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Research Article

Formulation and Evaluation of Floating Microspheres of Tizanidine Hydrochloride

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ABSTRACT

Microspheres are free flowing powders having particle size in the range of 1-1000µm with biologically active drugs intended for providing constant and prolonged therapeutical effect. Tizanidine Hydrochloride is a skeletal muscle relaxant, is a BCS class II drug with low bioavailability (40%) and short half-life (2.5 hours). It is better absorbed from the stomach, making it a suitable candidate for gastro-retentive formulations. To enhance its retention in the stomach and reduce dosing frequency, this study aimed to create optimized floating microspheres using ionotropic gelation techniques. The microspheres were developed using HPMC K4M and Eudragit RS100 as polymeric agents for controlling release. The formulation process was guided by Design Expert software (version 13, Stat-Ease). Comprehensive evaluations were conducted, including flow properties, buoyancy, release behaviour and drug entrapment. The best performing batch, F2 showed 99.3% release over 12 hours and good floating ability. Polymer concentration was positively correlated with both particle-size and buoyancy, with Eudragit RS100 having slightly greater buoyancy-enhancing effect than HPMC K4M. A balance between both the polymers produced an optimal buoyancy. Drug content and entrapment efficiency improved with higher polymers levels. The %drug release was the highest for the preparation with highest concentration of the polymers. The findings confirm that an appropriate blend of the chosen polymers enables successful formulation of gastro-retentive controlled-release microspheres of Tizanidine hydrochloride.

INTRODUCTION

Gastro-retentive systems are gaining importance for enhancing the absorption of drugs that have poor solubility in the intestine or degrade in alkaline conditions. They are mainly beneficial for drugs that dissolve poorly in the intestines or must be released specifically within the stomach[1].

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Microspheres, spherical particles composed of biodegradable polymers, are a common strategy for achieving gastro-retention. Such microspheres are capable of incorporating active pharmaceutical ingredients and allowing their gradual, controlled release. Floating microspheres, in particular, remain buoyant due to gas-releasing components like sodium bicarbonate that release carbon dioxide in acidic environments, aiding prolonged stomach retention[2].

Tizanidine hydrochloride, a centrally acting muscle relaxant, is classified as Biopharmaceutical Classification II with poor bioavailability (40%) and a short elimination half-life (2.5 hours). Since it has poor lower GI absorption[3], developing a stomach retentive system for its administration may enhance its therapeutic efficiency and reduce dosing frequency. In this study, rate retarding polymers HPMC K4M and Eudragit RS100 were incorporated to improve floatation and control the drug release. So, this research aims to increase its gastric residence time to improve absorption and reduce dosing frequency, ultimately supporting better patient adherence. Previous research on floating microspheres have highlighted their capability to improve therapeutic outcomes by improving drug uptake in the proximal GI region. In the current work, such established methods are refined using appropriate polymeric agents and supportive excipients. Literature review indicates that ionotropic gelation is a prominent method for developing floating microspheres using sodium alginate, a gas producing agent, and release rate slowing polymers.

MATERIALS AND METHODS

Chemicals used

Tizanidine hydrochloride was procured from Yarrow Chem Products. Sodium alginate was obtained from Isochem laboratories. HPMC K4M was obtained from Research-lab Fine Chem Industries. Eudragit RS100 was a gift sample from Evonik Roehm Pharma. Sodium bicarbonate and Calcium chloride from Isochem laboratories.

Preformulation Study

Preformulation studies were conducted to gather essential information about the physicochemical behaviour of the drug and its compatibility with selected excipients. These studies play a critical role in formulating a stable, effective dosage form.

Analytical Methods

Calibration Curve of TZN HCl in 0.1N HCl.

A primary stock solution was created by dissolving 10 mg of Tizanidine hydrochloride in 100 mL of 0.1N HCl. Aliquots from the primary solution were further diluted to prepare working concentrations of 2 to 12 µg/mL. Each sample's absorbance was measured at 320 nanometres, and the resulting data was used to plot a calibration graph with x-axis representing the concentration and y-axis the absorbance.[4]

Physicochemical properties of drug

Organoleptic evaluation

The pure drug was visually and physically examined for appearance, colour, odour, etc.

Determination of melting point by capillary method

The melting point was identified via capillary method. A small sample (0.1-0.2 grams) drug was loaded into a capillary tube and placed into the melting point apparatus. The temperature was gradually increased until the drug began to melt, and the melting point was recorded[5].

Solubility study

To know the solubility, saturation solubility studies were conducted using various solvents such as distilled water, ethanol, 0.1N HCl (pH 1.2), phosphate buffer (pH 7.4). Solubility was then calculated.

