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Formulation and Evaluation of Nebivolol Loaded Nanosponges for Oral Drug Delivery.

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ABSTRACT:
Nanosponges, characterized by their nanosized structures capable of encapsulating both hydrophilic and hydrophobic drugs, present a promising avenue for overcoming challenges associated with drug delivery, such as poor oral bioavailability. In this study, the focus was on formulating and evaluating Nebivolol-loaded nanosponges using the Emulsion Solvent Evaporation method with ethyl cellulose, PVA, β-Cyclodextrin, and dichloromethane as key components. FTIR analysis confirmed the absence of interactions between the drug and polymers. The Nebivolol nanosponges were assessed for various parameters including drug entrapment efficiency, particle size, surface morphology, and Zeta potential. Subsequently, Nebivolol-loaded capsules were subjected to a battery of tests including weight variation, in vitro disintegration, drug content, in vitro dissolution, and stability studies. The results demonstrated controlled release behavior over 24 hours, with zero-order kinetics observed. The study suggests that Nebivolol nanosponges hold promise for controlled drug delivery applications.

Introduction

Nanosponges have emerged as a highly promising and versatile tool in the field of drug delivery, offering a novel approach to address various challenges associated with conventional drug administration. Composed of microscopic particles with nanometer dimensions, nanosponges possess a unique three-dimensional structure that allows for the encapsulation of a wide range of substances, including both hydrophilic and hydrophobic drugs. This capability not only enhances the solubility of poorly soluble drugs but also facilitates their targeted delivery to specific sites within the body.[1,2]

The versatility of nanosponges stems from their ability to transport drugs through multiple mechanisms, including diffusion, degradation, swelling, and affinity-based mechanisms.[3] These mechanisms collectively contribute to the controlled release of the encapsulated drug, allowing for precise modulation of its pharmacokinetic profile. By exploiting these mechanisms, nanosponges can achieve sustained and controlled drug release, leading to improved therapeutic outcomes and reduced side effects compared to conventional dosage forms.[4,5]

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In recent years, there has been a growing interest in the development of targeted drug delivery systems, driven by advancements in pharmaceutical technology and the need to optimize therapeutic efficacy while minimizing systemic side effects. [6,7]Targeted drug delivery systems enable the selective accumulation of drugs at the site of action, thereby maximizing their efficacy while minimizing off-target effects. This is particularly relevant in the case of chronic conditions such as hypertension and heart failure, where precise control over drug delivery is essential for optimal treatment outcomes.[8,9]

Nebivolol, a beta-blocker, is widely used in the treatment of hypertension and heart failure due to its ability to reduce blood pressure and improve cardiac function. However, like many other drugs, Nebivolol faces challenges related to its poor solubility and bioavailability, which can limit its therapeutic efficacy. By formulating Nebivolol-loaded nanosponges, it is possible to overcome these challenges and enhance the drug's therapeutic efficacy through controlled release.[10,11]

In this context, the present paper aims to explore the formulation of Nebivolol-loaded nanosponges and evaluate their potential for controlled drug delivery.[12] Through a comprehensive analysis of the formulation parameters, characterization techniques, and in vitro evaluation studies, we seek to elucidate the feasibility and effectiveness of this novel drug delivery approach. Ultimately, the development of Nebivolol-loaded nanosponges holds promise for improving treatment outcomes in patients with hypertension and heart failure, paving the way for the development of next-generation targeted drug delivery systems.[13,14.]

1. Materials and Method[15]

Nebivolol received as a gift sample from Torrent Pharmaceuticals Ltd. Polyvinyl alcohol, Ethyl cellulose, β-Cyclodextrin, and Dichloromethane were obtained from research Lab Mumbai

Compatibility Studies using FTIR Spectroscopy:

FTIR spectral analysis of pure Nebivolol was conducted using a Jasco-FTIR-4100 spectrometer employing the KBr disk method. The obtained spectrum was compared with the standard spectrum of Nebivolol to assess any potential interactions.

2.1 Method of Preparation of Nebivolol Loaded Nanosponges:

Preparation of Nanosponges by Emulsion Solvent Diffusion Method:

The disperse phase comprising Nebivolol and a specified quantity of ethyl cellulose dissolved in the required amount of dichloromethane was slowly added to a definite amount of PVA in 100 ml of aqueous continuous phase. The mixture was stirred at 1000 rpm on a magnetic stirrer for 2 hours. Subsequently, the formed Nebivolol nanosponges were collected by vacuum filtration and dried in an oven at 40°C for 24 hours.

