

Formulation and Evaluation of Micro Sponges Loaded with Acyclovir Using an Antiviral Drug

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ABSTRACT

The main objective of the present research work was to develop and evaluate the anti-viral drug (Acyclovir) loaded micro sponges using polymers. Micro sponges of acyclovir were prepared by quassi-emulsion solvent diffusion method by using EC and HPMC as polymers. The prepared acyclovir micro sponges were subjected to IR, SEM, Particle size and Size distribution, Entrapment efficiency, *in vitro* dissolution studies and release kinetics. The IR Spectras revealed that, there was no interaction between the polymer and acyclovir. Acyclovir micro sponges was spherical in nature, which was confirmed by SEM. Acyclovir micro sponges with normal frequency distribution were obtained. A maximum of 95.67% drug entrapment efficiency was obtained in the acyclovir micro sponges. F5 formulations

ACV micro sponges show the maximum drug release. The coefficient of determination indicated that the release data was best fitted with Higuchi model kinetics. The release kinetics data implies that the release mechanism of all formulation was Non Fickian diffusion mechanism. On the basis of particle size, entrapment efficiency and morphology, *in vitro* release studies and its kinetics data, F5 (formulation) was selected as optimized formulation.

Keywords: Hydroxypropyl methyl cellulose, Ethyl cellulose, Acyclovir, Scanning electron Microscopy (SEM)

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INTRODUCTION

Viruses are the ultimate expression of parasitism. They are not only taking nutrition from host cell but also direct its metabolic machinery to synthesize new virus particles. Anti-viral drugs are a class of drugs which targets virus specific steps like cell penetration uncoating, virus assembly, maturation and reverse transcription etc. Anti-viral drugs classified as anti-herpes virus, anti-influenza virus, anti-hepatitis virus, and anti-retrovirus. Acyclovir is a first line antiviral drug which is used in the treatment of infection caused by Herpes Simplex Virus (HSV) (Healthline, 2021). Acyclovir is available as various dosage forms in the market such as capsules, creams, ointment, tablets and suspension (Yadav P and Nanda S, 2014).

Causative mechanism

HSV is a contagious virus that can be passed from person to person through direct contact. The microsphere-based polymeric microspheres uniquely overcome problems associated with above technologies. Microsponges are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it (Patel A, *et al.*, 2012; Ravi R, *et al.*, 2013). They are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance the stability, reduce side effects and modify drug release. The microsphere technology was developed by Won in the year 1987 and its original patents were assigned to Advanced Polymer Systems, Inc. Microsponges are polymeric delivery systems composed of porous microspheres (Hussain H, *et al.*, 2014; Saxena S and Nacht S, 2005). They are tiny sponge-like spherical particles with a large porous surface. They may enhance stability, reduce side effects and modify drug release favorably. Microsphere technology has many favorable characteristics, which make it a versatile drug delivery vehicle (Osmani RA, *et al.*, 2015). The Scanning Electron Microscopy of the microsphere particle reveals that its internal structure as the "bag of marbles". The porosity is due to the interstitial spaces between the marbles. The interstitial pores

can entrap many wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective and anti-inflammatory agents (Patel EK and Oswal RJ, 2012). These entrapped microsponges may then be integrated or formulated into product forms, such as creams, lotions, powders, soaps, capsules and tablets (Osmani AM, *et al.*, 2015). Although the microsphere size may vary, a typical 25 μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsphere, which can be loaded with up to its own weight of the active agent. The microsphere particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsphere materials (Ravi R and Senthikumar SK, 2013). Another safety concern is the potential bacterial contamination of the materials entrapped in the microsphere. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate into the tunnel structure of the microsponges (Pandey P, *et al.*, 2013; Kale S and Shalini R; 2013).

Advantages of micro sponges drug delivery system

- Enhanced product performance
- Extended release
- Reduced irritation and hence improved patient compliance
- Improved product elegance
- Improved formulation flexibility
- Improved thermal, physical and chemical stability
- Flexibility to develop novel product forms
- Non-irritating, non-mutagenic, non-allergenic and non-toxic
- Allows incorporation of immiscible substances

MATERIALS AND METHODS

Acyclovir was received as a gift sample from Medopharma Pvt Ltd. HPMC and EC dichloromethane, PVA, Glycerine was provided by East Point College of Pharmacy.

Drug excipient compatibility studies by FTIR

Excipients are the integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation (El-Helw AM and Bayomi MA, 2000).

The compatibility of drug acyclovir and polymers was established by infrared absorption spectral analysis (IR). Any changes in the chemical composition of the drug after combining it with the excipients were investigated with IR spectral analysis. In the present study, the potassium bromide (KBr) disc pellets method was employed.

