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Development of Sodium Alginate Beads of Telmisartan Using Emulsion Gelation Method: Formulation and *In-Vitro* Characterization

Sayali S. Shelar[1,*], Rajendra K. Surawase[2]

Abstract

Introduction: *The antihypertensive medication Telmisartan (TEL) is a member of BCS class II, which is distinguished by limited oral rate and extent and water solubility. By localizing the medication release in the stomach, gastro-retentive floating bead devices may be able to address the issues related to partial absorption and the low solubility of TEL. The preparation of TEL floating alginate beads was the aim of this investigation. The current work aims to extend the duration of TEL's gastric residence period. Two-tiered factorial layout was employed in the development and optimization of eight formulations of TEL alginate beads. The con. of calcium chloride, sodium alginate, and olive oil are independent variables, and the dependent parameters are the drug release, entrapment efficiency, and in vitro buoyancy. Several formulations of TEL alginate beads were made using the emulsion gelation process and calcium chloride is used as cross-linking agent. The in vitro buoyancy, in vitro drug release, and trapping efficiency of each formulation were assessed. The components' compatibility was established by DSC and FTIR spectroscopy.* ***Results:*** *The resultant beads showed excellent entrapment efficiency, prolonged drug release, and in vitro buoyancy. DSC and IR spectroscopy confirmed that TEL was safe to use with other ingredients. To assess the kinetics and the drug release, the drug release data was fitted to several mathematical models, including the Korsmeyer-Peppas model, the Higuchi equation, the zero-order, and the first-order models. First-order drug release was seen, and a non-Fickian mechanism was identified.* ***Conclusion:*** *We conclude that this novel approach to delivering TEL alginate beads is a potentially useful tool for improving medication solubility, oral bioavailability, and therapeutic efficacy, ultimately leading to improved patient adherence. The invitro dissolution study indicates that the F3 formulation has more drug release than other formulations. Finally, it is concluded that the F3 batch is the optimized formulation because it shows maximum drug release up to 98.13% as compared to other formulations due to concentration of oil and sodium alginate used as release rate retardant and gives a better result for drug release characteristics.*

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INTRODUCTION

Current study has indicated a growing interest in innovative dosage forms that are reusable in the abdomen for extended periods of time with consistency. Enhancing the floating bead's objective is to prolong stomach retention. Floating

drug delivery methods float on gastric juice for long lengths of time without changing the pace at which the stomach empties and enhancing rate and extent because they have a lower bulk thickness than gastric juice. Telmisartan (TEL), an oral hypertension medication, is classified in the Biopharmaceutical Classification System (BCS) class II. It is unique in that it has a low water solubility TEL solubility can be increased by various methods, including co-crystals, surface solid dispersions, while preparing it as floating which not only increases solubility but also helps the medication give sustained action [1, 2]. Constructing new TEL sodium alginate beads was the primary objective of the research to increase the medication's oral bioavailability. The principal aim of this work was to create novel floating alginate beads entrapped in TEL oil to enhance the drug's oral bioavailability. By utilizing the floating beads, the drug was able to release over time in the acidic environment of the stomach, increasing its solubility and absorption. When hydrocolloid molecules, such as alginate, gel with divalent ions, such as calcium, instantly become hydrated. A hydrocolloidal layer with a high viscosity is produced by this method [3].

Diffusion barriers are created as a result, which hinders the passage of tiny molecules like medications. The active ingredient is dispersed uniformly inside a matrix of polymers that controls the drug's rate of release [4]. Oral administration is the most practicable and advised way to get any drug into the systemic circulation. Recently, the pharmaceutical industry has demonstrated an increasing interest in Oral controlled release medication delivery can lead to more favorable therapeutic results, including easy dosage administration, patient compliance, and formulation flexibility [5].

MATERIAL AND METHOD

Material

Balaji Pharmaceuticals supplied the TEL medication; Modern Industries supplied the sodium alginate; Modern Industries supplied the calcium chloride; Modern Industries supplied Tween 80; and Modern Industries supplied the olive oil.