2.2 Preparation of Nebivolol Loaded Nanosponge Capsules (Punch Method or Manual Filling):[15,16,17.]

The powder containing Nebivolol nanosponges was placed on a sheet of clean paper or porcelain plate using a spatula, forming a cake with a depth approximately one-fourth to one-third the length of the capsule body. The base of the capsule was held vertically, and the open end was repeatedly pushed into the powder until the capsule was filled; then, the cap was replaced to close the capsule.

Table No. 1: Formulation of Nebivolol Loaded Nanosponge.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Nebivolol	100	100	100	100	100	100
Ethyl cellulose	400	600	900	1000	800	600
Polyvinyl alcohol	600	800	900	1000	1100	1200
β-Cyclodextrin	200	200	200	200	200	200
Dichloromethane (ml)	30	30	30	30	30	30

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Distilled water (ml)	100	100	100	100	100	100

Characterization of Nebivolol-Loaded Nanosponges:

Particle Size and Malvern Zeta Sizer:

The particle size of the Nebivolol-loaded nanosponges was determined using a Malvern zeta sizer. The average particle diameter was calculated using the formula: Average particle diameter = ∑ n * d / N, where n represents the total number of particles in a specific size range, d is the diameter of the particle in that size range, and N is the total number of particles.

Zeta Potential:

The zeta potential, which is indicative of the surface charge of the nanosponges, was measured using a zeta sizer equipped with laser Doppler microelectrophoresis. For analysis, the nanosponges were diluted tenfold with distilled water. A zeta potential value exceeding 30 mV in water indicates good stability of the nanosponges.

Percentage Yield:

The percentage yield of the prepared Nebivolol-loaded nanosponges was determined by accurately weighing the dried nanosponges from all batches. The measured weight of the prepared nanosponges was divided by the total amount of all excipients and drug used in the formulation and multiplied by 100 to obtain the total percentage yield.

Drug Entrapment Efficiency:

The drug entrapment efficiency of Nebivolol-loaded nanosponges was evaluated by selecting 100 mg of nanosponges from each batch. The nanosponge powder was placed in 100 ml of methanolic HCl and subjected to centrifugation at 1000 rpm for 30 minutes. The supernatant was filtered and analyzed by UV spectroscopy to determine the percentage entrapment efficiency using the formula: Percentage entrapment efficiency (%) = (Actual drug content / Theoretical drug content) × 100.

Shape and Surface Morphology:

Scanning electron microscopy (SEM) was employed to examine the shape and surface morphology of the Nebivolol-loaded nanosponges. Samples were deposited on glass slides and placed under vacuum. Subsequently, the nanosponges were coated with a thin layer of gold/palladium using a sputter coater unit. The morphology and size of the nanosponges were observed under SEM at an accelerated voltage of 15 kV.

RESULT AND DISCUSSION

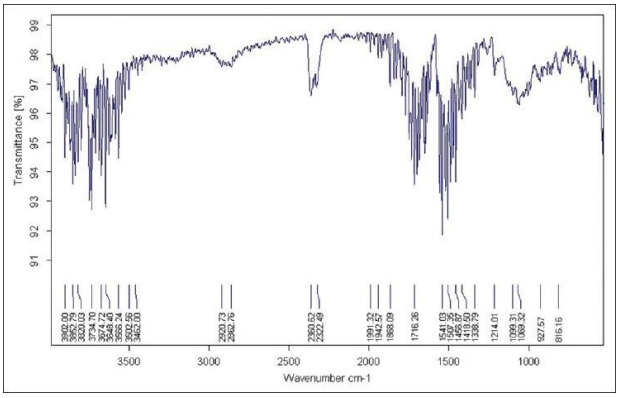

Figure 1 FTIR Spectra of Nebivolol

Interpretation of Nebivolol Infrared Spectrum:

The infrared (IR) spectrum of Nebivolol provides valuable information about the functional groups present in the molecule and allows for the identification of characteristic absorption bands.

Broad O-H Stretching:

The presence of a broad absorption band in the region of 3200-3600 cm^-1 indicates the presence of O-H stretching vibrations, which are typically associated with hydroxyl groups present in alcohols or phenols.

C-H Stretching:

The absorption bands observed in the region of 2800-3000 cm^-1 correspond to C-H stretching vibrations, which are characteristic of aliphatic and aromatic hydrocarbons present in the Nebivolol molecule.