Method of preparation of acyclovir micro sponge

Microsponges were prepared by Quasi emulsion solvent diffusion method. Internal organic phase was prepared by dissolving ethyl cellulose and Hydroxy propyl methyl cellulose and drug in dichloromethane with addition of 15 ml of glycerine (Abdelmalak NS and El-Menshaweh SE, 2012; Pavani S, et al., 2017). External phase was prepared by PVA and 150 ml water and heated at 40°C until it dissolved completely by using magnetic stirrer. The organic phase was added drop wise to the continuous stirring aqueous phase to form the discrete droplets at stirring speed 600 rpm to 750 rpm at temperature 40°C. The solution was filtered in Whatman filter paper and dried in hot air oven at 50°C for 2 hrs and sieved in a sieve No.30. (Hussein AA, 2014) (Table 1) (Figures 1 and 2).

Preformulation studies

Melting point determination: The melting point of acyclovir was found to be 256.05 degree.

Solubility study: The solubility of Acyclovir was determined by solvents such as alcohols,

0.1 N HCl, water. Acyclovir as slightly soluble in water, soluble in 0.1 N HCl, partially insoluble in alcohols.

Calibration curve of acyclovir

For the preparation of the calibration curve sample were prepared from stock solution (0, 2, 4, 6, 8, 10 µg/ml) the absorbance of the sample was taken at 252 nm using 0.1 N HCl (Figure 3).

Evaluation of micro sponges

Particle size analysis: Determination of the average particle size of acyclovir loaded micro sponges was determined with an optical microscope using a calibrated ocular and stage micrometer (Makwana R and Patel V, 2014). A minute quantity of microsponges was spread on a clean glass slide with a drop of liquid paraffin and a cover slip is placed on it. The average particle size was calculated by measuring 100 particles of each batch.

Where, d_{av} is the average diameter of particles (µm), n is number of particles per group, and d is the middle value (µm).

Scanning electron microscopy: Scanning electron microscopy of optimized micro sponge formulation was carried to determine the surface morphology. The sample was mounted directly onto the SEM sample holder using double sided sticking tape and images were recorded at differ-

ent magnifications at acceleration voltage of 10 kV using scanning electron microscope.

Loading efficiency: The microsponges was determined spectrophotometrically (λ_{max} =252 nm). A sample of Acyclovir microsponges (100 mg) was dissolved dissolved in 100 ml of phosphate buffer (pH 6.8) and kept for overnight. The drug content was determined and expressed as actual drug content in micro sponge. The loading efficiency (%) of the microsponges was calculated according to the following equation,

Loading efficiency=Actual drug content in microsponges × 100/Theoretical drug content

In vitro dissolution studies: *In vitro* drug release study was carried out using USP type-II dissolution test apparatus. The dissolution medium 900 ml of 7.4 phosphate buffer was maintained at 37 ± 1°C and stirred at 50 rpm. Aliquots of samples (5 ml) at an interval of 1 hour were withdrawn and filtered through Whatman filter paper. The samples were analyzed for Acyclovir content by UV-Visible spectrophotometer at 252 nm (Swetha A, et al., 2011). Data obtained was also subjected to kinetic treatment to obtain the order of release and release mechanism (Mehta M, et al., 2012; Kandalal A, et al, 2014). To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s. t), first order [Log(Q₀-Q) v/s t], Higuchi's square root of time (Q v/s. t_{1/2}) and KorsmeyerPeppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q₀-Q) is the cumulative percentage of drug remaining after time t.

RESULTS AND DISCUSSION

FTIR analysis

Fourier Transforms Infrared Radiation (FTIR) spectra of acyclovir and a mixture of acyclovir and the selected excipients were performed in conditions 40°C+2/75%+5 RH for one month storage. From the spectra of acyclovir, physical mixture of acyclovir and polymers. It was observed that all characteristic peaks of Acyclovir were present in the combination spectrum thus indicating compatibility of Acyclovir and polymer (Hussain H, et al., 2014) (Figures 4 and 5).

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed to characterize the surface of the formed micro sponge, the micro sponge particles are spherical for F1 and F5 formulation.

Loading efficiency

From the results obtained, it was observed that the F5 have higher entrapment as compared to other formulation like F1=89.34%, F2=85.65%, F3=91.48%, F4=88.67%, F5=95.88%, F6=92.43%, F7=94.34%.

Particle size distribution

It was found that particle size distribution was in the range of 30.77 µm to 47.71 µm, F5 formulation shows less particle size as compared to other formulations, F4 formulation has maximum particle size range to 47.71 µm, and increase in amount of polymer increased the particle size of micro sponges (Figure 6).

