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Formulation and *invitro* evaluation of nystatin organo gels

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ABSTRACT

The purpose of topical dosage form is to conveniently deliver drug across a localized area of the skin. To develop an ideal dosage form, one must take into account flux of the drug across the skin, nature of drugs, patient acceptability of the formulation, etc.., Nystatin is categorized as synthetic allylamine antifungal drug and is successfully used to treat Fungal disorders. On this contest, emulgel was formulated using carbopol 934 and HPMC, liquid paraffin as oil phase, emulsifying agents like tween 20 and span 20 and propylene glycol as permeation enhancersOn basis of quality of organogels produces total eight formulations F1 to F8 were selected. They were evaluated for physical appearance, pH, rheological study, spreadability, drug content and *in-vitro* drug permeation study. Thus, the formulated organogel had a distinct advantage over existing conventional dosage form in that the drug permeation was found to be rapid across the skin and hence the increased therapeutic response by bypassing 1st pass metabolism and with no gastrointestinal problems and patient compliance.

Keywords: Nystatin, Organo Gel Antifungal, First pass metabolism.

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.

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems1. The novel Transdermal drug delivery is 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 circulation2.

Gels

Gels are defined as a semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linkingintroduced[3].

METHODOLOGY

Calibration curve of Nystatin

Preparation of stock solution

Accurately weighed amounts of 100 mg of Nystatinwas transferred into a volumetric flask made up to 100 ml with pH 6.8 Phosphate buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock solution-1.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 ml with pH 6.8 Phosphate buffer which has given the solution having the concentration of 100mcg/ml.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of Nystatin (5-30mcg/ml) solutions. The absorbances of above solutions were recorded at λ_{max} (290nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

FORMULATION OF NYSTATIN ORGANOGEL

Gel preparation

The composition of Nystatinorganogel was shown in the formulation code table 1. The carbopolgel was prepared by dispersing 0.25g 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 50ml.

In case of Hydroxy Propyl Methyl cellulose gel was prepared by dispersing HPMC in hot purified water (80^0C) and the dispersion was cool, then the weight was adjusted to 50ml with purified water.

Organogel preparation

The continuous organic phase of organogel was prepared by dissolving span 20 and tween 20 in light liquid paraffin and heated upto 70^0-80^0C.Methylparaben, Propylparaben were mixed with propylene glycol and glutaraldehydeand and this added this mixture was dissolved in the aqueous phase. Then oil phase was mixed slowly with aqueous phase and final volume is made with purified water.

Organogel preparation

The obtained organic mixture was mixed with the gel and volume was adjusted to 50ml with water and subjected to homogenization for 45 minutes to get Nystatinorganogel 2% w/v.

Table 1. Formulation code

Ingredients (% w/v)	F1	F2	F3	F4	F5	F6	F7	F8
Nystatin (mg)	500	500	500	500	500	500	500	500
HPMC K15(ml)	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 934(ml)	-	-	-	-	0.25	0.25	0.25	0.25
Light liquid paraffin(ml)	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75
Tween 20(ml)	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20(ml)	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol(ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol(ml)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methylparaben(ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylparaben(ml)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Glutaraldehyde(ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Purified water (ml) (q.s)	50	50	50	50	50	50	50	50

Identification and authenticity of Nystatin pure drug

Physical appearance

The physical appearance of the drug was examined by organoleptic properties, and results were obtained as follows

Colour

White fine crystalline powder

Solubility studies

Table 2: Solubility studies

Solvents	Solubility
Water	Slightly soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Chloroform	Soluble

Determination of melting point

The melting point of nystatin was determined by capillary tube method and it was found to be 160^0C.This value matches the literature reference standard drug value.

Calibration curve of Nystatin

Table 3: Calibration curve of nystatin:

Conc.(µg/ml)	Absorbance
0	0
5	0.21
10	0.416
15	0.601
20	0.753
25	0.904
30	1.076

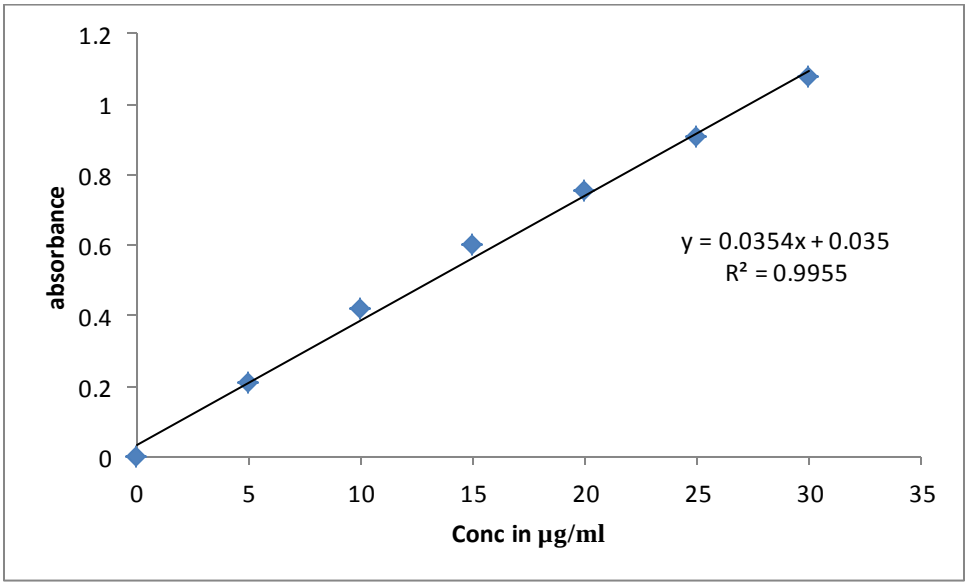

Figure 1: Calibration curve of Nystatin

DRUG-EXPIENT COMPATIBILITY STUDIES

FTIR study

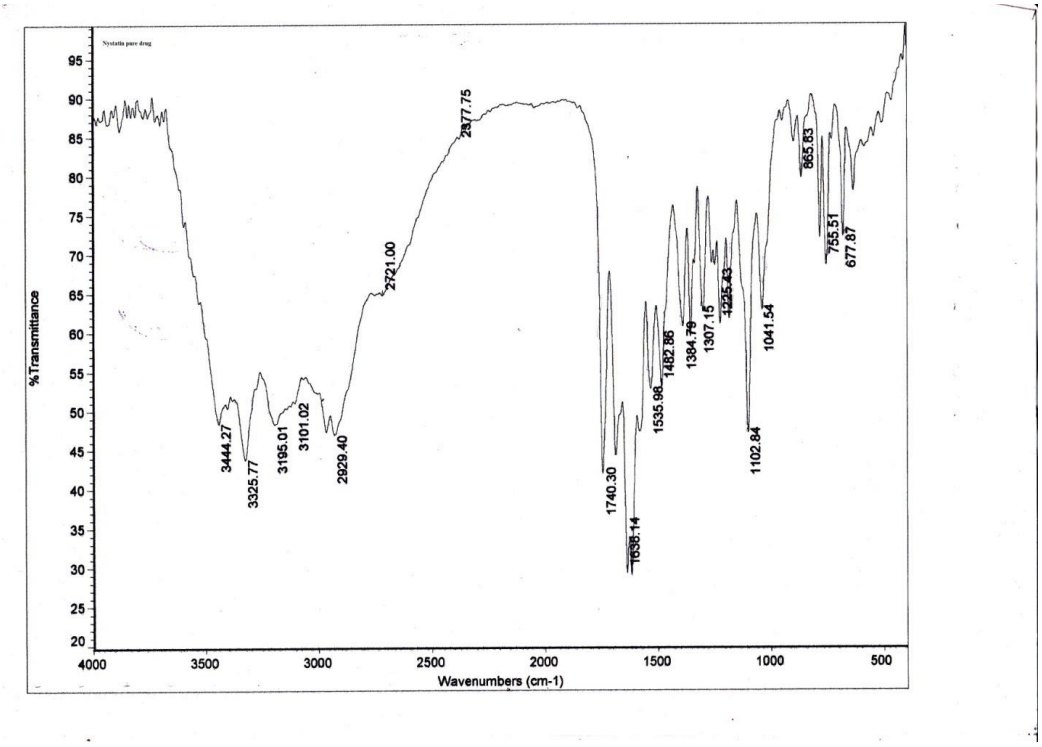

Figure no 2: FTIR of nystatin drug

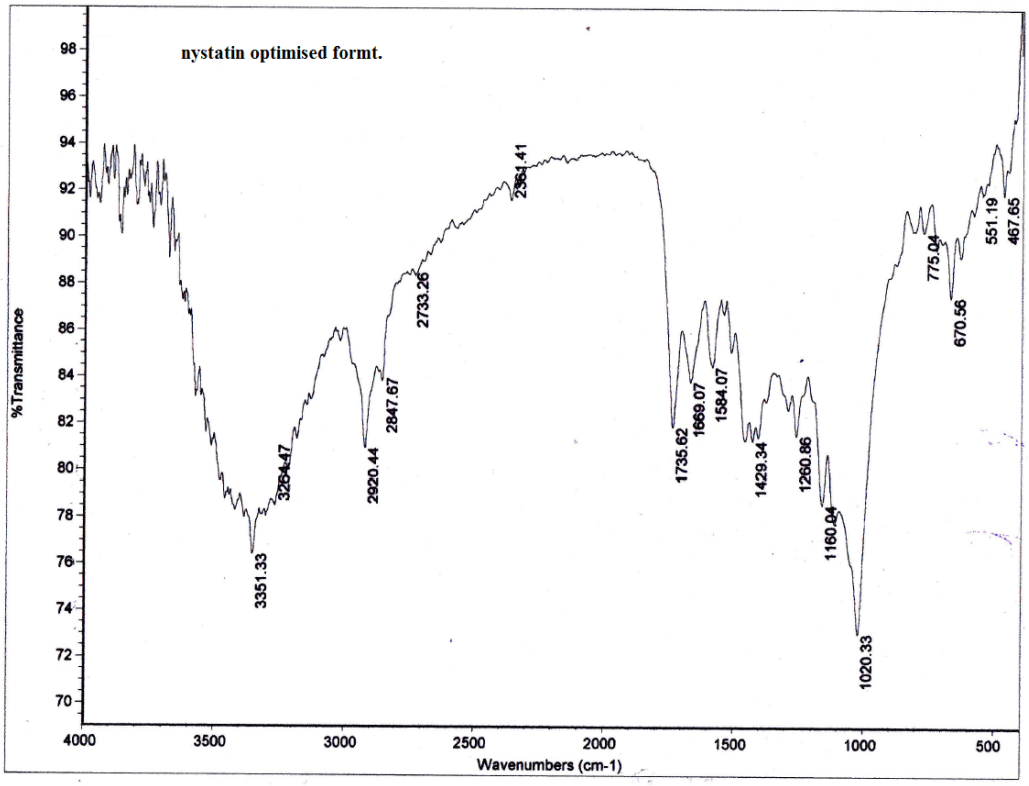

Figure no 3: FTIR of nystatin organogel optimized form

EVALUATION PARAMETERS

Physical appearance

Table 4. Physical appearance

Formulation code	Color	Homogeneity	Consistency	Phase separation
F1	Creamy white	Homogenous	Smooth	Not occurred
F2	Creamy white	Homogenous	Smooth	Not occurred
F3	Creamy white	Homogenous	Smooth	Not occurred
F4	Creamy white	Homogenous	Smooth	Not occurred
F5	Creamy white	Homogenous	Smooth	Not occurred
F6	Creamy white	Homogenous	Smooth	Not occurred
F7	Creamy white	Homogenous	Smooth	Not occurred
F8	Creamy white	Homogenous	Smooth	Not occurred

pH determination

Table 5.pH determination

Formulation code	pH
F1	6.4±0.43
F2	6.1±0.63
F3	6.7±0.25
F4	6.0±0.72
F5	6.3±0.11
F6	6.4±0.24
F7	6.7±0.88
F8	6.5±0.02

P^H evoluation of a topical dosage form is very important as it may cause irritation to the skin if varied from the normal p^H of the skin condition.Furthur more polymer like carbapol give consistency if the p^H was around 6 so all the formulations were evaluated for p^H.

Spreadability

Table 6.Spreadability studies

