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EVALUATION OF DRUG RELEASE FROM HPMC CARBOXYMETHYL GUAR GUM MATRICES

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ABSTRACT

The objective of present work was to study the feasibility of modified Guar gum - HPMC K4 M polymeric matrices as carrier for sustained stomach specific delivery of highly water soluble model drug, Verapamil HCl. Two types of modifications were carried out on native Guar gum. physical and chemical. In case of physical modification, Guar gum dispersions were exposed to microwave radiation, whereas, in case of chemical modification, carboxymethyl Guar gum was prepared using Williamson synthesis. The prepared modified Guar gum samples were characterized by FTIR for the evidence of carboxymethylation (in case of chemical modification) and molecular integrity (in case of physical modification). The prepared modified Guar gum samples were than combined with HPMC K4M and model drug followed by encapsulation in hard gelation capsules. The prepared hydrodynamically balanced (HBS) capsule dosage forms were than evaluated for in vitro buoyancy and drug release studies in 0.1 M HCl. The HBS formulations based on modified Guar gum-HPMC K4M exhibited excellent in vitro buoyancy (24 h) and were capable of sustaining the drug release for prolonged period. The drug release followed Korsmeyer-Peppas kinetics for chemically modified guar gum-HPMC K4M matrices and Zero order from physically modified Guar gum HPMC K4M matrices. Overall it may be concluded that modified guar gum-HPMC K4M matrices may constitute interesting polymeric carriers for sustained stomach specific release of drugs with absorption window in upper GIT.

KEYWORDS: Guar gum – HPMC K4 M, Verapamil HCl, 0.1 M HCl.

INTRODUCTION

Oral route is the most preferred route of administration for drugs exhibiting a "small absorption window" in gastrointestinal tract (GIT). For the drugs with absorption window in GIT, it is important that drugs not be delivered substantially beyond the desired site of action or absorption. To achieve this goal, controlled release systems often designed. These drug delivery systems not only control the rate at which it releases the drug over the time (temporal control) but also control on the location from which it is delivered (spatial control). Many of these controlled delivery systems utilize hydrophilic, polymeric matrices that provide useful levels of control to the delivery of sparingly soluble drugs. For soluble drugs and particularly for highly soluble drugs, such matrices do not provide adequate control over the drug release rate, instead resulting in a release that approximates first-order kinetics. That is, the rate of release is an inverse function of the square root of the elapsed time. With this pattern of release, most of the drug in the matrix is often released within the first hour in the acidic environment of stomach. For drugs like, Verapamil Hydrochloride (VHCL), whose solubility and thus absorption, decrease with increase in pH, the retention of the drug delivery system in the stomach and the rate at which the drug is released is very important. An approach to prolong the retention of VHCL in the stomach and to control its release rate from the dosage form is to engineer a polymer matrix capable of swelling and erosion in the acidic environment of stomach to form a swelled yet erodible hydrodynamically balanced mass. From such an *in situ* forming hydrogel, it is expected that the swelling of the polymer matrix will produce low density mass and continuous erosion causes a constant delivery rate of the drug from the matrix.

In the present investigation, pH independent swellable and erodible HPMC K4M and pH dependent swellable carboxymethylated Guar gum was used to engineer the polymer matrix. Guar gum (GG) is a polysaccharide similar in structure to cellulose. It is a polycationic copolymer consisting of glucosamine and N-acetylglucosamine units. GG, commonly obtained by partial deacetylation of chitin derived from the exoskeleton of crustaceans. Although GGJ is a very useful polymer with low toxicity, its limited solubility particularly at a physiological pH is a major obstacle for pharmaceutical and cosmetic applications. GG is a weak base with a pKa value of 6.2-7.0[6] due to the D-glucosamine residue, which leads to its insolubility at neutral and alkaline pH. GG dissolves in water at pH lower than 6.5, at which a substantial fraction of its amino groups are ionized. It is generally soluble in acidic solutions such as those of acetic acid, lactic acid and dilute hydrochloric acid.

Why carboxymethylated Guar gum ?

Natural gums are polysaccharides consisting of multiple sugar units linked together to create large molecules. Gums are frequently produced by higher plants as a result of their protection mechanisms following injury. Among various polymeric modifications of natural gums, carboxymethylation leads to formation of polyelectrolyte which increases the solubility of the polysaccharide. Other advantages of carboxymethylation are its cost effectiveness and then on toxicity of the products. Carboxylated polymers were expected to exhibit better water-binding capacity and increased water solubility. Further, carboxymethylation also confer a negative charge to otherwise neutral polymer molecules, which might come handy during the preparation of sustained drug delivery systems.

Gastroretentive Drug Delivery Systems

When a drug is taken orally it interacts with specific absorption sites located in different portions throughout the gastrointestinal tract (GIT), resulting in absorption of certain agents in stomach, the upper or lower intestine.[7] Therefore, gastroretentive drug delivery is an approach to prolong GRT, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects.[8] Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time GRT of drugs.[9] Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems etc.[10,11] The present work deals with gastroretentive approaches that have recently become leading methodologies in the field of Hydrodynamically balanced systems (HBS). In gastro retentive drug delivery systems stomach play key role in such systems.

Stomach and its physiology

The stomach is the most dilated part of the gastrointestinal tract and is composed of a thick muscular layer. The main function of the stomach is to act as a temporary reservoir for ingested food, to mix and reduce ingested solids to a semi fluid mass, known as chyme, by the action of acid and enzymatic digestion, and then emptying these contents at a controlled rate into the upper small intestine (duodenum).[12] This enables better contact of the ingested

material with the mucous membrane of the intestines and thereby facilitates absorption.[13] The stomach can be divided into three anatomical regions: the funds, the corpus or body and the antrum. The proximal region, made up of the funds and corpus, serves as a reservoir for ingested material, which gradually presses the gastric contents forward to the distal stomach and the duodenum, whereas the distal region (antrum) acts as a gastric homogenizer and grinder and it is coordinated with the corpus in the propulsion of gastric contents towards the pylorus.[14] The opening of the stomach to the duodenum is controlled by the pyloric sphincter, which allows liquids and fractions of chyme to empty while other material is retro pulsed into the antrum of the stomach and caught up by the next peristaltic wave (contraction of the distal stomach) for further size reduction before emptying.[14,16] Each section of the stomach is covered with a mucous membrane with a variety of secretory glands located beneath the epithelium and whose distribution varies from one region to another.[17] The gastric secretions include.[18,19]

- ***Acid* (HCl)** secreted by the parietal cells, which maintains the pH of the stomach between 1 and 3.5 in the fasted state.
- ***Gastrin*,** a hormone that stimulates gastric acid production and aids in gastric motility. The release of gastrin is stimulated by peptides, amino acids and distension of the stomach.
- ***Pepsins*,** which are proteases whose precursor, pepsinogen, is released by the gastric chief cells (or peptic cells). Pepsins break down proteins into peptides at low pH. The low gastric pH produced by the HCl leads to the hydrolysis of pepsinogen into pepsin; Pepsins are more efficient in cleaving peptide bonds between hydrophobic and preferably aromatic amino acids.
- ***Mucus*,** which is secreted by the surface mucosal cells and lines the gastric mucosa. The mucus protects the gastric mucosa from the combination of acid and the proteolysis action of pepsin.

Very little nutrient and drug absorption occurs in the stomach due to its small surface area compared to the small intestine. The rate of gastric emptying can be a controlling factor in the onset of drug absorption from the major absorptive site, which is usually the small intestine.

