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DEVELOPMENT AND CHARACTERIZATION OF MICROSPHERES FROM NATURAL GUMS FOR CONTROLLED DELIVERY OF ANTIHYPERTENSIVE DRUG

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ABSTRACT

The primary objective of this study was to develop and evaluate Propranolol HCl-loaded microspheres using natural polymers such as Carboxymethylated Xanthan Gum (CMX), Guar Gum, and Karaya Gum for sustained and controlled drug delivery. Propranolol HCl is a widely used beta-blocker for treating hypertension, arrhythmias, and epilepsy, but it requires frequent dosing due to its short half-life and low bioavailability. Controlled release formulations are therefore desirable to improve patient compliance and therapeutic efficacy. Microspheres were prepared by the emulsion cross-linking method and evaluated for various micromeritic properties, including particle size, bulk density, tapped density, and flow characteristics. The formulations were characterized for drug loading, entrapment efficiency, and in vitro release profiles. The results indicated that Formulation F4 exhibited the highest drug entrapment efficiency (92.19%) and a drug release profile best fitted to zero-order kinetics, suggesting a sustained and controlled release mechanism. The release followed a non-Fickian diffusion mechanism, indicating a combination of diffusion and polymer relaxation. The stability studies of the selected formulations, F1 and F8, demonstrated that the microspheres remained stable and compatible under the selected temperature and humidity conditions for 60 days. The results suggest that Propranolol HCl-loaded microspheres have the potential to serve as an effective oral controlled drug delivery system, improving the bioavailability, therapeutic efficacy, and patient compliance for chronic conditions requiring long-term medication. This study provides a promising approach to sustained drug release via microspheres, contributing to the field of oral drug delivery systems for improved management of diseases like hypertension.

KEYWORDS: Propranolol HCl, microspheres, controlled release, drug delivery, Natural polymers, Solvent evaporation; drug entrapment, zero-order kinetics.

1. INTRODUCTION

Recent advancements in drug delivery technologies are significantly transforming the landscape of drug discovery and development, fostering a more research-driven pharmaceutical industry on a global scale. Among these advancements, novel drug delivery systems (NDDS) offer numerous advantages, such as enhanced therapeutic outcomes by prolonging drug action and improving efficacy, better patient adherence due to reduced dosing frequency and user-friendly administration methods, and increased targeting efficiency that minimizes systemic side effects by directing drugs to specific sites.[1]

The oral route remains the most widely utilized and preferred method of drug administration, despite the availability of various other routes. Its widespread acceptance is largely due to its convenience, patient compliance, precise dosing, cost-effective manufacturing processes, and favorable product stability over time.[2]

Controlled Drug Delivery[3]

Controlled drug delivery systems are designed to release therapeutic agents at a defined rate, either at a specific site or throughout the body, for a predetermined duration. These systems enable continuous and predictable oral drug release as the formulation progresses through the gastrointestinal tract. In recent years, a new class of drug delivery technologies—termed controlled release systems—has emerged, offering significant advancements. Among these, osmotic pressure-driven delivery systems have gained regulatory approval and are now available on the market. These systems have demonstrated notable advantages in both pharmaceutical performance and clinical outcomes when compared to conventional sustained-release and immediate-release formulations.

Advantages of controlled drug delivery system[4]

Controlled release drug delivery systems have received much attention in past two decades as they overcome the

disadvantages of conventional therapy and offer some benefits like:

- Controlled administration of a therapeutic dose at the desired delivery rate.
- Constant blood levels of the drug, reduction of side effects.
- Minimization of dosing frequency.
- Enhancement of patient compliance.
- To obtain better therapeutic efficacy and diminished toxicity.

Disadvantages of controlled drug delivery system[4]

Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH dependent solubility.

- Poor in vitro-in vivo correlation.
- Possibility of dose dumping due to food.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.

Criteria for the Preparation of microspheres

Preparation of microspheres should satisfy certain criteria:

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

TYPES OF MICROSPHERES

Types of Microspheres

Bioadhesive Microspheres: These microspheres adhere to mucosal surfaces such as buccal, nasal, ocular, or gastrointestinal mucosa. This property enhances the residence time at the site of application, promoting prolonged drug release and improved therapeutic efficacy. Bioadhesion is facilitated by polymers like carbopol, chitosan, and polyacrylic acid.

