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FORMULATION AND EVALUATION OF GASTRORETENTIVE BEADS OF CIMETIDINE

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Abstract:
The present work aimed to develop and evaluate a gastroretentive sustained release dosage form of Cimetidine to prolong gastric residence time, achieve controlled plasma levels, and improve bioavailability for effective management of peptic ulcer. Preformulation studies confirmed the physicochemical properties of Cimetidine, including its crystalline nature, solubility profile, melting point (142–144 °C), partition coefficient (0.4), and λmax at 224 nm. Drug–excipient compatibility studies revealed no interaction, ensuring stability of the formulation. Cimetidine-loaded gastroretentive beads were prepared using the ionotropic gelation method with sodium alginate (2–4%) and gas-generating agents. The formulations exhibited percentage yields between 68.82–89.91%, particle sizes ranging from 174–267 µm, entrapment efficiencies of 71.28–94.32%, and swelling indices of 2.7–4.1. Floating ability studies in 0.1 N HCl (pH 1.2) demonstrated buoyancy values of 68.72–89.23%, with floating lag times of 37–55 seconds and total floating times exceeding 10 hours. Among all formulations, GB-1 showed superior performance with high yield (89.91%), smaller particle size (174 µm), maximum entrapment efficiency (94.32%), swelling index (4.1), and buoyancy (89.23%). In-vitro drug release studies confirmed sustained release, with GB-1 selected for kinetic modeling. The release profile best fitted the Korsmeyer–Peppas model (R^2 = 0.985), indicating diffusion-controlled release with possible swelling and erosion mechanisms. Stability studies over 30 days at 4 °C, 25 °C, and 40 °C confirmed the robustness of GB-1 with no significant variation in drug release. Overall, the optimized gastroretentive beads of Cimetidine (GB-1) demonstrated excellent floating ability, high entrapment efficiency and sustained release behavior, establishing their potential as a promising dosage form for prolonged gastric retention and improved therapeutic efficacy in peptic ulcer treatment

Keywords: *Cimetidine, Gastroretentive, Ulcer, Ionotropic gelation, Floating beads*

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INTRODUCTION:

The oral route is the preferred route for drug delivery[1]. Orally administered drugs which are promptly absorbed in the alimentary canal and rapidly lost from the blood are generally film coated or microencapsulated to prolong the drug release period and drug action[2]. Conventional oral drug administration does not usually provide rate-controlled release or target specificity[3]. Conventional drug delivery provides sharp increases of drug concentration at potentially toxic levels[4]. Drug concentration eventually drops off until re-administration. Incomplete drug release from the devices or too short residence time of pharmaceutical dosage forms in the upper position of small intestine will leads to low bioavailability of sustained release dosage forms[4]. To overcome these problems, various attempts have been made to develop floating systems which will float in the gastric contents for a long time[5]. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drug. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment[6]. It has applications also for local drug delivery to the stomach and proximal small intestines[7]. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[8].

The objective of this study is to develop a multi-unit gastroretentive sustained release dosage form of a water-soluble drug Cimetidine. In order to prolong the gastric residence time after oral administration at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability[9]. The floating dosage form containing Cimetidine as a drug was designed for the cure of peptic ulcer[10].

MATERIALS AND METHOD:

Cimetidine was obtained from Cipla Ltd. Indore (m.p.) as gift sample. Sodium bicarbonate was purchased from Himedia Pvt. Ltd. India, Sodium alginate from Swastik gum industries, India. Used solvents and reagents were belongs to L. R. grade.

Method of Formulation of Cimetidine Loaded Gastroretentive Beads

Cimetidine loaded gastroretentive beads were prepared using Ionotropic Gelation Method. Polymer solution was prepared by dissolving sodium alginate (2-4%) in distilled water, stirred until a clear solution formed. The drug was dispersed uniformly into the polymer solution, then added citric acid and $NaHCO_3$ to generate buoyancy. The mixture was dropped into a cross-linking solution (1% $CaCl_2$) using a syringe (20 G needle). The beads were formed instantly due to ionic cross-linking. The beads were kept suspended in the cross-linking solution for 30–60 minutes. The beads were filtered and washed with distilled water to remove excess ions. The beads were dried in air at room temperature for 24 - 48 hours then stored in a desiccator until evaluation.

