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Research Article

Carboxymethylation of Karaya Gum: Application in Gastroretentive Drug Delivery for Sustained Release of Model Drug

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ABSTRACT

Karaya gum (KG) is one of the least soluble of the gums. It does not dissolve in water to give a clear solution but instead absorbs water rapidly to form viscous colloidal sols. Carboxymethylation of karaya gum is expected to improve its aqueous solubility and gelling behavior. Another objective of the research is to evaluate the potential of carboxymethylated karaya gum (CMKG) as a drug release modulator (in acidic dissolution medium), when combined with hydroxypropyl methylcellulose (HPMC) K15M based polymeric matrices bearing propranolol HCl (PHCL). In the present study, KG was carboxymethylated using Williamson ether synthesis. Fourier transform infrared spectroscopy (FTIR) spectroscopy confirmed the formation of CMKG. The prepared CMKG was used in conjunction with HPMC K15M as a polymer matrix in the formulation capsule dosage form, using PHCL as a model drug. The filled capsules were then coated with gelucire 43/01 to convert them into hydrodynamically balanced (HBS) capsule dosage form. Dextrose and fructose were also added to the drug-polymer mix as osmogen to facilitate the drug release. The degree of substitution of CMKG was found to be 0.87. HBS capsule dosage forms remained buoyant on 0.1 HCl for up to 6 hours, the buoyancy was attributed to the gelucire 43/01 coating around the capsule shell. From the experimentation, it was observed that CMKG, when mixed with HPMC K15M at 1:3 ratios, extended the release of model drug from HBS capsule dosage forms in 0.1 HCl. At CMKG:HPMC K15M ratio 2:1, the release of PHCL from HBS capsules revealed fast drug release in 0.1 HCl. From the observations, it is evident that KG is amenable to carboxymethylation to form CMKG. It is also evident that it is advantageous to combine CMKG with HPMC K15M as release modulator to retard the release of PHCL in acidic dissolution medium.

INTRODUCTION

In recent years, the development and utilization of polymers isolated from natural sources have attracted increasing attention due to their sustainability, biodegradability, and biosafety. However, they evidence some drawbacks, such as variable chemical composition, uncontrolled rates of hydration, pH-dependent solubility, poor mechanical strength when combined with other polymers, and high susceptibility to microbial attack.^[1-3] Chemical modification provides an efficient route not only for removing such drawbacks but also for improving swelling and solubilization.^[4] Because of their improved

physicochemical properties chemically modified natural polymers have found numerous applications in drug delivery, biomaterials development, food and beverages, water purification, etc.^[5-9]

Karaya gum is an anionic polysaccharide that has diverse applications, such as, suspending agents, emulsifying agents, bulk laxatives, dental adhesive, etc. It is a heavily acetylated acidic polysaccharide composed of α -D-galacturonic acid and α -l-rhamnose residues in the main chain with 0-4 of the acid and 0-2 of rhamnose linkages.^[10] As the polymer is heavily acetylated, it is least soluble among the other plant-derived gums.

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KG swells in water to yield highly viscous dispersions; however, these dispersions show a permanent loss in viscosity on heating. KG has diverse applications, such as, suspending agent, emulsifying agent, bulk laxative, and dental adhesive, and so on. KG has earlier been chemically modified by thiolation,^[11] dodecenylsuccinic anhydride derivatives,^[12] grafting,^[13] and deacetylation.^[14] However, there are no literature reports on carboxymethylation of KG in pharmaceutical literature and applications. Thus, considering the same, the present study was designed with the objective of synthesizing CMKG and evaluating its potential as a release modifying polymer for gastroretentive delivery of model drug PHCL. CMKG was synthesized by Williamson ether synthesis, and characterized by FTIR and differential scanning calorimetry (DSC) studies.

MATERIALS AND METHODS

Materials

The PHCL was obtained as a gift from Akums Pharmaceuticals, India. Gum Karaya was obtained as dry gummy exudate from *Sterculia urens* Tree. HPMC K15M was purchased from Central Drug House and Sigma Life Science, respectively. All other reagents were of analytical grade.