Drug – Excipient compatibility

Compatibility between drug & the selected excipients was analyzed using FTIR spectroscopy. Spectra were recorded for pure drug, sodium alginate, Eudragit RS100, HPMC K4M and their physical mixtures. The KBr pellet technique was used, and spectra were analyzed across 400-4000 cm^{-1} range to identify any potential interactions or incompatibilities[6].

Formulation of floating microspheres

Microspheres were formulated via ionotropic gelation method. Sodium alginate was used to produce a mucilaginous polymer solution, into which Tizanidine hydrochloride was gradually introduced while stirring continuously. The release-modifying polymers were added in varying concentration and mixed thoroughly. Sodium bicarbonate was incorporated to generate carbon dioxide for buoyancy. The resulting suspension was added into calcium chloride solution drop wise, through a 23-gauge needle. The microspheres formed were allowed to harden for 30 minutes in the calcium chloride solution before being retrieved, rinsed and dried at room temperature[7]. The composition of floating microspheres is given in Table No.1.

Table No.1: Composition of floating microspheres of Tizanidine hydrochloride

Formulations	Tizanidine hydrochloride (mg)	Sodium alginate (%w/v)	HPMC K4M (mg)	Eudragit RS100 (mg)	Sodium bicarbonate (mg)	Calcium chloride (%w/v)
F1	6	4	60	30	50	2.5
F2	6	4	60	60	50	2.5
F3	6	4	30	30	50	2.5
F4	6	4	0	0	50	2.5
F5	6	4	60	0	50	2.5
F6	6	4	0	60	50	2.5
F7	6	4	30	30	50	2.5
F8	6	4	30	0	50	2.5
F9	6	4	30	30	50	2.5
F10	6	4	30	60	50	2.5
F11	6	4	30	30	50	2.5
F12	6	4	30	30	50	2.5
F13	6	4	0	30	50	2.5

Characterization of floating microspheres of Tizanidine hydrochloride

Micromeritic properties

Bulk density and Tapped density

A measured sample of the dried microspheres was poured into a 10 mL graduated cylinder. The initial volume was noted as bulk volume. Then tapped until the volume remained unchanged, noted as the tapped volume. Bulk and tapped densities were then calculated.

Carr's index, Hausner's ratio and angle of repose

Compressibility and flowability were assessed through Carr's index and Hausner's ratio using the bulk and tapped density values. The angle of repose was found via fixed funnel method, where particles flowed through a funnel and the slope angle formed by the heap was measured to evaluate flow characteristics[8].

Percentage yield

After air drying, the total weight of collected microspheres was measured. The percentage yield was then computed using the formula[9]:

% Yield = (Weight of Microspheres / Total Weight of Raw Materials) × 100

Particle size

The particle size was evaluated under an optical microscope equipped with a calibrated eyepiece micrometre. Approximately 100 microspheres were measured per batch to determine the average size[10].

***In vitro* buoyancy studies**

To determine floatation behaviour, microspheres (100 mg) were placed in 900 mL of 0.1N HCl in a dissolution apparatus paddle-type (USP type II) operating at 100 rpm and 37°C. Floating and sedimented particles were collected after 12 hours, dried, and weighed[11].

% Buoyancy = (Weight of Floating Particles / Total Weight of Particles) × 100

Drug content and Entrapment efficiency

To isolate the drug, microspheres were stirred in 0.1N HCl for 12 hours. After filtration, analysed at 320 nm using a UV spectrophotometer. Drug content and entrapment efficiency were then calculated using standard formulas[12].

***In vitro* drug release studies**

In vitro drug release testing was performed using 900 mL of 0.1N HCl maintained at 37±0.2°C with paddle speed 50 rotations per minute (USP type II apparatus). Samples of 2 mL were withdrawn at hourly intervals over a 12-hour period and replenished with equal volumes of fresh medium. Analyzed at 320 nm to quantify the released drug[13].

Optimization via Design Expert Stat-ease Software

Formulation optimization was carried out using Design-Expert software (version 13, Stat-Ease), where %drug release and entrapment efficiency were selected as the key response parameters[14].

Statistical analysis

The influence of independent variables on the responses was assessed through statistical tools, including ANOVA. To visualize the interaction effects and determine optimal formulation conditions, contour and response surface plots were generated. All experimental results are presented as the average of three independent trials and are expressed as mean ± standard deviation.

Stability studies

The optimized microsphere formulation was stored in sealed glass containers under two environmental conditions: (i) room temperature (27 ± 2°C, 60 ± 5% RH) and (ii) accelerated condition (45 ± 2°C, 70 ± 5% RH). Drug content and physical properties were evaluated at 30, 60, and 90 days[15].