Table 1: Formulation design

Sl. no	Ingredients	Formulation code						
		F1	F2	F3	F4	F5	F6	F7
1	Acyclovir (mg)	300	300	300	300	300	300	300
2	Hpmc+Ec (g)	3:3	3:4:5	3:6	3:12	3:9	3:10.5	3:7.5
3	Dichloromethane (mml)	70	70	70	70	70	70	70
4	Pva (mg)	225	225	225	225	225	225	225
5	Glycerine (%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Distilled water (ml)	450	450	450	450	450	450	450



Figure 1: Formulation of microsponge loaded acyclovir



Figure 2: Microscopic view of microsponge

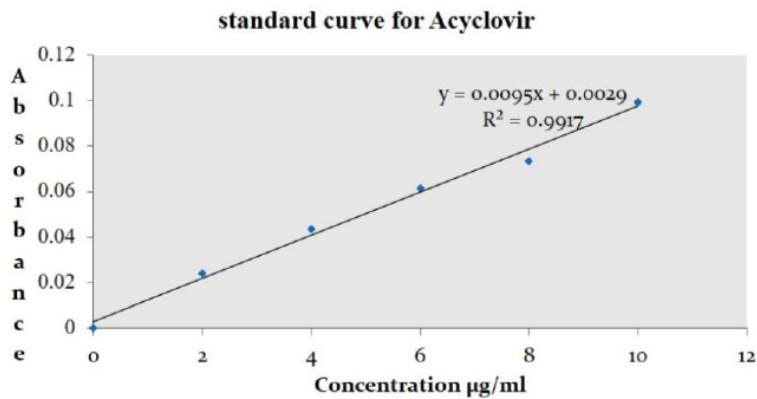


Figure 3: Calibration curve of acyclovir

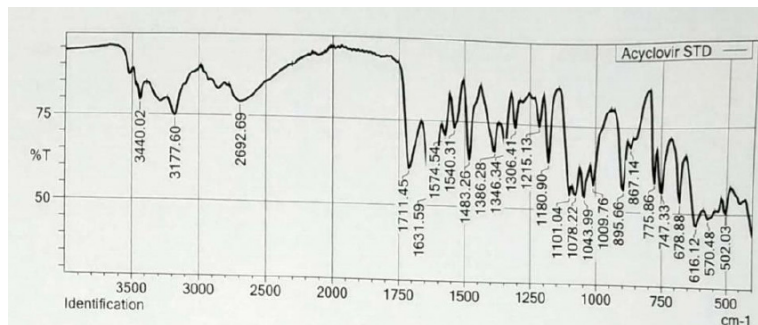


Figure 4: IR spectra of acyclovir (pure drug)

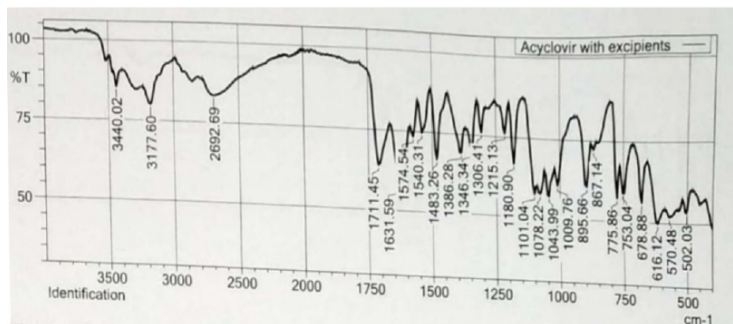


Figure 5: IR spectra of physical mixture of acyclovir and all excipients

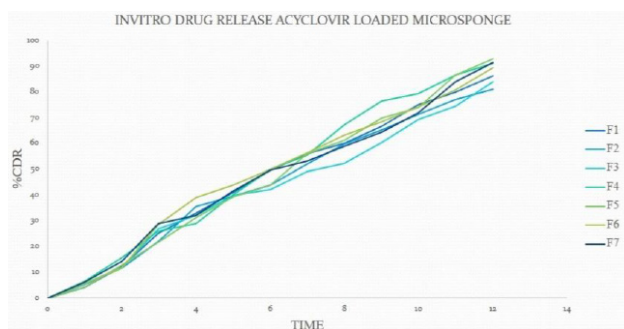


Figure 6: *In vitro* drug release of micro sponge (F1-F7)

Where dark blue: F1; Olive green: F2; Dark green: F3; Sea blue: F4; Light green: F5; Yellow: F6; Navy blue: F7

CONCLUSION

A maximum of 95.67% drug entrapment efficiency was obtained in the acyclovir micro sponges. F5 formulations ACV micro sponges show the maximum drug release. On the basis of particle size, entrapment efficiency and morphology, *in vitro* release studies and its kinetics data, F5 (formulation) was selected as optimized formulation.

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