Formulation and characterization of nystatin gel

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The main objective of this research is to develop and characterize a series of carbopol 934 (CP) hydroxypropyl methylcellulose (HPMC) and a combination of carbopol-HPMC as a gel base for topical delivery of nystatin. The drug level was held constant at 1.72% w/w and the level of propylene glycol which is used as a co-solvent and penetration enhancer was also kept constant at 2% w/w. The total level of the polymer was held constant at 1.5% w/w as a single polymer or combination of two polymers. The polymers combination selected were: carbopol 934 to HPMC at a ratio of 0:1, 1:0, 1:2, 2:1 and 1:1. The batch size was 500 g and triethanolamine was used to adjust the pH of the gel. The rheological study showed that formulation containing combination of 2 carbopol and 1 HPMC ratio gave the highest viscosity, and exhibited an apparent pseudoplastic thixotropic behavior.

The diffusion study indicated that gel formulation containing carbopol – HPMC at a ratio of 2:1 gave the highest percent drug diffusion compared to formulation containing low carbopol to HPMC ratio, carbopol alone or HPMC alone. Both in-vitro release and rheological study indicated that carbopol-HPMC had the best gel strength, physical properties and ability to diffuse the drug than carbopol or HPMC alone.

The results obtained in this study demonstrated that the combination of carbopol and hydroxypropyl methylcellulose can be used as a gel vehicle for nystatin topical application.

Key words: Nystatin Gel, Carbopol, HPMC, Rheological behavior, Diffusion, Semisolid.

There have been concerns related to the conventional topical dosage forms such as lotions, creams, ointment and powder in terms of drug diffusion or release from the vehicle and delivery through the skin. Creams and lotions often provide poor bioavailability of the drug because they are rapidly cleared from the skin and poorly release the drug from the base. Non-hydrophilic ointment are oleaginous, greasy and are not convenient to patients, and also medicated powders for topical application have short residence time on the skin.

Gels are semisolid systems in which the movement of the dispersion medium is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed phase. The increased viscosity caused by interlacing and consequential internal friction is responsible for the semisolid state. Also, a gel may consist of twisted matted strands often tied together by stronger types of Vander Waals Forces to form crystalline and amorphous regions throughout the system. Concentration of gel is usually between 0.5 to 2%, and gels maintain their viscosity over a wide range of temperature.

Among polymers used for formation of gel base is Carbomer resins (carbopol) and hydroxypropylmethyl-cellulose. Carbomer resins are alkylpentaerythritol cross linked acrylic acid-base polymer. A 1% w/w solution in water gives a pH of 3, viscosity of carbopol gel depends on the pH. An increase in pH to a range of 6-8 increases the viscosity and the adhesive properties of the gel. Hydroxypropylmethylcellulose is a partially substituted polyhydroxypropyl ether of cellulose. It is available in many grades, it is physiologically inert, does not irritate the skin and is not metabolized by the body.

The use of gel as a delivery system can increase the residence time of drugs on the skin and, consequently, enhance bioavailability (1). Gel delivery systems have several advantages such as the ease of administration, none greasy, patient compliance, high residence time on the skin and better drug release and diffusion (2-4). Recently, gel dosage forms have been used for several pharmaceutical applications such as periodontal pocket (5), ophthalmic delivery (6), liposomal gel for vaginal drug delivery (7) and as drug carrier for topical

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application of solid lipid nanoparticles (8).

A number of polymers have been investigated to develop gel forming systems (9-13) and the rheological properties and stability of different gel systems have been also investigated (14-18). However a nystatin gel delivery system for topical application had not been studied and is not available commercially.

The hypothesis of this research is that the use of triethanolamine can neutralize the acidic carbopol dispersion, which will help in the stability of both gel and drug. Also, the addition of HPMC to carbopol may give a gel of suitable physical properties, high viscosity, high drug release or dissolution and, consequently, good bioavailability.

The main objective of this study is to develop a nystatin topical gel formulation employing carbopol, HPMC, and mixtures of carbopol – HPMC at different ratios. Also, to describe physical properties, rheological behavior and to determine the amount of drug diffused from the different gel formulations.

