OPTIMIZATION, FORMULATION AND EVALUATION OF NEBIVOLOL LOADED HYDROGEL

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ABSTRACT

Hydrogels are cross- linked polymeric systems having capability of retaining large amount of water which makes it ideal carriers for topical and transdermal drug delivery. The study was designed to formulate and evaluate Nebivolol -loaded hydrogel. Nebivolol is a β1-adrenergic receptor blocker, is widely used in the management of hypertension. However administrating through oral associated with first pass metabolism and variable bio-availability hence incorporating this drug into hydrogel will enhance bio availability and promotes better patient compliance. In this work, hydrogel was prepared using ionotropic gelation method which provides mild processing conditions and efficient drug encapsulation. A three-factor, three-level Box–Behnken experimental design was employed to optimize the formulation design. Nine formulations were developed and evaluated for physicochemical and performance characteristics. Among them formulation F4 is the optimised formulation having superior properties. The optimised hydrogel exhibited a pH of 6.2 that is compatible with skin physiology and prevents skin irritation upon on application. The viscosity was found to be 33,166cP indicating proper consistency for topical application. And spreadability value of 13.6g cm/sec proves that ease of application and uniform distribution over the applied surface. The hydrogel was characterized further by FT IR, SEM and DSC. *In vitro* release studies revealed that optimised formulation achieved 96% drug release for a period of 10 hours indicating efficient drug diffusion from polymer matrix. Encapsulating Nebivolol in hydrogel enhances drug stability, provides controlled release, bypasses first pass metabolism thereby enhancing bio

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INTRODUCTION

Hydrogels are networks of three-dimensional, cross-linked, hydrophilic polymers that can absorb and hold a lot of water without losing their structural integrity. These materials, which resemble natural biological tissues due to their high water content, elasticity, and biocompatibility, can be made from synthetic or natural polymers.[1] Hydrogels have drawn a lot of interest in pharmaceutical and medicinal research because of these qualities. Because of their porous structure, which enables the regulated and prolonged release of medicinal substances, they are frequently utilized in drug delivery systems[2]

Nebivolol is a third-generation β1-selective adrenergic receptor blocker commonly used in the treatment of hypertension and other cardiovascular disorders. It reduces blood pressure by decreasing heart rate and cardiac output through selective β1-receptor blockade.[3] In addition to this action, Nebivolol stimulates endothelial nitric oxide release, which causes vasodilation and improves vascular function.[4] Due to this dual mechanism, the drug provides effective blood pressure control with better endothelial protection. Clinical studies have demonstrated that Nebivolol significantly lowers systolic and diastolic blood pressure in patients with hypertension.[5]The drug is administered orally and is primarily metabolized in the liver through the cyp2d6 enzyme pathway.[6]

Administering Nebivolol by the oral route has several limitations that may affect its therapeutic efficiency. One major disadvantage is first-pass metabolism in the liver, where the drug is extensively metabolized by the CYP2D6 enzyme, which can reduce its bioavailability and lead to variability in drug response among patients.[3] In addition, oral administration may cause slow onset of action, since the drug must dissolve, be absorbed through the gastrointestinal tract, and then enter systemic circulation. The oral route can also produce gastrointestinal side effects such as nausea, abdominal discomfort, or indigestion in some individuals.[6]

Hydrogels can be preferred for delivering Nebivolol due to their ability to provide controlled and sustained drug release, which helps maintain stable blood pressure levels.[7] They can bypass first-pass metabolism when used via alternative routes, improving nebivolol's bioavailability compared with oral tablets.[8] Being biocompatible and non-toxic, hydrogels are suitable for long-term cardiovascular therapy. Smart hydrogels can respond to physiological

stimuli like pH or temperature, releasing the drug when needed.[9] This controlled release reduces side effects such as dizziness or bradycardia by avoiding sudden high plasma concentrations. Additionally, hydrogels allow versatile administration routes, enhancing patient compliance and therapeutic efficiency.

