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ORIGINAL RESEARCH PAPER

Design and Development of Modified Released Microparticulate System of Flucanazole

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Abstract
The present investigation aims at developing novel fluconazone loaded chitosan micro particulate systems for the efficient handling of inflammatory bowel disease. Microspheres were prepared by emulsification-solvent evaporation method. The effects of the Fluconazole concentration and the ratio of chitosan on the percentages yield, drug encapsulation, particle size and in vitro drug release were studied. Drug-polymer interaction was investigated by means of FTIR spectroscopy. The results showed that there was no drug-polymer interaction. The microsphere were spherical, discrete and free flowing. The spherical shape of microspheres was confirmed from SEM photomicrographs. With increase in polymer concentration, the particle size was found to increase. The particles had good encapsulation efficiency and drug release (64.16±0.90 - 78.69±2.45%) at the end of 10 h. Increase in chitosan concentration had positive effect on drug encapsulation and negative effect on drug release. The developed microsphere showed controlled release and were following Higuchi's model. The release of fluconazole from the microspheres was Fickian diffusion without swelling.

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INTRODUCTION

Over last three decades, frequency and variety of fungus infections are increased due to change in medical and surgical care, mainly in intensive care units, which utilize invasive therapies for monitoring, coupled with the use of more potent immune suppressants and antibiotics.[1,2] These medical and procedural advances have increased the frequency of fungus infections. As a direct result of these therapeutic successes, the population of risk for fungal infections has greatly increased.[3]

In the early 1980s, systemic candidiasis recognized as a critical medical problem. The mortality is associated with candidiasis raised steadily 1988s, when it peaked at a rate of 6 per 1000,000 per population.[4] The advances in treatment of invasive candidiasis have lowered mortality stemming from Candidemia. Systemic candidiasis remains fourth common bloodstream infection.

Fluconazole is an antifungal agent used for a number of fungal infections, including candidiasis, blasotmycosis, coccidiodomycosis, cryptococcosis and also used to avoid candidiasis in individuals who are at high risks, for example, following organ transplantation, less birth weight babies, and persons with low blood neutrophil counts. It is administered by oral route or by intravenous injection.[5] Administration of an antifungal agent in the form of micro particulate system can release the drug in controlled manner and give efficient results. Microspheres are very small spherical particles with 1 to 1000 µm range. They can be manufactured from various natural or synthetic materials. Solid and hollow microspheres, due to their low density, find different applications. Hollow microspheres are mainly used as additives to lower the density of a material.[6] The goal of drug delivery system is to provide the therapeutic amounts of drug to the proper site in the body and maintain the desired drug concentration. Most convenient and commonly employed route for drug delivery has historically been by oral ingestion of drug which is easily absorbed from the GIT. [7]

EXPERIMENTAL

Materials

Fluconazole was procured as a gift sample from Park Pharmaceutical Ltd, India. Chitosan, Potassium dihydrogen orthophosphate were purchased from Central Drug House Ltd, New Delhi. N-hexane was purchased from RFCLs Limited, New Delhi. All other chemicals were of analytical reagent grade and were used as received.

Preparation of Flucanazole-loaded Microspheres

Chitosan microspheres containing fluconazole were prepared using solvent evaporation technique. An acetone/ liquid paraffin system was used in the preparation. Chitosan (300 mg) was dissolving in 20 mL of acetone and pure Fluconazole (500 mg) was dissolved in the polymer solution. The solution was filtered and magnesium stearate (50 mg) was dispersed into it by ultrasonication (Soniweld, Imeco Ultrasonic, Mumbai, India). This resulting dispersion was added drop-wise to a mixture of 100 mL liquid paraffin (light: heavy, 1:1) and 20 mL n-hexane with stirring at 1000 rpm using a mechanical stirrer (Remi, Mumbai, India). The stirring was continued for 1.5 h at room temperature, till acetone was evaporated totally. After complete evaporation of acetone, the microspheres were collected through vacuum filtration. The microspheres were washed 4-5 times with 40 mL of n-hexane for every wash, and dried at the room temperature in a desiccator for 24 h. A total of 15 batches of microspheres were prepared as shown in Table 1.