METHOD

Technique of Emulsion Gelation

Calcium chloride ($CaCl_2$) was used as a cross-linking agent during the emulsion-gelation process to create the TEL alginate beads. Using a magnetic stirrer, precisely the correct amount of sodium alginate was dissolved in distilled water at room temperature to create a sodium alginate solution with different concentrations. An O/W emulsion was formed by high shear mixing the sodium alginate aqueous solution, a specified amount of TEL (40 mg), and Tween 80 (0.5%) as an emulsifier for 20 minutes at 2000 rpm using a magnetic stirrer. The emulsion mixture was carefully blended and then extruded into a calcium chloride solution using a syringe G 22 needle. The mixture was allowed to contain the gel beads [6].

Solubility

TEL's solubility was examined in a variety of solvents, including water, 0.1 N Hcl, ethanol, and methanol [7].

Fourier Transform Infrared Spectroscopy (FTIR)

Using FTIR, the infrared spectra of calcium chloride and sodium alginate as well as TEL's drug combination were recorded, and spectral analysis was carried out to assess drug and excipient compatibility [8].

Differential Scanning Calorimetry (DSC)

DSC analysis was performed on 2–5 mg sample prepared as 1:1 ratio. The DSC of pure drug was measured using differential scanning calorimeter. Samples were heated between 30 and 320 degrees Celsius in an open aluminum pan at a rate of 10 degrees Celsius every minute under a 2-bar nitrogen flow [9, 10].

Table 1. The formulation's composition.

Formulation Code	Telmisartan	Sodium Alginate	Olive Oil	Tween 80	Calcium Chloride	Water (qs)
F1	40 mg	1%	5 ml	0.5%	5%	100 ml
F2	40 mg	4%	10 ml	0.5%	5%	100 ml
F3	40 mg	4%	40 ml	0.5%	5%	100 ml
F4	40 mg	4%	20 ml	0.5%	5%	100 ml
F5	40 mg	4%	25 ml	0.5%	5%	100 ml
F6	40 mg	1%	5 ml	0.5%	2%	100 ml
F7	40 mg	1%	30 ml	0.5%	2%	100 ml
F8	40 mg	1%	35 ml	0.5%	5%	100 ml

Optimization-2 Level Factorial Design

It involves formulation studies to optimize the drug release profile, stability, and bioavailability. This stage involves a comprehensive study of the TEL beads to determine their physical and chemical properties, stability, solubility, and compatibility with excipients. This information helps in selecting suitable excipients for the formulation [11]. The drug and polymer which is used for the formulation of beads are listed in Table 1.

Percentage Yield of Formulation

After drying, the percentage yield of beads generated is calculated by weight. To determine the overall percentage yield of the beads, the measured weight of the prepared beads was divided by the sum of all the non-volatile ingredients employed in their creation.

(Total weight of medication and excipients / Product weight) × 100 = Yield percentage (%) [12, 13]

Floating Lag Time

The resultant 20-bead sample was combined with a 0.1N Hcl solution in a beaker. At 37°C, the temperature is maintained consistently. A 12-hour period was used to measure the floating time. The test solution's buoyancy was not recognized until each bead sank to the top of the base. The test solution's buoyancy was not recognized until each bead sank to the top of the base. Additionally, the floating time, which indicates the time of appearance, and the floating lag time (FLT), which represents the length of formulation on the medium's surface [14].

Drug Composition and the Potency of Drug Entrapment

Using a mortar and pestle, 50 mg of the produced formulation was measured, crushed, and then dissolved in 25 ml of 0.1 N Hcl. This solution held true for a full day. This solution was kept to a total volume of 50 ml using mortar rinses. After filtering, the filtration was subjected to spectrophotometric analysis using a UV spectrophotometer [15].

***In-vitro* Drug Release Study**

The dosage of the drug supplied for the sustained release float beads was estimated to use the USP I dissolve instrument at 50 rpm. The dissolving medium was a 900 ml solution of 0.1N Hcl (pH 1.2), and the temperature was maintained at 37°C. At 0 minutes, one hour. A 5 ml sample was drawn from the USP dissolving device at each interval. Prior to undergoing a UV examination [16].

Swelling Study

Bead swelling experiments were conducted in dissolving media. To get rid of extra surface water, the beads were thoroughly filtered out at time t and then bottled. We weighed the swelling beads.