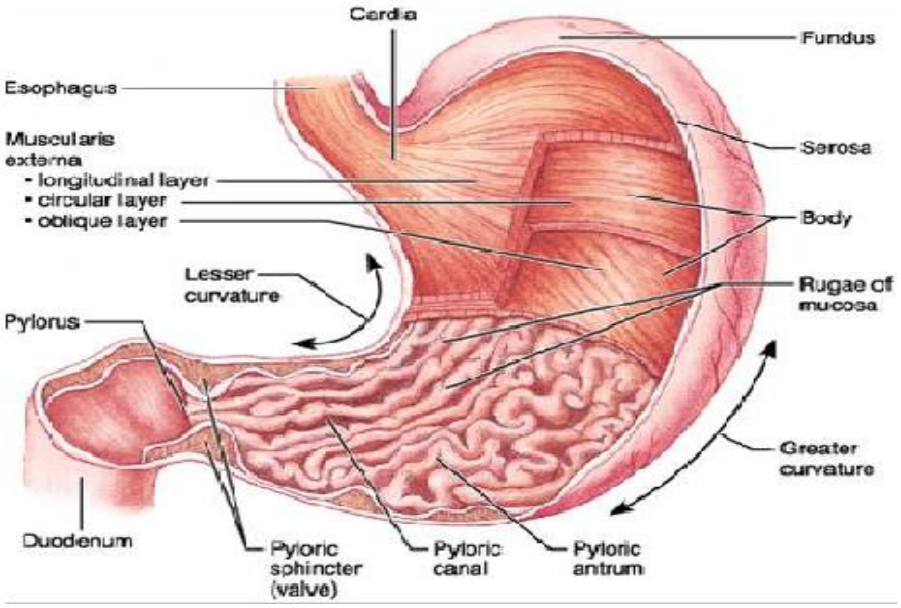

Fig. 1.1: Anatomy of Stomach.

A variety of gastroretentive drug delivery systems have been reported in the literature. These drug delivery systems are based on different modes of operation and have been variously named, for example as low density systems, swelling systems, ion exchange resins, osmotically controlled systems, bioadhesive forms etc.[20]

Gastroretentive Dosage Forms

Low Density Systems

The low density systems particularly, float once in contact with the gastric juice and allow prolonged residence time into the stomach by preventing premature emptying through the pylorus. They are usually made of biodegradable materials which disintegrate after a determined period of time and the residual form is then eventually emptied from the stomach.[21] Floating properties of drug delivery systems can be based on several principles, including inherent low density, low density due to swelling or to gas generation.[22]

Hydrodynamically Balanced Systems

Hydrodynamically balance systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form.[23,24]

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid at body temperature, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Figure 4).[25] Incorporation of fatty excipient gives low-density formulations and reduced penetration of water, reducing the erosion.[26]

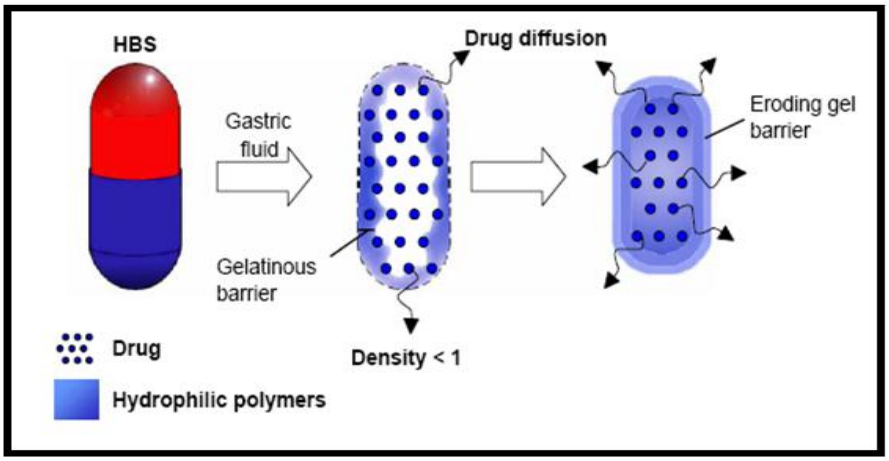

Figure 1: Hydrodynamically Balanced System (HBS).

MATERIALS AND METHODS

Materials

Verapamil Hydrochloride (VHCL) was obtained as gift samples from Dr. Reddy's Laboratories, India. Guar gum (GG) was procured from Sigma Aldrich, Brookfield. HPMC K4M was procured from Colorcon, India. All other chemicals used were of analytical grade. HPLC grade water was used in all the experimental work.

Table 1: Equipments.

Name of Equipments	Model,Name of company
Digital weighing balance	Citizen CY-220
UV–Visible Spectrophotometer	Shimadzu-1800, Kyoto, Japan
FT-IR Spectrophotometer	Shimadzu-8400S
USP dissolution apparatus type II	Electrolab-08L, Goregaon, Mumbai

Methods

Preparation of Carboxymethyl Guar gum (CMGG)

Purified guar gum was dispersed in 150 ml of isopropyl alcohol, in 250 ml of three neck flask equipped with a mechanical stirrer and contact thermometer for control of temperature. After the gum was well dispersed, the appropriate volume of NaOH solution (30%) was added at a rate of 1 ml within 15 min (total volume added 10 ml). After that required amount of Monochloroacetic acid (10 g) was added to the reaction mixture over a period of 10 min. The reaction mixture was heated and maintained at a specific temperature with continuous stirring for constant time to drive the reaction process to completion. After completion of reaction carboxymethyl guar gum was precipitated with the help of methanol and the precipitated product was purified.

Characterization

Characterization of (CMGG) by Fourier Transform Infrared Spectroscopy (FTIR)

The resulting products were characterized by FTIR (Nicolet spectrometer) spectroscopy and thermal gravimetric analysis (TA instrument, USA) in nitrogen atmosphere, at a heating rate of 20^0C /min.

Characterization of CMGG by Differential Scanning Calorimetry (DSC)

The CMGG samples were also characterized by DSC. For this purpose TA instruments Q-200 Differential Scanning Calorimetry instrument was used.

Determination of degree of substitution

The degree of substitution (DS) is the average number of sodium carboxymethyl groups bound per anhydroglucose unit. This method is used to determine the number of substituent groups added to the guar gum backbone. From the DS one can find how many hydroxyl groups is converted into carboxymethyl group. Degree of substitution markedly affects the properties of the compound. 1 gm. of Na- CMGG was dissolved in known amount of water. Then this solution was passed through regenerated Amberlite IRA 96 anion ex- change resin no. number of times till it become acidic. Then solution was divided into two equal parts labeled as solution 1 and solution 2. The exhausted resin was regenerated by passing 1 N HCl solution (3-4 times) followed by washing with distilled water to remove any excess acid. Solution1was taken into previously weighed beaker. The solution was heated until dryness on hot plate and then cooled and weighed Na-CMGG. Solution 2 was titrated against a standard

solution of NaOH. Note down the burette reading and find out the degree of substitution by following equation (1) & (2).

$$DS = \frac{0.162 \times B}{1 - 0.58 \times B} \quad (1)$$

Where,

$$B = \frac{Volume\ of\ 1N\ NaOH\ Used}{Weight\ of\ Sample} \quad (2)$$

Preparation of physically modified Guar Gum

Apart from chemical modification physically modified Guar gum was also prepared. Two types of microwave irradiated Guar gum were prepared. In first type (G-I), Guar gum was hydrated in deionized water and then placed in a refrigerator for two days at 2-8^{0}C. After that the Hydrogel was removed equilibrated to room temperature and the dried in a microwave oven.

Swelling of polymers

Accurately weighed amount of polymer/polymeric blend compositions with and without drug were put into bags made up of dialysis membrane (1000 Da molecular weight cut off, Sigma Aldrich). The bags were then heat sealed on both ends and put into 0.1 M HCl (pH 1.2) using USP type-II (Electrolab, India) at 37 ± 0.5°C and 50 rpm paddle speed. After predetermined time period (15 min, 30 min and 45 min), the bags were removed from the vessel, mopped with filter paper, and weighed on a digital balance(1 mg sensitivity, Citizen).

Preparation of hydrodynamically balanced (HBS) Capsule formulations

Single unit HBS capsules were prepared by physically blending VHCL with the required quantity of polymers using double cone blender for 15min (table 1), followed by encapsulation in hard gelatin capsules.

Table 2: Composition of Various HBS formulations.

Formulation code	GG	GG-I	GG-II	CMGG	HPMC K4M	VHCL
D1	50	---	---	---	150	80
D2	---	50	---	---	150	80
D3	---	---	50	---	150	80
D4	---	---	---	50	150	80

Determination of Drug Contents of HBS Capsules

Drug contents were determined by emptying 10 HBS capsules from each formulation as completely as possible. A powder equivalent to average weight was added to 100ml 0.1M HCl (pH 1.2, 37 ± 0.5 ^{0}C), followed by stirring for one hour at 500rpm (13). The solution was filtered through a 0.45μ membrane filter and diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 278 nm (VHCL).

