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Preparation and Evaluation of Anti-Viral Drug Entrapped Microspheres by Using Natural Gums as Rate Controlling Agent in Enhancing Bioavailability

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ABSTRACT

This study explores the preparation and assessment of microspheres formulated from natural gums, aiming for effectiveness, biodegradability, availability, and cost efficiency, using Lamivudine as the model drug. Lamivudine, with a biological half-life of 4 to 6 hrs and 86% of bioavailability, is known for treating HIV and also for chronic Hepatitis B. The microspheres are developed via solvent evaporation technique employing xanthan gum and guar gum. Compatibility was confirmed through FTIR analysis, showing no significant changes in characteristic peaks of Lamivudine and excipients across formulations. Particle size variation, surface morphology of particle, % of yield, % of drug entrapment efficiency, in-vitro drug release profiles, release kinetics, and stability were evaluated. The microspheres were pale yellow and free-flowing, with micrometric properties meeting standards for good flow. Scanning Electron Microscopy (SEM) revealed spherical shapes ranging from 100µm to 200µm. In-vitro drug release studies indicated a reduction in release rate with increasing xanthan gum concentration, following zero-order kinetics, suggesting diffusion-controlled release and stability. In conclusion, microspheres utilizing xanthan gum present a viable method for achieving controlled release of Lamivudine, potentially enhancing bioavailability and reducing dosing frequency.

Keywords: Lamivudine; Xanthan gum; microspheres; Solvent evaporation; and oral controlled drug delivery.

INTRODUCTION

Emerging DDT's are transforming drug discovery and development, fostering R&D-centric pharmaceutical industries to accelerate global progress. Novel drug delivery systems (NDDS) offer several advantages, including enhanced therapy through increased efficacy and prolonged drug action, improved patient adherence due to reduced dosing frequency and more convenient administration routes, and better site-specific delivery to minimize adverse effects[1,2].

Among various drug administration routes, the oral route is the most widely used. Despite the availability of different administration methods, oral delivery remains the preferred option. This preference is due to several factors such as patient acceptance, easy to administration, precise dosing, cost-effective manufacturing, and generally improved shelf-life of oral products.

Controlled Drug Delivery[3]

CDD refers to systems that release a drug at a predetermined rate, either locally or systemically, over a while. This approach enables continuous oral drug delivery with predictable and reproducible kinetics throughout the gastrointestinal tract. Recently, a new generation of pharmaceutical products known as controlled-release drug delivery systems has received regulatory approval. Often activated by osmotic pressure, these systems offer significant pharmaceutical and clinical advantages over traditional sustained-release and immediate-release products.

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Microencapsulation is a technique where solids, liquids, or gases are enclosed within microscopic particles by forming thin coatings of wall material around the substances. This method offers various strategies for delivering therapeutic agents to targeted sites in a sustained release manner. One effective approach is using microspheres as drug carriers[4,5].

Applications of Microencapsulation[6,7]:

- It is extensively used in designing controlled-release and sustained-release dosage forms.
- To mask the unpleasant taste of drugs such as Paracetamol and Nitrofurantoin.
- Many drugs are microencapsulated to minimize gastric and gastrointestinal tract irritation.
- Sustained release formulations of Aspirin have been shown to cause significantly less gastrointestinal bleeding compared to conventional preparations.
- Liquids can be transformed into a pseudo-solid state for easier handling and storage.

Microspheres[8,9]

Microspheres are solid, roughly sphere-shaped particles ranging from 1 to 1000µm in size. These are composed of polymeric, waxy, or any other protective type of materials that which can be easily biodegradable synthetic polymers or modified natural products like starches, gums, proteins, fats, and waxes. The choice of solvents for dissolving the polymeric materials depends on the solubility of both the polymer and the drug, as well as process the safety and economic considerations. Microspheres were characterized by their small size and large surface-to-volume ratio. At their smaller sizes, they exhibit colloidal properties, making their interfacial properties highly significant and often influencing their activity.

TYPES OF MICROSPHERES[10]

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
6. Biodegradable polymeric microspheres
7. Synthetic polymeric microspheres

Different methods of microsphere manufacturing are[11]

1. Spray Drying
2. Solvent Evaporation
3. Wet Inversion Technique
4. Hot Melt Microencapsulation
5. Polymerization techniques

- Normal polymerization
- Interfacial polymerization

6. Solvent extraction.

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METHODOLOGY[12,13,14,15,16,17,18]

PRE-FORMULATION DETERMINES:

Pre-formulation testing marks the initial phase in the systematic development of drug dosage forms. This process involves investigating the physical and chemical properties of a drug substance both alone and in combination with excipients. The primary objectives of pre-formulation testing are:

1. To identify and establish the essential physicochemical characteristics of a new drug substance.
2. To determine the drug's kinetic release rate profile.
3. To assess the drug's compatibility with various excipients.

Pre-formulation studies typically encompass physical tests and compatibility studies on drug samples.