In vitro Buoyancy Study

A suitable quantity of the floating beads was added to 100 milliliters of the pH 1.2 stimulated gastric fluid, and the combination was agitated using a magnetic stirrer. Filtration was used to separate the layer of buoyant beads.

Percent Buoyancy = Wf / Wf + Ws × 100.

RESULTS

Solubility

The TEL drug is freely soluble in ethanol, methanol, & practically insoluble in water. The solubility of TEL was checked in different solvents like Methanol, Ethanol, 0.1 N Hcl and water. TEL is sparingly soluble in water. Its solubility increases significantly in organic solvents like ethanol, methanol, and DMSO. This limited aqueous solubility affects its formulation and administration in pharmaceutical applications.

Fourier Transform Infrared Spectroscopy (FTIR)

TEL's infrared spectrum was captured. Figure 1(a) and (b) illustrates the 400–4000 cm^ scanning range and Table 2 displays the 1 cm^{-1} resolution that was attained.

Table 2. Range of functional group present in FTIR spectrum Telmisartan.

S.N.	Functional Unit	Ranges Observed (cm^{-1})	Regular Ranges (cm^{-1})
1	C–H stretching	634 cm^{-1}	900-650 cm^{-1}
2	C=O stretching	1248.12 cm^{-1}	1700 cm^{-1}
3	O–H stretching	3441.11 cm^{-1}	3500-3200 cm^{-1}
4	C–N stretching	1348.34 cm^{-1}	1300-1350 cm^{-1}

Thermal Gravimetry (DSC)

Using DSC, the medication TEL was verified while maintaining a heating rate of 1°C/min. As seen in Figure 1(c), the thermogram of TEL showed a pronounced endothermic peak with onset temp 293.34°C and peak temp 297.53°C, which is in line with its melting point.

Data Analysis

Evaluation of the dependent variables using both the full and reduced models. For the optimization of TEL by Factorial design was employed using State-Ease Design Expert 8.0.1 software. Total eight experiments were designed by considering three factors and two levels (high, low) sodium alginate, calcium chloride, and olive oil considered as independent factors and drug release and drug entrapment was dependent variables. Because to find the best optimization batch.

Table 3. Layout of actual design.

Run	Independent Variables			Dependent Variables	
	Olive Oil	*Sodium Alginate*	*Calcium Chloride*	*Drug Release*	*Drug Entrapment*
1	40.00	4	2	86	78.88
2	5.00	1	5	92.7	60.83
3	40.00	4	5	97.64	96.34
4	5.00	4	5	90.94	88.54
5	40.00	1	2	93.19	92.78
6	5.00	1	2	90.5	89.43
7	40.00	1	2	88.45	89.45
8	5.00	4	5	92.65	91.54

Full Model for Y1 (% CDR Drug Release)

Drug-release +91.51+1.97*A+1.47*B+2.00*C+0.19*A*B0.31*A*C+0.43*B*C+0.37*A*B*C

It was observed that the independent variable viz. A (sodium alginate) B (calcium chloride) and C (olive oil) had a positive effect on drug release Figure 2(a) and (b). It was observed that the independent variables A (sodium alginate), B (olive oil), and C (calcium chloride) had a positive effect on drug.

