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FORMULATION AND IN-VITRO EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM FOR CIPROFLOXACIN HCL DELIVERY

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ABSTRACT

Sustained release gastro retentive drug delivery systems enable delayed and ceaseless contribution of the medication to the upper pieces of the gastrointestinal tract and improve the bioavailability of drugs that are portrayed by narrow therapeutics window. Present examination depicts an impact of Medium Molecular Weight Chitosan and High Molecular Weight Chitosan in blend with Hydrophilic HPMC K4M for continued delivery of water soluble Ciprofloxacin HCl by gelation of polymer lattices. Different plans were set up by physical mixing of Ciprofloxacin HCl and polymer(s) in fluctuating proportion followed by embodiment into hard gelatin cases. Every one of the definitions aside from F1 stayed light in 0.1N HCl (1.2 pH) all through the investigation. Impact of Chitosan on drug release was additionally explored and it was discovered that the drug release was altogether unique in contrast with F1 which contain HPMC K4M just (P>1.7521). It was additionally seen that Chitosan has shaped polyelectrolyte complex (PEC) with HPMC K4M in-situ during the gelation of HBS preparations in 0.1 M HCl. Our outcomes recommended that Medium Molecular Weight Chitosan and High Molecular Weight Chitosan with HPMC K4M is an incredible material for stomach explicit sustained drug delivery of Ciprofloxacin HCl from hydrodynamically adjusted single unit capsules.

KEYWORDS: Gastroretentive, Ciprofloxacin HCl, Hydrodynamically balanced system, Chitosan, HPMC K4M.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and capacity to drag out and control the purging time is a significant resource for dosage forms, which live in the stomach for a more drawn out timeframe than ordinary dosage forms. A few troubles are looked in structuring controlled release systems for better ingestion and upgraded bioavailability. One of such troubles is the powerlessness to bind the dosage forms in the ideal territory of the gastrointestinal tract. [1, 2]

Gastric clearing occurs during fasting as well as bolstered states. The example of motility is though distinct in the 2 states. During the fasting state an interdigestive arrangement of electrical occasions occur, which go both through stomach and digestive tract each 2 to 3 hours. This is known as the interdigestive myloelectric cycle or moving myloelectric cycle. This is additionally partitioned into following 4 stages.[3]

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a blended meal, the example of withdrawals changes from fasted to that of sustained state. This is otherwise called stomach related motility design and includes constant withdrawals as in stage II of fasted state. These withdrawals bring about lessening the size of food particles (to under 1 mm), which are impelled toward the pylorus in a suspension structure. During the fed state onset of migrating myloelectric cycle (MMC) is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric clearing rates revealed that orally administered controlled release dosage forms are exposed to essentially 2 complications, that of short gastric residence time and irregular gastric emptying rate. Consequently, gastroretentive systems can stay in the gastric region for a few hours and henceforth essentially prolongs the gastric residence time of drugs.[3-6]

Gastroretentive drug delivery systems are characterized as frameworks that upsurge the retention of an oral dosage form in the stomach offering various focal points for drugs showing an absorption window in the GI tract, drugs that are inadequately dissolvable in the soluble alkaline medium, and drugs that are planned for local action on the gastro-duodenal wall.[7, 8] Gastro retention assists to give better accessibility of new products with new conceivable outcomes and substantial benefits for patients. In the course of the most recent three decades, different methodologies have been sought after to structure gastroretentive delivery systems including floating systems,[9] modified shape systems,[10] swelling and expanding systems, [11] bioadhesive systems, [12, 13] and high density systems. [14]

Hydrodynamically Balanced Systems (HBS) are proposed to drag out the stay of the dose structure in the gastro intestinal tract and help in upgrading the assimilation. Such systems are most appropriate for drugs having a superior dissolvability in acidic condition and furthermore for the drugs having explicit site of ingestion in the upper piece of the small digestive tract. To continue in the stomach for a prolonged period, the bulk density of dosage form must have less than 1.[15, 16]

These are single-unit dosage forms, containing at least one gel forming hydrophilic polymers. The polymers are blended in with sedate and for the most part directed in a gelatin case. The case quickly breaks down in the gastric liquid at internal heat levels, and hydration and expanding of the surface polymers creates a skimming mass. Drug release is constrained by the development of a hydrated limit at the surface (Figure 1). Consistent disintegration of the surface permits water penetration to the inward layers, keeping up surface hydration and buoyancy. [17, 18]

