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Investigation and Evaluation of an *in Situ* Interpolymer Complex of Carbopol with Polyvinylpyrrolidone as a Matrix for Gastroretentive Tablets of Ranitidine Hydrochloride

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Carbopol (CP) is a biocompatible bioadhesive polymer used as a matrix for gastroretentive (GR) tablets, however, its rapid hydration shortens its bioadhesion and floating when incorporated in effervescent formulae. The interpolymer complexation of CP with polyvinylpyrrolidone (PVP) significantly reduced the excessive hydration of CP, prolonging floating and maintaining the mucoadhesiveness. In early attempts, a lengthy process was followed to prepare such an interpolymer complex. In this study, an *in situ* interpolymer complexation between CP and two grades of PVP (K25 and K90) in 0.1 N HCl was investigated and characterized by Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC). Hence, directly compressed GR tablets of different combinations of PVP and CP with sodium bicarbonate (SB) as an effervescent agent were examined for prolonged gastroretention and sustained release of ranitidine hydrochloride (RHCl) as a model drug. Tablets were evaluated for *in vitro* buoyancy, bioadhesiveness, swelling, and drug release in 0.1 N HCl. All GR tablets containing PVP–CP combinations achieved more prolonged floating (>24 h) than CP tablets (5.2 h). Their bioadhesiveness, swelling, and drug release were dependent on the PVP molecular weight and its ratio to CP. Drug release profiles of all formulae followed non-Fickian diffusion. Formula containing the PVP K90–CP combination at a respective ratio of 1 : 3 (P_{90}C13) was a promising system, exhibiting good floating and bioadhesive properties as well as sustained drug release. Abdominal X-ray imaging of P_{90}C13 formula, loaded with barium sulfate, in six healthy volunteers showed a mean gastric retention period of 6.8±0.3 h.

Key words polyvinylpyrrolidone; carbopol; interpolymer complex; gastroretention; ranitidine hydrochloride

Extending the residence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released within the desired period of time is a real challenge in the development of an oral controlled release drug delivery system.[1)] Indeed, gastroretentive drug delivery systems (GRDDS) have received a significant interest in the past few decades. These systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. GRDDS ensure optimal bioavailability because they help in continuously releasing the drug before it reaches the absorption window.[2)]

Various approaches were developed to prolong the gastric-retention time (GRT) of oral dosage forms including floating,[3)] bioadhesive,[4)] and swelling drug delivery systems.[5,6)] The principle of floating preparation offers a simple and practical approach to achieve extended GRT with sustained drug release.[7)] To achieve floating systems, low density additives (*e.g.* fatty acids and fatty alcohols) and gas generating agents (effervescent type) were used.[8)] The effervescent type consists of polymeric matrix containing effervescent components, such as sodium bicarbonate (SB) that liberates carbon dioxide (CO_2) by aid of the acidic pH of the stomach to be entrapped in a gelling hydrocolloid maintaining prolonged buoyancy time with sustained drug release.[9,10)] Nevertheless, floating systems with an initial high density first settle down in the stomach and they are exposed to the risk of premature emptying even though their density decreases with time.[11)] Furthermore, floating systems need sufficient fluid in the stomach for tablet buoyancy.[12)] Since that, combined gastroretentive mechanisms were employed to enhance gastroretention including floating and bioadhesive approaches.[13,14)]

Bioadhesive polymers can be used to add bioadhesiveness to the floating systems in order to extend their GRT and counteract their premature gastric emptying. Commonly used bioadhesive polymers are polyacrylic acid (PAA) and its lightly crosslinked commercial forms, carbopol (CP), that exhibited strong bioadhesive properties and also appeared to be biocompatible.[15)] However, PAA has some limitations as a bioadhesive polymer including its rapid hydration that critically limits its use as a drug carrier, because it may be washed away by sufficient liquid flow supplied before the drug is delivered across the membrane.[10,16)] This excessive hydration of PAA can be significantly reduced by interpolymer complexation with polyvinylpyrrolidone (PVP).[17,18)] Strong hydrogen bonding between PAA and PVP can connect the component polymers in the interpolymer complex (IPC) imparting physicochemical characteristics which are different from individual polymers. The produced IPC showed limited solubility in water and maintained the mucoadhesiveness.[17)]

Mucoadhesive floating granules containing combination of PVP K30 and CP were prepared by wet and dry granulation

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techniques for delivery of acetaminophen.[19] However, multiparticulate systems as granules may release the drug at different sites of the GIT.[20,21]

Other studies reported a tedious process for preparation of PVP–CP IPC by reacting the aqueous dispersions of the two polymers and isolating the produced IPC to be dried and utilized as a matrix for controlled drug delivery of acyclovir.[22,23] But so far, no studies have been conducted to investigate the *in situ* interpolymer complexation between PVP and CP *via* hydrogen bonding between the carbonyl groups of the former and the non-ionized carboxyl group of the later within the tablet matrix in acidic medium. Hence, different combinations can be compressed into matrix tablets to examine the proposed *in situ* complexation between such polymers for gastroretension in acidic medium. Matrix tablet as a single dosage form could hinder the fast passage *via* the gastric pylorus due to the larger size than multiparticulate systems as granules.[24] Also, direct compression technique as an easy fast manufacturing process seems advantageous over the previously reported tedious process based on reacting the aqueous dispersions of the two polymers and separation of the IPC.

Ranitidine hydrochloride (RHCl) is H_2-receptor antagonist widely used in the treatment of gastric and duodenal ulcer. The short biological half-life of RHCl (*ca.* 2.5–3 h) favored its formulation as sustained release dosage forms.[25] However, the traditional approaches to sustained drug delivery are not suitable for RHCl, since, most of the drug releases at the colon where, the colonic metabolism of it is partly responsible for its poor bioavailability.[26] Moreover, the oral treatment of gastric disorders with RHCl promotes its local delivery to the receptor of the parietal cell wall. This local delivery increases the stomach wall receptor site bioavailability and the efficacy of the drug to reduce acid secretion.[27] As well, RHCl is absorbed mainly in the initial part of the small intestine.[28,29] Hence, GRDDS of RHCl utilizing the *in situ* interpolymer complexation between PVP and CP in purpose of improving its systemic and local delivery can be expected to efficiently reduce gastric acid secretion. Hydrogen bonding between these polymers can be maintained when the pH is lower than the pK_a of CP (6.0) as the majority of carboxyl groups of CP are non-ionized.[18] Decomplexation has been found to occur at basic medium (pH 7–8).[22,23] RHCl as an H_2-antagonist can cause intra-gastric acid reduction imparting median gastric pH less than 5.[30–32] Consequently, decomplexation would not be expected *in vivo* using RHCl as a model drug.