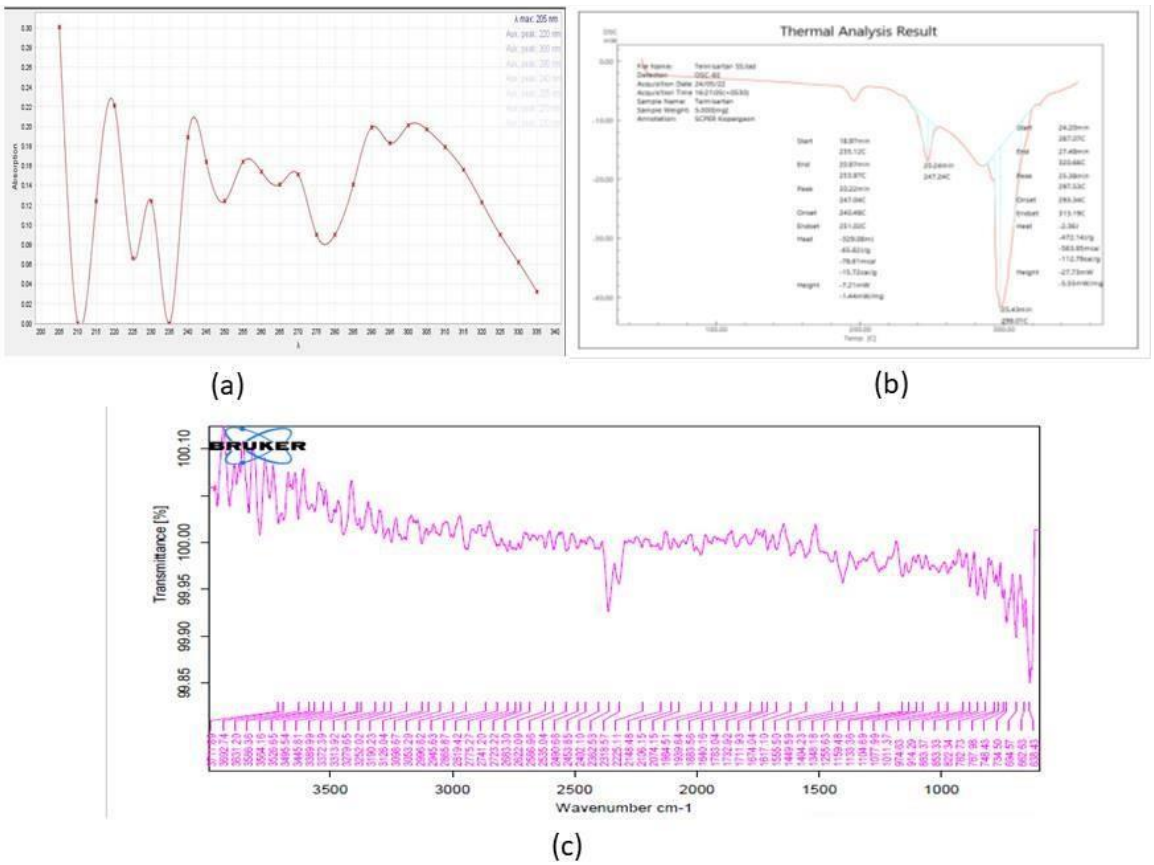

Figure 1. (a) UV spectrum of Telmisartan; (b) DSC curve of Telmisartan; (c) FTIR of Telmisartan.

The graphical representation shows the percentage of drug release after using three different polymers. The x-axis represents the independent variable, which is Polymer A (sodium alginate) & polymer B (olive oil), while the y-axis represents the dependent variable, that is percent drug release. The data obtained from the dissolution test are plotted on the graph, and curve shows the pattern of drug release.

Full Model for Y2 (Drug Entrapment Efficiency)

It was observed that the independent variable viz. A (sodium alginate), B (calcium chloride), and C (olive oil). Sodium alginate, calcium chloride, and olive oil had a positive effect on drug entrapment (Figure 2(c) and (d)). It was observed that the independent variable viz. A (sodium alginate), B (calcium chloride), and C (olive oil). Sodium alginate, calcium chloride, and olive oil had a positive effect on drug entrapment. Effect of sodium alginate, calcium chloride, and olive oil on drug release of TEL in 3D response surface plot confirmed. From the above Figure 3 response curve of Y1 (drug release). It is observed that as the concentration of sodium alginate increases from 1% to 4%, calcium chloride increases from 2% to 5% and olive oil increases from 5 ml to 40 ml drug release increases significantly.

Evaluation Telmisartan Beads Percentage Yield

F3 batch shows the highest percentage yield that is 91.92%. The percentage yields according to Table 3.

Drug Content and Drug Entrapment Efficiency

All prepared formulation shows uniformity of drug content. Into that F3 formulation shows the highest drug content, that is 97.64%. The drug content of all formulations are as listed in Table 3.

