Formulation and *In Vitro* Evaluation of Mucoadhesive Nystatin Vaginal Gel

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الخلاصة:

تم تحضير النيستاتين على شكل هلام مهبلي باستخدام قواعد مخاطية الالتصاق لتوفير خصوصية الالتصاق المخاطي ومن ثم زيادة فعاليته، كما تم تحضير صيغ مختلفة ومن ثم تقييمها من حيث تحرر الدواء خارج الجسم ومن حيث الخصائص الفيزيائية (قابلية الانتفاخ، اللزوجية، سلوك الانسيابية، الأس الهيدروجيني، قابلية الانتشار وقابلية الالتصاق المخاطي).

تم دراسة تاثير نوع وتركيز العوامل الجيلاتينية (2.5 و 3.5% من الكاربوكسي مثيل سيلولوز، 0.5 و1% من الكاربوبول 934 و 3 ، 4% صمغ زانثان) وكذلك تاثير اضافة توين 80 بتراكيز محتلفة (1, 3, 5 و10 %) على تحرر النيستاتين من الهلام المحضر ومقارنته مع المستحضر التجاري كريم نستاتين® المهبلي (شركة لايف فارما الايطالية).

وجد أن جميع الصيغ المحضرة لها خصائص فيزيائية مقبولة ولها قابلية على تحرر الدواء بعد مرور 5 ساعات أعلى من المستحضر التجاري، كما لوحظ ان الهلام الحاوي على الكاربوكسي مثيل سيلولوز قد أظهر أعلى تحرر للنيستاتين مقارنة بالانواع الاخرى للبوليمر، كذلك زيادة تركيز البوليمر ادت الى نقصان كمية النيستاتين المتحرر. ان اضافة 1% توين 80 ادت الى زيادة كمية النيستاتين المتحرر وان تحرر النيستاتين من الهلام الحاوي على الكاربوكسي مثيل سيلولوز ازداد بزيادة تركيز توين 80 (من 1الى 10%)، كما لوحظ ان الصيغة الحاوية على الكاربوكسي مثيل سيلولوز بتركيز 2,5% وتوين 80 بتركيز 5% هي الصيغة المختارة بسبب امتلاكها لخصائص فيزيائية مقبولة وقابلية جيدة على تحرر الدواء. لقد لوحظ ان تحرر الدواء من جميع الصيغ يتبع المرتبة صفر.

Abstract:

Nystatin was prepared as vaginal gels using mucoadhesive polymers to provide mucoadhesive property which in turns increase its effectiveness; different formulas were prepared which were evaluated for the in vitro drug release and for their physical properties (swelling index, viscosity, rheological behavior, pH, spreadability, and mucoadhesive characteristics). The influence of type and concentration of gelling agent [2.5 and 3.5 %w/w carboxymethylcellulose (CMC), 0.5 and 1% w/w carbopol 934 (CP 934), and 3 and 4% w/w xanthan gum], besides the effect of addition of different concentration (1, 3, 5, and 10%w/w) of tween 80 (TW.80) as a surfactant on

nystatin release from the prepared gels were investigated. All the prepared formulas were observed to have accepted physical properties and with higher release amount after 5 hours in comparison with Nystatin® vaginal cream (Lifepharma, Italy).

It was found that CMC containing gel produced the highest nystatin release compared with other polymer types used, also as the polymer concentration increased, the amount of nystatin released decreased. Addition of 1%w/w TW. 80 increased nystatin release, also the release from CMC containing gel was appeared to increase with increasing TW. 80 concentration (from 1 to 10% w/w), It was found that the formula containing CMC in a concentration of 2.5% w/w and TW. 80 in a concentration of 5% w/w was the formula of choice due to its optimum drug release and physical properties, rheological study revealed that this formula exhibited pseudoplastic flow with shearthinnig behavior and thixotrpy. All formulas were found to follow zero order release kinetics.

Key words: nystatin, mucoadhesive, vaginal gel

Introduction:

Over the last twenty years, extensive efforts has been made towards the administration and absorption of drugs via vaginal route, the first truly controlled drug delivery systems for use in the vagina were developed in 1970, when the first vaginal ring was used for delivery of medroxy progesterone acetate for contraception [1]. The vaginal route of drug administration has advantages over oral route because of the ability to by–pass first pass metabolism, ease of administration, and high permeability of low molecular weight drugs [2].

The currently available vaginal delivery systems, such as creams, foams, gels, irrigations, tablets…etc, have some limitations such as leakage, messiness and relatively low residence time owing to the self–cleaning action of the vaginal tract and often require multiple daily doses to ensure the desired therapeutic effect [3, 4]. Many different approaches have been tested to develop novel vaginal drug delivery systems that can meet both the clinical and the patients' requirements. Considerable attention has been focused on the development of controlled delivery systems providing a long-term therapeutic concentration of drugs following a single dose. Novel forms are liposomes, vaginal rings, cubic gels and formulations based on polystyrene elastomers [3].One interesting group of auxiliary agents is the mucoadhesive polymers, which are the basis of newly designed systems.

Bioadhesion may be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time [5].

The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems to retain drugs for treating largely local conditions, or to prolong the residence time in the vaginal cavity [6].