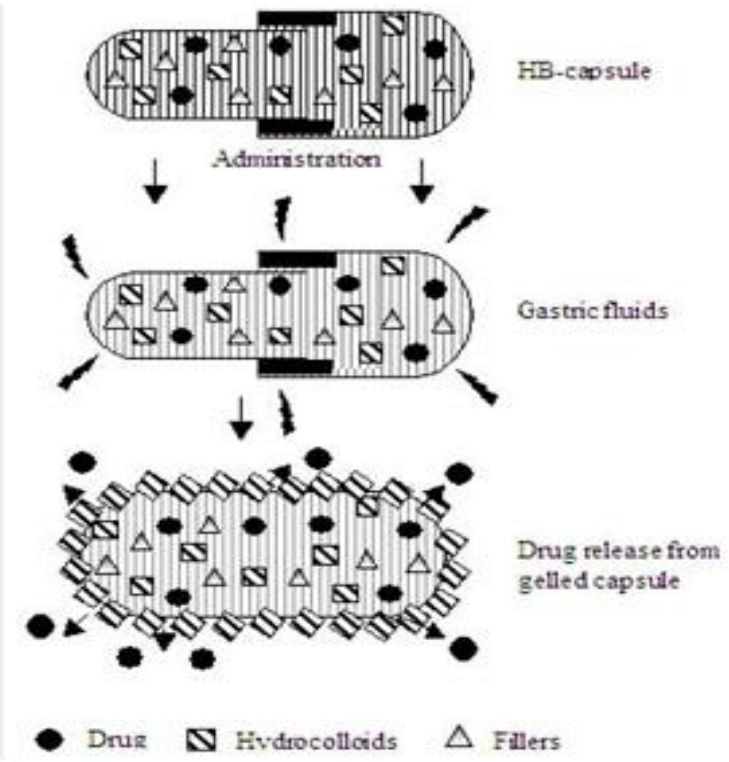

Figure 1: Working principle of HBS.

Ciprofloxacin HCl (CPHC), a first generation fluorinated 4-quinolones active against a broad range of bacteria. The most susceptible once are the aerobic gram negative bacilli but gram positive bacteria are inhibited at relatively higher concentration. CPHC is metabolized by hepatic metabolism and have a short half life of 3-5 hours necessitating high and frequent doses, which results in undesirable side effects. So there is a need to design a novel system that tends to release the drug at a controlled rate so as to increase the bioavailability and gastric retention time.

This investigation is based on development of HBS for CPHC by using gel forming polymers such as HPMC K4M, Medium Molecular Weight Chitosan and High Molecular Weight Chitosan to eradicate the problem associated with the therapy of CPHC.

MATERIALS AND METHODS

Collection of Materials

CPHC was obtained as a gift sample from Ranbaxy Research Laboratories, Gurgaon, India. Medium Molecular Weight Chitosan (MMWC), High Molecular Weight Chitosan (HMWC), HPMC K4M was purchased from Sigma Aldrich Chemicals Pvt. Ltd., Bangalore, India. All other reagents used were of analytical grade.

Determination of absorption maxima

Stock solution (1 mg/ml) of CPHC was prepared in 0.1N HCl and water. This solution was appropriately diluted with the same buffer/solvent to obtain a concentration of 10 µg/ml, the solution was kept in silica cuvette of 10mm. The UV spectrum was recorded in the range of 200-400 nm by using double beam UV-Vis spectrophotometer (1800 Shimadzu, Japan).

Preparation of calibration curve

A stock solution of 100 µg/ml of CPHC was prepared in 0.1N HCl and from it, standard solutions in the range of 1-12 µg/ml were prepared by appropriate diluting with 0.1N HCl. The absorbance of each standard solution was determined spectrophotometrically at 276.40 nm.

Preparation of HBS capsule containing CPHC

Single unit capsules were prepared by physically blending CPHC and HPMC K4M alone or in combination with other polymers in a Double Cone Blender for 15 min. followed by encapsulation in hard gelatin capsules.[19] The composition of various formulations is given in Table 1.

Table 1: Composition of HBS capsules containing CPHC along with and without release modifiers.

Formulation Code	HPMC K4M (in mg)	MMWC (in mg)	HMWC (in mg)	CPHC (in mg)
F1	95	-	-	190
F2	47.5	47.5	-	190
F3	47.5	-	47.5	190

In-vitro evaluation of HBS capsules: Prepared HBS capsules were evaluated for buoyancy, drug content, in-vitro drug release studies.