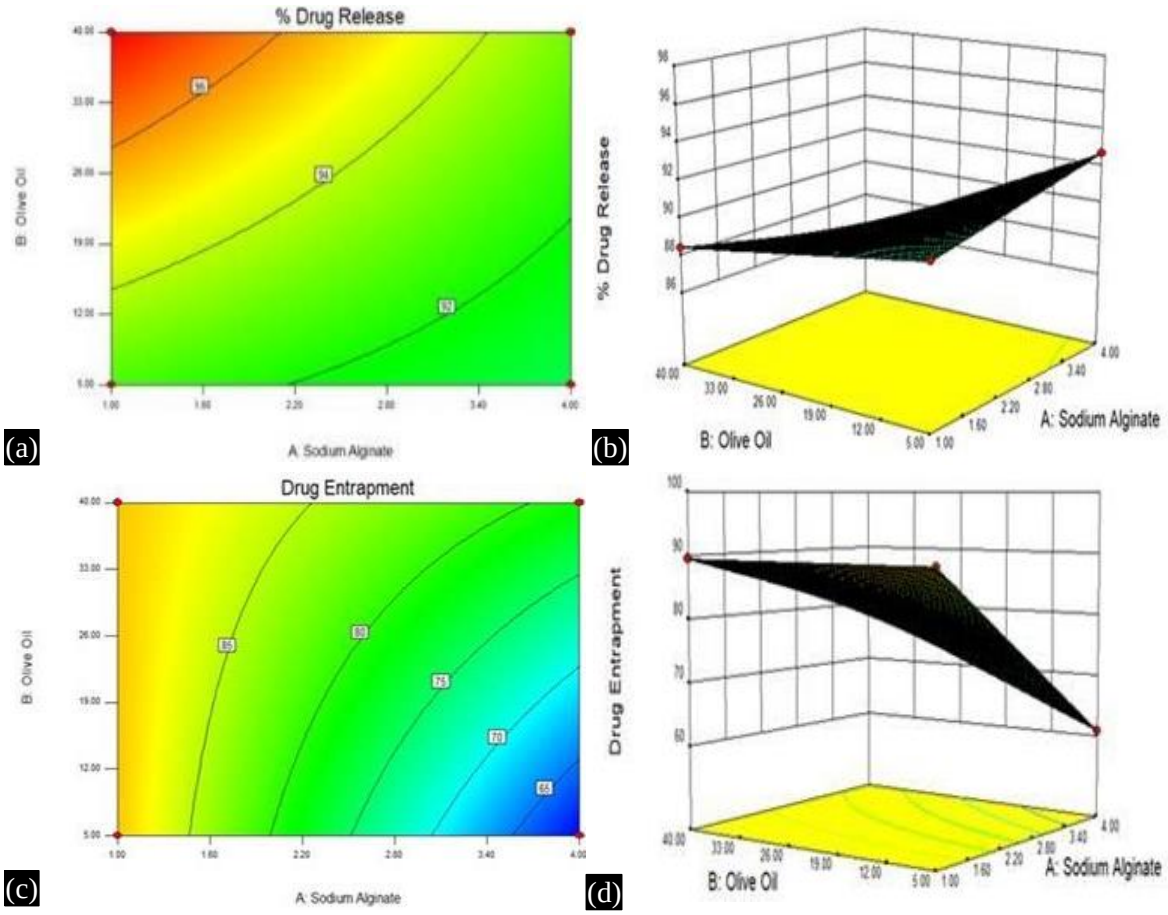

Figure 2. (a) Full model for Y1 (% CDR drug release); (b) 3D response surface plot (% drug release); (c) analysis of variance for response Y2 (drug entrapment) (d) 3D response surface plot (drug entrapment).

