International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 14 Issue 4 ǁ Jul. – Aug., 2025 ǁ PP. 17-26

Preparation And Evaluation of Nebivolol Microcapsule

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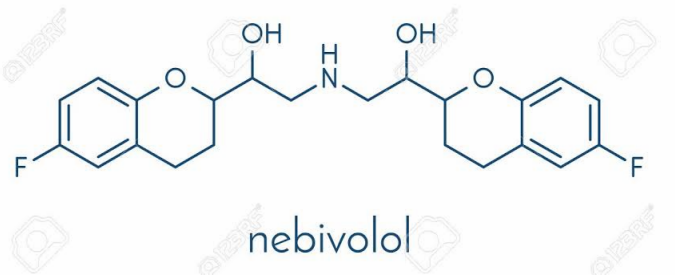
ABSTRACT:
Microencapsulation is an advanced technique used to protect, preserve, and deliver active materials in various industries like pharmaceuticals, cosmetics, fragrances, paints, coatings, detergents, food products, and agrochemicals. Polymeric materials are commonly used as microcapsule shells to provide effective barrier properties and achieve controlled release of the active ingredient inside.
However, these capsules have some significant limitations. They can suffer from unwanted leaching, and the polymers typically used are not biodegradable. Additionally, the energy cost involved in manufacturing microcapsules is an important factor to consider when designing these systems and their production processes. The encapsulation techniques e.g., solvent evaporation phase separation normally involves water insoluble polymers as carrier which require large quantity of organic solvents for the solubilization. As a result, the process becomes vulnerable to safety hazards, toxicity and increases the cost of production making the techniques non reproducible, economically and ecologically at an industrial scale. These concerns demand a technique free from organic solvent.
Thus, the objective of this study was to encapsulate Nebivolol with hydrophilic polymers such as sodium alginate, HPMC& methylcellulose. These polymeric dispersions form a homogenous film on drying and provide a controlled release of the drug from the polymer matrix.
In the present investigation, Nebivolol loaded microspheres prepared by hydrophilic polymers such as sodium alginate, HPMC, and methylcellulose with an objective of developing mucoadhesive microspheres of Nebivolol by Ionotropic gelation method.

Date of Submission: 11-07-2025 Date of acceptance: 24-07-2025

ABBREVIATIONS:
FT-IR Fourier transform infrared spectroscopy
UV-ultraviolet & visible
ML-milli-liters
Nm-nanometers
Pbs- phosphate buffer solution
Pka-dissolution constant
Ril-relative humidity
1%-elimination half-lite
I max - 'time to attain peak concentration
Hcl- hydrochloride
Gm – grams
Hypromellose-hydroxypropyl cellulose

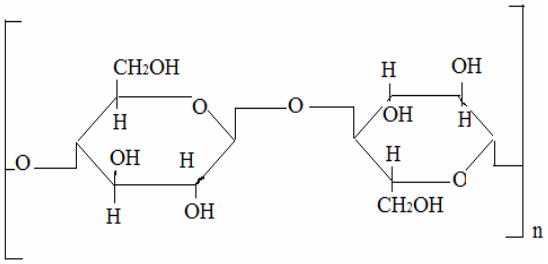
I. PREFORMULATION STUDIES

Structure



Molecular Formula**:** C22H25F2NO4
Molecular Weight**:** 405.5 g/mol
Appearance**:** White to off-white crystalline powder
Melting Point: ~245–250°C
Solubility: Slightly soluble in water; more soluble in methanol and ethanol
pKa: ~9.3
log P: ~3.3–3.4 (lipophilic)
UV λmax: ~281 nm
Thermal Behavior (DSC): Sharp endothermic melting peak at ~245–250°C
Crystallinity (XRD): Sharp diffraction peaks (crystalline nature)

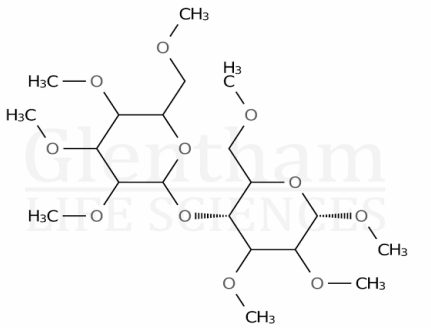
STRUCTURE: HPMC



Molecular Formula: Varies (general repeating unit: C56H108O30 for 2% substitution)
Molecular Weight: Varies depending on grade (typically ~10,000–1,500,000 Da)
Appearance: White or off-white, odorless, tasteless powder
Solubility: Soluble in cold water; forms viscous colloidal solution
pH (1% solution): ~5.5–8.0
Moisture Content: Typically <5%
Glass Transition Temperature (Tg): ~170–180°C
Thermal Stability: Decomposes above 200°C
Crystallinity: Amorphous

