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ADHESIVE AND SPREADING PROPERTIES OF PHARMACEUTICAL GEL COMPOSED OF CELLULOSE POLYMER

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Abstract

Salicylic acid (SA) is an ideal exfoliant for use on acne and acne-prone skin. It was chosen as the model drug. Samples were prepared by simple dispersing different hydroxypropyl cellulose (HPC) amounts (0.5-2%) in isopropyl alcohol solution and keeping in 4, 25 and 40°C. In all these systems viscosity, spreading, adhesive properties and drug release were characterized. The silastic membrane was employed as a barrier in Franz diffusion cell to study in vitro drug release. The concentration of drug was analyzed by means of UV spectrophotometer at the maximum wave length of 302 nm. The increasing in HPC concentration caused increased viscosity. A relationship between the viscosity and bioadhesive strength was shown by HPC gels. The results demonstrated that the flux of SA decreased with increase in pH and SA permeation conformed to the pH partition hypothesis. The results showed that increasing of the HPC concentration caused in a reduction of SA release rate SA from gels and increasing of HPC was related to an increased viscosity of formulation. Also an increase in the ratio of collodion: drug (2:1) and a decrease in the ratio of isopropyl alcohol: drug (less than 3:1) caused the decrease of transparency of gel and the release rate. The results showed that diffusion of SA gel followed peppas model.

Keywords:

Hydroxypropyl cellulose, Salicylic acid, Drug release rate, Adhesive, Spreading.

Introduction

Salicylic acid (SA) is a beta hydroxyl acid derived from the bark of the willow tree. Beta hydroxyl acids have a larger molecule than their cousin, alpha hydroxyl acids. The larger molecule size keeps the beta hydroxyl acid on the surface of the skin allowing it to more effectively penetrate and exfoliate within the pore. This action within the pores makes it an ideal exfoliant for use on acne and acne-prone skin. The larger molecule size of SA produces less irritation than alpha hydroxyl acids, making it a welcome alternative for those with sensitive skin. SA is used to treat many skin disorders, such as acne, dandruff, psoriasis, seborrhea dermatitis of the skin and scalp calluses, corns, common warts, and plantar warts, depending on the dosage form and strength of the preparation (1,2). Ultimate acceptability and clinical efficacy of such preparations require them to possess optimal mechanical properties (ease of removal from the container, spreadability on the substrate), rheological properties (viscosity, flowability), and other desired properties such as bioadhesion, desired drug release, and absorption (3). The efficacy of topical therapy depends on the absorption

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of formulation in a layer to deliver a standard dose. The optimum consistency of such a formulation helps ensure that a suitable dose is applied or delivered to the target site. A reduced dose would not deliver the desired effect, and an excessive dose may lead to undesirable side effects. The delivery of the correct dose of the drug depends highly on the spreadability of the formulation. The rate of spreading also depends on the viscosity of formulation, the rate of evaporation of solvent, and the rate of increase in viscosity with concentration that results from evaporation (4,5). Spreadibility is therefore an important characteristic of these formulations and is responsible for correct dosage transfer to the target site, ease of application on the substrate, extrudability from the package, and most important, consumer preference. Hydroxypropyl cellulose makes thinner gels with high tolerance for added drugs and salts, compatible with alcohols and glycols, hydrates and swells in water or hydroalcoholic solution. Polymers that adhere to skin surface can be conveniently divided into three broad categories: (1) polymers that become sticky when placed in water and owe their bioadhesion to stickiness; (2) polymers that adhere through non-specific, non-covalent interactions which are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant); and (3) polymers that bind to specific receptor sites on the cell surface. All three polymer types can be used for drug delivery (6). The purpose of the present investigation was to (a) prepare salicylic acid gels using hydroxypropyl cellulose, (b) study the spreading and adhesive properties of gels composed of hydroxypropyl cellulose, (c) investigation of different parameters effect on the release rate and flux of SA gel formulations.

Materials and methods

The following materials were used in the study: salicylic acid (Merck, Germany), hydroxypropyl cellulose (grade HPC-H, Nippon Soda, Japan), collodion (Merck, Germany), isopropyl alcohol, castor oil, camphor, all obtained from Merck (Darmstadt, Germany). Silastic membrane was provided by Biogene (Mashad, Iran). All other chemicals and solvents were of analytical grade.

Gel preparation

The composition of SA gels used is shown in Table 1. Hydroxypropyl cellulose (HPC) was dispersed in isopropyl alcohol and was stirred and homogenized with paddle stirrer for 30 min at 150-200 rpm. Then, SA dissolved in collodion and remainder of isopropyl alcohol was added to mixture. This mixture was stirred magnetically, until a homogenous solution was formed and gradually dispersed in HPC solution. Finally, water was added to formulation and stirred. Gel was formed at 20 min at 100 rpm, then it was stored at 4, 25 and 40°C. (Camphor and castor oil in gel formulations interacted with SA absorbance; therefore simple collodion was used instead of elastic collodion).

