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Research Article

Formulation and Evaluation of Fluconazole Microsponge using Eudragit L 100 by Quasi Emulsion Solvent Diffusion Method

Hans Mansi^{*1}, Dua Jagdeep Singh¹, Prasad D.N², Monika¹, Sharma Diksha¹¹Department of Pharmaceutics, Shivalik College of Pharmacy Nangal, Punjab, India²Department of Pharmaceutical Chemistry, Shivalik College of Pharmacy Nangal, Punjab, India

ABSTRACT

The aim of the present study is to formulate and evaluate the fluconazole microsponge by using Eudragit L 100. Microsponge was made because they provide controlled as well as target specific release of the drug. Thus study the effect of stirring rate on the formation of microsponge. Microsponge containing Fluconazole were prepared by quasi-emulsion solvent diffusion method at different stirring rate i.e 500, 800, 1000, 1200 and 1500 rpm. Particle size of prepared microsponge was observed in the range of 76.2 to 32.5 μ m. Scanning electron microscopy revealed the porous, spherical nature of the microsponges. The production yield, entrapment efficiency and drug content were found to be 78.24%, 82.76%, 81.36%. The impact of Drug: Polymer ratio and process variables i.e stirring speed and stirring time on the physical features of microsponges like production yield, mean particle size, entrapment efficiency were examined. It was shown that production yield, drug content and entrapment efficiency was found to be increase with increase in drug polymer ratio while drug: polymer ratio has reverse effect on particle size, as drug: polymer ratio increase, particle size decrease. As the polymer concentration increased, more amount of polymer surrounding the drug, thus increasing the thickness of the wall of the polymer matrix which lead to extended diffusion path and ultimately to lesser drug release or more sustained release. The effect of stirring rate on the morphology of microsponge. The formulation with higher drug to polymer ratio 1:8 (i.e F4) was chosen to investigate the effect of stirring rate on the morphology of microsponges. The dispersion of the drug and polymer within the aqueous phase was found to be dependent on the agitation speed. As the speed was increased the size of microsponges was reduced and the microsponges were found to be spherical and uniform.

Keywords: Novel drug delivery system, Microsponges, Eudragit L 100, Fluconazole, Quasi-emulsion solvent diffusion method.

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*Address for Correspondence:

Hans Mansi, Department of Pharmaceutics, Shivalik College of Pharmacy, Nangal, Punjab, India (Email: mansihns@gmail.com)

INTRODUCTION

A microsponge delivery system is a uniform, spherical, porous, highly cross-linked polymeric microspheres or tiny sponge-like spherical particles with large porous surface. They enhance stability, reduced side effects and modify drug release. It consists of micro-porous beads, typically 10-25 microns in diameter, loaded with active agents. Besides, they may enhance stability, modify drug release and reduce side effects favourably. Like a true sponge, each microsponge consists of a myriad of interconnecting voids of particles from 5-150 μ m within a non-collapsible structure, with a large porous surface¹.

Microsponge systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated products such as a gel, cream, liquid or powder².

Microsponge drug delivery system can confer increased efficacy for topically active agents with enhanced safety, improved aesthetic properties and extended product stability in an well-formed manner. Subjected over the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/gm. When applied to the skin surface, the microsponge drug delivery system discharges its active ingredient on a time mode and also in respond to other stimuli³. Microsponges have the capacity to adsorb or load a high degree of active materials into the particle or onto its surface. Its huge capacity for entrapment of actives up to 3 times its weight differentiates microsponges from different mode of dermatological delivery systems. Recently, microsponge delivery system has been successively addressed for the controlled release of drugs onto the epidermis with assurance that the drug remains chiefly localized and does not enter the systemic circulation in

major amounts and resulted in a new creation of highly efficacious and well tolerated novel products ².

It is unique technology for the controlled release of topical agents. Fluconazole is a triazole antifungal agent used for the treatment of systemic and superficial fungal infection. The purpose of the present investigation was to formulate and evaluate fluconazole loaded microsponges using Eudragit L 100 for the controlled release of drug and study the effect of stirring rate on the formulation of microsp sponge ⁴.

