RESEARCH ARTICLE

Studies on rheology and microbiological evaluation of hydrotropically gelled starch as topical vehicle for terbinafine hydrochloride

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The present study was aimed for the development and evaluation of hydrotropic starch gels of terbinafine hydrochloride which is an allylamine derivative of antifungal agent was formulated by using corn starch and sodium salicylate as hydrotropic salt. The gels were prepared in presence and absence of propylene glycol. The prepared gels were evaluated for *in vitro* drug release, rheological behavior and microbial studies. The degree of increase in the drug diffusion was found to be in order corn starch gel with propylene glycol was greater than corn starch gel without propylene glycol. The microbial studies were carried out in soya bean casein digest medium with *Candida albicans* as test organisms and were found to be 22.86 ± 0.58 and 20.22 ± 0.65 mm for TCSG (IV) and TCS (III), respectively. All the gels exhibited shear thinning. The rheogram indicated that the gel systems are pseudoplastic and exhibited thixotropy. The added propylene glycol has not appreciably altered the apparent viscosity values.

Key words: *Hydrotropy, starch gels, terbinafine HCL*

INTRODUCTION

Hydrotropic salts were reported as a class of compounds which are fairly in high concentrations, increases the solubility of variety of poorly soluble drugs in water.[1-4] Terbinafine hydrochloride is a drug of choic for treating dermatophytoses and especially, onychomycoses and more effective than either itraconazole or griseofulvin. Terbinafine hydrochloride is a antifungal agent of allylamine; which is synthetic derivative of 3-aminopropene, drug act by inhibiting squalaene epoxidase which plays key role in ergosterol biosynthesis which is essential component of fungal cell membrane.[5,6] As part of trials to explore pharmaceutical application of hydrotropy, the present work was aimed to develop terbinafine hydrochloride starch gels by using corn starch as vehicle and sodium salicylate[7-10] as a hydrotropic salt. The formulations were also evaluated for *in vitro* drug release, rheological behavior, and antifungal effectiveness.

EXPERIMENTAL

Materials

The materials used were terbinafine hydrochloride I.P. (Aurobindo Pharma ltd., Hyderabad), sodium salicylat (SD Fine Chemicals, Mumbai), corn starch (SD Fine Chemicals, Mumbai), and propylene glycol (SD Fine Chemicals, Mumbai).

Method

Construction of calibration curve

Accurately weighed quantity of terbinafine hydrochloride (100 mg) was dissolved in 50 ml of phosphate buffer pH 7.4 and kept on rotoshaker for 24 h and the volume was made up to 100 ml with phosphate buffer pH 7.4 to obtain 1000 mcg/ml. The above standard solution was further diluted with phosphate buffer pH 7.4 to obtain various dilutions (5, 10, 15, 20, 25, 30, 35, 40 mcg/ml). Absorbance was measured at 224 nm using Shimadzu-1700 spectrophotometer and a linear relationship was obtained.

Preparation of terbinafine hydrochloride starch gels

In the present work, corn starch was used (10% w/w) with sodium salicylate as hydrotropic salt in three different concentrations (9%, 10% and 11% w/w), and added propylene glycol (3% w/w) was used for best formulation and water for making up the volume to yield 100 gm of finished gel. Weighed quantity of sodium salicylate [Table 1] was dissolved in 40 ml of water along with 1 gm of terbinafine hydrochloride. Corn starch was weighed and dispersed in the remaining quantity of water and added to hydrotropic salts and drug solution. The mixture was stirred continuously till a translucent gel is

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obtained. The finished formulations were kept under vacuum to remove the entrapped air for a period of 48 h.

In vitro drug diffusion by dialysis method

In vitro drug release studies were carried out using a Keshary-Chein type diffusion cell. Hydrated (24 h) parchment membrane was used (0.3 mm thick) for partitioning and phosphate buffer pH 7.4 was used as diffusion media. The contents were stirred with the help of magnetic stirrer at a speed of 50 rpm. The samples were withdrawn at different time intervals for a period of 6 h. The samples were analyzed by measuring the absorbance at 224 nm using Shimadzu-1700 spectrophotometer.