Determination of pH

One g of gels were weighed and diluted 10 times with isopropyl alcohol. Then, pH of gels was measured with pH-meter (Table1).

Evaluation of gels content

One g of gels was dissolved in 10 mL of isopropyl alcohol and then SA was assayed by means of UV spectrophotometer at the maximum wave length of 302 nm (Table 1).

Measurement of viscosity of gels and effect of temperature

Viscosity of HPC was studied in different amounts of isopropyl alcohol. Also, aqueous solutions of HPC were prepared with various concentrations. Viscosity was judged in this case by a simple measurement of apparent viscosity on the Brookfield scale.

Table 1: Composition (%w/w) of salicylic acid gels

Constituents	Gels code				
	F_1	F_2	F_3	F_4	F_5
Salicylic acid	17	17	17	17	17
HPC	1	1.25	1	1	0.75
Collodion	17	17	17	34	34
Isopropyl alcohol(%95)	61.5	61.25	59	43	43
Water	3.5	3.5	6	5	5.25
pH	3.14	3.28	4.91	4.83	4.96
Mean content ± SD(mg/g)	168±0.11	165±0.31	169±0.57	170±0.74	169±0.36

* Each value is given as the mean of three experiments.

A Brookfield rotational digital viscometer DVLV-II was used to measure the viscosity (Pa.s) of gel formulations at 20°C. Spindle number 2 was rotated at 60 rpm. Also, effect of temperature on the viscosity was investigated in both solutions.

Adhesion strength measurement

The adhesion forces of SA gels were determined by means of adhesive force-measuring device shown in Fig. 1 (7), using tissue cut from mucosal area of rat hairless abdomen. The pieces of tissues stored frozen in phosphate buffer pH 7.4, and thawed to room temperature before use (8). At the time of testing, a section of rat skin was secured (keeping the mucosal side out) to the upper glass vial (C) using a cyanoacrylate adhesive (E). The diameter of each exposed mucosal membrane was 1.5 cm. The vials were equilibrated and maintained at 37°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). To expose tissue on this vial, a constant amount of 0.1 g SA gel (D) was applied. The height of the vial was adjusted so that the gel could adhere to the mucosal tissues of both vials. Immediately, a constant force of 1 N was applied for 10 minutes to ensure intimate contact between the tissues and the samples. The vial was then moved upwards at constant speed, and was connected to the balance. Weights were added at a constant rate to the pan on the other side of the

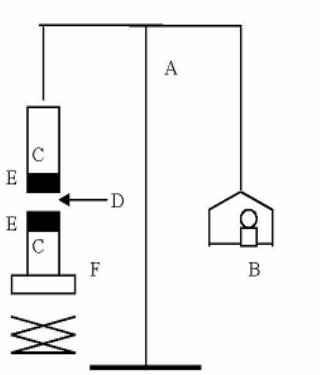

Fig. 1: Bioadhesive force measuring device: (A) modified balance; (B) Weights; (C) glass vial; (D) SA gel; (E) rat tissue; (F) height-adjustable pan.

modified balance of the used device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights that detached the tissues from the surface of each formulation using the following equation (7).

$$\textit{Detachment Stress (dyne/cm}^2\textit{)} = \frac{m.g}{A} \qquad (1)$$

Where m is the weight added to the balance in grams; g is the acceleration due to gravity taken as 980 cm/s^2; and A is the area of tissue exposed. Measurements were repeated thrice for each of the gel preparations, but before each measurement a fresh smooth gel surface was created. Effect of varying contact time (1, 2, 3, 5 and 10 min) was investigated for some of the gel preparations to optimize initial

contact time. In brief, formulations were allowed to be in contact with mucosa for carrying contact times (1, 2, 3, 5, and 10 min), and the bioadhesive force was determined as discussed above. Contact time that resulted in maximum bioadhesive strength was selected as optimum contact time required for adequate adhesion. All the above three experiments were conducted in triplicates.

Spreadability measurement

The parallel-plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations (Fig. 2). The advantages of the method are simplicity and relative lack of expense. On the other hand, the method is not very precise and sensitive, and data which it generates must be manually interpreted and presented. The spreadability behavior of various Witepsol suppository bases was tested between two Plexiglas plates at 37 ˚C, and optimum bases were selected on the basis of their spreading properties (9). Hadi et al. evaluated polyethylene glycol ointment bases spreadability using a parallel-plate extensiometer based on the sliding-plates design (10). Later, Vennat et al. validated the spreading-diameter measurements of hydrogels on the basis of cellulose derivatives and established the linearity of spreading-diameter measurement (11, 12).

