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Develop An Intragastric Floating Drug Delivery System of Clarithromycin to Sustain the Release of Clarithromycin

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ABSTRACT

This study aimed to develop an intragastric floating drug delivery system (FDDS) for clarithromycin to prolong its release and improve its bioavailability. Clarithromycin, a macrolide antibiotic, has a short half-life and is poorly absorbed in the gastrointestinal tract, necessitating the development of a controlled-release formulation. Floating beads were formulated using a combination of hydrophilic and hydrophobic polymers to achieve prolonged gastric retention. Various preformulation studies, including drug-excipient compatibility and solubility enhancement, were conducted. The beads were evaluated for buoyancy, drug release profiles, and in vitro dissolution rates. The results indicated that the optimised formulation provided sustained release for 12 h with excellent floating properties. This study underscores the potential of FDDS to enhance the therapeutic efficacy of clarithromycin by extending its gastric residence time and improving patient compliance.

Keyword: *Floating Drug delivery System, Clarithromycin, GIT.*

1. INTRODUCTION

Clarithromycin is a macrolide antibiotic known for its wide-ranging effectiveness and is frequently used to treat infections caused by Helicobacter pylori, respiratory tract infections, and other bacterial ailments. Its therapeutic potential is limited by its short biological half-life of 3-5 hours and instability in acidic conditions, which reduce its bioavailability. Conventional oral formulations of clarithromycin require frequent dosing, which may affect patient compliance. A floating drug delivery system (FDDS) offers a promising approach to enhance gastric retention of clarithromycin, enabling prolonged drug release and increased bioavailability. This study aimed to create and measure a gastro-retentive floating beads of clarithromycin, employing various polymers to achieve extended drug release and improved therapeutic outcomes.

2. MATERIALS AND METHODS

Is Clarithromycin (API), Hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M), Carbopol 934P, Sodium bicarbonate, Citric acid, Polyvinylpyrrolidone (PVP K30), Magnesium stearate, Talc, Microcrystalline cellulose (MCC), Distilled water.

Methods

Preformulation Studies

The compatibility of the drug with the excipients was assessed using Fourier-transform infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). Solubility tests were conducted at various pH levels.

Formulation of Floating beads

The floating Beads were formulated through the wet granulation technique. Different concentrations of HPMC and Carbopol were used to enhance buoyancy and drug release. Sodium bicarbonate and citric acid were incorporated as gas-generating agents to increase buoyancy. Evaluation of Floating Beads Buoyancy Studies: The in vitro floating behaviour was evaluated in 0.1N HCl. Swelling Index: This determined to assess the hydration capacity of the polymers. Drug Release Studies: These performed using a USP dissolution apparatus with 0.1N HCl as the medium. Kinetic Modelling: Drug release data were analysed using various mathematical models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas) to comprehend the release mechanism.

3. MATERIALS AND METHODS

Formulation Preparation

The formulation was developed using various excipients, each serving a specific functional role. Sodium alginate was used as a viscosity-increasing, thickening, and gelling agent, while calcium chloride (anhydrous) acted as the cross-linking agent. Light liquid paraffin functioned as a floating agent and oleaginous vehicle. Hydroxypropyl methylcellulose served as a low-viscosity hydrophilic matrix former, and methyl cellulose was used as a viscosity-enhancing agent. Two methods were employed for bead preparation: conventional alginate beads were prepared by the ionotropic gelation method without the use of mineral oil, as per standard procedures [1,2]. For oil-entrapped bead preparation, the emulsion gelation technique was adopted. In this method, sodium alginate was dissolved in distilled demineralised water under constant stirring. Various concentrations of mineral oil were added, followed by the incorporation of clarithromycin. The homogenised emulsion was then extruded dropwise through a 21G needle into a 1% calcium chloride solution and left undisturbed at room temperature for 30 minutes. The formed beads were rinsed twice with distilled water, filtered, and dried at room temperature for further evaluation [3,4].

CLARITHROMYCIN ALGINATE BEADS EVALUATION

Surface Morphology via SEMThe surface and internal structure of the dried beads were analyzed using a scanning electron microscope (SEM).[4]

The particle size of the clarithromycin-loaded calcium alginate beads was determined using an optical microscope by measuring 20 particles. The average particle size was then computed.