Material and Methods

All ingredients used in the manufacture of the gel were of compendial grades nystatin, USP, micropulverized, (donated by Bristol Myer Squibb, Puerto Rico, the assay potency was 5823 units / mg); carbopol 934, lot No. 020215599 (donated by Aventis Pharmaceutical CO., Puerto Rico); Methocel K4, Hydroxypropyl methyl cellulose, lot No. 14M92030901 K , (donated by Dow Pharmaceutical Inc, Midland, Michigan, U.S.A.); triethanolamine, lot No. 41HO539 (Purchased from Sigma, Aldrich Chemical Co., Midwawaukee, WI)., USA). Other reagents were purchased from Sigma Aldrich Chemical Corp, Milwawaukee, WI.)

Preparation of Gel Systems.

Nystatin, an antifungal drug was selected as a drug model in this study. The drug concentration in all formulations was kept constant at 1.72% w/w and the concentration of propylene glycol was also kept constant at 2% w/w. Propylene glycol was used as co-solvent and as a dispersion medium for the nystatin. Two formulations containing only one polymer at 1.5% w/w level (carbopol or Hydroxypropyl methyl cellulose) and three formulations containing combination of carbopol and Hydroxypropyl methyl cellulose (HPMC) at a ratio of 1:2, 2:1 and 1:1 for a total polymers level of 1.5% w/w were prepared. HPMC was added to carbopol to enhance the physical properties, viscosity and performance of the output gel product. Triethanolamine was used to neutralize and adjust the pH of the gel systems.

Hydroxypropyl methyl cellulose was added gradually while stirring (Dyna Mixer, model Freezemobile 5 EL, The Virtis Com Gardinar, NY.) to half the amount of hot water (90^0C). The remaining amount of water was cooled to 5^0C and was added to the dispersion of Hydroxypropyl methyl cellulose and mixing continued.

Carbopol was passed through screen No. 40, weighed and added while stirring in the mixture of HPMC, then the triethanolamine was added to adjust the pH of the gel.

Nystatin was dispersed in propylene glycol and transferred to the mixture of Hydroxypropyl methyl cellulose and carbopol while stirring.

Hydrogen Ion Concentration Measurement

A 0.3 g gel was dissolved in 100 ml distilled water and the pH was measured in triplicate's (pH Meter, Beckman Instrument, Model 50,serial NO. 430838 Fullerton, CA). The gels were protected from light and allowed to reach equilibrium for 2 hours at room temperature prior to the measurement of pH and evaluation of rheological behaviors. The drug content and the diffusion studies were performed after the gel reached equilibrium for 20 hours.

Rheological Study

Theory

Rheology describes the flow of liquid and the deformation of solids. Rheology includes the measurement of viscosity, which indicates resistance of a fluid to flow. High viscosity indicates high resistance to flow. Fluid systems are divided into Newtonian and non-Newtonian systems. Newtonian system show a linear relationship between shear rate and shear stress, where shear rate is the difference in velocity between two planes of liquid separated by a very small distance and shear stress is force per unit area. An Non-Newtonian system does not follow Newtonian law (viscosity = Shear stress / shear rate). Pseudoplastics are non-Newtonian systems exerted by polymer in solution. They are shear thining, have no yield value (do not need specific shear stress to flow), their curve begins at the origin and their viscosity decreases with the increase of shear rate. Plastic systems are also non-Newtonian exerted by flocculated disperse system, are shear thining, have yield value, their curve does not begin at the origin and their viscosity decrease with the increase of shear rate.

Thixotropy can be defined as an isothermal and comparatively slow recovery of consistency through shearing on standing of material. The rheogram of Thixotropy obtained by plotting shear stress versus shear rate shows the down curve (obtained by decreasing shear rate) is displaced to the left of the up curve (obtained by

increasing shear rate). Thixotropy materials undergo gel-to-sol transformation and exhibit shear thinning. Upon removal of stress, the structure starts to reform. This process is not instantaneous.