IR Spectroscopy

FT-IR spectroscopy evaluated the compatibility between the drug and its excipients. Infrared spectroscopy analysis was performed using a Thermos Nicolet FTIR, with spectra recorded in the 4000 to 400 cm-1 range. The samples, consisting of 1:1 drug-drug-excipient mixtures, were combined with KBr (200-400 mg) and pressed into disks under 5 tons of pressure for 5 minutes using a hydraulic press. Drug-excipient interactions were assessed by examining any shifts in the characteristic peaks of the drug in the spectra of the physical mixtures.

Determination of λmax

Lamivudine was dissolved in 0.1N HCL and phosphate buffer pH 6.8, further diluted with the same and scanned for maximum absorbance in a dual-beam UV spectrophotometer (Shimazu 1800) in the range from 200 to 400 nm, 0.1N HCL and phosphate buffer pH 6.8 as blank.

Standard Calibration Curve of Lamivudine

To prepare the first stock solution, 100 mg of lamivudine was accurately weighed and dissolved in 100 mL of 0.1 N HCl (pH 1.2) to achieve a 1000 µg/mL concentration. From this solution, 1 ml was pipetted into a 100 ml volumetric flask and diluted with 0.1 N HCl (pH 1.2) to form a second stock solution with a concentration of 10 µg/ml. Aliquots of the second stock solution were further diluted with pH 1.2 solution to obtain final concentrations of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, and 30 µg/ml. The absorbance of these solutions was measured using a two-beam UV spectrophotometer at 270 nm with a pH 1.2 solution as a blank. This procedure was repeated using phosphate buffer pH 6.8. Absorbance values were recorded and calibration curves were plotted. The maximum absorbance obtained from the plot was taken as λmax for the pure drug.

Table 01: Formulation of Microspheres

Formulation	Drug (mg)	Xanthan Gum (mg)	Guar Gum (mg)	Liquid Paraffin (ml)	Span 80 (v/v)
F1	100	15	-	200	0.5
F2	100	20	-	200	0.5
F3	100	25	-	200	0.5
F4	100	30	-	200	0.5
F5	100	-	15	200	0.5
F6	100	-	20	200	0.5
F7	100	-	25	200	0.5
F8	100	-	30	200	0.5
F9	100	-	35	200	0.5

Preparation of Lamivudine microspheres by Solvent evaporation technique [18,19]

Preparation of Microspheres

Microspheres were formulated using different ratios of drug to natural rubber (1:1.15, 1:1.20, 1:1.25). Initially, the gums were hydrated in 20 mL of water for 3 hours. A weighed amount of the drug (100 mg) was dispersed in 10 mL of methylene chloride and

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then mixed with an aqueous gum solution. This mixture of drug and gum was acidified with 0.5 ml of concentrated sulfuric acid to form a clear viscous solution.

The resulting solution was then emulsified to an oil phase by pouring into 200 mL of liquid paraffin containing 0.5% w/w. Span 80, emulsifying agent. This mixture was stirred mechanically at 1800 rpm for 210 minutes using a stirrer while heating to 50°C on a hot plate. 1.2% w/v was added to facilitate encapsulation. of dichloromethane together with 0.15% wt/vol. of glutaraldehyde as a cross-linking agent. Stirring and heating were continued for 2.5 hours until the aqueous phase was completely evaporated.

After this process, the oil phase was decanted and the collected microspheres were washed with water to remove residual surfactant and then washed three times with 100 mL aliquots of n-hexane. The microspheres were then filtered through Whatman filter paper, and dried in an oven at 80 °C for 2 h to obtain discrete, solid, free-flowing microspheres, which were then stored in a desiccator at room temperature.

EVALUATION OF LAMIVUDINE MICROSPHERES[20,21,22,23,24]

Micromeritic 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.

1. Bulk Density
2. Tapped Density
3. Carr's Compressibility Index
4. Hausner's ratio
5. Angle of Repose (θ)

Particle Size Determination[25,26]: The particle size of the microspheres was determined using the optical microscopy method. Approximately 100 microspheres were counted for particle size using a calibrated optical microscope.

Morphological Study using SEM[27,28]: The morphological study was performed using a scanning electron microscope (SEM). The microspheres were scanned and examined under a HITACHI SU 1500, Japan fine-coated, JEOL JFC-1100E ion sputter electron microscope. The sample was placed on a copper sample holder and sputtered with carbon and then with gold.