Carbonyl Stretching:

A sharp absorption band in the region of 1700-1750 cm^-1 indicates the presence of carbonyl stretching vibrations, which are typically associated with the carbonyl group (C=O) present in the Nebivolol molecule.

Aromatic C=C Stretching:

The presence of absorption bands in the region of 1600-1680 cm^-1 suggests the presence of aromatic C=C stretching vibrations, which are characteristic of aromatic rings present in the Nebivolol molecule.

C-O Stretching:

Absorption bands in the region of 1000-1300 cm^-1 correspond to C-O stretching vibrations, which are typically associated with the presence of ether or alcohol functional groups in the Nebivolol molecule.

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Evaluation Parameter

Evaluation of Nebivolol nanosponges:

Table No. 2: Average particle size of the Nebivolol nanosponges

Sr. No	Formulation Code	Particle Size (nm)	Standard Deviation*
1.	F1	191.58 ± 0.013	0.013
2.	F2	104.15 ± 0.016	0.016
3.	F3	84.29 ± 0.011	0.011
4.	F4	115.80 ± 0.016	0.016
5.	F5	136.22 ± 0.018	0.018
6.	F6	173.16 ± 0.017	0.017

*Each value is an average of three determinations.

Table No. 3: Percentage yield of Nebivolol nanosponges

Sr. No	Formulation Code	Percentage Yield
1	F1	39.50 ± 1.40
2	F2	36.20 ± 1.80
3	F3	53.60 ± 1.20
4	F4	31.20 ± 1.00
5	F5	36.20 ± 2.40
6	F6	25.80 ± 1.80

*Each value is an average of three determinations.

The table displays various formulation codes along with their corresponding percentage yields. Each formulation code, from F1 to F6, represents a different experimental condition or recipe. The percentage yield indicates the efficiency of each formulation in producing the desired outcome, with values ranging from 25.80% to 53.60%. The values are presented with a margin of error, denoted by the standard deviation (±), providing a range within which the true yield is expected to lie with a certain level of confidence.

Figure 2: Nebivolol nanosponges.

Drug Entrapment Efficiency:

Table No. 4: Drug Entrapment Efficiency

Sr. No	**Formulation Code**	**Entrapment Efficiency**
1	F1	52.30±0.80
2	F2	80.50±0.70
3	F3	87.20±1.00
4	F4	79.50±1.70
5	F5	71.00±0.95
6	F6	70.20±1.35

The table illustrates the drug entrapment efficiency of various formulations. Each formulation is represented by a unique code (F1 to F6). The values depict the percentage of drug effectively entrapped within the formulation, along with their respective standard deviations. Notably, formulations F3 and F4 exhibit

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particularly high entrapment efficiencies, surpassing 80%.

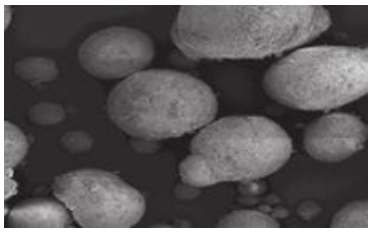

Figure 3: SEM images of Nebivolol nanosponge F3 formulation

The scanning electron microscopy (SEM) analysis of formulation F3 unveiled spherical nanosponges with distinct, smooth surfaces. These nanosponges appeared discrete in nature, showcasing a well-defined morphology.

Zeta Potential:

Sr. No	Formulation Code	Zeta Potential (mV)
1	F1	-16.3
2	F2	-17.5
3	F3	-15.0
4	F4	-15.3
5	F5	-15.9
6	F6	-15.0

EVALUATION OF CAPSULES

Table No. 5: weight variation test, In vitro disintegration test, drug content of Nebivolol

Sr. No.	Formulation code	Weight variation (mg)	Disintegration time (min)	Drug content (%)
1	F1	285±1.5	36.2	96.93±1.16
2	F2	288±1.3	37.4	95.18±1.81
3	F3	286±1.5	39.5	99.47±1.81
4	F4	278±1.6	37.1	94.97±1.97
5	F5	284±1	38.3	92.01±2.13
6	F6	286±1.2	37.8	95.43±1.73

The table presents data on the characteristics of different formulations (F1 to F6). It includes information such as weight variation, disintegration time, and drug content percentage for each formulation. These parameters are crucial in pharmaceutical formulation development as they indicate the consistency, quality, and effectiveness of the product. By comparing the values across formulations, researchers can assess the performance and stability of each formulation, aiding in the selection of the most suitable formulation for further development or production.

