




INTERNATIONAL JOURNAL OF EXPERIMENTAL AND BIOMEDICAL RESEARCH

Published by Pharma Springs Publication Journal Home Page: <https://pharmasprings.com/ijebr>

Formulation and evaluation of cidofovir loaded microspheres

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Article History:

Received on: 26 Jan 2024
Revised on: 01 Feb 2024
Accepted on: 02 Mar 2024

Keywords:

Cidofovir,
Microspheres,
In vitro dissolution studies,
FTIR,
DSC

Abstract

The study aimed to produce and assess cidofovir microspheres using the emulsion solvent diffusion method. Microspheres loaded with ethyl cellulose and HPMC were prepared. FTIR analysis confirmed stability with no drug-polymer interaction, and compatibility investigations ensured formulation compatibility. SEM determined particle size, with yields ranging from 84.44% to 87.62% and drug content from 64.8% to 97.2%. Particle sizes ranged from 20 μm to 210 μm , with drug loading capacities of 55.6% to 96.8% and entrapment efficiencies of 55.5% to 89.1%. Swellability studies showed a range of 0.6 to 1.6 seconds. Formulation CM8 exhibited optimal dissolution *in vitro* at 62.87%. Drug dissolution data were fitted to various models, with R² values ranging from 0.937 to 0.061. Up to 45 minutes of drug release was observed. Overall, cidofovir-loaded HPMC and ethyl cellulose microspheres showed favorable release properties under optimal conditions.



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eISSN: 2583-5254

DOI: <https://doi.org/10.26452/ijebr.v3i2.595>



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INTRODUCTION

The microspheres made of artificial polymers with distinctive particles that flow freely. They have a particle size of less than 200 micrometres and are biodegradable in the wild. When taken orally, the majority of medications come in standard dosage forms, which are limited in the short term because they can't confine and focus the system at the gastrointestinal tract [1]. Microspheres are widely used in parenteral and oral controlled medication delivery systems. A polymer that functions as both a carrier and a core material was needed. It is created for the formulation of microspheres amongst other approaches. The polymer ethyl cellulose is hydrophobic, inert, non-ionic, biocompatible, and has low toxicity. This is a well-researched technique for encapsulating materials

Table 1 Formulations of Cidofovir Microspheres

Sl.No	Ingredients	CM1	CM 2	CM 3	CM 4	CM 5	CM6	CM 7	CM 8	CM 9
1	Cidofovir	2.0	2	1.0	3	3.0	3	4	3.0	4
2	Ethyl Cellulose	2	2.0	2	2.0	3	3.0	3	3	3.0
3	HPMC	1.0	1.0	1.0	2	2.0	2	1.0	2	2.0
4	Ethanol	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
5	Distilled water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

to provide regulated release of medication. The polymer HPMC is swellable and non-ionic [2]. In controlled drug delivery systems, hydrophilic polymer gel matrix systems are commonly employed. Because of their flexibility, they are also employed to achieve a desired medication release profile at a reasonable cost. Natural polymers can be derived from a variety of sources, including proteins, chemically modified carbohydrates, and carbohydrates. The preparation methods are mostly determined by the medication, polymer type, and length of therapy. The aforementioned techniques encompass in situ polymerization, solvent evaporation, coacervation-phase separation, spray drying, as well as spray congealing [3].

MATERIALS AND METHODS

Cidofovir is a gift sample from Hetero drugs Limited, and other polymer mixtures such as HPMC (SD Fine Chemical Limited), ethanol (Ruchi Global Limited, Madhya Pradesh), and ethylcellulose (Rohm GmbH & CoKG, Germany).

METHODS:

Preformulation Studies:

Compatibility studies:

Studies on drug preformulation pertaining to drug and polymer interaction become unstable when drugs and polymers are prepared together. When using the proper polymer, they are crucial. [4] The compatibility of Cidofovir with the cellulose polymer was determined using FTIR Spectroscopy. (Jasco FTIR-401, Perkin Elmer, Japan).

Differential scanning calorimetry:

A plot of heat flux (rate) versus temperature at a given temperature rate is the result of a DSC. It offers details about the sample's physical characteristics. It might be amorphous or crystalline in nature. Thermogravimetric analysis indicates

that in certain formulations, there may be a drug-polymer interaction [5].