Drug Loading and Drug Entrapment[29,30,31,32,33]: Microspheres containing the equivalent of 50 mg of the drug were selected for evaluation. To determine the amount of entrapped drug, the microspheres were crushed and repeatedly extracted with aliquots of 0.1N HCl (pH 1.2). The combined extracts were transferred to a 100 ml volumetric flask and the volume was adjusted with 0.1 N HCl (pH 1.2). The solution was then filtered and the absorbance was measured spectrophotometrically (UV 1700, Shimadzu, Japan) at 212 nm against an appropriate blank, after appropriate dilution. The amount of drug loaded and entrapped in the microspheres was calculated according to the following formulas:

$$\% \text{ Drug loading} = \frac{\text{Weight of the drug loaded in the microspheres(DC)}}{\text{Total weight of the microspheres}} \times 100$$

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

(DC- Actual Drug Content)

Percentage yield[34]

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

In vitro drug release Study [35,36,37,38]

The prepared microspheres underwent in vitro drug release testing using a USP type II dissolution apparatus. The dissolution process was conducted in three sequential media: initially, 900 ml of 0.1 N HCl (pH 1.2) for the first 2 hours, followed by phosphate buffer (pH 6.8) for the subsequent 7 hours. The dissolution temperature was kept at 37 ± 0.5°C, with the basket rotating at 50 rpm. At predetermined intervals, 5 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium to ensure

sink conditions. The withdrawn samples were analyzed at 272 nm using a UV-visible double beam spectrophotometer to determine the percentage of drug released. This release study was conducted in triplicate to ensure accuracy.

Dissolution studies[39,40,41,42]:

Apparatus: LABINDIA USP Type II

Dissolution media: 0.1 N HCl (pH-1.2)

Speed: 100 rpm

Volume of medium: 900 ml Aliquots taken at each time interval-5 mL

Temperature: 37±0.5°C

Wavelength: 272 nm

Release Kinetics[43,44,45]: The matrix systems were reported to follow the release rate of Peppas and the diffusion mechanism for drug release. To analyze the release mechanism and release rate kinetics of the dosage form, the obtained data were fitted to zero-order, first-order, Higuchi matrix, Peppas and Hixson Crowell models. In this comparison of the obtained R-values, the most appropriate model was selected[46,47,48].

1. Zero Order Kinetics
2. First Order Kinetics
3. Higuchi Model
4. Korsmeyer-Peppas Model
5. Hixson–Crowell Model

Stability Studies[49,50]

Drug stability refers to the capacity of a formulation to maintain its physical, chemical, therapeutic, and toxicological properties within specified limits throughout its shelf life. Stability testing aims to evaluate how the quality of a drug substance or product changes over time when exposed to various environmental factors such as temperature, humidity, and light. This testing also helps establish appropriate storage conditions.

According to ICH guidelines, stability studies must specify the duration and storage conditions. For accelerated stability testing, conditions of 40°C with 75% relative humidity (RH) for six months are commonly used. In this study, accelerated stability testing of the optimal formulations was conducted in accordance with these ICH guidelines.

Procedure: In this study, a stability study was conducted for up to 60 days for selected formulations. The selected formulations were analyzed for physical appearance, drug entrapment and in vitro release study.

RESULTS AND DISCUSSION

IR Spectroscopy:

The FT-IR spectrum of the pure lamivudine drug was found to be similar to the standard.

lamivudine spectrum as in I.P. Individual FT-IR spectra of lamivudine pure drug, pure drug & xanthan gum and guar gum.

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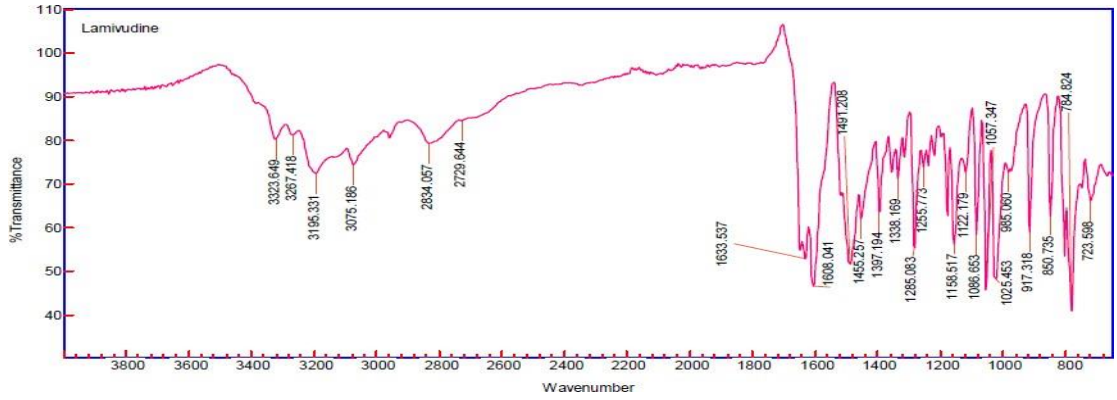