RESULTS AND DISCUSSION

Analytical method

Calibration curve of Tizanidine hydrochloride

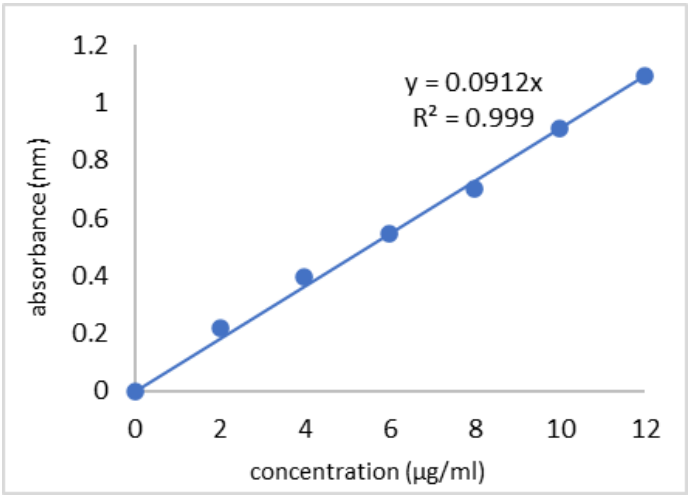

Figure No.1: Standard curve of Tizanidine hydrochloride in 0.1N HCl at 320nm

Physico-chemical properties of the drug

Organoleptic properties

Tizanidine hydrochloride appeared as an odorless, slightly yellowish-white powder with a bitter taste.

Determination of melting point

The melting point was 280 ± 1.5°C (mean ± Std. deviation, n=3), aligning with pharmacopeial specifications.

Solubility profile

Table No.2: Solubility profile of drug in different solvents

Name of the media	Saturation solubility of drug
Water	Slightly soluble
Ethanol	Soluble
0.1N HCl	Soluble
Phosphate buffer (pH 7.4)	Soluble

Drug-excipient compatibility studies: FTIR spectroscopy

FTIR analysis revealed characteristic peaks of Tizanidine hydrochloride including bands at 3066 cm^{-1} (aromatic C-H stretching), 1939 cm^{-1} (N-H bending), 1640 cm^{-1} (C=C stretch), and 811 cm^{-1} (C-Cl stretch). No additional peaks or significant shifts were observed in the spectra of the drug–excipient mixtures, indicating absence of any chemical interaction.