Methods

Synthesis of CMKG

The CMKG was synthesized from KG as per the synthetic procedure^[15] with some modification. Briefly, KG (2 grams) was dispersed in 100 mL distilled water. After the gum was well dispersed, an appropriate volume of sodium hydroxide solution (40% v/v) was added, at a rate of 1 mL within 15 minutes, with continuous stirring at room temperature. An aliquot of 15 mL monochloroacetic acid was added to the reaction mixture over a period of 10 minutes. The reaction mixture was heated to 70°C with continuous stirring for 4 hours. The reaction product was repeatedly extracted with ethanol (90% w/v) and separated by centrifugation (3,000 rpm for 15 minutes at 4°C). After the third extraction, the pH was adjusted to seven with glacial acetic acid. Finally, the precipitate was washed with water and dialyzed [dialysis membrane 1,000 kDa nominal molecular weight cut-off (MWCO, Sigma Aldrich, USA)] against distilled water for a couple of days (60 hours), and finally dried.

Characterization of CMKG

Both native and CMKG were characterized using FTIR, DSC, and X-ray diffraction.

FTIR

The KG and CMKG samples were subjected to FTIR spectroscopy in an FTIR spectrophotometer (PerkinElmer, version 10.6.0) in the range of 4,000 to 400 cm⁻¹ as KBr

pellets. Spectra were collected using a Perkin Elmer Spectrum One FTIR Spectrometer spectrophotometer (scan range 450–4,000 cm⁻¹, resolution 1 cm⁻¹).

DSC

The DSC thermograms of KG and CMKG samples were recorded using a differential scanning calorimeter (Q10 V9.0 Build 275, TA Systems, USA). About 7 to 8 mg of sample were crimped in a standard aluminum pan and heated in a temperature range of 40 to 250°C at a heating rate of 10°C per minute with a nitrogen purge of 50 mL/min.

¹³C Nuclear Magnetic Resonance (NMR) characterization

The solid-state ¹³C Cross Polarization Magic-Angle Spinning NMR (CP/MAS) NMR measurements were carried out on the 400 MHz Varian solid-state NMR spectrometer at IIT, Roorkee.

The high-resolution ¹³C CP/MAS NMR spectra were recorded at the resonance frequency of approximately 100 MHz with the use of 4 mm rotors and MAS frequency of 12,000 Hz and $\pi/2$ pulse duration of 1.9 μ s. In the CP experiments, the Hartmann-Hahn condition was achieved with the radio frequency field strength of 58 kHz, a contact time of 1 ms, and relaxation delay of 4 seconds between two consecutive scans. A high-power proton-decoupling field of 92 kHz was applied during data acquisition. The spectra were obtained at room temperature averaging over 5,000 to 33,000 scans. The chemical shifts were referenced to the Tetramethylsilane (TMS) using adamantane as an external standard.^[15]

X-ray Diffraction

Powder X-ray diffraction pattern of KG and CMKG were recorded employing X-ray diffractometer (Tabletop XRD, Miniflex 2, Rigaku, Japan). The sample powders were scanned from 0 to 80° diffraction angle range under the following measurement conditions: source, nickel filtered Cu-K radiation; voltage 30 kV; current 15 mA; scan speed 0.05 min⁻¹; division slit 1.25°; receiving slit 0.3 mm.

Determination of Degree of Substitution

The degree of substitution was determined by classical acid wash method.^[16-19] In brief, freshly precipitated CMKG (0.5 grams) was dispersed in hydrochloric acid reagent (20 mL) for 3 to 4 hours, followed by filtration and washing with 70% methanol to remove the acid followed by drying to constant weight in an oven at 70°C. The dried CMKG, so obtained, was well dispersed in 70% methanol, followed by the addition of an excess of sodium hydroxide (0.5 N) with stirring for 3 hours to dissolve the sample completely. The excess of sodium hydroxide was back titrated with hydrochloric acid (0.5 N) using phenolphthalein as an indicator. The degree of carboxymethyl substitution (DS) on KG was calculated using the following equation:

$$DS = \frac{0.162A}{1 - 0.058A}$$



Where A is the milliequivalent of sodium hydroxide required per gram of the CMKG sample.

