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FORMULATION AND *IN VITRO* EVALUATION OF FLUCONAZOLE SOLID DISPERSION INCORPORATED GEL

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ABSTRACT

The Goal of the present investigation was to design and evaluate gels for topical delivery of water insoluble antifungal agent Fluconazole with an aim to increase its penetration through skin and there by its flux. This is a broad spectrum imidazole derivative useful in the treatment of superficial and systemic fungal infections. The solubility of Fluconazole is increased by preparing solid dispersions with using mannitol, urea, polyethylene glycol 6000, polyvinyl pyrrolidone K30 and ß-cyclodextrin as carrier. Solid dispersion of Fluconazole was prepared by physical mixture method, solvent evaporation method, fusion method, Kneading Method and complex formation, in-vitro release profiles of all solid dispersions were comparatively evaluated and also studied against pure drug of Fluconazole. Faster dissolution was exhibited by solid dispersion containing 1:3 ratio of drug: mannitol by fusion method. The prepared solid dispersions were subjected for percent practical yield, drug content, infra red (I.R.) spectroscopic studies and differential scanning calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and mannitol. Drug - polymer interaction were investigated using differential scanning calorimetry (DSC). Gels have gained more and more importance because the gel-bases formulations are better percutaneously absorbed than creams and ointment bases. Therefore Fluconazole gel formulations were made with different polymers like carbopol 934, hydroxy propyl methyl cellulose, methyl cellulose, sodium carboxy methyl cellulose which Containing permeation enhancer namely sodium lauryl sulphate (0.25-1.0%) (250mg-1000mg) at different proportions. The formulated gels were evaluated for various physicochemical parameters

like, drug content, pH, viscosity, spreadability, extrudability, stability and in-vitro drug release. The in vitro drug release studies were carried out by using pH 5.0 citrate phosphate buffer containing 1% Tween 80. All the formulated topical preparation showed pH in the range of 6.5 to 7.4 and also showed good spreadability, extrudability. The formulation (FCS2) containing carbopol 934 (1%) with sodium lauryl sulphate 0.5% (500mg) showed best *in vitro* release of 98.95% at the end of 6 hrs.

Keywords: Fluconazole, Solid dispersion incorporated gels, Mannitol, Carbopol 934, *In-vitro* drug release

INTRODUCTION

The skin often has been referred to as the largest of the body organs. An average adult's skin has surface area of about $2m^2$. Its accessibility and the opportunity it affords to maintain applied preparation intact for a prolonged time have resulted in its increasing use as a route of administration whether for local, regional or systemic effects.

The extensive studies on release properties have revealed that the active ingredients in gel based formulations are better percutaneously absorbed than cream or ointment bases.

Fluconazole is a synthetic triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infection. Fluconazole inhibits the fungal cytochrome p450 enzyme 14α-demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of a fungal cytoplasmic membrane, and subsequent accumulation of 14α-demethyl sterols.

The major drawback of this drug is its insolubility in water. Increasing the water insoluble or slightly soluble compounds is a major concern for pharmaceutical researches.

The techniques generally employed to enhance the solubility of poorly water soluble drugs are use of surface active agent, hydrates and solvates, polymorphism, complexation, solid dispersion. Among this Solid dispersion is a unique technique used to increase solubility, dissolution and bioavailability of poorly water-soluble drugs. Conventional methods for preparing solid dispersion include physical mixture, fusion method, solvent evaporation method, melting solvent method and kneading method.

Hence, in the present investigation an attempt will be made to develop solid dispersion incorporated gels of Fluconazole to overcome solubility problems of drug and to treat fungal infections of skin more effectively.

MATERIALS AND METHODS

Fluconazole was procured as a gift sample from Rajesh chemicals co, Mumbai, India. Polyvinyl pyrrolidone, polyethylene glycol 6000, HPMC was purchased from Loba Chem Pvt. Ltd (Mumbai). Urea, mannitol, sodium laury sulphate,carboxy methyl cellulose, Triethanolamine were purchased from S.D. Fine chemical Pvt. Ltd, (Mumbai), ß-cyclodextrin, Carbopol 934, Methyl cellulose were purchased from Hi-Media Laboratories Pvt. Ltd. All the chemicals used in the present study were of AR Grade.

PREPARATION OF SOLID DISPERSIONS: Solid dispersions were prepared by various polymer and different method as shown in Table 1.

Table-1: Formulation ingredients, Preparation method of Fluconazole Solid Dispersions

Batch Code	Composition	Method	Ratio
F1	Fluconazole + Mannitol	Physical mixture	1:1
F2	Fluconazole + Urea	Physical mixture	1:1
F3	Fluconazole + PEG 6000	Physical mixture	1:1
F4	Fluconazole + PVP – K30	Physical mixture	1:1
F5	Fluconazole + ß-cyclodextrin	Physical mixture	1:1
F6	Fluconazole + Mannitol	Solvent evaporation method	1:2
F7	Fluconazole + Urea	Solvent evaporation method	1:2
F8	Fluconazole + PEG 6000	Solvent evaporation method	1:3
F9	Fluconazole + PVP – K30	Solvent evaporation method	1:3
F10	Fluconazole + ß-cyclodextrin	Solvent evaporation method	1:3
F11	Fluconazole + Mannitol	Fusion method	1:3
F12	Fluconazole + Urea	Fusion method	1:5
F13	Fluconazole + PEG 6000	Fusion method	1:5
F14	Fluconazole + PVP – K30	Fusion method	1:5
F15	Fluconazole + ß-cyclodextrin	Kneading method	1:1

Physical mixture[1]: Physical mixtures were prepared by mixing the appropriate amount of Fluconazole and polymer in pestle and mortar and pass through the sieve # 60.