Rhelogy Analysis

The rheological study of the different gel formulations were carried out with Programmable Rheometer (Digital Rheometert, model DV III, Brookfield, Engineering Lab Inc., Stouhton, MD). The viscosity (h) and the shear stress (t) of gel formulations of different composition were measured as a function of shear rate (D). Samples were left for 1 minute before measuring or decreasing the shear rate. The spindle was kept to rotate for 1 minute before measuring the shear stress and viscosity and the test was done in triplicates.

Drug Content

A weight of 0.3 g sample was introduced in 1000 ml volumetric flask and stirred on magnetic stirrer for three hours. A portion of the solution was filtered through a Whatman filter paper No.4 and 1 ml of the filtrate was transferred to a 100 ml volumetric flask and completed to volume with distilled water. The absorbance of the solution was determined at a wave length of 304 nm using UV spectrophotometer (DU 520, Beckman Coulter, single cell module) and the concentration of the drug in the sample was calculated using the slope and the intercept obtained from the standard curve of nystatin in distilled water.

Drug Release from Gel

A 0.3 g sample was placed in donor compartment of three individual assembled diffusion cell having a 1.435 cm^2 diffusional area. A cellulose ether membrane (simulate skin) was carefully cut and soaked in methanol for 10 minutes before placing in the outward face of one of the cells followed by assembling of the diffusion cell. One magnetic stirrer was added to each cell compartment. Each compartment was filled with 4 ml methanol and covered with paraffin film to avoid evaporation. Solutions were kept under constant agitation by means of magnetic stirrer. Samples of 1 ml were withdrawn from the receptor compartment and immediately replaced with 1 ml methanol. Sampling intervals were 15, 30, 45, 60, 90, 120, 180, 240 and 360 minutes. Gel formulation that gave highest or lowest drug release and diffusion were tested for 720, 1440 and 2880 minutes in triplicates.

Data Analysis and Statistical Evaluation

The paired T-test was used to determine if there is significant difference between the pairs of formalations compared.

One way ANOVA analysis was used to test the hypothesis that the means of several populations are equal.

Results

The rheological behavior of all gel formulations were investigated. The viscosity of the different formulations was compared as shown in Table 1. Gel formulations containing only carbopol showed approximate viscosity between 23,000 CP-132,000 CP while formulations containing combination of carbopol:HPMC at 1:1 ratio showed approximately viscosity between 25,000 CP to 165,000 CP and formulation containing carbopol:HPMC at 1 to 2 ratio showed approximate viscosity in the range of 14,000-75,000 cp. These data indicated that the incorporation of HPMC to carbopol increases the viscosity of the gel base. Gel formulations containing only HPMC gave an approximate viscosity between 900 CP to 600 CP while formulations containing carbopol:HPMC at a ratio of 1:2 gave a viscosity of approximately 13,000 CP to 75,000 CP. Formulations that gave the highest viscosity were 1 carbopol :1 HPMC and 2 carbopol :1 HPMC.

Table 1. Nystatin gels viscosity values

Speed (rpm)	Average viscosity (centipoise) CP:HPMC (0:1)	Average viscosity (centipoises) CP:HPMC (1:0)	Average viscosity (centipoises) CP:HPMC (1:2)	Average viscosity (centipoises) CP:HPMC (2:1)	Average viscosity (centipoises) CP:HPMC (1:1)
10	900	132267	75200	157667	164667
20	827	77933	44467	94467	92133
40	753	47467	27133	53833	52400
60	691	35311	20067	38533	36833
80	648	27767	16117	30467	29467
100	617	23227	13420	25367	24500
100	616	23147	13307	25533	24267
80	645	27467	15483	30167	28400
60	680	34200	18867	36833	35433
40	710	46333	14633	48467	48667
20	793	78333	38933	80367	84600
10	823	131467	61467	131600	145333

All formulations showed curves closed to the origin at low shear stress, and a decrease in viscosity as the shear rate is increased. Formulations containing only one polymer showed no thixotropy behavior because the up curve and down curve were superimposed indicating a rapid recovery of their structure as the shear stress is decreased. Formulations containing 2 carbopol:1 HPMC exhibited Non-Newtonian pseudoplastic behavior as shown in Figure 1.

