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Formulation and In -Vitro Evaluation of Flutrimazole Microspheres Loaded Transdermal Gel

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A b s t r a c t

Flutrimazole is a wide-spectrum antifungal drug. It is used for the topical treatment of superficial mycoses of the skin. Flutrimazole is an imidazole derivative. Present study was aimed to formulate and evaluate microspheres loaded transdermal gel containing Flutimazole as a model drug by employing Xanthan gum, Methocel K4M and Methocel K15M as polymers microspheres were prepared by using aqueous ionotropic gelation method. Different polymers, different drug to polymer(s) ratio(s) and other parameters were screened to study their effects on properties of microspheres and to optimize each parameter. The microspheres obtained were subjected to preformulation studies like bulk density, tapped density, angle of repose, carr's index, hausner's ratio the results obtained were with in the limit.The microspheres were characterized by Percentage yield, Drug entrapment efficiency, Particle size analysis, then the optimized microspheres formulation F8 were incorporated into the gel prepared with Methocel K100M, Sodium CMC and Guar gum as polymers and was evaluated by parameters like Visual inspection , pH measurement , Spreadability studies , Viscosity and in-vitro drug release by using franz diffusion cell for results from the diffusion results FG4 showed maximum percentage drug release of 96.85 hence it was considered as the optimized formulation.

Keywords: Flutrimazole, ionotropic gelation method,transdermal gel, Xanthan gum, Methocel K4M, Methocel K15M, Methocel K100M, Sodium CMC and Guar gum.

A r t i c l e I n f o

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C O N T E N T S

1. Introduction

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000µm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications[1]. In pharmaceutical industry developing a controlled dosage form has become increasingly important. Therefore various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. has been developed. Transdermal delivery has been emerged as a novel tool over injectables and oral routes as it increases the patient compliance and avoids the first pass hepatic metabolism. In transdermal drug delivery system the drug is delivered in a controlled rate into systemic circulation through the skin.

The intact skin is used as a port to administer a drug in transdermal gels but skin act as a barrier to ingress the material, it only allows a small material to penetrate over a period of time into systemic circulation[2]. Flutrimazole is a wide-spectrum anti-fungal drug. It is used for the topical treatment of superficial mycoses of the skin. Flutrimazole is an imidazole derivative. Its antifungal activity has been demonstrated in *in-vivo* and *in-vitro* studies to be comparable to that of clotrimazole and higher than bifonazole. It is an imidazole anti-fungal with dual anti-inflammatory and anti-fungal activity. It shows scarce transdermal penetration. It has the advantageous in the research of topical fungal infections with an inflammatory component. The present research work focuses on formulation of transdermal gels loaded with microspheres containing Flutrimazole.

2. Materials and Methods

Materials:

Flutrimazole (NATCO Pharma India), Xanthan gum (signet chemical corporation ,Mumbai, India), Methocel K 15M (Merck specialities Pvt Ltd, Mumbai, India), Methocel K 100M (Merck specialities Pvt Ltd, Mumbai, India), Calcium chloride (Sd fine chemicals Mumbai), Methanol (Sd fine chemicals Mumbai), Sodium hydroxide pellet (Sd fine chemicals Mumbai), Pottasium di hydrogen phosphate(Sd fine chemicals Mumbai), Carbopol 934(Sd fine chemicals Mumbai), Carbopol 940 (Sd fine chemicals Mumbai), Carbopol 974 (Sd fine chemicals Mumbai), Triethanolamine(Merck specialities Pvt Ltd), PEG (Merck specialities Pvt Ltd).

Method of Preparation

Ionotropic gelation method:

Batches of microspheres were prepared which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The Flutrimazole (300 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried. [3]

Characterization of Microspheres[4]

Percentage yield

The percentage of production yield was calculated from the weight of dried microsphe-res recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency:

Microspheres equivalent to 300 mg of the drug Flutrimazole were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 6.8. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 235 nm. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Particle size analysis:

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45x magnification

Micromeritic properties [5]

Bulk density, Tapped density and Hausner's ratio and Carr's index, were determined to assess the flow ability of the prepared microspheres.

