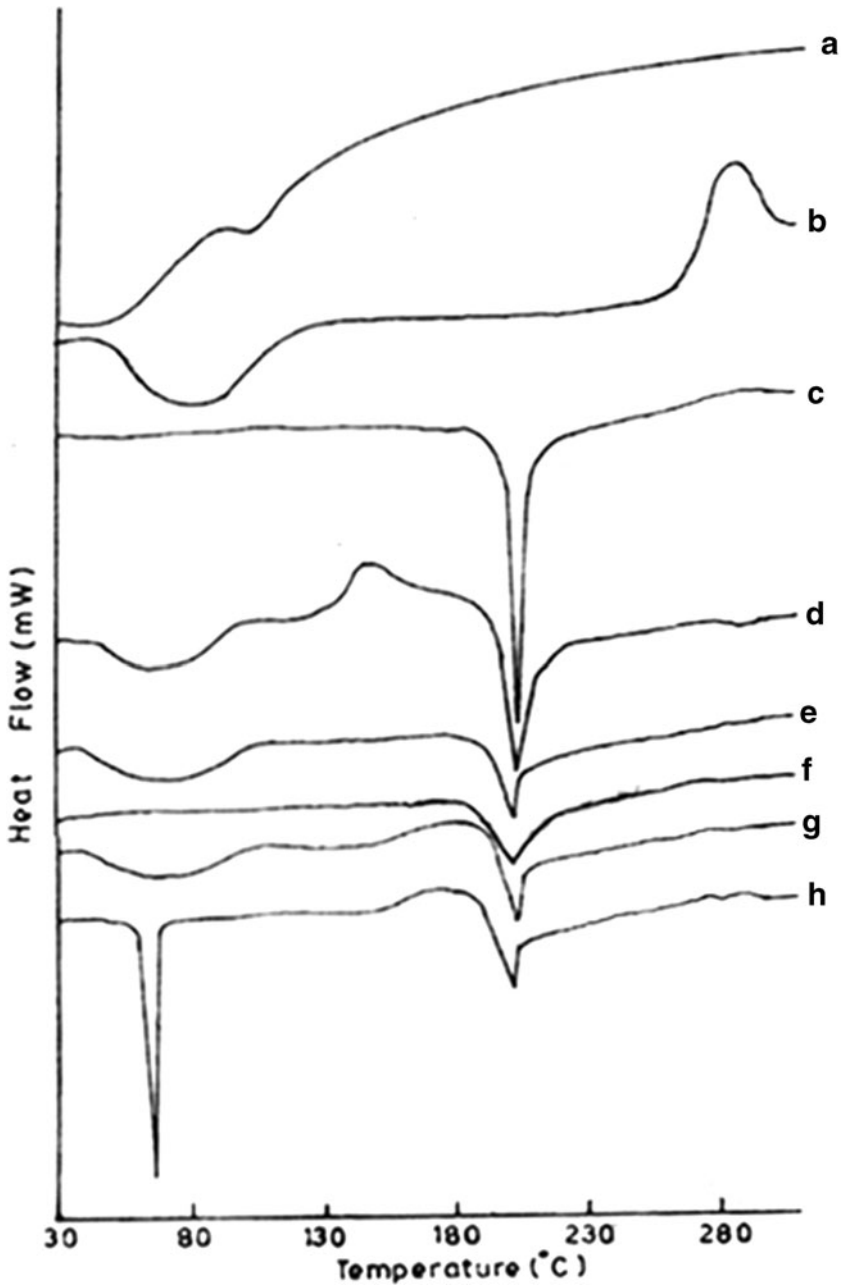


Fig. 4. DSC thermogram of **a** pure *C. fistula* gum, **b** pure CH, **c** CCG–CH interacted, **d** CH acetate film, **e** CCG–CH (70:30) film, **f** CCG–CH (70:30) film processed with microwave treatment, **g** CCG–CH (70:30) film processed with magnesium silicate, and **h** CCG–CH (70:30) film processed with magnesium silicate after microwave treatment

due to symmetrical deformations of CH_2 and C–OH groups. A similar peak was observed in the FTIR-ATR spectra of pure CCG. However, additional peaks at 1,316.46, 1,408.27, 1,462.66, 1,516.8, 1,547.87, and 1563.22 cm^{-1} characteristic of carboxymethyl moieties indicated conversion of pure *Cassia* gum into its carboxymethyl derivative (Fig. 3c).