Fusion method: Accurately weighed amount of mannitol, urea, PEG-6000, PVP-K30 and ß-cyclodextrin were melted in a porcelain dish at 80 - 85˚ and to this, calculated amount of Fluconazole were added with through mixing for 1-2 min followed by quick cooling.[2]It were kept in a dessicator under vacuum for 24 hrs. Then, solid dispersion formulations were pulverized using a porcelain mortar and pestle. The pulverized powder were sieve using # 60.[3]

Solvent evaporation method: The drug and the excipients were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40 - 45˚ with continuous stirring to obtain dry granules[2]. The resulting solid dispersion were stored in airtight container till further use.[4]

Kneading method: ß-cyclodextrin was added to the mortar, and small quantities of 50% v/v ethanol were added while triturating to get slurry like consistency. Then slowly the drug was incorporated into

the slurry, and trituration was continued further for 1 hrs. The slurry was then air dried at 25˚C for 24 hrs. Pulverized, and passed through sieve using # 100 and stored in a dessicator over fused calcium chloride.[5]

Evaluation of fluconazole solid dispersions:

Physical Appearance

All the batches of Fluconazole solid dispersions were evaluated for colour and appearance.

Percent Practical Yield (PY) [6]

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] ×100

Drug Content[7]

The Physical mixture and solid dispersion equivalent to 25 mg of model drug were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 261 nm by UV spectrophotometer. The actual drug content was calculated using the following equation as follows:

% Drug content = [Mact / Melt solvents] × 100

= Actual Fluconazole content in weight quantity of solid dispersion x 100

Theoretical amount of Fluconazole solid dispersion

***In-Vitro* Dissolution Study:[8]**

Dissolution studies were performed assuring sink condition according to the paddle method Dissolution Appratus using Campbell electronics, DR-6. The dissolution medium was 900 ml 5.0 pH citrate phosphate buffer containing 1% Tween 80 kept at 37˚C ± 0.5˚C. The solid dispersions equivalent 100 mg of Fluconazole was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the basket was rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 260 nm using PG Instruments limited, T-80 UV-visible spectrophotometer, the samples withdrawn were replaced by fresh buffer solutions. Each preparation was tested in triplicate and then means values were calculated.

Infrared spectroscopy (IR):[9]

FT-IR spectra of pure Fluconazole, mannitol, Gel formulation, carbopol 934, sodium laural sulphate with its Solid dispersions were obtained by Perkin-Elmer

FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm-1.

Differential scanning calorimetry (DSC):[10]

Thermal analysis of Fluconazole and the solid dispersion were carried out using differential scanning calorimetry method. Samples were examined using a Pyris 6 DSC (model) Perkin Elmer .Samples equivalent to approximately 3-4 mg Fluconazole were placed in aluminum pans and heated from 30 to 250˚C with a heating rate of 10˚C/min.

The onset temperature and peak temperature of the melting endotherm were to be reported

Preparation of solid dispersion incorporated gels:

Preparation of gels:

Gels were prepared by various polymers as shown in table 1 & 2. The polymer and purified water I.P. were taken in a glass beaker and allow to soaking for 24 hrs and solid dispersion containing equivalent amount of drug was dissolved in ethanol and other additives were added to the above soaked solution to get homogenous dispersion of drug in the gel[11].

Permeation Enhancers:

The permeation enhancers like sodium lauryl sulphate were incorporated in different concentration (0.25-1.0%) respectively (Table -5) was added by dissolving in little quantity of distilled water with the selected carbopol 934 formulation.

Table – 2: Formulation of Solid Dispersion Incorporated Fluconazole Gels

Ingredients	Carbopol gel	HPMC gel	Methyl cellulose gel	Sodium CMC gel
Fluconazole	1.0%	1.0%	1.0%	1.0%
Carbopol 940	1.0%	--	--	--
HPMC	--	10%	--	--
Methyl cellulose	--	--	5.0%	--
Sodium CMC	--	--	--	3.0%
Triethanol amine	0.50%	0.50%	0.50%	0.50%
Propylene glycol	10%	10%	10%	10%
Ethanol	2.5%	2.5%	2.5%	2.5%
Distilled Water (q.s.)	100ml	100ml	100ml	100ml

Table- 3: Formulation of Solid Dispersion in Fluconazole Gels with Permeation Enhancer

Ingredients	FCS1	FCS2	FCS3	FCS4
Fluconazole	1.0%	1.0%	1.0%	1.0%
Carbopol 934	1.0%	1.0%	1.0%	1.0%
.Triethanolamine	0.5%	0.5%	0.5%	0.5%
Sodium lauryl sulphate(mg)	250	500	750	1000
Propylene glycol	10%	10%	10%	10%
Ethanol	2.5%	2.5%	2.5%	2.5%
Distilled Water (q.s.)	100	100	100	100

Evaluation of gels:

Prepared gels of Fluconazole were evaluated for the following parameters.