MATERIALS AND METHODS

Materials

Sodium alginate, gelatine, carbapol940, triethanolamine, propylene glycol, $CaCl_2$, distilled water, Nebivolol.

Inotropic gelation method

1. Hydrogel Fabrication:

Dissolve sodium alginate in distilled water while stirring gently to prevent the formation of bubbles. This is crucial because the presence of air can compromise the gel structure during polymerization.[10] In another vessel, mix gelatine and Carbapol 940 with propylene glycol until a consistent solution is obtained. Previous studies indicate that the combination of these polymers enhances the mechanical strength and elongation properties of the hydrogel.[11] Merge the two mixtures and stir continuously to form a cohesive gel matrix, ensuring uniformity for the aquatic environment that mimics physiological conditions.[12] Adjust the pH to physiological standards using triethanolamine to ensure optimal drug compatibility. The pH is a critical factor influencing drug release profiles and tissue response.[9]

2. Integration of Nebivolol:

Introduce a specified quantity of Nebivolol into the hydrogel matrix, stirring continuously to achieve thorough distribution. Ensuring that the drug is homogeneously dispersed.[13] Allow the combination to homogenize on a magnetic stirrer for a minimum of 30 minutes at ambient temperature, promoting better interaction between the drug and the polymer network.

3. Cross-linking Phase:

Transfer the hydrogel mixture into petri plates and let it settle. This phase is for establishing the three-dimensional network structure that characterizes hydrogels.[8] Initiate the cross-linking of the hydrogel by applying a calcium chloride (CaCl2) solution to the surface and incubating it for 1 hour to structural integrity as this cross-linking is essential for maintaining the hydrogel's shape when hydrated.[7] Wash with distilled water to eliminate any residual calcium ions while maintaining the matrix's porosity, which is important for drug diffusion.

Optimization study

A three-factor, three-level Box–Behnken experimental design was employed using Design-Expert software to optimize the formulation variables affecting drug release. Propylene glycol (C), gelatine (B), and sodium alginate (A) were chosen as independent variables, and cumulative drug release (%) at 10 hours was regarded as the response. A total of 17 experimental runs were generated, including repeated center points, to quantify experimental error and model adequacy. Analysis of variance (ANOVA) was used to statistically assess the experimental data after it was fitted to a second-order quadratic polynomial model.

Table 1. Experimental design matrix of the Box–Behnken design and observed cumulative drug release

Std	Run	A:Sodium Alginate (mg)	B: Gelatin (mg)	C: Propylene Glycol (mL)	Drug Release (%)
13	1	450	450	3.5	88.9
3	2	300	600	3.5	96.0
6	3	600	450	2	87.4
10	4	450	600	2	91.3
17	5	450	450	3.5	88.9
7	6	300	450	5	86.1
12	7	450	600	5	84.8
1	8	300	300	3.5	92.6
8	9	600	450	5	84.2
4	10	600	600	3.5	90.8
2	11	600	300	3.5	94.2
11	12	450	300	5	85.8
5	13	300	450	2	86.4
15	14	450	450	3.5	88.9
9	15	450	300	2	90.3
14	16	450	450	3.5	88.9
16	17	450	450	3.5	88.9

Table 2: Formulation of Nebivolol loaded hydrogel

Formulation	Sodium alginate	Gelatine	Carbapol 940	propylene glycol	Drug	Triethanolamine	$CaCl_2$
F1	300	300	50 mg	3.5	100 mg	10mg	5 ml
F2	600	600	50 mg	3.5	100 mg	10mg	5 ml
F3	600	300	50 mg	3.5	100 mg	10mg	5 ml
F4	300	600	50 mg	3.5	100 mg	10mg	5 ml
F5	600	450	50 mg	2	100 mg	10mg	5 ml
F6	45	60	50	2	10	10mg	5