Therefore, the main objectives of this work were to study the *in situ* complexation between CP with two grades of PVP (K25 and K90) in 0.1 N HCl. As well, gastric buoyant matrix tablets containing PVP and CP with SB as an effervescent agent were prepared by direct compression. The effect of various ratios of PVP and CP on the floating, swelling ability, and *in vitro* drug release was investigated. Finally, the optimized formulation that combined both excellent buoyancy and sustained release characteristics was chosen for further *in-vivo* evaluation by X-ray study in human volunteers.

Experimental

Materials Polyvinylpyrrolidine (PVP) of different grades (K25 and K90) were supplied by Pharco Pharmaceutical Co., Alexandria, Egypt. Carbopol 934P (CP) and magnesium stearate were donated by Amriya Pharmaceutical Industries Co., Alexandria, Egypt. Sodium bicarbonate (SB), lactose monohydrate and hydrochloric acid were obtained from El-Nasr Pharmaceutical Chemicals Co., ADWIC, Cairo, Egypt). All other chemicals were of analytical grade.

Preparation of Polymer Complex Dispersions of PVP (K25 or K90) and CP in 0.1 N HCl (pH 1.2) at concentration of 2% (w/v) of each were first prepared. Appropriate volume of PVP and CP dispersions were mixed to obtain a weight ratio of 1 : 3, 1 : 2, 1 : 1, 2 : 1, and 3 : 1. Total polymer concentration was fixed at 2% (w/v) in each sample. Each polymeric mixture was stirred uniformly for 1 h and filtered. The residue consisting of PVP–CP complex was collected and weighted to represent the weight of fresh polymer complex.

Study of Polymer–Polymer Interactions In order to confirm the proposed interaction between PVP and CP within the tablet matrix in acidic medium, their physical mixture in ratio of (1 : 1 and 1 : 3) for PVP K25 and K90, respectively, were kneaded with 0.1 N HCl with subsequent drying in an oven at 40°C till constant weight. The dried complexes were ground into powder using a mortar and pestle, passed through a 200 μm sieve and then stored in tightly closed containers for further studies.

Fourier Transform Infrared (FT-IR) Spectroscopy The powder of the dried kneaded mixture was analyzed using FT-IR (Thermo Fisher Scientific, Inc., Waltham, MA, U.S.A.) according to the KBr disk method in comparison to PVP, CP, and their physical mixture. Each sample (2 mg) was mixed with 200 mg of potassium bromide (KBr). These mixtures were ground into fine powder and then compressed into KBr discs using a hydraulic press. Each KBr disc was scanned over a wave number region of 500–4000 cm^{-1} and the resolution was 4 cm^{-1}. The characteristic bands were recorded for all samples.

Differential Scanning Calorimetry (DSC) The powders were further analyzed using DSC (Pyris 6, PerkinElmer, Inc., U.S.A.). Temperature calibration was performed using indium as a standard. Samples (4 mg) were weighed directly in aluminum pans, which were then closed. The samples were kept for 1 min at 30°C, then heated from 30 to 400°C at a heating rate of 10°C min^{-1} under constant purging with dry nitrogen at 30 mL min^{-1}. Finally, they were kept for 1 min at 400°C.

Preparation of RHCl–GR Tablets GR tablets containing 168 mg RHCl (equivalent to 150 mg of ranitidine) were prepared by direct compression method using the formulae shown in Table 1. The required quantities of PVP, CP, and SB were individually passed through 200 μm sieve, mixed using a mortar and pestle for 10 min, and lubricated with 1% (w/w) of magnesium stearate. The blended powders were compressed into flat face tablets using a single punch tablet compression machine (Type EKO, Erweka-Apparatebau, GmbH, Germany), fitted with 10 mm flat-faced punches. The compression force was adjusted to give tablet hardness of 6–7 kg.

Evaluation of RHCl–GR Tablets Weight variation, content uniformity and friability percent of the prepared tablets were determined according to procedures mentioned in the U.S. Pharmacopoeia.[33]

***In Vitro* Buoyancy** The floating behavior of RHCl tablets was visually determined, in triplicate, according to the method described by Jaimini *et al.*[34] Briefly, the tablets were added separately into glass beakers containing 100 mL of 0.1 N HCl, and maintained in a water bath at 37±0.5°C. The tablets

Table 1. Tablet Formulations Studied

Formulae*	Formulae code	The weight of ingredients in each tablet (mg)			
		PVP K25	PVP K90	Carbopol 934P	Sod. bicarbonate
Carbopol	CP			212	60
PVP K25–CP 1 : 3	$P_{25}C13$	53		159	60
PVP K25–CP 1 : 2	$P_{25}C12$	71		141	60
PVP K25–CP 1 : 1	$P_{25}C11$	106		106	60
PVP K25–CP 2 : 1	$P_{25}C21$	141		71	60
PVP K25–CP 3 : 1	$P_{25}C31$	159		53	60
PVP K90–CP 1 : 3	$P_{90}C13$		53	159	60
PVP K90–CP 1 : 2	$P_{90}C12$		71	141	60
PVP K90–CP 1 : 1	$P_{90}C11$		106	106	60
PVP K90–CP 2 : 1	$P_{90}C21$		141	71	60
PVP K90–CP 3 : 1	$P_{90}C31$		159	53	60

* Each formulae contains 168 mg RHCl equivalent to 150 mg ranitidine base and 5 mg magnesium stearate as lubricant.

were observed for floating over 24 h. The time between tablet introduction and its buoyancy (floating lag time; FLT) and the time during which tablet remains buoyant (total floating time; TFT) were recorded.

***In Vitro* Bioadhesive Strength Measurement** Bioadhesive strength of tablets was evaluated using a modified 2-arm balance.[14,35,36] One metal holder was used to suspend the water collecting beaker to the balance and another to suspend a glass vial to the other side of the balance. The mucosal membrane used was a piece of rabbit stomach mucosa, 3×3 cm obtained from a local slaughter house and stored in Krebs buffer at 4°C upon collection after removal of the underlying fat and loose tissues. The experiments were performed within 3 h of procurement of the mucosa. The rabbit gastric mucosa was tied to an inverted 100 mL beaker and placed in a large one (250 mL). To maintain mucosal viability during the experiments, 0.1 N HCl was added into the large beaker up to the upper surface of the gastric mucosa and the temperature was adjusted at 37±0.5°C using thermostatically controlled water bath. Each tablet was attached to the glass vial with adhesive and then the beaker was raised slowly until contact between rabbit mucosa and the tablet. A preload of 50 g was placed on the vial for 5 min (constant preload time) to establish adhesion bonding between tablet and rabbit stomach mucosa. After completion of the preload time, preload was removed from the vial, and water was then added into the beaker from the burette in the other side till detachment of the tablet from the rabbit mucosa. The weight of water required to detach the tablet from the mucosa was noted as mucoadhesive strength.