Preparation of HBS Capsules

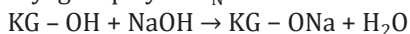
Single unit capsules were prepared by physically blending drug with the required quantity of polymer and other additives, as mentioned in Table 1, using double cone blender for 15 minutes. The powder mix was then encapsulated into hard gelatin capsules size 0. The HBS capsule formulations were then dip-coated with molten gelucire 43/01 maintained at 50°C. The coated HBS capsules were immediately put into the refrigerator (2–8°C) until further use.

In vitro Buoyancy of Formulations and Drug Release Study

In vitro buoyancy and drug release from HBS Capsules were evaluated simultaneously with a USP XXXI dissolution apparatus type II (paddle type, Electro Lab, Mumbai, India) at 50 rpm in 900 mL 0.1 M HCl at $37 \pm 0.5^\circ\text{C}$. At predetermined intervals, a 1 mL aliquot was withdrawn and replenished with an equal volume of fresh dissolution medium. The withdrawn samples were analyzed UV spectrophotometrically at 278 nm. HBS capsule formulations that sank within the first hour were discarded from drug release studies.

RESULTS AND DISCUSSION

Gum karaya is the common name given to the dried exudation of the *Sterculia urens* tree. It is partially acetylated polymer of galactose, rhamnose, and glucuronic acid with an molecular weight (MW) of approximately 9,500,000. Carboxymethylation of polysaccharides is carried out by Williamson ether synthesis, in which the polysaccharide alkoxide is reacted with monochloroacetic acid, and the primary and secondary alcohol groups are substituted by carboxymethyl group by an $\text{S}_\text{N}2$ reaction.^[18-20]



(Karaya gum)

$\text{KG} - \text{ONa} + \text{ClCH}_2\text{COONa} \rightarrow \text{KG} - \text{OCH}_2\text{COONa} + \text{NaCl}$
The yield of synthesized CMKG was 78.65%, and its appearance was off-white amorphous powder. The CMKG was characterized by FTIR and DSC studies. Fig. 1 shows the FTIR spectra of KG and CMKG in the frequency range of 4,000 to 400 cm^{-1} .

KG displayed a broad absorption band at 3,459 cm^{-1} due to presence of –OH of galactopyranose and glucopyranose

rings, a peak at 2,929 cm^{-1} corresponds to the C-H stretching mode of –CH₂ group, peaks at 1,730 and 1,620 cm^{-1} are due to C=O stretching vibrations of free carboxylic acids and the methylated galacturonic acid esters of the gum. The absorption peaks between 1,041 to 1,153 cm^{-1} were attributed to C-O and C-C stretching vibrations of pyranose rings of KG. The absorption peak at 1,428 cm^{-1} was due to deformation vibrations of CH₂ and C-OH groups, and peaks at 1,300 to 1,200 cm^{-1} were due to C-O-C stretching vibrations. The above observation corresponds to the findings by Sethi *et al.*^[21]

The spectra of CMKG (Fig. 2) shows a broad band from 3,459 to 33,435 cm^{-1} due to overlapping contributions of free and bonded OH groups of carboxylic acid. The peaks due to CO stretch of carboxylate ion appear at 1,641 and 1,412 cm^{-1} , while the CO stretch of carboxylic acid appears at 1,080 cm^{-1} . The bands at 1,025 cm^{-1} represented (C-O-C) stretching. The appearance of new absorption band at 1,563 cm^{-1} is suggestive of change in chemical environment brought by the carboxymethylation process.