In vitro buoyancy and drug release studies

In vitro release of VHCL from the HBS capsule formulations was performed in USP dissolution apparatus type II at 50 rpm. Evaluation of drug release was performed by using 900mL 0.1M HCl (pH 1.2) at 37 ± 0.5 ^{0}C. At predetermined intervals, one ml aliquot was withdrawn and replenished with an equal volume of fresh dissolution medium. Withdrawn samples were analyzed spectrophotometrically at 278 nm.

Drug Release Mechanism

Different kinetic models such as zero-order, first-order, and square root (Higuchi 1961) can be applied to interpretation of drug release kinetics. A zero order release refers to a uniform or nearly uniform rate of release of a drug from the solid dosage form after coming in contact with an aqueous environment, independent of the drug concentration in the dosage form during a given time period. Dosage forms with zero-order release generally provide maximum therapeutic value with minimal side effects. For many extended release formulations, the rate of drug release initially increases rapidly followed by decreased rate of drug release. This type of drug release is categorized as the first-order release. Such dosage form may not produce uniform concentration levels of the drug in the systemic circulation for a prolonged period of time (Paulo et al. 2001; Higuchi 1961). The Higuchi release equation predicts that the drug release is caused primarily by diffusion mechanism:

$$Q = K\sqrt{t} \qquad \text{Equation 1}$$

Where Q is the amount of the drug released in time t and K is the release constant from the equation. The data were also subjected to Korsmeyer-Peppas power law as in equation (2). The Korsmeyer-Peppas model provides an insight into the type of drug release mechanism taking place from swellable polymeric matrices (Paulo et al. 2001; Higuchi 1961):

$$\frac{Mt}{M\infty} = Kt^n \qquad \text{Equation 2}$$

Where $Mt/M\infty$ is the fraction of drug released in time t, $K$is the structural and geometric constant, and n, the release exponent, is estimated from linear regression fit of the logarithmic release data. Practically, one has to use the first 60% of a release curve to determine the slope obtained from equation (2) regardless of the geometric shape of the delivery device. A good fit to the Korsmeyer-Peppas equation indicates the combined effect of diffusion and relaxation mechanisms for the release.

Statistical Analysis

The differences in average data were compared by simple analysis of variance (one-way analysis of variance) or Student's t-test (Sigma Plot 11).

Statement of human and animal rights

This study does not contain any studies with human or animal subjects performed by any of the authors.

RESULT AND DISCUSSION

Guar gum (GG) is a non-ionic polysaccharide and is composed of galactose and mannose units (Fig 1). Its main chain consists of β-D-mannopyranose (β-D-mannose) units connected through 1,4-glycosidic linkages having side branches of β-D-galactopyranose (β-D-galactose) at every alternating mannose unit connected through 1,6-glycosidic linkages to the main backbone.

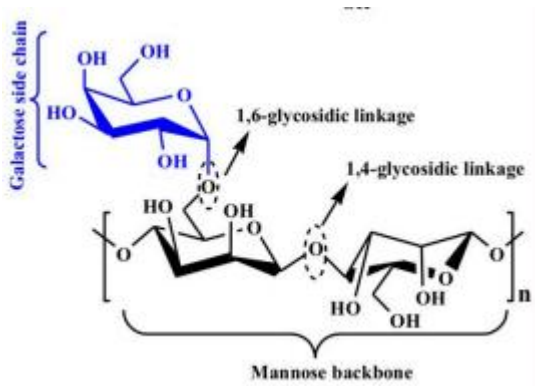

Figure 1: Chemical structure of Guar gum.

But due to the uncontrollable viscosity of the guar gum solution, uncontrollable rate of hydration, instability of its solutions for longer time and susceptibility to microbial contamination restricts its use in pharmaceutical industries.[10,11,12,13] To overcome these draw back guar gum should be chemically modified. In the present investigation, chemical

modification employed was carboxymethylation. Carboxymethylation of guar gum employed the Williamson ether synthesis procedure, which is a consecutive two-step reaction, proceeding with a strong base such as sodium hydroxide that deprotonates the free hydroxyl groups (particularly, the hydroxyl group of (-CH2OH) in guar gum) to form alkoxides, thereby increasing their nucleophilicity. Carboxymethyl groups are then formed in a reaction between guar alkoxides and Monochloroacetic acid.

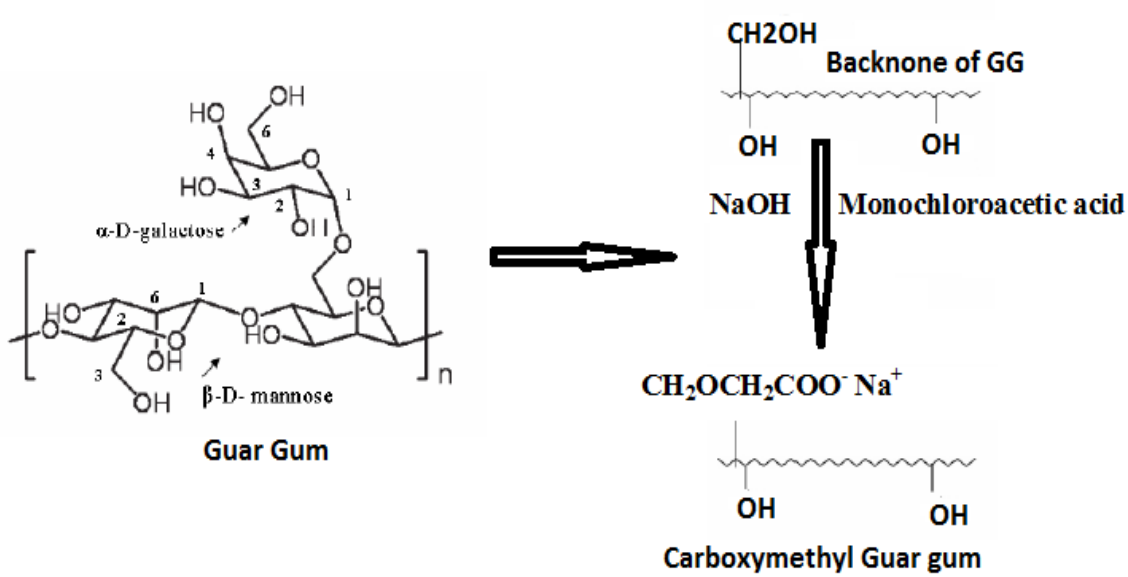

Figure 2: Conversion of Guar gum into N, O-Carboxymethyl Guar gum.

Properties of CMGG depend on degree of substitution and viscosity. Guar gum possesses three hydroxyl groups in its anhydroglucose unit, where one is primary the other two are secondary. The reactivity of primary hydroxyl is more than secondary hydroxyl groups, if we completely react three-hydroxyls, we will get the DS of "3". The derivatization of GG to CMGG was ascertained by FTIR study.

FTIR characterization of CMGG

The FTIR spectra of GG and CMGG are shown in Fig. 3. [**carbohydrate polymers**].

The FTIR spectrum of GG exhibited a broad absorption band at 3336.8 cm^{-1} due to OH stretching vibration. A sharp absorption band at 2919 cm^{-1} was assigned to CH_2 symmetrical stretching vibration. The absorption band appearing at 1640 cm^{-1} was due to OH bond belonging to water molecules. The CH_2 bending in GG was assigned to absorption at 1413 cm^{-1} and the bending of C O C appeared at 1017.7 cm^{-1} frequency region.

The absorption band due to OH stretching vibration in CMGG (g3) shifted to 3417 cm^{-1} and its intensity appeared to be reduced. This means that some of the OH groups of GG were involved in carboxymethylation. The band assigned to water (bending of water) which appeared at 1640 cm^{-1} in GG was absent in CMGG. In addition, a sharp new peak at 1410cm^{-1} was concerned with the symmetrical stretching vibration of carboxylate group in CMGG.

