Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Innovative Approach for Formulation of Fluconazole Nanogel

PATIL PRIYA *, TALELE SWATI, WAGH RAHUL, JADHAV ANIL

Sandip Institute of Pharmaceutical Sciences, Nashik, Maharashtra - 422213

ARTICLE DETAILS

Article history:
Received on 29 January 2019
Modified on 25 February 2019
Accepted on 07 March 2019

Keywords:
Fluconazole,
TDDS,
Eudragit S-100,
Glycerol,
Carbopol-940,
Cellophane Membrane.

ABSTRACT

Transdermal drug delivery is optimistic, but challenging system available for accessible as well systemic effect of the drug. Drug entry is followed by intercellular, transcellular or appendageal route. The intention of the present examination was to developed a nanogel with diminish particle size in order to ameliorate the bioavailability of the anti-fungal drug, Fluconazole. The present investigation is an endeavor to deliver the transdermal delivery of Fluconazole nanogel. Nanogel has been the frame having size extending from 100-400 nm. Glycerol and water ratio is 20:80 and co-solvent system is selected for performing Fluconazole nanogel using various polymers and has better permeability coefficient than alcohol: water cosolvent. Gels containing Fluconazole with Eudragit polymer appeared better permeability coefficient. Fluconazole nanogel formulated using carbopol with saturation enrich has shown better flux enrichment in comparison with nanogel formulated using Glycerol and Triethanolamine. Fluconazole nanogel with Eudragit and carpool as gelling agent has better flux enhancement with Triethanolamine.

INTRODUCTION

TDDS are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation. Transdermal delivery of drug is optimistic but challenging system available for accessible as well systemic effect of the drug. Drug entry is followed by intercellular, transcellular or appendageal route. The intercellular is the common pathway for drug permeation through skin. Transdermal administration represents a viable option for local and systemic delivery of diverse therapeutic compounds [1, 2]. Transdermal delivery is non-intrusive, imperative painless, does't require sterile preparation, and is effectively and promptly administered to the patient. Drug absorption through the skin is enrichment if the drug substance is in solution, if It has a favourable lipid/water partition coefficient. [2]

Author for Correspondence:
Email: priya.patil@sandippharmacy.org

Nanogel has both properties of solids and liquids. It consist of little sum of solid segments snared with polymers scattered in vast volume of fluid in which solids shape 3-D arrange framing the nanoscale measure prompting high surface region giving biconjugation of dynamic focusing on locales. Nanogel has been the frame having size running from 1-100nm. [1-3]

The nanogel of fluconazole has been used as anti fungal effect. Fluconzaole is the drug used is the most superior drug undergo 90% absorption in transdermal form. Fluconzaole provide better acceptability to the skin pH range. The study was conducted to plan and assess fluconazole nanogel which provides prolonged release, enlarge the residence time of drug on the skin thereby enhance bio-availability. [3 - 5]

MATERIALS AND METHODS

Preformulation

a) Melting Point

Determined by capillary method, for determination of melting point, drug was fill in a glass capillary and one end of capillary was sealed with the help of flame. The drug containing capillary was dipped into the liquid paraffin. Gradually increased the temperature and drug was starting to melt and melting point was then determined and reported.

b) Determination of λ_{max} of Fluconazole
The standard solution of active drug was prepared in phosphate buffer (pH 6.8) solution. The prepared solution was examined between the range 400-200 nm by UV- visible spectrophotometer.

c) Solubility Measurements
Normal solubility determinations carried out by the process. An excess amount drug was added and diffuses in excess amount of water in glass vial to form a saturated solution. The system was stirred for 24 hrs at 25°C and kept rest for 1hour to attain the equilibrium. The solution was filtered with membrane filter and diluted. The solubility was determined spectrometrically at 260 nanometers.

d) Infrared Spectrum
The IR spectra of fluconazole, Eudragit S-100 and binary mixture were recorded by using FTIR. KBr was mixed with dry sample of fluconazole in the ratio of 1:100. This mixture was triturate and form of a pellet by applying pressure in hydraulic press. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in (Perkin Elmer, Spectrum BX, USA) FTIR instrument and spectral analysis was done.

e) Differential Scanning Calorimetry
DSC was performed by Mettler -Toledo DSC 821e instruments. DSC scan for fluconazole was recorded at heating rate of 10°C/min in temperature range 50-300°C. Crystallinity of drug and excipient was measured by DSC.

