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The microsponge delivery system of Acyclovir: Preparation, characterization and *in-vitro* evaluation

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ABSTRACT

The aim of the present study was to develop and evaluate microsponge based topical delivery system of acyclovir for sustained and enhanced drug deposition in the skin. Microsponges containing acyclovir were prepared by an emulsion solvent diffusion method. The effect of formulation variable such as drug: polymer ratio, stirring speed, internal phase on the physical characteristics of microsponges were analyzed in order to optimize the formulation. These two microsponge formulation were prepared as gel in 0.35 %w/w carbopol and studied for pH, viscosity, spreadability, drug content, and in vitro release. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. The formulations were subjected to in vitro release studies and the results were evaluated kinetically and statistically. Developed microsponges were spherical and porous, and there was no interaction between drug and polymer molecules. Drug release through cellulose dialysis membrane showed diffusion controlled release pattern from microsponge based formulations by 8 h. acyclovir was stable in topical gel formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of viral infections and reduce the side effects.

Keywords: Microsponge; acyclovir, Porosity; Drug release.

INTRODUCTION

Acyclovir is commonly used in topical formulations for the treatment of Herpes labialis (cold sores). Acyclovir is available as a tablet, cream, ophthalmic ointment and i.v. Acyclovir topical cream is commonly associated with: dry or flaking skin or transient stinging/burning sensations. Infrequent adverse effects include erythemia or itch. The degree of irritation is believed to be related to the amount of acyclovir present in the skin, which the encapsulation of acyclovir can reduce the side effects to a great extent [1].

Preparation of sustained release dosage forms is one of the main objectives in drug formulation. Many controlled release dosage forms is are designed to release the drug at slow rates maintaining uniform selective therapeutic drug levels for an extended period of time. These dosage forms have the advantages of reducing the frequency of dosing, lowering the adverse effects and improving the patient compliance [2].

The successful formulation to control drug release for the required duration of time with optimum release pattern on various factors such as the ratio of polymer to drug, type of dosage form, and route of administration [3].

Polymeric microsponge and microspheres have received much attention as topical drug delivery systems in recent years and used to modify and retard drug release [4]. Their preparation results in the coating of the individual drug particles by inert polymeric materials, through which the drug would diffuse at a controlled and predictable rate to the surrounding medium [5].

There are two techniques used to produce polymeric microsponges drug delivery systems, which include a liquid – liquid suspension polymerization and quasi-emulsion solvent diffusion [6].

The main aim of the present work is to develop the acyclovir microsponges are prepared with various polymer concentrations by quasi-emulsion solvent diffusion method, for prolonged, relatively constant effective level of acyclovir and improve patient compliance.

MATERIALS AND METHODS

Acyclovir was received as a gift sample from orchid, Chennai. Ethyl cellulose was purchased from C. D. H New delhi. Poly vinyl alcohol was procured from qualigens fine chemicals, Mumbai and Dicholoromethane was purchased from alfa aesar, delhi. All other reagents used were of analytical grade.

Preparation of Acyclovir Microsponges

Acyclovir microsponges were prepared by quasi emulsion solvent diffusion method. In this method, the organic internal phase containing acyclovir and ethyl cellulose in 20 ml dichloromethane was gradually added in to 60ml of distilled water which contained different concentration (1, 1.5, 2%) of polyvinyl alcohol as emulsifying agent. The mixture was stirred for 8 hours, at 25^{o}c. The formed microsponge were filtered and washed with distilled water before being tray-tried at room temperature. For the evaluation of the effect of drug: polymer ratio on the physical characteristics of microsponge, different weight ratios of drug to ethyl cellulose (1:1, 1: 2, 1: 3) were employed. In all these formulations, the total amount of drug was kept constant [7].

Differential Scanning Calorimetry

Thermal analysis of MP, ethyl cellulose, and MP-loaded microsponge-based formulations were studied employing differential scanning calorimeter (Mettler Toledo DSC, USA). Samples (5 mg) were accurately weighed into aluminum pans and sealed. All samples were run at a heating rate of 10°C/min over a temperature range 25–300°C in atmosphere of nitrogen.

Scanning Electron Microscopy
The morphology of microsponges was examined using a scanning electron microscope (GEOL 5400, USA) operating at 20 kV. Dried microspheres were coated with gold– palladium alloy for 45 s under an argon atmosphere before observation.