Preformulation studies of methyl cellulose:

STRUCTURE: METHYL CELLULOSE
Molecular Formula: Varies (general repeating unit: C6H7O2(OH)3–x(OCH3)x, typically x ≈ 1.8)



Molecular Weight: Varies depending on grade (~10,000–100,000 Da)

Appearance: White, odorless, tasteless powder
Solubility: Soluble in cold water, forming a viscous solution; insoluble in hot water
pH (1% solution): ~5.5–8.0
Moisture Content: Typically <5%
Glass Transition Temperature (Tg): ~150–170°C
Thermal Stability: Decomposes above ~200°C
Crystallinity: Amorphous.

II. METHODOLOGY:

NEBIVOLOL MICROCAPSULES

Microcapsules were prepared by employing Sodium Alginate as the coat material in combination with polymers (drug: SA: polymer at ratios 2:2:1, 2:3:1 and 2:4:1).

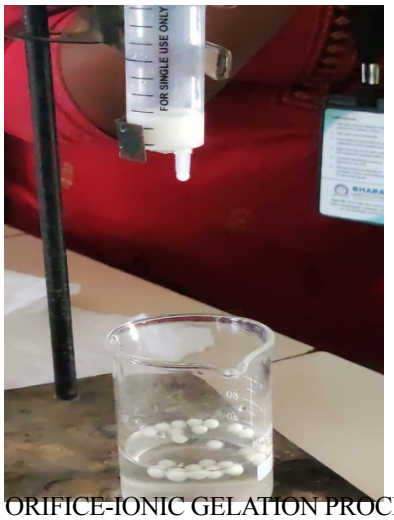


Fig 1: ORIFICE-IONIC GELATION PROCESS.

- Sodium Alginate (2.0 g, 3.0 g and 4.0 g) and polymer (1.0 g) were dissolved in purified water (25 ml) to form a homogenous polymer solution.
- To which core material, Nebivolol (2.0 g), was added and mixed thoroughly to get smooth viscous dispersion.
- Dissolving 10 grams of calcium chloride dihydrate in 100ml of water to get 10%(w/v) solution.
- The resulting dispersion was then added drop wise to 100 ml calcium chloride (10% w/v) solution through a syringe with a needle of No. 22 size.
- The added droplets were retained in the calcium chloride dihydrate solution.
- Filtration with Whatman filter paper the microspheres are obtained.
- Dry the sample in the hot air oven for 20 mins.
- Dried nebivolol microcapsules are obtained.

Fig2: OBTAINED NEBIVOLOL

Fig3: DRIED NEBIVOLOL

EVALUATIONPARAMETERSOFMICROCAPSULES:

FlowProperty: -

The flow properties were investigated by measuring the angle of repose of drug-loaded microcapsulesusingfixed-baseconemethodtoassesstheflowability.Thefixed-baseconemethod, a funnel was secured with its tip at a lcm height (H)above the graph paper that was placed on a flat horizontal surface. Microcapsules were carefully poured through the funnel until the apex of the conical pile just touched the tip of thefunnel. Measurethe height of thepiles (h)and the radiusof the base (o)with ruler.The angle of repose was determined by using the equation, and reported in Table

TAN OR $\theta = Tan^{-1}$

Particle size distribution

Particle size analysis of the microsphers was done by sieving method using Indian Standard Sieves 16,20,30,40,60 and 80#

Bulk Density

r= radius of the base of the pile, cm

Bulk density is the ratio of the microspheres to the bulk volume it occupies, expressed in gm/ml. 5 gm of the beads were weighed and poured into a 100mlmeasuring cylinder and the volume was measured.

Poured bulk density = Mass of microspheres by Volume of packing

Tapped density

Tapped density of microspheres determined by weighed accurately 5 gm of the microspheres were weighed and poured into a 100ml-measuring cylinder and the volume was measured. It was tapped mechanically for 100 times till a constant volume bulk volume obtained.