Formulation code	Spreadability (cm/sec)*
F1	3.0±0.01
F2	3.5±0.40
F3	3.2±0.55
F4	3.4±0.48
F5	3.5±0.62
F6	4.1±0.12
F7	2.5±0.75
F8	2.3±0.23

All the formulations were checked for the spreadability and the data was given in table 6.By taking the data consideration it was observed that concentration of span 20 and tween 20makes the difference in spreadability F7 were having maximum concentration of span 20 and ttween 20 compared to other formulations and the spreadability values found to be 2.5 ±0.75 the optimized formulation compared to other formulations.

Rheological studies (for 10rpm spindle 6)

Table 7: Rheological study data

Formulation code	Viscosity (cp)
F1	3600
F2	3300
F3	3900
F4	3650
F5	4300
F6	3100
F7	4800
F8	3100

The viscosities of all the formulations were measured using Brookfield viscometer at 10 rpm using spindle 6,it was found to be all the formulatons followed shear thinning effect with thixotropic property. It was observed that the viscosity of the formulation increases with the increase in organosion-gel ratio.

Drug content determination

Table 8: Drug content determination

Formulation code	Mean%
F1	98.41
F2	99.15
F3	98.02
F4	99.47
F5	98.83
F6	97.54
F7	98.74
F8	99.90

Drug content of all the formulations were carried out as per procedure in the methodology section.Drug content of all the formulations was found to be in the range 97.54%-99.90% as indicates in the table no.8.

