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Development and evaluation of a floating in situ gelling liquid formulation of a locally acting H₂-antagonist

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Abstract

In the present study, floating in situ gelling liquid formulation for controlled delivery of ranitidine was formulated using gellan gum (gelling polymer), calcium carbonate (gas-forming agent) and ranitidine. Gellan gum floating in situ gelling systems were prepared by dissolving varying concentrations of gellan gum in deionized water containing sodium citrate and calcium chloride, to which varying concentrations of drug and calcium carbonate were added and dissolved by continuous stirring. Prepared formulations were evaluated for viscosity, gelation behavior, floating properties (floating lag time and floating duration time), drug content and in-vitro drug release. Formulation variables such as concentration of gellan gum, calcium carbonate and drug significantly affected the formulation viscosity, floating behavior and in-vitro drug release. Analysis of the release kinetic data showed that the drug release from in situ gel followed a diffusion control mechanism.

Keywords

Floating systems

In situ gelling

Controlled delivery

Gellan gum

Ranitidine

1. Introduction

Oral formulations have earned a significant place among the various dosage forms developed so far for human administration (Mandal et al. 2016). In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric emptying time among many other reasons involved (Mudie et al. 2010; Nayak et al. 2010).

Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g. pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine (Prinderre et al. 2011; Thakar et al. 2013; Sugihara et al. 2014).

Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine (Nayak et al. 2010).

There are many drugs (e.g. captopril, metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area (Nayak et al. 2010; Kesarla et al. 2015). To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation (Mandal et al. 2016).

However, an oral sustained-controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time (Kumar and Philip, 2007).

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Apart from the systemic action, gastric retentive dosage forms had proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried *Helicobacter pylori*

from the submucosal tissue of the stomach (Nayak et al. 2010; Prinderre et al. 2011; Kim et al. 2014; Adebisi et al. 2015; Aoki et al. 2015).

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices (Singh and Kim, 2000).

FDDS has become increasingly attractive system for gastroretentive dosage forms because it can prolong gastric retention time and improve drug bioavailability (Sungthongjeen et al. 2008; Treesinchai et al. 2016). FDDS (single unit systems) are widely explored for gastroretention purposes and have a bulk density lower than gastric fluids (1.004 to 1.010 g/ml) and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Rosenzweig et al. 2013). While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system (Arora et al. 2005). After the required drug release, the used dosage form is emptied out from the stomach (Mayavanshi and Gajjar, 2008).

In addition to the single unit systems, In-situ gelling technique (also known as raft forming system) in combination with carbon dioxide bubble entrapment was also reported as another patient compliance design for gastroretention (Mandal et al. 2016).

This type of delivery system, initially as a solution form, contains an in situ gel forming polymer along with carbonates or bicarbonates as effervescent agents. When they come in contact with the gastric fluid, they swell and generate a viscous cohesive gel that contains entrapped carbon dioxide bubbles, causing the drug delivery systems to float (Foster et al. 2013; Prajapati et al. 2013).

H₂-antagonists or proton pump inhibitors are clinically used in treating chronic conditions like peptic ulcer and reflux oesophagitis. H₂-antagonists competitively inhibit histamine actions at all H₂-receptors, but are mainly used clinically as inhibitors of gastric acid secretion (Rang et al. 2003). Local availability of H₂-antagonists in stomach has a greater clinical significance in treatment of peptic ulcer.

Ranitidine (RT), a H₂-antagonist, is widely prescribed in active duodenal ulcers, gastric ulcers and gastroesophageal reflux disease. A conventional dose

of 150 mg can inhibit gastric acid secretion up to 5 hours and frequent administration leads to plasma fluctuations; hence, a sustained release dosage form of ranitidine is desirable. The short biological half-life of the drug (~2.5–3 hours) also favors development of a sustained release dosage form (Dave et al. 2004).

In the present study, an attempt was made to develop a floating in situ gelling liquid formulation using ranitidine for local release in the stomach. Floating in situ gelling liquid formulations were formulated using different concentrations of Gellan gum (gelling polymer) and calcium carbonate (gas-forming agent).