MATERIALS AND METHODS

Materials: Fluconazole gift sample obtained from Haustus Biotech. Pvt. Ltd., Tahliwal (Una), Dibutyl phthalate was procured from SD fine chem. Ltd. Mumbai, Polyvinyl alcohol was procured from Glaxo smith kline pharmaceuticals Ltd. Mumbai, Dichloromethane was procured from RFCL limited Gujrat India, Ethanol and KBr was procured from Central drug house (p) Ltd. New Delhi, and distilled water.

Method of Preparation of Fluconazole Microsponges

Fluconazole Microsponges were prepared by quasi-emulsion solvent diffusion method. To prepare the internal phase, fluconazole was dissolved in 20 ml of dichloromethane: ethanol (1:1) mixture to dissolve both the drug and the polymer (Eudragit L 100) and to this add 0.5 ml dibutyl phthalate as a plasticizer. The external phase containing 100 mg of PVA in water. The external phase was placed in the vessel with propeller stirrer rotating at different rpm, to this add slowly internal phase. The system was thermally controlled at 25° C in a water bath. Agitations up to 30 min permit the formation of microsponges and continue stirring for 8h to get desired rigid microsponges. After 8h stop stirring filter the rigid micro sponges through the filter paper (Whatmann filter paper 0.45 µm), washed with distilled water and dried at room temperature ^{5,6}. Fluconazole microsponges were prepared using various drug: polymer ratios i.e. 1:2, 1:4, 1:6, 1:8, 1:10 at different stirring rate of 500, 800, 1000, 1200 and 1500 rpm. The formula of various microsp sponge are shown in table 1.

Table 1 Micro sponge Formulations of Fluconazole Microsponges

Formulation Code	Drug: Polymer ratio	Drug (mg)	Eudragit L 100 (mg)	Ethanol+ Dichloro-methane (ml)	Polyvinyl alcohol (mg)	Distilled Water (ml)	Dibutyl phthalate (ml)	Stirring rate (RPM)
F1	1:2	100	200	20	100	150	0.5	500
F2	1:4	100	400	20	100	150	0.5	800
F3	1:6	100	600	20	100	150	0.5	1000
F4	1:8	100	800	20	100	150	0.5	1200
F5	1:10	100	1000	20	100	150	0.5	1500

Evaluation of microsponges

Production/ percentage yield: The dried microsponges of each batch are weight separately and percentage yield is calculated by using following equation:-

$$\text{Percentage yield} = \frac{\text{practical weight}}{\text{Theoretical weight}} \times 100$$

Entrapment efficiency (EE)/ Loading efficiency and Actual Drug Content: 100 mg of microsponges were accurately weighted. They were powdered and extracted with 100 ml of method. Further it was serially diluted with pH 7.4 phosphate buffer ^{7,8}. The resulting solution was analysed for fluconazole drug content by measuring absorbance in a UV spectrophotometer at 260nm using pH 7.4 phosphate buffer as blank. The studies were carried out in triplicate. The actual drug content and entrapment efficiency were deliberate as:

- **Actual drug content(%)**=(M_{act}/M_{ms})*100
- **Entrapment efficiency(%)**=M_{act}/M_{the}*100

Where M_{act} is the actual amount of fluconazole in weighed quantity of microsponges, M_{ms} is the weighed quantity of microsponges and M_{the} is the theoretical amount of fluconazole in microsponges.

Average size of microsp sponge

Particle size of all the prepared batches of microsp sponge was determined using optical microscopy at 10X and 40X. The microsponges were placed on glass and observe under optical microscope. The size of 50-100 microsponges was

measured using optical microscope. Then the particle size, shape and surface was calculated.

Scanning electron microscopy

Scanning electron microscopy is an electron optical imaging technology that confers photographic pictures and elemental knowledge. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as nano meter to deca meter, the sample is installed in an evacuated chamber and check in a controlled pattern by an electron beam. Interaction of the electron beam with the sample originate a kind of physical phenomena that when discover are used to form pictures and confer elemental information about the samples ^{9,10}. Microsp sponge were fixed on aluminium studs and coated with gold using a sputter coater SC 502, under vacuum [0.1 mm Hg]. The microsp sponge were then analysed by scanning electron microscopy (SEM).