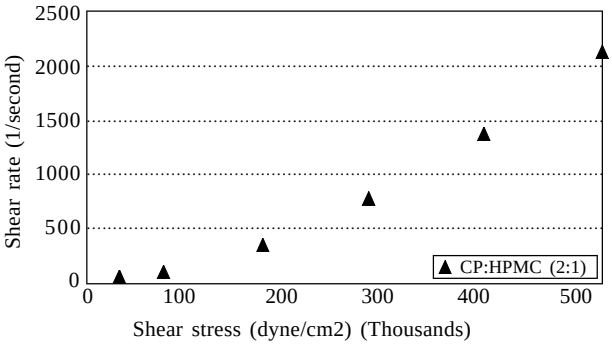

Figure 1. Shear rate versus shear stress for gel formulation containing 2 carbopol:1 HPMC

Formulations containing combination of carbopol and HPMC at a ratio of 2 carbopol:1 HPMC showed thixotropy behavior. The down curve was on the left of the up curve indicating that, upon application of shear rate, there was

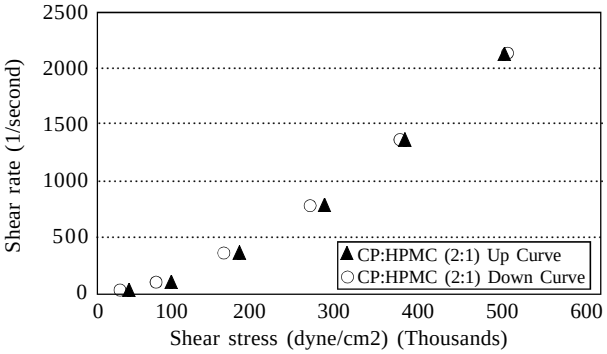

Figure 2. Thixotropy behavior for gel formulation containing 2 carbopol: 1 HPMC

break in the structure and upon equilibrium a recovery of the structure occurred (Table 1 and Figure 2).

The statistical analysis supported these data and indicated that there is no significant difference between the up and down curves for gel formulations formed of only one polymer, since p value was higher than 0.05, while there was significant difference (p value was less than 0.05) between the up and down curves for gel formulations composed of a combination of carbopol and HPMC (Figure 3 and Table 2).

Tables 3-5 show that as the ratio of carbopol to HPMC is increased in the gel formulations, the shear stress and the yield values are increased.

Table 3. Shear stress versus shear rate (flow curves) for up and down curves for formulations composed of combination of carbopol and HPMC at a ratio of 1:2

rpm	Angular velocity	Shear rate	Viscosity	Torque	Shear stress
10	1.042	20.85876	75200	18.89	15685.78
20	2.0944	83.8514	44467	22.23	37286.2
40	4.1888	335.4056	27133	27.3	91005.6
60	6.2832	254.6626	20067	30.10	151438.1
80	8.3776	1341.622	16117	32.23	216229.3
100	10.472	2096.285	13420	33.55	261321.4
100	10.472	2096.285	13370	33.27	278952.6
80	8.3766	754.6638	15483	30.97	207723.4
60	6.2832	20.85876	18867	26.30	14233882.2
40	4.1666	335.4056	24633	24.63	82620.46
20	2.0944	82.8514	38933	19.47	32645.86
10	1.042	20.85876	61467	15.37	12821.25

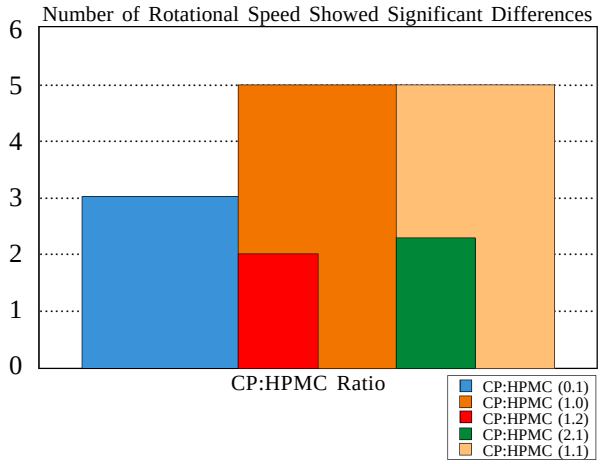

Figure 3. Statistical analysis for gel formulations containing only one polymer or combination of two polymers

All gel formulations have pH values between 5.59 and 7.84. The test was Performed in triplicates. The lowest pH value was 5.59 and was obtained from the gel containing only HPMC, while the highest pH value of 7.84 was obtained from gels containing only carbopol gel formulations containing combination of carbopol and HPMC, which gave values between 6.63 to 7.35. As the carbopol ratio is increased, the pH of the gel is slightly increased (Table 6).