	0	0	mg		0 mg		ml
F7	300	450	50 mg	5	100 mg	10mg	5 ml
F8	450	300	50 mg	5	100 mg	10mg	5 ml
F9	450	450	50 mg	3.5	100 mg	10mg	5 ml

Characterization and evaluation studies

Swelling Index: The swelling properties of hydrogels are typically determined using a gravimetric method. Hydrogel is prepared then let for drying. The weight of dried sample is recorded the sample is then added to 50 ml of buffer solution and the hydrogel is taken out at regular intervals and weighed with this the comparison is made between initial weight and final weight hence swelling index can be determined.[14]

Viscosity: The viscosity of hydrogel is measured using Brookfield viscometer, the prepared hydrogel is transferred into suitable container and ensure the spindle is immersed into hydrogel then spindle is lowered and allowed to rotate with fixed rpm note the readings.[15]

Spreadability: It is measured using a simple slip-and-drag method. In this procedure, a fixed amount of hydrogel is placed between two glass slides, and a known weight is placed on the upper slide to form a thin layer. Later an additional weight is tied to the upper slide, allowing it to move horizontally. The time taken for the upper slide to move is recorded, which shows the ease of spreading.

SEM: The SEM (Scanning Electron Microscopy) analysis of hydrogels is commonly used to study the surface morphology, porosity, and internal microstructure.[16]

DSC: The glass transition temperature (Tg) and melting or crystallization point can be found using Differential Scanning Calorimetry (DSC), which is frequently used to investigate the thermal characteristics of hydrogels.

Fourier Transform Infrared Spectroscopy (FTIR): It is frequently used to characterize hydrogels by identifying chemical bonds and functional groups present in the polymer network, which helps confirm hydrogel formation and molecular interactions.[17]

Drug content uniformity: It was evaluated to confirm that Nebivolol is evenly incorporated within each formulation. A fixed quantity of the dried hydrogel was weighed accurately and transferred into a known volume of phosphate buffer (pH 7.4). The mixture was kept in magnetic stirrer continuously for a predetermined time until complete extraction of the drug. The solution was filtered and analysed using UV–Vis spectrophotometry, and drug content was calculated using a calibration curve.[18]

***In vitro* drug release studies:** After precisely weighing a predetermined amount of the dry hydrogel and letting it hydrate evenly, it is put on a Franz diffusion cell. To do this, the Franz diffusion cell's donor and receptor compartments are separated by a semi-permeable membrane. To maintain continuous contact between the gel surface and the diffusion medium, the hydrogel formulation is placed in the donor compartment and phosphate buffer with a pH of 7.4 is placed in the receptor compartment. To maintain sink conditions, the receptor compartment is kept at 37°C ± 0.5°C and agitated continuously. To maintain a steady volume, take samples from the receptor compartment at regular intervals and replace them right away with an equivalent volume of new buffer solution. The withdrawn samples are filtered if necessary and analysed using UV–Vis spectrophotometry to determine Nebivolol concentration with the help of a calibration curve.[18]

RESULTS AND DISCUSSION

Optimization studies

The ANOVA results demonstrated that the quadratic model was statistically significant (Model F-value = 15.65, p = 0.0008), indicating that the model adequately described the relationship between formulation variables and drug release. The model exhibited an R^2 value of 0.9527, suggesting that 95.27% of the variation in drug release was explained by the selected variables. The Adjusted R^2 (0.8918) further confirmed good agreement between experimental and predicted values. The coefficient of variation was 1.20%, indicating excellent precision, while the Adequate Precision value of 15.59 confirmed an adequate signal for optimization (Table 3).