Bulk density: The product was tapped using bulk density apparatus for 1000 taps in a cylinder and the change in

volume was measured. Bulk density of the formulations was determined by using the following formula,

$$\text{Bulk Density} = \frac{\text{Total Weight}}{\text{Total Bulk Volume}}$$

Tapped density:

Tapped density is used to investigate packing properties of microcapsules into capsules. The tapped density was measured by employing the conventional tapping method using a 10mL measuring cylinder and the number of tappings was 100 as sufficient to bring a plateau condition. Tapped density was calculated using the following formula:

$$\text{Total Weight} = \frac{\text{Tapped Density}}{\text{Total Tapped Volume}}$$

Hausner's ratio:

It is another parameter for measuring flow ability of the microspheres. It is calculated using the following formula,

H = Bulk Density/ Tapped Density

Where, H = hausner's ratio

Compressibility index (carr's):

It is indirect measurement of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials since all of them can influence the consolidation index. It is also calledas compressibility index. It is denoted by CI and is calculated using the formula below.

Compressibility index = (1- Vo/V) * 100

Where, Vo = volume of microspheres before tapping

V = volume of microspheres after 100 tappings.

Production yield (%)

The production yield of microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres and % production yields were calculated as per the formula:

$$\%\ Yield = \frac{Actual\ Yield}{Theoretical\ Yield} \times 100\%$$

Evaluation of mucoadhesive property:

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 6.8 at 37^0C contained in a 1-litre vessel of the apparatus. At an interval of 1 hour up to 8 hours the machine is stopped and number of microspheres still adhering to mucosal surface was counted[6].

$$\%\ \text{Mucoadhesion} = \frac{\text{Number of microspheres adhered}}{\text{Number of microspheres applied}} \times 100$$

Gel forming polymers were soaked in water for 2 h and then dispersed by agitation at approximately600 rpm with the aid of magnetic stirrer to get a smooth dispersion. The dispersion was allowed to stand for 15 min to expel entrained air. To it the aqueous solution of triethanolamine (2% v/v) was added with slow agitation for adjusting pH to 6.5–7.5.At this stage permeation enhancersand microspheres containing drug equivalent to marketed formulation were incorporated into the gel base[7].

Evaluation of Flutrimazole microsphere gel

Visual inspection

The organoleptic properties, such as color, texture, consistency, homogeneity, and physical appearance of gel containing microspheres were checked by visual observation.

pH measurement

Gel formulation pH was recorded using digital pH meter. 5 g gel was dispersed in 45 ml distilled water at 27°C and solution pH was measured[8].

Spreadability studies

One of the requisite qualities for an ideal gel is to pursue excellent spreadability. Spreadability is used to express the extent of the area of skin or affected part to which gel readily spreads. A spreading value significantly affects therapeutic efficacy of the formulation. Expression of spreadability is given in terms of time (in seconds) taken by two slides to slip off from gel placed in between under application of specific load. Better spreadability is indicated by minimum time required for slides separation. Mathematical expression used for spreadability calculation was: Where,

$$S = \frac{M}{T}$$

S = Spreadability in g/s

M = Mass in grams

T = Time in seconds

Tube extrudability

One of the properties which an ideal gel should possess is good tube extrudability; so that when slight pressure is applied on tube, the formulation should extrude out uniformly with an ease. The technique adopted for examining gel extrudability was based upon percent quantity of gel extruded from the tube on finger pressure application. More the quantity extruded better the extrudability. Formulations were filled in clean, lacquered, collapsible aluminum tubes with 5 mm nasal tip opening and the pressure was applied on tubes using the first finger and thumb. Afterward tube extrudability was estimated in percentage by measuring the amount of gel

extruded through the tip and compared with marketed formulation considering its extrudability as 100%.