The FTIR-ATR spectrum of CCG and CH showed a characteristic peak at 1,516 cm^{-1} of NH_4^+ moieties and at 1,463.28 cm^{-1} of carboxylic moieties indicating linkages of CCG with CH (Fig. 3d). The additional weak peak at 1,626.5 cm^{-1} of N–H vibrations suggested some amide linkages between moieties of CCG and N–H moieties of CH. The FTIR-ATR spectra of films prepared by mixing magnesium silicate and coating solution (CH/CCG::30:70) indicated characteristic two strong bands at 1,000 and 662.85 cm^{-1} and one weak band at 3,204.14 cm^{-1} (Fig. 3e) suggesting hydrogen bond formation between primary alcoholic (–CH_2OH) and Si–O–Si or Mg–O. However, the films prepared by mixing EDTA-pretreated magnesium silicate and coating solution (CH/CCG:: 30:70) did not reveal these characteristic peaks indicating absence of hydrogen bond formation (Fig. 3f). These further explain the cause for enhanced *in vitro* 5-FU release from EDTA-pretreated magnesium silicate-coated tablets and reduced 5-FU release from CH/CCG (30:70) and magnesium silicate-coated 5-FU tablets.

Further, the DSC analysis was conducted to explore this overwhelming influence of magnesium silicate. Figure 4a shows a DSC thermogram of pure sodium CCG indicating one endothermic transition at 98.2°C. The DSC thermogram of chitosan powder indicated one exothermic transition at 311.5°C along with one endothermic transition below 100°C (Fig. 4b). This exothermic transition showed that chitosan degraded at 311.5°C. A sample was prepared by separately dissolving CH in acetic acid and CCG in water. These were mixed to obtain interaction precipitates of CCG–CH. These precipitates were dried at 50°C for 4 h and subjected to DSC analysis. The appearance of one endothermic transition at 206.03°C (Fig. 4c) was ascribed to electrostatic interaction between CCG and CH. However, the absence of a peak below 100°C showed the absence of hydrogen bonding or any other weak interactions between CH and CCG. The thermogram obtained from chitosan acetate films showed a broader endothermic peak below 100°C (with onset temperature of 40°C to end set temperature of 105°C) probably due to the combined influence of moisture and acetic acid (Fig. 4d). A similar peak was observed for dried CCG–CH (70:30) film in addition to electrostatic interaction peak at 206°C (Fig. 4e). However, the broad peak with onset temperature of 40°C to end set temperature of 105°C was diminished when the CCG–CH (70:30) film subjected to microwave treatment (Fig. 4f). This indicates

