Journal of Pharmacreations
PharmaCreations
ISSN: 2348-6295
Pharmacreations \ Vol 9 \ Issue 2 \ Apr - Jun - 2022
Jouranl Home page: www. pharmareations.com
Research article Open Access

DESIGN AND IN-VITRO CHARACTERIZATION OF FLUCONAZOLE EMULGELS

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ABSTRACT

The work was carried out to prepare Fluconazole ointment to achieve sustain release effect at site of administration making it the first oral dosage of fluconazole sulphate. Stability studies performed for optimized ointments formulations indicates that prepared Ointments have more stability at freezing temperature than that of room temperature. Based on the above data, it was confirmed that prepared Fluconazole Ointments (F3) can be considered as one of the promising approaches to reduce the dosing frequency and to maintain drug concentration at the desired site for longer time. Ointments improve the drug delivery, prolong the release, and improve the site specificity of the drug Fluconazole. Ointments creates a new opportunity for the well-controlled drug delivery of a number of drugs that have a problem of administration by other routes. It is generally agreed that classic are of little or no value as carriers for transdermal drug delivery because they do not penetrate the skin.

Keywords: Fluconazole, stability studies, dosing frequency, drug concentration, transdermal drug delivery

1. INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied lotions, creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption of the drugs through the skin, which lead to the idea of TDDS. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation.

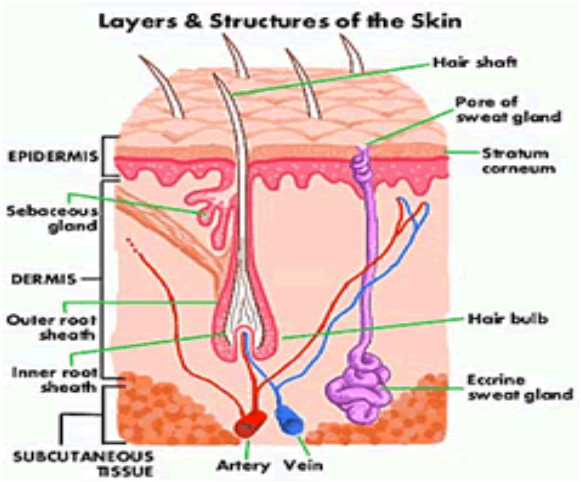


Fig 1: Anatomy of the skin[4]

2. LITERATURE REVIEW

Avish D Maru, Swaroop R Lahoti. Et., al., reported The formulation and evaluation of ointment containing sunflower wax, NNovare academic sciences, volume 12, issues 8, received 22 march 2019,

Andrej Dolenc, JulijanaKristl reported Drugs with low aqueous solubility and high permeability (BCS class II) present a high proportion of all drugs. This study examines the critical issues regarding engineering of a nanosuspension tailored to increase drug dissolution rate and its transformation into dry powder suitable for tabletting. Nanosuspensions of celecoxib, a selective COX-2 inhibitor with low water solubility, were produced by the emulsion-diffusion method using three different stabilizers (Tween® 80, PVP K-30 and SDS)

B Abismail, J.P Canselier, A.M Wilhelm, H Delmas, C Gourdon et., al Emulsification by ultrasound: drop size distribution and stability

Benita, ShunmugaperumalTamilvanan, et., al The potential of lipid emulsion for ocular delivery of lipophilic drugs Review ArticleEuropean Journal of Pharmaceutics and Biopharmaceutics, Volume 58, Issue 2, September 2004, Pages 357-368[2].

C. Solans, J. Esquena, N. Azemaret., al reported Highly concentrated (gel) emulsions, versatile reaction media Current Opinion in Colloid & Interface Science, Volume 8, Issue 2, June 2003, Pages 156-163[6].

3. DRUG PROFILE

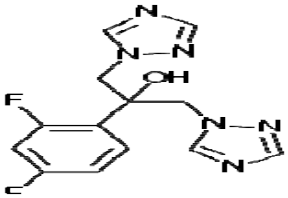
3 . 1 F L U C O N A Z O L E

Chemical Name: 2-(2,4-difluorophenyl)- 1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol.

Molecular formula: $C_{13}H_{12}F_2N_6O$

Molecular weight: 306.271

Structural formula: Fluconazole



Standards: Fluconazole contains not less than 99,0 % and not more than 101,0 % of $C_{13}H_{12}F_2N_6O$

4. AIM AND OBJECTIVES

The main aim of present research work is: Formulation of Flucanazole Emulgel using various emulsifying agents and gelling agents in different combinations ratios by suitable method. Evaluation of emulgel formulations for its physico-chemical properties like visual appearance, viscosity, pH, spreadability, drug content, etc.. In-vitro drug release permeation studies using Franz-Diffusion cell. To predict the surface morphology SEM studies were performed for the best formulation.

5. METHODOLOGY

5.1 Formulation design for Fluconazole emulgel preparation

The formulation code was designed according to a 2^3 factorial design so total eight Fluconazole emulgel formulations were prepared. The optimization in the formulation batches were made mainly based on three factors i.e., gelling agent, light liquid paraffin and emulsifying agent.