Morphology of the Particles:

The size distribution, shape, as well as particle size of the microspheres are ascertained using the following techniques [6].

Scanning Electron Microscopy [7]:

SEM stands for scanning electron microscopy. When assessing the general morphology and shape of the microspheres, it is quite helpful. Using scanning electron microscopy (SEM), the morphology and surface characteristics of ethyl cellulose microcapsules and coated microspheres were discovered. After the particles were freeze-dried, they were coated with gold palladium using a sputter coater (Balzers SCD 004, Liechtenstein) to produce a 20 nm thick coating, and they were examined under a microscope (JSM-6400, Tokyo, Japan).

Preparation of Cidofovir Microspheres:

Using distilled water as an external phase, the Cidofovir microspheres were produced via the Emulsion Solvent Diffusion technique. An excellent solvent, ethanol, which includes ciprofovir and has a concentration of polymers, such as HPMC and ethyl cellulose, makes up the internal phase.

In an organic solvent mixture including polymers in varying ratios, the drug as well as polymers were co-dissolved. Under agitation conditions, the drug solution was gradually injected using a syringe into the exterior water phase. For almost one hour, the system was continuously agitated at 800 rpm. In addition to the poor solvent absorbing into the excellent solvent. The droplets developed into microspheres as they steadily hardened. To keep the microspheres apart from the preparation system, the system was filtered. The finished

object was dried after being cleaned with distilled water. The procedure was done at room temperature the entire time. The drug-to-polymer ratio was displayed.

Evaluation of Microspheres:

Percentage production yield (PY)

$$\text{PY (\%)} = \frac{\text{Practical mass of microspheres}}{\text{Theoretical mass}} \times 100$$

Every formulation was tested three times, and the PY (%) was determined [8].

Entrapment efficiency [9]:

The Emulsion Solvent Diffusion Technique was used to prepare the microspheres. It underwent a 40-minute, 14,000 rpm centrifugation at 10°C. The HPMC as well as ethyl cellulose contain the appropriate amount of cidofovir. The amount that was discovered in the supernatant differed from the total amounts used to generate the microspheres. Using a UV spectrophotometer set at 490 nm, the amount of free Cidofovir in the supernatant was measured. The following equation is used to calculate it.

$$\%EE = \frac{M_{\text{Initial drug}} - M_{\text{Free drug}}}{M_{\text{Initial drug}}}$$

Drug loading efficiency:

After the drug loading efficiency was eliminated, the residual sediments (precipitations) were cleaned with distilled water and then mixed with a mixture of acetone and chloroform (2.5:2.5, v/v) in a 10 mL volumetric flask. This process was done to make sure that all of the drug was extracted completely from the microspheres, and after 30 minutes of sonication, the volume was adjusted to 10 ml using chloroform. The resulting mixture was then centrifuged at 14,000 rpm for 30 minutes at 10°C, and the supernatants were removed. The drug was then loaded as well as examined in triplicate for the loaded drug using a UV spectrophotometer at 490 nm [10].

Particle size determination:

Optical microscopy was used to measure the microspheres' particle size. For particle size, about 100 microspheres were counted. By suspending in water, the distribution of particle size was measured.

Equilibrium swelling studies of microspheres [11]:

A premeasured volume of microspheres was added to the pH 7.4 phosphate buffer. It is let to swell while maintaining its weight. Following their removal as well as blotting with filter paper, the weight variations of the microspheres were measured. The following formula was used to calculate the degree of swelling (α).

$$\alpha = \frac{w_g - w_o}{w_o}$$

Drug content determination:

To extract the medication, 50 mg of Cidofovir microspheres were crushed and suspended in water. The filtrate was tested spectrophotometrically for drug concentration at 490 nm after 24 hours, using water as the blank.

Micromeritic Properties of Cidofovir Microspheres [12-13]:

Bulk Density:

Sieve number 20 is used to filter the powder whose bulk density needs to be found. A 100ml graduated measuring cylinder is filled with precisely weighed 20gm, which is then carefully inserted. The cylinder is dropped three times, at intervals of two seconds, from a height of one inch onto a hard surface. The powder's volume is mentioned.