Preparation of Fluconazol Nanogel
Precisely weighed quantity of Drug, Eudragit S-100 (polymer), and Tween-80 as stabilizer are properly mixed with glycerol while stirring. Prepared aqueous phase containing carbopol-940 mixed in water with continuous stirring and then heat the solution. This drug containing stage is sonicated on Ultra sonic shower sonicator. The drug stage is included drop by drop into the watery stage amid homogenization to frame emulsion. The emulsion changed over into nanodroplets by homogenizer which framed O/W emulsion. Homogenization was preceded for one hour. Triethanolamine was added to form the gel with continuous stirring to nanogel. Then batch A1, A2, A3 was prepared at the highest rpm 8000 with different in composition. Whereas batches B1, B2, B3 and C1, C2, C3 prepared at different rpm such as 5000, 6000, 7000 using homogenizer which is shown in Tables 1. [6]

Table 1: Fluconazole Nanogel

Composition	A -1	A -2	A -3	B-1	B-2	B-3	C-1	C-2	C-3
Fluconazole (g)	100	100	100	100	100	100	100	100	100
Eudragit S100 (g)	0.15	0.20	0.25	0.15	0.15	0.15	0.25	0.25	0.25
Tween 80 (ml)	0.1	0.3	0.5	0.1	0.1	0.1	0.1	0.1	0.1
Glycerol (ml)	5	10	15	5	5	5	5	5	5
Carbopol (ml)	0.5	0.1	0.3	0.1	0.1	0.1	0.1	0.1	0.1
Water	70	30	50	30	30	30	30	30	30
Triethanolamine	2	3	4	2	2	2	2	2	2

Evaluation Parameters
a) Appearance: The prepared gel bases were, examined outwardly for clearness, color and presence of any particles.

b) Homogeneity: All prepared gels were tested and observed homogeneity by visual inspection after some time gels has been set at the bottom container. The samples were observed for their appearance and presence of any aggregates in the gel.

c) Measurement of Particle Size of Formulation: Measurement of particle size were determined by using Malvern Master sizer 2000 MS and then record particle size.

d) pH Measurement: The pH measurement was carried out by using calibrated digital type pH meter. Glass electrode was dipped into prepared solution and the reference electrode completely into gel system so as to cover the electrodes.

e) Drug Content: For the evaluation of the drug in gel, fluconazole was extracted from 1 gm of gel formulation with 50ml of phosphate buffer 6.8 and mixture was filtered through membrane filter (pore size 0.45µm). From this, 2ml was pipette out and made up to 10ml. then 1-10ml, the absorbance of the sample was determined spectrophotometrically at 260 nm. The concentration of fluconazole was estimated from the equation of calibration curve. [7]

f) *In Vitro* Release Studies The Franz Diffusion Cell apparatus is used to study drug release, which is consists of a cylindrical glass tube. 1 gm of gel proportional to 10 mg of fluconazole was spread consistently on the surface of cellophane layer (already absorbed medium for 24 hrs) and was settled to the one end of tube. The entire get together was settled so that the lower end of tube containing gel was simply contacts (1-2 mm profound) the surface of dispersion medium. The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37°±2° the contents were stirred using magnetic bar at 100rpm for a period of 24 hrs , 5 ml of samples were withdrawn at different time intervals and diluted up to 10ml of fresh buffer and the sample were analyse at 276 nm for fluconazole. [8, 9]