Physical appearance and homogeneity:

Gel formulation containing Fluconazole were visually inspected for clarity, color, homogeneity, presence of particles and fibers.

Determination of pH[8]:

The pH of gels was checked by using a digital Hanna Instruments, Ranchi pH meter at room temperature. Initially, the pH meter was calibrated using standard buffers of pH 4 and 9.2. Accurately 2.5 gm of gel was weighed and dispersed in 25 ml of purified water and then pH meter was dipped in the dispersion and the pH was noted.

Drug content analysis[9]:

The drug content of the prepared gels was carried out by dissolving accurately weighed quantity (0.5 g) of gel equivalent to 10 mg of drug was dissolved in 10 ml of methanol, the volume was made up to 100 ml and 5 ml of the above solution was further diluted to 25 ml with methanol. After suitable dilution absorbance of the solution was recorded by using PG Instruments limited, T-80 UV/ visible spectrophotometer at 261 nm.

Viscosity and Rheological studies[10]:

The viscosity of gels was determined by using Brookfield (DV-II+) viscometer. The gel was placed in the sample holder and the suitable spindle selected was lowered perpendicularly into the sample. The spindle was attached to viscometer and then it was allowed to rotate at a constant optimum speed at room temperature. The readings of viscosity of the formulation were measured after 2 minutes.

Gel Strength[10]:

The gel strength was measured by apparatus described by Chul Soon et al in which a fixed weight candle (30 g) was placed on the 15 ml gel in a 25 ml measuring cylinder and the time required to travel the candle down to 5 cm was noted.

Spreadability[11]:

The spreadability of the formulation was determined by an apparatus suggested by Muttimer *et al.*, it consist of a wooden block having a pulley at one end with fixed glass slide on block. An excess of ointment (3gm) placed on ground plate. The gel was sandwiched between this plates and another glass plate having the dimension of fixed ground plate and provided with the hook A 1kg weight was placed on the top of the two plates for 5 minute to expel air and to provide a uniform film of the gel between the plates. Excess of gel was

scrapped off from the edges. The top plate was then subjected to pull of 240 gms with the help of string attached to the hook and time required by the top plate to cover a distance of 10cm was noted. A shorter interval indicates better spreadability. Spreadability is measured by using the formula S=mxl/t (where S is spreadability, m is the weight tied to the upper slide, l is the length of the glass slide, and t is the time taken.)

Extrudability[12]:

In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity in percentage of gel extruded from tube on application of certain load. More the quantity extruded better was extrudability. The formulation under study was filled in a clean, lacquered aluminum collapsible one-ounce tube with a nasal tip of 5 mm opening. It was then placed in between two glass slides and was clamped. Extrudability was determined by weighing the amount of gels extruded through the tip when a constant load of 1 Kg was placed on the slides and gels extruded was collected and weighed. The percentage of gel extruded was calculated and grades were allotted (++ good; + fair).

***In-Vitro* Diffusion Study[12]:**

The apparatus consists of a glass cylinder with both the ends open, 10 cm in height, 3.7 cm in outer diameter and 3.1 cm in inner diameter was used as a permeation cell. A cellophane membrane soaked in distilled water (24 hours before use) was fixed to the one end of the cylinder with aid of an adhesive. Gels equivalent to 10 mg of Fluconazole was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 100 ml of citrate phosphate buffer of pH 5.0 containing 1% Tween 80 (receptor compartment). The whole assembly was fixed in such a way that the lower end of the cell containing gel was just touched (1-2 mm deep) to the diffusion medium, the medium in the compartment was agitated using a magnetic stirrer at the temperature 37±1ºC. Aliquots (5 ml) were withdrawn from the receptor compartment periodically (0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6 hours) and replaced with 5 ml of fresh buffer. After suitable dilution, the sample was analyzed by using PG Instruments limited, T-80 UV visible spectrophotometer at 261 nm.

IR Spectroscopy[5]:

FT-IR spectra of FCS2, and pure Fluconazole were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr

pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm-1.

Stability studies[13]:

Formulated gel preparations were kept at different temperature condition like ambient temperature 5±3˚C (refrigerator temperature), 45±2˚C at 75±5˚C (condition of accelerated stability testing) for span of three months. The following parameters of the gel such as color, pH, viscosity, spreadability, extrudability, and drug content and in-vitro drug release were studied.

RESULTS

Table 4: Drug content uniformity studies and percentage practical yield of Fluconazole solid dispersion

Formulation Code	Drug Content uniformity (%) Mean ± SD	% Practical Yield
F1	94.71	95.86
F2	93.476	94.75
F3	92.363	93.95
F4	95.653	95.10
F5	97.066	96.15
F6	94.170	93.75
F7	93.410	93.10
F8	94.803	91.25
F9	96.530	94.05
F10	93.346	93.05
F11	99.816	96.95
F12	86.240	85.15
F13	92.440	92.10
F14	98.347	95.50
F15	99.297	94.75

Table-5: *In-vitro* Drug Release Profile of Fluconazole Solid dispersion F1 to F5:

Time (T) (min)	F1 Cumulative % Drug release ± SD	F2 cumulative % Drug release ± SD	F3 cumulative % Drug release ± SD	F4 cumulative % Drug release ± SD	F5 cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000	0.000
10	15.59 ± 1.73	16.30 ± 2.24	14.66 ± 2.54	16.29 ± 2.79	23.11 ± 1.00
20	23.97 ± 3.37	27.33 ± 5.47	27.33 ± 1.31	28.93 ± 8.86	34.23 ± 1.89
30	34.88 ± 2.93	37.77 ± 1.46	36.17 ± 3.54	39.70 ± 3.17	43.99 ± 7.03
40	42.10 ± 4.51	46.98 ± 6.16	42.11 ± 1.73	47.99 ± 8.41	55.98 ± 0.85
50	45.22 ± 0.55	50.93 ± 7.36	48.17 ± 1.10	52.26 ± 6.01	62.97 ± 2.01
60	50.28 ± 1.62	55.99 ± 3.88	56.99 ± 1.66	55.99 ± 2.56	69.99 ± 4.04

***Average of three replicates**

Table-6: *In-vitro* Drug Release Profile of Fluconazole Solid dispersion F6 to F10:

me (T) (min)	F6 cumulative % Drug release ± SD	F7 cumulative % Drug release ± SD	F8 cumulative % Drug release ± SD	F9 cumulative % Drug release ± SD	F10 cumulative % Drug release ± SD
0	0.000	0.0000	0.000	0.0000	0.0000
10	49.99 ± 10.02	47.99 ± 3.02	53.48 ± 2.85	54.90 ± 2.03	49.99 ± 3.24
20	60.00 ± 5.07	56.94 ± 2.11	64.24 ± 4.08	61.98 ± 3.77	64.94 ± 1.51
30	69.99 ± 9.37	67.89 ± 1.46	69.57 ± 5.46	73.94 ± 0.70	70.92 ± 5.47
40	84.97 ± 2.59	90.09 ± 2.70	91.86 ± 2.06	87.97 ± 4.80	83.91 ± 4.56
50	93.97 ± 1.74	94.94 ± 1.60	97.35 ± 2.26	89.99 ± 2.07	92.95 ± 1.66
60	--	--	--	---	--

***Average of three replicates**

Table-7: *In-vitro* Drug Release Profile of Fluconazole Solid dispersion F11 to F15:

Time (T) (min)	F11 cumulative % Drug release ± SD	F12 cumulative % Drug release ± SD	F13 cumulative % Drug release ± SD	F14 cumulative % Drug release ± SD	F15 cumulative % Drug release ± SD	Pure Drug cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000	0.000	0.000
10	56.99 ± 3.27	47.99 ± 9.61	51.98 ± 4.28	53.89 ± 8.27	55.96 ± 2.01	14.98
20	67.96 ± 3.98	59.94 ± 4.40	58.94 ± 3.25	62.98 ± 4.23	65.97 ± 0.81	27.69
30	77.68 ± 7.80	66.95 ± 9.06	67.89 ± 6.09	71.91 ± 3.90	75.98 ± 5.07	38.70
40	97.77 ± 0.15	86.94 ± 1.20	88.96 ± 4.89	86.92 ± 6.65	89.93 ± 6.28	41.11
50	--	93.94 ± 2.53	94.99 ± 2.93	98.97 ± 0.53	97.93 ± 0.70	44.94
60	--	--	--	--	--	46.99