Bulk density = mass of powder/Bulk volume of powder

Angle of Repose:

A horizontal surface is used to support the bottom of an open-ended cylinder filled with powder. After that, the cylinder is raised vertically so that the powder can accumulate horizontally in a mound. By taking multiple measurements in different directions, the diameter at the base of the concentration is found. It is also measured how high the heap is.

Angle of repose = $\tan\theta = h/r$

Carr's Index:

It is the determination of tapped density and poured density.

A fixed quantity of powder is poured into an measuring cylinder and the volume is noted. The

tapped density is then determined as described under bulk density determination.

Carr's Index (%) = $\frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100$

True density:

It is the ratio between mass of powder and its true volume.

True density = $\frac{\text{weight of powder}}{\text{True volume}}$

Hausner's Ratio:

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

Tapped density:

Tapped density = $\frac{M}{V_T}$

In-vitro drug release studies [14]:

Using 500 cc of dissolve medium as well as the USP XXIV dissolution apparatus type II, in-vitro drug release tests were conducted. For 45 Mts, it is kept at 37 ± 0.5 °C, 50 rpm, and a pH 7.4 ± 0.2 phosphate buffer is used as the dissolving medium. The in-vitro release profile results for each formulation were plotted using the following data treatment methods:

1. Log cumulative drug remaining percentage against time using a first-order kinetic model
2. The Higuchi model's cumulative percent drug release versus the square root of time
3. Cumulative drug residual percentage over time (using a zero order kinetic model)
4. The Korsmeyer-Peppas model shows the log cumulative percent of drugs released vs log time.

Data Analysis:

The data was acquired and it was fitted in to the Zero order, First order, Higuchi matrix, and Korsmeyer as well as Peppas model in order to assess the mechanism for the release and release rate kinetics of the dosage form. After comparing the r-values, the best-fit model was chosen.

Zero order kinetics [15]:

In the event that the region remains unchanged and no equilibrium circumstances are reached, medication will be released gradually upon dissolution from pharmaceutical dosage forms

that do not disintegrate. The following equation can be used to express it.

$$Q_t = Q_o + K_o t$$

First order kinetics:

The following equation was fitted to the release rate data in order to examine the first order release rate kinetics.

$$\text{Log } Q_t = \text{log } Q_o + \frac{K_{1t}}{2.303}$$

Higuchi model:

Several theoretical models create this idea, to research the release of medications that are low solubility as well as water soluble. When they are included in solid matrices or semisolids, the equation is

$$Q_t = K_H \cdot t^{1/2}$$

4. Korsmeyer and Peppas release model:

The following equation is fitted to the release rate data in order to study this model.

$$M_t / M_\infty = K \cdot t^n$$

RESULTS AND DISCUSSION

Preformulation Studies:

Compatability studies

IR studies

FTIR is used to record the infrared spectrum of the pure Cidofovir sample. This is contrasted with Cidofovir's normal functional group frequencies.

Comparison of FT-IR Spectra of Cidofovir

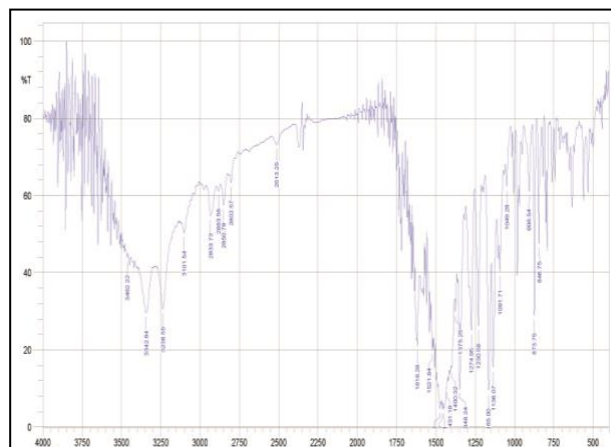


Figure 1: FTIR Spectra of Pure drug (Cidofovir)

Table 2 IR Interpretations for Pure Drugs and Polymers

Functional groups	Cidofovir	Drug + Ethyl Cellulose	Drug + Ethyl Cellulose + HPMC
O-H Stretch (Carboxylic acids)	2513.25	3566.38	3520.09
N-H Stretch (1°&2° amines)	3342.64	3419.79	3442.94
C-H Stretch (Aromatics)	2850.79	2974.23	3358.07
C-C Stretch (Alkynes)	1618.28	1348.24	1230.58
C-O (Alcohols and Ether)	1521.84	1274.95	1165.00