In-Vitro Drug permeation data

Table 9.% cumulative drug release data for F1 to F8

	% Cumulative drug release							
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	5.17	5.56	4.10	5.18	6.01	3.94	8.80	5.76
2	12.02	8.61	7.25	7.93	13.42	6.15	16.51	7.51
3	16.54	13.25	10.93	12.45	25.08	9.37	29.72	11.05
4	25.16	19.13	12.28	17.62	32.75	11.20	38.64	16.54
5	33.47	26.58	23.68	26.01	38.62	22.46	47.38	25.93
6	41.31	34.40	28.41	32.85	45.27	25.34	55.13	30.24
7	49.67	42.79	33.06	42.56	56.91	29.81	63.02	38.85
8	58.46	49.83	37.12	46.42	62.84	34.65	70.61	40.69

9	60.02	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	74.60	63.25	53.62	57.45	80.25	50.15	85.05	55.48
12	76.77	69.53	60.31	62.06	84.32	58.09	89.97	63.42

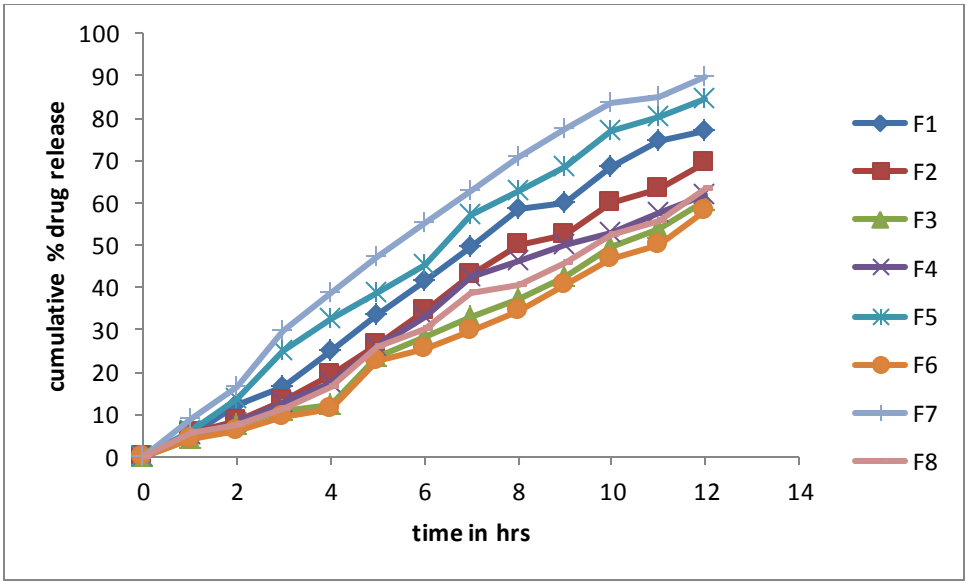

Figure 4: *In vitro* drug permeation graph

The optimized formulation F7 containing maximum concentration of span 20 and tween 20 showed highest % drug permeation at the end of 12 hrs and hence this formulation was selected as optimized formulation for further study.It was reavealed that span 20 and tween 20 concentrations were having positive effect on the drug permeation through the membrane.

Release kinetics of optimized formulation

Table no10: Release kinetics of optimized formulation:

	Zero order	First order	Higuchi	Peppas
	% CDR Vs T	Log % Remain Vs T	% CDR Vs √T	Log C Vs Log T
Slope	7.757527473	-0.14226443	29.57298225	1.343816675
Intercept	4.671758242	2.272945911	-15.3200226	0.639814304
Correlation	0.990176129	-0.82109574	0.976979985	0.908588553
R 2	0.980448767	0.674198227	0.95448989	0.825533159

CONCLUSION

Nystatin is categorized as antifungal drug and is successfully used to treat Fungal disorders. Nystatinmaximum wavelength is determined by UV-Visible spectrophotometer using 6.8 pH phosphate buffer and was detected to be 290 nm. Nystatinorganogels was formulated using light liquid paraffin as oil phase and emulsifying agents tween 20 and span 20 for emulsion and incorporated into gel using HPMC and carbopol 934 polymers in different ratios.The optimized formulation F7 showed a shear thinning with thixotropic property with better spreadability, viscosity and in-vitro permeability compared to other formulations.In the study it was observed that the concentrations of tween20 spann 20 and light liquid paraffin has shown effect on viscosity, spreadability and *in-vitro* drug permeability. Increased amount of liquid paraffin showed suppress activity of tween 20 and span 20.The surface morphology of the optimized formulation was observed by Scanning Electron Microscopic

study. Thus Nystatin organo gels which could increase the drug permeability across the skin and fast release of the drug could be successfully achieved.

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