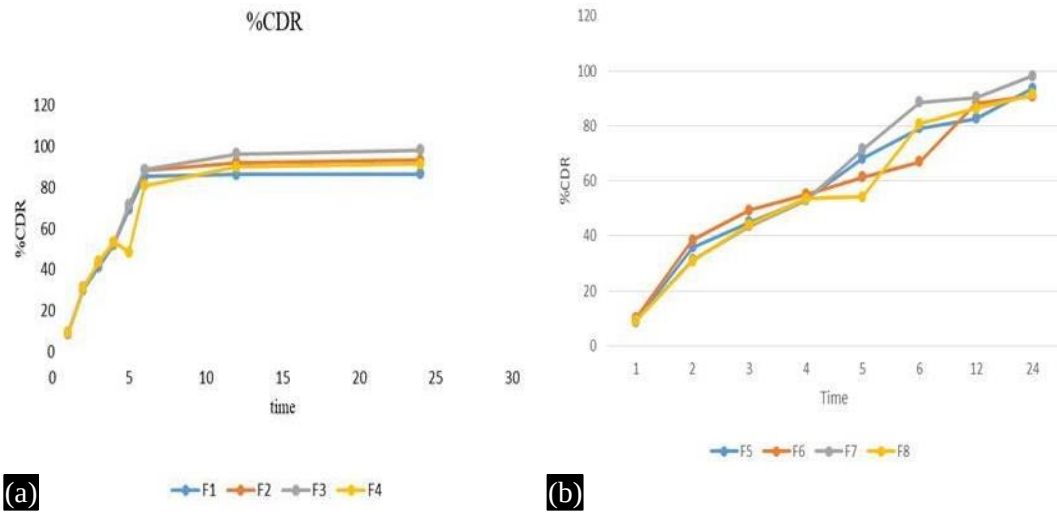

Figure 3 (a) Cumulative drug release of different batches (Batch F1–F4), (b) Cumulative drug release of different batches (Batch F5–F8).

Lag Time and Floating Time in Floating

For all formulas F1–F8, the FLT falls between 1.14 and 1.37 minutes, and the floating time can reach up to 12 hours. This can be attributed to the rise in olive oil concentration (Table 4).

Table 4. That affects the swelling of beads.

Batch No.	Percentage Yield %	Drug Entrapment	Floating Lag Time	Floating Time	Swelling Index
F1	78.9 ± 0.12	92.65 ± 0.13	1.37	Up to 12 hrs.	20.86
F2	81.70 ± 1.24	90.94 ± 0.12	1.40	Up to 12 hrs.	15.63
F3	91.92 ± 1.12	97.64 ± 0.12	1.35	Up to 12 hrs.	21.78
F4	84.88 ± 0.18	93.19 ± 0.13	1.38	Up to 12 hrs.	14.00
F5	74.84 ± 2.12	92.7 ± 0.09	1.15	Up to 12 hrs.	11.00
F6	84.94 ± 0.18	86 ± 0.12	1.30	Up to 12 hrs.	14.58
F7	84.33 ± 0.44	88.4 ± 0.12	1.25	Up to 12 hrs.	15.45
F8	90.49 ± 0.4	90.5 ± 0.06	1.30	Up to 12 hrs.	14.48

Swelling Study

All batches % swelling ratio were identified as being between 11% and 21.78%. The F3 batch shows highest swelling index because of the olive oil.

Study of Buoyancy *in vitro*

In 0.1 N HCL for 10 hr, that formulation F3 had the best floating ability (93.40%). This could be because of its low bulk density. The formulations' great floating ability is demonstrated by their range of floating abilities, which is 76.90%–93.40%. This has a strong floating ability due to addition of oil.

***In-vitro* Dissolution Study**

***In-vitro* Drug Release Study of Floating Beads of Telmisartan**

The dissolving profiles F1 to F8 and drug release profiles of formulations F1–F8 suggested sustained drug release. After 24 hours, the F3 formulation exhibited the maximum release out of the eight formulations. As a result, it was deemed an optimized formulation and was the focus of additional analysis and stability research (Table 5).

Table 5. Dissolution data of floating beads of Telmisartan % CDR for formulation batches.