***Average of three replicates**

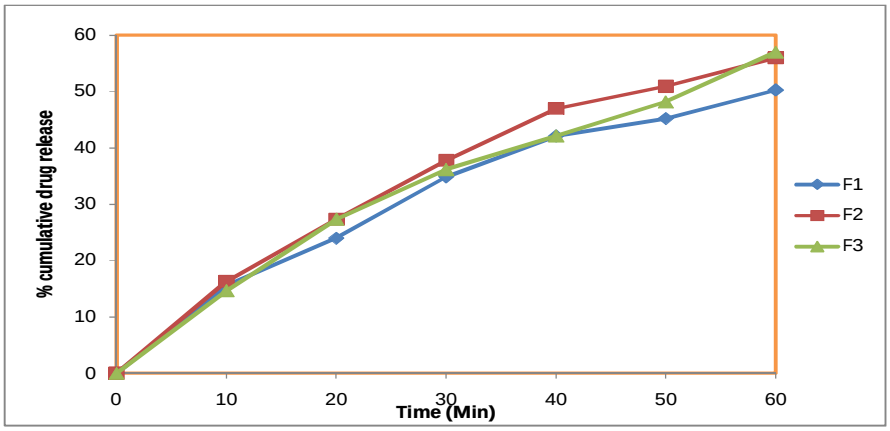

Figure -1: Release profile of Fluconazole from (F1, F2, and F3) solid dispersion

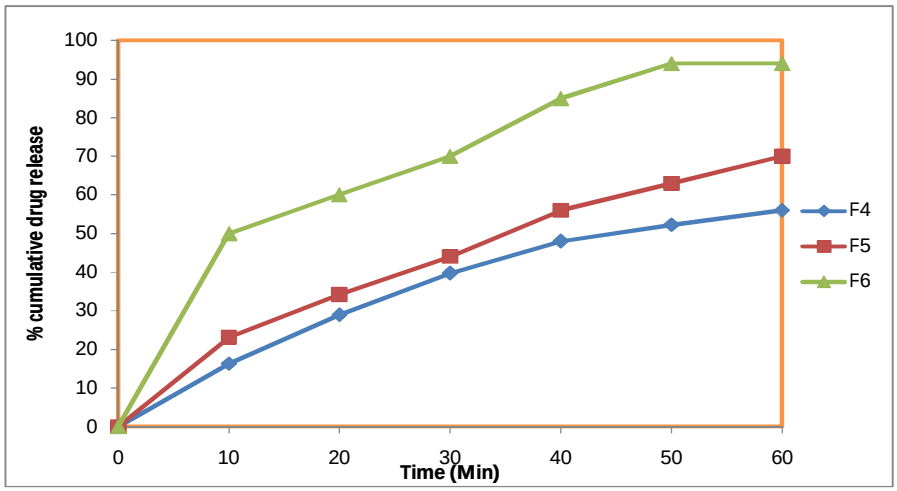

Figure -2: Release profile of Fluconazole from (F4, F5, and F6) solid dispersion

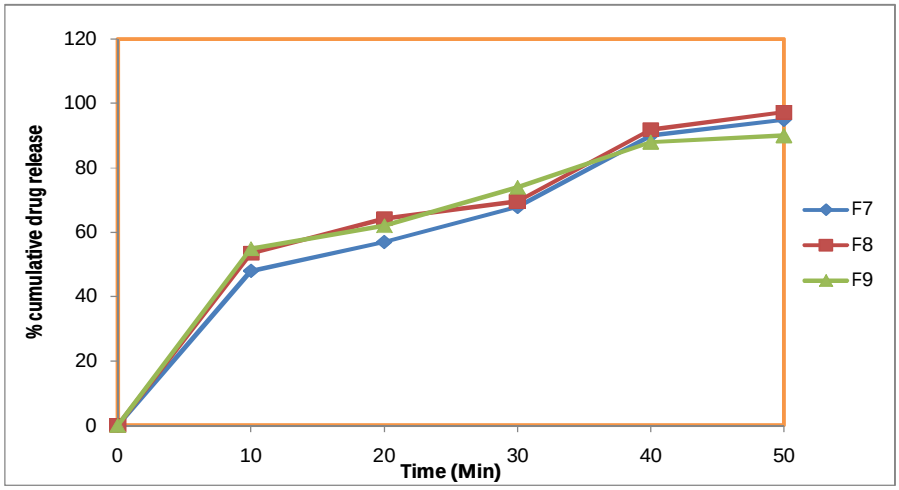

Figure -3: Release profile of Fluconazole from (F7, F8, and F9) solid dispersion

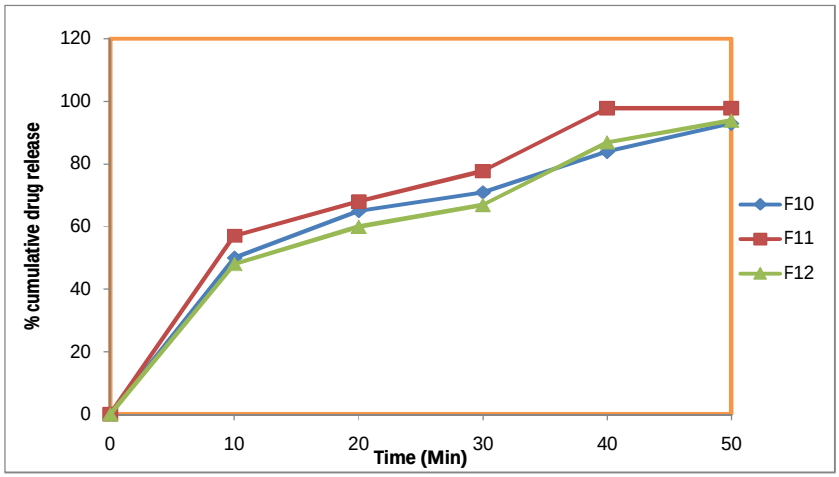

Figure -4: Release profile of Fluconazole from (F10, F11, and F12) solid Dispersion

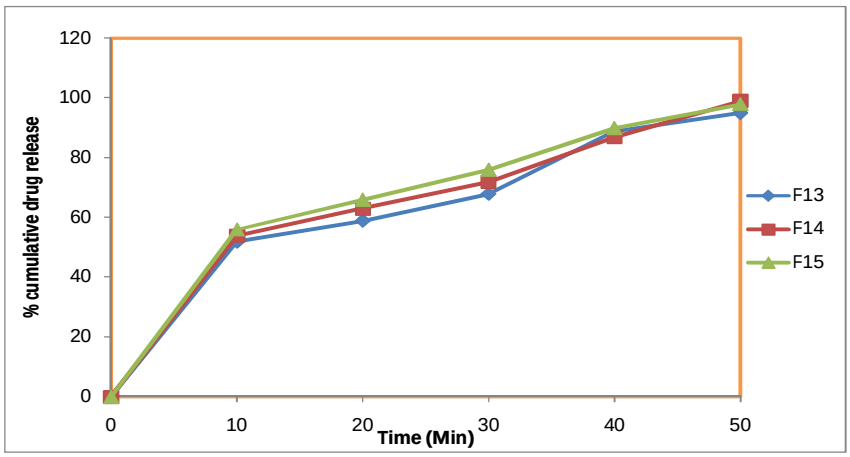

Figure -5: Release profile of Fluconazole from (F13, F14, and F15) solid dispersion