Magnetic Microspheres: These are engineered to respond to an external magnetic field, allowing site-specific drug delivery. Therapeutic magnetic microspheres are used to deliver anticancer drugs like doxorubicin to liver tumors. Diagnostic magnetic microspheres assist in imaging and detection of metastases using superparamagnetic iron oxide nanoparticles.

Floating Microspheres: Designed to remain buoyant on gastric fluids due to their low bulk density. This enhances gastric retention time and allows for slow, sustained drug release in the upper gastrointestinal tract. They are commonly used for drugs with poor colonic absorption such as ketoprofen.

Radioactive Microspheres: Used in radiotherapy, these microspheres deliver localized radiation to tumors without harming surrounding tissues. They are typically composed of yttrium-90 or other isotopes and are injected into arteries supplying the tumor site.

Methods of Microsphere Preparation

Various techniques are available for microsphere fabrication depending on the desired particle size, drug characteristics, and polymer properties.

Solvent Evaporation Method: Widely used for both hydrophilic and hydrophobic drugs. The drug and polymer are dissolved in an organic solvent, emulsified in an aqueous phase, and the solvent is evaporated under reduced pressure to form microspheres.

Emulsion Cross-Linking: Involves formation of a water-in-oil emulsion followed by chemical cross-linking of the dispersed phase using agents like glutaraldehyde. This method is suitable for heat-sensitive drugs.

Spray Drying: A solution of drug and polymer is sprayed into a hot air chamber, causing rapid solvent evaporation and formation of microspheres. It is a single-step, scalable process.

Coacervation-Phase Separation: This technique involves phase separation of polymer in solution leading to encapsulation of the drug. The process requires careful control of temperature and pH.

Ionotropic Gelation: Used mainly for natural polymers like alginate. The polymer is dropped into a solution containing multivalent ions (e.g., calcium), which causes gelation and microsphere formation.

Freeze Drying (Lyophilization): Often used as a post-processing step to improve stability and shelf-life, especially for protein-loaded microspheres.

2. MATERIALS AND METHODS

2.1. Collection

Propranolol HCl (Yarrow Chem Products, Mumbai) was used, and all other polymers and chemicals employed in the present study were of analytical grade.

Sl No.	Chemical name	Source
1	Propranolol HCl	Yarrow chem products, Mumbai
2	Carboxy methylated Xanthan Gum	Yarrow chem products, Mumbai
3	Guar gum	Finar Chemicals limited, india
4	Karaya gum	Prasol Chemicals Private Limited. india
5	Span 80	S D Fine Chem Limited, Mumbai
6	Glutaraldehyde	Prasol Chemicals Private Limited. india
7	Paraffin Liquid (light & heavy)	Research-lab Fine Chem Industries (Mumbai,India).
8	n-hexane	S D Fine Chem Limited, Mumbai

2.2. Pre-formulation Studies: Pre-formulation studies are a critical step in the rational design and development of pharmaceutical dosage forms. These investigations involve the assessment of the physical and chemical properties of a drug substance alone and in combination with potential excipients. The primary objective is to generate essential data that aids in the development of a stable, effective, and bioavailable formulation that can be reliably manufactured on a large scale. A comprehensive understanding of the physicochemical properties provides valuable insights for formulation design and may indicate the necessity for molecular modification or confirm the suitability of the compound for further development.

The specific objectives of pre-formulation studies include

- Establishing the key physicochemical characteristics of the new drug substance.
- Determining its kinetic drug release profile.
- Evaluating its compatibility with various pharmaceutical excipients.

Accordingly, the pre-formulation studies performed on the obtained sample of Propranolol HCl included physical characterization and compatibility analysis.

2.3. Infrared (IR) Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy was conducted to assess the compatibility between Propranolol HCl and selected excipients. The analysis was performed using a Thermo Nicolet FTIR spectrometer, and spectra were recorded over a wavenumber range of 4000 to 400 cm^{-1}. The samples (pure drug and drug-excipient physical mixtures in a 1:1 ratio) were mixed with potassium bromide (KBr, 200–400 mg) and compressed into discs using a hydraulic press at 5 tons pressure for 5 minutes. Any significant shifts or disappearance of characteristic peaks in the spectra of the physical mixtures, compared to the pure drug, were interpreted as potential interactions.