Drug Entrapment Efficiency and Drug Content Determination Clarithromycin beads were assessed for drug content. The drug-containing beads were extracted with 0.1N HCl for 24 h and then agitated for an additional 2 h. The resulting solution was filtered through a Whatman filter paper and analysed spectrophotometrically. Drug loading was calculated using the formula:

% Drug loading = (Amount of drug in beads/Amount of beads) × 100

Peppas utilised the value of n to categorise assorted liberation mechanisms, finding that n = 0.5 signifies Fickian diffusion, n values ranging from 0.5 to 1.0 indicate anomalous transport (which includes diffusion, erosion, and swelling mechanisms or mixed-order kinetics), and n values of 1 or above denote case-II transport (associated with the erosion and relaxation of the swollen polymer layer)[5]. These four models are primarily used to predict drug liberation kinetics from extended-release formulations. Additionally, there are other specific models for describing drug release kinetics, such as the Cube Root Law or Hixson-Crowell model, which account for the release rate from monolithic drug particles applicable for the pure liquefaction of drug particles following direct and absolute beads erosion or disintegration, as well as the Weibull model, Baker-Lonsdale model (a modified Higuchi model), and Hopfenberg model (a modified Peppas model). It was essential to determine the maximum possible strength of alginate that could be used to create the beads with the available syringe (21G needle) for extrusion, as the literature indicates that the gel strength of alginate is a key factor in controlling drug release. [6]

PREPARATION AND OPTIMIZATION OF ALGINATE BEADS

Production of Calcium Alginate Beads: Effect of Sodium Alginate and Calcium Chloride Concentrations on the Formation of Spherical Alginate Beads: Calcium alginate beads were created experimentally using the ionotropic gelation method.

Table 1: Formulation of calcium alginate gel beads with variable prototype of sodium alginate and calcium chloride

S. No.	Sodium alginate Concentration (%w/w)	Calcium chloride (%w/w)	Distilled water(upto) (g)
1	1	1	10
2		3	10
3		5	10
4		7	10
5		1	10

6		3	10
7	2	5	10
8		7	10
9		1	10
10		3	10
11	3	5	10
12		7	10
13		1	10
14		3	10
15	4	5	10
16		7	10

Observations

The surface characteristics and morphology of the prepared calcium alginate beads were initially assessed through visual inspection. It was observed that alginate solutions with concentrations below 3% w/w resulted in non-spherical beads due to insufficient viscosity, which failed to support proper bead formation. Conversely, increasing the sodium alginate concentration beyond 3% w/w produced a highly viscous solution, which hindered smooth drop formation during extrusion. Consequently, a 3% w/w sodium alginate concentration—exhibiting a gel-like texture—was found to be optimal and was thus selected for all subsequent formulations. The calcium chloride concentration was also evaluated; however, increasing its concentration beyond 1% w/w showed no significant effect on bead sphericity. Therefore, 1% w/w calcium chloride was standardized for future formulations. It was crucial to determine the highest feasible alginate concentration that could be extruded using the available 21G syringe needle, as literature reports that alginate gel strength plays a key role in modulating drug release [7]. In line with this, it was also noted that increasing alginate concentration decreased drug release from the beads, owing to the enhanced gel strength which slows down drug diffusion [8].Further, oil-encapsulated calcium alginate beads were prepared using the emulsion gelation method. To improve buoyancy—a primary objective of the study—various formulations were developed by incorporating different concentrations of liquid paraffin as a floating agent. These trials were carried out while maintaining a consistent 1:1 ratio of drug to sodium alginate to evaluate the effect of paraffin concentration on both buoyancy and drug entrapment efficiency [9].

Table 2. Preparation of floating gel beads with varying amounts of mineral oil (Liquid Paraffin).

Formulation	Clarithromycin (mg)	Sodium alginate (mg)	Liquid Paraffin	Distilled water (g)
1	300	300	0	10
2	300	300	5	10
3	300	300	10	10
4	300	300	15	10
5	300	300	20	10
6	300	300	25	10
7	300	300	30	10

OBSERVATION: Initial trial batches were checked for mean diameter, drug loading, Entrapment Efficiency and Buoyancy.