Tapped density =

SurfaceStudybyScanningelectronmicroscope(SEM):

The surface morphological details of the microcapsules were determined by using a scanning electron microscope (SEM) model JSM, 35CF JEOL, Japan. The samples were dried thoroughly in vacuum desiccators before mounting on brass specimen studies. The samples were mounted on a specimen studies using double sided adhesive tape, and gold-palladium alloy of 120AKness was coated on the sample using spatter coating unit (Model E5100 Polaron, UK) in an argon ambient of 8-10 pascal with plasma voltage about 2Kv and discharge current about 20mA.The sputtering was done for nearly 3minutes to obtain uniform coating on the samples to enable good quality SEM images. The SEM operated at low accelerating voltage of about 15Kv with load current of about 80mA.Thecondenserlenspositionwasmaintainedbetween4.4-5.1.Theobjectivelensaperturehas a diameter of 240 microns and the working distance WD= 39mm.

DrugEntrapmentEfficiency (DEE):

Drug entrapment efficiency of Microcapsules was performed by accurately weighed 50mg of microcapsulesweresuspended100mlofphosphatebufferpH7.2±0.1.Theresultingsolutionwas kept for 24 hours. Next day it was stirred for 15 min and subjected for filtration.After suitable dilution, Nebivolol content in the filtrate was analysed spectrophotometrically at 276nm using Shimadzu 1201 UV. visible spectrophotometer.

The obtained absorbance was plotted on the standard curve to get the exact Concentration of the entrappeddrug.Calculatingthisconcentrationwithdilutionfactorwegetthepercentageofactual drug encapsulated in microcapsules

Thedrugentrapmentefficiencywasdeterminedusingfollowingrelationship:

%DEE= X100

In-Vitro Dissolution Studies:

The physicochemical property of most drugs that has greatest influence on their absorption characteristicsfromtheGITisdissolutionrate."Thedrugisexpectedtoreleasefromthesolid dosageforms(granules,tablets,capsulesetc.) andimmediatelygointomolecularsolution.This process is called as dissolution".

Drug Release Studies: -

Themethodis specifiedin USPfordrugreleasestudywasfollowed: -

Apparatus: -USPXIIIdissolutionratetestapparatusemployingtheroundbottom dissolution vessel and rotating

basket assembly.
AcidStage: -900mlofsimulatedgastricfluidTS(acidbufferpH1.2.
Bufferstage: -900mlofpH6(duodenalfluid)andsimulatedintestinalfluidTS (phosphate buffer pH 7.4.)

Fig 4 8 dissolution USPXIIIRotating basket apparatus

Dissolution Conditions:

Volume of dissolution media	Dilutionfactor	pH condition	Time{h}	StimulatedG1 region
900 ml	10	1.2	2	stomach
900 ml	10	7.4	7	Liversmall intestine

Procedure: -
Microcapsules equivalentto2gofnebivolol andwereevaluatedforin-vitrodissolution studies.ThestudywascarriedoutinaUSPXIIIrotatingbasketapparatus.Dissolutionfluidconsists of900mlofsimulatedgastrointestinalfluidsofincreasingpHnamelypH1.2(-2hr),pH6.0(1hr)and pH7.2 (upto 10 hrs)maintained temperatureare370c±0.5°C and the basket wasrotated at aconstant speed of 75rpm. Liquids of sampleswerewithdrawn afterpredeterminedperiodsoftimeandthesamevolumeoffresh medium wasaddedimmediatelytothetestmedium.Thewithdrawalsampleswerefilteredthrougha0.45µm membrane filter. The drug content was determined in the filtrate after appropriate dilution and analyzed at 276nm spectrophotometrically using Shimadzu 1201 UV-visible spectrophotometer.

Fig 5 UV visible spectrophotometer

Correspondingconcentrationsinthesampleswerecalculatedfromstandardplotandcalculate cumulative percentage of drug release from each formulation.