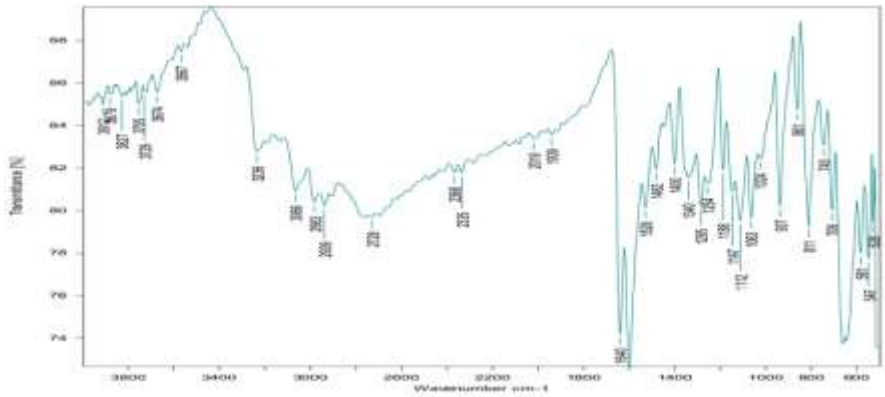

Figure No.2: FTIR spectrum of Tizanidine hydrochloride

Figure No.3: FTIR spectrum of Sodium alginate

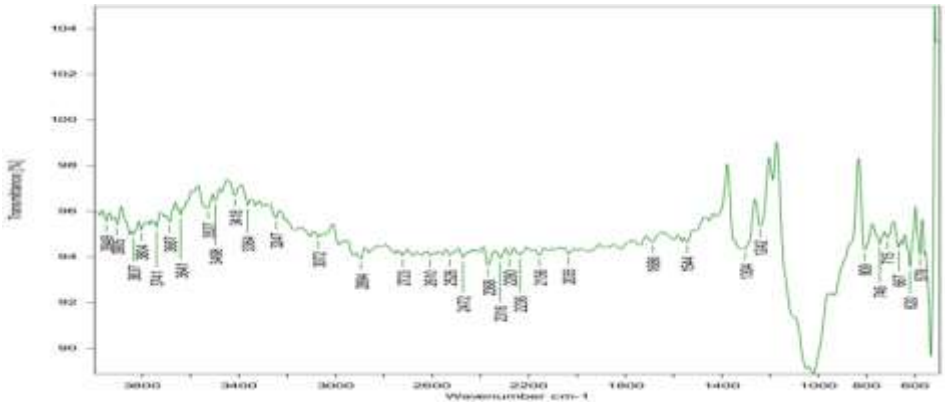

Figure No.4: FTIR spectrum of HPMC K4M

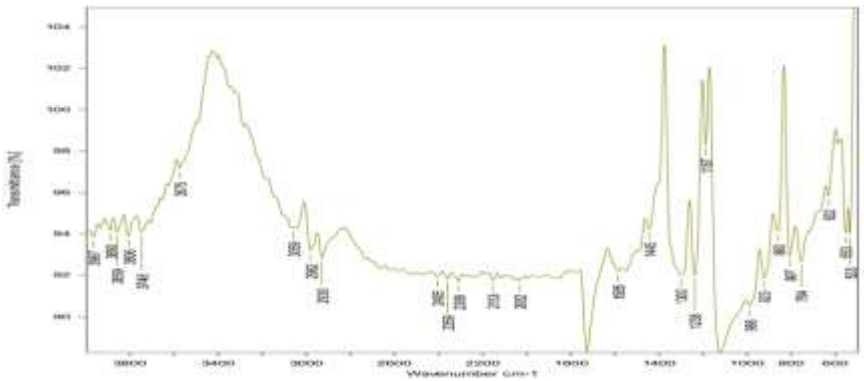

Figure No.5: FTIR spectrum of Eudragit RS100

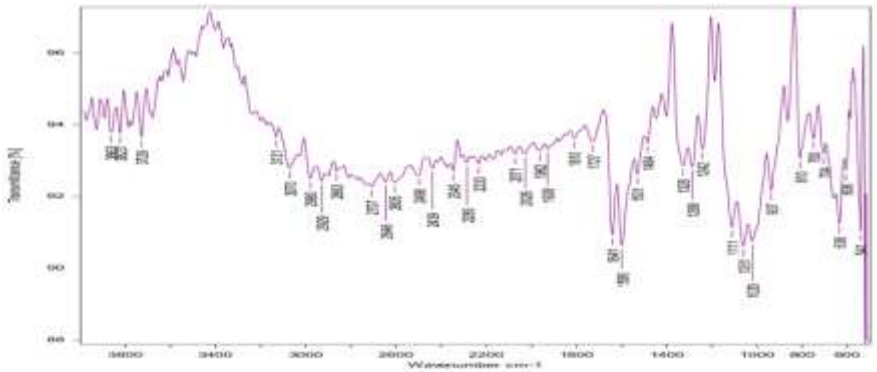

Figure No.6: FTIR spectrum of physical mixture of drug and polymers

Micromeritic studies of prepared microspheres

The microspheres demonstrated good flow characteristics as indicated by Carr's index, Hausner's ratio, and angle of repose. These values suggest that the flow properties were suitable for further processing.

Table No.3: Micromeritic study of floating microspheres of tizanidine hydrochloride

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Angle of repose (°)
F1	0.2041±0.005	0.2283±0.0036	10.56±3.42	1.109±0.049	26±1.15
F2	0.2135±0.0053	0.248±0.004	14.11±3.48	1.165±0.046	26.31±0.323
F3	0.2236±0.0057	0.259±0.0045	13.6±3.54	1.157±0.048	27.71±0.580
F4	0.2399±0.014	0.286±0.005	12.02±4.81	1.198±0.091	29.77±0.38
F5	0.2179±0.005	0.252±0.004	13.75±1.150	1.159±0.016	27.58±0.381
F6	0.2194±0.0045	0.2568±0.003	14.54±1.772	1.17±0.024	27.7±0.55
F7	0.2236±0.0057	0.259±0.0045	13.6±3.54	1.157±0.048	27.71±0.580
F8	0.2152±0.003	0.2446±0.003	12.014±0.161	1.136±0.0023	28.11±0.894
F9	0.2236±0.0057	0.259±0.0045	13.6±3.54	1.157±0.048	27.71±0.580
F10	0.2213 ±0.005	0.255±0.0046	13.38±3.63	1.124±0.051	25.64±0.311
F11	0.2236±0.0057	0.259±0.0045	13.6±3.54	1.157±0.048	27.71±0.580
F12	0.2236±0.0057	0.259±0.0045	13.6±3.54	1.157±0.048	27.71±0.580
F13	0.2221±0.0031	0.260±0.004	14.76±0.103	1.173±0.002	29.76±0.57

Percentage yield, *In vitro* buoyancy, Drug content and entrapment efficiency

Percentage yields ranged between 75.6% and 87%, with formulation F2 exhibiting the highest yield. *In vitro* buoyancy tests showed that floating capacity varied from 65.7% to 91.2%. Increased polymer content improved floatation, particularly in formulations containing higher proportions of Eudragit RS100. The most effective buoyancy was observed in formulations using an optimized ratio of the two polymers, attributable to the water-repelling (hydrophobic) characteristics of Eudragit RS100 and the gel-forming, water-attracting (hydrophilic) nature of HPMC K4M.