Table 7 shows the drug content in 0.3 g of the different gel formulations. Gels containing

Table 2. Analysis of variance, means comparison using student's test for comparing up and down curves of the same formulation

Ratio of CP to HPMC in gel formulation	10 rpm	20 rpm	40 rpm	60 rpm	80 rpm	100 rpm
0:1	24.3621	7.1571	-0.0750	5.44719	-1.29401	-3.36454
1:0	-1087.59	-123.524	-4327.72	295.099	146.528	-24.705
1:2	10506.1	4770.17	2028.10	986.405	279.515	-114.114
2:1	23067.9	10712.2	2657.68	872.235	-373.752	-247.216
1:1	11701.7	4338.12	502.13	1138.24	974.120	-59.326

Table 4. Shear stress versus shear rate (flow curves) for up and down curves for formulations composed of combination of carbopol and HPMC at a ratio of 2:1

rpm	Angular velocity	Shear rate	Viscosity	Torque	Shear stress
10	1.042	20.85876	15766	39.42	32887.37
20	2.0944	83.8514	94467	47.23	78211.9
40	4.1888	335.4056	53833	53.83	180558.9
60	6.2832	254.6626	38583	57.80	290794.1
80	8.3776	1341.622	30467	60.93	408752.1
100	10.472	2096.285	25367	63.42	531764.6
100	10.472	2096.285	25533	62.83	535244.4
80	8.3766	754.6638	40167	60.33	404727.2
60	6.2832	20.85876	36833	44.25	277964.9
40	4.1666	335.4056	49467	94.47	165915.1
20	2.0944	82.8514	80367	40.18	67388.85
10	1.042	20.85876	131600	32.90	27450.12

Table 5. Shear stress versus shear rate (flow curves) for up and down curves for formulations composed of combination of carbopol and HPMC at a ratio of 1:1

rpm	Angular velocity	Shear rate	Viscosity	Torque	Shear stress
10	1.042	20.85876	164667	41.17	34347.49
20	2.0944	83.8514	92133	46.07	77254.81
40	4.1888	335.4056	523200	52.40	175752.5
60	6.2832	254.6626	36833	55.25	277964.9
80	8.3776	1341.622	29467	58.93	1395335.9
100	10.472	2096.285	24500	61.25	513589.8
100	10.472	2096.285	24267	60.67	508705.5
80	8.3766	754.6638	28400	56.80	3811020.8
60	6.2832	20.85876	35433	53.15	267399.6
40	4.1666	335.4056	448667	58.67	163231.8
20	2.0944	82.8514	84600	42.30	70938.28
10	1.042	20.85876	145333	36.33	30314.66

only one polymer gave the lowest percent drug diffusion compared to gels containing combination of two polymers.

Percent drug diffused from formulations containing only HPMC at 6 hours was 7.6%, formulations containing only carbopol gave 5.4%; formulations containing carbopol:HPMC (1:2) gave 8.8%; and formulations containing carbopol:HPMC (1:1) gave 19% drug diffusion. As the carbopol ratio is increased in the formulation, the percent drug diffused is increased. Formulations containing 2 carbopol : 1 HPMC or 1 carbopol : 1 HPMC gave the highest percent drug diffusion. The combination of carbopol and HPMC modified the characteristics of the gel structure and enhanced the drug diffusion from the gel matrix as shown in Figure 4. The statistical analysis supported the diffusion data and showed significant differences (Table 8 and Figure 5).