2.4. Solubility Analysis

Solubility analysis was performed to identify an appropriate solvent system for dissolving Propranolol HCl and the excipients used in the formulation of microspheres. The solubility behavior of the drug in various solvents facilitated the selection of suitable media for both formulation and analytical purposes.

2.5. Melting Point Determination

Melting point determination is a preliminary test used to assess the purity of a drug substance. Even minor impurities can significantly alter the melting point range, often resulting in a decrease and broadening of the temperature interval. The melting point of Propranolol HCl was determined using Thiele's tube apparatus.

2.6. Estimation of Propranolol HCl by UV-Visible Spectrophotometry

A UV-Visible spectrophotometric method was employed for the quantitative estimation of Propranolol HCl. The drug exhibited maximum absorbance at a wavelength of 289 nm in 0.1 N hydrochloric acid (HCl).

Preparation of Stock Solution

An accurately weighed quantity of 100 mg of Propranolol HCl was dissolved in 0.1 N HCl and the volume was made up to 100 mL in a volumetric flask. From this solution, 10 mL was further diluted to 100 mL with 0.1 N HCl to obtain a final concentration of 100 µg/mL, which served as the stock solution.

Standard Calibration Curve

Standard solutions containing 10, 20, 30, 40, and 50 µg/mL of Propranolol HCl were prepared by suitable dilutions of the stock solution with 0.1 N HCl. The absorbance of each solution was measured at 289 nm against 0.1 N HCl as the blank using a UV-Visible spectrophotometer. All measurements were performed in triplicate, and the mean absorbance values were used to construct a calibration curve. A linear regression analysis was conducted to derive the regression equation and correlation coefficient, which were subsequently used for the quantitative estimation of Propranolol HCl in the test samples.

Preparation of Propranolol HCl Microspheres by Solvent Evaporation Technique

Microspheres containing Propranolol HCl were prepared using the solvent evaporation technique with varying drug-to-natural gum ratios of 1:1.15, 1:1.20, and 1:1.25.Initially, the required quantity of natural gum was dispersed in 20 mL of distilled water and allowed to hydrate for 3 hours. Simultaneously, 100 mg of Propranolol HCl was dissolved in 10 mL of methylene chloride. The hydrated gum solution was then added to the drug solution to form a uniform drug–gum dispersion. To this dispersion, 0.5 mL of concentrated sulfuric acid was added to facilitate the formation of a

clear and viscous solution. This mixture was then slowly emulsified into 200 mL of liquid paraffin containing 0.5% w/w Span 80, which acted as the emulsifying agent. The system was stirred mechanically at 1800 rpm for 210 minutes using an overhead mechanical stirrer while maintaining the temperature at 50 °C with the aid of a thermostatically controlled hot plate. Following emulsification, 1.2% w/v dichloromethane was introduced as the encapsulating agent, along with 0.15% w/v glutaraldehyde as the cross-linking agent. Stirring and heating were continued for an additional 2.5 hours to ensure complete evaporation of the aqueous phase and solidification of microspheres. The resultant microspheres were collected by decanting the oil phase and washed thoroughly with distilled water to remove residual surfactant. This was followed by triple washing with 100 mL aliquots of n-hexane to eliminate residual oil and unreacted materials. The washed microspheres were filtered using Whatman filter paper and dried in a hot air oven at 80 °C for 2 hours. The final product—discrete, solid, and free-flowing microspheres—was stored in a desiccator at room temperature until further use.

Formulation of Microspheres

Formulations	Propranolol HCl (mg)	Carboxy methylated Xanthan Gum (CMX)(mg)	Guargum (mg)	Karaya gum (mg)	Liquid Paraffin (ml)	Span 80 (v/v)
F1	40	25	-	25	250	0.75
F2	40	50	-	25	250	0.75
F3	40	75	-	25	250	0.75
F4	40	100	-	25	250	0.75
F5	40	-	25	25	250	0.75
F6	40	-	50	25	250	0.75
F7	40	-	75	25	250	0.75
F8	40	-	100	25	250	0.75

3. Physicochemical evaluations[12]

a) MicrospheresMicromeritic Studies

The prepared microspheres are characterized by their micromeritic properties such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

b) Bulk Density

The bulk density is defined as the mass of powder divided by bulk volume.