Table 3 Interpretation of the DSC Spectrum

Sl.No	Drug & Excipients	Exothermic peak	Endothermic peak
1	Cidofovir(CM1)	122.5°C & -10.65 mw	-----
2	Drug+ethyl cellulose+Hpmc (CM2)	121.9°C & -9.29 mw	286.2°C & -7.50 mW

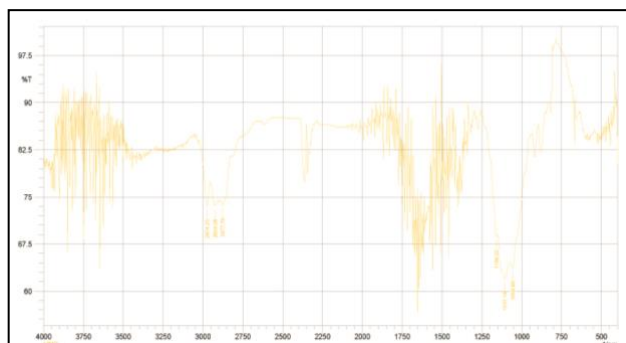


Figure 2: FTIR Spectra of Ethyl cellulose

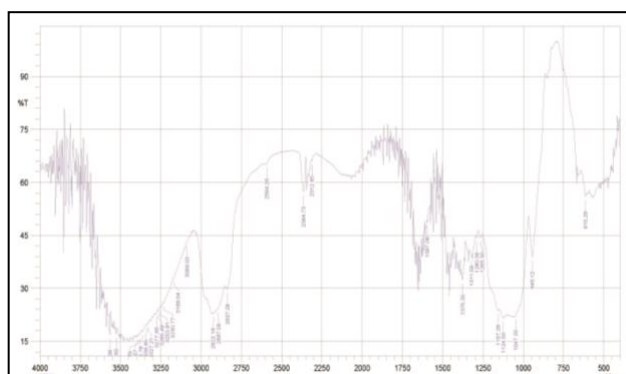


Figure 3: FTIR Spectra of HPMC

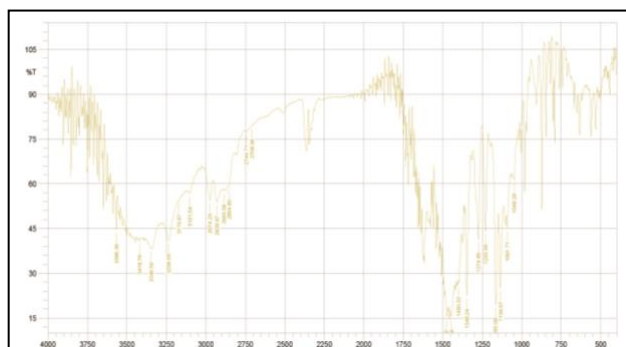


Figure 4: FTIR Spectra of Drug + Ethyl cellulose

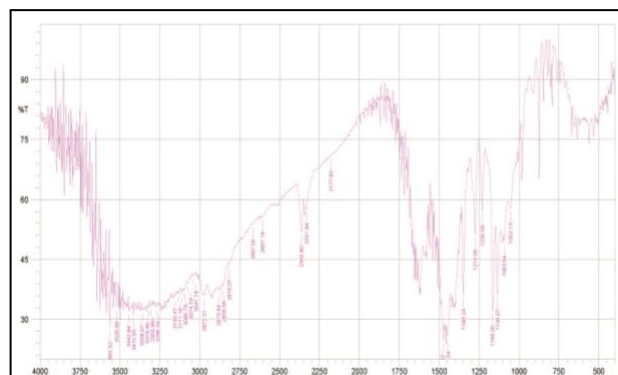


Figure 5: FTIR Spectra of Drug + EC + HPMC

Differential scanning calorimetry:

The exothermic peak in the spectra of the pure drug from the DSC sample is 122.50°C and -10.65 mW. The mixed sample contains drug (cidofovir), ethyl cellulose, as well as HPMC. The exothermic peak is 121.90 °C and -9.29 mW, while the endothermic peak of the mixture is 286.2 °C and -7.50 mW. The compatibility of the medication along with excipients reveals that the formulation is not compatible. It is suitable for the formulation of microspheres.