In-vitro buoyancy studies

Prepared capsules were immersed in 0.1N HCl (pH 1.2) in USP paddle type apparatus at 50 rpm. The floating lag time and time for which the capsules remained buoyant was observed.[19]

Effect of release modifiers

MMWC and HMWC were used at same concentration as mentioned in Table 1. These polymers were physically blended separately with HPMC K4M and CPHC and filled into the hard gelatin capsules.

Determination of drug content of capsules

Drug content was determined by emptying 10 same formulations filled in hard gelatin capsules as completely as possible. A powder equivalent to average weight was added to 100ml of 0.1N HCl (pH 1.2) at 37˚C±0.5˚C, followed by stirring for one hour at 500 rpm. The solution was filtered through 0.45µ membrane filter, diluted suitable and the absorbance of resultant solution was measured spectrophotometrically at 276.40 nm.

In-vitro drug release studies

In-vitro release of CPHC from the HBS capsule was performed in USP dissolution apparatus type II at 50 rpm. Evaluation of drug release was performed by using 900ml of 0.1N HCl (pH 1.2) at 37˚C±0.5˚C. At predetermined intervals, 1ml aliquot was withdrawn and replenished with an equal volume of fresh dissolution media in order to maintain the sink conditions perfectly. Withdrawn samples after suitable dilutions were analyzed spectrophotometrically at 276.40 nm.

Drug release Kinetics and Mechanism

Different kinetic models (Zero Order, First Order and Higuchi's Model) were applied to the release data to interpret the drug release kinetics and to know the mechanism of drug release from these HBS capsules with the help of equations 1, 2 and 3.

Zero order equation: $Q = Q_o - k_o t$ (eq.1)

First Order equation: $L_n Q = L_n Q_o - k_1 t$ (eq.2)

Higuchi's equation: $Q = k_H t^{½}$ (eq.3)

In these equations, Q_o is the intial drug concentration, Q is the amount of drug released at time t and k_o, k_1, k_H are the rate constant for zero order, first order and Higuchi's model, respectively.[20]

To confirm the exact mechanism of drug release from HBS capsules, the data were fitted according to the korsmeyer-peppas model. Korsmeyer et al. used a simple empirical equation to describe the general solute release behavior from controlled release polymer matrices:-

$$\mathbf{Mt/M\infty = Kt^n}$$

Where, Mt/M∞ is the fraction of drug released, K is the kinetic constant, t is release time and n is the diffusional exponent for drug release. The value of n gives an indication of the release mechanism: when n=1, the release rate is independent of time (zero-order, case II transport).

n=0.5 stands for fickian diffusion and when 0.5<n<1.0, diffusion and non-fickian transport are implicated. Lastly, when n>1.0, super case II transport is apparent. n is the slope value for log (Mt/M∞) vs log time curve.[21]

RESULT AND DISCUSSION

Estimating absorption maxima of CPHC

For estimating CPHC absorption maxima was determined by UV spectrophotometer and the absorption maxima was found to be 276.40 nm in 0.1N HCl (pH 1.2). The spectra and wavelength of maximum absorbance (λ_{max}) were showed in Figure 2 and Table 2 respectively.