The bulk density was calculated by dividing the weight of the samples in grams by the finalvolume in cm

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres before tapping}}$$

c) Tapped Density

Tapped density is the volume of powder determined by tapping by using a measuring cylinder containing weighed amount of sample. The cylinder containing Known amount of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume.

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres before tapping}}$$

d) Carr's Compressibility Index

This is an important property in maintaining uniform weight. It is calculated using following equation.

$$\% \text{ Compressibility Index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} X 100$$

Lower the compressibility values indicate better flow.

e) Hausner's ratio

A similar index like percentage compressibility index has been defined by Hausner. Values less than 1.25 indicate good flow, where as greater than 1.25 indicates poor flow. Added glident normally improves flow of the material under study. Hausner's ratio can be calculated by formula,

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

f) Angle of Repose (θ)

Good flow properties are critical for the development of any pharmaceutical tablet, capsules or powder formulation. It is essential that an accurate assessment of flow properties be made as early in the development process as possible so that an optimum formulation can be quickly identified. Interparticle forces between particles as well as flow characteristics of powders are evaluated by angle of repose. Angle of repose is defined as the maximum angle possible between the surface and the horizontal plane.

$$\tan \theta = h/r \text{ , } \theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height of the pile and, r = radius of the powder cone respectively.

Angle of repose affects particle size distribution, as larger the particle size, it will flow freely and vice-versa. It is a helpful parameter to monitor quality of powdered or granular pharmaceutical formulations. For good

flowing materials, the angle of repose should be less than 30°.

g) Particle Size Determination: The particle size of the microspheres was determined by using optical microscopy method. Approximately 100 microspheres were counted for particle size using a calibrated optical microscope.

h) Morphological Study using SEM: The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron Microscope HITACHI SU 1500, Japan connected with Fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbon followed by Gold.

i) Drug Loading and Drug Entrapment: Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100 mL volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 212 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

$$\text{Drug content} = \frac{\text{Absorbance} \times \text{Bulk Volume} \times \text{Dilution Factor}}{1000}$$

$$\%\ \text{Drug loading} = \text{Drug content} \times 100$$

$$\%\ \text{Drug entrapment} = \frac{\text{Amount of drug actually prsent(DC)}}{\text{Theoretical drug loaded expected}} \times 100$$

J) Percentage yield

$$\%\ \text{yield determined by following equation} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

k) In vitro drug release Study

The prepared microspheres were subjected to *in vitro* drug release sequentially in three different suitable dissolution media. USP type II dissolution apparatus was used. The dissolution medium for the first 2 hr was 900 ml of 0.1 N HCl (pH 1.2) and continued in phosphate buffer pH 6.8 for the next 7 hrs The temperature of dissolution medium was maintained at 37 ±0.5 °C and the basket was rotated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh dissolution medium to maintain sink conditions. The samples were analyzed at 272 nm, for the percentage drug release using an UV Visible double beam spectrophotometer. The release study was performed in triplicates.

Release Kinetics: The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit modelwas selected.

Zero order: Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation:

$$Qt = Qo + Kot$$

First Order Kinetics: To study the first order release kinetics the release rate data were fitted to the following equation.

$$\text{Log } Qt = \log Qo + K1t / 2.303$$

Higuchi Model: Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$Qt = KH \times t1/2$$

Korsmeyer-Peppas Model: To study this model, the release rate data is fitted to the following equation.

$$Mt / M = K.\ tn$$

Hixson–Crowell Model: To study the Hixson–Crowell model, the release rate data are fitted to the following equation.

$$Wo\ 1/3 - Wt\ 1/3 / Ks\ t$$

4. RESULTS AND DISCUSSION

IR Spectroscopy: The FT-IR spectrum of the Propranolol HCL pure drug was found to be similar to the standard spectrum of Propranolol HCL as in I.P. The individual FT-IR spectra of the pure drug Propranolol HCL, as well as the combination spectra of the drug and polymers. All the characteristic of peaks of Propranolol HCL were present in spectrum of drug and polymers, indicating compatibility between drug and polymers.