Table 6. pH values for nystain gel formulations

	CP:HPMC (0:1)	CP:HPMC (1:0)	CP:HPMC (1:2)	CP:HPMC (2:1)	CP:HPMC (1:1)
Average pH value (n=3)	5.59	7.84	7.15	7.35	6.83

Table 7. Drug content in mg per 0.3 g gel

Gel formulations	Mg nystatin per 0.3 g gel
CP:HPMC (1:0)	3.927
CP:HPMC (0:1)	3.45
CP:HPMC (2:1)	1.962
CP:HPMC (1:2)	1.536
CP:HPMC (1:1)	1.856

Formulation of 1 carbopol: 0 HPMC and formulation containing 2 carbopol: 1 HPMC that showed highest and lowest percent drug diffusion were tested for diffusion over 24 hours as shown in Figure 6. The different parameters such as flux or the amount of material flowing through a unit cross section S of a barrier in unit time t were calculated (Tables 8 and 9).

A plot of percent drug diffused versus square root of time for all formulations showed a linear relationship which indicated that the drug is released from the gel system by diffusion model as shown in Figure 7, which presents gel system containing 2 carbopol: 1 HPMC.

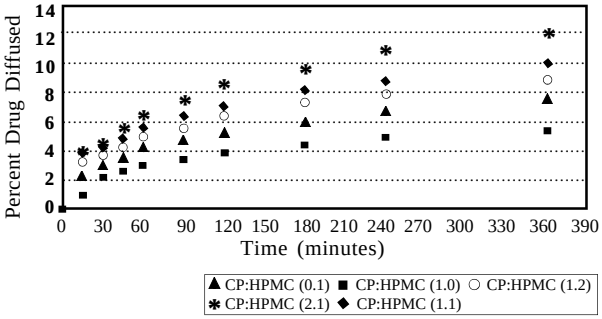

Figure 4. Drug diffusion from gel formulations containing different ratios of carbopol and HPMC.

Discussion

The use of carbopol with HPMC polymer offers an effective and successful gel base for the topical delivery of nystatin as a gel. Formulations containing only one polymer gave non-Newtonian pseudoplastic behavior and showed superimposed up and down curves flow. Thixotropy behavior was apparent in formulations containing polymer combinations. The percent drug diffused from gel formulations containing only one polymer was low compared

Table 8. Diffusion data for nystatin gel formulations at 360 minutes

Gel formulations	Flux (j) mg/sec/cm²	Diffusion coefficient (D) cm/sec²	Amount of drug diffused per unit surface area (Q) mg/cm²	Partition coefficient (K)	Permeability coefficient (P) cm.sec
CP:HPMC (0:1)	4.1841 e-6	1.1969 e-7	9.0682 e-1	15.14	1.4137 e-3
CP:HPMC (1:0)	3.8715 e-6	9.5206 e-8	8.3624 e-1	17.27	8.2219 e-4
CP:HPMC (1:2)	3.2262 e-6	1.4548 e-7	6.9686 e-1	9.81	7.1848 e-4
CP:HPMC (2:1)	1.5488 e-6	2.1250 e-7	7.6665 e-1	7.68	8.1800 e-4
CP:HPMC (1:1)	3.5488 e-6	1.7144 e-7	7.6665 e-1	9.28	7.964 e-4

Table 9. Diffusion data for nystatin gel formulations at 2880 minutes

Gel formulations	Flux (j) mg/sec/cm²	Diffusion coefficient (D) cm/sec²	Amount of drug diffused per unit surface area (Q) mg/cm²	Partition coefficient (K)	Permeability coefficient (P) cm.sec
CP:HPMC (1:0)	7.6623 e-6	2.2477 e-8	1.324	10.09	1.134 e-2
CP:HPMC	6.8667e-6	1.8003 e-8	1.1847	8.32	1.5617 e-4

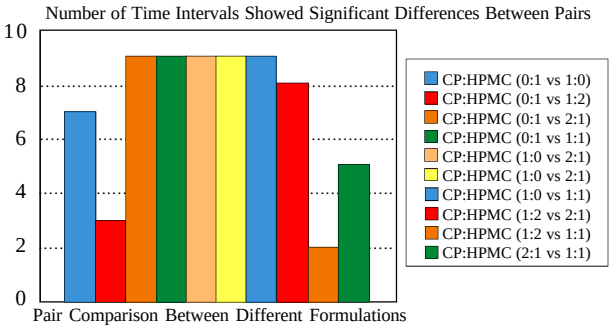

Figure 5. Students t test for drug diffusion from different gel formulations.