The most commonly used mucoadhesive polymers that are capable of forming hydrogels are synthetic polyacrylates, polycarbophil, chitosan, cellulose derivatives, hyaluronic acid derivatives, pectin, tragacanth, carrageenan and sodium alginate [7,8].

Vaginitis is a common gynecological problem in women of all age groups. It may result from microbial infections, contact dermatitis, atrophic vaginitis or allergic reactions [9]. The infectious vaginitis is of three types: candidiasis, trichomoniasis, and bacterial vaginosis. Vaginal infections are usually characterized by vaginal discharge, vaginal irritation, or vulvar itching, and bad vaginal odor [10,11].

Nystatin is a polyene antifungal antibiotic used for the prophylaxis and treatment of candidiasis of the skin and mucous membranes [12]. Nystatin is produced by growth of certain strains of *streptomyces noursei*, it contains not less than 5000 units per mg of the dried substance; it is characterized as a very slightly soluble to practically insoluble in water [13].

The present study involves preparation and in vitro evaluation of long acting mucoadhesive vaginal gels of nystatin using three different polymers namely carboxymethylcellulose, carbopol 934, and xanthan gum, each of them was used in two different concentrations. Tween 80 was added as a surfactant in different concentrations.

Materials and Methods:

Nystatin, xanthan gum and methyl paraben were supplied by Samara Drug Industry. Carboxymethylcellulose (BDH chemicals Ltd, Pool, England). Sodium hydroxide and disodium hydrogen phosphate (Fluka AG, Switzerland). Carbopol 934 (J.T.Baker,India), tween 80 (Merk-Schuncherdt, Germany), citric acid (Al-Pharma pharmaceutical company Amman Industrial Estate), and Nystatin® vaginal cream (Lifepharma–Italfarmaco Group, Milano, Italy).

Equipments:

Sartorius balance (Werke-GMBH, type 2842, Germany), pH meter (Hanna Instruments, pH211 Microprocessor, Italy), USP dissolution apparatus, type II (Copley Scientific TLD, England), rotational viscometer (Fungilab, Spain), spectrometer (Biotech engineering management co. LTD, U.K), and electrical mixer (Janke and Kunkel, RF16).

Methods:

Preparation of Nystatin Vaginal Gels:

Gels were prepared by cold mechanical method described by Schmolka et al (1972) [14]. The preservative (methyl paraben), the surfactant (tween 80), and sodium hydroxide (in carbopol 934 containing gels) were dissolved in

water. The required quantity of polymer (carboxymethyl cellulose, carbopol 934, or xanthan gum) was weighed and sprinkled slowly on the surface of purified water and left for two hours, after which it was continuously stirred by electrical mixer, till the polymer soaked in water, the final gel was left overnight to ensure hydration, Finally the drug was added to the prepared gel with continuous stirring till the drug get dispersed in the gel completely [14,15].

Different formulas of nystatin vaginal gel were prepared as shown in (Table-1). The prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were kept in dark and cool place [16,17].

Evaluation of Nystatin Vagina gel:

In Vitro Nystatin Release Test from Gel Bases:

A basket with 2.5 cm in diameter was enclosed with a multifold filter paper (dialysis cell) in order to be filled with 1 g of the prepared nystatin gel. After connecting to stirrer motor, the dialysis cell was immersed to about 1 cm of its surface in 500 ml of citrate-phosphate buffer pH 4.2 (the collecting medium) [9,18]. The system maintained at 37^{o}C, the collecting medium was stirred at 100 r.p.m for 5 hours; samples were withdrawn from the collecting medium after 0.5, 1, 1.5, 2, 3, 4, and 5 hours and replaced with an equal volume of the fluid solution [18]. The samples were then analyzed spectrophotometrically for their drug content at λ max of 306 nm [19]. Experiments were repeated three times for each of the gel formula.

Effect of Polymer Type and Concentration on Nystatin Release from Gel Bases:

The effect of polymer type and concentration on the release of nystatin from gel bases was studied using 2.5 and 3.5% w/w CMC, 0.5 and 1% w/w carbopol 934, and 3 and 4% w/w xanthan gum .

Effect of Addition of Surfactant and its Concentration on Nystatin Release from Gel Bases:

Tween 80 was used to study the effect of surfactant addition on nystatin release from gel bases using different concentrations of tween 80 (1, 3, 5, and 10% w/w).

Mechanism of Nystatin Release and Release Kinetic from Gel Bases:

The mechanism of nystatin release from the prepared mucoadhesive gels was analyzed by fitting the release data into different kinetic equations including:

zero order:

$Q = Q_o + K_o t$ ----------eq. (1)

first order:

$\log Q = \log Q_o + K_1 t/2.303$ ----------eq. (2)

Higuchi equation:

$Q = K_2 t^{1/2}$ ----------eq. (3)

and Peppas equation:

$\text{Log } M_t/M_\infty = \log K + n \log t$ ----------eq.(4)

Where Q is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution, M_t/M_∞ is the fraction of drug released at time t, n is release exponent indicative of release mechanism, K_o, K_1, K_2, and K are the zero, first, Higuchi, and Peppas release constants respectively[20].