The spreading capacity of the gel formulations was measured 48h after preparation by measuring the spreading diameter of 1 g of the gel between two 20 × 20 cm glass plates after 1 min. The mass of the upper plate was standardized at 125 g. Also, a similar apparatus used to assess the spreadability of Lyncomycin hydrochloride gels (13). The following equation was used for the purpose:

$$S = m \times \frac{1}{t} \qquad (2)$$

In which S is the spreadability of gel formulation, m is the weight (g) tied on the upper plate, l is the length (cm) of the glass plates, and t is the time taken (s) for the plates to slide the entire length. DePaula et al. evaluated the spreadability of various ointment formulations by compressing the sample under several glass plates of known weight (15). Twenty plates were subsequently placed over the sample at 1-min intervals. The spreading areas reached by the sample were measured in millimeters in the vertical and the horizontal axes. The results were expressed in terms of the spreading area as a function of the applied mass according to the following equation:

$$S_i = d^2 \times \frac{\pi}{4} \qquad (3)$$

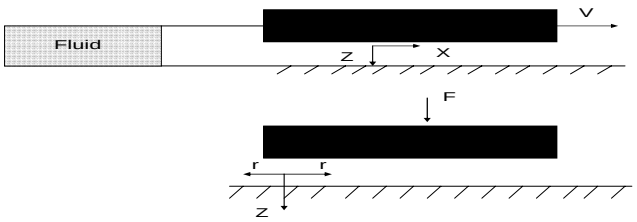

Fig. 2: Schematic representation of finger geometry as two parallel plates (14) V = finger velocity, Z = thickness of sample, X = shearing stress, F = shear force between the fingers, r = radius of the finger.

In which S_i is the spreading area (mm^2) resulting from the applied mass i (g), and d is the mean diameter (mm) reached by the sample. The spreading area was plotted against the plate weight to obtain the spreading profiles.

Assay procedures

Analytical method for the assay of SA

In order to determine the standard calibration curve of SA, a stock of 1 mg/mL was prepared. Then, dilutions were made to prepare a series of solutions containing SA in different concentrations. In these solutions, absorbance values at 302 nm (λ_{max}) were determined UV spectrophotometrically. Plotting the concentration values (x) versus absorbance values (y) calibration curve of SA was determined. Analytical parameters for the assay of salicylic acid were calculated using ANOVA test.

Recovery studies

To study the accuracy, reproducibility, precision, and to check the interference from excipients used in the formulation of the above method, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the gels. Mixtures were analyzed spectrophotometrically. Percentage recovery was calculated after three experiments.

Drug release studies

The release studies were conducted using Franz diffusion cells (ERWEKA® HDT6, Germany). Silastic membrane was fitted into place between the chambers of cells. The receptor phase composed of isopropyl alcohol and the temperature was maintained at 37°C. Preliminary experiments showed no interactions of the receptor phase with either the membrane or the formulations placed on the donor side. The receptor phase was stirred at 700 rpm during the study. A pre-determined amount of gel was mounted on the donor side of Franz cell (16). Samples were assayed spectrophotometrically at 302 nm. The initial volume of the medium was maintained by adding 3 mL of dissolution medium after each sampling. Each test was carried out in triplicate and the mean of three observations was reported.

Statistical analysis

Where appropriate, results were evaluated using a one-way ANOVA. For inter-comparisons of candidate formulations the Tukey HSD (honestly significant difference) test was then conducted (using SPSS version 13), Where $p<0.05$ was taken to represent a statistically significant difference (17).

Results and discussion

The effect of temperature on the viscosity

At 20 °C, a 0-3% aqueous dispersion and isopropyl alcohol of HPC was prepared and their viscosity was measured (Fig. 3). Aqueous solutions are transparent and have smooth viscosity. Relationship between the concentration of isopropyl alcohol solution and its viscosity is similar to that of aqueous solution (Fig. 3).

Viscosity changes in isopropyl alcohol solutions at certain temperatures. The relationship between temperature and viscosity of solution is shown in Fig. 4. Viscosity is gradually decreased with elevation of temperature, and suddenly dropped at a temperature above 45˚C.

Such a process is due to limited solubility, but it is reversible. Viscosity of isopropyl alcohol solution decreases with elevation of the temperature, but unlike aqueous solution, rapid fall in viscosity due to gelation was not observed (Fig. 4).

The effect of pH

At 20°C, a 0-3% aqueous dispersion of HPC exhibited pH values between 2 to 5, depending on its concentration. In general, increase of HPC caused increase in gel viscosity (Fig. 5). pH of all formulations

was adjusted to 7. Aqueous solutions of HPC are stable between pH 6-8 with the viscosity of solutions being relatively unaffected.
However, at low pH, aqueous solutions may undergo acid hydrolysis, which causes chain scission and hence, a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration (6).