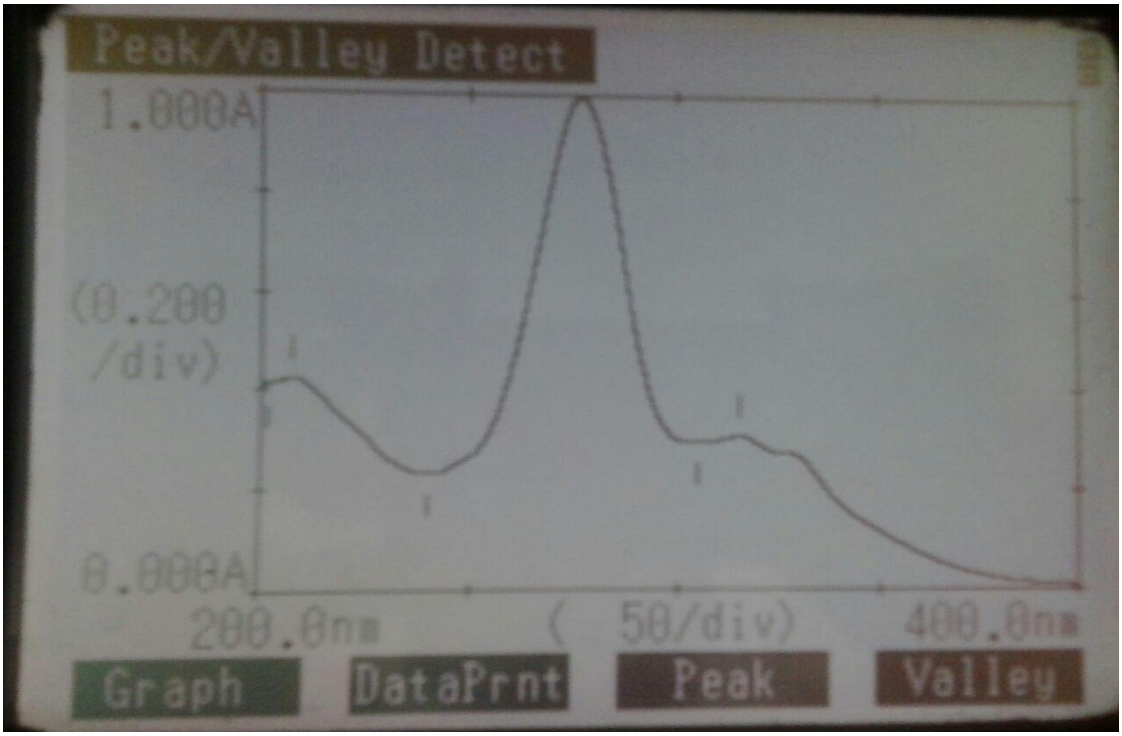

Figure 2: λ_{max} of CPHC.

Table 2: Wavelength of maximum absorbance by CPHC (λ_{max}).

Solvent	λ_{max}
Water	276.40 nm
0.1N HCl	276.40 nm

Estimation of CPHC

Standard calibration curve of CPHC was prepared in 0.1N HCl (pH 1.2) at 277.40 nm, using UV spectrophotometer. The calibration curve and absorbance were showed in Figure 3 and

Table 3, respectively. Table 4 represents the statistical parameter related to standard curve of CPHC in 0.1N HCl (pH 1.2)

Table 3: Calibration curve data of CPHC.