Tablet Swelling Study Water-uptake was studied for all tablet formulations according to the method adopted by Dorozynski *et al.*[37] Briefly, tablets were individually weighed and each one was transferred into a beaker containing 200 mL of 0.1 N HCl. All beakers were put into a thermostatically controlled water bath adjusted at 37±0.5°C. At the specified intervals of time; 1, 2, 3, 4, 6, 8, 10 and 12 h, each tablet was removed from the medium, gently wiped with filter paper to remove surface water, and re-weighed. The mean weights of tablets were determined, and the degree of swelling was calculated according to the following equation:

$$\% \text{ Water uptake} = (W_s - W_d / W_d) \times 100$$

where, W_s, the weight of swollen tablet; W_d, the weight of dry tablet.

Drug Release Studies Drug release was performed using a USP type II apparatus (Dissolution Apparatus USP Standards, Scientific, DA-6D, Bombay, India) at 75 rpm for 12 h. Each tablet was placed in 900 mL 0.1 N HCl as a dissolution medium that maintained at 37±0.5°C. At appropriate time intervals 1, 2, 3, 4, 6, 8, 10, and 12 h, aliquots of 5 mL of sample was withdrawn and an equal volume of fresh medium was added to maintain the volume constant. The samples were diluted, filtered using millipore filter (Gelman GN-6 Metricel membrane filter, 0.45 μm pore size and 47 mm diameter, U.S.A.) and analyzed spectrophotometrically at a wavelength of 313 nm using an UV/Vis (JASCO, V-530, Japan). The cumulative % of RHCl released at each time interval was calculated using the equation obtained from the calibration curve for RHCl. The release was described by plots of percentage cumulative drug released *versus* time.

Analysis of Drug Release Data The dissolution profiles of all RHCl formulae in 0.1 N HCl were fitted to zero-order, first-order and Higuchi model.[38] Also, Korsmayer–Peppas kinetics model was used to describe the release mechanism applying the equation $m_t/m_\infty = kt^n$ where, m_t/m_∞ is the fraction of drug released, k is kinetic constant, t is release time, and n is the diffusional exponent for drug release and it equals the slope of $\log m_t/m_\infty$ *vs.* log time curve giving an indication of the release mechanism.[39] The model with the highest correlation coefficient (r^2) was considered to be the best fitting one.

***In Vivo* Studies in Healthy Volunteers** After giving informed written consent, six healthy male volunteers with age of 23 to 27 years and weight from 62 to 70 kg participated in this study. The studies were approved by Mansoura University Protection of Human Subjects Committee and the protocol complies with the declarations of Helsinki and Tokyo for humans. Complete medical history, physical examination, hematological and biochemical laboratory analyses were carried out to confirm the health status of the volunteers. The study was supervised by expert radiologist and physician. No medicine was allowed to be administered by subjects for one week prior to and during the course of the study.

Abdominal X-Ray Imaging In order to make the optimized formulation X-ray opaque, an amount of 50 mg of the drug was replaced with barium sulfate keeping all other

ingredients constant. Our preliminary study using different amounts of barium sulfate (10, 20, 30, 40, 50 mg) showed that, 50 mg of this compound was sufficient to allow X-ray visibility but not to hinder tablet buoyancy. After overnight fasting, the volunteers were allowed to have a low calorie food. Half an hour later, a radiograph was made, just before the administration of the tablet, to ensure the absence of radio-opaque material in the stomach. Next, a barium sulfate-labeled tablet was administered to every subject with 200 mL of water. The volunteers were asked to take 200 mL water after every 1 h. At different time intervals (1.5, 3, 4.5, 7 h post-administration of tablets), the volunteers were exposed to abdominal X-ray imaging (KOX-15 E Toshiba, Japan) in a standing position keeping the distance between the source of X-rays and the subject constant for all images. Therefore, the movements of the GR tablets could be easily observed and the mean GRT was determined.[40)]

Statistical Analysis The resulting data are represented as the mean±standard deviation (S.D.). Statistical analysis of the data was carried out using one way ANOVA followed by Tukey–Kramer multiple comparisons test at a level of significance of $p<0.05$ with Instat Graphpad prism software (version 4.00; Graphpad Software, San Diego, CA, U.S.A.).

Results and Discussion

In order to confirm the interpolymer complexation between CP and either of PVP K25 or PVP K90 in 0.1 N HCl, five different weight fractions of CP to PVP including 1 : 3, 1 : 2, 1 : 1, 2 : 1, and 3 : 1 corresponding to CP concentrations of 25, 33.33, 50, 66.66, and 75%, respectively were used and the weight of fresh PVP–CP complexes produced was determined (Fig. 1). In case of PVP K25, the amount of the fresh complexes augmented with the increase in CP concentration, up to a weight ratio of 1 : 1 (50% CP) possibly due to a maximum interaction between the polymers and consumption of free polymer molecules towards the formation of an insoluble complex. Further

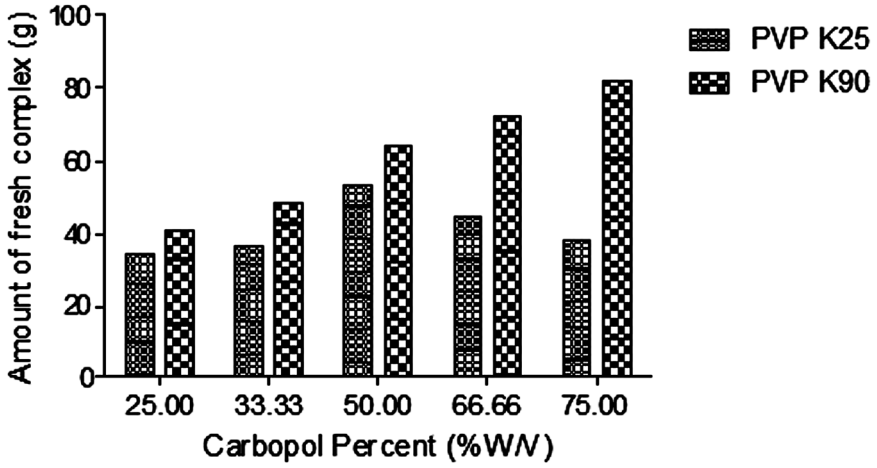

Fig. 1. Amount of Fresh PVP–CP IPC Produced from Interaction between CP and Different Grades of PVP