In vitro dissolution studies: The release of fluconazole from microsp sponge was investigated in pH 7.4 phosphate buffer as dissolution medium (900ml) using USP type I apparatus. A sample of microsp sponge equivalent to 100mg of fluconazole was taken in the basket. A speed of 52 rpm and temperature of 37± 0.5 °c was maintained throughout the experiment. At fixed intervals, aliquots (5ml) were withdraw and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using Double beam UV spectrophotometer at 260 nm against blank. The studies were carried out in triplicate ^{11,12}.

Kinetic Modelling

Data obtained from in-vitro release studied was evaluated to check the goodness of fit to various kinetics equations for quantifying the phenomena controlling the release from microspheres. The kinetic models were used like zero order, first order, and Higuchi and Korsmeyer - peppas model. The goodness of fit was evaluated using the correlation coefficient value (R^2)^{13,14}.

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. cumulative of drug released versus time (zero order kinetic models).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log of cumulative drug release versus log time (Korsmeyer – peppas model)

Zero Order Kinetics: It gives the system in which the drug release rate is independent on its concentration¹⁵.

$$Q_t = Q_0 + K_0 t$$

Where

Q_t = Amount of drug dissolved in time t.

Q_{0s} = Initial amount of drug in the solution,

K_0 = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Q_t versus t will give a

Straight line with a slope of K_0 and an intercept at zero.

First Order Kinetics

It gives the drug release from the systems in which the release rate is dependent on concentration¹⁷.

$$\log Q_t = \log Q_0 + kt/2.303$$

Where

Q_t = released amount of drug in time t.

Q_0 = initial amount of the drug containing solution

k = first order release constant

If the first order drug release kinetic is followed, then a plot of $\log (Q_0 - Q_t)$ versus t will be

Straight line.

With a slope of $kt/2.303$ and an intercept at $t=0$ of $\log Q_0$.

Higuchi Model

It explains the fraction of drug release from a matrix is proportional to square root of time.

$$M_t/M_\infty = kt^{1/2}$$

Where

M_t And M_∞ = cumulative amounts of drug release at time t and infinite time,

And k = Higuchi dissolution constant reflection formulation characteristics. If the Higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will be straight line with slope of k ¹⁶.

Korsmeyer- Peppas model (Power Law)

The power law explains the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$$M_t / M_\infty = kt^n$$

$$\log [M_t / M_\infty] = \log k + n \log t$$

Where M_t and M_∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t),

k = constant incorporating structural and geometrical characteristics of CR device,

n = diffusion release exponent indicative of the mechanism of release for drug Dissolution.

To characterize the release mechanism,

The dissolution data { $M_t / M_\infty < 0.6$ } versus $\log t$ will be linear with slope of n and intercept gives the value of $\log k$. Antilog of $\log k$ gives the value of k ¹⁸.

Table 2 Interpretation of diffusion release mechanisms

n	Mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (Non- Fickian) diffusion
0.89	Case II transport
Above 0.89	Super case II transport

Effect of Formulation Variables on the Formation of Microsponges

Effect of drug: polymer ratio

In order to evaluate the effect of drug on the formation of microspunge, different Eudragit polymer to Fluconazole ratios (1:2, 1:4, 1:6, 1:8 and 1:10) were used to prepare microsponges. The formed microsponges were evaluated for their appearance, drug content, particle size and entrapment efficiency¹⁹.

Effect of stirring speed on the formation of microsponges

In order to evaluate the effect of stirring speed on the formation of microsponges, were prepared with different RPM of 500, 800, 1000,1200 and 1500, the formed microsponges were evaluated for their drug content and particle size^{20,21}.

RESULT AND DISCUSSION

Standard curve of fluconazole and absorption maxima

A precise, sensitive and accurate method for estimating fluconazole was developed using UV visible spectrophotometer.

Preparation of standard stock solution

Accurately weigh 100 mg fluconazole was taken in a clean And dry 100ml volumetric flask and was dissolved in 7.4 phosphate buffer. Then 1 ml of above solution was taken and then dissolve in another 100ml of 7.4 phosphate buffer (stock solution) than from the stock solution 1ml of solution was taken and dissolve in 100ml of 7.4 phosphate buffer to make 1µg/ml solution. After that 1,2,3,4,5,6,7,8,9,10µg/ml solutions were made by dissolving 1,2,3,4,5,6,7,8,9,10µg/ml solutions in 10 ml 7.4 phosphate buffer.