Table 3. Analysis of variance (ANOVA) for the quadratic polynomial model of cumulative drug release

Source	**F-value**	**p-value**	**Significance**
Model	15.65	0.0008	Significant
A	2.23	0.1789	NS
B	0.00	1.0000	NS
C	23.16	0.0019	Significant
AB	10.19	0.0152	Significant
AC	1.85	0.2156	NS
BC	0.88	0.3791	NS
A^2	5.68	0.0486	Significant
B^2	39.50	0.0004	Significant
C^2	62.76	<0.0001	Significant
Model summary statistics and goodness-of-fit parameters for the quadratic model			
Std. Dev.	1.07	**R^2**	0.9527
Mean	89.08		**Adjusted R^2**

C.V. %	1.20		Predicted R^2
		Adeq Precision	15.5912

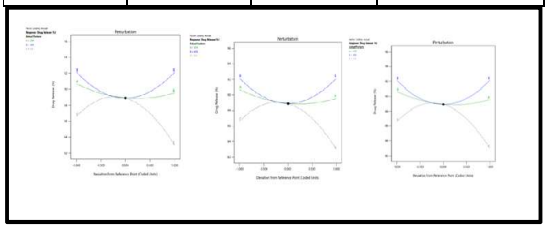
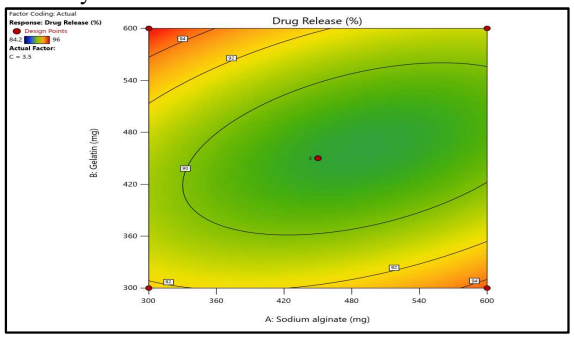


Figure 1. Perturbation plot showing the effect of sodium alginate (A), gelatin (B), and propylene glycol (C) on cumulative drug release (%)

Response Surface Analysis

Three-dimensional response surface and contour plots illustrated the interaction among sodium alginate, gelatine, and propylene glycol on drug release. The plots indicated that moderate concentrations of sodium alginate and higher gelatine concentration improved drug release, whereas excessive propylene glycol produced a nonlinear effect due to increased matrix viscosity.



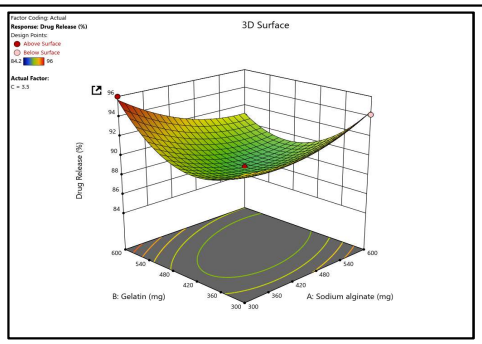


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Figure 2 Three-dimensional response surface plot showing the interactive effect of sodium alginate (A) and gelatin (B) on cumulative drug release (%)

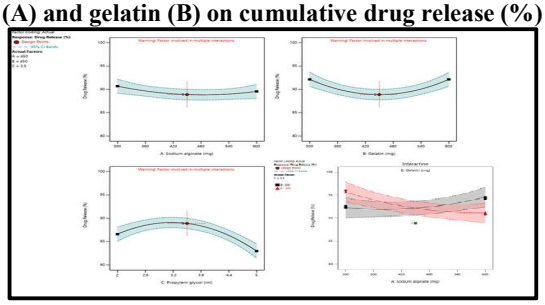


Figure 3: Contour plot showing the interaction of variables

The optimized formulation consisted of 300 mg sodium alginate, 600 mg gelatin, and 3.5 mL propylene glycol, producing approximately 96.0% cumulative drug release after 10 h. The experimental response closely matched the predicted value, confirming the validity of the optimization model. The improved release profile may be attributed to the balanced polymer concentration together with the plasticizing effect of propylene glycol, which enhanced matrix hydration and drug diffusion.