Figure 01: IR Spectrum of pure drug Lamivudine

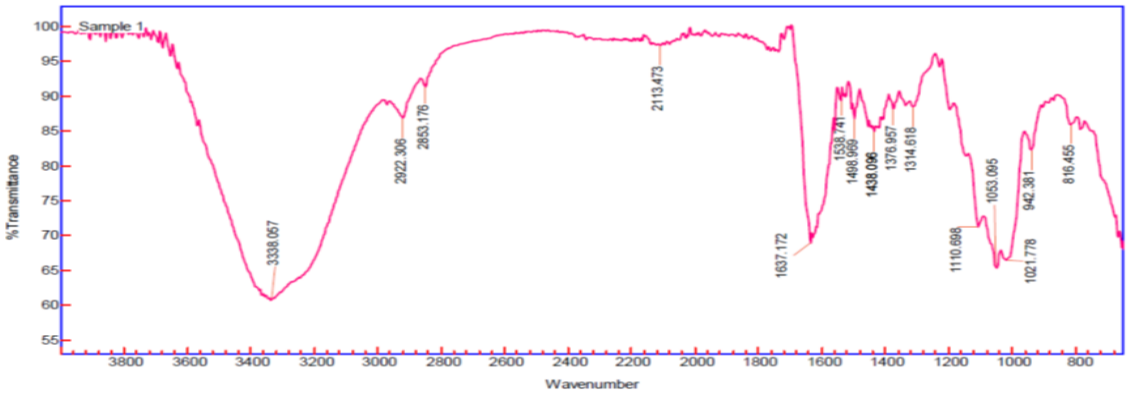

Figure 02: IR Spectrum of Lamivudine with xanthan gum + guar gum

Micromeritic Properties: Table 10 presents the results for all formulations (F1 to F9) of Lamivudine microspheres, evaluated across various parameters including bulk density, tapped density, % Compressibility Index, Hausner's Ratio, and Angle of Repose. The % Compressibility Index for these formulations ranged from 11 to 18, suggesting that all formulations exhibit good flow properties. The Angle of Repose values for formulations F1, F2, F5, and F6 were between 25 and 30 degrees, indicating favorable flow characteristics.

Table 02: Micromeritic properties of Lamivudine microspheres

Formulation Code	Bulk Density ($g/cm^{3)}$	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	The angle of Repose (θ)
F1	0.4354±0.004	0.5211±0.008	13.58±1.22	1.162±0.03	26.98±0.24
F2	0.4887±0.009	0.5686±0.005	14.36±1.33	1.159±0.04	25.75±0.25
F3	0.5554±0.016	0.6211±0.009	16.21±1.26	1.183±0.012	32.95±0.18
F4	0.4716±0.008	0.5365±0.006	11.88±1.35	1.141±0.018	33.83±0.15
F5	0.5420±0.014	0.622±0.002	12.22±1.05	1.145±0.03	28.68±0.37
F6	0.6201±0.011	0.7211±0.013	13.42±1.03	1.158±0.09	27.09±0.17
F7	0.4654±0.016	0.5198±0.009	12.35±1.22	1.146±0.04	33.63±0.65
F8	0.4109±0.018	0.5798±0.012	15.19±1.04	1.230±0.024	34.55±1.08
F9	0.5446±0.017	0.6541±0.013	15.39±0.85	1.179±0.027	37.13±1.52

Particle Size Analysis: The average particle size of the microspheres, measured using optical microscopy with a stage micrometer and ocular micrometer, is summarized in Table 11 and illustrated in Figure 8. For formulations F1 to F4, which utilized Xanthan gum, the mean particle size ranged from 278 ± 7.14 µm to 913 ± 6.35 µm. In contrast, for formulations F4 to F9 that used Guar gum, the mean particle size varied from 572 ± 12.51 µm to 991 ± 10.73 µm. As the concentration of polymers increased from F1 to F9, the particle size of the microspheres also increased. This growth in particle size is attributed to the increased viscosity of the polymer solution at higher concentrations, which reduces the efficiency of stirring and consequently affects the particle size.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 113-126. ijppr.humanjournals.com ISSN: 2349-7203

Table 03: Average Particle Size of Lamivudine Microspheres

Formulation code	Average particle size (µm)±SD
F1	920±6.55
F2	938±11.31
F3	448±12.36
F4	282±7.18
F5	986±10.68
F6	752±12.32
F7	648±8.71
F8	588±11.52
F9	563±12.42