RESULT AND DISCUSSION:

Gastroretentive sustained release dosage form of drug Cimetidine was developed. In order to prolong the gastric residence time after oral administration at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. The floating dosage form containing Cimetidine as a drug was designed for the cure of peptic ulcer. In the preformulation study the Cimetidine was assessed for color, odor and taste visually and found Cimetidine was white, solid odorless, slightly bitter, crystalline powder. Solubility of Cimetidine was tested in various solvents at room temperature and observed by the UV-visible spectrometer inspection. The melting point was observed at 142 – 144 ^{O}C. The partition coefficient of the Cimetidine was found 0.4 which indicated the hydrophilic nature of drug. The λmax of Cimetidine was found at 224nm. The calibration curve of Cimetidine in 0.1N HCl was prepared. Study of Cimetidine drug-excipient mixture was performed and found no interaction. One-month study no change was observed in the physical characteristics of the drug in presence of the excipients.

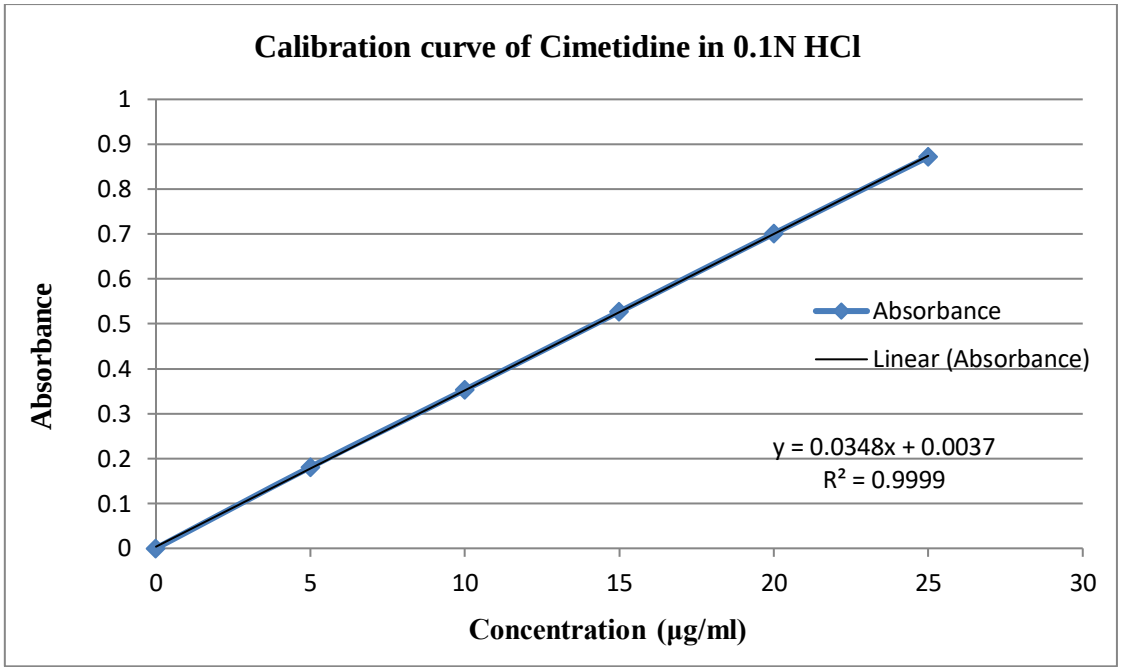

Figure 1: Calibration curve of Cimetidine (0.1 N HCl)

Physical Compatibility studies of Cimetidine with excipients:

Compatibility study of Cimetidine drug-excipient mixture was performed. The observations were given in the table below. after one-month study no change was observed in the physical characteristics of the drug in presence of the excipients. This shows that there is no incompatibility between drug and excipients.