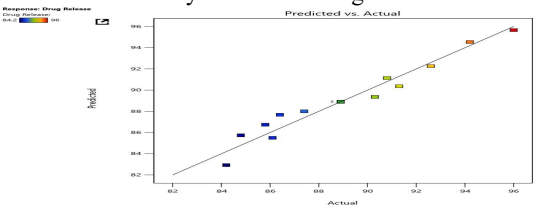


Figure 4: Predicted versus actual plot showing the agreement between predicted and experimental cumulative drug release values.

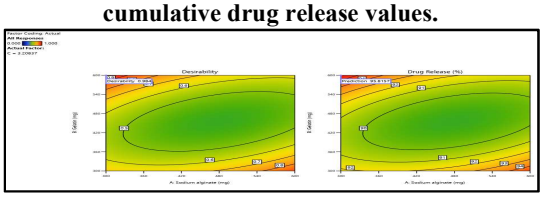


Figure 5. Desirability plots illustrating the optimized formulation and predicted cumulative drug release.

Swelling index: The prepared hydrogel swelling index was found to be **356%**, indicating a moderate water absorption capacity. The hydrogel shows a well-developed porous structure and good hydrophilic nature. The observed swelling index confirms that the polymer network is adequately cross-linked.

Viscosity: The hydrogel viscosity was found to be **33166 cp**, indicating a moderate consistency. This suggests that the formulation has good thickness and structural integrity. The viscosity value shows that the hydrogel can spread easily while still remaining stable on the surface without flowing excessively. This balance is essential for effective topical application and ensures better retention at the site of use.

Spreadability: The hydrogel showed a spreadability value of **13.6**, indicating good ease of application. This suggests that the formulation can be easily spread on the skin with minimal effort, ensuring uniform distribution.

pH: pH was found 6.2 which is favorable for skin penetration and skin pH

FTIR: Both FTIR spectra indicate the presence of hydroxyl (–OH) functional groups, evidenced by the broad absorption bands in the 3200–3500 cm^{-1} region, along with aliphatic C–H stretching near 2900 cm^{-1} and strong C–O stretching bands around 1000–1100 cm^{-1}. The absence of a prominent carbonyl peak near 1700 cm^{-1} suggests that compounds such as aldehydes, ketones, or carboxylic acids are unlikely. Spectrum 2 shows a broader and more intense O–H

band compared to Spectrum 1, indicating stronger hydrogen bonding, which may be due to a higher concentration of hydroxyl groups or increased intermolecular interactions (e.g., a polyalcohol or more hydrated sample). Overall, both spectra are consistent with alcohol-type compounds, with Spectrum 2 representing a more strongly hydrogen-bonded system than Spectrum 1.

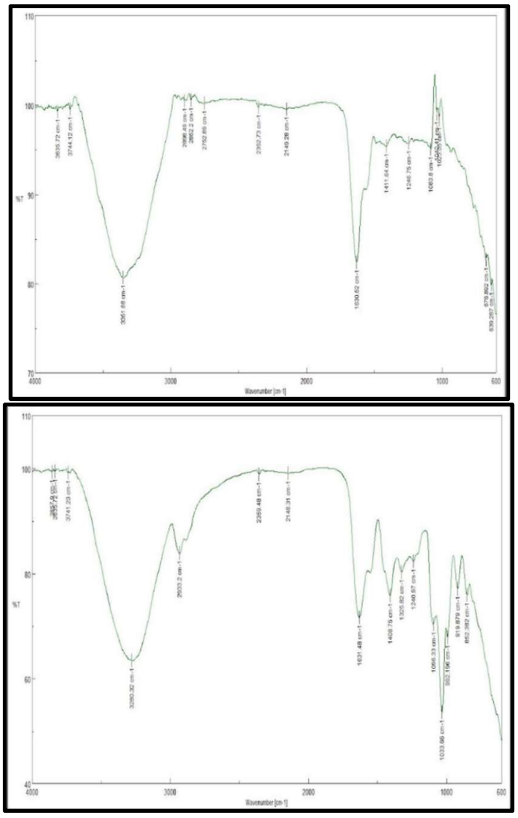
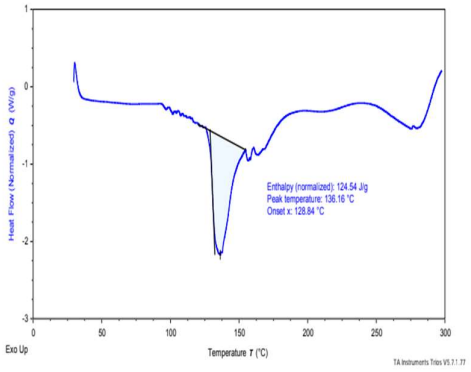