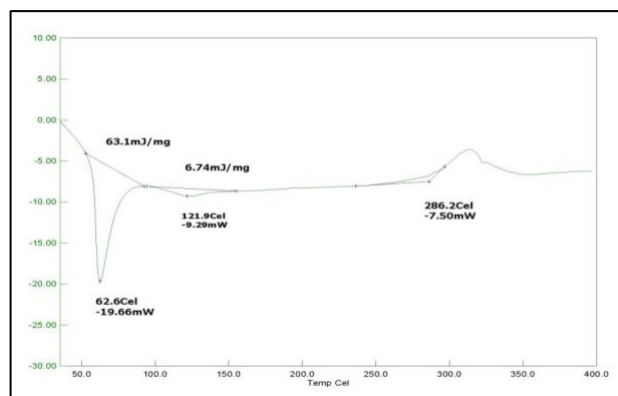


Figure 6: DSC spectrum of pure drug Cidofovir

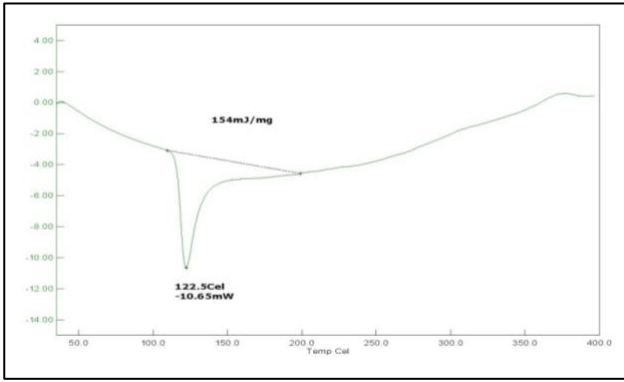


Figure 7: DSC spectrum of Mixtures (Drug + EC + HPMC)

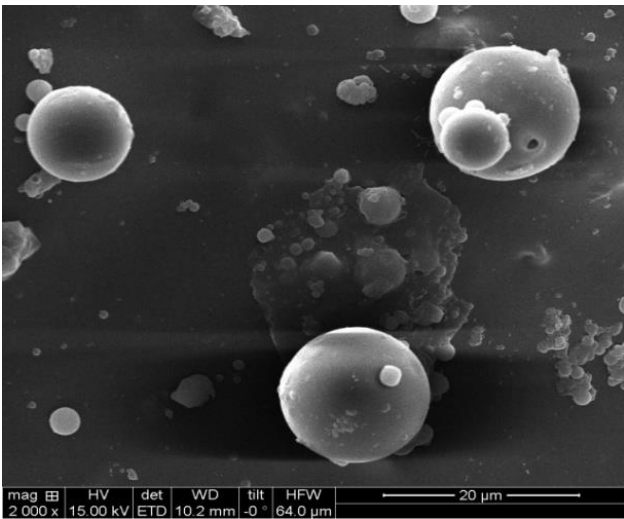
Morphology of the Particles:

The particle size, size distribution, as well as shape of Cidofovir microspheres are determined using the methods described below.

SEM

The morphology and structure of microspheres were determined using scanning electron microscopy (SEM), as well as photomicrographs were made at appropriate magnifications. Scanning electron microscopy was used to acquire pictures of the optimised formulation.

Shape and Surface Morphology



Figures 8: SEM samples of the best formulations of CM 8.

Evaluation of Cidofovir Microspheres

Percentage Yield

The production yield of Cidofovir microspheres utilising HPMC as well as ethyl cellulose is listed in Table 4 and Figure 9.