Drug entrapment efficiency
The acyclovir microsponges' equivalent to 100mg of acyclovir were accurately weighed and crushed. The powdered of microsponges were dissolved in ethanol (10ml) in volumetric flask (100ml) and made the volume with 0.1 N Hcl. This solution is then filtered through whatmann filter paper No.44. After suitable dilution the absorbance was measured at 254nm using spectrophotometer and the percentage drug entrapped was calculated.

The amount of acyclovir encapsulated in microsponge was estimated by using the following formula.

$$\text{Encapsulation efficacy (\%)} = \frac{\text{Amount of drug released from lysed acyclovir microsponge}}{\text{Amount of drug initially taken to prepare acyclovir microsponge}}$$

Preparation of acyclovir microsponge gel
Accurately weighed amount of carbopol 940 was taken and dissolved in water using propeller. In another beaker, microsponges containing Acyclovir (free or entrapped, equivalent to) drug dissolved in ethanol and added to carbopol solution by stirring, followed by addition of PEG 400. Neutralized the carbopol solution by slowly adding triethanolamine solution with constant stirring until the gel is formed. The pH of the final gel formed was determined.

Physiochemical study of acyclovir microsponges gel:
The study includes determination of pH, viscosity, spreadability and tube extrudability [8].

Determination of pH:
The gel pH was measured by using digital type pH meter (HICON) by dipping the electrode completely in the microsponge gel so as to cover the electrode. This is to confirm that the pH of the formulation is near to skin pH.

Viscosity:
A brook field viscometer (Brookfield engineering laboratories, INc) was used to measure the viscosity (cps) of the microsponge gel at a controlled temperature (25^{o}c) spindle number 21 was rotated at 100rpm.

Spreadability:
Spreadability of the formulation was determined by an apparatus, which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pully at one end. A rectangular ground glass plate (20cm×20cm) was fixed on the block. Two grams of the formulation was sandwiched between the ground plates. The movable glass plate is provided with hook. A 300gm weight was placed on the tip of two plates for five minutes to expel air and to provide a uniform film of the formulation between the plates. Excess of the

formulation was scrapped off from the edges. The top plate was then subject to pull off a 30gm, initially with the help of a string attached to the hook and moves over the pulley. The time required by the top plate to move at distance of 10cms was noted. A shorter time interval indicates better spreadability. In case the slide did not move with 30gms, weight was increase gradually. In case the slide was moving fastly, the weight was decreased gradually.

The spreadability was calculated by using the following formula

$$\text{Spreadability} = \frac{\text{weight tied to the upper side} \times \text{length of glass slides}}{\text{Time taken in seconds}}$$

Tube extrudability:

The apparatus used t measure is extrudability apparatus. A closed collapsible tube containing formulation was pressed firmly at the crimped end by keeping weight. When cap was removed, formulation extruded until the pressure dissipated. Weight in grams required to extrude a 0.5cm ribbon of the formulation in 10seconds was determined. The experiments were repeated thrice and the average value is reported.

Drug release studies

In vitro release studies were carried out using Franz diffusion cells with a receptor compartment volume of 20 ml and an effective diffusion area of 3.14 cm^2. Cellulose dialysis membrane (Himedia, Mumbai, India) was soaked in receptor media (0.1N Hcl) for 24 h before experiment. A predetermined amount of acyclovir microsponges gel was placed on the donor side. The receptor medium was continuously stirred at 600 rpm and thermo-stated at 32±0.5°C with a circulating jacket. At predetermined time intervals, 2 ml samples were withdrawn from the receiver compartment and replaced with an equal volume of fresh 0.1N Hcl . The collected samples were analyzed by UV analysis (254nm) to determine acyclovir content. The drug release data were analyzed to determine the release kinetics (zero-order and first-order) as well as diffusion controlled mechanism (Higuchi model) using linear regression analysis [9].

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

The thermograms of acyclovir, ethyl cellulose and poly vinyl alcohol and physical mixture of acyclovir, ethyl cellulose, poly vinyl alcohol,are shown in Figures. 1, 2, 3 and 4. Acyclovir showed characteristic endothermic peaks at 120.61ºC,150.48ºC and 254.07ºC. ethyl cellulose showed a broad peak at 264.9ºC, poly vinyl alcohol showed characteristic peak at 205.78. The thermogram of Physical mixture of acyclovir, ethyl cellulose, poly vinyl alcohol exhibited all characteristic peaks of acyclovir, thus indicating that there was no change in the crystallinty of acyclovir.