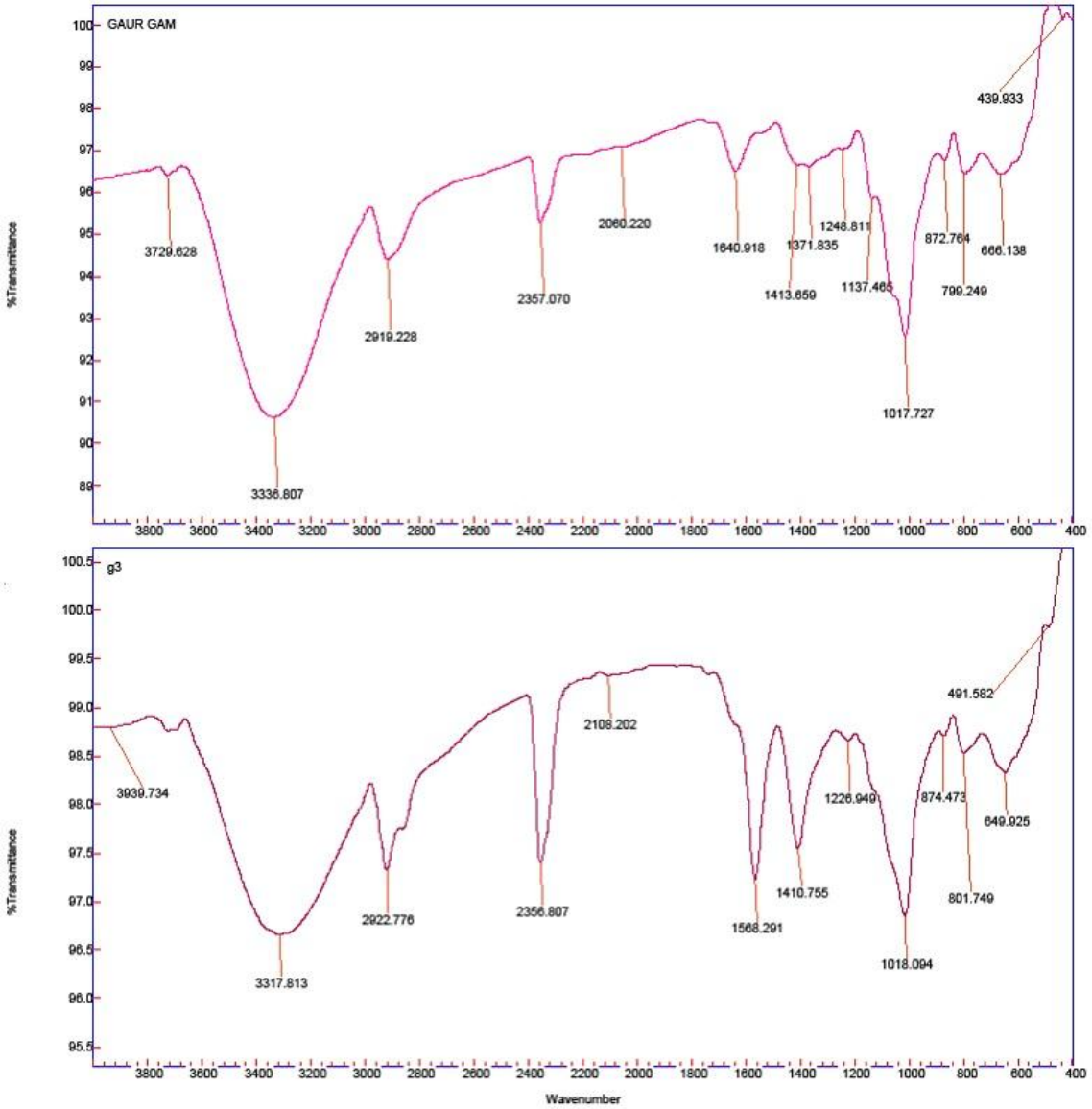

Figure 3: FTIR spectra of Guar gum (GG) and Carboxymethyl Guar gum (CMGG).

Besides chemical derivatization, microwave irradiated guar gum was also prepared and evaluated with respect to drug delivery applications. The reason for preparing microwave irradiated guar gum was the uncontrollable viscosity of native guar gum solutions. For this reason, guar gum needs to be depolymerized to give lower molecular weight fractions

suitable for desired pharmaceutical applications. Microwave radiation is a well known technique which has been reported to cause depolymerization of guar gum. A domestic microwave (IFB Solo 20PM2S 20 Liters 800 Watts Microwave Oven) with a rated power of 800W was used in the work. Two types of microwave irradiated samples were prepared, namely G-I & G-II. In case of G-1, a 2% w/v aqueous dispersion of guar gum was prepared by hydrating the native guar gum in deionized water for 12 hr. The prepared dispersion was then kept in microwave oven until all the water was removed from the dispersion. G-II was prepared in somewhat different manner, in this the guar gum solution prepared in the same manner as mentioned above, was kept in refrigerator at 4^0C FOR TWO DAYS before drying in the microwave oven. The dried samples were then crushed and pass through the mesh no 40 to get free flowing powder. The FTIR spectra of microwave irradiated guar gum samples GG-I (g2) and GG-II (g1 new) is given below (figure 3).

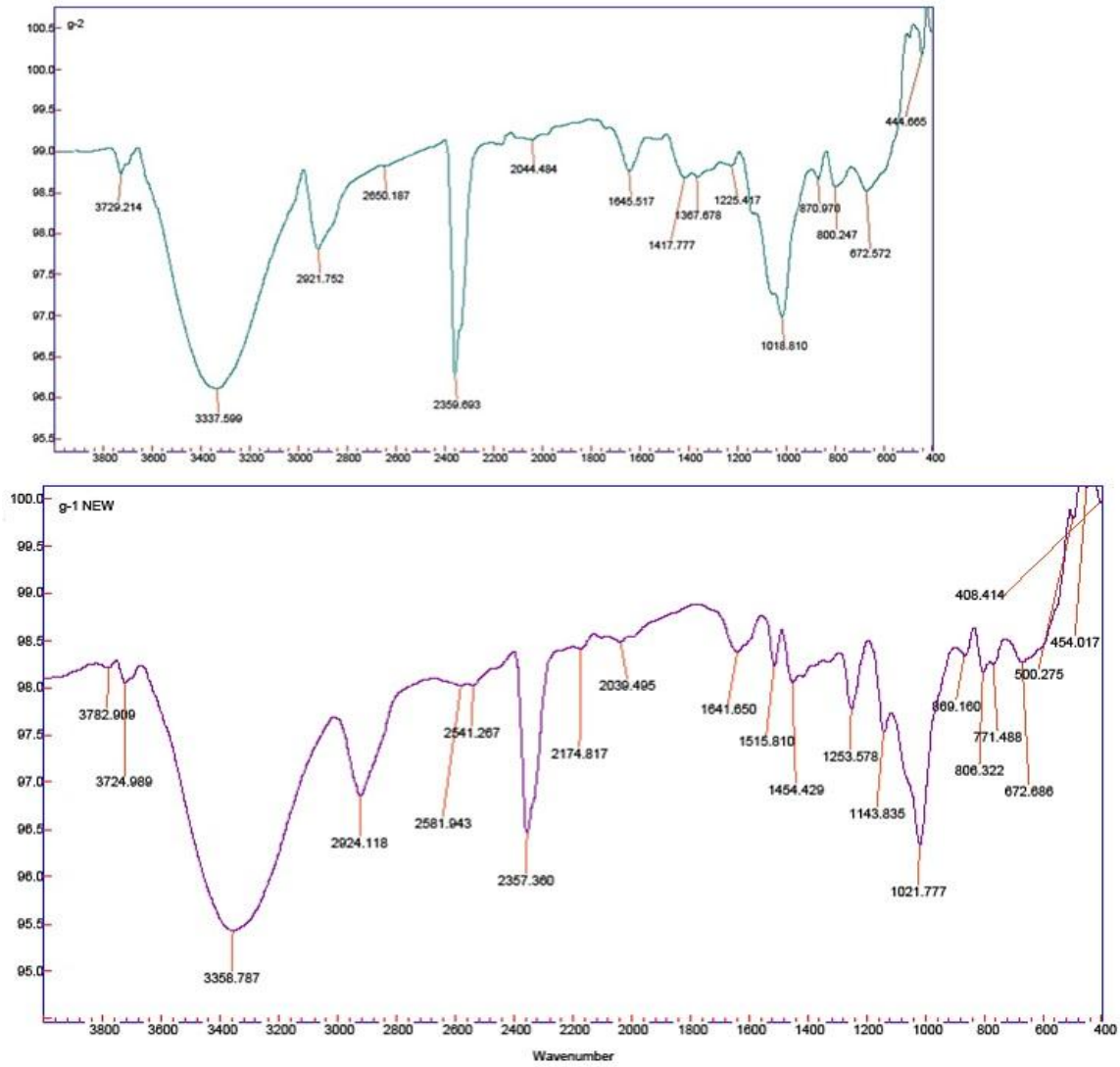

Figure 4: FTIR SPECTRUM of GG-I (g2) and GG-II (g1 new).