Table No. 1: Physical drug-polymer compatibility studies

S. No.	Drug-Excipient	Initial	30 Days study			Comments
			Condition			
			CS	RT	Oven	
1.	Drug (Cimetidine)	White Color	NC	NC	NC	Compatible
2.	Drug + All ingredient	White Color	NC	NC	NC	Compatible

CS = Cool Store (2-8 ^{O}C), **RT** = Room Temperature, **Oven (45 ^{O}C), NC** = No Change

Formulation of Cimetidine loaded gastroretentive beads

Cimetidine loaded gastroretentive beads were prepared using Ionotropic Gelation Method. Polymer solution was prepared by dissolving sodium alginate (2-4%) in distilled water, stirred until a clear solution formed. The beads were dried in air at room temperature for 24 - 48 hours then stored in a desiccator until evaluation

Table No. 2: Composition of Cimetidine loaded gastroretentive beads

S. No.	Ingredients	GB-1	GB-2	GB-3	GB-4	GB-5
1	Cimetidine(mg)	200	200	200	200	200
2	Sodium Alginate (%)	2.0	2.5	3.0	3.5	4.0
3	Citric acid (mg)	20	20	20	20	20
4	$NaHCO_3$ (mg)	40	40	40	40	40
5	Water	q. s.	q. s.	q. s.	q. s.	q. s.
6	$CaCl_2$ (%)	2.5	2.5	2.5	2.5	2.5

Evaluation of Cimetidine Loaded Gastroretentive Beads

Cimetidine loaded gastroretentive beads were evaluated and found. Percentage yield of all the formulations ranged from 68.82 % - 89.91%. As shown in result, gastroretentive beads containing Cimetidine have good percentage yield. The mean particle sizes of the Cimetidine gastroretentive beads ranged from174 µm – 267 µm. The gastroretentive beads formulation GB-1 with smaller particle size than other formulation. The microphotograph image of the optimized formulation is shown in figure. The prepared gastroretentive beads were spherical in shape with distinct pores of the slightly rough surface of beads. Entrapment efficiency of all the formulations ranged from 71.28 % to 94.32 %. Swelling index of all the formulations ranged from 2.7 to 4.1 %. Floating ability of the prepared beads was evaluated in 0.1 N HCl (pH 1.2). The floating ability of the beads is directly related to the amount of gas generating agent added, in order to make the beads to float onto the surface of the media. Floating capacity (% Buoyancy) of all the formulations ranged from 68.72 % to 89.23 %.

All the formulations showed a total floating time more than 10 h and floating lag time was observed between 37 sec to 55 sec.

Table No. 3: Evaluation of Cimetidine loaded gastroretentive beads

Formulation code	Percentage (%) yield	Particle size (µm)	(%) Entrapment Efficiency	Swelling Index
GB-1	89. 91	174	94.32	4.1
GB-2	80.52	193	85.13	3.7
GB-3	78.31	232	87.27	3.5
GB-4	68.82	249	76.99	3.0
GB-5	75.34	267	71.28	2.7