Particle Size Analysis of Microsponge

The Microsponges were subjected to microscopic examination (S.E.M) for characterizing size and shape of the Microsponges. SEM images showed the microsponges to be porous and it's have spherical shape. The pores were induced by the diffusion of the solvent from the surface of

the microsponges. The mean particle size of acyclovir microsponges were shown in the table. Photographs were given in Fig No. 1.

Fig no 1: DSC Thermograms - Etylcellulose

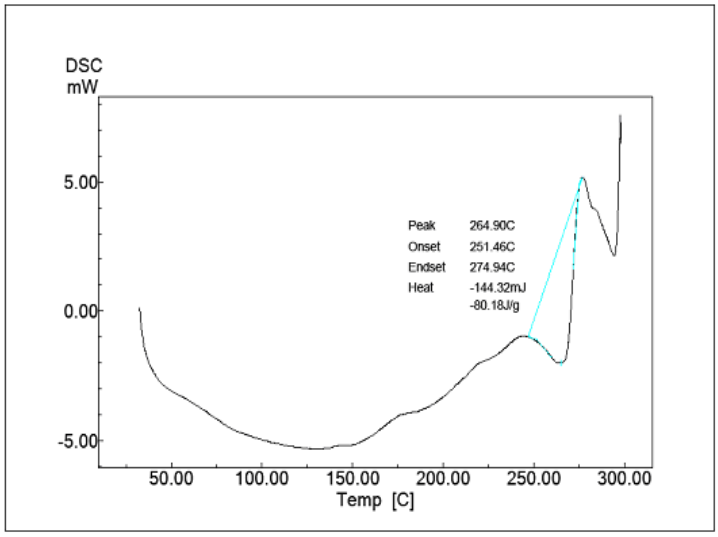


Fig no 2: DSC Thermograms – Acyclovir+PVA+Ethyl alcohol

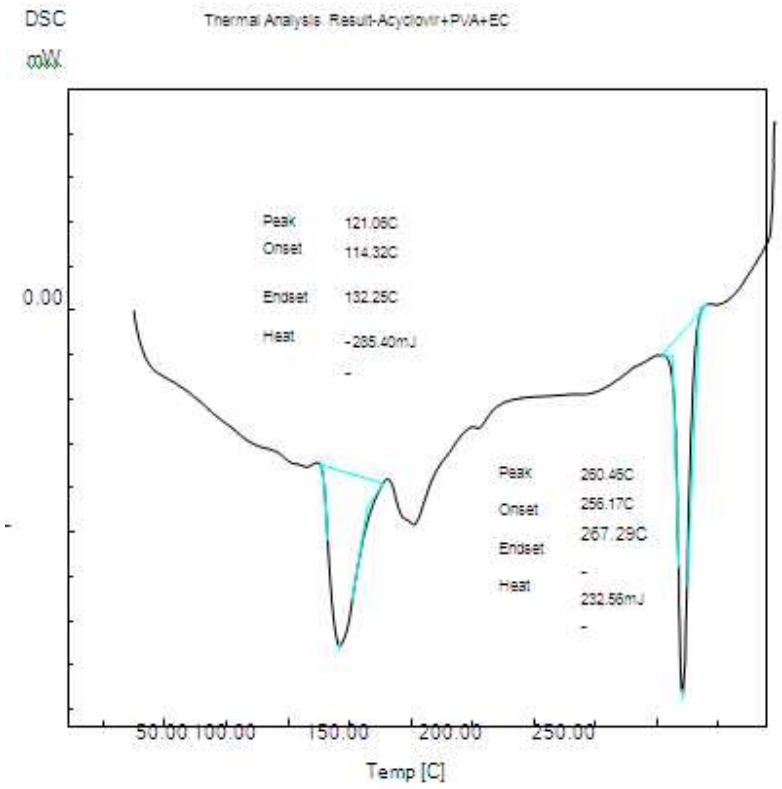


Fig no 3: DSC Thermograms – PVA (poly vinyl alcohol)