Drug content and entrapment efficiency improved alongside polymer concentration. Higher polymer loading likely due to a more stronger entrapment matrix, minimizing drug loss during gelation and curing. These observations highlight the critical role of polymer ratio optimization in maximizing drug entrapment. As shown in Table 4, formulations with higher yet balanced polymer content demonstrated better drug incorporation and retention.

Particle size

The average particle size across batches ranged from 502 µm to 683 µm. An upward trend in particle size was noted with increased polymer concentration, likely due to elevated solution viscosity, which caused the formation of larger droplets during extrusion and subsequently produced bigger microspheres after ionic crosslinking.

Table No.4: Evaluation and characterization of prepared floating microspheres

Formulations	Percentage yield (%)	Particle size (µm)	In-vitro buoyancy (%)	Drug content (%)	Drug entrapment efficiency (%)
F1	85.8±1.29	651±2.12	85.3±1.31	82.8±0.25	96.6±0.21
F2	87±1.35	683±1.81	91.2±1.25	83.1±0.11	97±0.13

F3	83.9±1.24	610±1.02	68±1.35	81±0.14	94.6±0.16
F4	75.6±2.56	502±1.64	65.7±0.95	75.5±0.18	88.2±0.22
F5	85.1±1.86	576±2.14	76±1.21	78.4±0.21	91.5±0.23
F6	81.05±2.75	569±1.53	82.6±0.81	77.7±0.20	90.8±0.25
F7	83.9±1.24	610±1.02	68±1.35	81±0.14	94.6±0.16
F8	78.8±3.15	522±2.16	70.8±1.43	77±0.19	89.9±0.22
F9	83.9±1.24	610±1.02	68±1.35	81±0.14	94.6±0.16
F10	86.1±2.48	648±1.52	88.6±1.46	80±0.28	93.5±0.32
F11	83.9±1.24	610±1.02	68±1.35	81±0.14	94.6±0.16
F12	83.9±1.24	610±1.02	68±1.35	81±0.14	94.6±0.16
F13	78.4±2.23	517±1.48	84.1±1.27	76.4±0.25	89.1±0.28

In vitro drug release studies

Drug release profiles indicated drug release extending upto 12 hours. Formulation F2 exhibited the most prolonged release, achieving 99.3% release by the end of the testing period. In contrast, formulations with lower polymer content showed faster release, with some completely releasing in 8 hours. The results confirm that increasing polymer concentration retards drug diffusion, thereby supporting extended release.

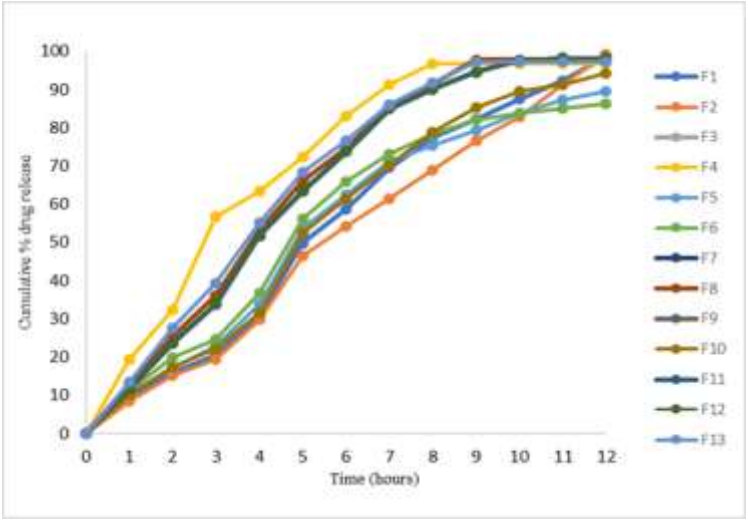

Figure No.7: *In vitro* drug release study of formulation F1 – F13

Optimization

Quadratic models provided the best statistical fit for drug content and entrapment efficiency based on ANOVA results.