In vitro wash-off test

The mucoadhesive property of the microspheres was evaluated by in vitro washoff test which is a simple and quick method. pieces of tissue (pig stomach, about 2 x 5 em. and small intestine, about 2 x 15 cm, obtained from slaughter house and stored in Tyrodes solution) were tied onto a plastic slide (about 2 x 15 cm) using rubber bands Microspheres were spread (25 No) onto each wet, rinsed tissue specimen, and counted. Immediately thereafter, the prepared two slides were connected with suitable support onto one of the groves of a USP tablet disintegrating test apparatus, permitting a slow, regular up and down movement (-30min-1) in a test fluid (0.IN HCI, pH 1.2) kept at 37°C. At given intervals, the motor was stopped and number of microspheres still adhering onto the tissue was counted. The results obtained can be used as a measure of bioadhesion(Jeevana et al., 2009).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) study of drug loaded microspheres was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug-excipient compatibility study. The analysis was performed at a rate 50 C min' from 500°C to 2000°C temperature range under nitrogen flow of 25 ml min-!.

Fourier Transforms Infrared Radiation measurement (FT-IR)

The FT-IR spectra acquired were taken from dried samples. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm' resolution. The results were the means of 16 determinations. A quantity equivalent to 2mg of pure drug and drug loaded microspheres were selected separately. Scanning electron microscopy (SEM)

Morphological characterization of the microspheres was done by using Scanning electron microscope (JEOL JSM -5200). The samples were coated to 200A° thickness with gold-palladium using prior to microscopy. Microspheres before dissolution study were only subjected to SEM study.

FTIR analysis measures the range of wavelengths in the infrared region that are absorbed by a material. This is accomplished through the application of infrared radiation (IR) to samples of a material. The sample's ability to absorb the infrared light's energy at various wavelengths is measured to determine the material's molecular composition and structure.

Unknown materials are identified by searching the IR spectrum against a database that has a wide range of reference spectra. Materials can be quantified using the FTIR materials characterization technique as long as a standard curve of known concentrations of the component of interest can be created.

Fourier Transform Infrared Spectroscopy Analysis can be used to identify unknown materials, additives within polymers, surface contamination on a material, and more. The results of the tests can pinpoint a sample's molecular composition and structure.

A simple device called an interferometer is used to identify samples by producing an optical signal with all the IR frequencies encoded into it. The signal can be measured quickly.

Then, the signal is decoded by applying a mathematical technique known as Fourier transformation. This computer-generated process then produces a mapping of the spectral information. The resulting graph is the FTIR spectrum which is then searched against reference libraries for identification.