Characterization of Microspheres

Determinations of tapped density and bulk density

Microspheres of different formulations (1 g) were taken into a 10 mL graduated measuring cylinder individually and the volume was noted down. The measuring cylinder was tapped 50 times using USP bulk density equipment (ETD 1020, Electrolab, Mumbai, India). The bulk density and tapped density were calculated using the following formula:

Bulk density = Weight of the microspheres / Initial volume (1)

Trapped density = Weight of the microspheres / Final volume after trapping (2)

Hausner's ratio

The Hausner's ratio was determined using the following formula:

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density} \quad (3)$$

Table 1. Details of different batches of microspheres containing fluconazole depicting formulation and process variables

Formulation code	Drug: Chitosan ratio	Liquid paraffin (light) : Liquid paraffin (heavy) : n-hexane ratio	Speed (rpm)
F1	1:1.25	40:30:15	700
F2	1:1.75	40:30:15	700
F3	1:1.25	50:40:25	700
F4	1:1.75	50:40:25	700
F5	1:1.25	40:30:15	1100
F6	1:1.75	40:30:15	1100
F7	1:1.25	50:40:25	1100
F8	1:1.75	50:40:25	1100
F9	1:1	45:35:20	900
F10	1:2	45:35:20	900
F11	1:1.5	35:25:10	900
F12	1:1.5	55:45:30	900
F13	1:1.5	45:35:20	600
F14	1:1.5	45:35:20	1300
F15	1:1.5	45:35:20	900

Angle of repose

The determinations of angle of repose can be done by the material poured through a funnel, which's fixed at a position as its lower tip was at height of 2 cm above the surface. The microsphere were poured through the funnel to make a heap. The height (h) and radius (r) of the heap were measured. The angle of repose was determined by following formula:

$$\theta = \tan^{-1}(h/r) \quad (4)$$

Carr's index

The Carr's index determined by using following formula:

$$\text{Carrs index} = [\text{Tapped density} - \text{Bulk density} / \text{Tapped density}] \times 100 \quad (5)$$

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectral data of optimized formulations was taken for determination of probable molecular interaction between the excipients and drug through the KBr disc technique.

Particle size and morphology

The particles size of the developed microspheres was determined by means of the optical microscope (7001-IMS Vaiseshika, Ambala, India). The surface morphology of the drug-overloaded microsphere was studied using a scanning electron microscope (SEM; EVO-50, ZEISS, UK).

Determination of entrapment efficiency and drug loading

Accurately weighed (10 mg) microsphere were taken into 25 mL phosphate buffer (pH 6.8) for the determination of entrapment efficiency and drug loading, which were calculated using following formula:

Drug loading (%) = [Drug weight within the microspheres/ Weight of microspheres] × 100 (6)

Drug entrapment (%) = [(Total drug – Drug in microspheres) / Weight of microspheres] × 100 (7)

In vitro release of drug from microspheres and modelling of releases data

The drug release profile of different batches of formulations was determined using USP type II dissolution apparatus (DS8000, Lab India, Mumbai, India) in phosphate buffer of pH 6.8 at 37±0.5°C. The samples were withdrawn at different time intervals and the drug content was determined spectrophotometrically at 260 nm.

RESULTS AND DISCUSSION

Characterization of Microspheres

Microspheres of batches F11, F12 & F13 were not formed, which might be due to very low shear of stirring in case of F13, insufficient solvent in case of F11 or excess amount of solvent in case of F12, which led to precipitation and agglomeration of the polymers. The physical properties and drug loading of different batches of microspheres are given in Table 2.