Response 1: in-vitro drug release

Table No.5: Fit Summary: *In-vitro* drug release

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0002		0.7908	0.6602	
2FI	0.3591		0.7894	0.3836	
Quadratic	**0.0018**		**0.9557**	**0.7645**	**Suggested**
Cubic	0.0575		0.9802	0.0414	**Aliased**

Response 2: Drug entrapment efficiency

Table No.6: Fit Summary: drug entrapment efficiency

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	**< 0.0001**		**0.8908**	**0.8062**	**Suggested**
2FI	0.3984		0.8885	0.6778	
Quadratic	**0.0115**		**0.9600**	**0.7931**	**Suggested**
Cubic	0.0957		0.9781	-0.0611	**Aliased**

Table No.7: ANOVA for Quadratic model for response 1: in-vitro drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	927.60	5	185.52	52.74	< 0.0001	significant
A-HPMC K4M	608.03	1	608.03	172.85	< 0.0001	
B-EUDRAGIT RS100	178.21	1	178.21	50.66	0.0002	
AB	15.60	1	15.60	4.44	0.0732	
A^2	46.90	1	46.90	13.33	0.0082	
B^2	31.38	1	31.38	8.92	0.0203	
Residual	24.62	7	3.52			
Lack of Fit	24.62	3	8.21			
Pure Error	0.0000	4	0.0000			
Cor Total	952.22	12				

Table No.8: ANOVA for quadratic model for response 2: drug entrapment efficiency

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	56.47	5	11.29	58.58	< 0.0001	significant
A-HPMC K4M	41.08	1	41.08	213.07	< 0.0001	
B-EUDRAGIT RS100	11.48	1	11.48	59.55	0.0001	
AB	0.4225	1	0.4225	2.19	0.1823	
A^2	0.3938	1	0.3938	2.04	0.1961	
B^2	3.48	1	3.48	18.05	0.0038	
Residual	1.35	7	0.1928			
Lack of Fit	1.35	3	0.4499			
Pure Error	0.0000	4	0.0000			
Cor Total	57.82	12				

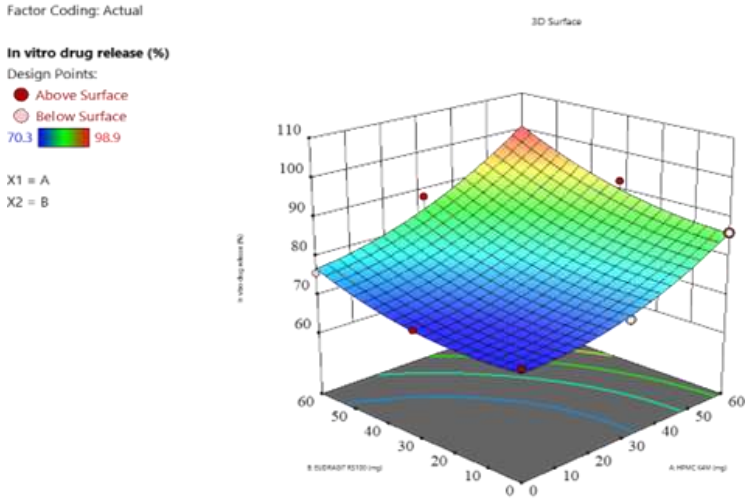

Figure No.8: 3-D response surface plot for the effect of concentration of HPMC K4M and Eudragit RS100 on *in-vitro* drug release

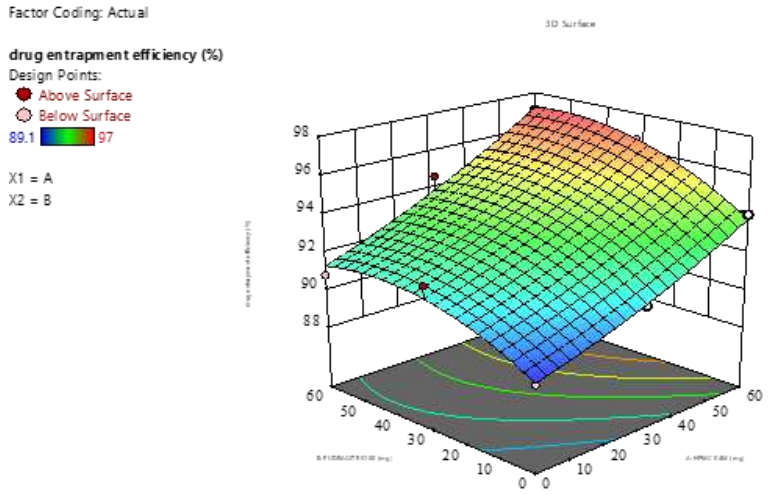

Figure No.9: 3-D response surface plot for the effect of concentration of HPMC K4M and Eudragit RS100 on drug entrapment efficiency

The desirability function method, a common tool for multi-response optimization, calculates an overall desirability score between 0 and 1 to assess goal achievement. A higher score indicates better satisfaction of response objectives. The numerical optimization tool generated six sets of optimal solutions. Among these, the software determined the ideal combination to be 59.98mg of HPMC K4M and 55.945mg of Eudragit RS100 achieving a maximum desirability score of 1.0.