2. Materials and Methods

2.1. Materials

Ranitidine (RT) was a kind gift from Medical Union Pharmaceuticals, Abu Sultan, Ismailia, Egypt, Gellan gum (Phytigel)[®] and calcium carbonate (CaCO₃) were supplied from Sigma Company for pharmaceuticals, Cairo, Egypt, Sodium citrate and Calcium chloride were supplied from El-Nasr Pharmaceutical Chemicals Co., (Egypt), All other reagents were of analytical grade.

2.2. Preparation of in situ floating systems

Gellan based in situ floating systems were prepared according to the method reported before (Rajinikanth et al. 2007; Rajinikanth and Mishra, 2008). Gellan gum solution of different concentrations (0.25–1.0% w/v) were prepared in deionized water containing sodium citrate (0.25% w/v) and calcium chloride (0.016% w/v). Low level of cations present in the solution was sufficient to hold the molecular chains together and inhibit hydration. The gellan gum was dispersed in deionized water, heated to 90°C with continuous stirring and then cooled below to 40°C. After cooling below 40°C, various concentrations of calcium carbonate and drug were added and dispersed well with continuous stirring. The resulting formulations were finally stored in amber color narrow mouth bottles until further use.

2.3. Measurement of Viscosity:

The viscosity of the prepared formulations was determined using a Brookfield viscometer DV-II (Brookfield, USA) using spindle cp 40. Viscosity was measured at different angular velocities at a temperature of 25±1°C. Viscosity measurement for each sample was done in triplicate, with each measurement taking approximately 30s.

2.4. In vitro gelation study:

The gelation studies were carried out as described previously (Rohith et al. 2009) with minor modification. The gelation cells were cylindrical reservoirs capable of holding 3ml of the gelation solution (simulated gastric fluid (SGF), 0.1 mol L⁻¹ HCl of pH 1.2, without enzymes). Within the cells located at the bottom was a 250 µl transparent plastic cup to hold the gel sample in place after its formation. Then, 100µl of the preparation was carefully placed into the cavity of the cup using micropipette, and 2ml of the SGF was added slowly in reservoir. Gelation was observed by visual examination.

2.5. Floating behavior:

The floating behavior of the prepared formulations was carried out as described previously (Rohith et al. 2009). The floating properties (floating lag time and floating duration time) of the formulations were determined in the SGF (0.1 mol L⁻¹ HCl, pH 1.2). The time in minutes taken by the formulation to emerge on the dissolution medium surface (floating lag time) and floating duration time was noted.

2.6. Drug content:

Ranitidine content inside the prepared formulations was carried out as described previously (Rohith et al. 2009). Ten mL of the solution was added to 900 mL of the SGF (0.1 mol L⁻¹ HCl, pH 1.2) and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with the SGF and the drug concentration was determined by using a UV-visible

spectrophotometer (UV-1800 PC Shimadzu, Tokyo, Japan) at 226 nm against a suitable blank solution.

2.7. In-vitro release:

The release profile of ranitidine from the formulations was carried out as described previously (Rohith et al. 2009). A USP paddle dissolution test apparatus with a paddle stirrer speed set at 50 rpm was used in this experiment. The dissolution medium used was 900 mL of the SGF (0.1 mol L⁻¹ HCl, pH 1.2) and temperature was maintained at 37 ± 0.2 °C. Ten mL of the formulation were placed into a Petri dish (4.5 cm internal diameter) which was kept in the dissolution vessel and the SGF was carefully added to the vessel avoiding any disturbance of the Petri dish. At each time interval, a precisely measured sample of the dissolution medium was pipetted out and replenished with fresh medium. Ranitidine content in the sample was determined spectrophotometrically. Each study was conducted in triplicate.

2.8. Mechanism of drug release:

In order to analyze the mechanism of drug release from the formulations, the in vitro dissolution data were fitted to zero-order ($F = k_0t$), first-order ($F = e^{-kt}$), Higuchi diffusion ($F = k\sqrt{t}$) release models, where F is the fraction of drug released ($\leq 60\%$), k is the release constant and t is time.

3. Results and Discussion

3.1. Evaluation of formulations:

The composition of the prepared formulations is

Table 1: Formulation variables.