S. no.	Concentration (µg/ml)	Absorbance (nm)
0	0	0
1	2	0.177
2	4	0.286
3	6	0.424
4	8	0.583
5	10	0.733
6	12	0.965

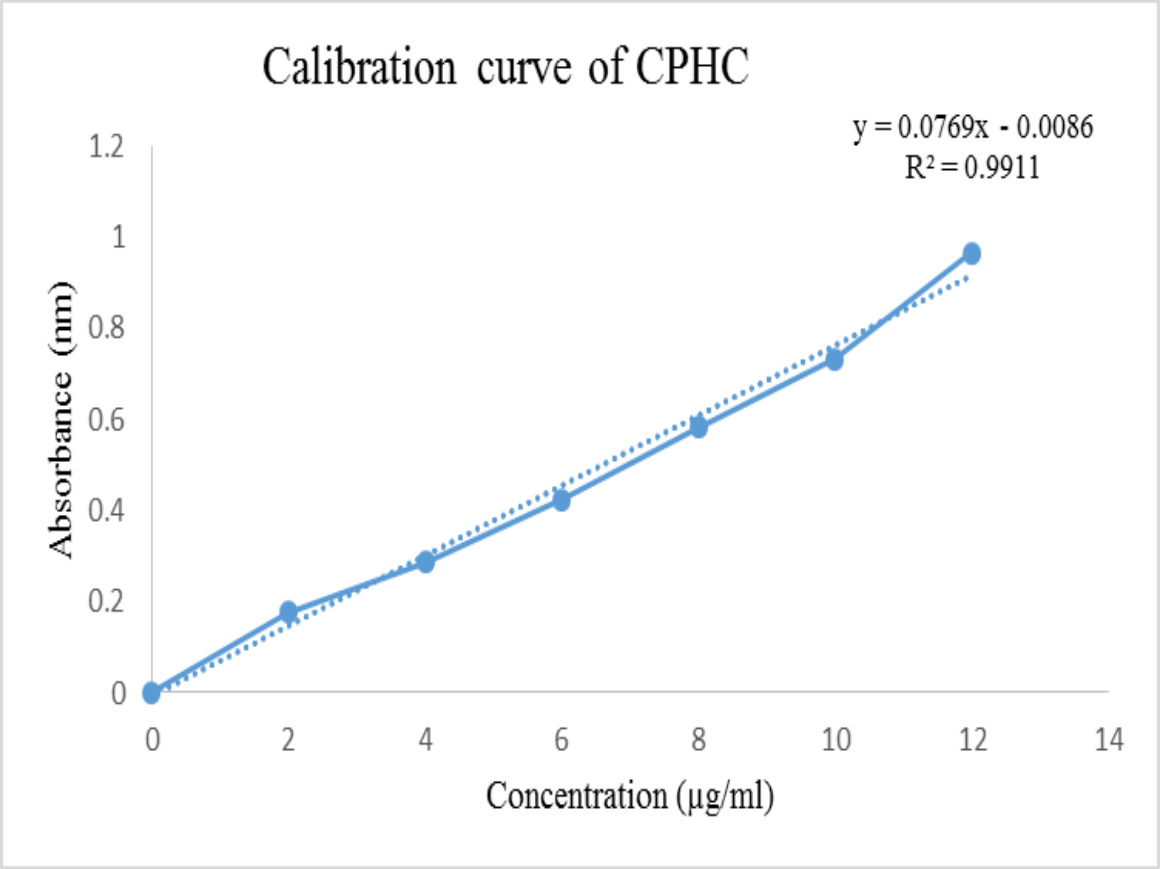

Figure 3: Calibration curve of CPHC 0.1N HCl at 276.40 nm.

Table 4: Statistical parameter related to standard curve of CPHC in 0.1N HCl (pH 1.2)

S. no.	Parameter	Values
1	Regression Coefficient	0.991
2	Intercept on Y-axis	0.008
3	Equation of Line	y = 0.076x - 0.008

In-vitro buoyancy studies

From the in-vitro buoyancy studies it was observed that all formulations exhibited immediate buoyancy with no lag time. When HBS formulations filled in hard gelatin capsules and placed in 0.1N HCl, the disruption of capsule shell begins and it was observed that as the dissolution medium penetrated through the disrupted capsule shell, the outer layer of the polymer matrix hydrated to form gel. For efficient buoyancy, swelling of polymer is very vital. The purpose of incorporating HPMC K4M into the HBS formulation was to increase the porosity of the polymer matrix in order to improve the hydration and subsequent gel formation. HPMC K4M alone (F1) has good floating behavior for upto 4 hours after that the gel formed was got burst and mixed with dissolution media, this could be attributed to the weak gel network formed due to the hydrophilicity of HPMC K4M. HPMC K4M in combination with MMWC or HMWC exhibited good floating behavior throughout the experiment. This is due to the fact that chitosan contains –NH2- groups bound to polymer chains. In the presence of acidic gelation medium, the polymer chains in Chitosan absorb dissolution medium and the binding of H^+ causes the polymer to swell ($NH3^+$). Figure 4-9 showed the floating behavior of HBS capsules in the time range of 1-6 hours, respectively. Further, there must be a balance between swelling and water acceptance. In our case, during swelling of the hydrophilic cellulose derivative (HPMC K4M), the macromolecular chains absorb water, leading to an expansion of the network formed and to formation of a quasi-equilibrium structure. This three-dimensional network structure usually is held together by physical chain entanglements, hydrogen bonds, tie junctions, or tie points produced by various types of forces. Upon further absorption of water, these gels may start disentangling, indicating a competitive phenomenon of swelling and dissolution. Beyond that time, HPMC K4M gel thicknesses were no longer sustained.[22-24] Hence, addition of release modifiers such as MMWC and HMWC are necessary to incorporate into formulation along with HPMC K4M. Chitosan forms gel in the acidic medium, swelling of chitosan polymers resulted in increase in bulk volume. The air entrapped in the swollen chitosan maintains the density less than unity which ultimately confers buoyancy to the dosage forms.[25-29]

Figure 4: F1, F2, F3 remained buoyant in first hour.

Figure 5: F1, F2, F3 remained buoyant in second hour. F2 and F3 starts to form gel.

Figure 6: F1, F2, F3 remained buoyant in third hour. Gel formed by F2 is firmed but not firmed in case of F1.