Table 3. Characterization of prepared calcium alginate gel beads

Formulation	Concentration of oil (Liquid Paraffin) (%w/w)	Mean Diameter (mm)± S.D.	Drug loading (%)	Entrapment efficiency (%)	Floating Time (hrs)
1	5	1.80	6.14	72.56	>12
2	10	2.16	8.18	79.21	>12
3	15	2.23	6.28	87.9	>12
4	20	2.35	9.5	90.2	>12
5	25	2.38	9.58	88.57	>12
6	30	2.5	8.64	77.68	>12

4. OBSERVATION

The key factor that enhanced both the proportion of drug content and the efficiency of entrapment was the quantity of oil incorporated into each batch's formulation. Batches with 10% and 30% oil were excluded because the 10% oil batches exhibited a prolonged floating lag time, whereas the 30% oil batches faced issues with oil leakage. Following the preparation of these batches, two oil concentrations were selected: 15% and 20%. As the oil concentration increased from 5% to 15% w/w, the floating percentage consistently increased owing to its hydrophobic properties; however, when the oil concentration exceeded 20% w/w, the buoyancy percentage declined. With 10% oil, some of the drug diffused into the surrounding medium during the gellification of the alginate beads. However, increasing the oil concentration to 15% enhanced the barrier effect of the entrapped oil droplets, safeguarding the drug from diffusion and thereby boosting the drug content in the beads. When the oil content was increased to 20% and 30%, the larger oil volume occupied most of the bead space, hindering sufficient drug entrapment. Thus, it was concluded that an intermediate optimal oil level is crucial for preparing beads with maximum drug content. The optimal mineral oil level (20%) was selected for further formulation. As the oil concentration increased, the bead diameter gradually increased. An increase in mineral oil concentration resulted in higher entrapment efficiency in clarithromycin-loaded alginate beads; however, once the mineral oil concentration surpassed the optimal level, the entrapment efficiency decreased. [9-11]

Preparation of floating alginate beads of Clarithromycin Different drug-to-sodium alginate ratios (D/Na alginate) were assessed with a constant liquid paraffin concentration of 20% (w/w) to improve drug entrapment efficiency.

Table. 4: Formulation of floating calcium alginate gel beads using various sodium alginate concentrations.

Formulation	Drug (%w/w))	Sodium alginate(%w/w)	Liquid Paraffin (%w/w)	Distilled water (g)
F1	1	2	20	10
F2	1	2.5	20	10
F3	1	3	20	10
F4	1	3.5	20	10
F5	1	4	20	10

OBSERVATION: The prepared beads were evaluated for Mean Diameter, Drug loading, and entrapment efficiency.

Table 5. Characterisation of prepared calcium alginate gel beads with assorted sodium alginate concentrations.

Formulation	Drug: sodium	Mean Diameter±	Drug loading	Entrapment	Floating time

	alginate	S.D.(mm)	(%)	Efficiency(%)	(hrs)
F1	1:2	1.21	14.12	90.71	>12
F2	1:2.5	1.24	12.34	87.5	>12
F3	1:3	1.35	7.29	85.56	>12
F4	1:3.5	1.23	9.96	82.14	>12
F5	1:4	1.56	8.54	78.58	>12

In Vitro Dissolution Study

The in vitro dissolution study was conducted to evaluate the drug release behavior of formulations containing different ratios of sodium alginate and the drug. The study was performed using the USP Type I (Basket) dissolution apparatus. Each formulation was tested in 900 mL of 0.1N hydrochloric acid (HCl) as the dissolution medium, maintained at a temperature of 37 ± 0.5°C to simulate physiological conditions. The basket rotation speed was set at 50 rpm. At predetermined time intervals, 5 mL samples were withdrawn from the dissolution vessel for analysis and replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were analyzed to determine the drug release profile of the various formulations.