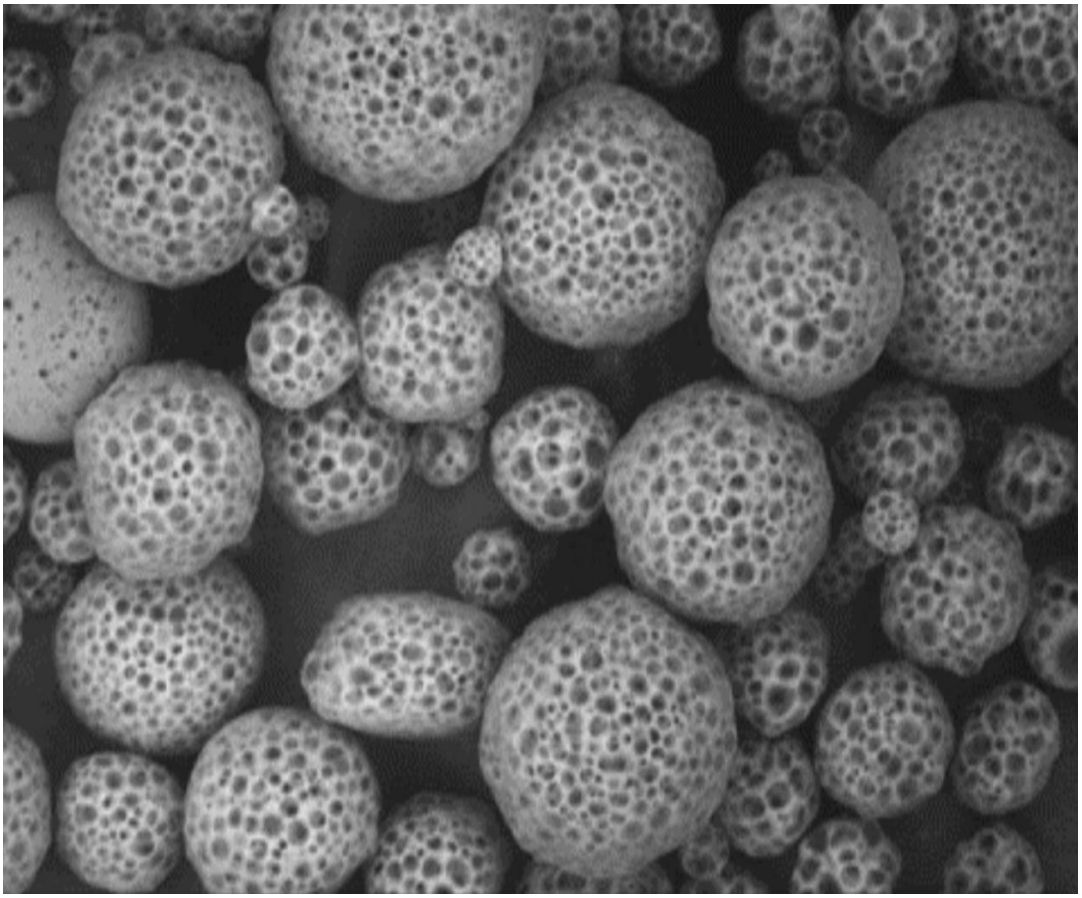

Figure 2: Surface morphology of optimized formulation of GB-1

Table No. 4: Buoyancy test of Cimetidine loaded gastroretentive beads

Formulation code	Floating Lag Time (sec)	Total Floating Time (hours)	Buoyancy (%)
GB-1	37 sec	10 h	89.23
GB-2	42 sec	10 h	79.28
GB-3	46 sec	9 h	78.57
GB-4	46 sec	10 h	68.72
GB-5	55 sec	10 h	71.35

***In-vitro* drug release study**

Formulation GB-2, GB-3, GB-4 and GB-5 were having the lower drug release in the desired time so these are not included in further study. Formulation GB-1 was subjected for the further kinetic study.