Rheological behavior of terbinafine hydrochloride gel formulations

Formulations TCSG (IV) and TCS (III) were evaluated for rheological behavior. The viscosity of gels was determined by using Brookfield synchro-electric RVT model digital viscometer at room temperature with the following variables. Spindle No. SC4 28/13R was used with 12-ml volume adapter. Eight spindle speeds 0.5, 1, 2.5, 5, 10, 20, 50, and 100 (rpm) was used. The shear stress (dyn/cm^2) and shear rate (s^{-1}) was calculated.

Rheogram

In the present work, the shear rate (s^{-1}) was considered as independent variable and shear stress (dyn/cm^2) was considered as dependent variable.

Stress-shear rate rheogram

Both ascending and descending rheograms were drawn for low- and high-shear rate values to ascertain whether gels systems show thixotropy. The data was plotted as Casson plots[11] in which square root of shear-stress are plotted against the square root of shear rate. The intercepts on the stress axis gives the yield values in dyn/cm^2.

Microbiological evaluation

The microbiological evaluation for TCS (III) and TCS (IV) formulations was carried out using agar cup plate method. Soya bean casein digest medium[12] was used with *Candida albicans* as test organisms.

Table 1: Formulation of terbinafine hydrochloride hydrotropically gelled bases of starch

Ingredients	Formulation code			
	TCS (I)	TCS (II)	TCS (III)	TCSG (IV)
Terbinafine hydrochloride (%)	1	1	1	1
Corn starch (%)	10	10	10	10
Sodium salicylate (%)	9	10	11	11
Propylene glycol (%)	-	-	-	3
Water up to gm	100	100	100	100

Formulation code: T, terbinafine hydrochloride; C, corn starch; S, sodium salicylate; G, propylene glyco

RESULT AND DISCUSSION

In vitro diffusion of drug from the starch gel vehicle is shown in Table 2. The percent drug release at 6 h was found to be 27.39, 35.8, 45.68 and 71.20 for TCS (I), TCS (II), TCS (III) and TCSG (IV), respectively. Addition of propylene glycol (TCSG IV) has enhanced the rate of diffusion. The degree of increase in the drug diffusion was found to be in the following order: TCSG (IV) > TCS (III) > TCS (II) > TCS (I). The apparent viscosity (cp) values were found to be 116700 and 3050; 159700 and 3875, respectively, for TCS (III) and TCSG (IV) at low shear rate 0.14 s^{-1} and high shear rate 28 s^{-1} [Tables 3 and 4]. Stress-shear rate data was plotted for TCS (III) and TCSG (IV) containing propylene glycol as percutaneous enhancer; which showed that the effect of added propylene glycol has not appreciably altered the viscosity values. The gels were found to exhibit shear thinning property when shear rate is increased. The ascending and descending rheograms are not superimposed and can be considered as thixotropic in nature with hysteresis loop as shown in [Figures 1 and 2]. The stress-shear rate data was also plotted as Casson plots for TCSG (IV) and TCS (III) formulations [Figures 3 and 4]. The plots in both systems gave intercepts on stress axis which indicate yield values and were found to be 13234 and 15437 dyn/cm^2

Table 2: *In vitro* diffusion of terbinafine hydrochloride form hydrotropically gelled base of starch

Time (h)	percent drug release			
	TCS (I)	TCS (II)	TCS (III)	TCSG (IV)
0.5	10.85 ± 0.28	11.43 ± 0.16	11.85 ± 0.10	15.76 ± 0.16
1	11.35 ± 0.13	14.10 ± 0.38	14.45 ± 0.23	23.95 ± 0.22
1.5	12.50 ± 0.29	14.10 ± 0.28	14.45 ± 0.17	23.55 ± 0.19
2	13.16 ± 0.21	15.25 ± 0.36	16.01 ± 0.05	31.45 ± 0.18
2.5	15.33 ± 0.22	15.89 ± 0.34	16.22 ± 0.07	16.59 ± 0.14
3	16.10 ± 0.11	16.28 ± 0.20	25.05 ± 0.32	36.95 ± 0.09
3.5	19.05 ± 0.18	18.20 ± 0.11	33.05 ± 0.29	43.05 ± 0.12
4	22.10 ± 0.17	21.63 ± 0.24	35.45 ± 0.18	59.95 ± 0.19
4.5	23.86 ± 0.14	25.68 ± 0.30	39.15 ± 0.01	61.15 ± 0.28
5	24.19 ± 0.29	29.15 ± 0.27	41.5 ± 0.10	64.66 ± 0.21
5.5	26.20 ± 0.21	33.16 ± 0.16	42.95 ± 0.13	69.02 ± 0.18
6	27.39 ± 0.18	35.8 ± 0.14	45.68 ± 0.05	71.12 ± 0.19