Procedure: From stock solution 1,2,3,4,5,6,7,8,9,10ml were withdrawn separately in different 10ml volumetric flasks and volume made in each case up-to 10ml of 7.4 phosphate buffer to produce the concentration 1,2,3,4,5,6,7,8,9,10µg/ml. Absorbance of these solutions were recorded at λ_{max} 260nm against (distilled water) blank using UV-visible spectrophotometer and standard curve was plotted between concentration v/s absorbance.

DETERMINATION OF ABSORPTION MAXIMA (λ_{max})

UV scan of fluconazole in phosphate buffer pH 7.4 was done. Analysis by UV spectrophotometer depicted absorption maxima of fluconazole at λ_{max} was 260 nm at pH 7.4 of phosphate buffer.

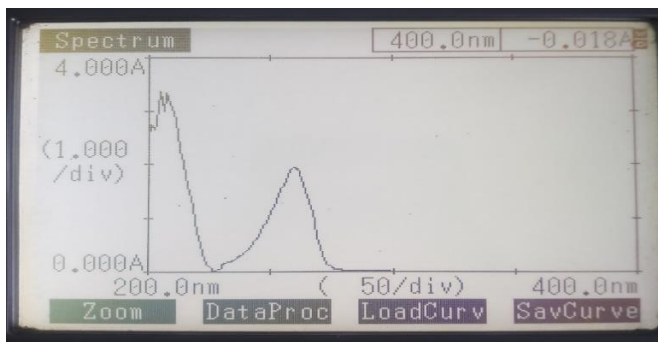


Fig. 1 Absorption spectra of Fluconazole

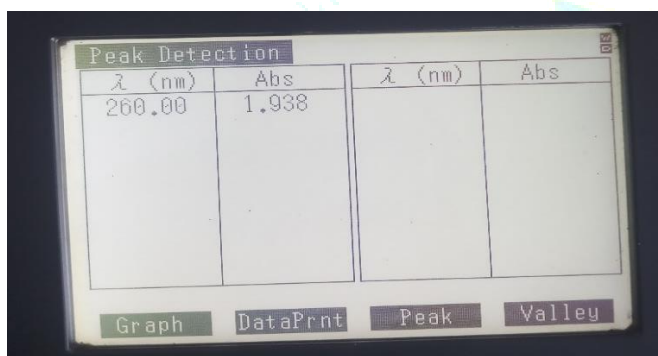


Fig. 2 Absorption maxima of Fluconazole

CONSTRUCTION OF CALIBRATION CURVE

Table 3 Calibration curve data for Fluconazole

conc. (µg/ml)	Absorbance
1	0.008
2	0.009
3	0.01
4	0.011
5	0.014
6	0.016
7	0.019
8	0.022
9	0.024
10	0.026

STANDARD CURVE OF FLUCONAZOLE IN PHOSPHATE BUFFER pH 7.4

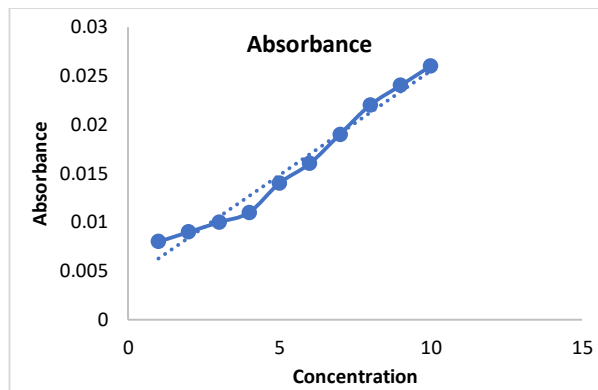


Fig. 3 Calibration curve of Fluconazole

Evaluation of microsponges

Production/Percentage yield (%)

The production yields of fluconazole are shown in fig 4. Production yield calculated for all microsponges ranged from 44.17 to 78.24%. The readings are mean of three different measurements \pm SD. It was found that production yield increases with increase in drug: polymer ratio.