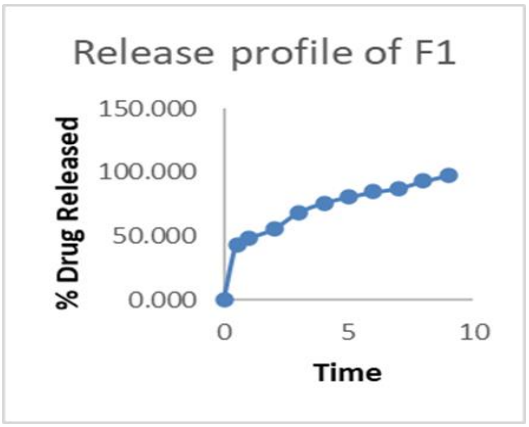
Table.6 the Cumulative % of drug release from all formulations.

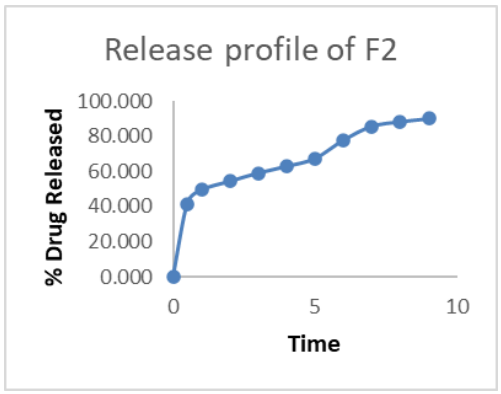
Time (hours)	Cumulative % of Drug Released ± S.D				
	F1	F2	F3	F4	F5
0.5	43.22±0.72	41.63±0.45	38.33±0.40	39.95±43	44.80±0.28
1	48.23±0.74	49.47±0.34	45.63±0.35	48.16±0.28	47.85±0.29
2	55.32±0.23	54.32±0.11	49.47±0.36	50.08±0.19	51.26±0.21
3	68.48±0.89	59.07±0.19	58.62±0.20	58.17±0.41	55.64±0.18
4	75.91±0.30	62.89±0.30	64.43±0.76	63.29±0.32	59.15±0.19
5	80.64±0.12	67.38±0.75	66.19±0.32	68.65±0.37	63.76±0.35
6	84.63±0.30	77.89±0.41	69.84±0.42	76.84±0.38	66.95±0.32
7	87.45±0.24	85.75±0.38	78.38±0.41	79.86±0.45	71.27±0.31
8	93.07±0.19	88.35±0.29	85.98±0.32	81.17±0.19	78.78±0.36
9	97.55±0.19	90.05±0.18	89.56±0.38	85.14±0.35	80.58±0.20

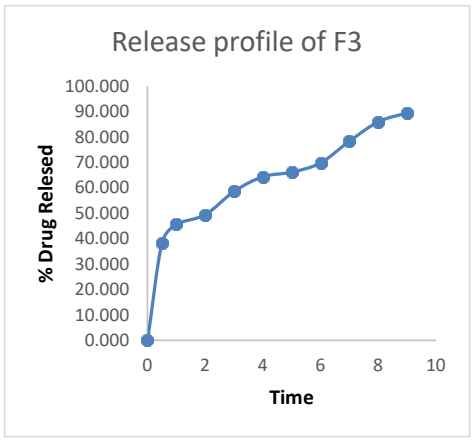
OBSERVATION: The alteration in drug release was linked to an increase in alginate content. As the amount of alginate increased, the cross-linking between sodium alginate and calcium chloride became stronger, leading to more drugs being trapped and less being released. The entrapment efficiency of the formulations varied from 78.58 to 90.71. Fig: 6.2.6 % Drug release profile of various explicates.[12-15]