*Average of three replicates; *Each sample of 1 gm gel contains 100 mg of drug; *Drug content analyzed at 224 nm

Table 3: Viscosity (cps) for hydrotropically gelled starch with out propylene glycol (TCS III)

Speed (rpm)	Shear rate (s^{-1})	Square root of shear rate	Apparent viscosity up curve (cps)	Shear stress up curve (dyn/cm^2)	Square root of shear stress up	Apparent viscosity down (cps)	Shear stress down curve (dyn/cm^2)
0.5	0.14	0.37	116700	16338	127	86700	12138
1	0.28	0.52	70200	19656	140	52200	14616
2.5	0.7	0.83	36500	25550	159	28300	19810
5	1.4	1.18	21300	29820	172	17900	25060
10	2.8	1.67	13100	36680	191	11450	32060
20	5.6	2.36	8100	45360	212	7500	42000
50	14	3.74	4560	63840	252	4430	62020
100	28	5.29	3050	85400	292	3050	85400

Table 4: Viscosity (cps) for hydrotropically gelled starch added propylene glycol (TCSG IV)

Speed (rpm)	Shear rate (s^{-1})	Square root of shear rate	Apparent viscosity up curve (cps)	Shear stress up curve (dyn/cm^2)	Square root of shear stress up	Apparent viscosity down (cps)	Shear stress down curve (dyn/cm^2)
0.5	0.14	0.37	159700	22358	149.52	128700	18018
1	0.28	0.52	90200	25256	158.92	76200	21336
2.5	0.7	0.83	45700	31990	178.85	39700	27790
5	1.4	1.18	27800	38920	197.28	24500	34300
10	2.8	1.67	17200	48160	219.45	15400	43120
20	5.6	2.36	10800	60480	245.92	9850	55160
50	14	3.74	6040	84560	290.79	5660	79240
100	28	5.29	3875	108500	329.39	3875	108500