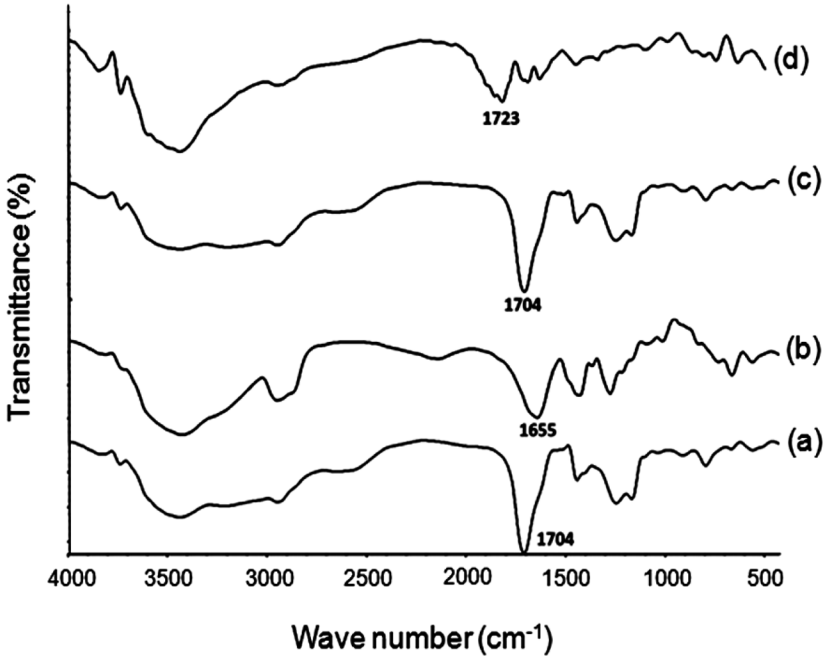

Fig. 2. FT-IR of (a) CP, (b) PVP K90, (c) PVP K90–CP Physical Mixture (1 : 3) and (d) Kneaded PVP K90–CP Mixture (1 : 3)

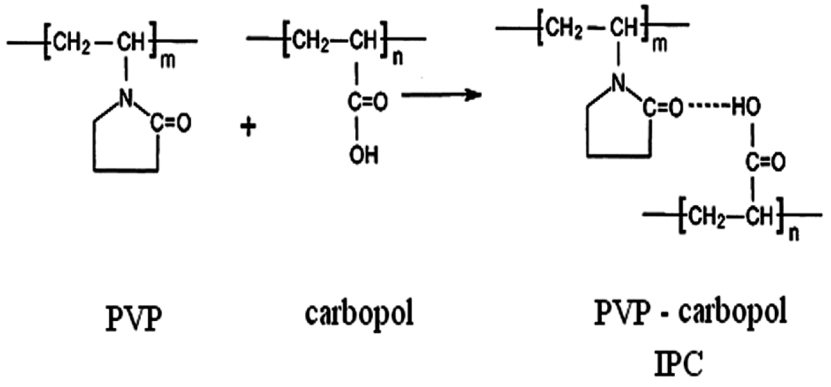

Fig. 3. Reaction between PVP and CP

increase in CP concentration decreased the amount of the produced IPC of PVP K25 and CP. Regarding IPC with PVP K90, the increase in CP concentration from 25 to 75%, resulted in higher amount of PVP K90–CP complex in contrast to PVP K25. At the same weight ratio of the two polymers, the amount of fresh IPC with PVP K90 was higher than that with PVP K25. These results indicated that, the molecular weight (MW) of PVP and its ratio to CP played important roles in the complexation process. Similar results were previously reported by Tan *et al.*[41]

Figure 2 shows the FT-IR spectra of PVP K90, CP, their physical mixture and kneaded mixture with 0.1 N HCl. The spectrum of PVP K90 showed a band at 1655 cm^{-1} which is characteristic to C=O group. CP spectrum exhibited an absorption band at 1704 cm^{-1} possibly due to intramolecular hydrogen bonding between its carboxyl groups.[42] The spectrum of PVP K90–CP physical mixture showed the characteristic bands of carboxylate group of CP, however, such band appeared less sharp and shifted to higher wave number at 1723 cm^{-1} in case of their kneaded mixture. This behavior may be attributed to the hydrogen bonding between carboxyl group of CP and carbonyl group of PVP K90 after breaking of some of the CP intramolecular hydrogen bonds as proposed in Fig. 3. Similar findings were previously demonstrated in studying the interaction between PVP and PAA.[17,42]

Figure 4 shows the DSC thermograms of PVP K90, CP, their physical mixture, and kneaded mixture with 0.1 N HCl. In case of the PVP K90 thermogram, a sharp endothermic peak at 77.8°C was noted indicating the presence of bound water or moisture. The DSC thermogram of CP showed two endothermic peaks at 73.8 and 236.5°C as well as an exothermic one at 300°C at which the decomposition of CP may have occurred.[43–45] The thermogram of PVP K90–CP physical mixture showed endothermic peaks of the two polymers at 75 and 233.6°C. However, their kneaded mixture exhibited broadening and shifting of CP endothermic peak at 236.5 to 245°C with disappearance of its exothermic peak at 300°C. This effect assigned to the formation of strong intermolecular forces owing to hydrogen bonding between carboxyl and carbonyl groups of CP and PVP K90, respectively. Similar effect was previously reported in case of chitosan–CP IPC.[46] The same FT-IR and DSC results were also obtained in case of PVP K25–CP (data not shown). This indicates that complexation could occur between CP and different grades of PVP during dissolution in 0.1 N HCl.