g) Spreadability: Spreadability is dictated by mechanical assembly proposed by Mutimer. It comprise of wooden square, which is given by a pulley toward one side. By this technique, spreadability is estimated based on 'Slip" and 'Drag". A ground glass slide is settled on this square. An example of 0.1 g of nanogel under examination is put on this ground slide. The gel is settle on the shoreline formulation was squeezed between two slides and a 1kg weight is put on the top point of two slides and left for around 5 minutes to remove air and to give a uniform film of the nanogel between two slides. Overflow of the gel is rejected from edges. The best plate is then exposed to pull the weight. With help of string connects to the snare and the time required by best slide to cover the separation is noted. A shorter interim demonstrate better spreadability. Spreadability was calculated by using the formula. [10]

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

Where, S= spreadability, L=Length of glass slide,
M=weight tied to upper slide,
T=Time taken to separate the slides.

h) Extrudability: It is a standard experimental test to quantify the power required to expel the material from cylinder. The strategy connected for assurance of associated shear in the locale of the rheogram comparing to a shear rate surpassing the yield esteem and showing plug stream. The technique get for assessing nanogel plan for extrudability depends on the amount in level of nanogel and nanogel expelled from lacquered aluminum collapsible cylinder on use of weight in grams required in any event 0.5cm strip of nanogel in 10 seconds. The estimation of extrudability of every definition demonstrates the triplicate and midpoints esteem is introduced.

Extrudability= Applied weight to extrude the nanogel from tube (in gm)/ Area (in cm2). [11]

i) Rheological Studies: Brookfield viscometer was used for determination of viscosity of gel. The spindle was inserted into the gel surface. After that add 3gm of gel process perform in Stability chamber and maintained Room temperature. The process is conducted by using spindle no.61, 63 and 64. Then the readings were taken at different rpm such as 50, 100, 150, 250rpm and viscosity was measured. All the evaluation parameter performed for the three batches, the result for the batch A-1 was found to be satisfactory as compare to other batch. [12, 13]

RESULT AND DISSCUTION

Preformulation Studies

Characterization of Fluconazole

a) Organoleptc Properties

Fluconazole exhibits white to off-white crystalline powder.

b) Melting Point

Result for melting point is shown in the Table 2. The melting point is found to match with standard value, indicating that, the drug was in pure form.

Table 2: Melting point of Fluconazole

Drug	Melting Point range	
	Standard	Observed
Fluconazole	140-142°C	138-140°C

c) FTIR Spectroscopy

The FTIR spectrum for is shown in Fig. 1 and in Fluconazole interpretation of FTIR spectra is given in Table 3. FTIR spectrum of drug sample showed all the peaks corresponding to the functional groups present in the structure of Fluconazole.

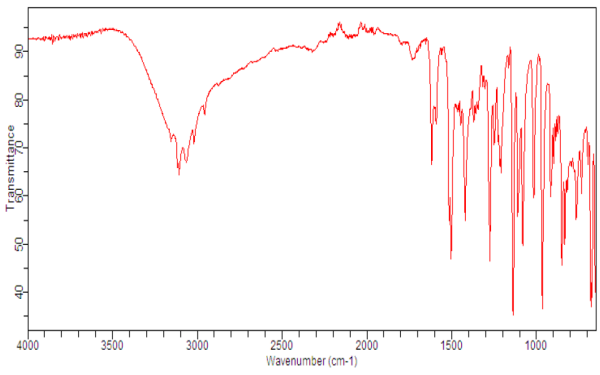

Figure 1: FTIR spectrum of pure Fluconazole

Table 3: Interpretation of FTIR spectrum of pure Fluconazole

Peaks CM^{-1}	Groups
3107	O-H
1249	C-O
2875	Aliphatic C-H
1249	Asymmetric C-O-C
1042	Symmetric C-O-C

From FTIR spectrum it was concluded that the drug sample was in pure form.

d) Differential Scanning Calorimetry Studies Pure Drug- Fluconazole

DSC thermogram of Fluconazole is shown in the Fig. 2. DSC studies indicate a sharp endothermic peak at 282 ºC corresponding to the melting point of the sample which matches with the melting point of Fluconazole.

