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PREPARATION AND EVALUATION OF MICROPARTICLES CONTAINING FLUCONAZOLE FOR CONTROLLED RELEASE

***Nagendra R.**

Research Scholar, JJT University, Jhunjhunu, Rajasthan.

***Corresponding Author: Nagendra R.**

Research Scholar, JJT University, Jhunjhunu, Rajasthan.

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ABSTRACT

The present study aimed at preparation and Evaluation of microparticles for controlled release of Fluconazole using blend of polymers in the treatment of candidiasis. The microparticles of Fluconazole were prepared by spray drying technique. The prepared microparticles were evaluated for drug polymer compatibility, the results shown that there were no significant interactions. The encapsulation efficacy was ranging from 56-96%. The *in-vitro* drug release studies indicate the release of drug in a controlled manner over a period of 12 hrs. It was found that the Fluconazole release rate increased with a decreased amount of polymers. This can be adjusted by maintaining the concentration of the polymers. The formulation FC2 was found to be optimum formulation.

KEYWORDS: Fluconazole, Cancer, spray drying, Controlled release.

INTRODUCTION

Controlled drug delivery systems containing polymeric carriers has gained increased interest in last two decades, because they can be fabricated into films, rods capsules and microparticles[1] they mask the unacceptable taste or odor of drugs, they stabilize drugs sensitive to oxygen, moisture or light, they eliminate incompatibilities among drugs.

Fluconazole, commonly known as "*Diflucan"*, is an antifungal drug used for the treatment of both systemic and superficial fungal infections in a variety of tissues. It was initially approved by the FDA in 1990. This drug is an "*azole*" antifungal, in the same drug family as "Ketoconazole" and "Itraconazole". Fluconazole has many advantages over the other antifungal drugs including the option of oral administration. The side effect profile of this drug is minimal. It has been demonstrated as an efficacious treatment for vaginal yeast infections in one single dose.[2] Here an attempt was made to reduce the dosing frequency and to maintain the drug level at therapeutic concentration range, by formulating a Controlled drug delivery system in the form of microparticles using blend of hydrophilic and lipophilic polymers.

METHODS

Preparation of Microparticles

The microparticles were prepared by spray drying technique. Various formulations and process variables that could affect the preparation and properties of the microparticles were identified and optimized to get small, discrete and spherical microparticles. The formulation variables included concentration of drug: polymers ratio, amount of solvent used, types of excipients and its solubility.

Different parameters such as temperature of inlet air, drying temperature, concentration of different polymers and drug, feed rate, inlet air pressure and aspiration were optimized during the process. Optimum drying conditions were employed for the process i.e,

Inlet temperature	:	82°C
Feed-flow rate (ml/min)	:	5-6 ml/min
Compressed spray air flow	:	10 L/min
Air pressure	:	1.5 kg/cm^2

Table 1: Formulation chart of Fluconazole microparticles.

Formulation code	Chitosan (mg)	Carbopol 71G(mg)	Chitosan-carbopol 71G physical mixture (1:1) (mg)	IPEC (mg)
FA1	50	---	---	----
FA2	100	---	---	----
FB1	---	50	---	---
FB2	---	100	---	---
FC1	---	---	50	---
FC2	---	---	100	--
FD1	---	---	---	60
FD2	---	---	---	70

Angle of repose

Angle of repose was assessed to know the flowability of microparticles, by a fixed funnel method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged above the graph paper of height which was placed on a flat horizontal surface. Drug loaded microparticles were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The radius (r) and height of the pile (h) were then determined. The angle of repose (θ) for samples were calculated using the formula,

$$\text{Angle of repose } (\theta) = \tan^{-1} (h / r) \qquad (1)$$

Angle of repose represents whether the given sample was free flowing or not. The relationship between angle of repose and flowability is shown in Table 9. The mean of three determinations was used to calculate the angle of repose from each of the formulation.

Drug loading and encapsulation efficiency

100 mg of microparticles were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffers. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution was diluted to 10 ml and absorbance was measured. The drug content was calculated by using the formula.[7, 8]

$$\text{Amount of drug} = \frac{\text{Conc. from standard graph X dilution factor}}{1000}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of microparticles. It is further calculated by using formula

$$\% \text{ Encapsulation Efficiency} = b/a \times 100$$

Where, 'a' is the theoretical drug content and 'b' is the drug entrapped.

In vitro drug release studies

Release of Fluconazole was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time intervals and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy.[9,10]

RESULTS AND DISCUSSION

Micromeritic properties of fluconazole Microparticles

Generally, the microparticulate drug delivery systems are formulated as single unit dosage forms in the form of capsule or tablet. Such microparticulate systems should possess the required and better Micromeritic properties. The obtained data angle of repose (θ) and % compressibility index (CI) along with related parameters are presented in Table 2. The values of θ^0 and CI ranged from 23.3 to 28.3 and 11.35 to 14.22% respectively indicating that the obtained values were well within the limits. This result clearly shows that the prepared microparticles have reasonably good flow potential.