Solubility analysis: The Propranolol HCL is freely soluble in water; sparingly soluble in methanol; practically insoluble in acetone. It was soluble in 0.1N HCL (pH 1.2) and phosphate buffer (pH 6.8). Solubility analysis is important because the drug has to dissolve in the solvents and also in thedissolution medium used.

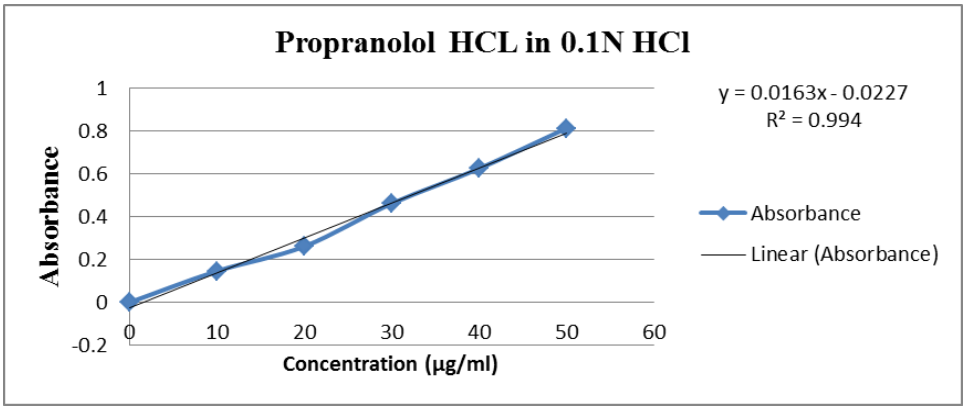
Melting point determination: The melting point of the obtained drug sample was found to be 161^0C which is within thereported range of 160-162^0C. It complies with the purity of the drug sample.

Determination of λmax in 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8): Propranolol HCL was dissolved in 0.1N HCL(pH 1.2) and phosphate buffer(pH 6.8), further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (shimadzu 1800) in the range from

200 to 400 nm, using pH 1.2 and pH 6.8 as blank. The λmaxof drug was found to be 284 nm.

Standard calibration curve of Propranolol HCL: The concentration and absorbance values of the solutions are shown in Table and the calibration curve in The present analytical method obeyed Beer's law in the concentration range of 10-50 mg/mL and suitable for the estimation of propranolol HCl from different sample solutions. The correlation coefficient (r) value was found to be 0.999 in O.IN HCl, indicated a positive correlation between the concentration of propranolol HCl and the respective absorbance values. The regression line describing the relation between concentration and absorbance was as follows: y = 0.0208X + 0.0002 Where, y is the absorbance at 289 nm and x is the concentration of propranolol HCl in |ig/mL

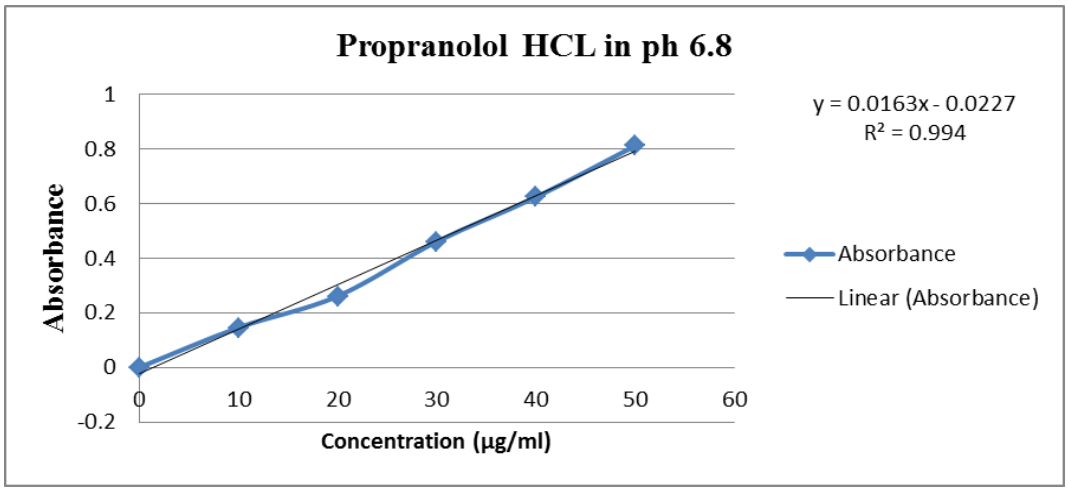
Sl No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.206±0.0020
3	20	0.417±0.002
4	30	0.627±0.002
5	40	0.835±0.004
6	50	0.997±0.003