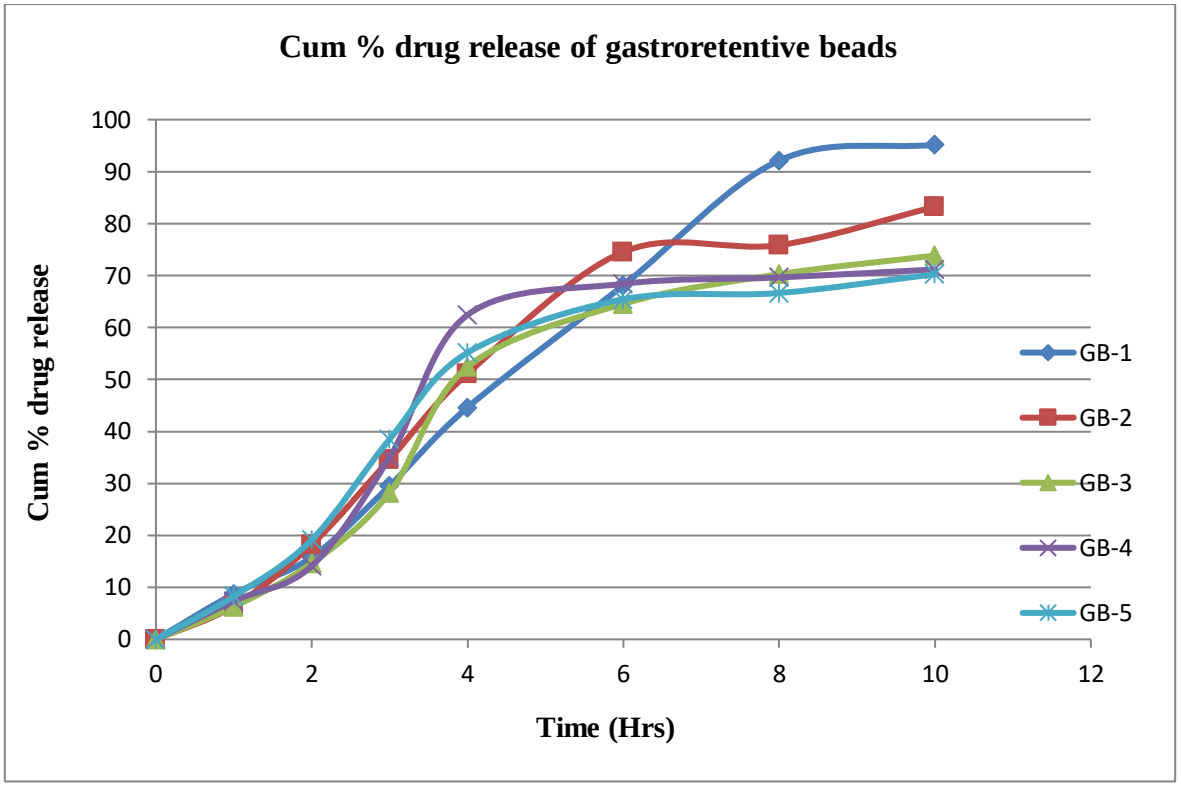

Figure 3: Cumulative percentage of drug release of gastroretentive beads

Kinetic Modeling of Optimized Formulation GB-1

A good fit (high R^2 value) model was Korsmeyer –Peppas, suggested the release mechanism involve diffusion through a polymeric matrix, possibly combined with swelling or erosion.