Viscosity

The viscosity of the gel formulation was measured with a Brookfield viscometer (Brookfield, USA; Capcalc Version 2.2) using 1x model and cone number 01, with an angular velocity of 5 rpm at 25 ºC. An average of five readings was used to calculate viscosity.

***In Vitro* Drug Release**

In vitro drug release studies of the microspheres, emulgel formulations and commercial cream product were carried out using modified Franz diffusion cell during 12 h. Mixture of PBS pH 7.4: ethanol (70:30) was used as receptor medium and sink condition was determined. The receptor phase was kept at a constant temperature of 37°C and stirred by a magnetic stirrer. Spectra/Por 2® dialysis membrane, MWCO: 12–14kDa (Spectrum Lab., USA) was used as the diffusion membrane. At appropriate time intervals, 0.5 ml of samples were collected and replaced by an equal volume of fresh receptor medium. Flutrimazole content was analyzed by UV at a wavelength of 235 nm.[9]

Drug release kinetics

The release data obtained from various formulations was studied further for fitness of data in different kinetic models like Zero order, First order, Higuchi equation and Korsmeyer-Peppas models.[10]

3. Results and Discussion

Calibration curve

Suitable analytical method was developed for Flutrimazole using UV spectroscopy and analytical wavelength of λ_{max} at 235 nm was identified in pH6.8 buffer solution. Calibration curve was constructed in this media. The method has shown good reproducibility. Beer Lambert's law was obeyed in the range of 1 to 5ug\ml and pH 6.8 buffer solution.

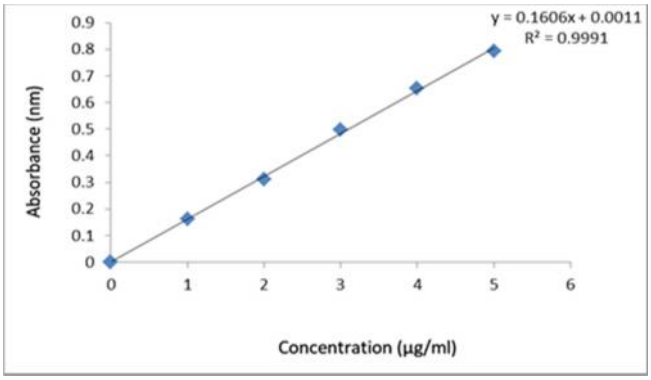

Fig 1: Standard graph of Flutrimazole in simulated gastric fluid pH 6.8

Evaluation and Characterization of Microspheres

Percentage Yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and Microspheres lost during the washing process. The percentage yield was found to be in the range of 72 to 83%.

Table 3: % yield of the formulations

Formulation	% yield
F1	82.25
F2	72.06
F3	81.19
F4	78.36
F5	76.15
F6	75.91
F7	78.25
F8	81.34
F9	80.16

Table 4: Pre formulation parameters

Formulation Code	Mean particle size (µm)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner'sRatio	Carr'sindex (%)	Angle ofrepose (^{0})
F1	651	0.52	0.53	13.21	1.14	22.53
F2	709	0.51	0.55	12.79	1.06	23.16
F3	681	0.53	0.52	14.63	1.08	24.81
F4	653	0.52	0.54	13.08	1.11	22.17
F5	712	0.57	0.51	13.72	1.09	24.51
F6	716	0.52	0.53	13.63	1.11	24.67
F7	678	0.51	0.51	15.18	1.13	22.57
F8	663	0.53	0.52	14.62	1.11	23.16
F9	781	0.52	0.52	15.08	1.08	22.09

Table 5: Percentage entrapment efficiency

Formulation Code	% Entrapmentefficiency	Formulation Code	% Entrapmentefficiency
F1	72.51	F6	76.85