Table 1: Formulation code for gel preparation (Fluconazole 1% w/w)

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Guar gum	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 934	-	-	-	-	0.25	0.25	0.25	0.25
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Formulation code for emulsion preparation (Flucanazole 1% w/w)

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Flucanazole	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Light liquid paraffin	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75
Tween 20	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylparaben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Purified water (q.s)	20	20	20	20	20	20	20	20

Table 3: Final formulation code

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Fluconazole	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Guar gum	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 934	-	-	-	-	0.25	0.25	0.25	0.25
Light liquid paraffin	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75

Tween 20	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylparaben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Purified water (q.s)	50	50	50	50	50	50	50	50

5.2 Formulation of Fluconazole emulgel

5.2.1 Gel preparation

The composition of Flucanazole emulgel 1% w/w was shown in the formulation code table. The carbopol gel was prepared by dispersing 1.25g of carbopol 934 in purified water with constant stirring at a moderate speed and soaked overnight. The gel was obtained by neutralizing the dispersion with tri ethanol amine and pH is adjusted to 6.5 and purified water was added to adjust the weight to 50g.

In case of guar gum gel was prepared by dispersing guar gum in hot purified water (80^0C) and the dispersion was cooled, then weight was adjusted to 50g with purified water.

5.2.2 Emulsion preparation

The oil phase of emulsion was prepared by dissolving span 20 in light liquid paraffin and heated upto 70^0-80^0C.

Aqueous phase was prepared by dissolving tween 20 and drug in 5ml ethanol and heated upto 70^0-80^0C.

Methylparaben, propylparaben were mixed in propylene glycol and glutaraldehyde and this added this mixture was dissolved in aqueous phase.

Then oil phase was mixed slowly with aqueous phase and final volume is made with purified water.

5.2.3 Emulgel preparation

The obtained emulsion was mixed with the gel and weight was adjusted to 50g with water and subjected to homogenization for 45 minutes to get flucanozole emulgel 1% w/w

5.3 Evaluation parameters

5.3.1 Physical appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and phase separation.

5.3.2 pH evaluation

pH evaluation is an important criteria especially for topical formulations. The pH of emulgel should be between 5-7 to mimic the skin conditions. If the pH of prepared emulgel is acidic or basic, it may cause irritation to the patient.

pH of prepared emulgel was measured using digital pH meter by dipping the glass electrode into the emulgel. The measured pH of each formulation was done in triplicate and average values were recorded.

5.3.3 Rheological studies

The viscosity of gel during handling, transport and storage is an important criterion. The viscosity of different emulgel formulations was determined at 25^0C using Brook field viscometer. The emulgels were rotated using spindle 6 at10 rpm and viscosities were measured.

5.3.4 Spread ability test

One of the criteria for a dermatological preparation is to meet the ideal qualities is that it should possess good spreadability. Spreadability is the term expressed to denote the extent of area to which the gel readily spreads on application to skin or the affected area. The therapeutic efficacy of the formulation also depends on the spreadability values. Hence determination of spreadability is an important emulgel evaluation parameter, spreadability is measured as:

$$S = M \times L/T$$

Where,

M = weight to be taken
L = length of the slide
T = time taken

The spreadability if each sample was evaluated in triplicate by using fabricated spreadability apparatus which consists of two glass plates. 0.5g of the sample was placed on lower plate and upper plate was placed on the top of the sample. Force was generated by adding increasing weight slowly at 1 minute interval into the pan connected to the upper plat, each sample was tested three times at constant temperature and exerted weight and the mean values of the spread surface area on lower plate were calculated.

5.3.5 Drug content determination

Drug concentration in emulgel was measured by UV-Visible spectrophotometer. celecoxib content in emulgel was measured by dissolving accurately weighed (1g) of emulgel in 6.8pH phosphate buffer by Sonication and diluted to 10 folds prior to absorbance. Absorbance was measured at 260nm using UV-Visible spectrophotometer 1700 (Shimadzu, Japan). The test was conducted in triplicate and the average % drug content was determined.

5.3.6 Determination of globule size

The globule size analysis of the optimized formulation were determined by treating the emulgel sample with scarlet red dye and spreaded over as a thin film on the glass slide and observed under the 10X microscope.

5.3.7 Isolation of egg membrane

Egg was taken and made a small hole on the tip portion of the egg. The contents of the egg were removed via that hole. Then egg shell was washed internally with water and dipped into 0.1N Hcl solution for four hours. The outer shell of the egg would dissolve and egg membrane was isolated from it.

5.4 In-vitro drug permeation study

In-vitro permeation study was carried out using keisshary chein cell having capacity of 16ml volume. Egg membrane was isolated and used for the study. Pre weighed (1.5g) emulgel was spread evenly on to the egg membrane. The egg membrane was clamped between donor and receptor compartment. The receptor compartment was filled with 16ml of 5.5pH phosphate buffer maintained at 37ºC and stirred by using magnetic stirrer. The sample (2ml) was collected at suitable time intervals and analyzed for drug content by UV-Visible Spectrophotometer 1700 (Shimadzu, Japan) at 260nm after appropriate dilutions as discussed earlier. The same procedure was opted for flucanazole emulgel 1% w/w prepared by using carbopol 934 and Guar gum.