Formulation Code	Formulation Composition				
	Gellan Gum (% w/v)	CaCO ₃ (% w/v)	RT (%w/v)	Na Citrate (% w/v)	CaCl ₂ (% w/v)
Effect of Gellan concentrations					
H ₁	0.25	0.75	1	0.25	0.016
H ₂	0.5	0.75	1	0.25	0.016
H ₃	0.75	0.75	1	0.25	0.016
H ₄	1	0.75	1	0.25	0.016
Effect of CaCO ₃ Concentrations					
H ₅	0.5	0.5	1	0.25	0.016
H ₆	0.5	0.75	1	0.25	0.016
H ₇	0.5	1	1	0.25	0.016
H ₈	0.5	2	1	0.25	0.016
Effect of RT Concentrations					
H ₉	0.5	0.75	2	0.25	0.016
H ₁₀	0.5	0.75	3	0.25	0.016

shown in **Table 1**. The two main pre-requisites of in situ gelling systems are optimum viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol-gel transition due to ionic interaction. Moreover, the in situ formed gel should preserve its integrity without dissolving or eroding for prolonged period to facilitate sustained release of drugs locally. The developed formulations met all the pre-requisites to become an in situ gelling floating system, gelled and floated instantaneously at the pH conditions of the stomach. Sol to gel transformation of gellan occurs in the presence of either monovalent or divalent cations in contact with the gastric fluids.

Either sodium bicarbonate and calcium carbonate could be used as a gas-forming agent. Calcium carbonate was selected in this study as the gas producing agent because it is established that formulations containing calcium carbonate produce a significantly stronger gel than those containing sodium bicarbonate (Choi et al. 2002). This is due to the internal ionotropic gelation effect of calcium on gellan (Kedzierewicz et al. 1999). The calcium carbonate present in the formulation as insoluble dispersion is dissolved and releases carbon dioxide on reaction with acid of the stomach, and the in situ released calcium ions results in formation of gel with floating characteristics. The released carbon dioxide is entrapped in the gel network of the formulation, and the gel rises to the surface of the dissolution medium (in vitro) or the stomach (in vivo) (Deshpande et al. 1997).

3.2. Viscosity and gelling properties:

The rheological properties of the solutions are of importance in view of their proposed oral administration. In the selection of the concentration of the gelling polymer, a compromise is sought between a sufficiently high concentration for the formation of gels of satisfactory gel strength for use as a delivery vehicle, and a sufficiently low concentration to maintain an acceptable viscosity for ease of swallowing (Rajinikanth et al. 2007).

The solutions showed a marked increase in viscosity with increasing concentration of gellan gum (0.25 – 1 % w/v) as shown in **Table 2**. The observed increase in viscosity with increase in concentration has been noted previously for gellan gum and was attributed to a consequence of increasing chain interaction with an increase in polymer concentration (Deasy and Quigley, 1991). All polymer concentrations showed evidence of shear thinning behavior, the effect being more pronounced at higher concentrations (Rajinikanth et al. 2007).

Increasing the calcium carbonate content, which is the source of cations, simultaneously increased the viscosity of the formulation at all polymer concentrations studied (**Table 2**). Since the calcium carbonate is present in the formulations as insoluble dispersion, an increase in its concentration proportionally increased the number of particles dispersed, thus contributing to increased viscosity (Rohith et al. 2009).

Table 2: Characteristics of RT floating in situ gelling systems.

Formulation Code	Viscosity (m Pa s)*	Gelation (s)	Floating		Drug content (%)*
			Lag time (s)	Duration time (h)	
Effect of Gellan concentrations					
H₁	245.23 ± 4.01	27	45	> 24	99.4 ± 0.6
H₂	292.13 ± 8.42	25	36	> 24	101.9 ± 1.1
H₃	326.74 ± 9.16	20	31	> 24	104.4 ± 0.4
H₄	413.32 ± 11.32	14	24	> 24	100.7 ± 0.2
Effect of CaCO ₃ Concentrations					
H₅	240.87 ± 11.14	38	47	> 24	102.1 ± 0.3
H₆	292.13 ± 8.42	25	36	> 24	98.9 ± 0.12
H₇	342.17 ± 12.9	16	28	> 24	102.3 ± 0.3
H₈	593.15 ± 9.65	10	16	> 24	98.3 ± 0.22
Effect of RT Concentrations					
H₉	303.31 ± 14.51	19	45	> 24	103.8 ± 0.17
H₁₀	384.15 ± 7.65	15	57	> 24	100.2 ± 0.05

* Mean ± SD (n = 3)

The gelation study was conducted in the SGF (0.1 mol L⁻¹ HCl, pH 1.2). All the formulations showed immediate gelation when contacted with SGF. Most of the formulations are gelled within 40 s after contact with SGF and the gelling time was ranged from 10 s–38 s (**Table 2**). The formulation containing highest concentrations of calcium carbonate (2.0%w/v) has lowest gelation time (10 s), whereas formulation containing lowest calcium carbonate has highest gelation time (38 s) as shown in **Table 2**. This could be explained by the fact that calcium carbonate being present in the formulation as insoluble dispersion which becomes soluble in the acidic medium and release calcium ions, that cause gelation of gellan.