Physical Properties of RHCl Tablets The physical properties of different RHCl tablets are summarized in Table 2. All tablet formulae showed acceptable physicochemical properties complying with the specifications of U.S. Pharmacopoeia[33] for weight variation, drug content, and friability. The weight of the tablets ranged from 438.8 to 446.7 mg. Drug uniformity results were found to be good among different batches ranging from 96.5 to 103.3%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

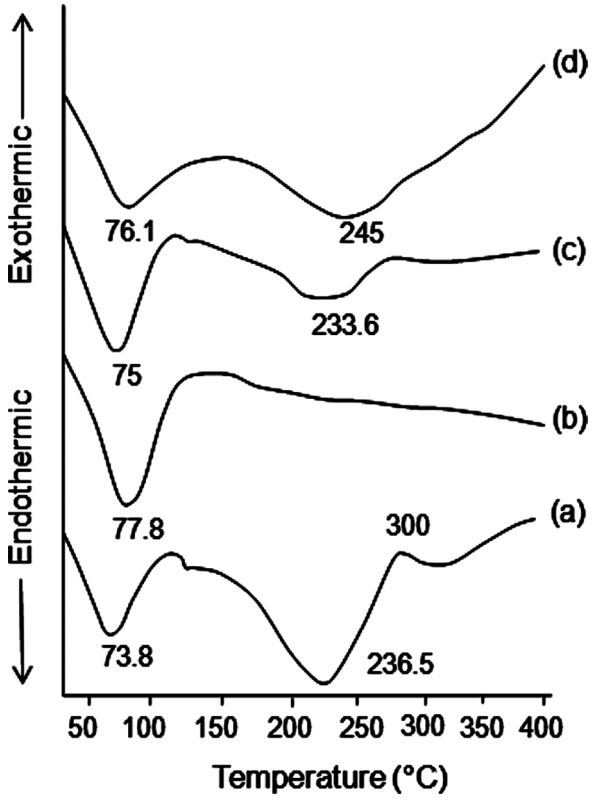

Fig. 4. DSC of (a) CP, (b) PVP K90, (c) PVP K90–CP Physical Mixture (1 : 3) and (d) Kneaded PVP K90–CP Mixture (1 : 3)

***In Vitro* Buoyancy Studies** When effervescent CP tablets was formulated using 20 mg SB, instant floating was observed possibly due to the entrapment of the resultant CO_2 within the CP gel layer.[47] However, these tablets maintained flotation for only about 5.2 h. This behavior could be attributed to the hydrophilicity of CP that promoted water penetration into the tablet matrix leading to an increase in its density with subsequent decrease in floating time.[48] Increasing the amount of SB

Table 2. Physical Properties of RHCl–GR Tablets

Formulae code	Tablet weight (mg)	Drug content (%)	Tablet friability (%)	Floating lag time (FLT; s)	Total floating time (TFT; h)	Bioadhesive force (g)
CP	441.2±2.3	99.1±1.2	0.34±0.09	Immediately	5.2±0.7	33.1±3.2
$P_{25}C13$	440.3±4.1	103.3±0.5	0.34±0.05	Immediately	>24	36.4±2.1
$P_{25}C12$	442.3±1.3	100.6±3.5	0.22±0.01	Immediately	>24	37.5±1.1
$P_{25}C11$	446.6±1.0	101.5±1.2	0.45±0.03	<20	>24	38.2±2.3
$P_{25}C21$	439.9±0.5	98.8±1.0	0.56±0.06	<20	>24	27.1±3.0
$P_{25}C31$	438.8±3.2	99.3±3.2	0.45±0.03	<20	>24	22.6±2.0
$P_{90}C13$	439.9±5.2	102.2±5.6	0.23±0.04	Immediately	>24	42.7±0.7
$P_{90}C12$	443.2±5.7	99.7±2.9	0.34±0.02	Immediately	>24	40.8±3.8
$P_{90}C11$	445.9±4.8	96.5±4.1	0.28±0.08	<20	>24	38.1±1.4
$P_{90}C21$	438.9±1.2	99.8±3.2	0.45±0.06	<20	>24	28.8±2.3
$P_{90}C31$	446.7±7.2	98.8±4.6	0.65±0.03	<20	>24	24.6±3.2

Each value represents the mean±S.D. (n=3).

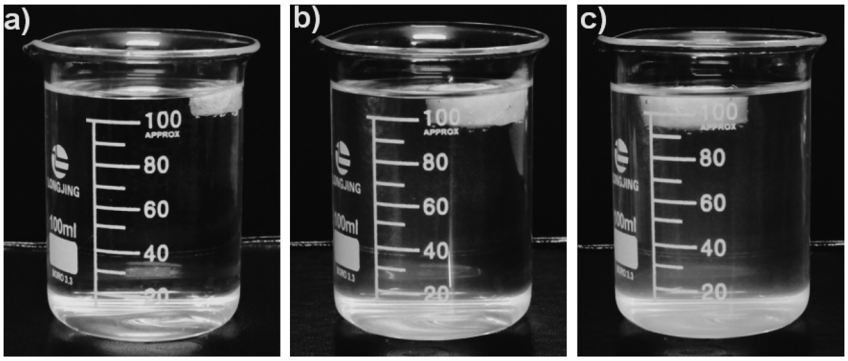

Fig. 5. Photographs of $P_{90}C13$ Floating Tablet in 0.1 N HCl

a: <5 s after immersion, b: 12 h after immersion, c: 24 h after immersion.

to 60 mg had no significant effect on the TFT of this formulation. On the other hand, the PVP (K25 & K90) matrices did not float even by increasing SB content from 20 to 60 mg and eroded after 4 h of the acidic soaking.

Effervescent PVP K25–CP matrix tablets of ratio 1 : 1 formulated with 20 mg SB exhibited significantly higher FLT (166.3±12.5 s) and TFT (12 h) than that of CP tablets. These results can be explained on the basis that the resulting IPC is more hydrophobic in nature due to shielding of the hydrophilic carboxyl and carbonyl groups of CP and PVP, respectively through hydrogen bonding.[17] The increase in SB amount in PVP K25–CP matrix tablets to 40 and 60 mg shortened FLT to 66 and <20 s, respectively, and prolonged TFT (>24 h). Since the instant floating was observed for 60 mg SB level, this amount was selected for the formulation of all PVP K25–CP or PVP K90–CP combinations in different ratios of 1 : 3, 1 : 2, 1 : 1, 2 : 1, and 3 : 1.

FLT and TFT were estimated for all the prepared formulations and the results are illustrated in Table 2. The FLT for the prepared formulations was <20 s except for CP and those containing high CP ratio; $P_{25}C13$, $P_{90}C13$, $P_{25}C12$, and $P_{90}C12$ that floated immediately. All the prepared PVP–CP combinations remained buoyant for more than 24 h. Therefore, it can be said that the CO_2 generated was trapped in the tablets and protected within the gel formed by hydration of polymers decreasing tablet density below 1, hence, maintaining tablet buoyancy.[49] Photographs taken during *in vitro* buoyancy study of $P_{90}C13$ formula in 100 mL 0.1 N HCl at different time intervals are shown in Fig. 5.