Table 2. Physicochemical properties of developed microspheres

Formulation code	Bulk density (g/cm³)	Tapped density (g/cm³)	Hausner's ratio	Angle of repose	Carr's index	Particle size (µm)	Drug loading (%)	Drug entrapment (%)
F1	0.124 ± 0.032	0.205 ± 0.068	1.650± 0.521	33.25± 0.42	19.51± 1.36	33.62	4.53	60.15 ±2.14
F2	0.134 ± 0.021	0.169 ± 0.098	1.270 ± 0.413	29.21± 0.35	20.71± 0.56	43.11	4.67	56.11 ±1.51
F3	0.144 ± 0.079	0.150 ± 0.051	1.046 ± 0.309	28.21± 0.22	14.40± 0.24	33.04	7.05	69.41 ±4.26
F4	0.127± 0.053	0.149 ± 0.013	1.173± 0.032	31.51± 0.23	14.76± 0.54	39.74	7.11	71.32 ±5.45
F5	0.131± 0.032	0.151 ± 0.092	1.152± 0.142	27.32± 0.29	13.24± 0.4	32.83	5.94	65.25 ±3.05
F6	0.137± 0.017	0.158 ± 0.142	1.153± 0.215	24.29± 0.33	13.29± 0.32	36.57	7.54	73.22 ±3.12
F7	0.129± 0.112	0.168 ± 0.026	1.302± 0.124	29.64± 0.56	23.21± 0.32	31.90	6.72	68.43 ±2.31
F8	0.132± 0.078	0.163 ± 0.061	1.234± 0.041	34.21± 0.61	19.01± 0.41	37.69	6.97	75.95 ±4.25
F9	0.121± 0.018	0.153 ± 0.074	1.264± 0.056	33.16± 0.10	20.91± 0.44	36.10	4.94	59.25 ±3.05
F10	0.139± 0.015	0.193 ± 0.011	1.388± 0.192	26.22± 0.25	27.97± 0.64	47.03	8.59	81.02 ±2.14
F14	0.123± 0.041	0.161 ± 0.017	1.308± 0.121	28.29± 0.32	23.60± 0.54	38.90	7.14	68.43 ±3.54
F15	0.128± 0.022	0.164 ± 0.032	1.281± 0.081	27.12± 0.11	21.95± 0.43	33.25	6.90	72.22 ±2.34

Hausner's ratio is connected to inter-particle frictions. It is not direct measures of bulk density, and shape, size surface area, cohesiveness of the particles and moisture content. Higher Hausner's ratio and fine particles indicate greater cohesion between particles, low range Hausner's ratio indicate high-quality flow ability. It is well known that particle size and shape influences flow ability. The fine particles (<100 mm) be likely to exist much cohesive and consequently fewer free-flowing, while superior denser particles be liable to free-flowing.

FTIR spectroscopy

In spectrum of optimized formulation (formulation F15), the major peaks of fluconazole were present (Figure 1). The FTIR result confirms that nearby was no boundary between polymer and the drug. The broadening and slight shift the peaks might be due to the minor ionic interactions.

Particle size and morphology

From the SEM micrographs it is apparent that the fluconazole loaded microspheres were predominately spherical in appearance and had small particle size (31.90 μm to 47.03 μm). The surface was observed to be smooth, dense (Figure 2).