Standard Calibration Curve of Propranolol HCL in 0.1N HCl

Concentration vs. absorbance values of propranolol HCl in 0.1 N HCl pH 6.8 Phosphatebuffer at 284 nm

Sl No	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.146
3	20	0.261
4	30	0.461
5	40	0.624
6	50	0.812



Standard Calibration Curve of Propranolol HCL in pH 6.8

Micromeritic Properties: The results of all formulations F1 to F9 of Propranolol HCL microsphere are shown in Table 10: Which were evaluated for variable parameters such as bulk density, tapped density, % Compressibility index, Hausner's ratio and angle of repose. The % Compressibility index was in the range of 11-18 for all

the formulations F1 to F9 indicating good flow property. The values of angle of repose for formulations F1,F2, F5 and F6 was found to be in the range of 25-30 which indicated the good flow potential.

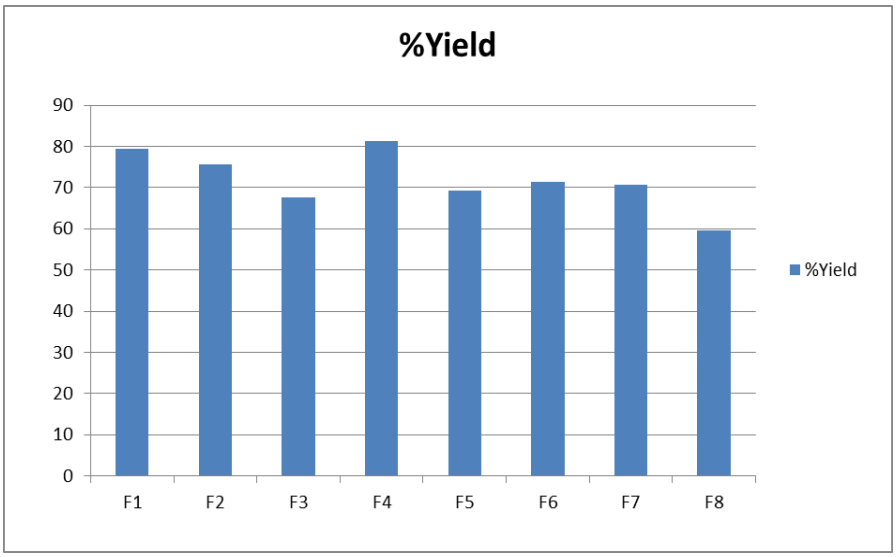
Micromeritic properties of Propranolol HCL microspheres

Formulation Code	Bulk Density (g/cm$^{3)}$	Tapped Density(g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.5426±0.005	0.5216±0.009	14.65±1.12	1.158±0.02	26.93±0.23
F2	0.6986±0.008	0.5184±0.004	15.24±1.22	1.166±0.05	25.74±0.24
F3	0.6234±0.015	0.6423±0.008	17.16±1.82	1.193±0.011	32.94±0.17
F4	0.5813±0.009	0.5436±0.005	13.94±1.42	1.131±0.019	33.81±0.14
F5	0.5418±0.013	0.6813±0.001	13.36±1.22	1.141±0.02	28.67±0.36
F6	0.6268±0.011	0.7316±0.012	14.56±1.32	1.156±0.08	27.08±0.16
F7	0.5576±0.014	0.5348±0.008	13.47±1.32	1.142±0.03	33.61±0.64
F8	0.7154±0.013	0.5485±0.011	16.24±1.41	1.229±0.023	34.54±1.07

Particle Size Analysis: Average particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer. The mean particle size for the formulation F1 to F4 containing Xanthan gum was found to be in range from 278±7.14µm to 913±6.35µm. For formulation F4 to F9 containing Guar gum the mean particle size was found to be in range from 572±12.51µm to 991±10.73 µm respectively. With increase in polymers concentration in the microspheres from F1 to F9, the particle size of microspheres increases respectively. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency.