Table No.9: Desirability table showing solutions suggested and their desirability

Number	HPMC K4M	EUDRAGIT RS100	*Invitro* drug release	Std Err (*In vitro* drug release)	drug entrapment efficiency	Std Err (drug entrapment efficiency)	Desirability	
1	**59.988**	**55.945**	**99.188**	**1.508**	**97.251**	**0.353**	**1.000**	**Selected**
2	59.062	57.375	99.210	1.513	97.125	0.354	1.000	
3	59.590	57.832	99.768	1.556	97.184	0.364	1.000	
4	59.891	58.426	100.242	1.594	97.213	0.373	1.000	
5	60.000	60.000	101.049	1.667	97.201	0.390	1.000	
6	59.706	56.120	99.077	1.500	97.216	0.351	1.000	

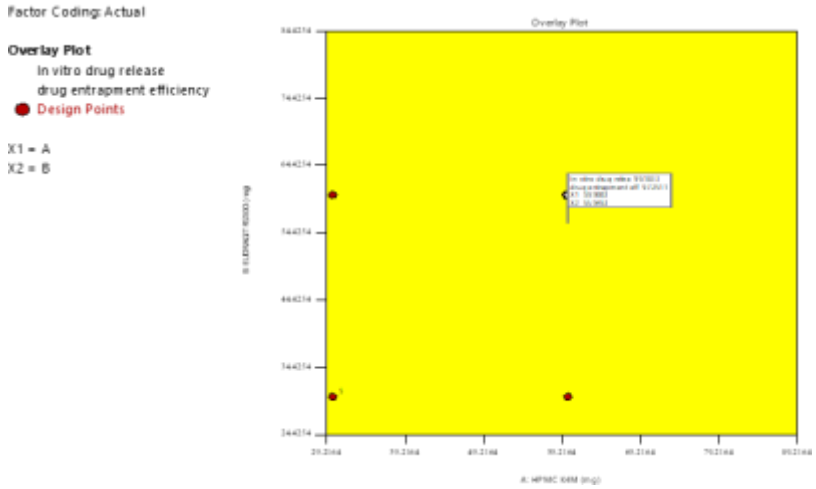

Figure No.10: Overlay plot of optimized formulation of floating microspheres of Tizanidine hydrochloride

The overlay plot (refer to Fig. 10) was utilized to identify the optimal design space for the formulation. The yellow area represents the area that satisfies the predetermined criteria. Experimental values obtained from three replicate trials closely matched the predicted outcomes, affirming model reliability.

Figure No.11: Photograph of optimized formulation- F2

Kinetic Studies

The drug release kinetics of formulation F2 were assessed using various mathematical models.