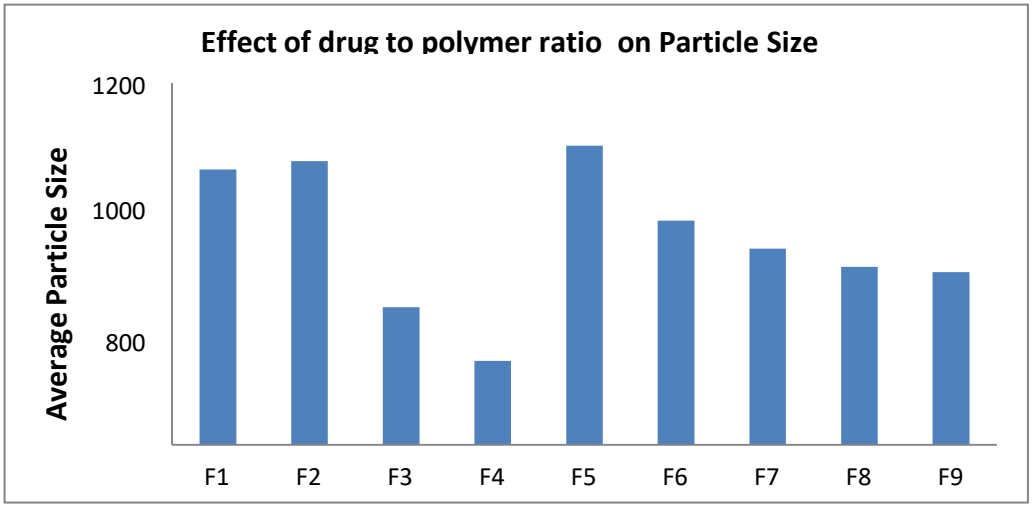

Figure 03: Comparison of Avg. Particle Size of the Prepared Microspheres

Scanning Electron Microscopy: The shape and surface morphology of the microspheres were examined using a Hitachi SU 1500 scanning electron microscope (SEM) from Japan. The SEM analysis indicated that all prepared microspheres were spherical. Microspheres containing Guar gum were smooth, spherical, and exhibited slight aggregation, whereas those made with Xanthan gum appeared porous, rough, and more distinctly spherical. Scanning electron photomicrographs of formulations F1 and F5 are depicted in Figure 9.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 113-126. ijppr.humanjournals.com ISSN: 2349-7203

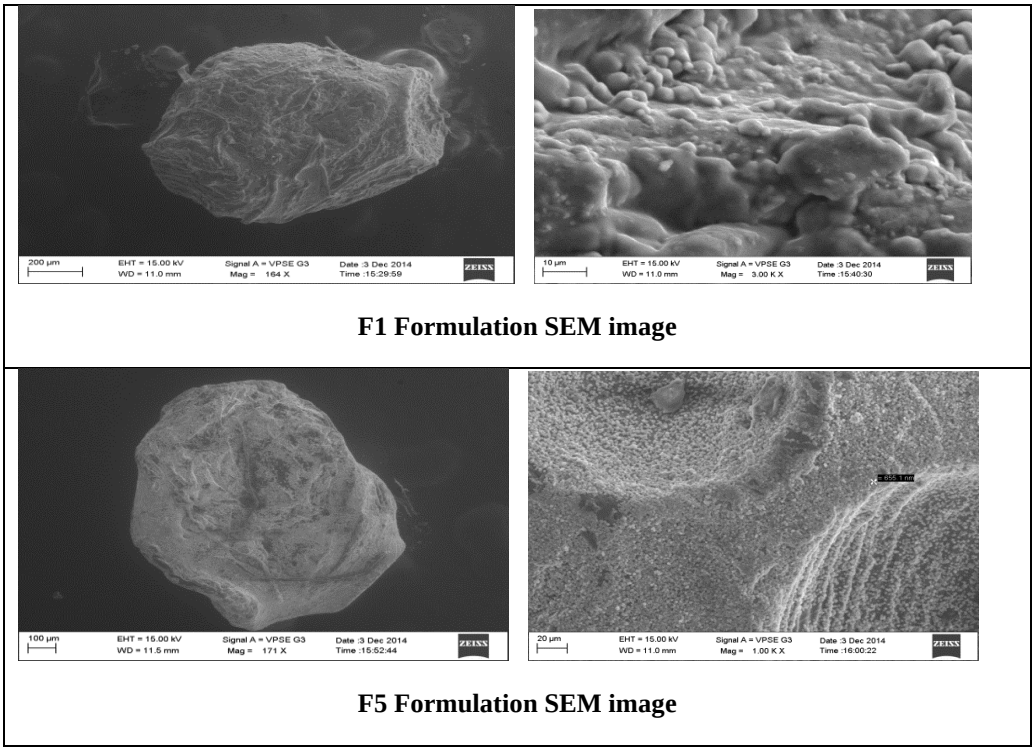

Figure 04: SEM images of F1 and F5 formulation Drug Loading and Drug Entrapment:

The values for % drug loading and % entrapment efficiency. With increasing polymer concentration, % drug loading decreased, while % entrapment efficiency increased. This trend is attributed to the higher viscosity of the polymer solution, which affects the diffusion characteristics of the polymers and influences the drug's ability to remain entrapped within the microspheres. The permeability properties of each polymer may also impact how much drug diffuses into the surrounding medium during microsphere preparation. Comparative data for % drug loading and % entrapment efficiency are illustrated.