Table 4 Production yield of Fluconazole microsponges

Formulation Code	Percentage Yield
F1	44.17
F2	56.47
F3	64.38
F4	78.24
F5	77.36

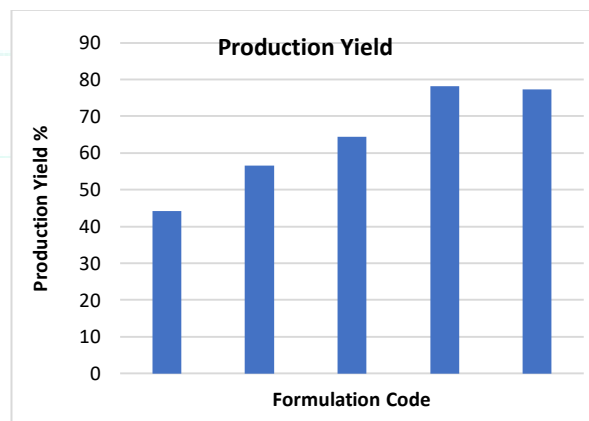


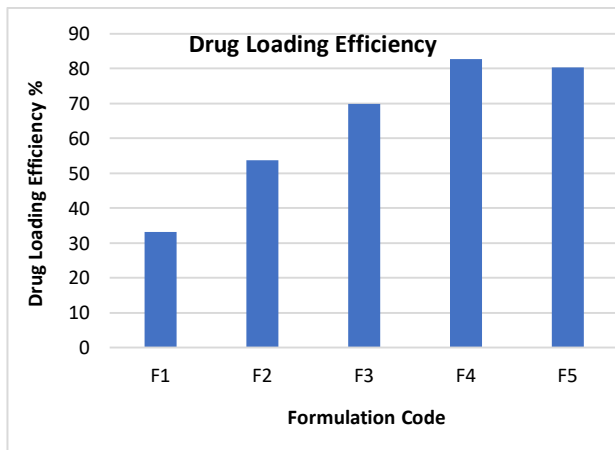
Fig. 4 Production yield of Fluconazole microsponges

Encapsulation efficiency/Loading efficiency (%)

The loading efficiency of fluconazole microsponges formulations are shown in fig. 5. The loading efficiency calculated for all microsponges range from 33.17 to 82.76% - the highest loading efficiency. The was found for the formulation F4 where a greater amount of drug was encapsulated. It is indicated that fluconazole/ Eudragit L 100 ratio (1:8) had the optimum capacity for drug entrapment.

Table 5 Encapsulation efficiency/ loading efficiency (%) of Fluconazole microsponges

Formulation Codes	Drug Loading Efficiency
F1	33.17
F2	53.74
F3	69.94
F4	82.76
F5	80.38

**Fig. 5 Encapsulation efficiency of Fluconazole microsponges****Size Analysis of Microsponge**

The average particle size of Fluconazole microsponge is ranges from 76.2 to 32.5. It was observed that as the ratio of drug to polymer increased, the particle size decreased. This could be due to the reason that in high drug to polymer ratio, the amount of polymer available per microsponge was comparatively less. In high drug: polymer ratio less polymer amount surround the drug and decreasing the thickness of

polymer wall and microsponges with smaller size were obtained.

Table 6 Average Particle Size of Microsponge

Formulation Code	Average Particle Size (μm)
F1	76.2
F2	64.4
F3	58.7
F4	32.5
F5	34.6