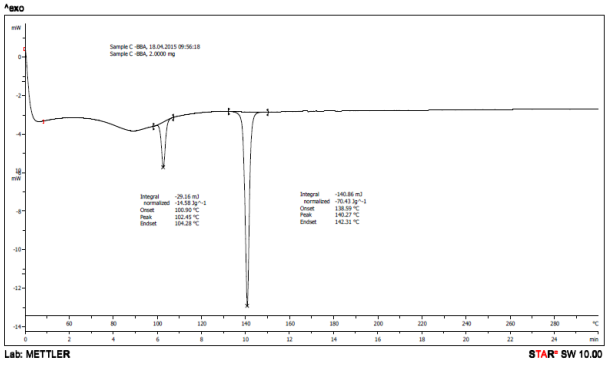

Figure 2: DSC Thermogram of Fluconazole

e) UV Spectroscopy: Determination of λmax

After studying the UV spectra of Fluconazole, it was found that drug shows absorbances at 260 nm but maximum absorbance was at 260 nm when solution is prepared in distilled water. So 260 nm was considered as λmax. UV spectra Fluconazole is shown in Fig. 3.

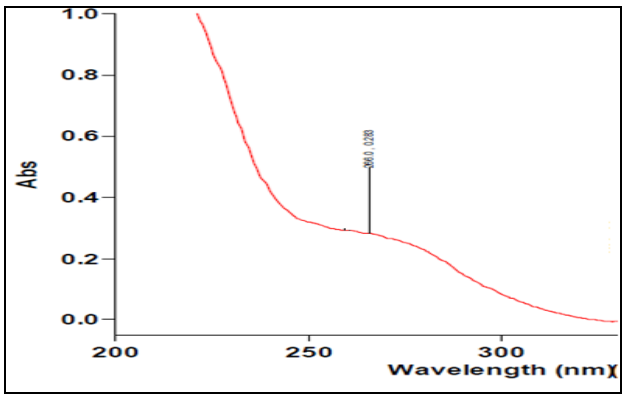

Figure 3: UV Spectra of Fluconazole

f) Effect of Change in pH on λ_{max}

λ_{max} of drug was observed by making its solution in different pH to check the effect of pH on λ_{max}. Result of the same is given in Table 4.

Table 4: Effect of pH on λ_{max}

Drug solution in Ph	λmax
6.8	260nm
7.4	260nm

There was no significant change in λ_{max} of Fluconazole at different pH. So calibration plot can be constructed by using distilled water and can be used for quantitative evaluation purpose; though the medium of evaluation of release is phosphate buffer pH 7.4.

g) Calibration Curve of Fluconazole

The calibration curve for Fluconazole in phosphate buffer 6.8 and its observation values are in Table 5. The graph of absorbance vs. concentration was found to be linear in the concentration range of 4-24µg/ml at 260 nm. The R^2 of the calibration curve was found to be 0.999.

Table 5: Calibration curve values of Fluconazole

Sr. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	4	0.1548
3	8	0.3173
4	12	0.4842
5	16	0.6303
6	20	0.7963
7	24	0.9237
R^2	**0.999**	
Slope	**25.61**	
Intercept	**-0.1020**	

h) Determination of Solubility

The solubility data of Fluconazole in distilled water at 25°Cand 0.9%w/v NaCl and in different room temperature is given in Table1. The results showed that drug was equally soluble in distilled water at 25°C and has same solubility in from solubility data it can be concluded that Fluconazole shows pH independent solubility and solubility of drug will not change during manufacturing at temperature 25°C and also during absorption. So the drug will remain soluble throughout the buffer and was finalize as it removed tailing and gave the peak with high plate count (Table 6).