The values of tapped density ranged between 0.599 to 0.443 g/cm^3. Density difference between the formulations is negligible and the density values of formulations were well within the limits, indicating that the prepared microparticles were non-aggregated and spherical in nature.

Table 2: Micromeritic properties of fluconazole Microparticles.

Formulation	Mean size (µm) (±S.D*)	θ ° mean ± SD*	CI% mean ± SD*	Tapped density gm/cm^3 mean ± SD*
FA1	1.26 ± 0.6	23.3 ± 0.9	11.35 ± 0.86	0.599 ± 0.02
FA2	1.16 ± 1.4	25.7 ± 0.8	14.01 ± 0.46	0.545 ± 0.02
FB1	1.28 ± 0.6	26.3 ± 0.5	14.61 ± 0.66	0.534 ± 0.04
FB2	1.13± 0.8	24.3 ± 0.8	13.63 ± 0.23	0.415 ± 0.02
FC1	1.36 ± 1.5	23.9 ± 1.1	14.22 ± 0.14	0.592 ± 0.06
FC2	1.51 ± 0.5	28.3. ± 0.8	11.45 ± 0.66	0.516 ± 0.02
FD1	1.48 ± 0.7	27.9.± 0.9	12.22 ± 0.68	0.535 ± 0.02
FD2	1.47 ±0.4	26.4±0.6	12.26 ± 0.34	0.465 ± 0.05

Drug loading and encapsulation efficiency

The test for drug content was carried out to ascertain uniform distribution of the drug in the formulation. Drug loading and entrapment efficiency increase with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Fluconozole in the microparticles and the deviation is within the acceptable limits. The decrease in the drug content in the product probably can be due to the loss of drug with the evaporation of the solvent.

Table 3: Drug loading and encapsulation efficiency of prepared microparticles.

Formulation	Drug loading (%) mean ± SD*	Encapsulation efficiency (%) mean ± SD*
FA1	57.74±0.23	95.23±0.36
FA2	42.26±0,18	70.43±0.25
FB1	40.68±0.24	67.80±0.24
FB2	33.85±0.21	56.41±0.17
FC1	50.38±0.29	83.96±0.21
FC2	57.82 ±0.27	96.36 ±0.19
FD1	42.84±0.19	71.4±0.27
FD2	51.32±0.28	85.5±0.23

In- vitro drug dissolution

Release of Fluconazole was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. The sample were withdrawn at different time intervals 1,2,3,4,6,8,10 and 12 hrs filtered through whatman filter paper and replaced equal volume of dissolution medium. Sample was suitably diluted and analyzed for Fluconazole using UV-visible spectrophotometer. The percentage of Fluconazole release was calculated.

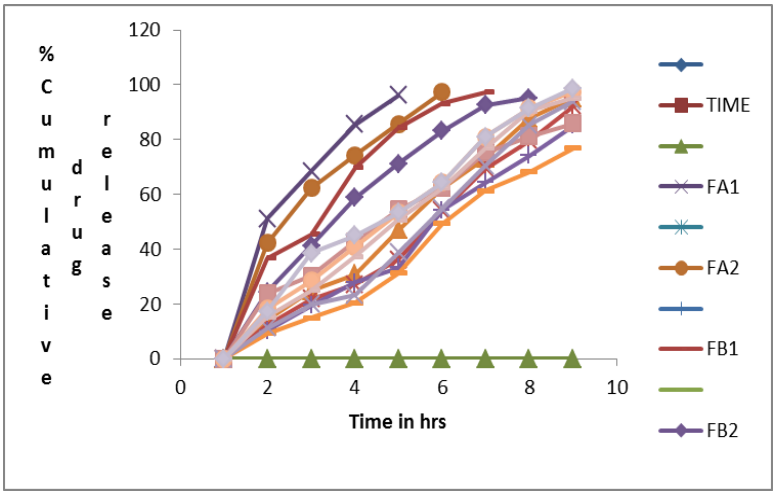

Figure 1: *In-vitro* drug release profile of the formulations.

CONCLUSION

The objective of this study was to prepare and evaluate microparticles loaded with fluconazole for controlled release using different ratios of drug to natural polymers and prepared microparticles were characterized. The method is simple, rapid, and economical and does not imply the use of toxic organic solvents. The method used was suitable for both water-soluble and insoluble drugs. The formulation (FC2) produced discrete spherical microparticles. The DSC thermogram obtained for the pure drug and formulation shows no significant shift in the endothermic peaks confirming the stability of the drug in the formulation. From the results of drug loading and encapsulation efficiency, it can be inferred that there was a proper and uniform distribution of drug in the micro particles. The *in vitro* drug release data showed the release of a drug in a controlled manner.

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