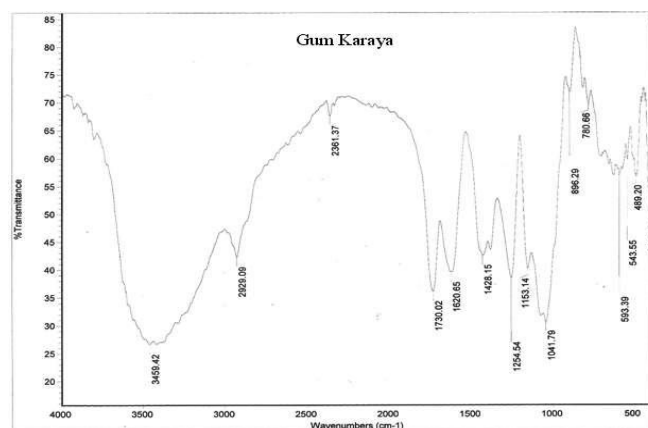


Fig. 1: FTIR spectra of KG

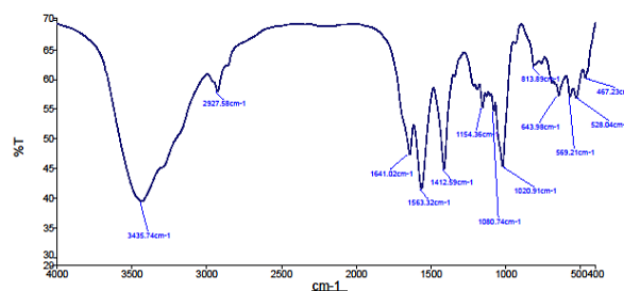


Fig. 2: FTIR spectra of CMKG

Table 1: Composition of formulations containing PHCL

Formulation code	Propranolol HCl (mg)	HPMC K15 M (mg)	KG (mg)	CMKG (mg)	Dip coatings with molten gelucire 43/01
R	100	75	25	-	-
R1	100	75	25	-	One
R2	100	75	-	25	One
R3	100	50	-	50	One

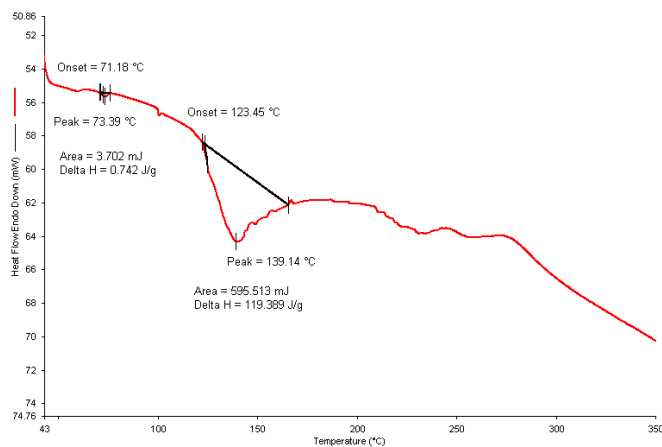


Fig. 3: DSC thermogram of KG

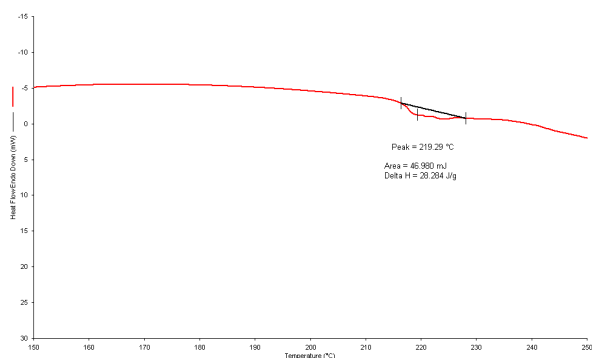


Fig. 3A: DSC thermogram of CMKG

Figs 3 and 3A exhibits the DSC thermograms of KG and CMKG. The thermal curve of KG showed a broad endotherm at 139°C, attributed to the glass transition temperature of the polymer.

The DSC curve of CMKG (Fig. 3A) shows a broad endotherm at 219°C. The shift in the endothermic peak indicates that modification of GG has taken place on carboxymethylation.

¹³C NMR Spectra of KG

The results of solid-state ¹³C NMR spectra of carboxymethylated KG exhibited (Fig. 4) intense peaks at $\delta = 181.818$ ppm [due to C=O (carboxylic acid moieties)]. The peak at 103.56 ppm corresponds to C1 carbon in the β -glycosidic bond, while the broad signal at 82.05 ppm (due to ring carbon of galactopyranose ring of KG). The signals of C5, C2, carbons are at 72.206 and 75.674. The peak at 60.923 is due to -CH₂OH. The signal at 21.748 ppm is due to the acetyl residues in the polysaccharide. The signals at 25.11, 26.193, and 31.859 are due to aliphatic carbons.