Lower concentrations of calcium carbonate were excluded from the study. Gellan formulations with low calcium carbonate concentrations (less than 0.5%, w/v) formed weak gels and such vehicles are not suitable as oral liquid formulations, as they will be removed earlier from the stomach by the peristaltic movements (Rajinikanth et al. 2007; Rajinikanth and Mishra, 2008).

Gellan formulations containing high concentration of calcium carbonate is expected to produce a strong gel in short gelation time of the delivery system in the stomach. In addition, combinations of high polymer and calcium carbonate concentrations will demonstrate adequate gel strength, indicating that they will withstand the shear forces likely to be encountered in the stomach. Thus, such vehicle will have longer residence time than oral solutions. Ideally, an in situ gelling delivery system should be a free flowing liquid to allow reproducible oral administration as a liquid (Rajinikanth and Mishra, 2008).

3.3. Floating properties

The floating properties of the prepared formulations was evaluated in the SGF (0.1 mol L⁻¹ HCl, pH 1.2). The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were evaluated and are shown in **Table 2**.

The mechanism of floatation is explained as follows: Upon contact with an acidic medium, gelation and cross linking by Ca⁺⁺ ions occurred to provide a gel barrier at the surface of the formulation. The calcium carbonate effervesced, releasing carbon dioxide and calcium ions. The released carbon dioxide is entrapped in the gel network producing buoyant formulation

and then calcium ion reacted with gellan produced a cross linked three-dimensional gel network that might restrict the further diffusion of carbon dioxide and drug molecules and has resulted in extended period of floating and drug release, respectively (Miyazaki et al. 1999).

The floating ability of the formulation mainly depends on calcium carbonate and gellan concentrations. The lowest level of calcium carbonate which produced a buoyant gel system for the duration of drug release study was found to be 0.75% (w/v) at all polymer levels. On increasing the calcium carbonate concentration, the floating lag time was reduced and duration of floating was increased. The increase in the amount of Ca⁺⁺ and CO₂, content at increased calcium carbonate concentration, is responsible for the observed reduction in floating lag time and increased duration of floating.

Similarly, an increase in the polymer concentration resulted in decreased floating lag time and an increase in floating duration of the prepared systems (Singh and Kim, 2000)

The floating lag time varied with the formulation variables. Formulation H8 (Gellan gum 0.5 % w/v, CaCO₃ 2 % w/v) exhibited the least floating lag time (16 s) while formulation H10 (Gellan gum 0.5 % w/v, CaCO₃ 0.75 % w/v) exhibited the highest lag time (57s) (**Table 2**). The decrease in the floating lag time of formulation H8 can be attributed to the availability of an increased amount of CO₂ as the concentration of calcium carbonate was increased, being entrapped in the formed gel to give rapid floatation.

As the drug concentration was increased from 1–3 % w/v, the floating lag time also increased from 36 to 57 seconds. It appears that with higher polymer content, excipients and drug, the bulk density of the gel increased, resulting in extension of the lag time. Irrespective of formulation variables, the floating duration time was found to be > 24 hours.

3.4. In-vitro drug release:

The In-vitro drug release study was conducted on the formulations for a period of 8 h during which the highest drug release of 96.28 ± 0.3 % (n = 3) was observed with formulation H1 (Gellan gum 0.25 % w/v, drug 1 % w/v) and the least drug release of 69.34 ± 0.1 % with H8 (Gellan gum 0.5 % w/v, drug 1 % w/v) during the 8 h dissolution study. The obtained results were represented in **Figures (1 – 3)**