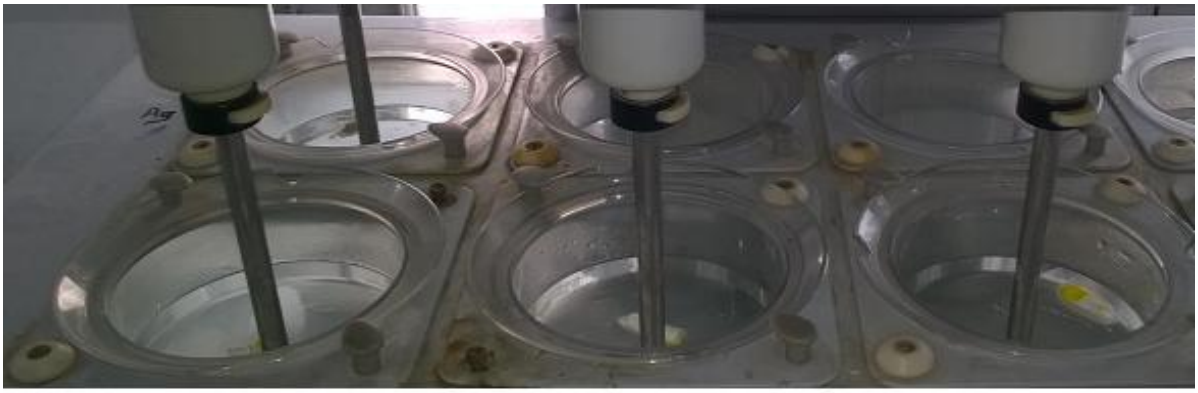

Figure 7: F1, F2, F3 remained buoyant in fourth hour. Gel formed by F1 starts to loosen its strength whereas F2 has firmed gel. F3 has formed firmed gel.

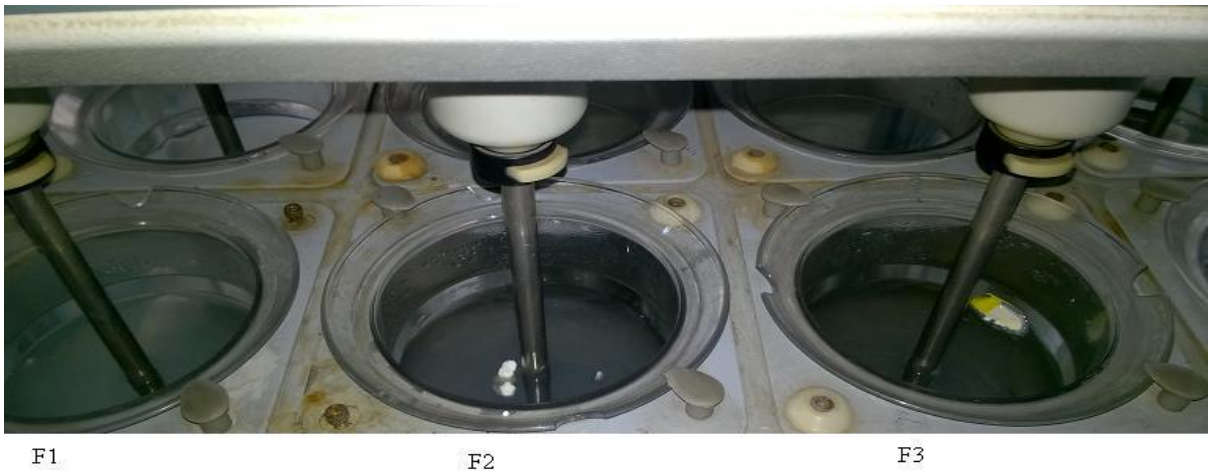

Figure 8: F2, F3 remained buoyant in fifth hour. Gel formed by F1 disappeared whereas gelled formed by F2 and F3 is firmed.

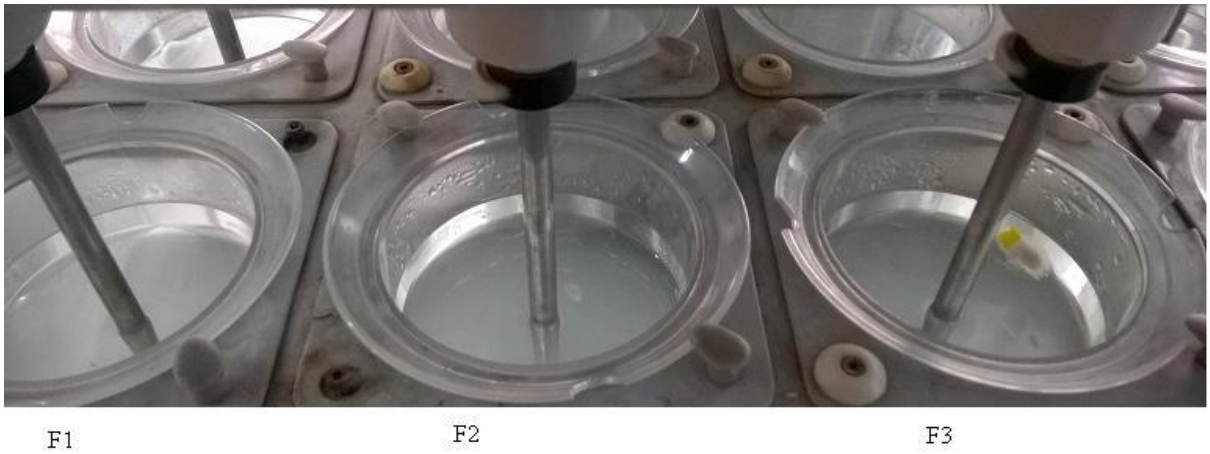

Figure 9: F2, F3 remained buoyant in sixth hour. F2 gel starts loosen its strength whereas F3 has firmed gel.