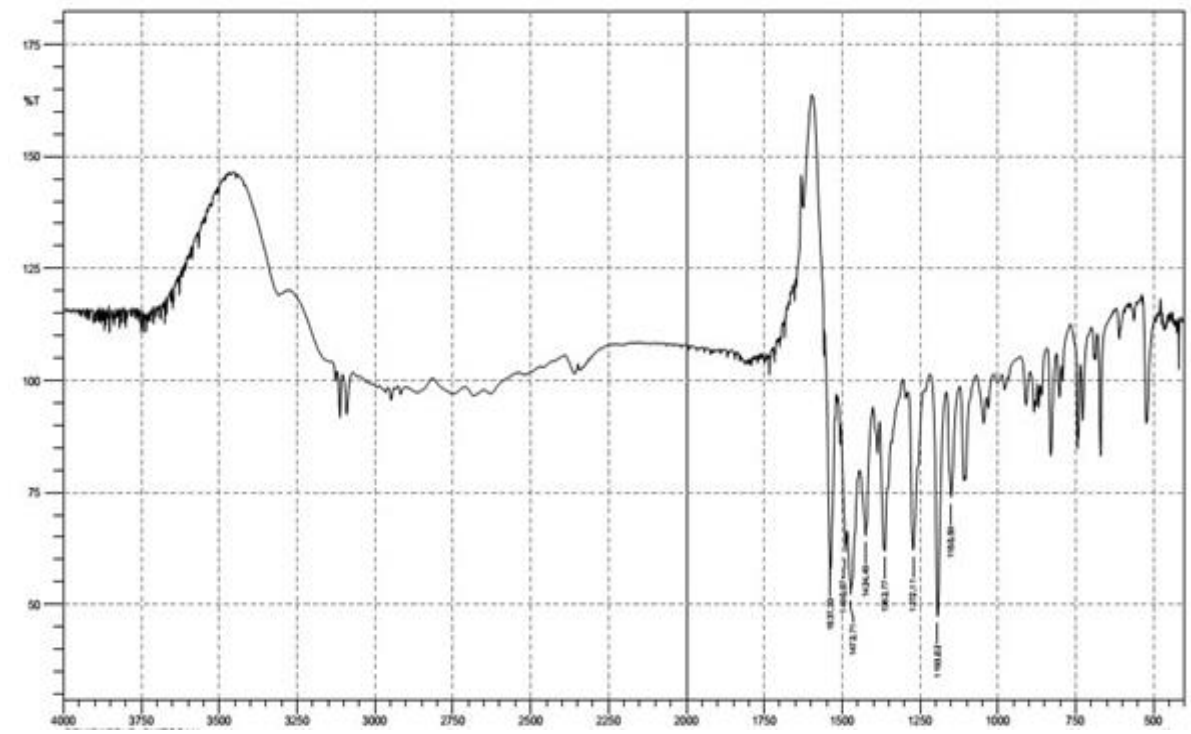

Figure 1. FTIR spectrum of optimized microspheres (Batch F15)

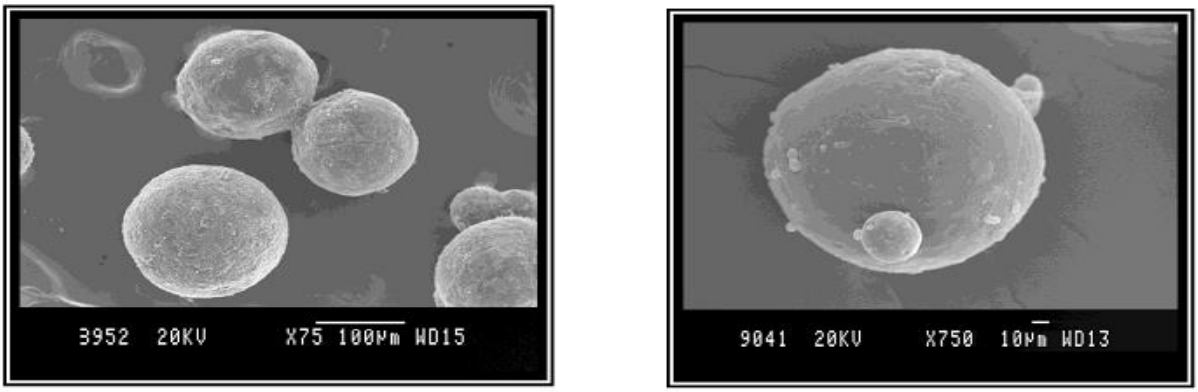

Figure 2. SEM micrograph of optimized microspheres (Batch F15)

In vitro fluconazole release from the microspheres

The in vitro release profiles of different batches of microspheres are given in Figures 3 and 4. A primary rupture release might be there responsible for the release of surface drug. Stirring velocity has a positive effect on drug release at lower polymer concentration. A sustained drug releases was practical form all the formulations during 10 h dissolution study. Formulation F9 showed highest drug release (79.69±2.45%) after 10 h. The rate of release was decreased with an increase in polymers concentration.