Average Particle Size of Propranolol HCL Microspheres

Formulation code	Average particle size (µm)±SD
F1	913±6.35
F2	940±11.28
F3	456±12.42
F4	278±7.14
F5	991±10.73
F6	743±12.24
F7	650±8.69
F8	590±11.46

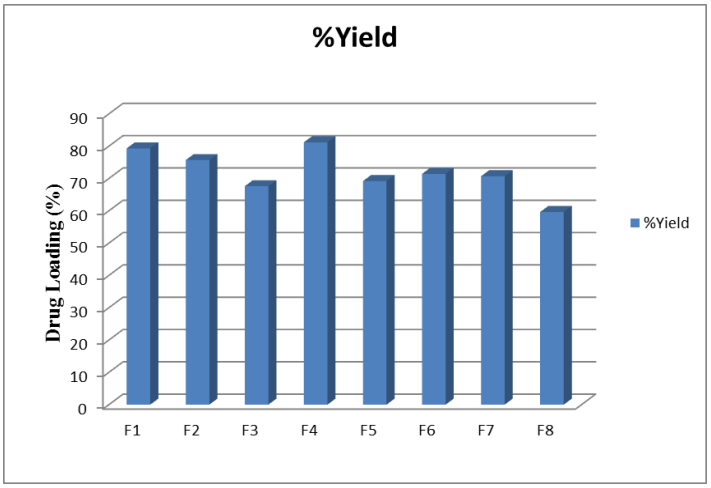


Comparison of Avg. Particle Size of the Prepared Microspheres

Drug Loading and Drug Entrapment

Formulation Code	Actual Drug Content (mg)	Theoretical Drug Content (mg)	Total Weightof Microspheres (mg)	% Drug Loading	%Drug Entrapment
F1	19.01	25.01	50	21.12	78.21
F2	13.25	16.71	50	27.51	82.52
F3	11.29	12.49	50	22.59	90.49
F4	19.61	25.02	50	38.46	92.19
F5	13.91	16.76	50	37.89	73.62
F6	11.43	12.52	50	32.76	78.45

F7	19.69	25.1	50	29.54	84.81
F8	14.23	16.69	50	28.22	86.90



Comparison of % Drug Loading of the Prepared Microspheres

***In-vitro* drug release studies**

Dissolution studies on all the Eight formulations of Propranolol HCL microspheres were carried out using a USP dissolution apparatus Type II. 0.1N HCl (pH 1.2) and pH 6.8 was used as the dissolution medium. The *in-vitro* drug release data of different formulations are shown in Table. No.14 and Figure.No.13. The cumulative percent drug release after 12 hours was found to be in the range of 81.203, 79.138,76.498 and 82.641% for the formulations F1, F2, F3 and F4 respectively whereas cumulative percent drug release after 12 hours was 71.658, 80.754,74.744,69.903 % for formulations F5 to F8 respectively. The cumulative drug release significantly decreased with increase in polymer concentration. The increased density of the polymer matrix at higher concentrations results in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix.

In–vitro drug release for Propranolol HCL Microspheres in 0.1N HCL (pH 1.2)and (pH 6.8) phosphate buffer

Time (hrs)	CUMULATIVE % DRUG RELEASE OF FORMULATION							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	18.215	16.557	14.472	17.215	13.959	16.959	16.553	14.141
2	27.410	25.765	24.433	35.765	22.537	26.557	20.535	18.370
3	35.714	32.406	31.723	42.406	29.126	39.146	25.844	23.465
4	46.375	38.389	37.073	48.389	31.821	38.811	31.817	29.634
5	53.038	43.050	41.369	53.050	34.497	44.477	32.497	31.050
6	58.590	54.998	49.069	64.998	49.073	51.063	39.136	39.360
7	62.606	62.318	53.716	72.318	45.702	56.712	54.469	48.156
8	69.620	68.331	65.697	76.331	64.340	63.350	61.803	59.691
9	76.663	72.994	69.020	79.994	67.619	71.669	68.447	66.313
10	81.203	79.138	76.498	82.641	71.658	80.754	74.744	69.903