Table 6: Solubility criteria in various solvent

Parameter	1	2	3	Mean
Solubility in water at 25^{0}c (mg/ml)	1.90	1.33	1.76	1.66
Solubilty in 0.9% w/v NaCl (mg/ml)	1.67	1.26	1.10	1.34
Phosphate buffer pH 6.8	590.5	588.9	518.8	566.9

i) Stability Batches Evaluation

The stability studies were carried out on optimized formulation. The samples were stored at 40^{o}C±2^{o}C and 75%±5% relative humidity for three months as per ICH guidelines. After 1, 2 and 3 months samples were withdrawn and tested for appearance, pH, particle size, drug content, spread ability, extrudability, viscosity is shown in Table 7, 8 and 9.

Table 7: Batches Evaluation (Batch A)

Evaluation parameter	A-1	A-2	A-3
Appearance	Clear	Clear	Clear
Homogeneity	Homogenous	Homogenous	Homogenous
Partical size (nm)	159	192	220
pH	6.2±0.00	6.5±0.02	6.8±0.20
Drug content ±SD	98.8±0.02	96.5±0.02	97.8±0.04
In vitro drug release (%)	96.72±0.0784	94.75±0.963	92.78±0.77
Skin irritation test	No irritation	No irritation	No irritation
Spreadability (g.cm/s)	5.3±0.4	5.7±0.5	5.0±0.5
Extrudability (g)	277±0.6	266±0.4	251±0.6
Viscosity in cp at 50(rpm)	9892	8890	8800

Table 8: Batches Evaluation (Batch B)

Evaluation parameter	B-1	B-2	B-3
Appearance	Clear	Clear	Clear
Homogenicity	Homogenous	Homogenous	Homogenous
Particle size(nm)	159	165	280
pH	6.3±0.01	6.5±0.02	6.7±0.20
Drug content ± SD	97.8±0.01	96.5±0.09	94.8±0.05
In Vitro drug release(%)	96.72±0.0784	95.75±0.963	95.78±0.77
Skin irritation test	No irritation	No irritation	No irritation
Spread ability (g.cm/s	6.4±0.4	6.1±0.6	6.4±0.6
Extrudability(g)	259±0.4	267±0.9	280±0.1
Viscosity In cp 50(rpm) at	9765	8982	8978

Table 9: Stability Batches Evaluation

Evaluation parameter	Initial observation			After one month (40 ^{o}C, 75%)		
	C-1	C-2	C-3	C-1	C-2	C-3
Appearance	Clear	Less Clear	Clear	Clear	Clear	Clear
Homogeneity	Homogenous	Homogenous	Homogenous	Homogenous	Homogenous	Homogenous
pH	6.4±2	6.8±2	6.2±2	6.9±2	6.9±2	6.6±4
Partical size (nm)	159	167	179	169	158	156
Drug content ±SD	97.3±0.019	96.6±0.14	96.5±0.092	97.7±0.095	97.7±0.095	97.7±0.095
Spreadibility (gcm/s)	5.12	6.98	5.3	6.6±0.5	5.5±0.2	5.5±0.2
Extrudability (gm)	220	235	214	358	225	227
In vitro drug release (%)	96.65±0.903	91.92±0.861	94.56±0.85	92.32±1.10	96.02±1.0	96.38±0.39
Viscosity (cp)	9498	8588	9760	9453	9495	9440

j) Market product evaluation

Product name- Serrini

Market product were evaluated for appearance, homogeneity, particle size measurement, pH measurement, drug entrapment, drug content, skin irritation study, in vitro drug release, spread ability, extrudability, rheological study is shown in Table 10.