FTIR spectra give better idea about the chemical structure identity and any structural changes occurring during the treatment. Analysis of the control (native) guar gum and GG-I & GG-II was performed and the obtained results have been given in Fig. 4.

It can be observed from the figure that the guar gum subjected to has a spectrum super imposable over that of the control (native) guar gum. The peaks observed in the spectral region between the 800 cm^{-1} and 1200 cm^{-1} shows highly coupled C—OH and C—O—C stretching modes of polymer backbone. The peak near the spectra 3342 cm^{-1} was due to the O—H stretching vibration of polymer and water involved in hydrogen bonding.[49] The region between 500 cm^{-1} and 700 cm^{-1} represented the crystallinity of the polymer.[50] Appearance of small new peaks was observed in microwave treated guar gum possibly attributed to marginal changes. The results have clearly established that there are no major changes in the functional groups and chemical structure. The treatment only breaks the polymer structure giving possible viscosity reduction without any changes in the functional properties.

DSC characterization of CMGG

The DSC thermograms of Guar Gum and CMGG's were recorded and compared. The DSC was carried out 20^0C/min under continuous flow of dry Nitrogen gas. The thermograms were recorded in the range of 50-200^0C for Guar Gum and 50-500^0C for CMGG. The thermogram of Guar gum exhibited a broad endothermic peak at 122.40^0C attributed to the loss of water due to vaporization.

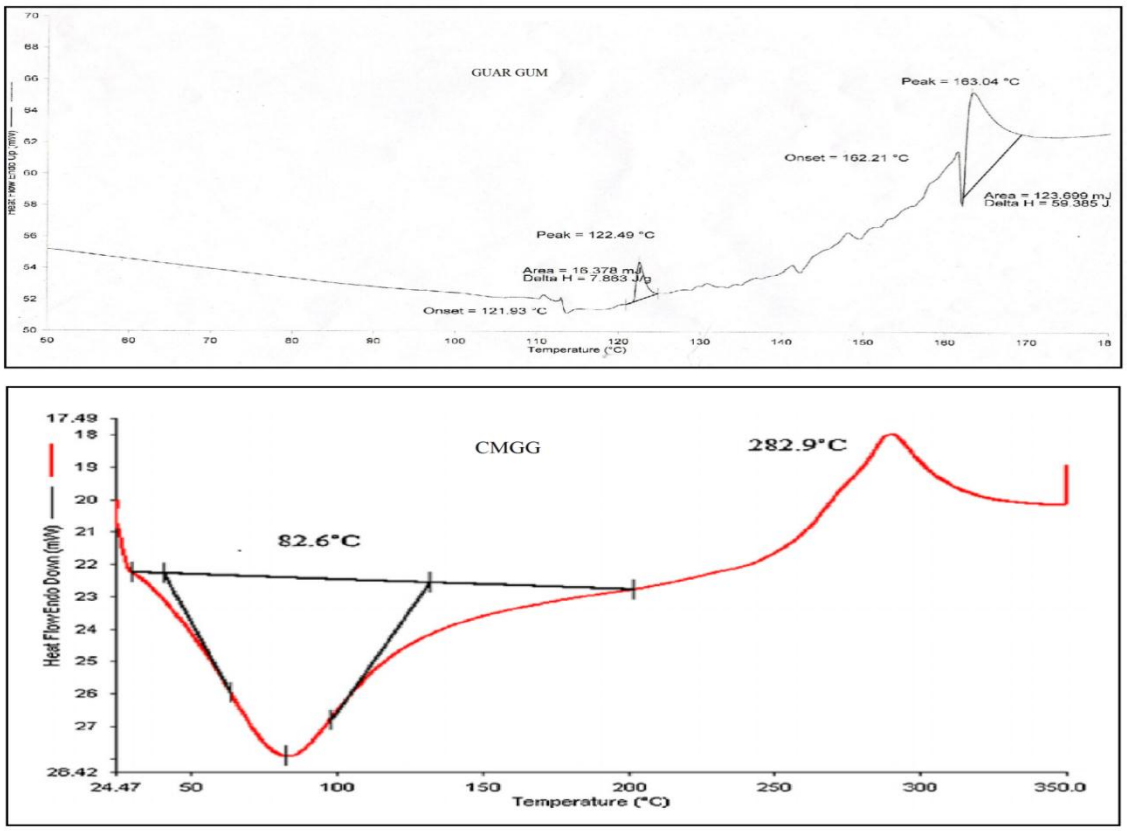

Figure 5: DSC spectra of Guar gum (GG) and Carboxymethyl Guar gum (CMGG).

Determination of Degree of Substitution (DS) [carbohydrate polymers]

GG possesses numerous hydroxyl groups in its structure. The hydroxyl groups can be substituted with carboxymethyl groups by reacting in alkaline medium with Monochloroacetic acid since, there is an average of 3 OH groups per sugar unit the degree of substitution should theoretically be 3. In the present study, however, the degree of substitution was found to be 0.71 ± 0.11. From the work of various researchers, it appears that the DS in guar gum rarely exceeds. Although, there are a number of OH groups in GG, carboxymethylation occurs primarily at free CH_2OH groups (i.e. the C6 position of units) due to steric resistance. The steric hindrance by OH groups present in GG is probably responsible for low DS.

Swelling studies

Quick hydration and subsequent gel formation is a foremost and important property of polymeric excipients to be used in sustained release formulations. In the present investigation polymers used were GG, modified GG (GG-I, GG-II & CMGG) and HPMC K4M. HPMC is a non ionic hydrophilic cellulose derivative containing methoxyl and hydroxypropyl groups

that supports its hydration properties. GG is also a non ionic polymer which swellsin polar solvents like water by forming strong hydrogen bond. The hydrogen bonding activity is due to the presence of hydroxyl groups in guar gum molecule. The rate of guar gum viscosity development increases with decreasing pH and increasing temperature. A temperature range of 25-40^{0}C is desirable for maximum viscosities of guar gum dispersion.**[Guar gum: processing, properties and food applications)\].** Further, hydration rates of guar gum are reduced in the presence of dissolved salts and other water binding agents. GG-I & GG-II are microwave irradiated guar gum samples. Microwave radiation has been reported to cause depolymerization of polymers, which may result in decrease in intrinsic viscosity of the guar gum. Carboxymethyl guar gum (CMGG) is an anionic polymer. The most important properties of CMGG include degree of substitution (DS) and its viscosity. The DS of CMGG was found to be around 0.71, whereas, its viscosity (2% w/v, in water as determined by Brookfield viscometer) was found to be 8600 cps.

In vitro swelling studies were carried out in 0.1 M HCl (pH1.2) using USP type II (Electrolab, India) at 50 rpm paddle speed and 37 ± 0.5°C temperature. The results are displayed in Table 2.

Table 2: Swelling of polymer(s) or compositions with or without drug in 0.1 M HCl(pH 1.2).