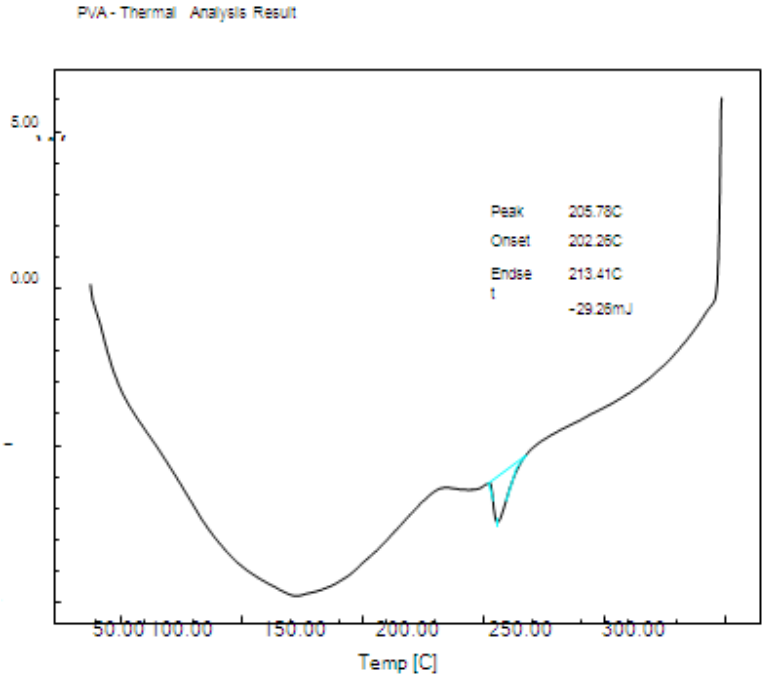


Fig no 4: DSC Thermograms – Acyclovir

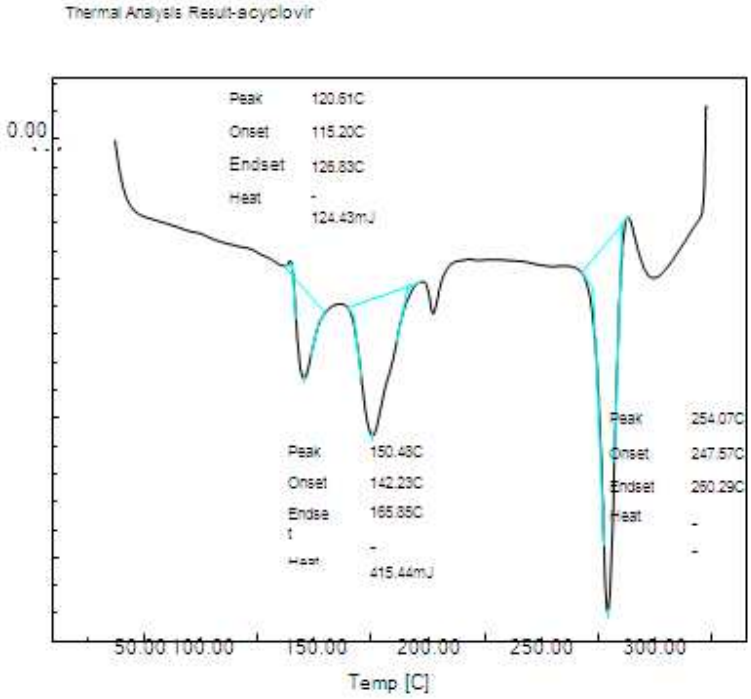
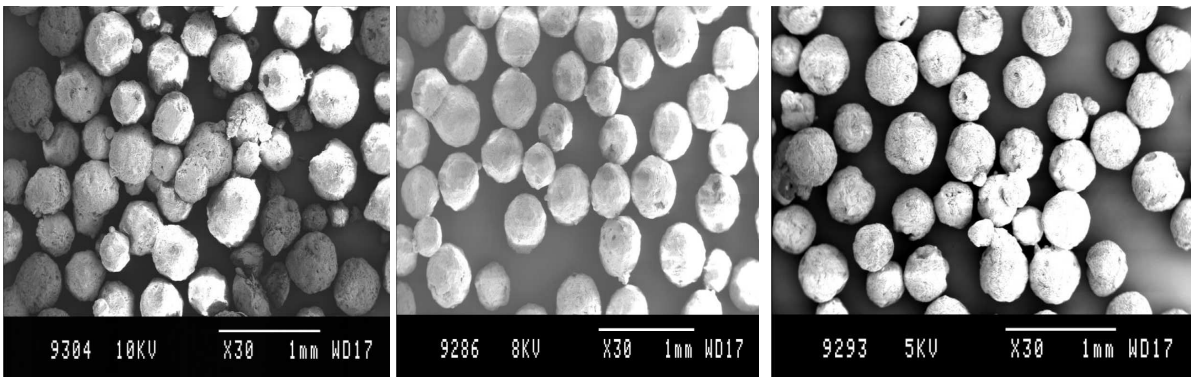