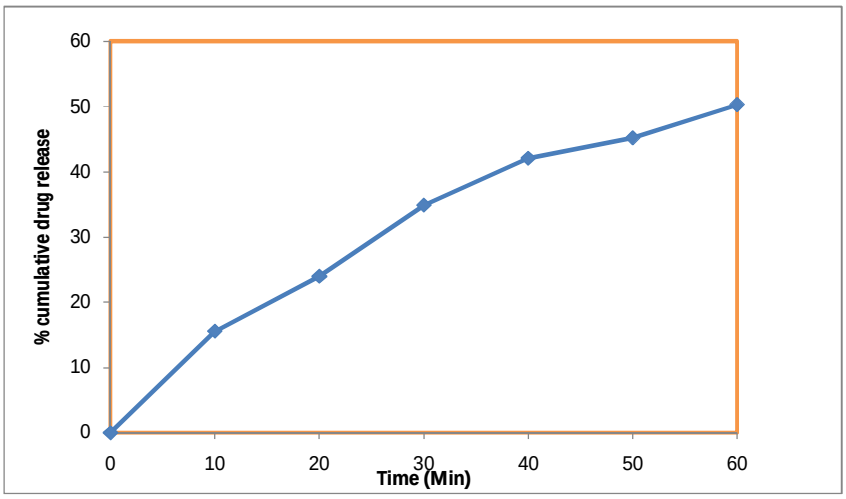

Figure-6: Release profile of Fluconazole pure drug Evaluation of solid dispersion incorporated in fluconazole gel formulations

Table- 8: Physical Parameters and Drug Content of Formulations

Sl.NO	Formulation code	Physical Appearance	Homogeneity	pH	%Drug Content (Mean+SD)
1	Carbopol 934 gel	White Translucent	++	6.67	98.15 ± 0.15
2	HPMC gel	White Translucent	++	6.50	97.05 ± 0.34
3	MC gel	White Translucent	++	6.64	96.18 ± 0.49
4	NaCMC gel	White Opaque	++	7.28	95.05 ± 0.29
5	FCS1	White Opaque	++	7.63	96.64 ± 0.68
6	FCS2	White Translucent	++	7.66	98.96 ± 0.89
7	FCS3	White Translucent	++	6.33	97.36 ± 0.72
8	FCS4	White Translucent	++	6.54	97.15 ± 0.62
9	PD	White Translucent	++	7.15	94.45 ± 0.72
10	MP	White Translucent	++	6.71	98.91 ± 0.31

++ GOOD, + FAIR

Table-9: Rheological Properties Of The Formulations

S. NO	Formulation code	Viscosity(CPS)	Spreadability (gm-cm/sec)	Extrudability
1	Carbopol 934 gel	2450	13.50	++
2	HPMC gel	7630	14.75	++
3	MC gel	5450	15.25	++
4	NaCMC gel	9010	16.15	++
5	FCS1	5970	14.85	++
6	FCS2	7455	13.70	++
7	FCS3	9750	16.10	++
8	FCS4	8410	14.90	++

++ GOOD, + FAIR

Table- 10: *In-Vitro* %Drug Release of Fluconazole From Gel

Time (T) (min)	Fluconazole from Carbopol 934 gel	Fluconazole from HPMC gel	Fluconazole from Methyl cellulose gel	Fluconazole from NaCMC gel
	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000
0.5	26.18	22.12	17.09	17.92
1	34.57	29.14	21.92	26.95
2	40.79	38.62	31.21	31.90
3	50.77	40.09	35.05	40.00
4	54.99	46.81	45.92	47.01
5	64.50	58.15	53.99	54.71
6	70.52	65.55	61.02	63.10

All values are represented as mean ± standard deviation (n=3)

Table-11: *In-Vitro* %Drug Release Study Of Fluconazole From Fcs1 Gel- Fcs4 Gel

Time (T) Hrs	FCS1	FCS2	FCS3	FCS4	Pure Drug (PD) gel	Marketed Preparation (MP) gel
	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD	cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000	0.000	0.000
0.5	32.98	40.00	32.58	30.99	3.30	3.99
1	43.97	46.98	38.41	44.74	5.45	8.98
2	51.93	59.74	51.65	49.77	8.01	10.95
3	67.54	73.08	71.20	70.52	9.94	16.48
4	72.87	80.09	80.19	82.85	11.97	17.92
5	82.35	90.76	88.78	88.29	14.44	22.80
6	91.93	98.97	95.07	95.60	15.87	24.90

All values are represented as mean ± standard deviation (n=3)

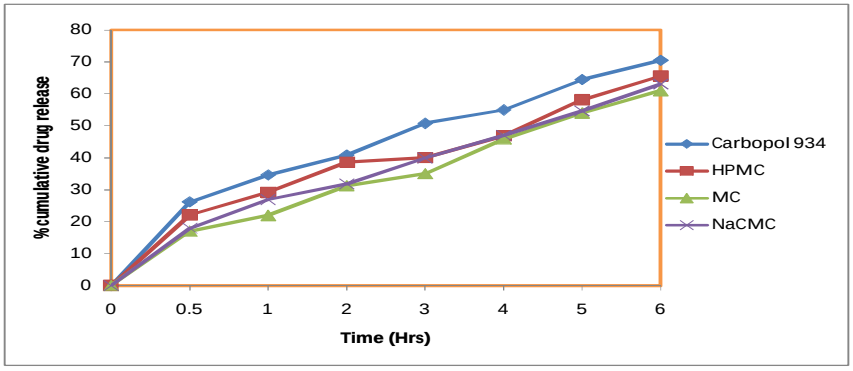

Figure-7: Cumulative percent drug release of Fluconazole from Carbopol 934, HPMC, MC, and NaCMC Gel