Bioadhesive Properties Bioadhesion of GR dosage forms is very important to overcome the highly variable residence times at various sites in the GIT, thus, improving their efficacy. The bioadhesion of CP may be explained by the presence of carboxylic acid groups which form strong hydrogen bonds with mucin, high molecular weight, and sufficient chain flexibility.[50] As well, PVP was reported to have certain mucoadhesivity.[51]

Table 2 compares the bioadhesive forces of PVP–CP matrix tablets to those containing CP only. The bioadhesive force of PVP–CP matrix tablets increased as the ratio of CP was raised for both PVP grades, that could be referred to the greater bioadhesion of CP compared to PVP. Similar results were previously reported.[41] In addition, the bioadhesive forces of PVP–CP tablets at ratios of 1 : 1, 1 : 2, and 1 : 3, were greater than that containing CP alone. Similarly, it has been reported that the bioadhesive forces of the PVP–PAA IPC were higher than that of commercial CP 971.[17] Another investigation demonstrated that, the combination of PVP with PAA was assumed to dehydrate some polymeric acid groups of the PAA molecule facilitating the interaction with the glycoproteins of the mucin. This resulted in an extended intermolecular network between the combined macromolecules and mucin imparting a greater mucoadhesion index.[52]

Swelling Study Swelling is a vital factor to measure the hydration ability of the formula which in turn affects its buoyancy, adhesion ability of swellable polymers and drug

release kinetics. The percentage swelling in 0.1 N HCl up to 12 h for formulations with various ratios of CP and PVP was measured, and illustrated in Fig. 6. There was an increase in the percentage swelling with higher amounts of CP. This effect may be due to the presence of hydrophilic groups in CP molecules that are responsible for their ability to absorb water. The hydration of these hydrophilic groups resulted in water entry into the polymer network leading to their expansion and hence, an ordering of the polymer chains.[53] Accordingly, $P_{25}C13$ formula showed the highest percentage swelling (254.0%) within 5 h. Tablet matrices with lower CP content, namely, $P_{25}C12$ and $P_{25}C11$ exhibited a significant reduction ($p<0.05$) in the percentage swelling to 140.3 and 75.6%, respectively. Meanwhile, further decrease in CP content as in case of $P_{25}C21$ and $P_{25}C31$ formulae resulted in non-significant decrease in the maximum percentage swelling compared to $P_{25}C11$ (Fig. 6a).

The swelling profiles of PVP K90–CP matrix tablets can be divided into two distinct phases: rapid swelling phase (0–5 h) followed by a slower swelling one between 5 and 12 h (Fig. 6b). $P_{90}C13$ tablets showed the highest percentage swelling (356.3%) after 7 h that could be due to the high content of CP in addition to the high MW of PVP used. Thus, the test medium uptake of the prepared matrices depended on the ratio of PVP to CP and the MW of PVP used. Further decrease of the CP content in PVP K90–CP tablets significantly ($p<0.05$) decreased the percentage swelling that probably still be attributed to the fewer hydrophilic groups and subsequent lower water uptake.

Drug Release Profiles

Effect of Molecular Weight of PVP

The effect of MW of PVP on drug release from tablets containing combinations of PVP and CP at a respective ratio of 3 : 1 ($P_{25}C31$ and $P_{90}C31$) was studied and the results are shown in Fig. 7a. A slower drug release was observed with $P_{90}C31$ tablets compared to those with $P_{25}C31$. Nearly, a complete drug release from $P_{25}C31$ formula occurred within 10 h, whereas, only 80.7% of the drug released from $P_{90}C31$ tablets within this period. Therefore, it can be claimed that the MW of PVP influenced the drug release pattern from the prepared matrix tablets and the higher MW of PVP K90 compared to that of PVP K25 facilitated stronger interaction with CP and more viscous gel.[54,55] The lower swelling and higher erosion of $P_{25}C31$ tablets as observed from swelling study could also account for the higher dissolution rates compared to those of $P_{90}C31$. This resulted in a shorter pathlength for drug diffusion into the release medium. The rapid hydration of $P_{25}C31$ tablets may be responsible for the earlier release in the dissolution medium, while, in the later times, the release could be attributed to the erodible properties of the matrix as shown from the swelling study (Fig. 6a).

PVP K90 could impart a higher swelling of $P_{90}C31$ compared to that of $P_{25}C31$ providing a continuous viscous matrix filling the interstices between particles that might maintain the integrity of the tablets and retard further liquid penetration sustaining the drug release.[56] As well, the high swelling rate led to increase in the tablets dimensions, drug diffusion pathways and thus decreasing diffusion rates.[57]

Effect of PVP–CP Ratio

The effect of various ratios of PVP K25 to CP on the drug release was studied and the results are illustrated in Fig. 7b. The decrease in CP content in matrix tablets with PVP K25 lowered the drug release as has been noted with formulae containing PVP K25–CP at respective ratios of 1 : 3, 1 : 2, and 1 : 1 ($P_{25}C13$, $P_{25}C12$, and $P_{25}C11$) that released 95.9, 78.6, and 70.0% of the drug after 8 h, respectively. Further decrease in