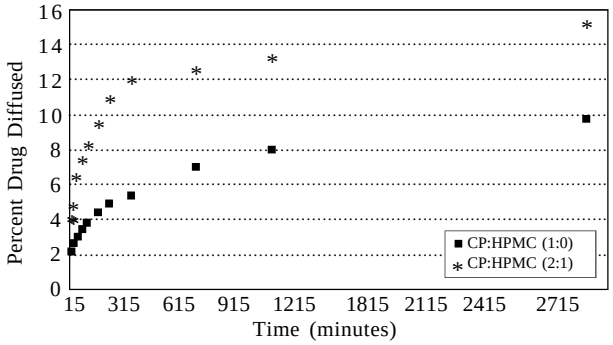

Figure 6. Comparison of drug diffusion profiles up to 24 hours from formulations, Containing CP:HPMC (0:1) versus formulation containing CP:HPMC (2:1).

to formulations containing combination of polymers.

The physical properties for gels containing one polymer are different from gel bases containing combination of two polymers. Carbopol polymer gave a gel base of highest pH value and highest viscosity. The addition of HPMC to carbopol enhanced the gel base properties. Formulations containing 2 carbopol : 1 HPMC gave a gel of highest viscosity structure and best drug diffusion. The long residence time of the gel combined with the ability of the gel to release the drug in sustained matter will assist in enhancing bioavailability. Change in the ratio of the incorporation of the two polymers affects the rheological behavior and the release profile of the drug from the gel.

This study offers the formulator flexibility in the design of gel systems with desirable rheological properties and drug release.

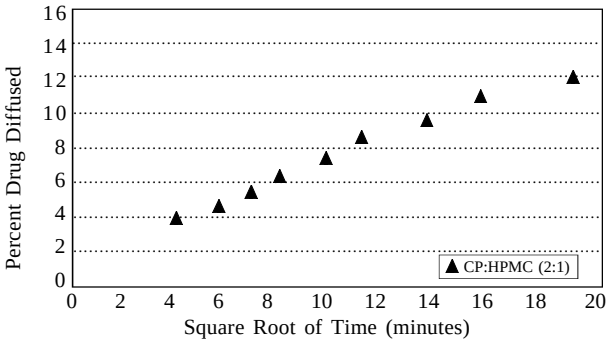

Figure 7. Square root of time plot for formulation composed of CP:HPMC (2:1).

Resumen

El objetivo principal de este estudio es desarrollar y caracterizar una serie de polímeros de carbopol 934, hidroxipropil metil celulosa (HPMC, por sus siglas en inglés) y una combinación de carbopol-HPMC como gel base para la aplicación tópica de nistatin. Los niveles de la droga permanecieron constantes en 1.72% P/P y el nivel de glicol de propileno, usado como co-solvente y para aumentar la penetración de la droga, también se mantuvo constante en 2% P/P. El nivel total del polímero se mantuvo constante en 1.5% P/P al usar un solo polímero o una

combinación de dos polímeros. Se seleccionaron combinaciones de polímeros de carbopol 934-HPMC en proporciones de 0:1, 1:0, 1:2, 2:1 y 1:1. El tamaño del lote fue de 500 gramos y se utilizó trietanolamina para ajustar el pH del gel. El estudio reológico mostró que la formulación de carbopol-HPMC en proporción de 2:1 tuvo la mayor viscosidad y exhibió un comportamiento aparentemente seudo-plástico tixotrópico.

El estudió de difusión indicó que la formulación de gel que contiene carbopol-HPMC en proporción 2:1 posee un mayor por ciento de difusión de la droga al compararlo con las formulaciones que contenían menos carbopol que HPMC, carbopol solo o HPMC solo.

Los resultados obtenidos en este estudio demuestran que la combinación de carbopol e hidroxipropil metil celulosa se puede utilizar como vehículo para la aplicación tópica de nistatina.

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