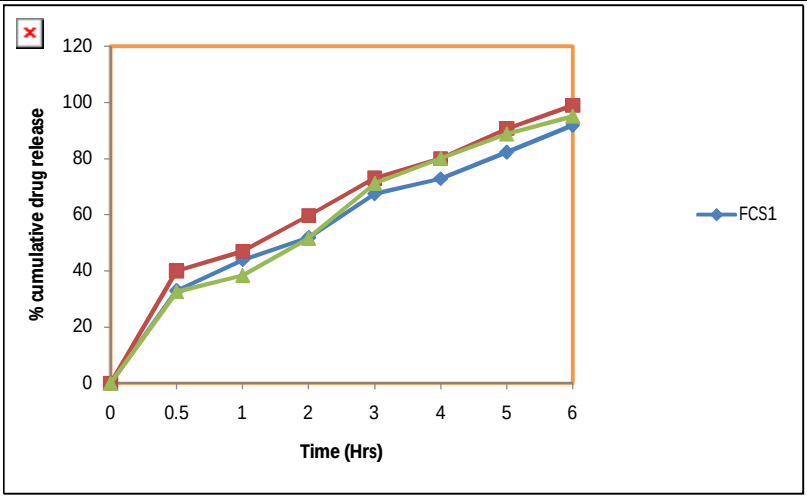

Figure- 8: Cumulative percent drug release of Fluconazole from FCS1, FCS2, FCS3, and FCS4 Gel

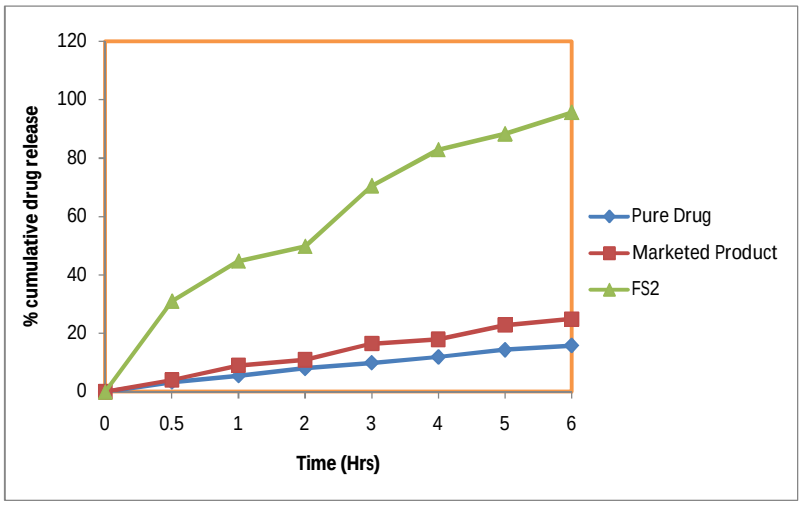

Figure- 9: Cumulative percent drug release of Fluconazole from formulation FS2, Pure drug (PD) and Marketed preparation (MP)

DISCUSSION

In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly soluble drug, Fluconazole by solid dispersion method using mannitol,urea, polyethylene glycol (PEG) 6000, polyvinylpyrrolidone K30, ß-cyclodextrin as carrier. Solid dispersion of Fluconazole was prepared by Physical mixture, solvent evaporation method, Fusion method and kneading method. The prepared solid dispersion were evaluated for number of parameters like DSC, FT-IR, percent practical yield, drug content uniformity studies, and *In- vitro* drug release studies etc.

With the advent of medicated topical applications for transdermal drug delivery, the skin is now viewed as a potential portal of entry. Topical application of the drug at the affected site offers potential advantages of delivering the drug directly to the site of action. Topical fungal infection can best be treated by application of gels over the skin surface, from which the drug released continuously to the desired site.

Differential Scanning Calorimetry (DSC) Studies:

The drug Fluconazole subjected for DSC study, it started melting of 141.9˚C and completed at 144.5˚C, suggesting that these narrow rang of melting is due to the present of single compound in the pure form.

The polymer Mannitol subjected for DSC study, the peak of melting point of mannitol was at 172.4^{o}C.

DSC thermogram of pure drug Fluconazole shows a endothermic peak at 141.9^{o}C and 141.7^{o}C in solid dispersion with mannitol (F11) which indicates that there is negligible change in the peak.From this point we concluded that there is no interaction between drug with mannitol and any other excipients used in the solid dispersion F11.

Infrared (IR) Spectral analysis studies:

FT-IR study was carried out to study the interaction of drug with polymers.The peaks at 3408 cm^{-1} is due to -NH stretching , 3063 cm^{-1} is due to C-H stretching,1584 cm^{-1}is due to C-N cm^{-1} stretching. These are the prominent peaks of the drug fluconazole. All these peaks were also found in the gel formulation (FCS2) and solid dispersion with mannitol (F11).