Drug Content

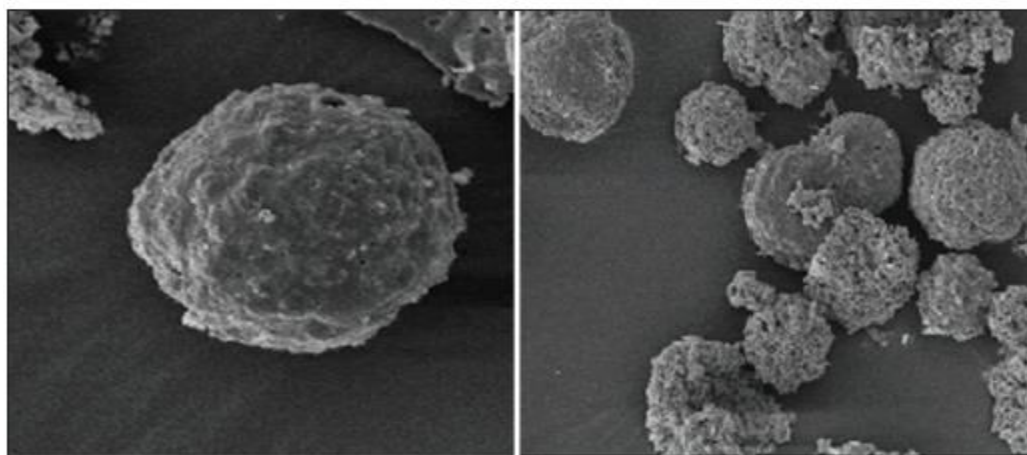
The drug content was determined by using phosphate buffer (pH 7.4) with the help of UV spectrophotometer by dissolving the formulation in phosphate buffer for 24 hours and then sample was taken and analyzed in UV-spectrophotometer. It was revealed that the formulation F4 have the greater drug content. The drug content from F1-F5 ranges between 37.44 to 81.36%.

Table 7 Drug Content of Microsponges

Formulation Code	Drug Content (mean \pm S.D) n=3
F1	37.44
F2	53.57
F3	69.35
F4	81.36
F5	80.24

Scanning electron microscopy

The SEM photographs of the microsponges are shown in fig. 6. SEM images showed the microsponges are porous and spherical in shape. No intact drug crystal are seen visually and inner structure was porous with void spaces. The pores were induced by the diffusion of the solvent from the surface of the microsponges.

**Fig. 6 Images showing structure and porosity of microsponge**

In-vitro dissolution studies

It was observed as the concentration of Eudragit was increased, the percent release of fluconazole decreases. The

increase in Eudragit concentration leads to the increased density of polymer matrix into the microsponges which result in an increased diffusional path length.