Determination of Gel pH:

The pH of the prepared gel was measured by putting the tip of the electrode surface to the gel surface and the results were taken as a mean of three determinations [21].

Viscosity Measurement:

The viscosity of different gel formulas was measured and the rheogram of the selected formula was obtained at 25°C using rotational viscometer. The prepared formulas were sheared with spindle R7, the viscosity was measured at rotational speed of 6 r.p.m. The rheogram was obtained by measuring the viscosity over the range of speed setting from 2 to 30 r.p.m. with 30 seconds between each two successive speeds, and then in descending order [22]. Measurements were repeated three times for each of the gel formula.

Spreadability Measurement:

Concentric circles of different radii were drawn on graph paper and a glass plate was fixed on to it. Gel (5.0 g) was transferred to the centre of the lower plate and spread over an area of 2 cm diameter. A glass plate of 100±5 g was placed gently on the gel and the spread diameter was recorded after one minute; subsequent glass plates were added and the spread diameter was recorded after one minute of each addition. Results were presented as the spreading area being a function of the applied mass [21]. The experiment was repeated three times and the average spreading area was reported.

Swelling Index Measurement:

The swelling index of the prepared gels was determined by weighing the dry gel of each formula and recording their weights before placing them separately in weighed beakers. The total weight was recorded (W1). Four milliliters of citrate-phosphate buffer pH 4.2 were added to each beaker and then placed in an incubator at 37°C. After time intervals of 0.5, 1, 1.5, 2, 3, 4, and 5 hours, excess water was carefully removed, and the swollen gel was weighed (W2) [23]. The experiment was repeated three times and the average W1 and W2 were reported. The swelling index was determined from the following equation:

Swelling index = (W2-W1) / W1 ----------eq.(5)

Mucoadhesive Strength Measurement:

The mucoadhesive strength of each formula was determined by measuring the weight required to detach the gel from the sheep vaginal mucosal tissue by using a modified chemical balance. A section of vaginal mucosa was

cut from the sheep's vaginal cavity and instantly fixed with mucosal side out onto each glass vial using a rubber band. The vials with vaginal mucosa were stored at 37^{o}C for five minutes, and then one of them was connected to the balance in an inverted position, while the second one was placed on a height adjustable pan. Fixed amount of sample of each gel formula was placed onto the vaginal mucosa of the second vial, and then the height of this vial was adjusted so that the mucosal surfaces of both vials come in intimate contact between tissues and the gel. Then weight was kept rising in the pan until vials get detached. Measurements were repeated three times for each of the gel formula [24].

Statistical Analysis:

Results are given as a mean ± standard deviation (S.D), n=3. The results were analyzed statistically using Student's *t*-test or one way analysis of variance (ANOVA). Significance was determined at $P < 0.05$. Statistics were done using Microsoft Excel (2007).

Results and Discussion:

Swelling Index Measurement:

Swelling index was measured for all formulas over a time of 5 hours. The swelling index was significantly ($p<0.05$) affected by polymer type as shown in (figure-1); formulas containing CMC (F1 and F4) swelled rapidly at the beginning in citrate – phosphate buffer pH 4.2 due to the faster hydration of CMC, but could not remain their matrix integrity up to 5 hours due to erosion of gel matrix [23], while formulas containing xanthan gum (F3 and F6) showed constant increasing in swelling index up to 5 hours because xanthan gum have high degree of swelling due to water uptake and small degree of erosion due to polymer relaxation [25], formulas containing carbopol 934 (F2 and F5) showed less swelling index at the beginning but a highest swelling index was observed at the end of 5 hours, this is attributed to the property of carbopol to retain water which increases the swelling degree and form thick swollen mass [26].

In addition it was found that as polymer concentration increased, swelling index was increased significantly ($p<0.05$) as found in (F4, F5, and F6) compared with (F1, F2, and F3) respectively (figure 1). Also it was found that swelling index was affected by the presence of surfactant and its concentration (figures 2 and 3, respectively). The swelling index of formulas containing 1% w/w tween 80 as a surfactant (F7, F8, and F9) was significantly ($p<0.05$) less than that of formulas free from tween 80 (F1, F2, and F3) respectively, also it was found that increasing tween 80 concentration led to a significant ($p<0.05$) decrease in swelling index (F7, F10, F11, and F12), this may be due to formation of aggregation of surfactant molecules within or over the network of gel matrix, which greatly decreased the hygroscopisity of polymer network and then decreased water absorption [27].

Viscosity measurement:

Viscosity is an important parameter for characterizing the gel as it affects the spreadability, extrudability, and release of drugs [28]. The viscosity of the prepared gels was significantly ($p<0.05$) affected by polymer type and it was found in the following order: carbopol 934> xanthan gum > CMC as found in (F2, F3, and F1) and (F5, F6, and F4) respectively as shown in table (2). It was observed that increasing polymer concentration led to a significant ($p<0.05$) increase in gel viscosity (F4, F5, and F6) compared with (F1, F2, and F3) respectively.