Figure 6 FTIR spectra of Nebivolol loaded hydrogel

DSC:



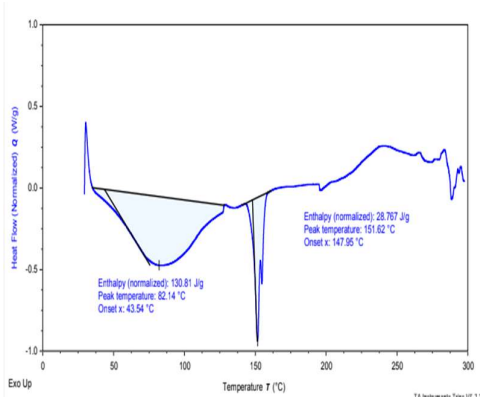


Figure 7 DSC of Nebivolol loaded hydrogel

The DSC thermograms indicate that the formulation (fig -7.1) exhibits two distinct endothermic transitions, including a sharp melting peak at higher temperature, confirming the presence of a well-defined crystalline phase. In contrast, the blend (fig-7.2) shows a single, broadened endothermic peak shifted to a lower temperature, with the disappearance of the sharp melting transition observed in the formulation. This shift and peak broadening suggest improved homogeneity and possible solid-state interaction between components, leading to reduced crystallinity or partial amorphization. Such behaviour is generally considered favourable for enhancing uniform dispersion and potentially improving solubility.

SEM:

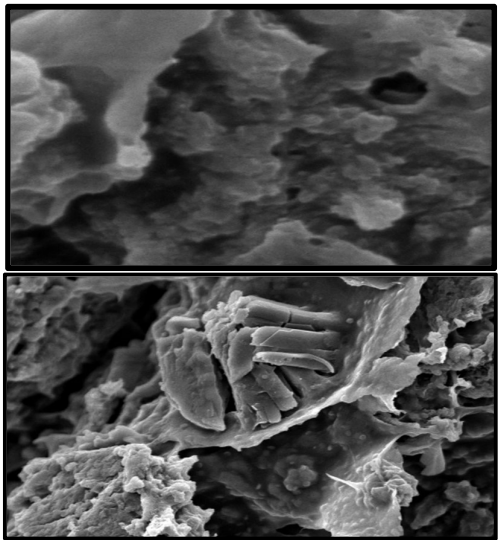


Figure 7 SEM of Nebivolol loaded hydrogel

The SEM analysis of the hydrogel reveals a heterogeneous morphology characterized by layered, sheet-like structures along with a rough and highly porous surface. The presence of folded flakes and aggregated regions indicates effective polymer chain entanglement and cross-linking, confirming the formation of a stable three-dimensional network. Additionally, the observed interconnected pores and void spaces suggest a high surface area, which is favourable for water uptake, swelling behaviour, and drug loading. Overall, the porous and cross-linked

architecture of the hydrogel supports efficient diffusion and controlled drug release, demonstrating its suitability for drug delivery applications.

Drug content: The drug content varied from varied from 84.90% to 96.00 %. In comparison to the other formulations, Formulation F4 showed the peak drug concentration.

***Invitro* drug release studies:** *In-vitro* analysis of diffusion of **of Nebivolol loaded hydrogel** results values were presented in the table below. The cumulative drug diffusion percentage from formulations F1 – F9 ranges from 76.05 to 96.00. Among all, formulation 'F4' exhibits sustained drug release of 96% within 10 hrs.