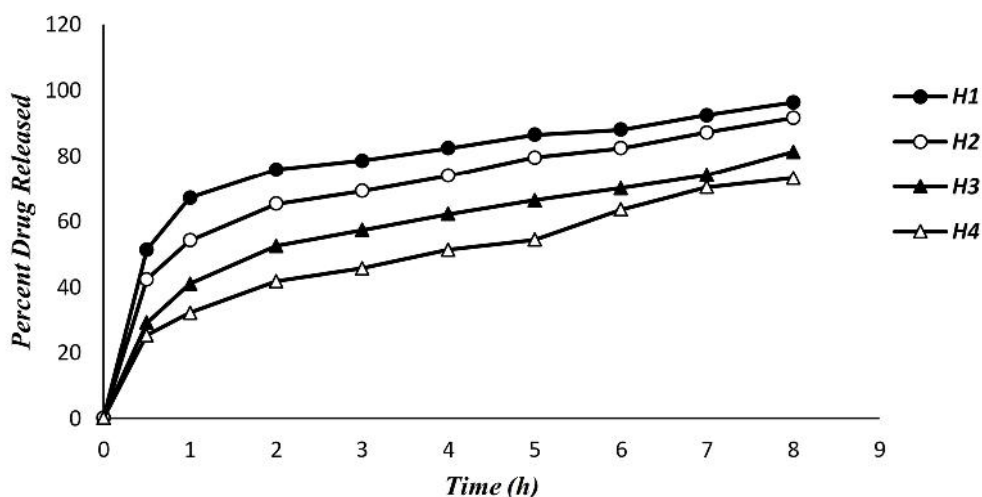


Figure 1: Effect of gellan gum concentration on the in-vitro drug release.

3.4.1. Effect of polymer concentration on in vitro drug release:

It was also noted that increasing the polymer concentration in the prepared formulation caused a significant ($P < 0.01$) decrease in rate and extent of drug release (Figure 1). This effect is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse (Rajinikanth et al. 2007; Rajinikanth and Mishra, 2008).

Another explanation for this effect is that increasing the polymer concentration, more polymeric chains are available for crosslinking with the calcium ion. As the crosslinking increases, it forms a stronger gel, across which drug diffusion becomes difficult (Celine et al. 2006).

The release of drug from these gels was characterized by an initial phase of high release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of moderate release. This bi-phasic pattern of

release is a characteristic feature of matrix diffusion kinetics (Lemoine et al. 1998). The initial burst effect was considerably reduced with increase in polymer concentration.

3.4.2. Effect of calcium carbonate concentrations on in vitro drug release:

Calcium carbonate (0.5–2.0 % w/v) was used as a gas-forming agent and a source of cations for gelation in the formulation. The desired floatation (> 24 h) was achieved with calcium carbonate concentration of 0.75 % w/v while a concentration up to 2.0 % w/v provided sustained release of ranitidine (Figure 2).

The drug release decreased as the concentration of calcium carbonate in the formulation was increased. This may be attributed to the fact that as the concentration of calcium ions increases, cross-linking also increases.

3.4.3. Effect of drug loading on in vitro drug release:

Ranitidine was incorporated in three different

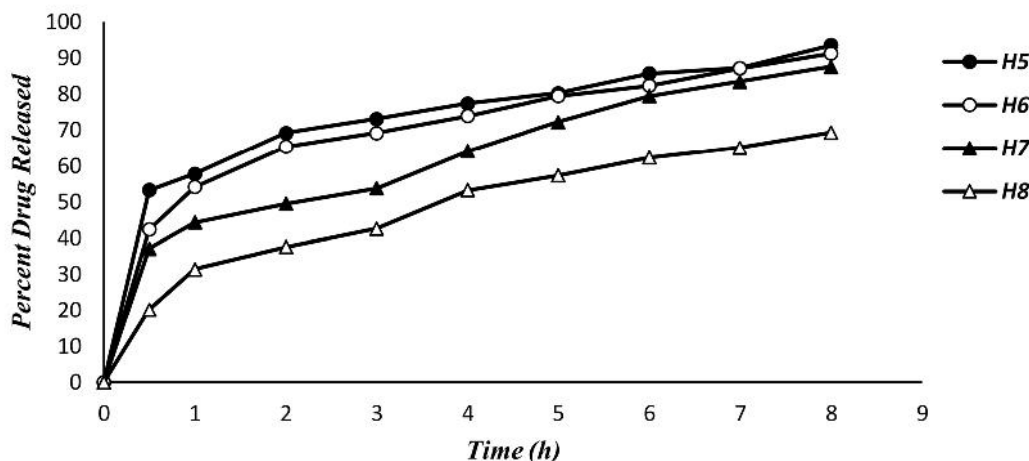


Figure 2: Effect of calcium carbonate concentration on the in-vitro drug release.