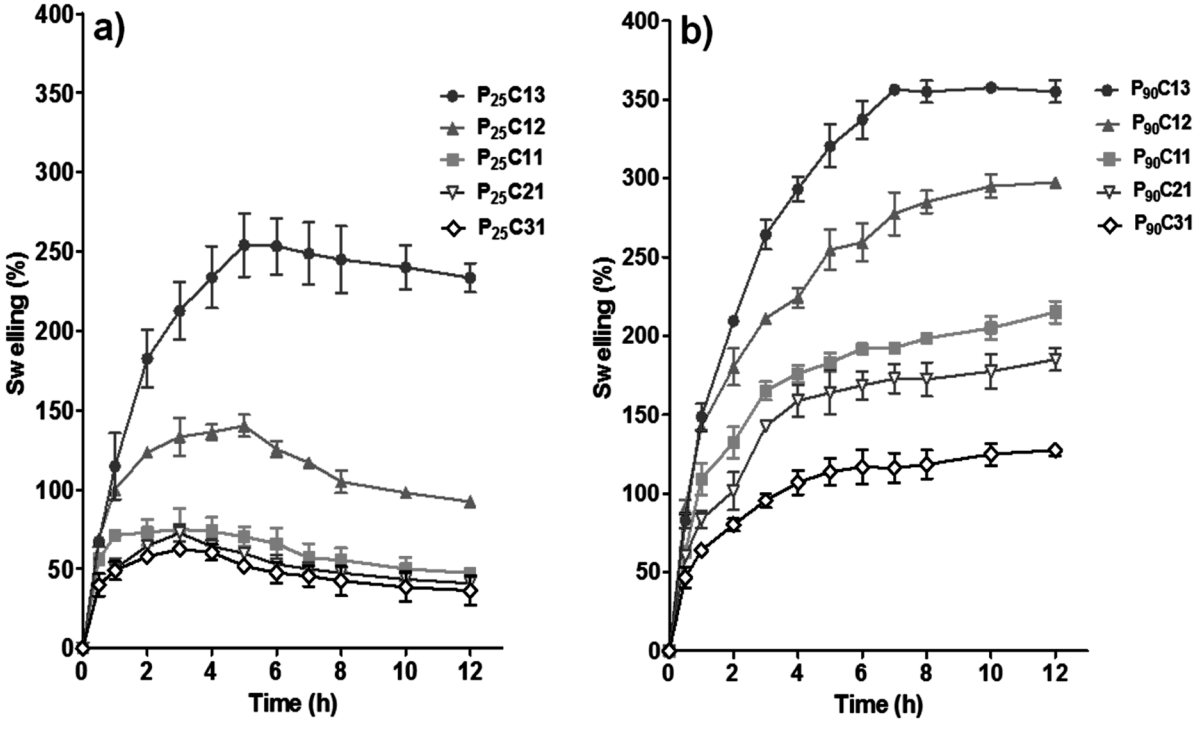

Fig. 6. Swelling Profiles of Tablets Containing (a) PVP K25–CP Combination in Different Ratios and (b) PVP K90–CP Combination in Different Ratios

Each point represents the mean±S.D. ($n=3$).

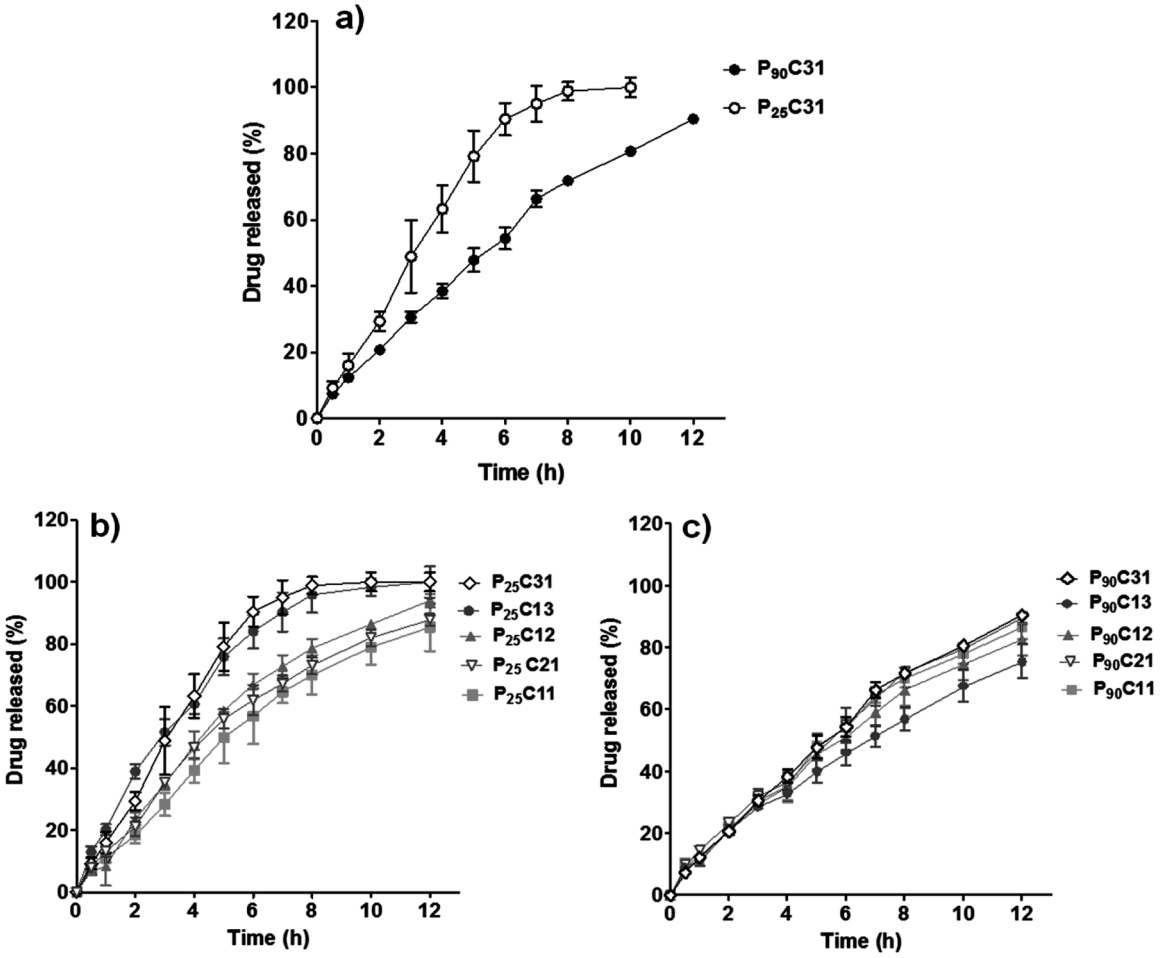

Fig. 7. Release Profiles of RHCl from Tablets Containing (a) PVP K25–CP and PVP K90–CP Combination at 3 : 1 Ratio, (b) PVP K25–CP Combination in Different Ratios and (c) PVP K90–CP Combination in Different Ratios

Each point represents the mean±S.D. (n=3).