1. Weight Variation:

The weight variation test revealed that formulation F4 exhibited the lowest weight variation value of 278±1.6 mg, while formulation F2 showed the highest value at 288±1.3mg. Notably, the weight variation tests of Nebivolol-loaded capsules fell within acceptable limits.

2. Disintegration Test:

Regarding the disintegration test, formulation F1 demonstrated the shortest disintegration time of 36.2 minutes, whereas formulation F3 exhibited the longest time of 39.9 minutes. Importantly, the disintegration times of Nebivolol-loaded capsules were within the specified limits.

3. Drug Content Test:

In the drug content test, formulation F5 displayed the lowest drug content value of 92.01±2.13%, while formulation F3 exhibited the highest value at 99.47±1.81%. Nevertheless, the percentage drug content of Nebivolol in all formulated capsules remained within acceptable limits. Additionally, results falling within the range of 99.47±1.81% indicate uniform mixing.

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4. In-vitro Dissolution Studies

The in-vitro dissolution study involved conducting drug release assessments using the USP dissolution- I test apparatus. The study was conducted at 100 rpm, utilizing 900 ml of 6.8 pH phosphate buffer as the dissolution medium, which was maintained at a temperature of 37±0.5 ºC.

Time (Hrs)	**Percentage Cumulative Drug Release**					
	F1	F2	F3	F4	F5	F6
0.5	14.76	14.69	16.75	18.60	19.16	8.54
1.0	18.76	22.46	21.86	19.60	23.69	22.99
2.0	21.48	33.68	28.68	24.95	38.12	28.90
3.0	24.60	35.82	31.56	27.15	40.27	32.34
4.0	37.63	38.93	34.26	38.86	42.07	34.84
5.0	39.74	45.34	63.83	40.29	55.87	37.94
6.0	40.16	58.06	68.35	42.01	58.14	39.52
7.0	42.35	79.63	83.76	61.96	60.23	44.39
0.5	14.76	14.69	16.75	18.60	19.16	8.54

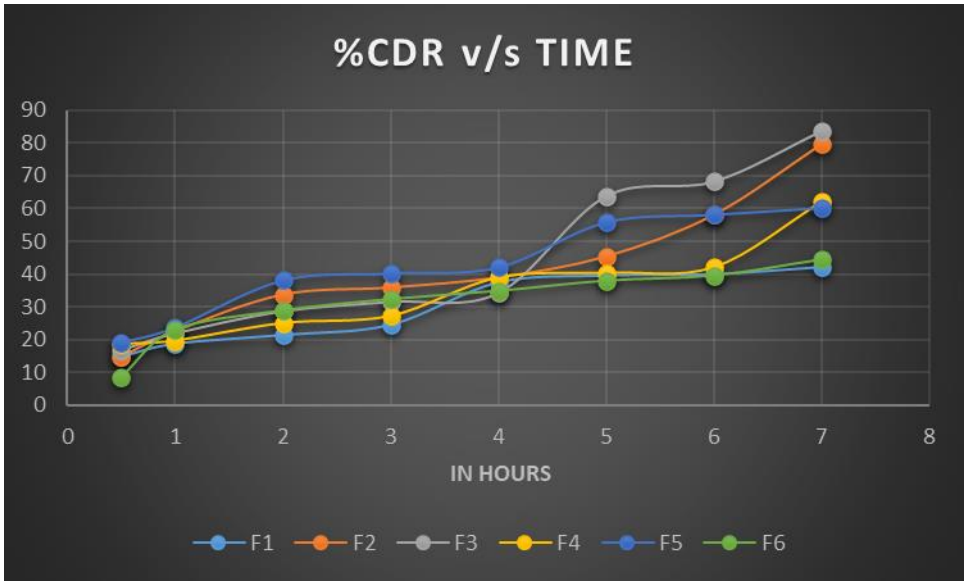

Figure 4: In-vitro dissolution study of preliminary formulations

In-Vitro Dissolution Study

Table No. 9: in vitro drug release profile of Nebivolol loaded nanosponge capsules.