The addition of 1%w/w tween 80 resulted in a significant ($p<0.05$) decrease in the viscosity (F7, F8, and F9) compared with tween 80 free formulas (F1, F2, and F3) respectively, also increasing the concentration of tween 80 resulted in a significant decrease ($p<0.05$) in gel viscosity (F7 , F10, F11, and F12), this is due to the fact that when surfactant is added, a collapse of the chains occurs; as soon as the chains no longer overlap and then the viscosity is reduced. Thus any change in viscosity reflects a change in polymer conformation (extension or shrinkage) [29].

The rheogram of the selected formula of choice (F11) was drawn (by plotting the shear rate versus shear stress) as shown in figure (4), it was observed that F11 possessed pseudoplastic flow with thixotropic behavior, where the down curve was displaced with regard to the up curve, showing at any rate of shear on the down curve a lower shear stress than it had on the up curve; a hysteresis loop was formed between the two curves. Thixotropy, or time dependent flow, occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurement [30]. It is noteworthy that thixotropy is a desirable characteristic in pharmaceutical preparations in order to deliver an initially thick product as a thinner, easily spreadable material [15].

In Vitro Nystatin Release from Gel Bases:

Effect of Polymer Type:

The effect of polymer type on nystatin release from gel bases was shown in figure (5). It was observed that the amount of nystatin released was significantly ($p<0.05$) influenced by the type of polymer base used and it was found in the following order cmc > xanthan gum > carbopol 934 (F1, F3, and F2) and (F4, F6, and F5) respectively, this may be due to the higher viscosity of carbopol 934 and xanthan gum compared with CMC based gels which was responsible for hindering drug release from gel matrix [29].

Effect of Polymer Concentration:

It was found that the amount of drug released was decreased significantly ($p<0.05$) with increasing polymer concentration (F4, F5, and F6) compared with (F1, F2, and F3) respectively, this could be attributed to an increase in the density of the polymer matrix and an increase in the diffusional path length

which the drug molecules have to traverse [31] (figure-5).

Effect of Addition of Surfactant and its Concentration on Nystatin Release from Gel Bases:

Tween 80 was added as a surfactant in a concentration of 1%w/w in order to enhance nystatin release from gel bases. Since formulas containing the lower concentrations of polymers showed more drug release, tween 80 was added to them for further enhancement of drug release (F7, F8, and F9) as shown in (figure-6).

The addition of tween 80 produced a significant ($p<0.05$) increase in nystatin release in formulas (F7, F8, and F9) compared with tween 80 free formulas (F1, F2, and F3) respectively this may be attributed to the effect of surfactant on drug solubility and partitioning which could help in increasing drug release in presence of emulsifying type of surfactants [29].

Different concentrations of tween 80 were used to study the effect of surfactant concentration on nystatin release from gel bases as shown in figure (7), a significant ($p<0.05$) increase in nystatin release was obtained when the concentration of tween 80 was increased from 1% to 3% w/w, and from 3% to 5% w/w, while further increase in tween 80 concentration to 10% w/w produced no significant ($p>0.05$) increase in nystatin release.

The release of nystatin from gel formulas was compared with that of the marketed Nystatin® (Lifepharma – Italy) vaginal cream (containing nystatin 100000U/4g) as shown in table (3); it was found that all gel formulas gave higher release amount than that of the marketed cream.

Determination of Nystatin Release Kinetics:

The release kinetic models of nystatin from different gel formulas were shown in (Table-4). Based on the correlation coefficient (R^2) value in various models, the model that gives the higher (R^2) values is considered as the best fit of the release data [32]. It was found that nystatin release from all formulas best fit zero order kinetics since the regression coefficient (R^2) of zero order equation was higher than those of first and Higuchi's equations.

Furthermore, the release data were also analyzed according to the well known exponential Peppas equation, in which the slope values (n) for the prepared formulas were calculated to identify the release mechanism, when $n=0.45$ indicates Fickian diffusion release, $0.45<n$ indicates anomalous (non-Fickian) transport, and $n>0.89$ to a super case II transport. The slope values (n) of all the prepared formulas were found to be more than 0.89 indicating super case II transport, where the drug release involves polymer relaxation and chain disentanglement which suggests that the availability of free drug molecules able to diffuse remain constant over time producing the zero order release kinetic [33], which further supported the results obtained by using the correlation coefficient (R^2) values.

pH measurement:

The pH of all gel formulas were measured and listed in table (2), it was found that the pH of all formulas were within the limits of vaginal preparations in order to be not irritant to the vaginal mucosa [34,21].

Spreadability Measurement:

Spreadability is an important property of vaginal preparations from patient compliance point of view. The spreading area for different formulas were plotted versus mass applied, all formulas were observed to have good spreadability.

The spreadability of the prepared gels was significantly ($p<0.05$) decreased as the polymer concentration increased (F4, F5, and F6) compared with (F1, F2, and F3) respectively (figure 8), this is due to the fact that an increase in polymer concentration increases the repulsion between chains, increases the cross linking between chains, and reduces the spreadability [35].