Table 04: Drug Loading and Drug Entrapment of Lamivudine Microspheres

Formulation Code	Actual Drug Content (mg)	Theoretical Drug Content (mg)	Total Weight of Microspheres (mg)	% Drug Loading	%Drug Entrapment
F1	18.18	25	50	39.46	79.18
F2	14.65	15.77	50	26.5	83.47
F3	12.29	12.5	50	21.70	91.30
F4	18.42	25	50	22.06	93.22
F5	14.86	15.87	50	36.48	74.52
F6	12.36	12.5	50	31.76	79.54
F7	18.88	25	50	28.54	85.78
F8	15.22	15.87	50	29.22	87.84
F9	12.42	12.5	50	24.22	93.58

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
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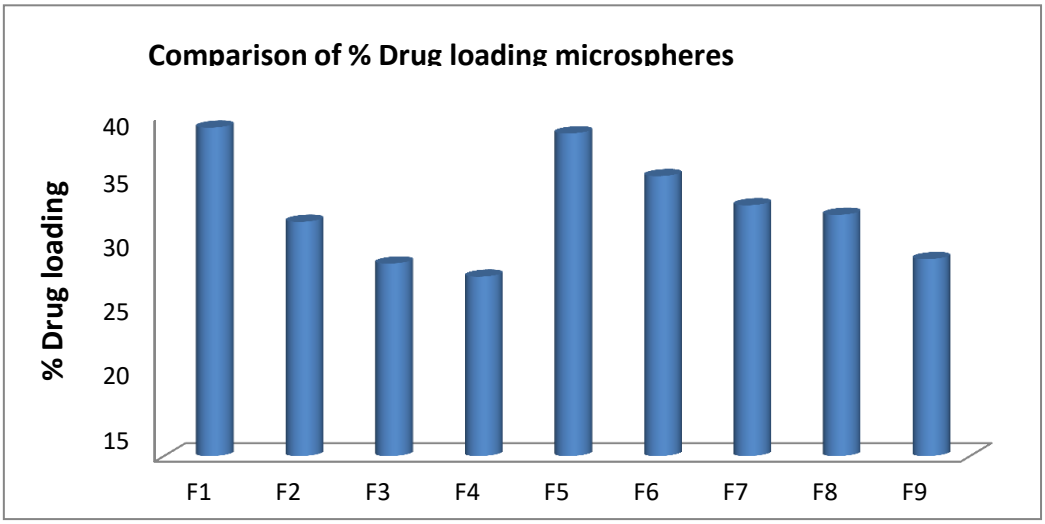

Figure 05: Comparison of % Drug Loading of the Prepared Microspheres

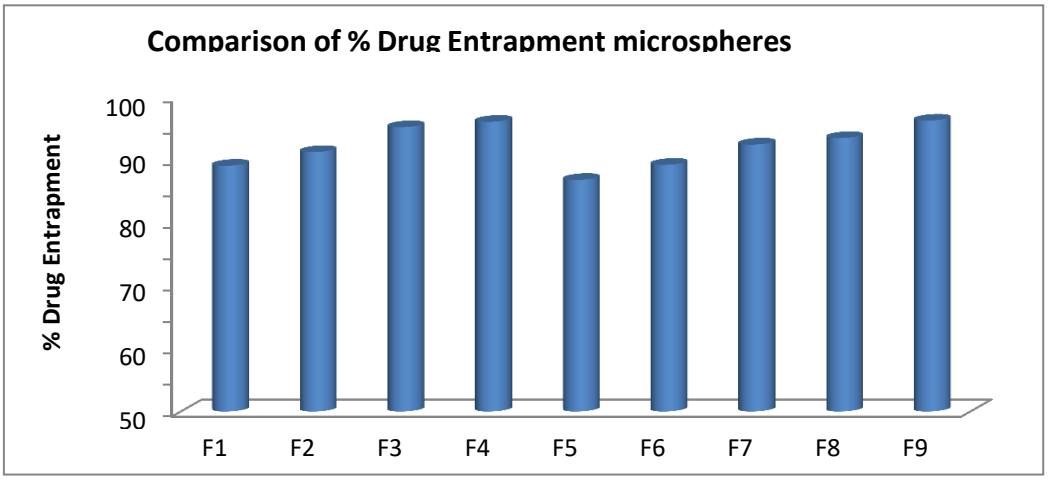

Figure 06: Comparison of % Drug Entrapment of the Prepared Microspheres % yield:

The percentage yield of various formulations Fl to F9 was calculated and found to be 79.21%, 75.73%, 67.68%, 61.54%, 81.13%, 71.4%, 70.70%. , 59.68% and 55.50%. The practical yield percentage decreased slightly with increasing polymer ratio. Results of all F1 to F9 microsphere preparations.