The ¹³C spectrum of KG was also recorded in a similar manner (spectra not shown). ¹³C NMR spectra showed intense characteristic peaks at $\delta = 101.2$ and 100.34 ppm (due to anomeric carbons of KG), at 82.023 ppm (due to ring carbon of galactopyranose ring of KG), at 71.84 ppm (due to -C-O-C- bond of KG), and 23.39 and 19.66 ppm [due

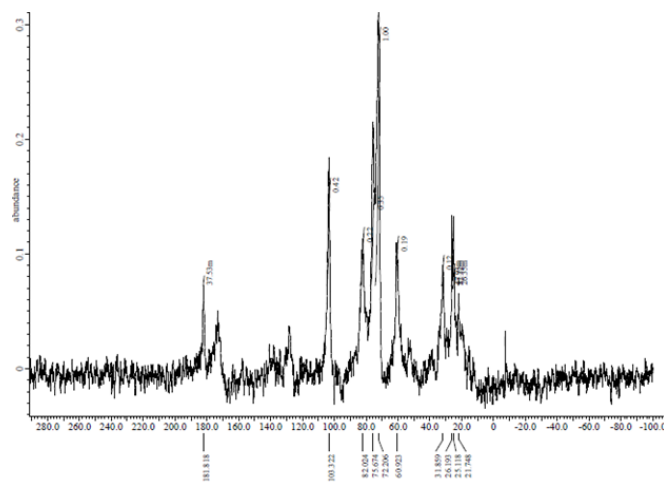
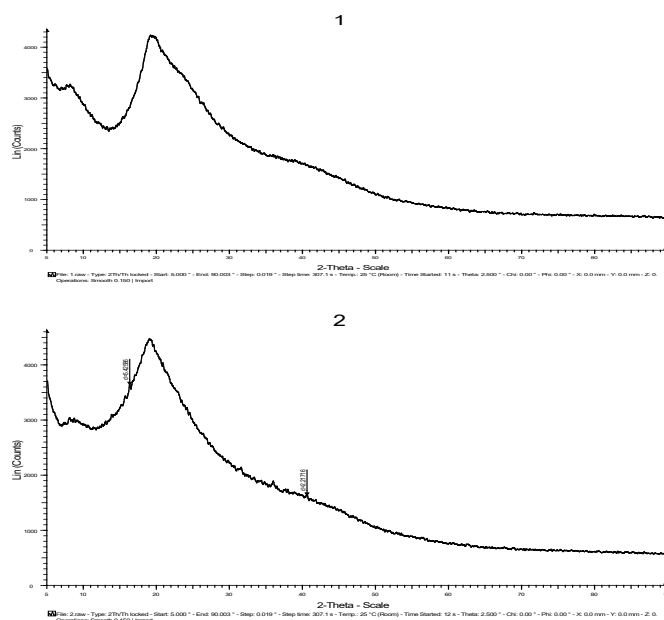
Fig. 4: ¹³C spectra of CMKG

Fig. 5: X-ray diffractogram of (1) KG; (2) CMKG

to methyl carbon (CH₃) of rhamnose and acetyl residues in the KG].^[11]

Fig. 5 displays the X-ray diffraction pattern of KG and CMKG. The diffractogram of KG is typical of amorphous materials with no sharp peaks, while diffractogram of CMKG shows the typical characteristic peaks appearing at around 16 and 42° (2 θ scale), which indicates the increase in crystallinity of KG on carboxymethylation.