Addition of 1% w/w tween 80 resulted in a significant ($p<0.05$) increase in the spreadability (F7, F8, and F9) compared with (F1, F2, and F3) respectively (figure 9). Also increasing the concentration of the added surfactant (from 1 to 10% w/w) resulted in a significant ($p<0.05$) increase in the spreadability (F7, F10, F11, and F12) as shown in figure (10), which can be explained by that the added surfactant will increase the adhesive forces between the gel molecules and the spreading surface and at the same time decrease the cohesive forces between polymer molecules themselves which in turns results in increasing spreadability [20].

Mucoadhesive Strength Measurement:

The mucoadhesive strength is an important physicochemical parameter for vaginal gels. All formulas appeared to have good mucoadhesive strength (figure 11). The mucoadhesive strength of the prepared gels was significantly ($p<0.05$) affected by polymer type and it was found in the following order: carbopol 934 > cmc > xanthan gum; as found in (F2, F1, and F3), and (F5, F4, and F6) respectively, this is due to the fact that mucoadhesive strength depends on the polymer structure, molecular weight, and other physicochemical properties which were varied according to the polymer type [36,37]. The mucoadhesive strength was significantly ($p<0.05$) increased by increasing the polymer concentration (F4, F5, and F6) compared with (F1, F2, and F3) respectively, because at lower concentrations of the polymer chains, there is inadequate and unstable interaction amongst the polymer and the mucosal layer resulting in poor mucoadhesive properties [5].

The influence of surfactant (tween 80) addition and its concentration on the mucoadhesive strength was appeared to be non significant ($p>0.05$); as found in (F7, F8, and F9) compared with (F1, F2, and F3) respectively, and (F7, F10, F11, and F12) respectively.

Formula No.	Ingredients (g)							
	Nystatin	Carboxymethyl cellulose	Carbopol 934	Xanthin gum	Sodium Hydroxide	Methyl Paraben	Tween 80	Distilled water
F1	0.5	2.5	-	-	-	0.4	-	**Up to 100**
F2	0.5	-	0.5	-	0.2	0.4	-	**Up to 100**
F3	0.5	-	-	3	-	0.4	-	**Up to 100**
F4	0.5	3.5	-	-	-	0.4	-	**Up to 100**
F5	0.5	-	1	-	0.4	0.4	-	**Up to 100**
F6	0.5	-	-	4	-	0.4	-	**Up to 100**
F7	0.5	2.5	-	-	-	0.4	1	**Up to 100**
F8	0.5	-	0.5	-	0.2	0.4	1	**Up to 100**
F9	0.5	-	-	3	-	0.4	1	**Up to 100**
F10	0.5	2.5	-	-	-	0.4	3	**Up to 100**
F11	0.5	2.5	-	-	-	0.4	5	**Up to 100**
F12	0.5	2.5	-	-	-	0.4	10	**Up to 100**

Table-1: Composition of Different Formulas of Nystatin Vaginal Gels (%w/w).

Formula No.	Viscosity (cp) at 6 r.p.m.	pH
F1	40150	6.8
F2	234836	7.08
F3	110926	6.36
F4	90102	6.75
F5	259992	6.66
F6	145248	6.36
F7	38294	6.23
F8	200183	6.7
F9	90347	5.04
F10	37150	5.06
F11	35132	4.86
F12	34136	4.53

Table-2: The Viscosity & pH of Different Formulas of Nystatin Vaginal Gels

Formula No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	Nystatin Vaginal Cream
% Nystatin Released	7.6	4.72	5.46	6.1	4.5	5.0	9.26	5.8	6.9	10.7	24.3	24.46	4.13

Table-3: % Nystatin Released from Different Formulas after 5 hours in Citrate – Phosphate Buffer at pH 4.2 &37°C.

Formula No.	Zero order		First order R^2	Higuchi R^2	Peppas	
	R^2	K			R^2	n
F1	0.9962	0.0783	0.9872	0.9271	0.9952	0.9173
F2	0.9966	0.0489	0.9876	0.9233	0.9914	0.9437
F3	0.9979	0.0559	0.978	0.9137	0.9954	0.9337
F4	0.9966	0.0626	0.9776	0.9261	0.9951	0.9888
F5	0.9949	0.0474	0.9862	0.929	0.9903	0.9651
F6	0.9914	0.0523	0.9744	0.9169	0.9813	0.9539
F7	0.998	0.0937	0.981	0.9212	0.9937	0.9678
F8	0.9986	0.0579	0.978	0.9144	0.9934	0.9147
F9	0.9982	0.0711	0.9842	0.9145	0.9954	0.9617
F10	0.9947	0.1114	0.9756	0.9307	0.9923	0.9789
F11	0.9986	0.2417	0.9774	0.9106	0.9967	0.9111
F12	0.9989	0.245	0.9754	0.9116	0.9966	0.9136

Table-4: Kinetic Treatment of the Release Data of Nystatin from Different Formulas.