Table 05: Practical Yield of Lamivudine Microspheres

Formulation Code	Theoretical Wt. (mg)	Practical Yield (mg)	%Yield
F1	1000	754	79.19
F2	1500	1096	75.68
F3	2000	1298	67.91
F4	1000	765	61.49
F5	1500	1098	81.21
F6	2000	1277	71.39
F7	1000	757	70.69
F8	1500	1078	59.71
F9	2000	1309	55.49

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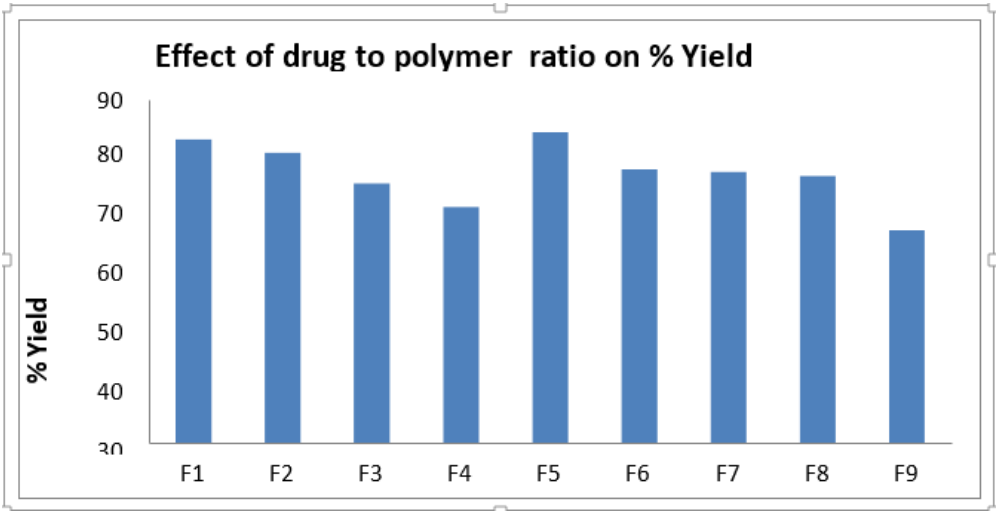

Figure 07: Comparison of % Yield of the Prepared Microspheres

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

Table 06: *In–vitro* drug release for Lamivudine 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	F9
0	0	0	0	0	0	0	0	0	0
1	18.114	17.004	14.584	13.869	17.118	16.848	16.442	14.232	13.182
2	27.528	26.645	24.522	22.478	35.674	26.665	20.424	18.261	17.174
3	32.698	31.351	31.698	29.236	42.604	39.235	25.733	23.353	22.322
4	46.464	37.459	37.114	31.545	48.498	38.722	31.906	29.523	27.654
5	52.110	42.925	41.426	34.434	53.141	44.577	32.586	31.161	30.663
6	58.145	54.889	49.121	49.136	64.889	51.152	39.245	39.471	37.213
7	64.512	62.401	53.803	45.824	72.209	56.622	54.354	48.267	44.633
8	68.247	68.412	65.796	64.410	76.123	63.261	61.712	59.780	49.323
9	76.248	73.898	69.212	67.796	79.885	71.778	68.556	66.222	65.679
10	80.698	78.241	76.298	71.498	82.235	80.665	74.565	69.184	63.679

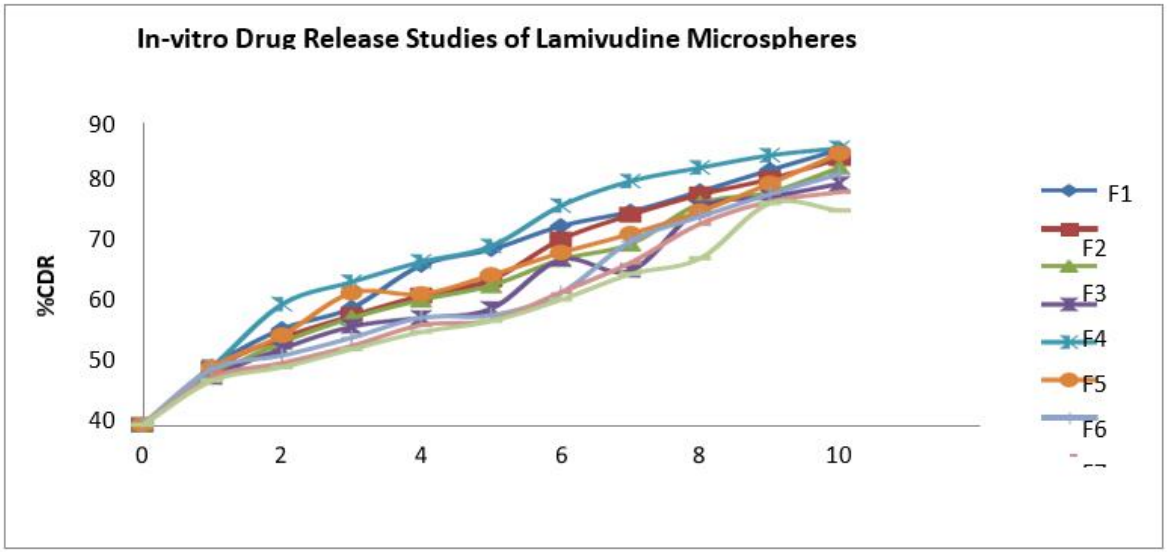

Figure 08: Comparative *In-vitro* Dissolution Profile of Lamivudine Microspheres

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 8, August 2024 pp 113-126. ijppr.humanjournals.com ISSN: 2349-7203