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	0.156 ± 1.01	0.162 ± 1.18	0.171 ± 1.02	0.163 ± 0.01	0.16 ± 0.01	0.181 ± 1.01	0.0.154 ± 0.01	0.161 ± 0.02
2	0.548 ± 0.11	0.562 ± 0.01	0.57 ± 0.02	0.562 ± 0.01	0.654 ± 0.1	0.702 ± 0.01	0.564 ± 0.01	0.544 ± 0.01
3	0.748 ± 0.11	0.781 ± 0.01	0.792 ± 0.03	0.799 ± 0.02	0.815 ± 0.1	0.896 ± 0.01	0.766 ± 0.03	0.657 ± 0.12
4	0.948 ± 0.16	0.956 ± 0.01	0.962 ± 0.01	0.972 ± 0.1	0.966 ± 0.1	0.769 ± 0.2	0.987 ± 0.4	0.879 ± 0.1
5	1.256 ± 0.16	1.291 ± 0.01	1.299 ± 0.01	0.876 ± 0.02	1.238 ± 0.2	1.114 ± 0.01	1.132 ± 0.01	1.113 ± 0.23
6	1.548 ± 0.01	1.601 ± 0.03	1.609 ± 0.01	1.468 ± 0.01	1.435 ± 0.2	1.213 ± 0.01	1.453 ± 0.2	1.456 ± 0.2
12	1.555 ± 0.01	1.69 ± 0.09	1.78 ± 0.01	1.658 ± 0.1	1.699 ± 0.1	1.65 ± 0.2	1.160 ± 0.01	1.459 ± 0.02
24	1.568 ± 0.16	1.172 ± 0.24	0.171 ± 0.12	1.163 ± 0.23	1.16 ± 0.1	1.181 ± 0.2	1.212 ± 0.3	1.49 ± 0.1

Drug Release Kinetics

Because the higher correlation coefficient (R^2) for first order indicated that the value of R^2 for first order varied from 0.9461 to 0.9767, the drug release from the beads followed first-order kinetics rather than zero order and the Higuchi model. Thus, it was believed to be a first-order release pattern that all formulations adhered to. The value of the exponent (n) approached 0.592 in the Korsmeyer-Peppas model, suggesting that all formulations exhibit the non-Fickian release mechanism (Table 6 and Figure 4).

Stability Study

The best formulation's stability experiments showed that when it was stored at room temperature and at a temperature and humidity of 40°C and 75% RH, there were no appreciable changes in the physical properties. As indicated in Table 7, no appreciable changes in physical attributes or the percentage of CDR at 12 hours were noticed over the course of a month [17, 18].

Table 6. Curve fitting data of drug release rate profile of formulation F1–F8.

Model		Formulation Code							
		F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***
Zero order	R^2	0.6664	0.7144	0.7542	0.7589	0.7276	0.7319	0.7744	0.6349
First order	R^2	0.9461	0.9467	0.9474	0.9426	0.9745	0.9590	0.9767	0.9495
Higuchi model	R^2	0.8772	0.8858	0.8967	0.8976	0.9257	0.9365	0.9338	0.8851
Korsmeyer-peppas model	n	0.574	0.599	0.620	0.620	0.585	0.578	0.610	0.550

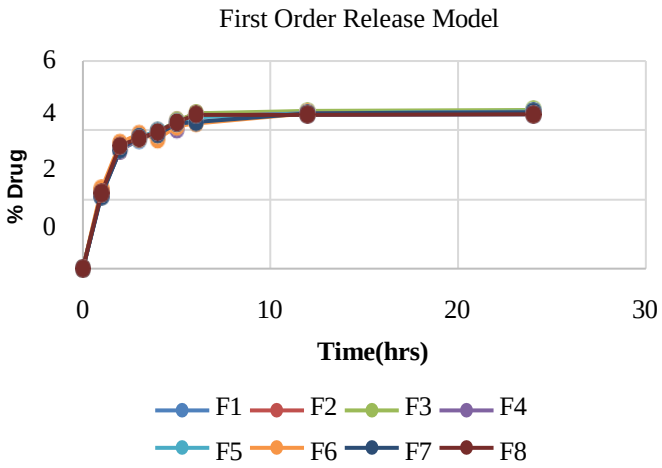

Figure 4. First order kinetic.

Table 7. Stability study of optimized formulation.

Stability (40°C ± 2°C and 75% RH ± 5%)	% CDR	Drug Content	Floating Duration
Initial	98.13	97.64	Up to 12 hrs.
15 Days	98.09	97.47	Up to 12 hrs.
30 Days	97.80	97.31	Up to 12 hrs.