Degree of Substitution

The KG possesses numerous hydroxyl groups in its structure. The hydroxyl groups can be substituted with carboxymethyl groups by reacting in alkaline medium with monochloroacetic acid. From the degree of substitution, one can find how many hydroxyl groups are converted into carboxymethyl group. The reactivity of primary



Table 2: Physicochemical attributes of HBS capsule formulations

Formulation code	Average fill per capsule (mg)	Average weight of filled capsule	Average weight of gelucire 43/01 coated capsule	% drug content
R	200 ± 8.3	302 ± 7.6	367 ± 6.9	99.82 ± 3.76
R1	200 ± 6.6	304 ± 5.6	371 ± 5.4	99.18 ± 3.11
R2	200 ± 6.9	301 ± 4.6	368 ± 7.1	99.79 ± 3.41
R3	200 ± 6.8	301 ± 5.4	372 ± 6.8	99.29 ± 4.76

**Fig. 6:** Gelucire 43/01 coated HBS capsule formulations

hydroxyl is more than secondary hydroxyl groups; if we completely react three-hydroxyls, we will get the DS of “3.”^[16-19] The sample of CMKG was found to have degree of carboxymethyl substitution of 0.87 ± 0.14 , as determined by classical acid-wash method.

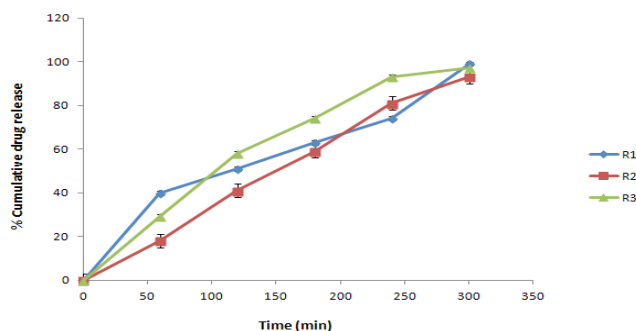
Development of HBS Capsule Formulations bearing PHCL

Selection of Model Drug

Highly water-soluble drugs are very difficult to formulate into a sustained-release oral dosage form. The problem becomes more pronounced when the drugs exhibited an absorption window in upper gastrointestinal tract (GIT) or instability/ reduced solubility in the alkaline environment of small intestine.^[22-24] PHCL is such a medicinal agent. The drug showed pH-dependent solubility; at pH 1.2, the solubility of PHCL is 225 mg/mL.^[25] For sustained stomach specific release of such drugs, it would be desirable to provide a drug delivery system that inherently has the property of extended gastric residence coupled with release retarding properties. Such a system will ensure the availability of the entire absorption window for highly soluble absorption window limited compounds or complete dissolution of drugs in the acidic environment of the stomach, thereby improving drug bioavailability. In the present investigation, an attempt has been made to study the feasibility of polymeric matrices composed of nonionic HPMC and CMKG as carriers for sustained stomach specific delivery of PHCL.

Preparation of HBS Capsules

Various HBS capsule formulations were prepared in two steps. In the first step, drug-polymer mix (Table 1) was

**Fig. 7:** % cumulative drug release in 0.1 HCl (pH 1.2)

encapsulated in hard gelatin capsule size 0, using hand-operated capsule filling machine. These filled capsules were then dip-coated by dipping into molten gelucire 43/01 (Fig. 6).

The lipid (gelucire 43/01) formed a thin hydrophobic coating around the capsules, which ultimately provides immediate buoyancy to the HBS formulations, when immersed in acidic dissolution medium. Few physicochemical attributes of HBS formulations are given in Table 2.

In vitro Buoyancy and Drug Release Studies

The *in vitro* buoyancy and drug release studies (Fig. 7) were performed in triplicate using USP (type II) dissolution apparatus at 50 rpm in 900 mL 0.1 HCl (pH 1.2) maintained at $37 \pm 0.5^\circ\text{C}$.

With the exception of formulation R, all other formulations (R1, R2, and R3) remained buoyant for the entire duration of release study. Formulation R composed of HPMC K15 M, KG, and the drug could not float for more than one hour and released almost 80% of drug before sinking in the acidic dissolution medium. This could be explained as propranolol is highly hydrophilic, which further reduces the strength of the aqueous gel layer due to high diffusional driving force and consequently increased erosion. As a result, hydrogel lost its integrity and became distorted, leading to burst release and premature sinking of the formulation.^[26] Considering the observation, in the present study, to improve the buoyancy and to address the problem of burst release, we have decided to coat the capsule formulations (R1, R2, and R3) with molten gelucire 43/01.