Polymer(s)	Wt of polymers (mg)	Wt of polymers (mg)		
		After 15 min	After 30 min	After 45 min
Guar gum (GG)	50	220	230	250
GG-I	50	210	220	230
GG-II	50	234	245	270
CMGG	50	220	250	245
HPMC K4M	150	170	185	205
HPMC K4M + GG	150+50	230	252	307
HPMC K4M + GG-I	150+50	211	241	272
HPMC K4M + GG-II	150+50	219	245	267
HPMC K4M + CMGG	150+50	221	254	271
HPMC K4M + GG+VHCL	150+50+80	315	330	347
HPMC K4M + GG-I+VHCL	150+50+80	290	312	345
HPMC K4M + GG-II+VHCL	150+50+80	292	326	346
HPMC K4M +CMGG+VHCL	150+50+80	320	350	384

From the results of swelling studies it was observed that both native guar gum and modified guar gum (G-I, G-II & CMGG) swells to about 5 times to their weights in about 45 min.

HPMC K4M swells to a significantly lesser extent. Mixtures of HPMC K4M and GG, GG-I & GG-II showed even better swelling compared to native and modified guar gum (s). This could be attributed to the formation of strong hydrogel network due to reduced erosion of gel layer. Addition of Verapamil HCl into the polymer matrices resulted in significant increase in swelling. This could be explained as swelling of hydrogel upon exposure to physiological fluids depends upon the osmotic pressure within the hydrogel caused by the hydrophilicity of the constituting polymers, the static charges on the polymer, and the counter ions within the hydrogel matrix. At acidic pH drug exist in cationic form (Verapamil H+). Increase in total ionic contents in the hydrogel network resulted in increased magnitude of osmotic and electrostatic forces, leading to increased ingress of aqueous medium and thus increased swelling.

Determination of water holding capacity of hydrogels

In order to investigate the strength of formed hydro gels, water holding capacity (% WHC) of various drug-polymer mixes correspond to formulation table 1 was determined. Drug-polymer mixes were put into hard gelatin capsules, which were than immersed in different flasks of USP dissolution apparatus type II (Electrolab, Mumbai, India) at 25 rpm, at 37 ± 0.5°C temperature, containing 500 mL of 0.1 M HCl for 8 h. the results are depicted in table 3. and figure 4.

Table 3: % WHC of various formulation mixes.

Formulation Code	Initial weight of formulation mix plus weight of empty hard gelatin capsule (mg)	Weight of formulation mix after 8 hr of swelling in 0.1 M HCl at 37^0C (mg)	% WHC
D1	385	6490	99
D2	385	5780	96
D3	385	6212	94
D4	385	8452	99

The % WHC ranged from 94-100%. Although HPMC K4M, native GG and modifies guar gum (s) not only swell in water but also becomes soluble in it (erosion) but during the study, it was observed that polymeric mass acquired the shape of a well formed mechanically strong cylinders which retained its shape for up to 24 hr.

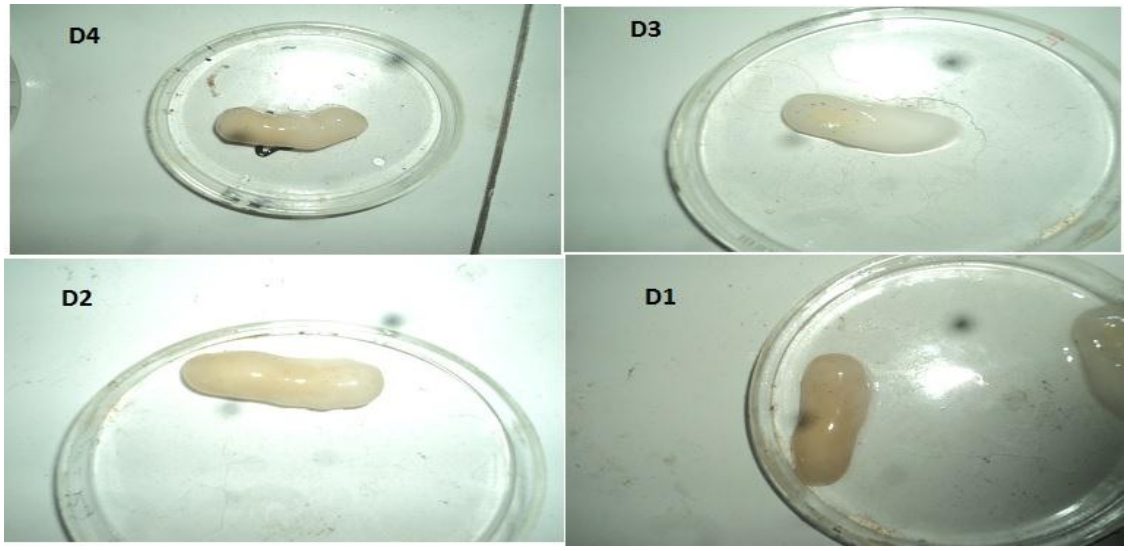

Figure 4: % WHC OF Guar gum (GG), Carboxymethyl Guar gum (CMGG),GG-I (g2) and GG-II (g1 new).

***In vitro* buoyancy studies**

The buoyancy of hydrodynamically balanced (HBS) capsule formulations is governed by both swelling of the encapsulated hydrocolloid upon contact with dissolution medium and the presence of voids in the matrix, which varies from polymer to polymer. The swelling of carrier system resulted in an increase in bulk volume. The air entrapped in swollen carrier maintains the density lower than unity, which ultimately confers buoyancy to the dosage form.[17] In the present study, a combination of pH independent (HPMC K4/GG/GG-I/GG-II) and pH dependent (CMGG) polymers were used. It was hypothesized that upon exposure to acidic dissolution medium, aqueous acidic medium (0.1 M HCl) penetrates the capsule shell initiating surface hydration of the pH-independent hydrocolloid gelling agent (HPMC in combination with GG/GG-I/GG-II) to form a gel layer and trapping air within the less dense powder bulk to account for the buoyant behavior of the capsule. On the other hand, the presence of anionic polymer (CMGG) in HPMC matrix gradually exposes the drier matrix that hydrates to replenish the gel layer. Upon exposure to acidic dissolution medium, hard gelatin capsule shell dissolved slowly in approximately 15 min. During this time period, the contents of the capsule shell gradually exposed to the dissolution medium slowly begin to form gel. Complete gel formation took around 1 hr and characterized by the formation of cylindrical gelled body with solid core in the centre. After around three hr of exposure, solid core became fully hydrated to form a translucent cylindrical gelled mass. No lag time was observed in all the formulations studied (Table 2). With the exception of formulation D, all the formulations remained buoyant up to 24h.

Table 4: In vitro floating characteristics of HBS formulations.

Formulation Code	Floating lag time (s)	Duration of floating (h)	Comments
D	**Nil**	**12**	Remained floated as irregular mass for up to 12 hr
D1	NIL	24	Remainedfloated for more than 24 h as well formed cylindrical mass
D2	NIL	24	
D3	NIL	24	
D4	NIL	24	

Determination of Drug Contents of HBS Capsule Formulations

The drug content determination test is done to ensure that each HBS capsule formulation contains equal amount of drug. For this purpose encapsulated contents of 10 HBS capsules from each formulation were emptied as completely as possible. The contents so removed were then put into 100 ml 0.1 M HCl (pH 1.2, 37 ± 0.5^0C) and stirred for one hour at 500 rpm. The solution was filtered through a 0.45 μ membrane filter and diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 290 nm. Drug contents of various formulations are given in Table 3. All capsule formulations were found to contain drug contents within limit.

***In vitro* drug release studies**

In vitro drug release from HBS formulations were carried out in triplicate using 0.1 M HC(37^0C) as dissolution medium at 50 rpm. In case of all the formulations release studies were carried out for the duration of 8 hr. The in vitro release data are depicted in figure 5.7.