Drug content of capsules

Drug contents of all formulations were determined UV spectrophotometrically and were found to be in the range of 98 to 99%. Table 5 showed the drug content and drug remaining in the gel matrix. Experiment was conducted in triplicate.

Table 5: Drug contents in various HBS formulations.

Formulation Code	Drug Content	% Drug Release	Drug Remaining in the Gel Matrix (%)
F1	99.13±1.02%	98.91±2.39%	1.09±1.76%
F2	98.23±1.31%	68.26±1.14%	31.74±2.42%
F3	98.12±1.63%	47.36±1.99%	52.64±2.89%

In-vitro drug release studies

In-vitro release studies were carried out in 0.1N HCl (pH 1.2) and it revealed that all formulations remained buoyant throughout the experiment except F1 which remained buoyant only for 4 hours. All formulations except F1 are capable of sustaining the release of CPHC from HBS capsules even though the solubility of CPHC in water was very high. The retardation in drug release was attributed to the PEC formation between Chitosan and HPMC K4M. This PEC formation is expected to retard the dilution of outer gel layer of swellable and erodible hydrogel, thereby, retarding the diffusion of PHCL. It has been reported that the PECs formed between a polycation (e.g. Chitosan) and polyanion exhibit a very high degree of ordering and crystal like properties, and have quite compact structures and are little affected by pH variation of the dissolution medium. [30] Keeping this in view, it is expected that, if these complexes are formed in situ, it might be possible to overcome the initial burst release of CPHC. It was observed that as the imbibition of the acidic dissolution medium in to the capsule shell, formation of gel layer around the polymer matrix was initiated. Initially drug particles located at the surface of the polymer matrix dissolved and released rapidly. Thereafter, it was expected that the drug release would retard as drug particles located at successively increasing distances from the surface of the polymer matrix will be dissolved and released by diffusion through the gel layer.

Formulation F1 which contains only HPMC K4M releases 98.91±2.39% of CPHC in 4 hours. It may attributed to the absorption of dissolution medium by the macromolecular chains of HPMC K4M strong enough which leads to the expansion of three-dimensional network and disentanglement of polymeric chains causes weakened density and strength of gel layer, resulting in rapid erosion and burst release of drug. Table 6 and 7, Figure 10 showed the % cumulative drug release.

However formulation F2 and F3 which contains HPMC K4M along with MMWC and HMWC, respectively releases 68.26±1.14% and 47.36±1.99% CPHC with less standard deviation, in 6 hours (Table 6 and 7, Figure 10 showed the % cumulative drug release). In case of Formulation F2, the polymer matrix was made up of MMWC and HPMC K4M which got hydrated within 2 hour which leads to the formation of gel while in case of Formulation F3 (HMWC and HPMC K4M) it took 3 hours to get hydrated. The early onset of gelation was attributed to the HPMC K4M and as the acidic dissolution medium penetrates deeper to the gel surface layer, the MMWC got protonated and swells which resulted in increase of bulk volume but due to the low viscosity of MMWC in comparison to HMWC (high viscosity resulted in thicker gel layer formation which increases the diffusion path length of the drug), matrices become more porous as dissolution proceeds and the diffusion path length for the drug become less and hence the gradual erosion of gel were take place which results in faster diffusion of the CPHC in comparison to Formulation F3.

Statistical Analysis

% cumulative drug release from F1, F2, F3 was treated with one way ANOVA (SPSS statistics 17.0 software) and there was found a significant difference in the release of drug which was attributed to the gelation strength of various polymers ($P<1.7521$ at 95% confidence interval). No significant difference in the release of drug from the formulation F1 and F2 ($P>0.6368$) but F1 and F3, F2 and F3 were statistically different ($P<2.8166$, $P<1.9665$ respectively at 95% confidence interval) in releasing the drug from the gelled polymer matrices which could be attributed to the high viscosity of HMWC in comparison to MMWC and HPMC K4M, that resulted in thicker gel layer formation around the drug particles hence increasing the diffusion path length of the drug that's why the release of the drug was seem to be sustained.