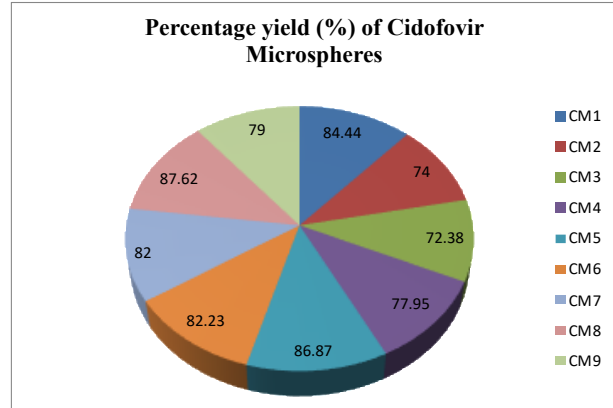


Figure 9: Percentage yield of Cidofovir microspheres

Encapsulation efficiency

Drug entrapment efficiency (%EE)

Percentage entrapment efficiency of CM 1: 91.1%, CM 2: 87.1%, CM 3: 77%, CM 4: 66%, CM 5: 63.9%, CM 6: 60.8%, CM 7: 58.8, CM 8: 54.5, as well as CM 9: 51.8% The CM 8 demonstrates good formulation and high efficiency. Results can be seen in Table 4 and Figure 10.

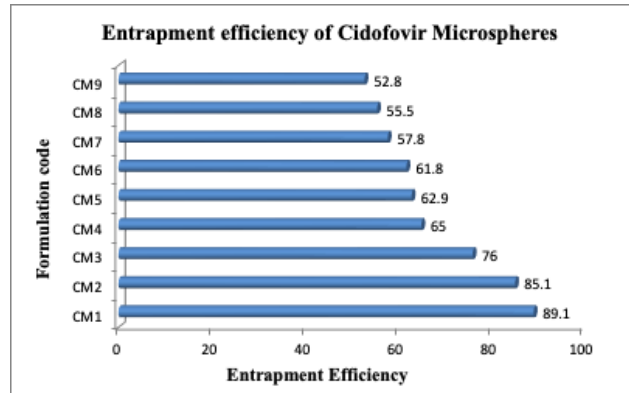


Figure 10: Entrapment efficiency of Cidofovir Microspheres

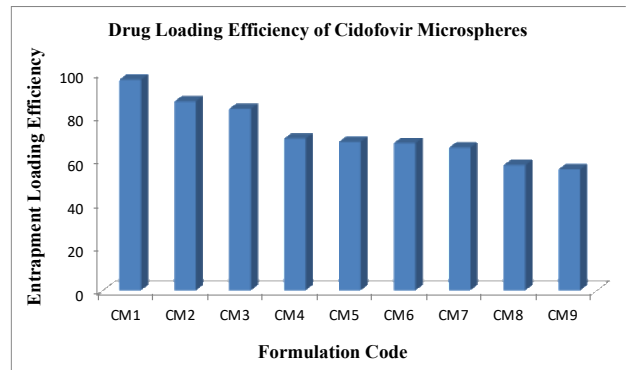


Figure 11: Drug Loading Capacity of Cidofovir microspheres

Entrapment Loading (%EL)

The percentage of CM 1-97.9%, CM 2-87.9%, CM 3-84.3%, CM 4-71.9%, CM 5-70.4%, CM 6-68.8%, CM 7-64.8, CM 8-56.8, and CM 9-54.8% that were entrapped. The CM 8 demonstrates excellent formulation and strong efficacy. Outcomes as displayed in Figure 11 and Table 4.

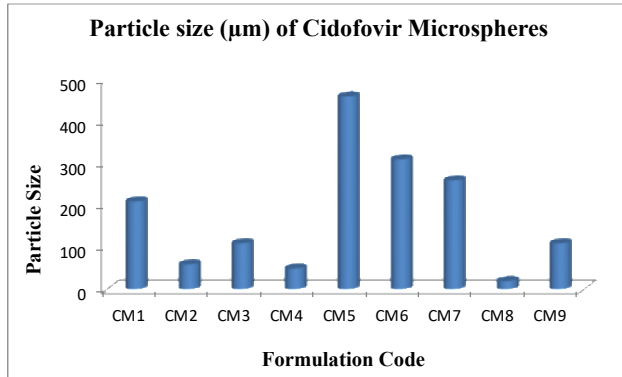


Figure 12: Particle Size of Cidofovir microspheres

Particle size

CM 1 (200 µm), CM 2 (50 µm), CM 3 (100 µm), CM 4 (45 µm), CM 5 (450 µm), CM 6 (300 µm), CM 7 (250 µm), CM 8 (10 µm), and CM 9 (100 µm) depict the particle size distribution of microspheres. Results are displayed in Figure 12 and Table 4.

Equilibrium swelling studies of microspheres.