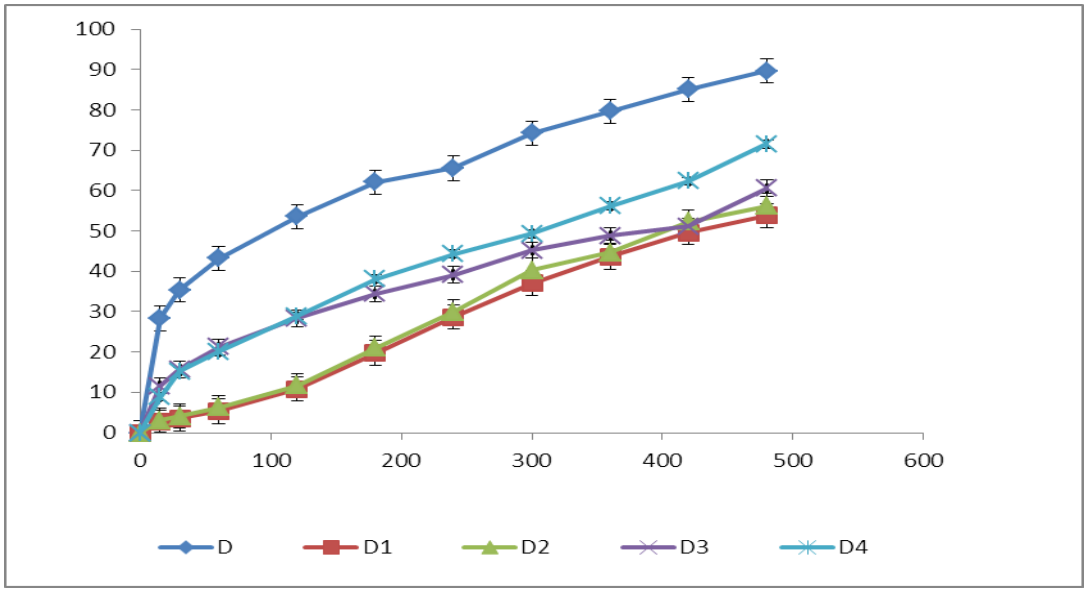

Figure 5.7.: In vitro % cumulative drug release from various formulations.

There was burst release of drug from Formulation D (release profile not depicted in figure), with more than 53% drug was released at the end of 1st hr. After that, the drug was released in a sustained manner for up to 8 hr. although gel formation was rapid but it seems that high diffusional driving force coupled with increased magnitude of osmotic and electrical forces (generated due to ionization of drug, Verapamil H+) weakens the diffusive barrier leading to rapid drug release initially. As the concentration of drug reduced in the hydrogel matrix, the magnitude of osmotic and electrical forces also went down leading to sustained drug release thereafter. Another reason for initial fast drug release could be attributed to the surface area of the resultant Drug-polymer matrices, which could not be large enough to cover the drug particles at the matrix surface. Hence, there might be a greater possibility of higher degree of drug releases. From formulation D1 & D2, drug release was significantly retarded compared to formulation D ($p<0.05$). Here only 6% drug was released at the end of 1st h compared to formulation D; where around 35% drug was released at the end of first hour. And at the end of 8th h about 53% drug was released. This could be attributed to the formation of a stronger gel layer of the resultant matrix, reducing the diffusion and erosion of HPMC K4 M gel layer. From formulation D3, initially there was comparatively rapid drug release with about 21% drug was released at the end of 1st h ($p<0.05$, compared to formulation D, D1 & D2). However after that the drug release was sustained with about 60% drug was released at the end of 8th hr. The higher drug release during the 1st hr could be attributed to the increased depolymerization of GG due to microwave irradiation of refrigerated GG dispersion, which might have caused the formation of few lower viscosity regions in the HPMC gel network.

From formulation D4, drug release was more uniform compared to formulations D, D1 & D2. Here about 20% and 71% drug was released at the end of 1st and 8th h. Incorporation of anionic polymers into HPMC matrices have been reported to retard the drug release in acidic media due to formation of insoluble mass that act as a barrier to drug diffusion.

Drug release kinetics

Release Kinetics

The release data were put into various kinetics models and results are depicted in table 5. From the kinetic data, it was observed that all the formulations D, D3 and D4 followed Korsmeyer –Peppas release mechanism, which provides an insight into the type of drug release mechanism taking place from swellable polymeric devices.Formulations D1 & D2 followed zero order release mechanism. This model describes that the drug release rate from

the formulations is independent of the concentration of the drug. The n values ranged from 0.33-0.95. Formulations D & D3 followed Fickian diffusion, whereas, formulations D1, D2 & D4 followed non-Fickian release mechanism.

Table 5: drug release kinetics from various HBS formulations.

Formulation Code	Drug release kinetic				
	Zero order	First order	Higuchi	Korsmeyer-Peppas	n value
D	0.9632	0.8854	0.7263	0.9955	0.33
D1	0.9925	0.9003	0.5326	0.9761	0.95
D2	0.9912	0.9044	0.5715	0.9755	0.91
D3	0.9768	0.8815	0.9863	0.9955	0.46
D4	0.9867	0.8630	0.9624	0.9948	0.57

REFERENCES

1. Sonia Lefnaoui, NadjiMoulai-Mostefa. Synthesis and evaluation of the structural and physicochemical properties of carboxymethyl pregelatinized starch as a pharmaceutical excipient. Saudi Pharmaceutical Journal, Available online 4 February 2015.
2. Nabais T1, Brouillet F, Kyriacos S, Mroueh M, Amores da Silva P, Bataille B, Chebli C, CartilierL. High-amylose carboxymethyl starch matrices for oral sustained drug-release: in vitro and in vivo evaluation. Eur J Pharm Biopharm, 2007 Mar.; 65(3): 371-8.
3. Fernanda M. Carbinatto Ana Dóris de Castro, Raul C. Evangelista, Beatriz S.F. Cury. Insights into the swelling process and drug release mechanisms from cross-linked pectin/high amylose starch matrices. Asian Journal of Pharmaceutical Sciences, February 2014; 9(1): 27–34.
4. Lemieux M1, Gosselin P, MateescuMA. Carboxymethyl high amylose starch as excipient for controlled drug release: mechanistic study and the influence of degree of substitution. Int J Pharm., 2009 Dec. 1; 382(1-2): 172-82.
5. Mihaela Friciu M1, Canh Le T, Ispas-Szabo P, MateescuMA. Carboxymethyl starch and lecithin complex as matrix for targeted drug delivery: I. Monolithic mesalamine forms for colon delivery. Eur J Pharm Biopharm, 2013 Nov; 85(3 Pt A): 521-30.
6. *Mohammad Reza Saboktakin, Roya M. Tabatabaie, Abel Maharramov, Mohammad Ali Ramazanov. Synthesis and characterization of chitosan-carboxymethyl starch hydrogels as nano carriers for colon-specific drug delivery. J Pharm Educ Res., December 2010; 1: 2.
7. Fabien Brouillet, Gilles Baylac, Louis Cartilier, and Bernard Bataille. High-amylose sodium carboxymethyl starch matrices for oral, sustained drug release: development of a

spray-drying manufacturing process. Drug Development and Industrial Pharmacy, July 2010; 36(7): 795-805.

8. Paulo Costa, Jose Manuel Sousa Lobo. Servic¸o de Tecnologia Farmaceutica, Faculdade de Farmacia da Universidade do Porto Rua Anıbal Cunha, 164, 4050-047 Porto, Portugal
9. S. Gupta, B. Shah, B. Sanyal, P.S. Variyar, A. Sharma, Role of initial apparent viscosity and moisture content on post irradiation rheological properties of guar gum, Food Hydrocoll, 2009; 23: 1785–1791.
10. B.V. McCleary, A.H. Clark, I.C.M. Dea, D.A. Rees, The fine structures of carob and guar galactomannans, Carbohydr. Res., 1985; 139: 237–260.
11. K.T. Roberts, The physiological and rheological effects of foods supplemented with guar gum, Food Res. Int., 2011; 44: 1109–1114.
12. M. Dogan, A. Kayacier, E. Ic, Rheological characteristics of some food hydrocolloids processed with gamma irradiation, Food Hydrocoll, 2007; 21: 392–396.
13. T. Miyazawa, T. Funazukuri, Noncatalytic hydrolysis of guar gum under hydrothermal conditions, Carbohydr. Res., 2006; 341: 870–877.
14. T. Shaikh, S. Sasi Kumar, Pharmaceutical and pharmacological profile of guar gum an overview, Int. J. Pharm. Pharm. Sci., 2011; 3: 38–40.
15. M.S. Butt, N. Shahzadi, M.K. Sharif, M. Nasir, Guar gum: a miracle therapy for guar gum: a miracle therapy for hypercholesterolemia hyperglycemia, Crit. Rev. Food Sci. Nutr., 2007; 47: 389–396.
16. Tayal, R.M. Kelly, S.A. Khan, Rheology and molecular weight changes during enzymatic degradation of a water-soluble polymer, Macromolecules, 1999; 32: 294–300.
17. Y. Cheng, R.K. Prudhomme, Enzymatic degradation of guar and substituted guar galactomannans, Biomacromolecules, 2000; 1: 782–788.
18. Q. Wang, P.R. Ellis, S.B. Ross-Murphy, The stability of guar gum in an aqueous system under acidic conditions, Food Hydrocoll, 2000; 14: 129–134.
19. Y. Cheng, K.M. Brown, R.K. Prudhomme, Preparation and characterization of molecular weight fractions of guar galactomannans using acid and enzymatic hydrolysis, Int. J. Biol. Macromol, 2002; 31: 29–35.
20. T.T. Reddy, S. Tammishetti, Free radical degradation of guar gum, Polym. Degrad. Stab., 2004; 86: 455–459.
21. A.V. Mohod, P.R. Gogate, Ultrasonic.
22. Juhi Dubey, Department of Pharmaceutics, IFTM University, Moradabad 244001, India Received 29 May 2015; Revised 9 July 2015; Accepted 14 July 2015.