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Table 4: In vitro drug release kinetics of Nebivolol loaded hydrogel formulations from F1 to F9

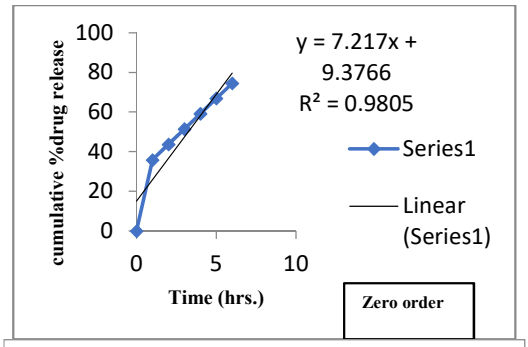
Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00±0.00	0.00±0.01	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	22.40±0.03	30.60±0.02	27.80±0.01	35.80±0.04	18.50±0.02	25.20±0.02	16.20±0.01	23.40±0.03	21.40±0.03
2	29.80±0.01	39.40±0.01	35.90±0.02	43.60±0.02	26.70±0.01	33.80±0.02	25.70±0.02	27.80±0.01	29.80±0.01
3	37.10±0.02	47.80±0.04	44.60±0.02	51.40±0.03	34.5±0.01	41.90±0.03	30.51±0.01	35.10±0.02	37.10±0.02
4	45.20±0.02	55.10±0.04	52.30±0.01	59.20±0.02	42.80±0.02	49.60±0.02	38.80±0.02	42.20±0.02	46.20±0.02
5	53.60±0.04	62.40±0.03	60.10±0.01	66.90±0.01	50.90±0.03	57.80±0.03	45.90±0.03	53.60±0.04	50.90±0.04
6	61.40±0.03	69.20±0.04	68.7±0.02	74.50±0.03	59.30±0.04	65.20±0.02	54.30±0.03	61.40±0.03	61.30±0.03
7	69.80±0.01	75.60±0.04	75.20±0.02	80.80±0.05	67.50±0.02	72.60±0.01	62.50±0.02	68.80±0.01	69.50±0.01
8	76.50±0.02	82.10±0.03	81.60±0.03	86.40±0.03	74.80±0.03	79.10±0.03	69.20±0.03	76.50±0.02	76.60±0.02
9	82.	88.70	87.30	91.20	81.20	85.60	71.20	82.	82.

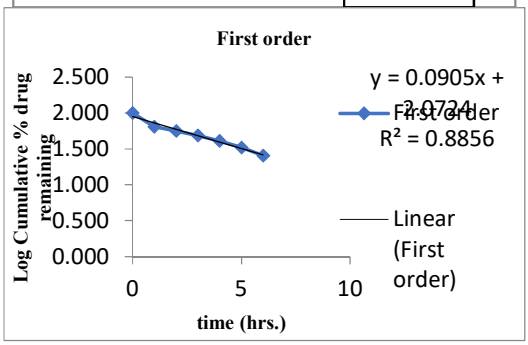
	40±0.03	±0.02	±0.01	±0.02	±0.02	±0.02	±0.04	40±0.03	30±0.03
10	88.90±0.03	94.20±0.02	92.60±0.02	96.00±0.02	87.40±0.01	91.30±0.02	78.40±0.01	84.90±0.03	86.60±0.03

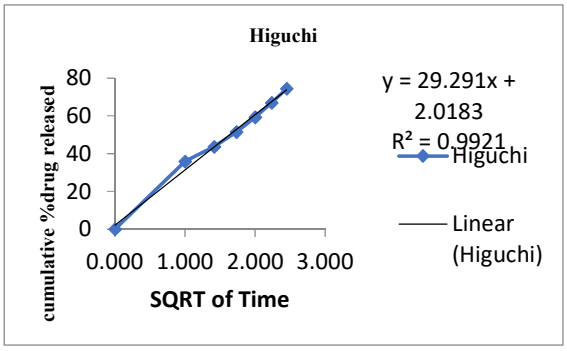
***Invitro* drug release kinetics:** The drug kinetics of Nebivolol loaded hydrogels was evaluated by applying zero-order, first order, Higuchi and Korsemeyer Peppas kinetic models.