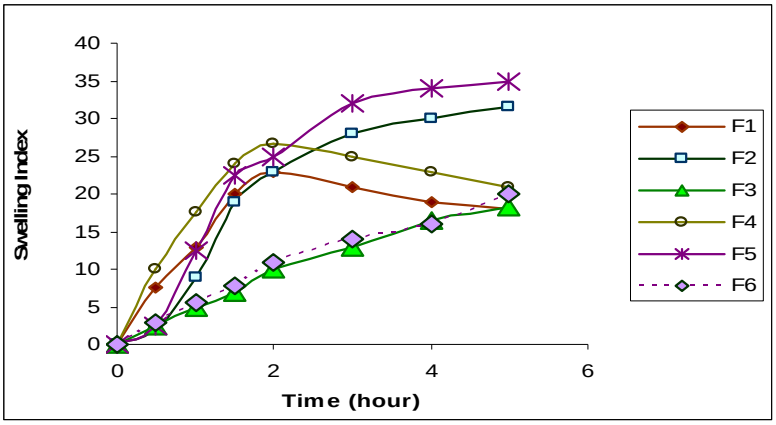

Figure-1: The effect of Polymer Type & Concentration on the Swelling Index of Nystatin Vaginal Gels at pH4.2 &37°C (Mean ± SD, n=3).

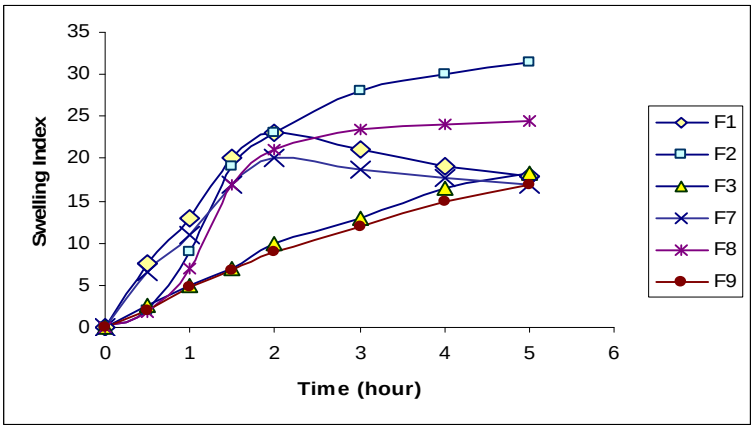

Figure-2: The effect of Addition of Surfactant (1% tween 80) on the Swelling Index of Nystatin Vaginal Gels at pH4.2 &37°C (Mean ± SD, n=3).

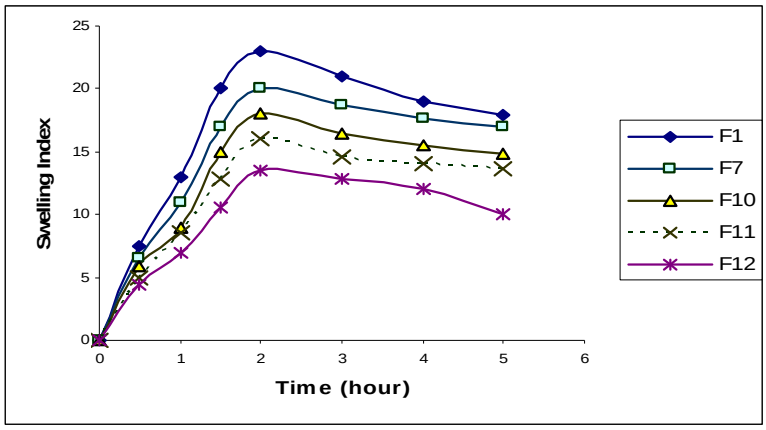

Figure-3: The effect of Surfactant (tween 80) Concentration on the Swelling Index of Nystatin Vaginal Gels at pH4.2 &37°C (Mean ± SD, n=3).

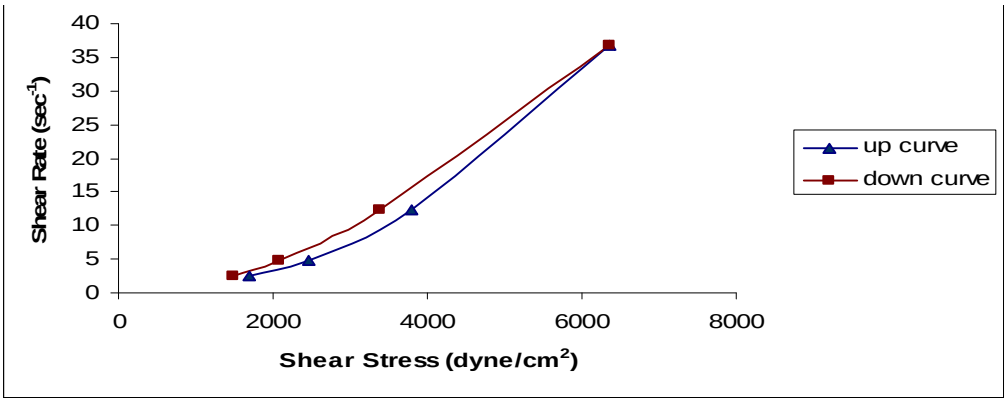

Figure-4: Rheogram of Formula 11 at 25°C (Mean ± SD, n=3).