As a consequence, formulations R1, R2, and R3 remained floated on the dissolution medium for up to 6 hours. It was observed that as the HBS capsule formulations

were put into dissolution medium, the lipid coating around the capsule begins to erode, causing the penetration of dissolution medium inside the capsule shell leading to gel formation due to presence of hydrophilic polymer matrix (HPMC/KG or HPMC/CMKG). The whole system behaved like a lipid embedded polymeric raft, which floats over the surface of the dissolution medium and releases the drug slowly over an extended period of time. The purpose of adding dextrose and fructose to the formulation mix was to give impetus to the drug release from a lipid embedded hydrogel structure due to the generation of osmotic pressure. From formulation R1, about 40, 51, 74, and 99% drug was released at the end of 1st, 2nd, 4th, and 6th hour, respectively. Here also, there was initial burst release of PHCL from the formulation. But later on, drug was released in an extended manner for up to 6 hours. This could be attributed to slow erosion of capsule shell due to lipidic coating, and consequently delayed penetration of dissolution medium inside the capsule. Up to 15 minutes, there was no drug release. After about 30 minutes, there was surge in drug release. This could be attributed to the fast disintegration of capsule shell due to rapid erosion of thinly coated lipid. The effect of dextrose and fructose on drug release is also not ruled out. These osmogens were added to impart osmotic pressure to the gel network. Once the capsule shell was completely disintegrated into pieces (beginning of 45th minute), the penetration of dissolution medium became relatively easy in the polymer matrix; this has caused not only the hydration of polymer but also dissolution of osmogens. Dissolution of osmogens has resulted in development of osmotic pressure within the partially formed gel network. Once the raft structure was fully formed, after about 60 minutes, the drug was released in a uniform manner for up to 6 hours. After that, formulations sank.

In case of formulation R2, the KG was replaced in the polymer matrix with equal amount of CMKG in the HBS capsules. From formulation R2, about 18, 59, 81, and 93% drug was released at the end of 1st, 3rd, 4th, and 6th hour, respectively. The drug release was statistically ($p > 0.05$) different from R1. This could be attributed to the controlled diffusion of drugs through the hydrophobic-hydrophilic polymeric raft, effectively countering the high diffusion driving force that might be exerted by highly hydrophilic PHCL.

In case of formulation R3, the CKG concentration was increased to 50 mg, drug release was increased compared to R1 and R2 ($p < 0.05$). From formulation R3, about 29, 58, 74, and 93% drug was released at the end of 1st, 2nd, 3rd, and 4th hour, respectively. This could be attributed to the formation of highly hydrophilic drug-polymer gel due to increase in concentration of CKG, embedded in lipid raft; the drug release was modulated by osmogen and diffusion driving force exerted by the highly hydrophilic drug. This leads to a comparatively faster release of drug from the HBS capsules.

CONCLUSIONS

In this study, we have prepared and evaluated gelucire 43/01 coated HBS capsules for the sustained stomach specific delivery of highly hydrophilic model drug PHCL. In this study, three approaches were combined: for prolonged floating, coating of gelucire 43/01 on the hard gelatin capsules; release retardation by hydrophilic HPMC/KG or HPMC/CMKG based polymer matrix; and release facilitation by osmogens, dextrose, and fructose. Observations from this study suggested that all these approaches worked in conjunction and brought about a drug delivery system, which was not only capable of floating up to 6 hours but also retarded the release of the highly hydrophilic model drug. Another peculiarity of this work is that a very small amount of polymer was used in the polymer matrix. This polymer matrix formed a weak hydrogel upon exposure to dissolution medium, but the release retarding effect of the formed hydrogel was augmented by the hydrophobic gelucire 43/01, and at the same time, osmogens prevented the excessive retardation of drug release by osmotic effect. We propose that the prepared HBS capsule formulation may constitute a potential carrier for sustained stomach specific release of hydrophilic drugs.

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