6. RESULTS AND DISCUSSION

6.1 Identification of authenticity of fluconazole pure drug

6.1.1 Physical appearance

Physical appearance of the drug was examined by organoleptic properties and results were obtained as follows:
Color: White powder
Odor: Odorless
State: crystalline powder

6.1.2 Determination of melting point (Table 1)

Compound name	Melting point (^{0}C)	
	Standard	Observed
fluconazole	138^{0}C -140^{0}C	138^{0}C

6.2 Evaluation parameters

6.2.1 Physical appearance

Formulation code	Color	Homogeneity	Consistency	Phase separation
F1	Creamy white	Homogenous	Smooth	-
F2	Creamy white	Homogenous	Smooth	-
F3	Creamy white	Homogenous	Smooth	-
F4	Creamy white	Homogenous	Smooth	-
F5	Creamy white	Homogenous	Smooth	-
F6	Creamy white	Homogenous	Smooth	-
F7	Creamy white	Homogenous	Smooth	-
F8	Creamy white	Homogenous	Smooth	-

6.2.2 pH determination

Sl.no	Formulation code	pH
1	F1	6.31
2	F2	6.22
3	F3	6.47
4	F4	6.50
5	F5	6.48
6	F6	6.32
7	F7	6.61
8	F8	6.56

6.2.3 Spread ability studies

Table 4: Graph for spreadability (F1 to F8)

S.no	Formulation code	Spreadability (g.cm/sec)
1	F1	16.84
2	F2	15.92
3	F3	17.01
4	F4	15.10
5	F5	19.38
6	F6	18.41
7	F7	20.30
8	F8	17.62

6.2.4 Rheological studies (for 10rpm spindle 6)

Table 5: Rheogram for formulations F1 to F8

S.no	Formulation code	Viscosity (cps)
1	F1	1824
2	F2	1800
3	F3	2056
4	F4	2137
5	F5	1682
6	F6	1674
7	F7	1670
8	F8	1682

6.2.5 Drug content determination

Table 6: Drug content for F1 to F8

S.no	Formulation code	Drug content%
1	F1	85.74
2	F2	86.27
3	F3	81.50
4	F4	89.50
5	F5	89.43
6	F6	82.51
7	F7	83.12
8	F8	88.96

6.3 In-Vitro Drug permeation data

Table 7: % cumulative drug release data for F1 to F8

Time (hrs)	% Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	6.17	5.56	4.10	5.18	6.01	3.94	8.80	5.76
2	10.82	8.61	7.25	7.93	13.42	6.15	16.51	7.51
3	17.54	13.25	10.93	12.45	25.08	9.37	29.72	11.05
4	25.26	19.13	12.28	17.62	32.75	11.20	38.64	16.54
5	32.47	26.58	23.68	26.01	38.62	22.46	47.38	25.93
6	40.31	34.40	28.41	32.85	45.27	25.34	55.13	30.24
7	49.07	42.79	33.06	42.56	56.91	29.81	63.02	38.85
8	54.46	49.83	37.12	46.42	62.84	34.65	70.61	40.69
9	66.02	52.32	42.62	49.83	68.56	40.65	77.54	45.65
10	68.32	59.82	49.53	52.64	76.85	46.74	83.45	52.25
11	73.65	63.25	53.62	57.45	80.25	50.15	85.05	55.48
12	75.86	69.53	60.31	62.06	84.32	58.09	89.97	63.42

6.4 Standard calibration linearity curve of Flucanazole in pH 6.8 Phosphate buffer

Flucanazole (100mg) was dissolved in buffer,volume was made up to 100 ml in volumetric flask using Phosphate buffer pH 6.8. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml. Absorbance of each solution was measured at --nm using Shimadzu UV-1700 UV-Vis double beam spectrophotometer with Phosphate buffer pH 6.8 as a reference standard.

S.No	Concentration	Absorbance
1	0	0
2	2	0.103
3	4	0.210
4	6	0.317
5	8	0.421
6	10	0.520

7. SUMMARY

The work was carried out to prepare Fluconazole ointment to achieve sustain release effect at site of administration making it the first oral dosage of fluconazole sulphate. The pre-formulation studies like UV analysis of fluconazole, FTIR were complied with USP standards. The FTIR spectra revealed that there was no interaction between the drug and excipients. The Formulation F3 containing 1% of xanthum gum has maximum drug release maintain the sustainity. *In-vitro* skin permeation study studies showed that, Ointments were found to increase the membrane permeation and deposition showing a sustain effect. Stability studies performed for optimized ointments formulations indicates that prepared Ointments have more stability at freezing temperature than that of room temperature. Based on the above data, it was confirmed that prepared Fluconazole Ointments (F3) can be considered as one of the promising approach to reduce the dosing frequency and to maintain drug concentration at the desired site for longer time.

8. CONCLUSION

Finally, it can be concluded from the results of present study that Ointments improve the drug delivery, prolong the release, and improve the site specificity of the drug Fluconazole. Ointments creates a new opportunity for the well-controlled drug delivery of a number of drugs that have a problem of administration by other routes.

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