Phosphate buffer (pH7.4) was added to 100 mg of preweighed microspheres, which were then let to swell to a constant weight. Following their removal as well as blotting with filter paper, the microspheres' weight changes were measured and reported, as shown in Table 4 and Figure 13.

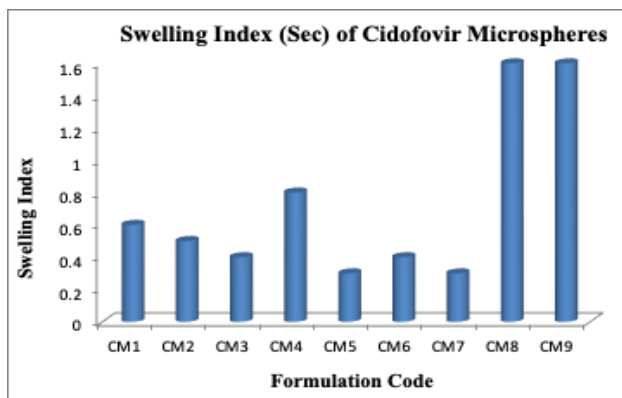


Figure 13: Swelling index of Cidofovir microspheres.

Percentage drug content Determination:

The drug content distribution of the microspheres was represented by the formula as shown in Table 4 and Figure 14. The drug content is CM 1 (65.8%), CM 2 (69.2%), CM3 (90.3%), CM4 (89.7%), CM 5 (75.2%), CM 6 (85.2%), CM 7 (88.5%), CM 8 (98.2%), CM 9 (70.4%).

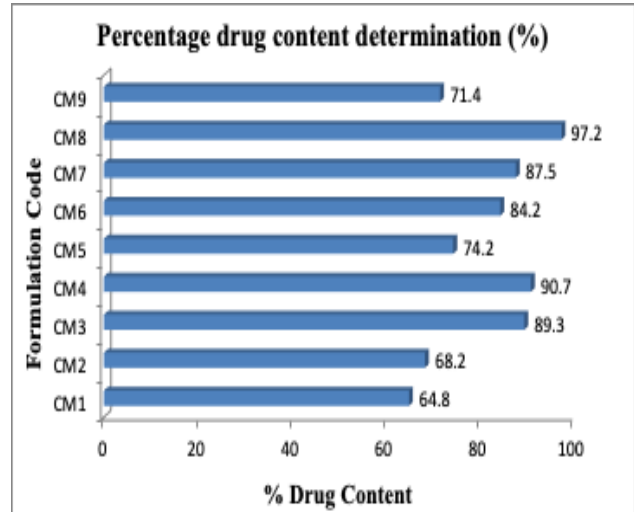


Figure 14: Percentage drug content of Cidofovir microspheres.

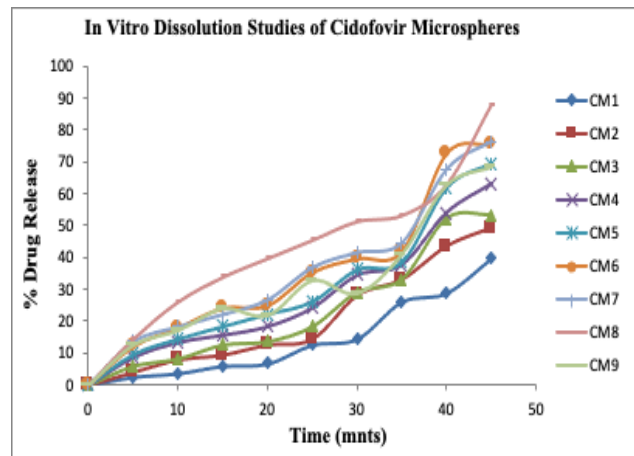


Figure 15: In vitro dissolution studies of Cidofovir microspheres

In vitro dissolution Studies:

The invitro drug dissolution data was fitted to many mathematical models, including zero order, first order, Higuchi matrix, and Korsmeyer Peppas model, in order to comprehend the mechanism of drug release rate kinetics of the drug from dosage forms. Table 5 shows the compliance with the values.