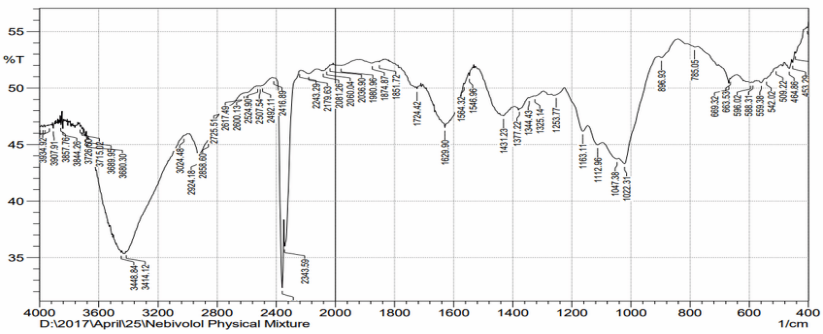


FIG 6 FTIR SPECTRAL GRAPH

III. RESULTS

Fig 6.3 FTIR SPECTRA

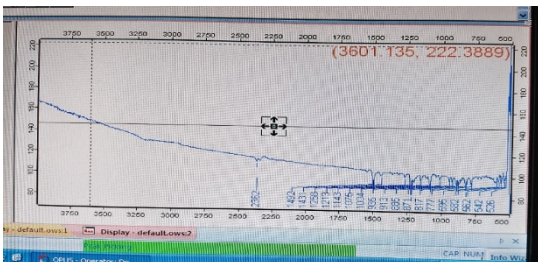


Fig7 PURE DRUG NEBIVOLOL FTIR SPECTRA

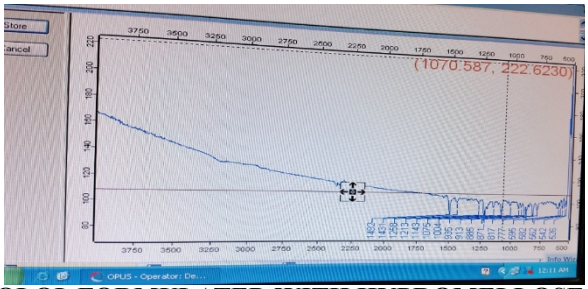


Fig8 NEBIVOLOL FORMULATED WITH HYPROMELLOSE POLYMER

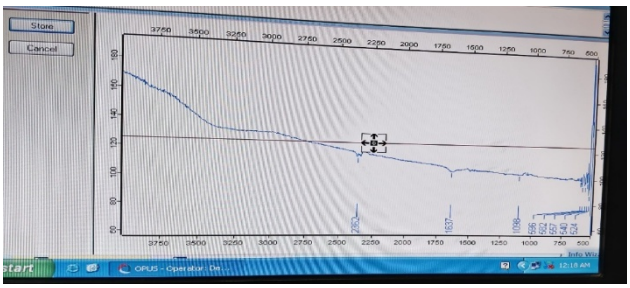


Fig 9NEBIVOLOL FORMULATED METHYL CELLULOSE POLYMER

Table1: Angle of Repose for Nebivolol Microcapsules with HPMC and Methyl Cellulose

Formulation Code	Polymer Used	Angle of Repose (°)	Flow Property
F1	HPMC	28.5 ± 0.4	Excellent
F2	HPMC	30.0 ± 0.5	Good
F3	HPMC	31.5 ± 0.3	Good
F4	Methyl Cellulose	33.8 ± 0.6	Good
F5	Methyl Cellulose	36.2 ± 0.5	Passable
F6	Methyl Cellulose	38.0 ± 0.7	Poor

Table2:Flow property table for the six nebivolol microcapsule formulations using the angle of repose, Carr's index, and Hausner's ratio.

Formulation Code	Polymer	Carr's Index (%)	Hausner's Ratio
F1	HPMC	14.3	1.17
F2	HPMC	16.7	1.20
F3	HPMC	15.2	1.18
F4	Methyl Cellulose	15.9	1.19
F5	Methyl Cellulose	16.7	1.20
F6	Methyl Cellulose	17.1	1.21

Table3: Particle Size Analysis for Nebivolol Microcapsules

Formulation Code	Polymer Used	D10 (µm)	D50 (µm)	D90 (µm)	Average Particle Size (µm)
F1	HPMC	45 ± 2	85 ± 3	120 ± 4	83 ± 3
F2	HPMC	48 ± 3	88 ± 2	125 ± 5	87 ± 4
F3	HPMC	50 ± 2	90 ± 4	130 ± 3	90 ± 3
F4	Methyl Cellulose	52 ± 3	95 ± 4	135 ± 4	95 ± 4
F5	Methyl Cellulose	55 ± 2	100 ± 5	140 ± 6	98 ± 5
F6	Methyl Cellulose	58 ± 3	105 ± 3	145 ± 5	102 ± 4

Table 4 : Bulk Density and Tapped Density for Nebivolol Microcapsules

Formulation Code	**Polymer Used**	**Bulk Density (g/cm³)**	**Tapped Density (g/cm³)**
F1	HPMC	0.42 ± 0.01	0.49 ± 0.02
F2	HPMC	0.40 ± 0.02	0.48 ± 0.01
F3	HPMC	0.39 ± 0.01	0.46 ± 0.01
F4	Methyl Cellulose	0.37 ± 0.02	0.44 ± 0.02
F5	Methyl Cellulose	0.35 ± 0.01	0.42 ± 0.01
F6	Methyl Cellulose	0.34 ± 0.02	0.41 ± 0.02

Table 5 : SEM Analysis of Nebivolol Microcapsules

Formulation Code	**Polymer Used**	**Particle Shape**	**Surface Morphology**	**Observed Size (µm)**	**Porosity**
F1	HPMC	Spherical	Smooth surface	80–100	Low
F2	HPMC	Spherical	Slightly wrinkled	75–95	Low
F3	HPMC	Spherical	Smooth with slight dents	85–105	Low
F4	Methylcellulose	Nearly spherical	Rough surface, porous areas	90–110	Moderate
F5	Methylcellulose	Irregular	Wrinkled and cracked	85–100	Moderate
F6	Methylcellulose	Spherical	Slightly rough, porous	80–110	Moderate