23. J.M. Wasikiewicz, S.G. Yeates, Green molecular weight degradation of chitosan using microwave irradiation, Polym. Degrad. Stab., 2013; 98: 863–867.
24. M. Vodenicarova, G. Drimalova, Z. Hromadkova, A. Malovikova, A. Ebringerova, Xyloglucan degradation using different radiation sources: a comparative study, Ultrason. Sonochem, 2006; 13: 157–164.
25. N.M. Beylerian, L.R. Vardanyan, R.S. Harutyunyan, R.L. Vardanyan, Kinetics and mechanism of potassium persulfate decomposition in aqueous solutions studied by a gasometric method, Macromol. Chem. Phys., 2002; 203: 212–218.
26. P.R. Gogate, I.Z. Shirgaonkar, M. Sivakumar, P. Senthilkumar, N.P. Vichare, A.B. Pandit, Cavitation reactors: efficiency assessment using a model reaction, AIChE J., 2001; 47: 2526–2538.
27. O. Solomon, Z.Z. Ciutta, D'etermination de la viscosit'eintrins'eque de solutions de polym'eres par une simple d'etermination de la viscosit'e, J. Appl. Polym. Sci., 1962; 6: 683–686.
28. G. Robinson, S.B. Ross-Murphy, E.R. Morris, Viscosity-molecular weight relationship intrinsic chain flexibility, and dynamic solution properties of guar galactomannan, Carbohydr. Res., 1982; 107: 17–32.
29. B.K.Tiwari, K. Muthukumarappan, C.P. O'Donnell, P.J. Cullen, Rheological properties of sonicated guar, xanthan and pectin dispersions, Int. J. Food Prop., 2010; 13: 223–233.
30. C. Leonelli, T.J. Mason, Microwave and ultrasonic processing: now a realistic option for industry, Chem. Eng. Process.: Process Intensif., 2010; 49: 885–900.
31. Atique, M. Iqbal, AKM Bhouse. Ethanobotanical study of cluster fig. Fitoterapia, 1985; 56(4): 236-240.
32. A.M. Ali, N. Hussain, S.A. Haq. Sterol composition of guar seed oil. Pakistan J Scientific and Industrial Res., 1977; 20(4/5): 279-281.
33. Andrea Dario Frias, Valdemiro C. Sgarbieri. Guar gum effect on blood serum lipids and glucose concentration of wistar diabetic rats. Ciencia Techno De alimentos, 1998; 18(2): 1-10.
34. Anonyms. "Guar Production" Vernon Agricultural Research & Extension Center, Texas A & M Univ. 2006.
35. C.K. Kokate, A.P. Purohit, S.B. Gokhale. Pharmacognosy, Nirali Prakashan, 2007; 138-139.
36. C.P. Khare. Indian Herbal Remedies. Springer, new York, 2004; 171-72.

37. D.T. Coxon, J.W. Wallis, N.S. Levitt, W.P Jakson. 3- epikatonic acid from guar meal, Cyamopsistetragonoloba. Phytochemistry, 1980; 19: 1247-1248.
38. G.P. Kaushal, I. S. Bhatia. A study of polyphenols of seeds and leaves of Guar (Cyamopsistetragonoloba). J Sci Food and Agri., 1982; 33: 461-470.
39. HM Mukhtar, S.H. Ansari, M. Ali, A.Z Bhat, T. naved. Effect of aqueous extract of Cyamopsistetragonoloba Linn. beans on blood glucose level in normal and alloxan-Induced diabetic rats. Indian journal of Experimental Biology, 2004; 42(12): 1212-1215.
40. Zui L. Chang. Verapamil. Analytical Profiles of Drug Substances, 1988; 17: 643-674.
41. Hamann SR, Blouin RA, McAllister RG Jr. Clinical pharmacokinetics of verapamil. Clin Pharmacokinet, 1984 Jan-Feb; 9(1): 26-41.
42. McAllister RG Jr, Kirsten EB. The pharmacology of verapamil. IV. Kinetic and dynamic effects after single intravenous and oral doses. Clin Pharmacol Ther., 1982 Apr.; 31(4): 418-26.
43. McTavish D1, Sorkin EM. Verapamil. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs., 1989 Jul; 38(1): 19-76.
44. Pharmacology of Antihypertensive Therapeutics. edited by Detlev Ganten, Patrick J. Mulrow, Springer-Verlag, Berlin, Heidelberg, 1990.
45. Pubchem Substance and Compound Databases; Pub Chem CID=62969, https://pubchem.ncbi.nlm.nih.gov/compound/Verapamil_hydrochloride (accessed March 22, 2017).
46. Chen GL, Hao WH. Factors affecting zero-order release kinetics of porous gelatin capsules. Drug Dev Ind Pharm., 1998 Jun; 24(6): 557-62.
47. Chen GL, Hao WH. In vitro performance of floating sustained-release capsule of Verapamil. Drug Dev Ind Pharm., 1998 Nov.; 24(11): 1067-72.
48. Sawicki W. Pharmacokinetics of Verapamil and norverapamil from controlled release floating pellets in humans. Eur J Pharm Biopharm, 2002 Jan.; 53(1): 29-35.
49. Sawicki and Głód. Preparation of floating pellets with Verapamil hydrochloride. Acta Pol Pharm., 2004 May-Jun; 61(3): 185-90.
50. Nguyen CN, Christensen JM, Ayres JW. Formulation of sustained-release Verapamil HCl and Diltiazem HCl semisolid matrix capsules. Pharm Dev Technol., 2008; 13(2): 115-25.
51. Anand Patel*, Moin Modasiya, Dushyant Shah, and Vishnu Patel. Development and In Vivo Floating Behavior of Verapamil HCl Intragastric Floating Tablets. AAPS Pharm Sci Tech., 2009 Mar.; 10(1): 310–315.

52. H. V. Gangadharappa, M. Rahamath-Ulla, T. M. Pramod-Kumar & F. Shakeel*. Floating drug delivery system of verapamil hydrochloride using karaya gum and HPMC. Clinical Research and Regulatory Affairs, 2010; 27: 1.
53. Bertram, H. C., Karlsson, A. H., Rasmussen, M., Dønstrup, S., Pedersen, O. D., & Andersen, H. J. (2001). The origin of bi-exponential T2 relaxation in muscle myowater. Journal of Agricultural and Food Chemistry, 2001; 49: 3092–3100.
54. Bertram, H. C., Andersen, H. J., & Karlsson, A. H. (2001). Comparative study of low-field NMR relaxation measurements and two traditional methods in the determination of water holding capacity of pork. Meat Science, 2001; 57: 125–132.
55. Brøndum, J., Munck, L., Henckel, P., Karlsson, A. H., Tornberg, E., & Engelsen, S. B. (2000). Prediction of water-holding capacity and composition of porcine meat with comparative spectroscopy. Meat Science, 2000; 55: 177–185.