Table 6: In-vitro characteristics of HBS capsules

Formulation Code	Duration of drug release (hours)	% Cumulative drug release	Floating time (hours)
F1	4	98.91±2.39%	4
F2	6	68.26±1.14%	6
F3	6	47.36±1.99%	6

Table 7: Cumulative percent drug release.

Time (hours)	F1	F2	F3
0	0	0	0
1	11.14±1.30 %	12.53±2.20 %	5.57±1.20
2	40.40±1.92 %	27.86±1.12 %	11.14±2.12

3	61.30±1.98 %	36.22±1.32 %	18.11±1.98
4	98.91±2.39 %	41.79±2.23 %	29.25±2.89
5	-	47.36±2.14 %	37.61±2.74
6	-	68.26±1.14 %	47.36±1.99

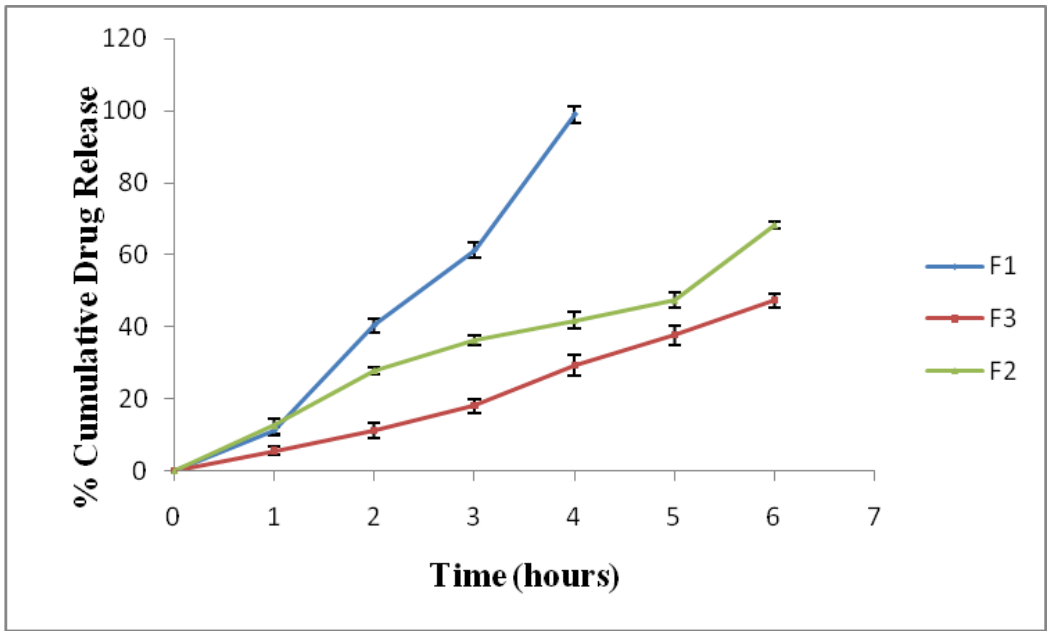

Figure 10: % Cumulative drug release from various formulations.

Mechanism of drug release

Table 8 represents drug release kinetics from the formulations. Zero order kinetics seemed to be the most appropriate model describing release kinetics from all formulations (F1 to F3) with coefficient of correlation in the range of 0.967 to 0.985. On the other hand, n values for formulation F1 and F3 (1.549, 1.216 respectively) was found to be greater than 1, indicated that the CPHC release was by non-fickian diffusion with super case-II transport mechanism, possibly owing to the chain disentanglement with erosions/spaces in the polymeric chains of the blended polymers. n-value of 0.860 for Formulation F2 indicates anamolous diffusion, possibly refers to both diffusion of drug through erosion in the polymeric chains of the blended polymers.

Table 8: Drug release kinetics of HBS formulations consisting of CPHC.

Formulation Code	Drug Release Kinetics				
	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	n value
F1	0.971	0.688	0.810	0.988	1.549
F2	0.967	0.919	0.916	0.969	0.860
F3	0.985	0.961	0.842	0.993	1.216

CONCLUSION

HBS based on HPMC K4M alone and in combination with MMWC and HMWC were prepared and evaluated. The prepared HBS systems showed sufficient promise to be developed into efficient vehicle for gastroretentive delivery of CPHC. Our results showed that HPMC K4M in combination with MMWC and HMWC, which is relatively less explored polymeric combination, is an excellent material for the sustained delivery of CPHC.

Conflicts of interest

The authors confirm that this article has no conflicts of interest.

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