Table6: Drug Entrapment Efficiency (DEE) for Nebivolol Microcapsules

Formulation Code	Polymer Used	DEE (%)
F1	HPMC	92.3 ± 1.2
F2	HPMC	91.0 ± 1.4
F3	HPMC	89.8 ± 1.3
F4	Methyl Cellulose	88.5 ± 1.5
F5	Methyl Cellulose	87.0 ± 1.6
F6	Methyl Cellulose	85.5 ± 1.4

Table: 7 Differential scanning calorimetry

Sample	Thermal Event	Interpretation
Pure Nebivolol	Sharp melting endotherm ~250°C	Crystalline nebivolol
HPMC/Methyl Cellulose	Broad endotherm ~80–120°C	Moisture evaporation, polymer relaxation
Nebivolol-HPMC/MC Microcapsule	Reduced or shifted melting peak	Possible drug–polymer interaction, partial amorphization

Table 8: Standard curve of Nebivolol in 0.1N HCL

Concentration (µg/ mL)	**Absorbance**
0	**0**
10	**0.125**
20	**0.207**
30	**0.319**

40	**0.426**
50	**0.522**

Table 9: Standard curve of Nebivolol in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.121
20	0.231
30	0.336
40	0.437
50	0.541

Table 10: Dissolution Data of Nebivolol microcapsules Prepared with HPMC

TIME (hr)	CUMULATIVE percent of drug released
0	0
1	28.28
2	35.15
3	40.55
4	49.47
5	52.82
6	68.83
7	72.02
8	86.52
9	90.91
10	92.11
11	96.22
12	99.08

Table 11: Dissolution Data of Nebivolol Microcapsules Prepared with Methylcellulose

TIME(hr)	CUMULATIVE percent of drug released
0	0
1	15.61
2	19.59
3	28.12
4	38.45
5	50.61
6	56.18
7	68.92
8	73.29
9	82.72
10	86.24
11	90.17
12	95.54

IV. SUMMARY:

Nebivolol, a beta-blocker used for hypertension and heart failure, was successfully microencapsulated using hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC) as polymer matrices. The aim was to develop sustained-release oral dosage forms that improve patient compliance and maintain therapeutic drug levels over extended periods. Microencapsulation was performed using a solvent evaporation technique, where nebivolol was dispersed with either HPMC or MC in an organic solvent and emulsified in an aqueous phase. After solvent evaporation, microcapsules formed with spherical and uniform shapes.

Characterization studies revealed that HPMC-based microcapsules (formulations F1–F3) generally had smaller particle sizes and superior flow properties compared to MC-based microcapsules (F4–F6). Bulk and tapped density measurements supported these findings, with HPMC microspheres showing better

compressibility and handling characteristics. The angle of repose values for HPMC formulations suggested excellent flow, which is advantageous for further processing like tablet compression.

Drug entrapment efficiency (DEE) was higher for HPMC formulations, typically around 90%, indicating more efficient drug loading compared to MC-based microcapsules. Differential scanning calorimetry (DSC) studies of the microcapsules revealed reduced or broadened melting peaks of nebivolol, suggesting potential drug–polymer interactions or partial amorphization within the polymer matrix. This could enhance the solubility and release profile of the drug.

Overall, HPMC-based microcapsules offered smoother surfaces, smaller particle sizes, and higher DEE than MC-based formulations. These observations highlight the suitability of HPMC for developing nebivolol microcapsules with improved sustained-release properties. The study confirms the potential of these polymer-based microcapsules to optimize nebivolol delivery in controlled-release oral formulation

V. CONCLUSION:

The present study successfully demonstrated the preparation of Nebivolol microcapsules using Methylcellulose and HPMC as polymers through the orifice ion gelation technique. The formulated microcapsules exhibited good encapsulation efficiency, uniform size distribution, and satisfactory flow properties. Evaluation studies confirmed the sustained drug release potential of the microcapsules, with the release rate being influenced by the polymer type and concentration. HPMC-based microcapsules showed a more controlled and prolonged release profile compared to Methylcellulose formulations, making them a promising candidate for sustained drug delivery. Overall, the orifice ion gelation method proved to be a simple, reproducible, and effective technique for the microencapsulation of Nebivolol, enhancing its pharmaceutical properties for improved therapeutic efficacy.

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