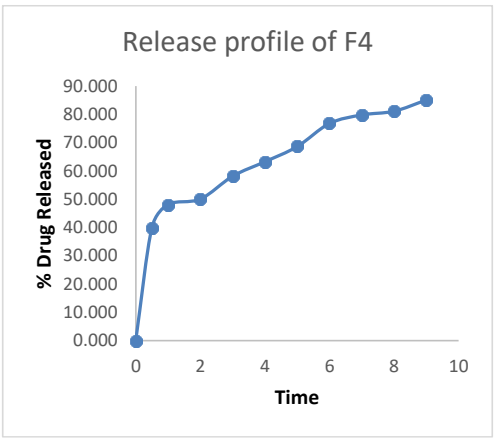
COMPARISON

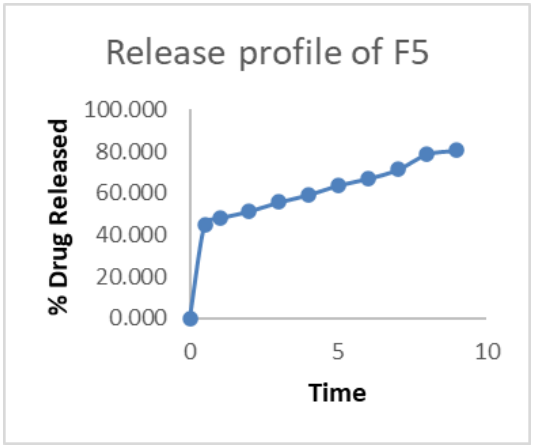
Fig: 1. Percentage Drug release profile of various Formulations.











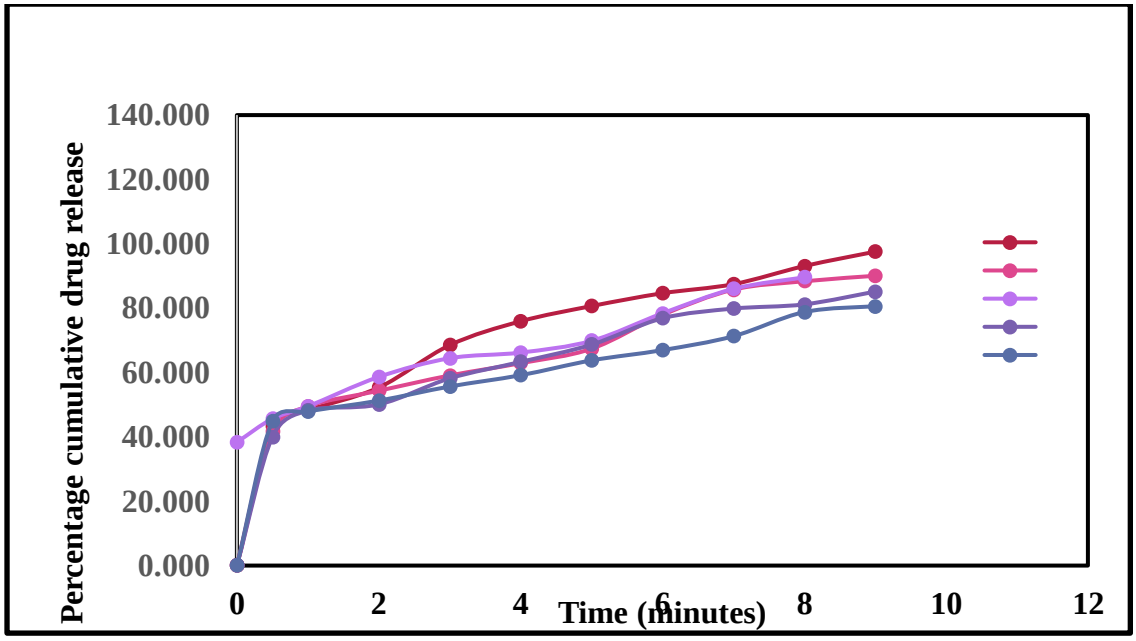


Fig: 2 Comparison of Drug Release Profiles of All Formulations.

Table.7 Synchronic statistics of regression and invariability of the mathematical models for the dissolution data of the explicate.