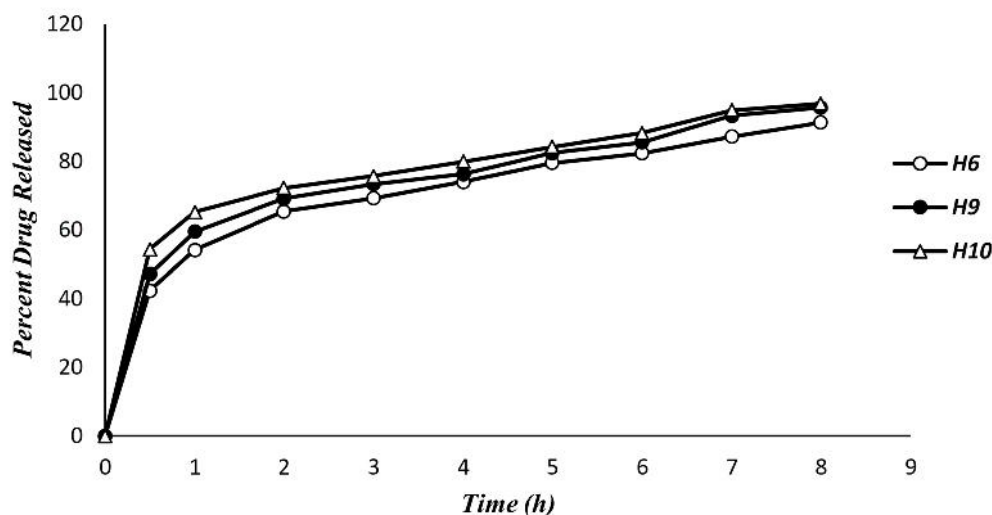


Fig. 3: Effect of ranitidine concentration on the in-vitro drug release.

concentrations (1, 2 and 3 % w/v) to evaluate the effect of drug loading on the release profile (**Figure 3**). An initial burst release was observed from the studied formulations H6 (drug 1 % w/v), H9 (drug 2 % w/v) and H10 (drug 3 % w/v). However, at the end of 8 hours, the drug release from the formulations was in the range of 91–96 %. The results indicated that there was an increase in the rate and extent of in vitro drug release with increase in Ranitidine concentrations.

3.5. Mechanism of drug release:

In order to investigate the mode of drug release from floating in situ gels the release data were analyzed using the mathematical models mentioned before. The obtained results were represented in **Table 3**. The examination of the coefficient of determination (R^2) was used to determine the mechanism of release. As shown in **Table 3**, the coefficient of determinations (R^2) for the zero-order model ranges from 0.884 to 0.9351 and that for the Higuchi model ranges from 0.9579 to 0.9944, suggesting the drug release

followed diffusion controlled mechanism from the prepared preparations.

4. Conclusion

In the present study, various in situ liquid oral formulations of ranitidine were prepared. The study has shown that release of the drug can be controlled by modifying the composition parameters such as the initial drug loading, concentration of gas-forming agent and polymer content.

The behavior of prepared formulation was evaluated and by observing the results of the evaluation parameters, it can be stated that floating in situ gelling systems have the capability of forming gels in stomach and sustaining the drug release from these gels over the period of at least 8 h.

5. Conflict of interest

The authors report no declaration of conflict of interest.

Table 3: In-vitro drug release kinetics analysis.

Formulation Code	R^2		
	Zero Order	First Order	Higuchi Diffusion
H ₁	0.8975	0.8342	0.9640
H ₂	0.9201	0.8629	0.9761
H ₃	0.9315	0.8801	0.9821
H ₄	0.9054	0.9098	0.9646
H ₅	0.9351	0.9110	0.9579
H ₆	0.9201	0.8629	0.9761
H ₇	0.9012	0.9625	0.9939
H ₈	0.8824	0.9863	0.9931
H ₉	0.9025	0.9773	0.9944
H ₁₀	0.9312	0.9654	0.9830

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