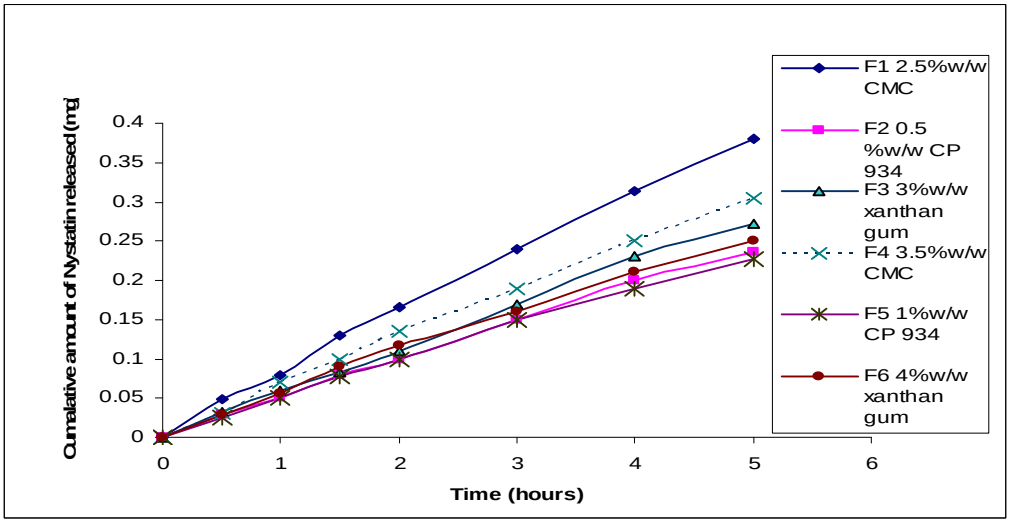

Figure-5: The Effect of Polymer Type & Concentration on the Release Profile of Nystatin in Citrate-Phosphate buffer pH 4.2 at 37^{o}C (Mean ± SD, n=3).

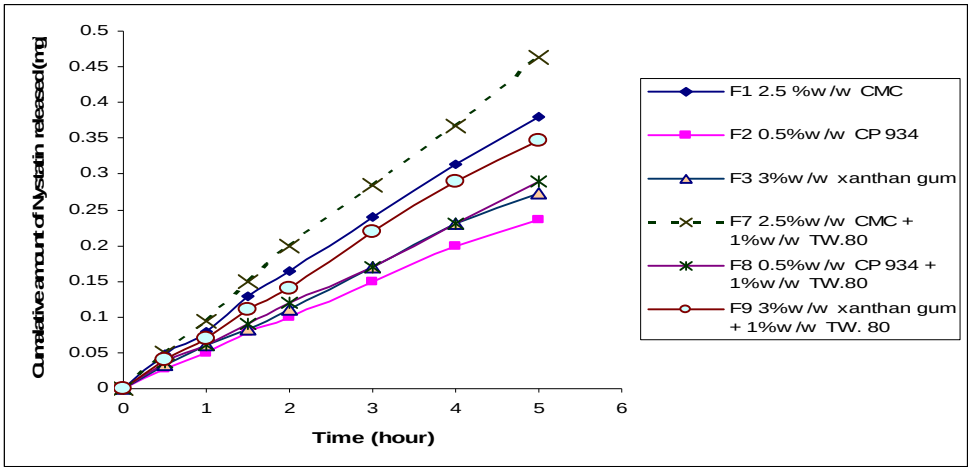

Figure-6: The Effect of addition of Surfactant (1%w/w tween 80) on the Release Profile of Nystatin in Citrate-Phosphate buffer pH 4.2 at 37^{o}C (Mean ± SD, n=3.

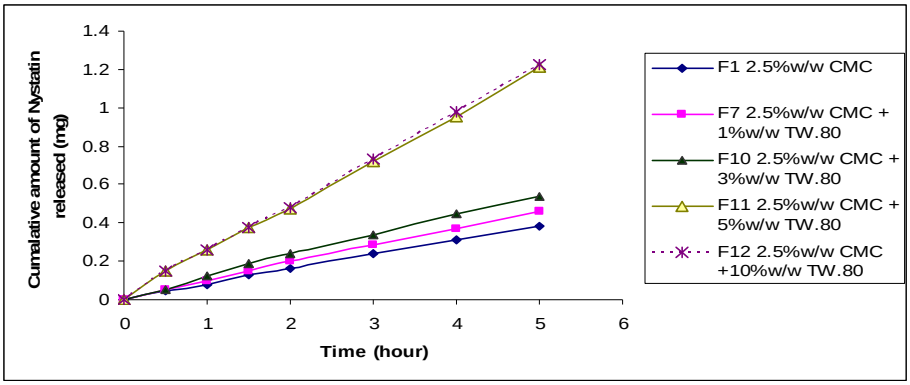

Figure-7: The Effect of Surfactant (Tween 80) Concentration on the Release Profile of Nystatin in Citrate-Phosphate buffer pH 4.2 at 37°C (Mean ± SD, n=3).