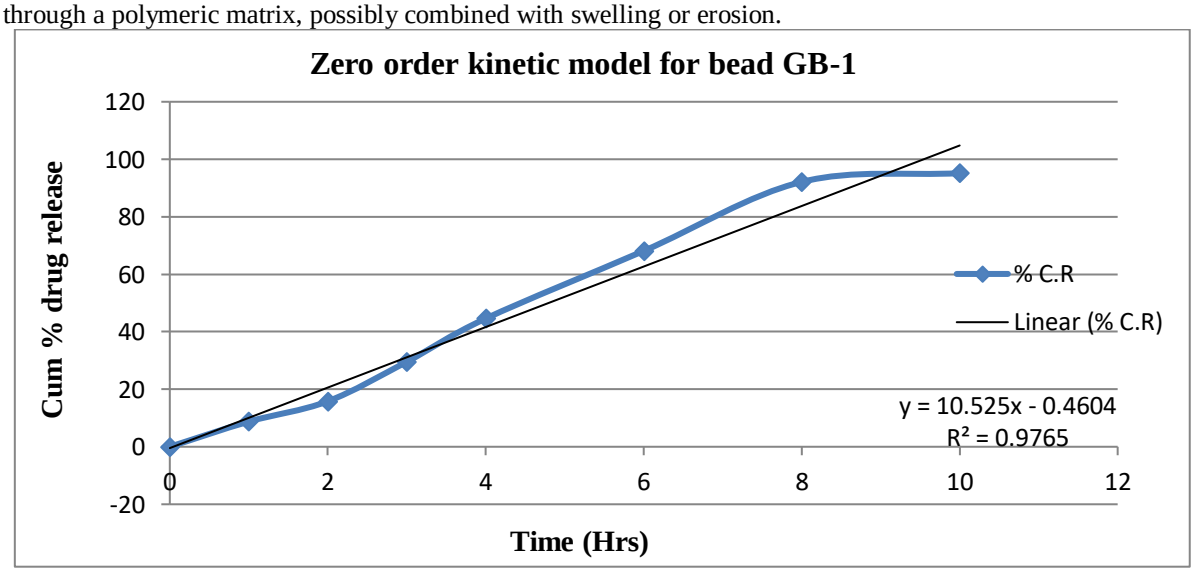

Figure 4: Zero order kinetic model for bead GB-1

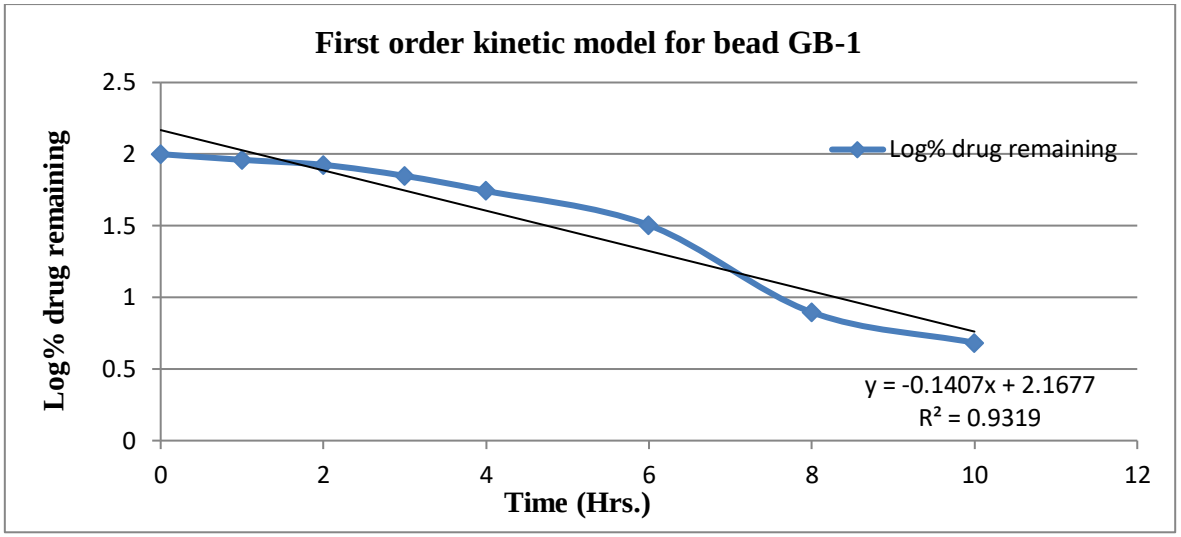

Figure 5: First order kinetic model for bead GB-1

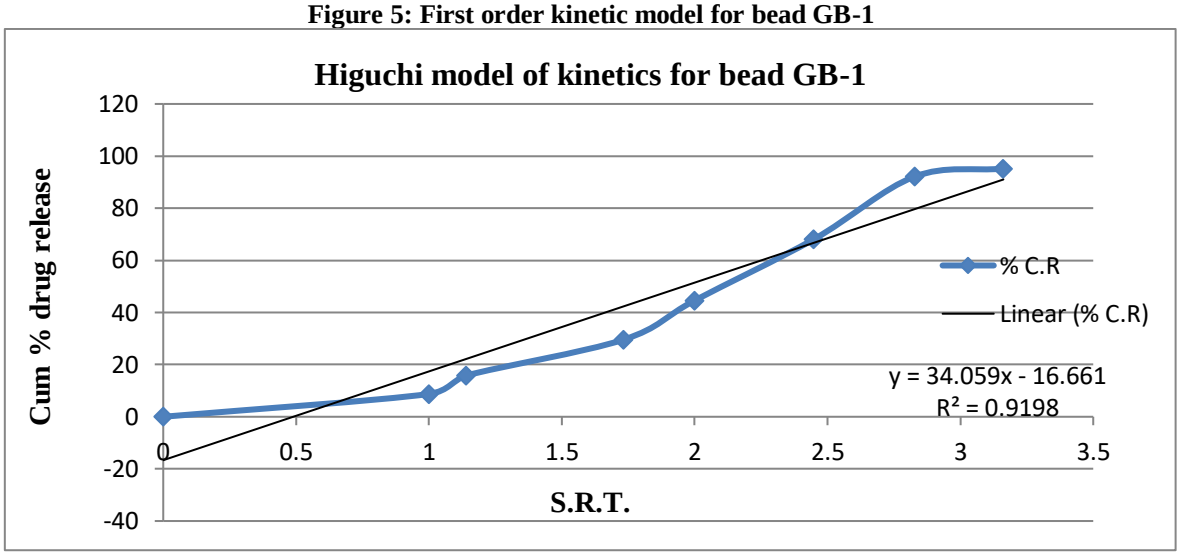

Figure 6: Higuchi model of kinetics for bead GB-1

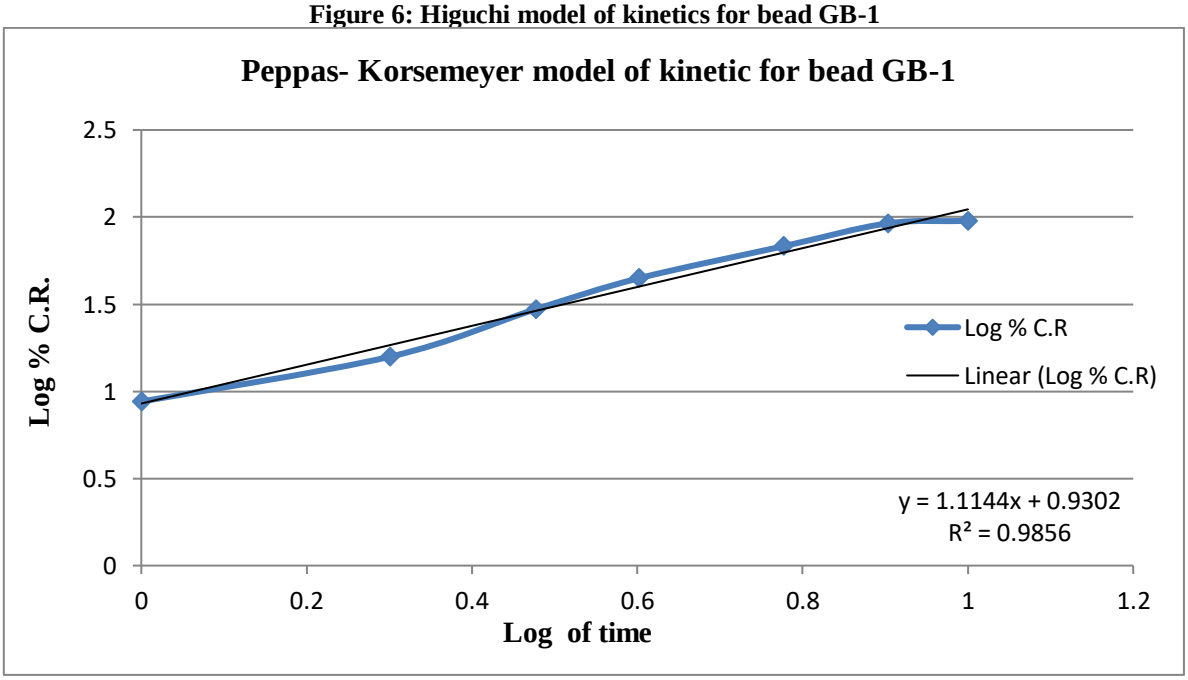

Figure 7: Peppas- Korsemeyer model of kinetics for bead GB-1

Table No. 5: Curve fits for optimized release systems GB-1

Model	Equation	R^2
Zero order	y = 10.52x – 0.460	R^2 = 0.976
First order	y = -0.140x + 2.167	R^2 = 0.931
Higuchi	y = 34.05x – 16.66	R^2 = 0.919
Korsmeyer –Peppas	y = 1.114x + 0.930	R^2 = 0.985

A good fit (high R^2 value) model was Korsmeyer –Peppas, suggested the release mechanism involve diffusion through a polymeric matrix, possibly combined with swelling or erosion.

Stability Studies

Stability studies of gastroretentive beads GB-1 suggested formulation was stable on all condition.

Table No. 6: Stability studies of gastroretentive beads GB-1

Time (Days)	% Drug release		
	4 °C	25 °C	40 °C
0	95.18	95.18	95.18
15	94.41	95.31	94.32
30	94.02	95.14	94.06

CONCLUSION:

The gastroretentive beads of Cimetidine prepared using ionotropic gelation demonstrated promising results for controlled gastric retention. The preformulation studies confirmed Cimetidine's physicochemical compatibility with selected polymers, and its hydrophilic nature favored incorporation into hydrogel matrices. Formulation with sodium alginate and calcium carbonate provided effective buoyancy, sustained drug release, and acceptable drug entrapment efficiency. Evaluation results - such as floating ability, swelling index, and *in-vitro* release supported its potential as a robust delivery system for enhanced therapeutic efficacy and patient compliance.

CONFLICT OF INTERESTS

There are no any conflicts of interest.

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