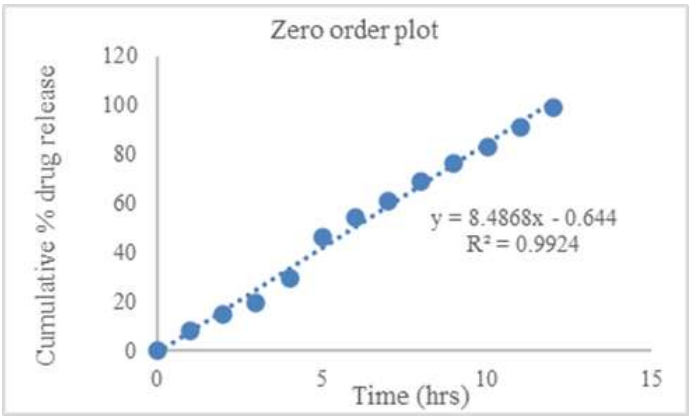

Figure No.12: Zero order plot for optimized formulation

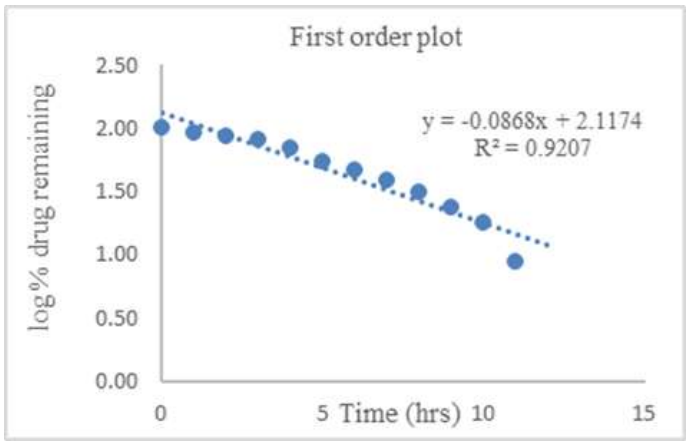

Figure No.13: First order plot for optimized formulation

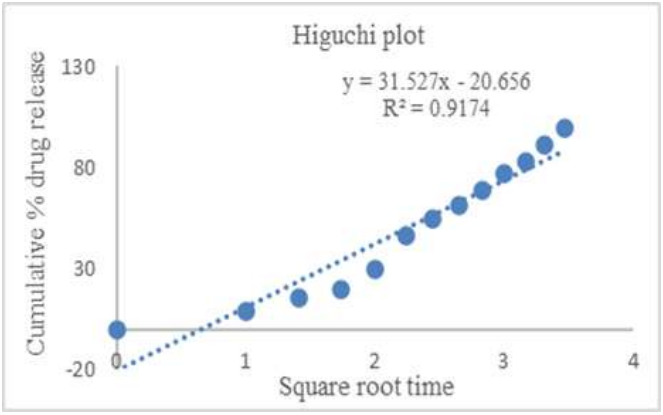

Figure No.14: Higuchi plot for optimized formulation

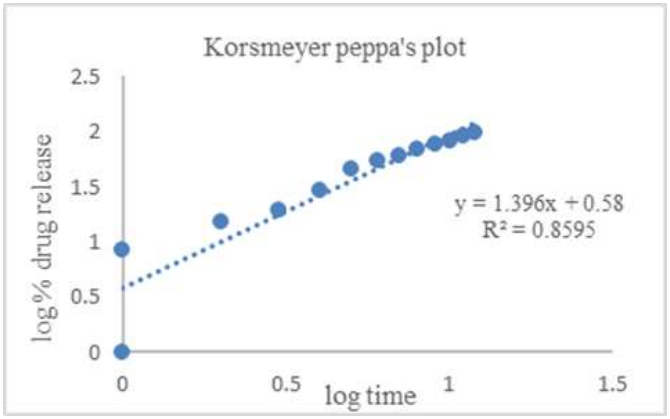

Figure No.15: Korsmeyer peppa's plot for optimized formulation

The zero-order model exhibited the highest correlation coefficient ($R^2 = 0.9924$), indicating a consistent, controlled release over the 12-hour period. This pattern suggests that, release mechanism was primarily governed by matrix erosion and polymer degradation rather than passive diffusion. Other kinetic models, such as Higuchi & Korsmeyer-Peppas, displayed comparatively lower correlation values, reinforcing the conclusion that formulation F2 followed a zero-order, controlled release profile.

Stability studies

Stability studies conducted at both room and accelerated conditions over three months revealed no significant changes in physical appearance or drug content. This confirmed the physicochemical stability of the final microsphere formulation during the study period.

Table No.10: Stability study data

Storage condition	Sampling interval	Physical appearance	Drug content (%)
40±2°C, 70±5% RH	0 days	No change	83.1 ± 0.13
	30 days	No change	83.09 ± 0.15
	60 days	No change	83.08 ± 0.12
	90 days	No change	83.06 ± 0.13
25±2°C, 60±5% RH	0 days	No change	83.1 ± 0.16
	30 days	No change	83.1 ± 0.13
	60 days	No change	83.1 ± 0.11
	90 days	No change	83.09 ± 0.14

CONCLUSION

Tizanidine hydrochloride-loaded floating microspheres were effectively formulated using ionotropic gelation method. The developed microsphere batches exhibited excellent flowability, efficient drug encapsulation, and controlled release profiles. Increasing polymer

concentration led to larger particle sizes, improved floatation, and enhanced entrapment efficiency. Among all tested batches, formulation F2 was identified as optimal, delivering 99.3% drug release over 12 hours and showing consistent buoyancy.

Kinetic modelling confirmed zero-order release, ensuring uniform and controlled delivery. Stability evaluations confirmed that the microspheres maintained their integrity and drug content under storage. These findings suggest that floating microspheres of Tizanidine hydrochloride offer a promising strategy for prolonging gastric retention, improving drug absorption, and reducing dosing frequency, ultimately contributing to better patient compliance.

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