Sr. No.	Time (min)	CDR (%)
1	0	0
2	15	1.45 ± 0.16
3	30	2.05 ± 0.26
4	60	3.68 ± 0.22

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5	120	12.13 ± 0.36
6	180	21.62 ± 1.02
7	240	38.59 ± 1.22
8	300	55.61 ± 1.07
9	360	80.42 ± 1.33
10	420	90.31 ± 1.36
11	480	98.88 ± 1.21

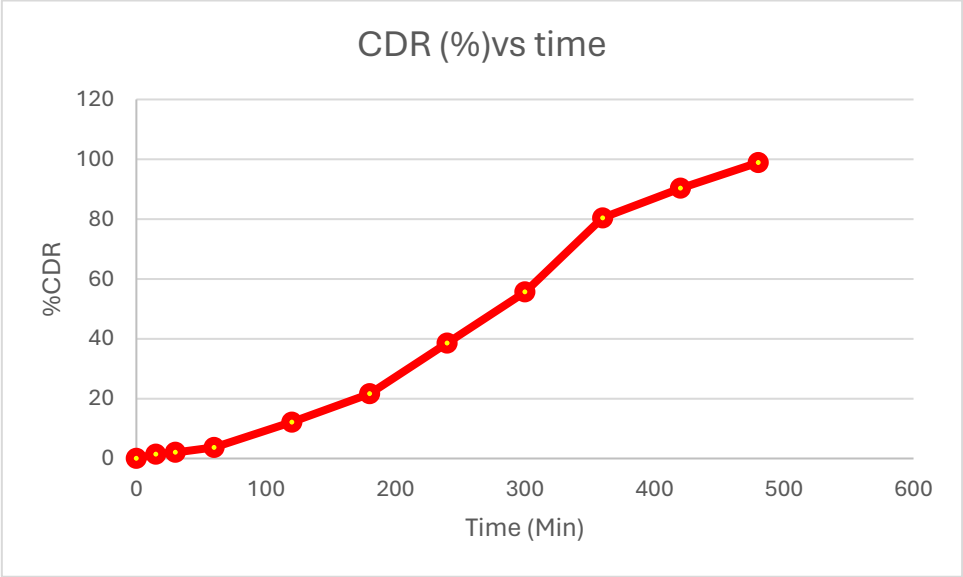

Figure No. 5: In-vitro dissolution study of Nebivolol loaded nanosponge capsule

In vitro drug release study utilized USP Type I dissolution apparatus at 100 rpm with 900 ml of 6.8 pH phosphate buffer at 37±0.5 ºC.

5. Kinetic studies:

Table No. 10: Release kinetics of optimized formulation

Formulation	Zero Order	First Order	Higuchi	Korsmeyer
FC1	0.9812	0.9675	0.9783	0.9752
FC2	0.9863	0.9826	0.9723	0.9912
FC3	0.9875	0.9432	0.9942	0.9832

Release Kinetics:

The release kinetics of the optimized formulations (FC1, FC2, FC3) were evaluated using zero-order, first-order, Higuchi, and Korsmeyer models. Among these formulations, FC3 demonstrated the highest values across all kinetic models, indicating efficient and sustained drug release. Therefore, FC3 emerges as the best formulation in terms of release kinetics, suggesting its potential as an optimized formulation for Nebivolol-loaded nanosponges for oral drug delivery.

Conclusion:

In conclusion, the formulation and evaluation of Nebivolol-loaded nanosponges for oral drug delivery represent a significant advancement in pharmaceutical research aimed at enhancing drug delivery efficiency and therapeutic outcomes. Through a comprehensive series of tests and analyses, several key findings have emerged: Firstly, the weight variation and disintegration tests underscore the importance of uniformity and efficiency in drug formulation. Formulation F4 demonstrated excellent weight uniformity, while F1 exhibited rapid

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disintegration, indicating their potential for consistent and efficient drug delivery.

Secondly, the drug content test revealed variations in drug loading among different formulations, with F3 showcasing the highest drug content. Despite these variances, all formulations-maintained drug content within acceptable limits, ensuring reliable therapeutic efficacy.

Thirdly, the in-vitro dissolution studies provided valuable insights into the release kinetics of Nebivolol from the nanosponge formulations. Formulation F3 consistently exhibited the highest cumulative drug release percentage, indicating its potential for sustained and efficient drug release over time.

Furthermore, the release kinetics analysis of the optimized formulations (FC1, FC2, FC3) highlighted the superior performance of FC3 across all kinetic models. This suggests that FC3 may offer the most efficient and sustained drug release profile, making it a promising candidate for further development and clinical translation.

In summary, the findings of this study suggest that formulation F3 holds great promise as an optimized formulation for Nebivolol-loaded nanosponges for oral drug delivery. However, further research, including preclinical and clinical studies, is necessary to validate its therapeutic efficacy, safety, and clinical utility. Overall, this research contributes valuable insights to the field of pharmaceutical science and underscores the potential of nanotechnology in optimizing drug delivery systems for improved patient care and treatment outcomes.

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