Drug Release Kinetic Model										
Formul-ation code	Zero Order		First Order		Higuchi		Hixson Crowell		Koresmeyer-Peppas	
	R^2	K	R^2	K	R^2	k	R^2	K	R^2	K
F1	0.9568	7.1055	0.9252	0.1105	0.9852	24.512	0.643	0.0826	0.9719	0.2874
F2	0.9738	6.1116	0.9689	0.0989	0.9418	20.435	0.7843	0.1826	0.9281	0.2457
F3	0.9694	5.6412	0.9394	0.0994	0.9806	19.291	0.883	0.1958	0.9717	0.2567
F4	0.9852	5.978	0.9647	0.101	0.9724	20.193	0.9223	0.1656	0.9478	0.2542
F5	0.9984	3.9905	0.9921	0.0698	0.9788	13.434	0.9241	0.1188	0.9355	0.1721

R^2 = correlation coefficient; k = release rate constant; n= release rate exponent

Here is your interpretation rewritten into a coherent and professional paragraph:

Interpretation
To analyze the drug release mechanism of the floating beads, various kinetic models—including Zero-order, First-order, Higuchi's, and Korsmeyer-Peppas equations—were applied. Among these, the in vitro drug release data of clarithromycin-loaded beads best fit the Higuchi model, indicating that the drug release followed a diffusion-controlled mechanism. The Higuchi equation describes drug release as a process governed by Fick's law, where the release is proportional to the square root of time. This model is particularly applicable to systems where the drug is uniformly dispersed within a swellable polymer matrix. The Higuchi equation is represented as:

$Qt = Kh * t^{1/2}$

Where *Qt* is the amount of drug released at time *t*, and *Kh* is the Higuchi dissolution constant that incorporates the structural and geometric characteristics of the formulation. The value of the release exponent (*n*) further helps in understanding the drug release mechanism from the matrix system [16–19].

The Clarithromycin entrapment efficiency and control of drug release from the beads of Drug/ sodium alginate ratio was tried to improve by increasing the viscosity of sodium alginate solution using Hydroxpropyl methyl cellulose(HPMC).

Table 8 Different formulations prepared using HPMC:

Formulation	Amount of Clarithromycin (mg)	Amount of HPMC (mg)	Amount of sodium alginate (%)	Liquid paraffin (ml)
F1	250	500	1	2
F2	250	500	2	2
F3	250	500	3	2
F4	250	-	3	2

OBSERVATION: Prepared beads were evaluated for Mean Diameter, drug loading and entrapment efficiency.

Table 9 Characterization of prepared floating alginate beads using Hydroxypropyl methyl cellulose:

Formulation	Mean Diameter± S.D. (mm)	Drug Content (%)± S.D.	Entrapment Efficiency(%)± S.D	Floating time (hrs)
F1	2.25	31.19	81.68	>12
F2	2.35	36.74	83.11	>12
F3	2.23	32.24	80.08	>12
F4	2.45	32.04	80.10	>12

INTERPRETATION: Various kinetic models were employed to examine the release behaviour of the floating beads. Investigation of the release kinetics of clarithromycin beads indicated that in vitro drug release was best described by Higuchi's equation. All data conformed to Higuchi's equation, which depicts drug release as a diffusion process governed by Fick's law, reliant on the square root of time. This model is applicable to systems in which drugs are evenly distributed within a swellable polymer matrix. Qt = Kh t1/2 where Qh denotes the amount of drug dissolved over time t, K1/2 is the first-order release constant that encompasses the structural and geometrical characteristics of the formulation, and n is the release exponent indicating the drug release mechanism.[20]

Table.10 Release profiles of formulations:

Time (hours)	Cumulative % of Drug Released = S.D			
	F1	F2	F3	F4
0.5	45.39±0.26	34.47±0.26	48.9±0.31	37.62±0.30
1	56.7±0.17	50.40±0.45	51.08±0.48	48.65±0.16
2	68.74±0.45	57.27±0.32	62.55±0.30	55.27±0.15
3	71.72±0.46	64.41±0.37	68.36±0.30	60.01±0.16
4	73.14±0.28	70.64±0.36	70.79±0.39	68.92±0.32
5	74.61±0.29	78.18±0.41	78.83±0.27	75.29±0.32
6	80.95±0.44	84.63±0.29	81.60±0.30	78.88±0.21
7	82.06±0.36	91.34±0.12	87.48±0.17	81.60±0.53
8	93.14±0.22	95.85±0.48	91.25±0.29	90.57±0.18
9	96.31±0.15	98.16±0.49	94.54±0.19	92.35±0.17

OBSERVATION:

The in vitro dissolution tests performed on the prepared batches were designed to assess the dependent variable, specifically the proportion of drug released at different time intervals. The results from these experiments showed that the floating alginate beads offered a disciplined liberation of clarithromycin for almost 12 h. Among the various preparations, F2 demonstrated the highest cumulative release percentage, indicating its effectiveness in sustaining clarithromycin release for 9 h. Thus, it can be concluded that a novel sustained-release system of oil-entrapped calcium alginate beads was developed and produced using an emulsion-gelation technique, with its morphological and release characteristics thoroughly evaluated. The beads exhibited superior sustaining abilities compared to traditional beads owing to the inclusion of HPMC K100M. Therefore, the oil entrapment method is a promising strategy for developing multiparticulate systems, even for drugs that are not water soluble. There was no significant change in the normal diameter of the beads after incorporating the polymer. The average diameter of the prepared alginate beads ranged from 2.25–2.45.

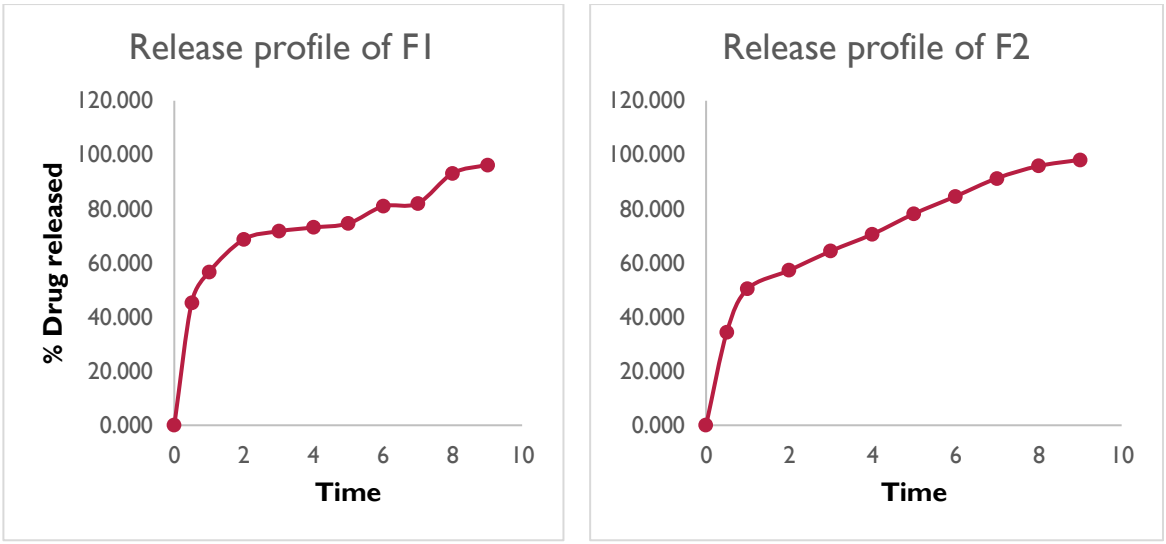


Fig 3. graph of release profie of formulations

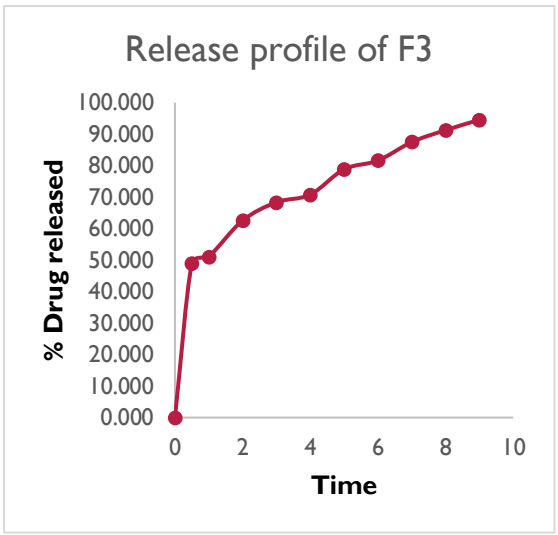
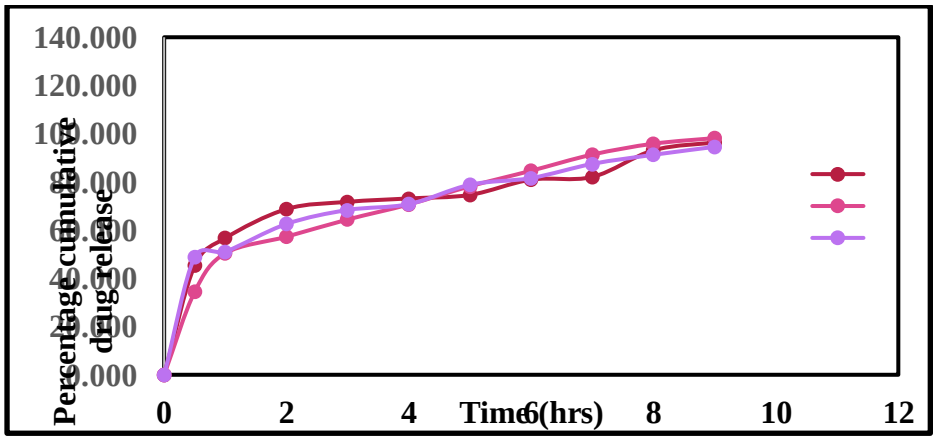


Fig:4 Percentage Drug released of Formulations F1, F2 and F3.



Tabel:11 DRUG RELEASE KINETICS

Drug Release Kinetic Model										
Formul-ation code	Zero Order		First Order		Higuchi		Hixson Crowell		Koresmeyer-Peppas	
	R^2	k	R^2	K	R^2	k	R^2	k	R^2	K
F1	0.8342	4.8193	0.7747	0.0747	0.9213	17.22	0.924	0.6289	0.96	0.2111
F2	0.9593	7.8289	0.8818	0.1269	0.9835	26.953	0.9757	1.0056	0.9786	0.3392
F3	0.9745	5.8645	0.9476	0.0881	0.9875	20.072	0.9857	0.7052	0.9667	0.2259

SUMMARY & CONCLUSION

This study explored the physical and chemical traits of potential drug molecules, as well as their derived properties, such as the solid and solution characteristics of compounds that aid in the evolution of suitable drug delivery systems. Clarithromycin is characterised as a white or off-white crystalline powder that is odourless, with a melting point