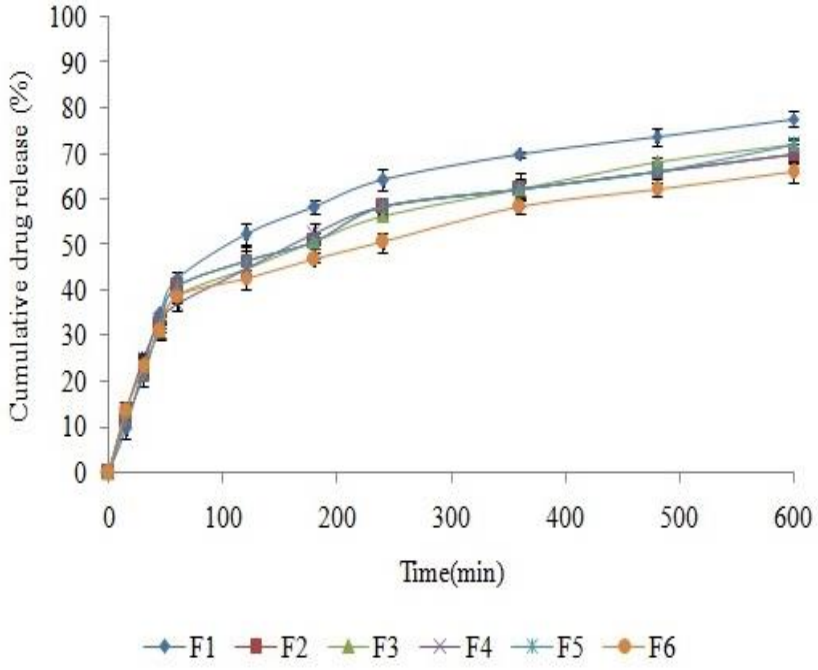

Figure 3. *In vitro* drug release profiles of different batches of microspheres (F1-F6)

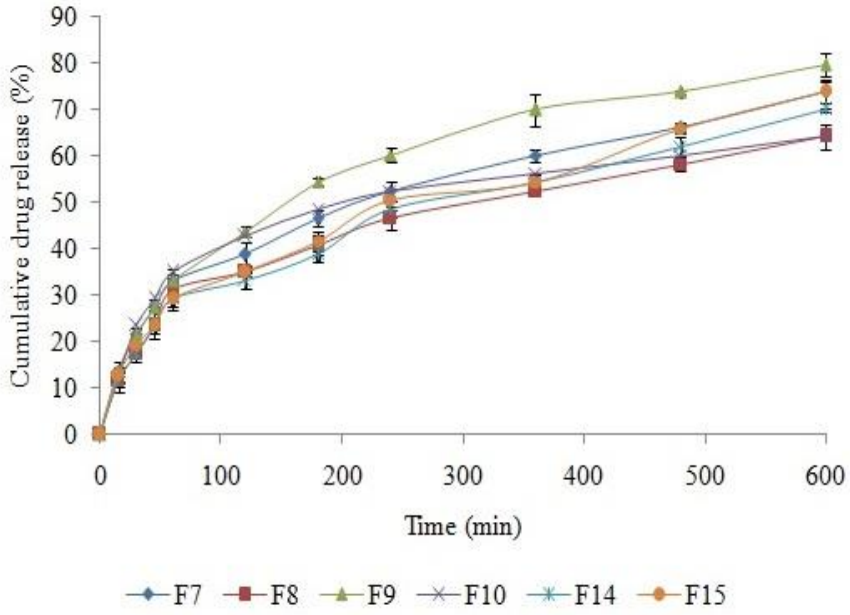

Figure 4. *In vitro* drug release profiles of different batches of microspheres (F7-F15)

CONCLUSION

The developed microsphere formulation for the drug fluconazole is an appropriate drug delivery system for Fluconazole. The optimized batch exhibited idea physical properties, surface properties, drug entrapment and sustained release of the entrapped drug, and might be used for efficient treatment of IBD.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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