It clearly indicates that there is no drug interaction with any excipients used in the gel formulation

Percent Practical yield:

Solid dispersions of Fluconazole were prepared by different method using carriers like Mannitol, Urea, PEG-6000, PVP-K30, and ß-cyclodextrin. In the present work, total 15 formulations were prepared and their complete composition is shown in

Table 1. All the Solid dispersions prepared were found to be fine and free flowing powders. The results of percent practical yield studies are shown in Table-4.The percentage Practical yield of the prepared solid dispersions was found to be in the range of 85.15 – 96.95. The maximum yield was found to be 96.95% in F11.

Drug Content Uniformity Studies:

The actual drug content of all the 15 formulations is shown in Table-4.The drug content of the prepared Solid dispersion formulations was found to be in the range of 86.24 – 99.81% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found to be 99.81% in F11.

***In Vitro* Dissolution study:**

Drug release from solid dispersions and fusion method was faster than pure drug, Figure 1-9 shows the plot of cumulative percent released as a function of time for different formulations. Cumulative percent drug released after 40 minutes were 42.10 – 97.77 for F1 to F15 formulation, while it was 41.11% in 40 minutes for pure drug Fluconazole. Formulation F11 were showed highest dissolution of 97.77 at 40 minutes.

In vitro release study revealed that there was a marked increase in the dissolution rate of Fluconazole from all solid dispersions when compared to pure Fluconazole itself. From the *in-vitro* drug release profile, it can be seen that formulation F-11 containing mannitol (1:3 ratio of drug: mannitol) show higher dissolution rate compared with other formulations. The increase in dissolution rate was in the order of Mannitol > Urea > ß-cyclodextrin >PEG – 6000 > PVP – K30.

Drug applied externally to the affected site provides great advantage of delivering drug directly to the site of action. Local infection can be treated by application of products, where there is a continuous of drugs.

Here the preparation and evaluation of Fluconazole solid dispersion were done and the best solid dispersion i.e. F11(1:3 ratio of Fluconazole : mannitol) by fusion method were chosen and incorporated into gels by using Carbopol 934, HPMC, Methyl cellulose and NaCMC as gelling agents.

In-vitro diffusion profile of Fluconazole from gels containing different polymer like Carbopol 934, HPMC, Methyl cellulose and NaCMC are 70.52,65.55,61.02 and 63.10% respectively drug release in 6 hrs. (Shown in Figure-7) Carbopol 934 shown highest release of 70.52% as compared to HMPC, Methyl cellulose and NaCMC.

Here the preparation and evaluation of Fluconazole solid dispersion incorporated gels were done and the best drug release

was Carbopol 934. Carbopol 934 was chosen for the study with different permeation enhancer viz. SLS are shown in Table 3. From the result, it is clearly evident that all the gel formulations showed good extrudability, homogeneity, and spreadability. The drug content was in the range of 95.05% to 98.91%.

The formulations viscosity ranged from 2450 to 8410 cps, and pH of all the formulations was between pH 6 and pH 7.6. This lies in the normal pH range of the skin. Fig. 7 depicts the *in vitro* diffusion profile of Fluconazole from gels containing carbopol 934 and different concentrations of permeation enhancer sodium lauryl sulphate (0.25-1.0%). Sodium lauryl sulphate of 0.5 % concentration was shown maximum of (98.95%) drug release over a period of 6hrs. Further in SLS concentration of 0.75% and 1.0% level showed decrease in drug release. In fact the drug release was found to be slightly decreased.

Amongst the all formulations the highest release of Fluconazole was given by FCS2 i.e. 98.95%.

The pure drug and marketed preparation showed a cumulative percent release of 15.87 and 24.90% respectively.

Spreadability:

Spreadability plays an important role in patient compliance and help in uniform application of gel to the skin. Gels should spread easily. All the formulations were found to have better spreadability.

CONCLUSION

The data obtain from the study of development and evaluation of Fluconazole solid dispersion incorporated gels, Solid dispersions of Fluconazole were prepared by different method using carriers like mannitol, Urea, PEG- 6000, PVP-K30, and ß-cyclodextrin and Carbopol 934, HPMC, MC, NaCMC as gelling agents, the following points can be concluded:

The dissolution rate of Fluconazole from solid dispersion i.e., F1-F15 was significantly higher than that of pure drug.

Solid dispersion prepared by Fusion method showed faster drug release than the dispersion prepared by Solvent evaporation method then by Kneading method followed by physical mixture.

The general trend indicated that there was increase in dissolution rate for solid dispersion in the following order of Mannitol > Urea > ß-cyclodextrin >PEG – 6000 > PVP – K30.

IR studies indicated that no chemical interaction between drug and polymer took place during preparation of solid dispersion of Fluconazole.

DSC studies indicated that Fluconazole was homogeneously distributed within the carrier in an amorphous state and no drug

crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product.

Fluconazole solid dispersion incorporated gels were translucent, opaque and milky white in appearance, the pH, and drug content, extrudability, spreadability and viscosity were found in acceptable range.

In-vitro drug release of Fluconazole solid dispersion incorporated gels formulation Carbopol 934 shown higher drug release as compared to HMPC, Methyl cellulose and NaCMC.

Based on this study the effect of permeation enhancer on Fluconazole release, an optimum of 0.5% SLS were found to be more suitable to give a better formulation having good drug release characteristics and consistency.

The IR study showed that there was no chemical interaction between Fluconazole and polymer for FCS2 formulation.

From overall formulation, FCS2, which was formulated using Carbopol 934 polymer with 0.5% SLS Permeation enhancer was found to be the best formulation.

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