CONCLUSION

The current study was to create and enhance TEL floating alginate beads, which would increase the solubility and bioavailability of medicines by extending their residence duration in the gastrointestinal area. TEL's systemic absorption can be improved and prolonged, and it can be controlled due to alginate beads' gastro-retentive properties.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Zhang Y, Jiang T, Zhang Q, Wang S. Inclusion of telmisartan in mesocellular foam nanoparticles: Drug loading and release property. Eur J Pharm Biopharm. 2010;76(1):17–23. doi: 10.1016/j.ejpb.2010.05.010.
2. Reda WW, Mohamed AM, Razaak A, EL-Gindy G, Fathalla D. Formulation and assessment of celecoxib floating beads in capsule using 2^ 3 full factorial design. J Adv Biomedical Pharm Sci. 2022;5(3):101–112. doi: 10.21608/JABPS.2022.136094.1157.
3. Sharma M. Formulation and evaluation of sodium alginate beads by emulsion gelation method. AJP. 2017;11(01). doi: 10.22377/AJP.V11I01.1096.
4. Rasel MA, Hasan M. Formulation and evaluation of floating alginate beads of diclofenac sodium. Dhaka Univ J Pharm Sci. 2012;11(1):29–35. doi: 10.3329/dujps.v11i1.12484.
5. Takka S, Gürel A. Evaluation of chitosan/alginate beads using experimental design: formulation and in vitro characterization. Aaps Pharmscitech. 2010;11(1):460–466. doi: 10.1208/s12249-010-9406-z.
6. Krishna BS, Gavini V, Meenakshi BM, Mounika B, Rajitha B, Balamani B. Controlled release microbeads of zidovudine incorporated with natural waxes: Design and characterization. Am J PharmTech Res. 2015;6(1):1–13.
7. Telmisartan: Uses, interactions, mechanism of action | DrugBank Online [Internet]. Drugbank.com. DrugBank; 2016 [Accessed from October 2024]. Available from: https://go.drugbank.com/drugs/DB00966
8. Sharma YR. Elementary organic spectroscopy. S. Chand Publishing; 2007.
9. Bairagi PD, Gondkar SB, Saudagar RB. Formulation development and evaluation of floating wax microspheres of tizanidine hydrochloride. Asian J Pharm Pharmacol. 2018;4(5):673–679. doi: 10.31024/ajpp.2018.4.5.19.
10. Montgomery DC. Design and analysis of experiments. 10th edition John Wiley & Sons; 2017.
11. More KS, Sonawan MP, Kor VB, Bhamare DB. Formulation development and evaluation of wax incorporated floating beads of dapagliflozin. Int J Pharm Sci Nanotechnol (IJPSN). 2023;16(5):6953–6957. doi: 10.37285/ijpsn.2023.16.5.3.
12. Birajdar AA, Deshmukh MT, Shete RV. A review on gastro-retentive floating microspheres. JDDT. 2021;11(1-s):131–138. doi: 10.22270/jddt.v11i1-s.4518.
13. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS PharmSciTech. 2005;6:E372–E390. doi: 10.1208/pt060347.
14. Bairagi PD, Gondkar SB, Saudagar RB. Formulation development and evaluation of floating wax microspheres of tizanidine hydrochloride. Asian J Pharm Pharmacol. 2018;4(5):673–679.
15. Pund AU, Shendge RS, Pote AK. Current approaches on gastroretentive drug delivery systems. JDDT. 2020;10(1):139–146.
16. Uthumansha U, Prabahar K, Gajapathy DB, El-Sherbiny M, Elsherbiny N, Qushawy M. Optimization and in vitro characterization of telmisartan loaded sodium alginate beads and its in vivo efficacy investigation in hypertensive induced animal model. Pharmaceutics. 2023;15(2):709. doi: 10.3390/pharmaceutics15020709.
17. Thakur S, Sharma B, Verma A, Chaudhary J, Tamulevicius S, Thakur VK. Recent progress in sodium alginate based sustainable hydrogels for environmental applications. J Clean Prod. 2018;198:143–159. doi: 10.1016/j.jclepro.2018.06.259.
18. Council GC. The GCC guidelines for stability testing of drug substances and pharmaceutical products. Publication (online). Edition Two; 2011;1428:22.