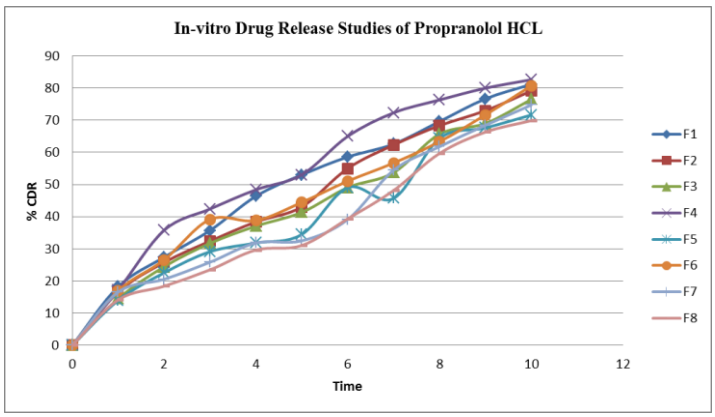


Figure Comparative *In-vitro* Dissolution Profile of Propranolol HCL Microspheres

Release Kinetics: Model Fitting Release Profile of Propranolol HCL Microspheres

Formulation code	Mathematical Models (Kinetics)						Best Fit Model
	Korsmeyer–Peppas		Higuchi	Hixson–Crowell	First order	Zero order	
	R^2	N	R^2	R^2	R^2	R^2	
F1	0.929	0.456	0.961	0.966	0.889	0.983	Zero order
F2	0.935	0.449	0.968	0.966	0.899	0.984	Zero order
F3	0.923	0.441	0.949	0.908	0.867	0.952	Zero order
F4	0.939	0.439	0.974	0.973	0.984	0.994	Zero order
F5	0.949	0.454	0.974	0.966	0.913	0.988	Zero order
F6	0.935	0.421	0.961	0.942	0.887	0.966	Zero order
F7	0.969	0.446	0.990	0.989	0.934	0.991	Zero order
F8	0.979	0.410	0.988	0.988	0.947	0.992	Zero order

5. SUMMARY AND CONCLUSION

The present study successfully formulated Propranolol HCl-loaded microspheres using natural polymers such as Carboxymethylated Xanthan Gum (CMX), Guar Gum, and Karaya Gum via the emulsion cross-linking method. A total of eight formulations were prepared and evaluated for critical parameters including particle size, drug loading, entrapment efficiency, and percentage yield.

- FTIR study indicated that the drug is compatible with all the excipients.
- Among the formulations, Formulation F4 demonstrated the highest drug entrapment efficiency (92.19%) and satisfactory particle size (278 µm), making it suitable for controlled oral drug delivery.
- However, its lower yield and drug loading compared to other batches indicate a need for further process optimization. On the other hand, Formulation F1 and F5 offered a more balanced profile with high drug loading (38.46% and 37.89%) and good production yields (79.31% and 81.19%), though with slightly larger particle sizes.
- The micromeritic evaluation of the prepared Propranolol HCl microspheres revealed acceptable flow and packing characteristics. The **bulk density** of the formulations was found to be in the range of **0.42 to 0.56 g/cm³,** while the **tapped density** ranged **from 0.50 to 0.64 g/cm³.** The calculated **Carr's Index** varied between **12.5% and 21.8%,** indicating fair to good flow properties. Similarly, the **Hausner ratio** values were observed between **1.14 and 1.28,** which further supports acceptable flowability and compressibility.
- Overall, the results suggest that the selection of polymer type and ratios significantly affects the performance of microsphere formulations.
- The in vitro drug release profiles of formulations F1 to F8 were analyzed using various kinetic models to understand the release mechanism. Among the models tested, all formulations showed the best fit to the **zero-order kinetic model**, indicating a consistent and controlled release of the drug over time, independent of concentration. Furthermore, the release mechanism was found to follow a **non-Fickian (anomalous) diffusion**, suggesting that the drug release was governed by a combination of both **diffusion** and **polymer relaxation or erosion** processes.
- The study concludes that microspheres offer a promising approach for sustained and controlled release of Propranolol HCl, potentially improving therapeutic outcomes and patient compliance in chronic conditions like hypertension.

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