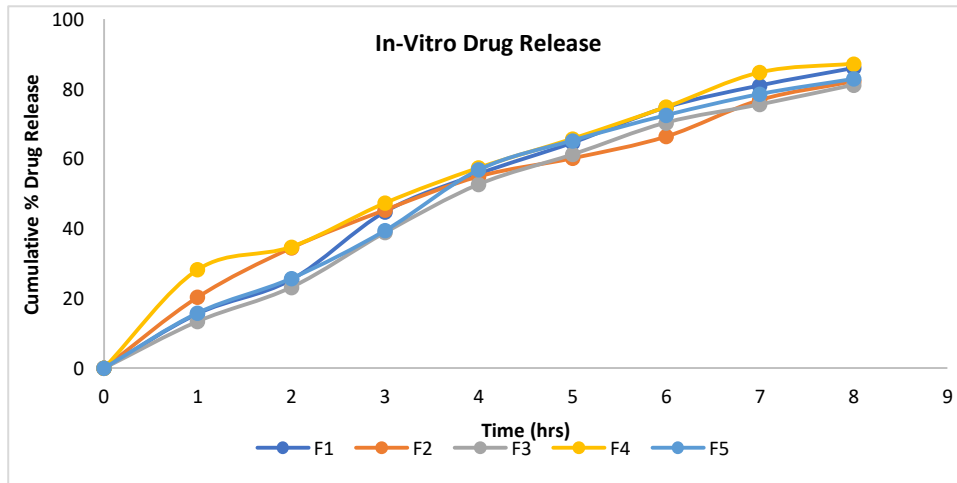


Fig. 7 In-Vitro Drug Release of Fluconazole Microsponge

Drug release kinetic of Fluconazole microsponges

Zero order release kinetics

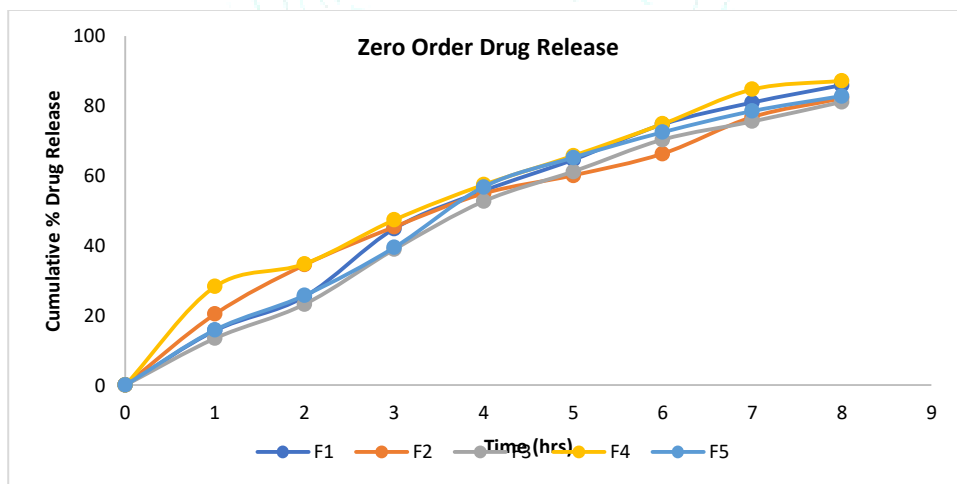


Fig. 8 Zero order release kinetic of Fluconazole microsponges

First order release kinetics

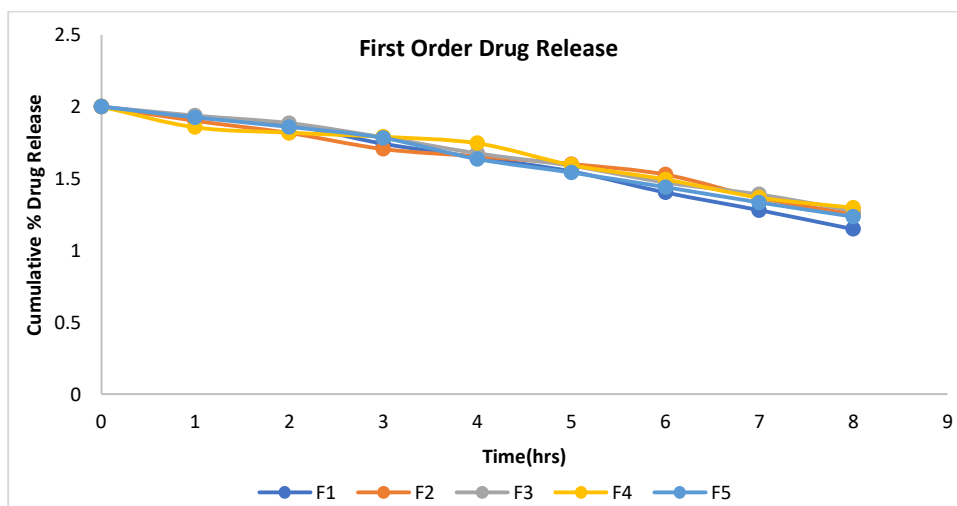


Fig. 9 First order release kinetic of Fluconazole microsponge

Higuchi release kinetics

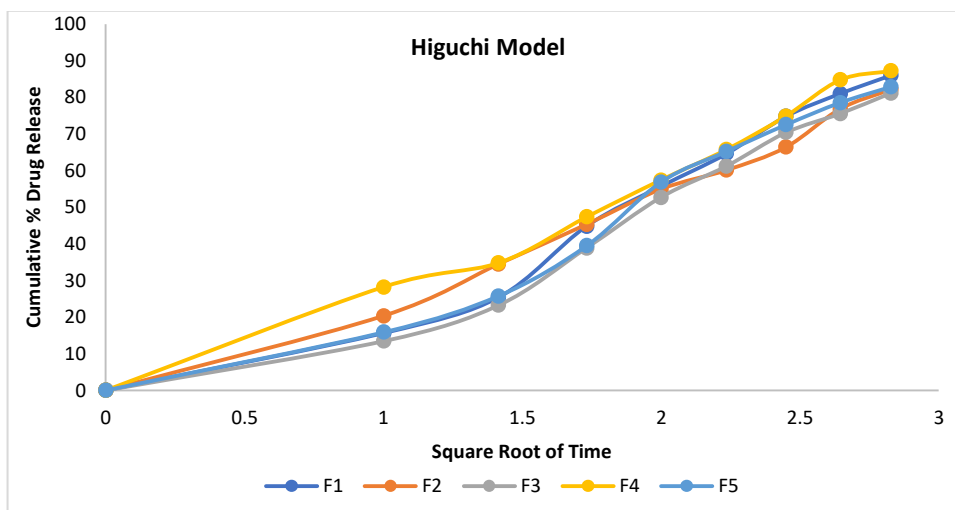


Fig. 10 Higuchi release kinetic of Fluconazole micro sponge

Peppas release kinetics

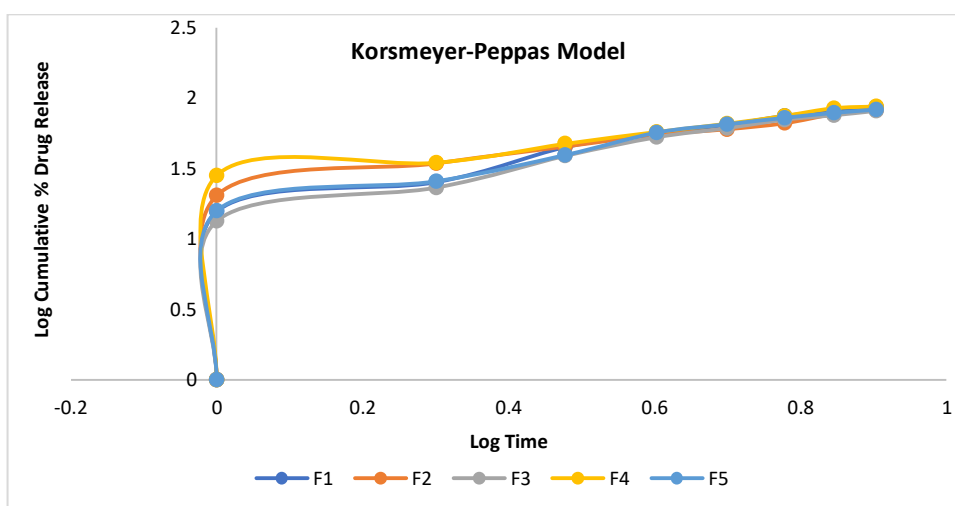


Fig. 11 Peppas release kinetic of fluconazole micro sponge

The mechanism of drug release from the formulation during the dissolution was determined using the zero order, first order, Higuchi equation and Peppas equation. All formulations were best fitted to zero order and Peppas plot. The best formulation F4 follows zero order kinetics.

Effect of Formulation Variables on the Formation of Microsponges

Effect of drug: polymer ratio

Production yield, entrapment efficiency and drug content was analysed to be increase with increase in drug polymer ratio, the drug: polymer ratio has reverse effect on particle size, as drug: polymer ratio increase, particle size decreases.

Effect of stirring rate on the morphology and yield of microsponges

The effect of stirring rate on the morphology of microsponges. The formulation with higher drug to polymer ratio was chosen to investigate the effect of stirring rate on the morphology of microsponges. The stirring rate was varied in the range of 500 to 1500 rpm. The dispersion of the drug and polymer into the aqueous phase was examined to be dependent on the agitation speed. As the speed was increased the size of microsponges was reduced and the

microsponges were found to be spherical and uniform. As increases in the drug: polymer ratio particle size was decreases, which could be correlated with the kinetics of micro sponge formation in the presence of comparatively lower concentrations of the polymer. It was also noted that at higher stirring rate, the production yield was increased.

Effect of polymer concentration

As the polymer concentration increased, more amount of polymer surrounding the drug, thus increasing the thickness of the wall of the polymer matrix which lead to extended diffusion path and ultimately to lesser drug release or extended release.

CONCLUSION

The aim of present study was to make the micro sponge of fluconazole so that the drug is able to release in a controlled and targeted manner. Fluconazole is formulated as microsponges by quasi-emulsion solvent diffusion method using polymer Eudragit L 100. Varied drug: polymer ratio and stirring rate reflected remarkable effect on the particle size, drug content and encapsulation efficiency. It was observed that as the drug to polymer ratio was increased, the particle size decreased. The mechanism of drug release from

the formulation F4 during the dissolution was determined using the zero order, first order, Higuchi equation and Peppas equation. All formulations were best fitted to zero order and Peppas plot. The best formulation F4 follows zero order.

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