Table 10: Marketed Product Evaluation

Evaluation Parameter	Market Product (serrini)
Appearance	Clear
Homogenicity	Homogenous
Particle size(nm)	162
pH	6.3 ± 0.2
Drug content ± SD	96.08 ± 0.42
In vitro drug release (%)	94.72 ± 0.920
Skin irritation test	No irritation
Spreadability (g.cm/s)	7.1 ± 0.5
Extrudability(g)	282 ± 0.7
Viscosity in cp at 50(RPM)	8898

CONCLUSION

The novel nanogel form represents an effective and better carrier for the topical preparations. The prepared nanogel formulation showed the better penetration in the skin may be due to the enhanced contact between the drug and the skin resulting from more surface area and hydration. The prepared formulation proves to be the better alternative for the oral administration of Fluconazole (antifungal) and eliminates the limitations of the drug like gastric disturbances, low bioavailability, short half life and first pass effect. The formulations of Fluconazole nanogels were prepared using glycerol: water solvent and carbopol used to maintain the viscosity. The use of nanogels allow the improvement of the biopharmaceutical parameters of entrapped drugs. Nanoscale form of the gel had made tunable nanoscale dimensions, drug loading capacity and providing surface area for conjugation of active targeting moieties. The production of the formulation is also proved to be better and cost effective in comparison with oral dosage forms.

REFERENCES

[1] Talele S, Nikam P, Ghosh B, Deore C, Jaybhave A, Jadhav A. A research article on Nanogel as topical promising drug delivery for Diclofenac sodium, Indian journal of pharmaceutical education and research, 2017, 51(4); 580-587.

[2] Abrar. B, Shaikh. A, Formulation and *in vitro* evaluation of NSAIDs gel, International journal of current pharmaceutical research, 2012, 4; 56-58.

[3] Dinda. S. C, Advances in Pharmaceutical Techonology, School of Pharmaceutical Education and Research, 2011; 69-82.

[4] Alvarez-Lorenzo, c, concherio ,a. intelligent drug delivery systems:polumeric micelles and hydrogels,Mini-Rev. Med.Chem,8, 2008; 1065-1074.

[5] Alvarez-Lorenzo, C., Concheiro, A., Molecularly imprinted gels and nanoparticle and microparticles. Manufacture and applications. In: Arshady, R., Kono, K. (Eds.), SmartNano- and Microparticles. Kentus Books, London, 2006; 279-336.

[6] Benson. H. A, Transdermal drug delivery:. Penetration enhancement techniques, Curr Drug delivery, 005; 2-23.

[7] Boinpally, R.R., Zhou, S.L., Poondru, S., Devraj, G., Jasti,, B.R. Lecithin vesicles for topical delivery of diclofe-nac‟, Eur. J. Pharm. Biopharm., 2003, 56; 389-392.

[8] Ansari, K.A., Vavia, P.R., Trotta, F., Cavalli, R., Cyclodextrin-based nanospongesfor delivery of resveratrol*: in vitro* characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech, 2011, 12; 279–286.

[9] Cavalli, R., Akhter, A.K., Bisazza, A., Giustetto, P., Trotta, F., Vavia, P., Nanosponge formulations as oxygen delivery systems. Int. J. Pharm.2010, 402; 254–257.

[10] Dua. K, Pabrija. K, Acelofenac Topical dosage forms; *In vitro* and *in vivo* characterization, Acta Pharm, 2010; 60-467.

[11] Bhaskar. K, Anbu. J, Lipid Nanoparticles for Transdermal delivery of flubiprofen, formulation , *in vitro*, *ex vivo* and *in vivo* studies, lipids; BioMed Central, 2009; 8-79.

[12] Benson H.A, Elastic liposomes for dermal and transdermal drug delivery, Current drug delivery, 2009, 6; 217-226.

[13] Chowdary, K.P.R., Mohapatra, P., and Murali Krishna, M.N., Evaluation of olibanum and its resin as rate controlling matrix for controlled release of diclofe-nac‟, Indian Journal Pharm. Sci., 2009,68(4); 497-500.