F2	78.07	F7	69.07
F3	81.65	F8	75.02
F4	78.05	F9	73.14
F5	77.61		

Table 6: *In-vitro* release studies

TIME (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	6.08	7.08	6.02	5.03	6.05	6.03	5.36	6.52	7.36
1	11.36	13.52	11.63	9.84	11.34	11.64	10.64	11.36	13.64
2	20.57	22.36	21.15	15.62	18.97	20.12	18.91	19.15	22.92
3	29.14	31.91	29.82	21.18	26.82	29.67	26.08	26.18	30.15
4	37.08	39.05	37.14	28.67	34.16	36.34	35.64	32.46	37.34
5	45.29	47.83	46.57	36.91	41.07	42.91	40.87	39.72	46.67
6	52.17	56.47	54.03	44.13	48.13	49.05	49.64	46.67	52.61
7	58.08	64.08	60.92	52.84	53.14	53.17	55.19	52.19	60.94
8	63.34	71.32	66.17	59.07	59.97	60.36	62.21	61.24	68.92
9	72.26	78.54	72.64	62.35	65.15	69.73	69.67	70.34	76.52
10	78.05	83.61	79.13	69.91	72.63	73.18	73.15	80.16	82.34
11	82.34	87.12	88.81	74.07	79.64	79.16	77.64	88.17	89.67
12	89.08	91.05	93.06	81.13	84.08	83.08	85.18	97.05	92.01

Evaluation of microspheres loaded topical gel

Visual inspection: The organoleptic properties, such as color, texture, consistency, homogeneity, and physical appearance of gel containing microspheres were checked by visual observation.

Table 7: Physical parameters of microspheres loaded topical gels of Flutrimazole:

Formulationcode	% Drugcontent	Spreadability (gm.cm\sec)	Viscosity (cps)	pH	Extrudability
FG1	96.13	13.25	219.23	6.58	96.51
FG2	95.15	14.63	217.18	6.93	97.49
FG3	96.73	13.91	220.67	6.78	97.63
FG4	95.12	14.75	215.57	6.83	96.14
FG5	96.83	14.36	217.63	7.26	98.87
FG6	96.45	14.18	218.18	6.97	97.69
FG7	97.18	13.79	219.14	7.18	98.13
FG8	96.63	14.82	220.15	7.06	97.85
FG9	97.14	15.35	218.67	6.63	97.64

***In-Vitro* Release Studies**

Table 8: In-vitro cumulative percentage drug release profile for Flutrimazolemicrospheres loaded gels

Time (hrs)	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	FG9
0.5	6.52	7.36	7.13	6.03	5.36	6.13	7.03	6.15	8.63
1	11.69	13.18	12.94	11.45	9.91	11.92	14.65	11.93	12.15
2	19.15	18.64	21.57	17.91	16.52	19.15	21.87	20.15	18.94
3	26.64	25.97	28.47	26.14	23.67	27.18	29.64	29.76	23.82
4	35.97	34.15	34.64	34.57	31.86	36.64	35.81	37.64	31.16
5	44.15	43.64	43.85	41.62	39.28	43.87	42.13	46.63	39.82
6	52.62	52.97	51.14	47.14	47.71	52.64	51.78	55.98	46.15
7	59.49	61.81	59.63	56.98	53.67	59.28	58.94	64.47	55.25
8	65.37	67.02	65.08	65.82	61.83	65.14	65.11	71.05	63.72
9	73.62	73.63	72.14	74.97	70.15	73.63	74.63	78.12	71.96
10	79.83	76.12	81.63	81.14	76.05	81.17	81.45	83.15	78.21
11	85.12	81.16	84.15	88.15	83.14	86.64	85.92	87.02	85.72
12	89.35	84.15	89.32	96.85	89.37	90.94	88.05	91.13	89.63