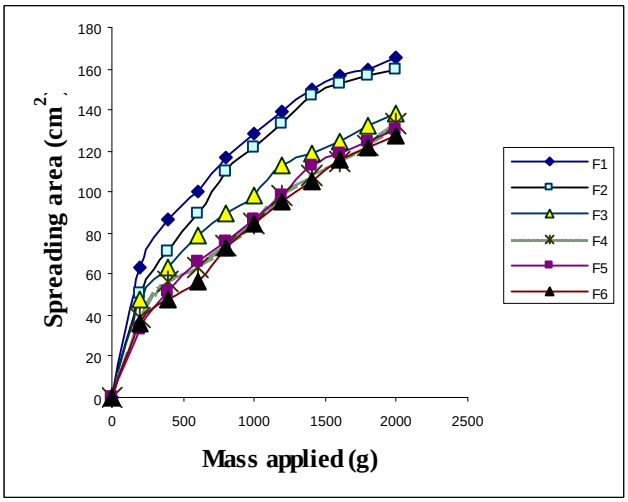

Figure-8: The Effect of Polymer Concentration on the Spreadability of Nystatin Vaginal Gels (Mean ± SD, n=3).

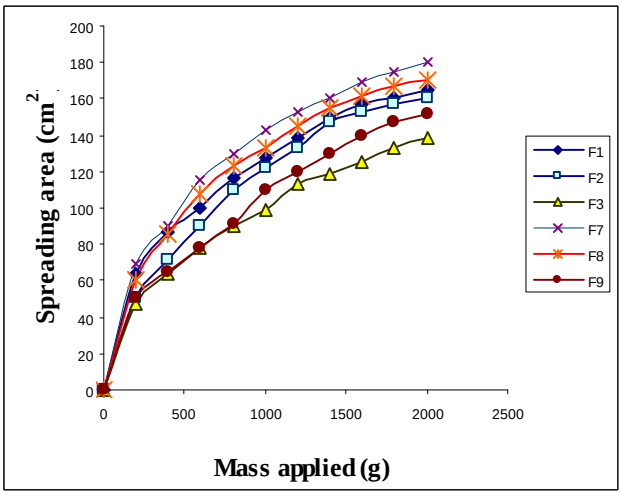

Figure-9: The Effect of addition of Surfactant (1%w/w tween 80) on the Spreadability of Nystatin Vaginal Gels (Mean ± SD, n=3)

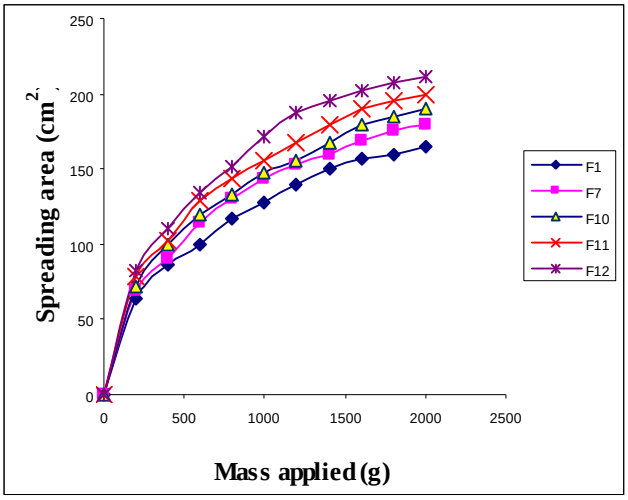

Figure-10: The Effect of Surfactant (tween 80) Concentration on the Spreadability of Nystatin Vaginal Gels (Mean ± SD, n=3).

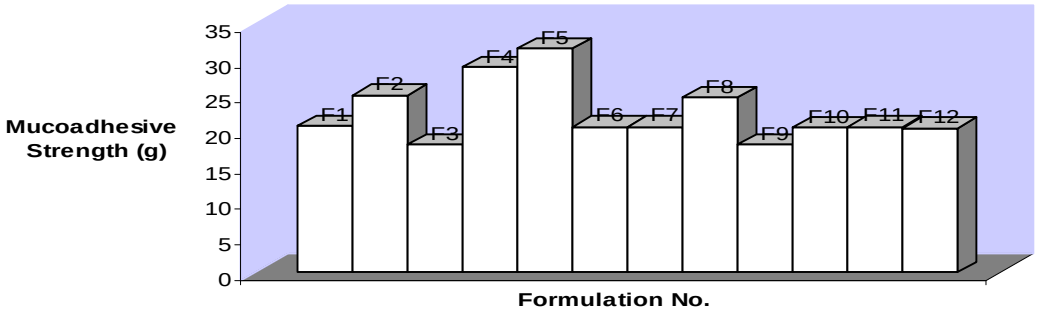

Figure-11: Mucoadhesive Strength of Different Formulas of Nystatin Vaginal Gels (Mean ± SD, n=3).

Conclusion:

Nystatin was formulated as a vaginal gel using mucoadhesive polymers to provide mucoadhesive property which increases its effectiveness. The drug release from the prepared gels was affected by polymer type and concentration, addition of surfactant, and surfactant concentration; all the prepared formulas released nystatin in amount higher than that of the marketed vaginal cream. The optimum nystatin release was obtained using 2.5% w/w CMC as gelling agent and 5% w/w tween 80 as a surfactant (F11) and this formula exhibited shear–thinning behavior with thixotropy. The mechanism of drug release from the gel matrix for all formulas followed zero order release kinetic.

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