Table 3. Mathematical Modeling and Release Kinetics of RHCl from the Prepared GR Tablets

Formula code	Zero order	First order	Higuchi model	Korsmeyer–Peppas		Drug transport mechanism
	Correlation coefficient (r^2)			r^2	Diffusional exponent (n)	
$P_{25}C13$	0.963	0.947	0.977	0.998	0.750	Non-Fickian
$P_{25}C12$	0.982	0.991	0.938	0.967	0.727	Non-Fickian
$P_{25}C11$	0.993	0.988	0.932	0.983	0.692	Non-Fickian
$P_{25}C21$	0.977	0.996	0.953	0.991	0.705	Non-Fickian
$P_{25}C31$	0.963	0.915	0.945	0.992	0.763	Non-Fickian
$P_{90}C13$	0.987	0.974	0.954	0.994	0.662	Non-Fickian
$P_{90}C12$	0.994	0.976	0.948	0.994	0.682	Non-Fickian
$P_{90}C11$	0.993	0.979	0.935	0.987	0.689	Non-Fickian
$P_{90}C21$	0.994	0.958	0.943	0.996	0.689	Non-Fickian
$P_{90}C31$	0.996	0.961	0.937	0.990	0.696	Non-Fickian

CP amount ($P_{25}C21$ and $P_{25}C31$) increased the drug release rate. Accordingly, $P_{25}C11$ formula showed the slowest release which could be attributed to the maximum complexation between PVP K25 and CP at this ratio upon tablet hydration in the acidic medium forming an insoluble IPC. In accordance, the maximum amount of fresh complex of PVP K25 and CP was obtained at weight ratio of 1 : 1 (Fig. 1). This could allow slower solvent penetration into the matrices and more controlled drug diffusion.[58] Beyond 1 : 1 weight ratio of the two polymers, the imbalance of complexation sites between carboxyl and carbonyl groups may reduce the shielding effect for hydrophilic groups within the complex. This may be referred to less complex formation resulting in less control of solvent penetration and drug diffusion, hence, enhancing the drug release.[19,58]

The influence of the PVP K90–CP ratios on RHCl release

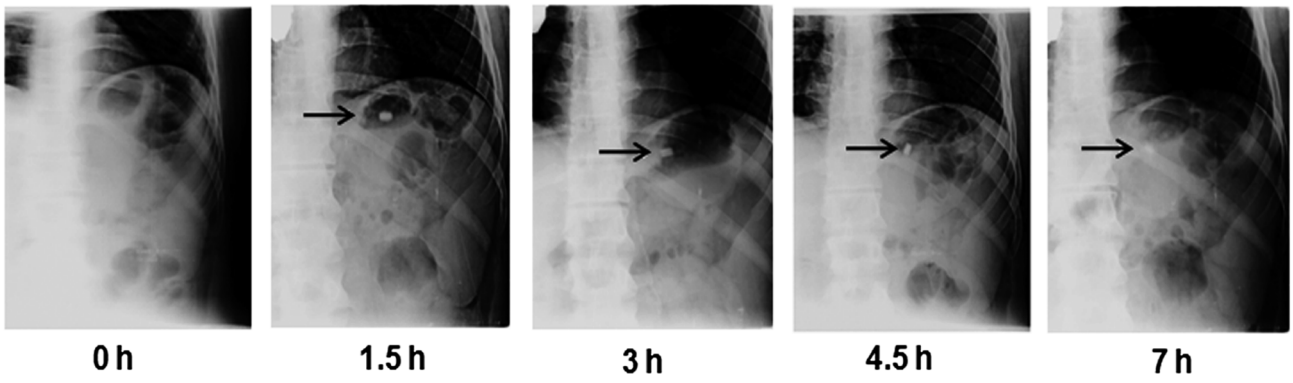

Fig. 8. X-Ray Imaging of RHCl–GR Tablet ($P_{90}C13$ Formula)
The location of tablet is represented with an arrow.

from the GR tablets was depicted in Fig. 7c. The slowest release pattern was obtained when PVP K90 and CP were incorporated at a ratio of 1 : 3 allowing the release of 56.8% of the drug after 8 h. Matrices containing lower CP content as in case of $P_{90}C12$ and $P_{90}C11$ formulae significantly ($p<0.05$) exhibited higher drug release after 8 h of 66.4 and 70.1%, respectively. However, further lowering in the amount of CP did not significantly modify the drug release rate. This behavior is different from those containing mixtures of PVP K25 and CP. This might be explained on the basis that PVP K90 has higher MW than PVP K25, thus, produced a complex of higher viscosity withholding the tablet shape and integrity efficiently for an appreciable period and subsequently, prevented its erosion in the release medium.

Kinetic Modeling of Drug Release The data obtained from *in vitro* dissolution studies were fitted to different kinetics models as zero-order, first-order, and Higuchi equation. The obtained r^2 values were ≥ 0.915 suggesting that the drug release from all the tested formulations in 0.1 N HCl may follow any one of these models (Table 3).

To determine the mechanism of drug release, the data were fitted according to Korsemeyer–Peppas equation. For a matrix tablet, when (n) value equals 0.45, a diffusion-controlled drug release can be expected. In case of (n) value of 0.89, a swelling-controlled drug release may have been encountered. Values of (n) between 0.45 and 0.89 can be considered as an indicator for both mechanisms (anomalous transport). The obtained (n) values ranging from 0.662 to 0.763 with r^2 values ≥ 0.967 suggested that the combination of matrix erosion and diffusion of the drug in the hydrated matrices controlled RHCl release, in acidic medium, from matrix tablets containing PVP–CP mixtures.[39] Similar finding was previously reported for RHCl release from GR alginate beads in acidic medium.[59]

The Mean Gastric Retention Period $P_{90}C13$ formula showed excellent floating, mucoadhesive and swelling characteristics with initial faster hydration rate which may promote the interpenetration of the tablet matrix within the gastric mucosa. Furthermore, it exhibited a promising initial drug release followed by a controlled behavior for a desired period of time. Based on these findings, $P_{90}C13$ was chosen for *in vivo* evaluation *via* determination of gastric retention using X-ray imaging. The radiographic images taken at different periods post-administration of the barium sulfate-loaded tablet in one of the volunteers illustrated that the tablet slightly moved downwards after 3 h, then appeared nearly at the same position in the stomach till the end of 7 h as shown in Fig. 8. This behavior could be related to its bioadhesive nature. The appearance of RHCl–GR tablet in stomach of the subject till 7 h confirmed its buoyancy and the proposed *in situ* interpolymer complexation of PVP and CP employing RHCl as a model drug. The mean gastric retention time was calculated for the six volunteers and was found to be 6.8 ± 0.3 h.

Conclusion

Tablets containing PVP K90–CP at a respective ratio of 1 : 3 ($P_{90}C13$) experienced promising FLT, TFT, swelling ability, bioadhesion force, and sustained RHCl release rates indicating an *in situ* complexation between the two polymers. They showed *in vivo* gastric retention period of 6.8 ± 0.3 h in six healthy human volunteers. It is worth noting that the *in situ* complexation between CP and PVP, particularly K90, in gastric fluid may offer an ideal milieu for novel GR tablet formulations with prolonged drug release. Consequently, drugs having narrow absorption window in the stomach or upper part of the small intestine would be suitable candidates to be incorporated into these systems.

Conflict of Interest The authors declare no conflict of interest.

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