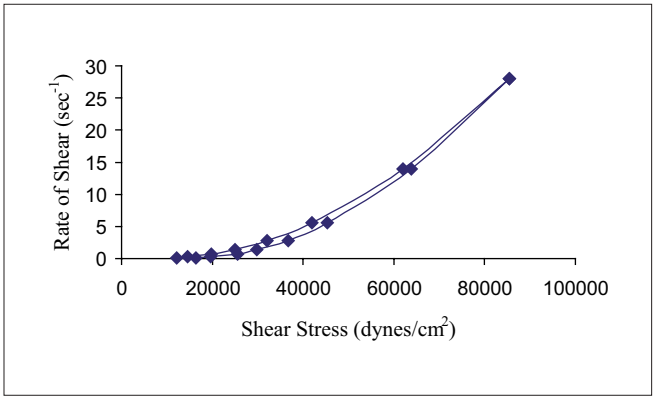

Figure 1: Rheograms showing thixotropy behavior for TCS (III) formulation

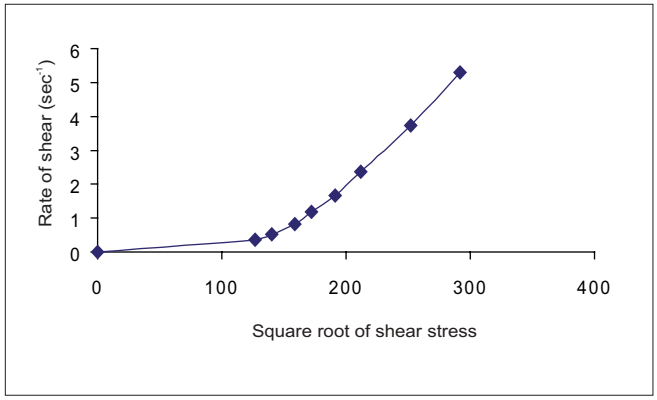

Figure 3: Casson plots showing shear thinning for TCS (III) formulation

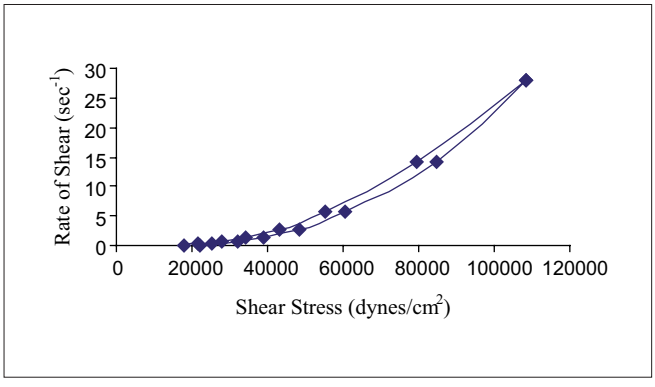

Figure 2: Rheograms showing thixotropy behavior for TCSG (IV) formulation

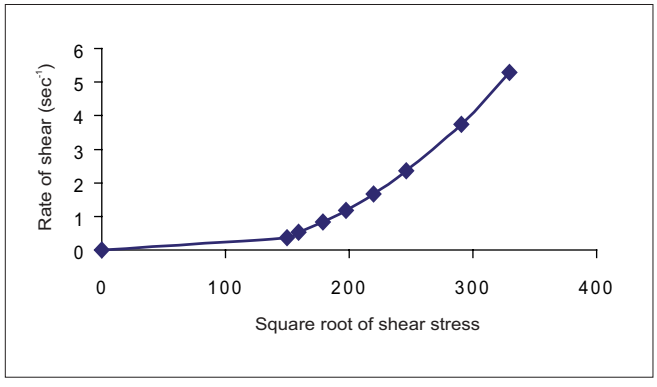

Figure 4: Casson plots showing shear thinning for TCSG (IV) formulation

for TCSG (IV) and TCS (III), respectively. The rheologic data has thus indicated that hydrotropically gelled starches are thixotropic in nature and exhibited yield value. The systems gave pseudoplastic flow with considerable shear thinning tendency and can be expected to exhibit better spreadability. The zone inhibition values were found to be 22.86 ± 0.58 and 20.22 ± 0.65 mm for TCSG (IV) and TCS (III), respectively. The result indicated that the added propylene glycol gel systems gave comparatively better antifungal activity.

ACKNOWLEDGEMENTS

The authors are very much thankful to M/s Arubindo pharmaceutical Ltd, Hyderabad and Principal of Luqman College of Pharmacy, Gulbarga, for providing facilities to carry out the work.

REFERENCES

1. Darwish A, Florence AT, Saleh AM. Effects of hydrotropic agents on the solubility, precipitation and protein binding of etoposide. J Pharma Sci 2006;78:577-81.
2. Agrawal S, Pancholi SS, Jain NK, Agrawal GP. Hydrotropic solubilization of nimesulide for parenteral administration. Int J Pharma 2004;274:149-55.
3. Maheshwari RK, Chavda V, Sahoo K, Varghese S. Novel application of hydrotropic solubilization in the spectrophotetri analysis of diclofenac sodium in solid dosage form. Asian J Pharma 2006;1:30-2.
4. Maheshwari RK, Ajmera A. Novel application of hydrotropic solubilization in the spectrophotetri analysis of diclofenac sodium in solid dosage form. Asian J Pharma 2006;1:60-2.
5. Sweetman, Sean C. Martindale: The complete drug reference. 33rd ed. p. 394-1.
6. Richard P, Howland M, Harvey A. Lippincotts Illustrared Pharmacology. 3rd ed. p. 410-1.
7. Cooper and Gunn's "Dispensing for pharmacutical students, 12th ed. CBS Publication and Distributors; 2000. p. 29,92,207.
8. Indian Pharmacopaeia. Delhi: Controller of Publication; 1996. p. 701.
9. Brittain HG. Analytical profiles of drug substances and excipients. Academic press, An umprint of Elsevier; 2005. p. 427.
10. British Pharmacopoeia. Compound Benzoic acid ointement, 1980;2:697.
11. Casson N. A flow equation for pigment oil suspension of the printing ink type-in Rheology of dispersers systems. *In*: Mill CC, editor. London: Pergamon Press; 1959. p. 84.
12. Pharmacopoeia of India. vol 2. Delhi: Controller of Publications; 1985. p. A107.

Source of Support: Nil, **Conflict of Interest:** None declared.