Table 5: Cumulative drug percentage release profile of optimized formulation(F4)

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumulative % drug remaining	log time	log Cumulative % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0	2	0	0	100	4.642	0
1	35.8	64.2	1	1.808	0	1.554	35.8	4.004	0.638
2	43.6	56.4	1.4142	1.751	0.301	1.639	7.8	3.835	0.807
3	51.4	48.6	1.7320	1.687	0.477	1.711	7.8	3.649	0.993
4	59.2	40.8	2	1.611	0.6	1.722	7.8	3.443	1.1
5	66.9	33.1	2.2360	1.520	0.699	1.825	7.7	3.211	1.431
6	74.5	25.5	2.4449	1.407	0.778	1.872	7.6	2.943	1.699
7	80.8	19.6	2.6458	1.283	0.845	1.907	6.3	2.678	1.964
8	86.4	13.6	2.8284	1.134	0.903	1.937	5.6	2.387	2.255
9	91.2	8.8	3	0.944	0.954	1.960	4.8	2.065	2.577
10	96	4	3.1622	0.602	1	1.982	4.8	1.587	3.055







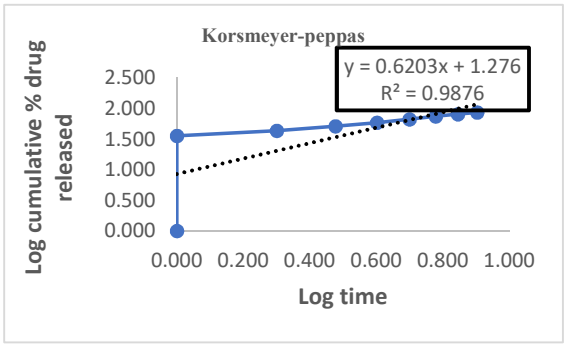


Figure 8 Drug kinetics of Nebivolol loaded hydrogels

The Higuchi model exhibited the highest correlation coefficient (R^2 = 0.9921), indicating that the drug release predominantly follows a diffusion-controlled mechanism, where Nebivolol diffuses through the hydrated polymeric matrix of the hydrogel. This suggests that the porous network of the hydrogel governs the release of the drug according to Fickian diffusion principles. The First-order model also showed a high degree of linearity (R^2 = 0.9721), suggesting that the drug release rate is influenced to some extent by the concentration of the drug remaining within the hydrogel matrix. In contrast, the Zero-order model showed a comparatively lower correlation (R^2 = 0.8845), indicating that the release was not maintained at a constant rate throughout the study period.

The Korsmeyer–Peppas model demonstrated the lowest correlation coefficient (R^2 = 0.5131), indicating that this model does not adequately describe the release kinetics of the optimized formulation under the present experimental conditions. Overall, the optimized hydrogel formulation exhibited a sustained drug release profile with approximately 96% cumulative drug release after 10 hours, demonstrating its suitability as a controlled-release delivery system. The predominance of Higuchi kinetics confirms that diffusion through the hydrated polymer matrix is the principal mechanism governing Nebivolol release, which may contribute to prolonged therapeutic action and improved patient compliance.

CONCLUSION

The optimized hydrogel achieved 96% drug release within 10 hours, demonstrating efficient and prolonged release characteristics. Release kinetic studies suggested that drug diffusion occurred in a controlled manner. By avoiding hepatic first-pass metabolism and providing sustained delivery, the hydrogel system may improve Nebivolol bioavailability and therapeutic effectiveness. Therefore, the developed formulation can be considered a potential and patient-friendly approach for long-term hypertension treatment.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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