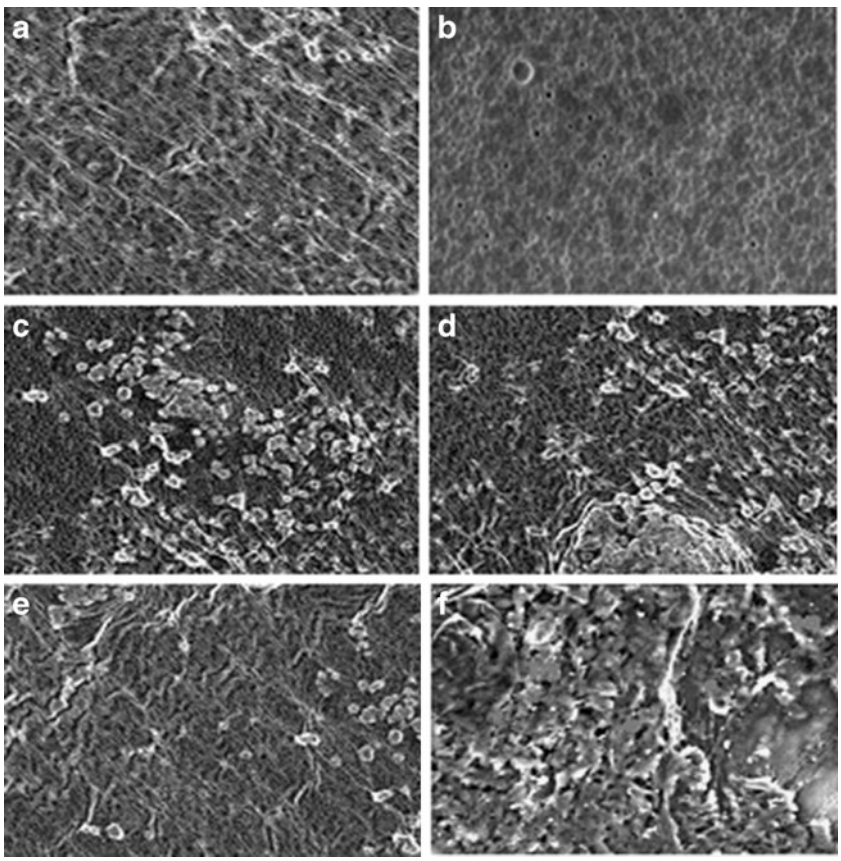


Fig. 5. SEM photograph of coated tablet surface containing **a** CCG–CH (70:30), **b** CCG–CH (70:30) after sequential pH treatment, **c** CCG–CH (70:30) with magnesium silicate, **d** CCG–CH (70:30) with magnesium silicate after sequential pH treatment, **e** CCG–CH (70:30) with EDTA-treated magnesium silicate, and **f** CCG–CH (70:30) with EDTA-treated magnesium silicate after sequential pH treatment

that microwave treatment did not only remove bound water, but it also evaporated free acetic acid. Further, the CCG–CH (70:30) films containing magnesium silicate showed endothermic transitions at 55°C and 206°C as observed in films prepared without magnesium silicate (Fig. 4g). However, appearance of sharp peaks at 65.68°C and 206°C in films of CCG–CH (70:30) containing magnesium silicate subjected to microwave treatment suggested interaction of magnesium silicate with CCG–CH (70:30) films (Fig. 4h). Hence, these findings were in accordance with those obtained with FTIR investigations. This further depicts the intercalation of magnesium silicate into the CCG–CH films that inhibited the *in vitro* release of 5-FU from tablets.

The surface behavior of CCG–CH (70:30)-coated tablets was examined using SEM analysis. The SEM photograph (Fig. 5a) of CCG–CH (70:30)-coated tablets appeared rough and uneven, and showed weak broken lines. The coated CCG–CH (70:30) tablets subjected to sequential pH treatment (i.e., pH 1.2, pH 7.4, and pH 6.8) revealed holes and weakened coat surface (Fig. 5b). The freshly coated tablets containing CCG–CH (70:30) and magnesium silicate appeared smooth (Fig. 5c). This appearance was preserved in the tablets after sequential pH treatment (Fig. 5d). However, the smoothness was lost when CCG–CH (70:30) containing EDTA-treated magnesium silicate was used to coat tablets (Fig. 5e and f).

CONCLUSIONS

The use of dusting powders for prevention of sticking as well as penetration of moisture during aqueous tablet coating is not new. However, the nonuniform spreading of dusting powders during the aqueous coating process leads to inconsistent *in vitro* release of drugs, specifically if the coating is for modified-release tablets. The developed aqueous coating formulation could be suggested to consist of a blend of adhesive force enhancer system (CCG–CH, 70:30) and a cohesive force reduction system (CCG–CH (70:30) containing magnesium silicate). The results indicated that coating the tablets with adhesive system (CCG–CH, 70:30) was not suitable for delivering 5-FU in the colon, probably due to its hydrophilic nature. The coating of cohesive force strength reduction system over these tablets significantly reduced the release of 5-FU from these tablets to 6% in acidic pH, thus complying with the requirement of enteric release. FTIR and DSC analysis strongly indicated the role of hydrogen bonding between primary alcoholic (–CH_2OH) groups of carboxymethylated *Cassia fistula* gum and Si–O–Si or Mg–O moieties of magnesium silicate in reducing the release of 5-FU from coated tablets in acidic pH.

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