Fig No. 5. SEM Photograph of acyclovir loaded microsponge formulations



The effect of various polymer concentrations on the produced microsponge.

The formulation variables were altered and optimized to obtained the microsponge with maximum drug entrapment and desired size. The drug entrapment efficiency of all the formulation was in the range between 38.46 – 71.87%.

Table 1: Microsponge formulation prepared by quasi-emulsion solvent diffusion method

Ingredients	Microsponges Constituents Formulation					
	F1	F2	F3	F4	F5	F6
Acyclovir (gm)	1	1	1	1	1	1
Ethyl cellulose (gm)	1	1	1.5	1.5	2	2
Dichloromethane (ml)	5	5	5	5	5	5
Glycerol (ml)	1	1	1	1	1	1
PVA (gm)	1	2	1	2	1	2
Distilled Water (ml)	200	200	200	200	200	200

Table 2- Effect of the Drug to Polymer in Physical Characterization

S. No	Formulation code	Mean diameter (µm)	Encapsulation efficacy (%)	Production yield (%)
1	F1	58	38.46±1.2	87.78
2	F2	58.2	53.29±0.8	88.18
3	F3	55.8	48.30±0.9	90.05
4	F4	56.6	71.87±1.9	91.5
5	F5	53.8	52.74±1.2	90.5
6	F6	54.8	62.18±1.4	92.8

The values are mean ±S.D (n=3)

Drug entrapment efficiency was high in F4 formulation with desired size was obtained. The results showed that the ratio of polymer played an important role in the encapsulation efficacy of microsponges. Drug entrapment efficiency of microsponge increases with increase in concentration of polymer ratio. However further increase in the polymer concentration (1:2) had no appropriate increase in percentage of encapsulation efficacy, it may due to approaching system saturation.

The concentration of emulsifier (PVA) has a key role to play in the preparation of microsponges. When the concentration of emulsifier was increased from 1-2%, the drug encapsulation efficacy was increased.

Table 3: Formulation of the acyclovir microsponges gel

Ingredients	Formulation- 1	Formulation - 2
Acyclovir Microsponge eqv. to acyclovir 1.0%w/w	1.0	1.0
Carbopol 940 (gms)	0.5	0.5
Ethanol (gms)	15	15
PEG 400 (gms)	15	15
Triethanolamine (gms)	5	5
Water q.s(gms)	100	100

Characterization of acyclovir microsponges gel

The formulated microsponges gels were evaluated for pH, viscosity, drug content, spreadability and tube extrudability. The results are shown in table.

Table 2- Characterization of acyclovir microsponges gel

S. No	Formulation code	pH	Viscosity (cps)	Drug Content (%)	Spreadability (g.cms)	Extrudability (g)
1	F1	6.72	40500	90.16	32	460
2	F2	6.62	41000	89.85	31	500
3	F3	6.56	41000	91.06	35.5	540
4	F4	6.8	42500	93.04	35	530
5	F5	6.78	42600	85.68	31	510
6	F6	6.58	42800	87.44	30	520

Drug permeation studies

Comparative study of the diffusion profile of the drug from six prepared formulations with different polymer concentration (1%, 1.5%, 2%). A maximum percentage of 69.81% was obtained from formulation F-1 during 6 hrs study.