Release Kinetics:

Table 07: Model Fitting Release Profile of Lamivudine Microspheres

Formulation code	Mathematical Models (Kinetics)						Best Fit Model
	Korsmeyer–Peppas		Higuchi	Hixson–Crowell	First order	Zero order	
	R2	n	R2	R2	R2	R2	
F1	0.9399	0.4621	0.9522	0.9771	0.8981	0.9982	Zero-order
F2	0.9525	0.4501	0.9786	0.9563	0.8898	0.9844	Zero-order
F3	0.9393	0.4521	0.9984	0.9830	0.8867	0.9144	Zero-order
F4	0.9533	0.4734	0.9814	0.9173	0.9480	0.9524	Zero-order
F5	0.9434	0.4745	0.9874	0.9576	0.9310	0.9777	Zero-order
F6	0.9239	0.4132	0.9861	0.9324	0.8487	0.9747	Zero-order
F7	0.9768	0.4046	0.9819	0.9889	0.9401	0.9899	Zero-order
F8	0.9672	0.4219	0.9577	0.9767	0.9984	0.9889	Zero-order
F9	0.9776	0.4835	0.9668	0.9807	0.9247	0.9988	Zero-order

Stability study: Stability testing was performed on lamivudine microspheres from formulations F1 and F5 under conditions of 40°C and 75% relative humidity for 60 days. The samples were evaluated after 15, 30, 45 and 60 days for physical appearance, entrapment efficiency and drug release profiles. The results of these stability studies showed no significant changes in the physical appearance, drug entrapment, or in vitro release characteristics of the microspheres.

Table 08: Stability Studies for Formulations Stored at 40ºC/75% RH

Tested after days	% Drug entrapment		% CDR	
	F1	F5	F1	F5
15	78.12	73.26	81.723	82.175
30	77.37	73.29	80.234	82.147
45	77.41	72.23	81.173	81.765
60	78.26	72.32	81.69	82.251

SUMMARY

The primary goal of a drug delivery system is to deliver a therapeutic dose of a drug to a target site in the body and to maintain the desired plasma concentration over a period of time. The project was structured into several phases, starting with an extensive review of the theoretical and technical literature, as detailed in Chapters 3 and 4. This was followed by the acquisition and standardization of materials for the formulation of microspheres.

The microspheres were developed using two types of polymers, xanthan gum and guar gum, using a solvent evaporation technique. The formulations were then evaluated for various parameters including percent yield, particle size, morphology, drug entrapment and in vitro drug release. Most formulations met acceptable criteria across these parameters, with changes in drug to polymer ratio resulting in different microsphere sizes and improved drug entrapment efficiency.

The release mechanism was analyzed by fitting the drug diffusion data to several kinetic models. The results showed that the drug release best fits a zero-order kinetic model and follows a non-Fickian diffusion mechanism. Stability studies of selected formulations over 60 days showed no significant changes in physical appearance, drug entrapment or in vitro release profiles.

Formulations F1 and F5 proved to be the most promising for oral administration of lamivudine, meeting all evaluated parameters. However, to determine the absorption patterns and bioavailability of the drug from these microspheres, in vivo studies are necessary to establish a correlation between in vitro and in vivo results. Overall, these microspheres represent a viable candidate for controlled release drug delivery systems in the current environment of advanced formulation technologies.

CONCLUSION

This study presents an innovative approach to formulate Lamivudine microspheres using natural gums such as xanthan gum and guar gum aimed at improving the treatment of HIV and chronic hepatitis B. The microspheres were prepared by solvent evaporation method and various evaluation parameters were investigated to achieve controlled drug release. Details of preparation and assessment are given in previous chapters.

Key findings of the study include:

• Micrometric analysis showed that the mean particle size of the microspheres ranged from 278 ± 7.14 µm to 991 ± 10.73 µm.

• Scanning electron microscopy (SEM) revealed that the microspheres containing guar gum were smooth, spherical and showed slight aggregation. In contrast, xanthan gum microspheres were porous, rough, and distinctly spherical.

• The entrapment efficiency in % increased with the viscosity of the polymer solution.

• Drug release kinetics for formulations F1 to F9 were best described by a zero-order model, with a release mechanism following a non-Fickian diffusion pattern.

• Stability studies showed that formulations F1 and F5 remained stable and compatible under selected temperature and humidity conditions for 60 days. No significant changes in drug entrapment or in vitro release characteristics were observed.

Overall, the formulated microspheres show promise as an oral controlled drug delivery system capable of prolonging drug retention in the gastrointestinal tract.

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