of 219°C, and shows slight solubility in methanol, ethanol, and acetonitrile. The infrared spectrum of clarithromycin was obtained using FT-IR spectroscopy, and the drug sample was identified using the KBr disc method. The compatibility between the polymer and drug was also evaluated, with the FT-IR spectra showing no shifts, deletions, or broadening of peaks, leading to the conclusion that there was no chemical interaction. DSC thermograms of clarithromycin and its mixtures with excipients were obtained using a DSC-60 Shimadzu instrument. These thermograms show a clear endothermic peak at 227°C. When the sodium alginate concentration exceeded 3% w/w, the solution became excessively viscous, hindering droplet formation. The calcium chloride concentration was consistently maintained at 1% w/w for all formulations. The gel strength of alginate is crucial for controlling drug release. Initial trial batches were assessed for mean diameter, drug loading, entrapment efficiency and buoyancy. This study focused on the use of oil to prepare floating alginate bead batches for clarithromycin. The oil concentration was selected to enhance the drug content and entrapment efficiency. Batches with 10% and 30% oil were rejected because of prolonged floating lag times and oil leakage problems. Two oil concentrations were selected: 15% and 20%. The floating percentage increased with increasing oil concentration, whereas the buoyancy percentage decreased as the oil concentration increased. The increased oil concentration shielded more drugs from diffusion, thereby boosting the drug content in the beads. However, the larger oil volume occupied most of the bead space, limiting the entrapment of a sufficient drug volume. An optimal level of 20% mineral oil was selected for further formulation development. The reduction in drug release was attributed to the simultaneous increase in alginate, as more drug remained entrapped, reducing release. The entrapment efficiency of the formulations ranged from 78.58 to 90.71. The study concluded that an intermediate optimal oil level is essential for preparing beads with maximum drug content

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