Table 3 - Comparative percentage drug release of Acyclovir microsponge formulations

S. No	**Time in hours (hrs)**	Comparative percentage drug release					
		F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
1	0.25	3.6	2.54	2.64	1.35	0.54	1.45
2	0.5	6.18	5.81	3.32	2.42	1.04	4
3	0.75	11.6	10.90	4.78	3.82	1.63	9.81
4	1	14.54	13.45	6.40	4.46	2.82	09.36
5	2	24.36	22.54	15.76	14.89	10.50	16.27
6	3	36.72	33.45	32.56	29.78	17.18	26.9
7	4	47.27	44.72	48.59	42.94	29.56	35.27
8	5	58.90	52.72	54.64	52.96	38.34	43.27
9	6	69.81	60	58.04	61.06	46.64	52.36

Fig No. 6. Comparative diffusion profile of acyclovir microsponge formulations

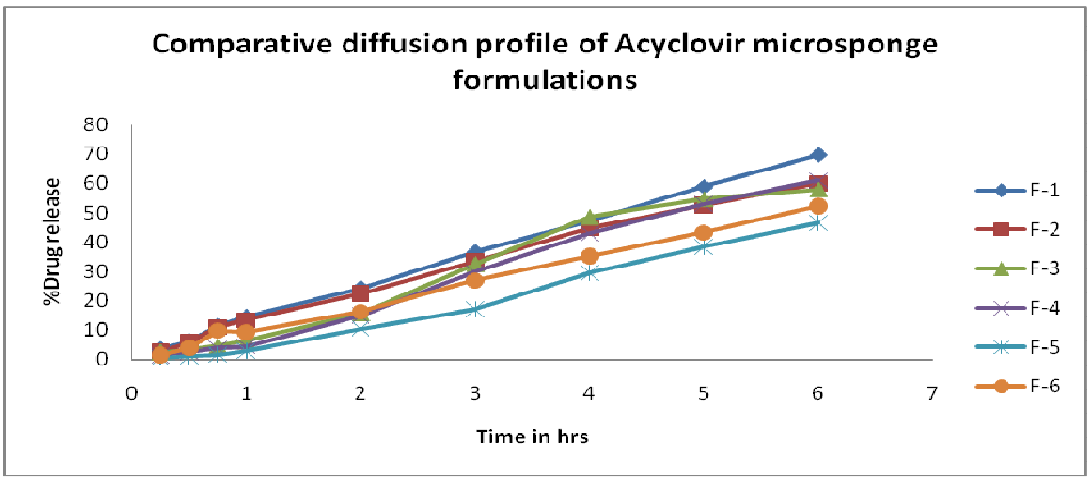


Table 4- *In vitro* release kinetic parameters (Correlation Coefficient) of acyclovir microsponge formulation

Drug : polymer ratios	Kinetic Models		
	Zero order	First Order	Higuchi Equation
Formulation-1	0.919	0.932	0.991
Formulation-2	0.956	0.946	0.996
Formulation-3	0.986	0.870	0.993
Formulation-4	0.937	0.973	0.983
Formulation-5	0.954	0.990	0.990
Formulation-6	0.963	0.972	0.995

In order to obtain meaningful information for the release, the drug release data were fitted to various kinetic models. Table (4) summarizes the correlation coefficient (r) for the different release kinetic models of acyclovir microspheres. Models with higher r values were judged to be more appropriate models for the release data. The linear relationship between the logarithms of the percentage drug remained to be released from the microspheres as well as the relationship between the amount of acyclovir released and square root of time, indicated that the drug release appeared to fit either first order or Higuchi diffusion model. Higuchi plots were found to be of highest linearity with correlation coefficient greater than that of the zero order kinetics and corresponded to that of the first order kinetics indicating that the drug release mechanism from these microsponges was diffusion controlled. Kinetic Studies revealed that release of Acyclovir from developed microsponges was found to be very close to zero-order kinetics indicating that the concentration was nearly independent of drug release.

CONCLUSION

Acyclovir microsponge formulations were formulated by using ethyl Cellulose (different ratios) and Poly vinyl alcohol as an emulsifier. Drug entrapment efficiency of Microsponges increases with increase in concentration of ethyl cellulose. It was observed that an increase in the polymer concentration produced more number of microsponges per ml of the dispersion formed, resulting in increased percentage of drug entrapment up to pre-saturation extent. However, further

increase in the polymer concentration had no proportionate increase in percentage drug entrapment due to approaching system saturation.

The in-vitro Diffusion study of formulations F_1 to F_6 shows a retarded release with increase percentage of ethyl cellulose. Kinetic studies shows that Higuchi plot were found to be highest linearity with correlation coefficient greater than that of the zero order kinetics and corresponded to that of the first order kinetics indicating that the drug release mechanism from these microsponges was diffusion controlled.

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