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

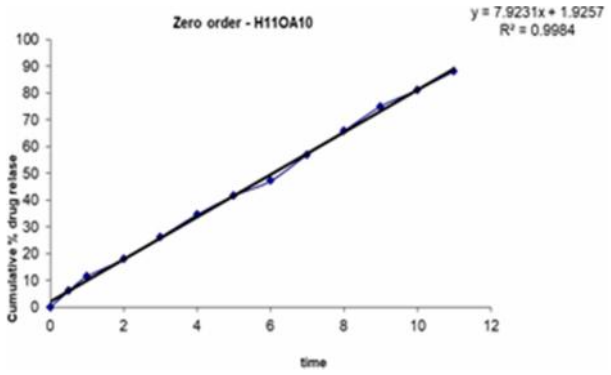

Fig 2: Zero order release kinetics graph

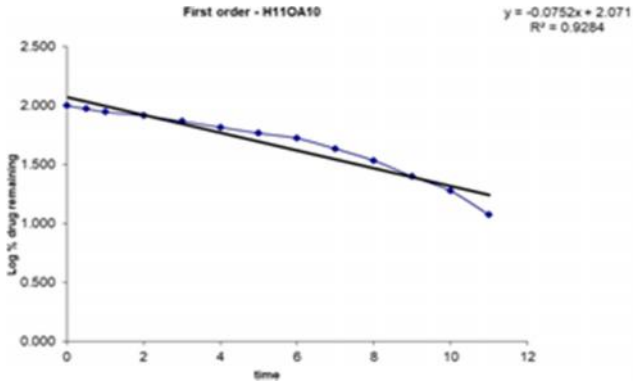

Fig 3: First order release kinetics graph

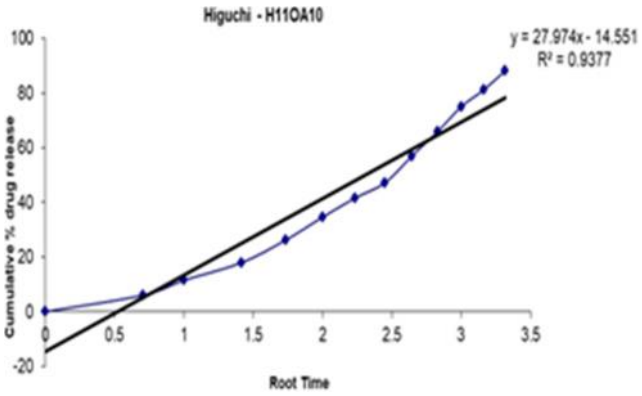

Fig 4: Higuchi release kinetics graph

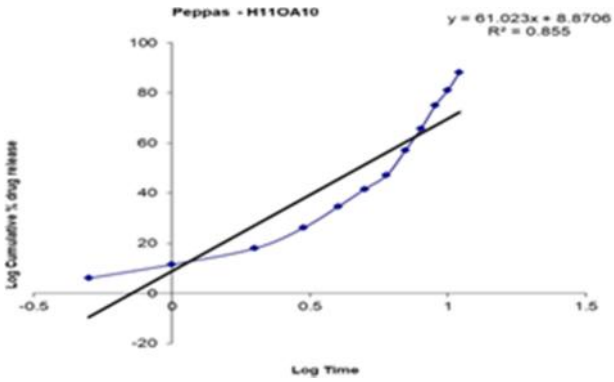

Fig 5: Kars mayer peppas graph

4. Conclusion

The aim of the present study is to formulate and evaluate microspheres loaded transdermal gel containing Flutimazole as a model drug by employing Xanthan gum, Methocel K4M and Methocel K15M as polymers microspheres were prepared by using aqueous ionotropic gelation method. Different polymers, different drug to polymer(s) ratio(s) and other parameters were screened to study their effects on properties of microspheres and to optimize each parameter. The microspheres obtained were subjected to preformulation studies like bulk density, tapped density, angle of repose, carr's index, hausner's ratio the results obtained were within the limit. The microspheres were characterized by Percentage yield, Drug entrapment efficiency, Particle size analysis, then the optimized microspheres formulation F8 were incorporated into the gel prepared with Methocel K100M, Sodium CMC and Guar gum as polymers and was evaluated by parameters like Visual inspection , pH measurement , Spreadability studies ,Viscosity and in-vitro drug release by using franz diffusion cell for results from the diffusion results FG4 showed maximum percentage drug release of 96.85 hence it was considered as the optimized formulation.

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