Table 4 Evaluation of Cidofovir microsphere properties

Formulation code	% yield (%)	Drug Content	Entrapment Efficiency (%)	Drug Loading capacity (%)	Particle size(μm)	Swellability Studies (Sec)
CM1	84.44	64.8	89.1	96.8	210	0.6 Sec
CM 2	74	68.2	85.1	86.8	60	0.5 Sec
CM 3	72.38	89.3	76	83.4	110	0.4 Sec
CM 4	77.95	90.7	65	69.8	50	0.8 Sec
CM 5	86.87	74.2	62.9	68.3	460	0.3 Sec
CM 6	82.23	84.2	61.8	67.7	310	0.4 Sec
CM 7	82	87.5	57.8	65.6	260	0.3 Sec
CM 8	87.62	97.2	55.5	57.6	20	1.6 Sec
CM 9	79	71.4	52.8	55.7	110	1.6 Sec

Table 5 In Vitro dissolution Studies

Sl.no	Time	% of Drug release								
		CM1	CM2	CM3	CM4	CM5	CM6	CM7	CM8	CM9
1	5	2.53	4.07	5.95	8.69	9.59	12.15	13.63	14.43	12.59
2	10	3.64	7.95	8.23	13.37	14.43	17.96	18.31	26.07	17.21
3	15	5.95	9.45	12.58	15.63	18.33	24.17	22.17	33.82	24.09
4	20	6.67	12.59	13.63	18.33	22.17	24.95	26.73	39.65	21.95
5	25	12.57	14.43	18.31	24.17	26.07	35.33	36.87	45.39	32.93
6	30	14.41	28.07	29.04	34.33	36.09	39.65	41.49	51.23	28.85
7	35	26.05	33.07	33.07	37.65	38.43	41.97	44.61	53.13	41.24
8	40	28.8	43.47	52.06	53.91	61.65	72.65	67.63	62.87	62.87
9	45	39.63	49.21	53.13	62.87	69.27	75.55	76.29	87.93	68.62

Table 6 Release kinetics of Cidofovir Microspheres

Model (1)	Equations (2)	CM 1		CM 2		CM 3		CM 4	
		R ²	m	R ²	m	R ²	M	R ²	m
Zero order	$M_0 - M_t = kt$	0.655	69.4	0.939	1123	0.007	15.93	0.202	72.88
First order	$\ln M = \ln M_0$	0.494	0.061	0.540	0.067	0.257	0.038	0.352	0.044
Higuchi's Matrix	$M_0 - M_t = kt^{1/2}$	0.516	4508	0.767	7420	0.023	212.0	0.189	515.5
Kosmeyer Peppas	$\log(M_0 - M_t) = \log k$	0.835	2.354	0.884	2.545	0.572	1.709	0.663	1.813

Table 7 Release kinetics of Cidofovir Microspheres (Continued)

CM 5		CM 6		CM 7		CM 8		CM 9	
R ²	M	R ²	m	R ²	m	R ²	M	R ²	M
0.928	1414	0.917	15.49	0.949	154.4	0.937	1593	0.945	139.7
0.438	0.062	0.481	0.052	0.465	0.051	0.399	0.061	0.478	0.051
0.803	9618	0.798	1057	0.848	1067	0.899	11409	0.836	960.9
0.806	2.517	0.835	2.032	0.827	2.033	0.785	2.560	0.838	2.018

CONCLUSION

Creating Cidofovir microspheres for a sustained drug delivery system was the goal of the current project. Formulation CM 8 appears to have excellent morphological properties based on the

results. The best formulation, according to the percentage yield of microspheres, entrapment efficiency, drug loading efficiency, swelling index, and particle size measurements were found to be (20 μm), 57.6%, as well 54.5 %, respectively. The

best formulation for drug content was determined to be 97.2, and several Release kinetic studies were used to suit the in vitro drug release data in a sustained way over a 45-minute duration. The concentration of ethyl cellulose was shown to have a significant impact on every evaluation parameter. Therefore, the Cidofovir microspheres that have been created could be a viable option for safe and efficient long-term drug delivery.

ACKNOWLEDGEMENTS

The authors are thankful to the Secretary & Correspondent & Principal of Jagan's Institute of Pharmaceutical Sciences, Jangalakandriga (V), Muthukur (M) Nellore-524 346, SPSR Nellore (Dist) Andhra Pradesh, for providing the necessary facilities to carry out this work.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Funding Support

The authors declare that they have no funding for this study.

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