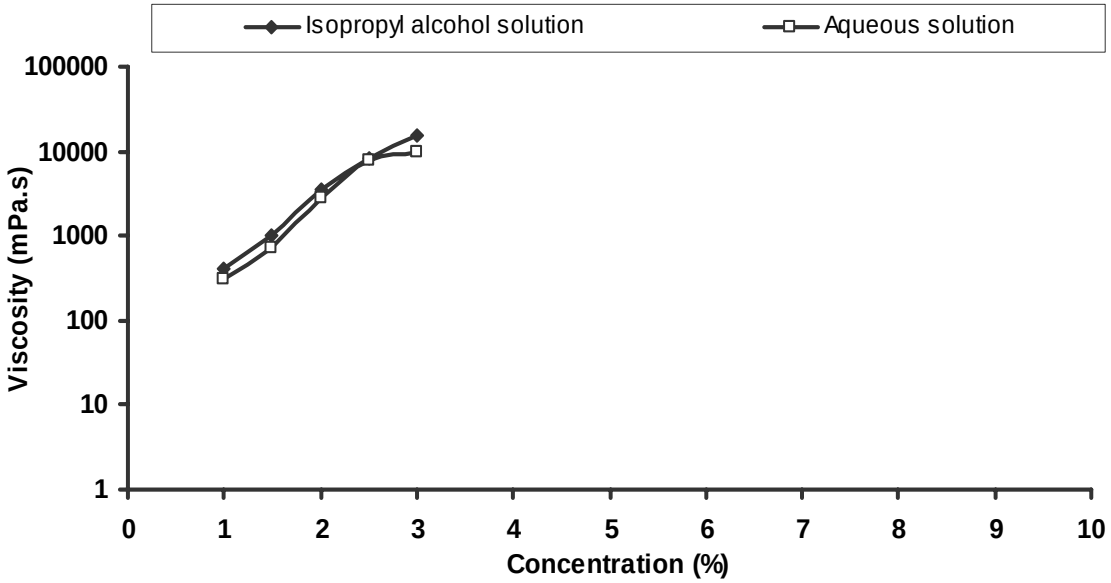

Fig. 3: Viscosity vs. concentration of water and isopropyl alcohol solution of HPC at 20°C.

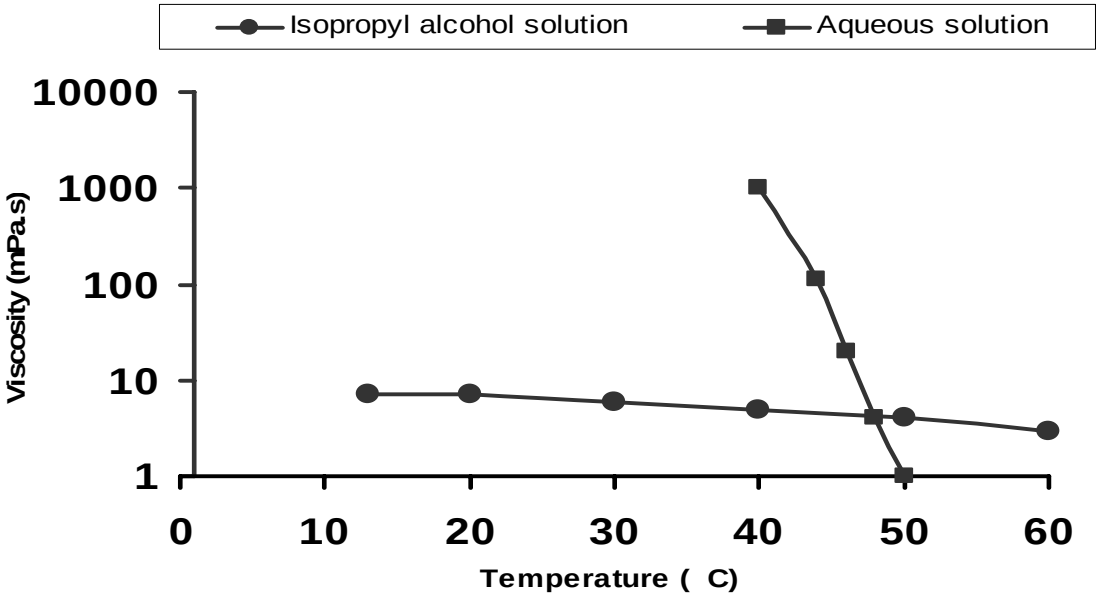

Fig. 4: Viscosity vs. temperature of 2% aqueous and isopropyl alcohol solution of HPC.

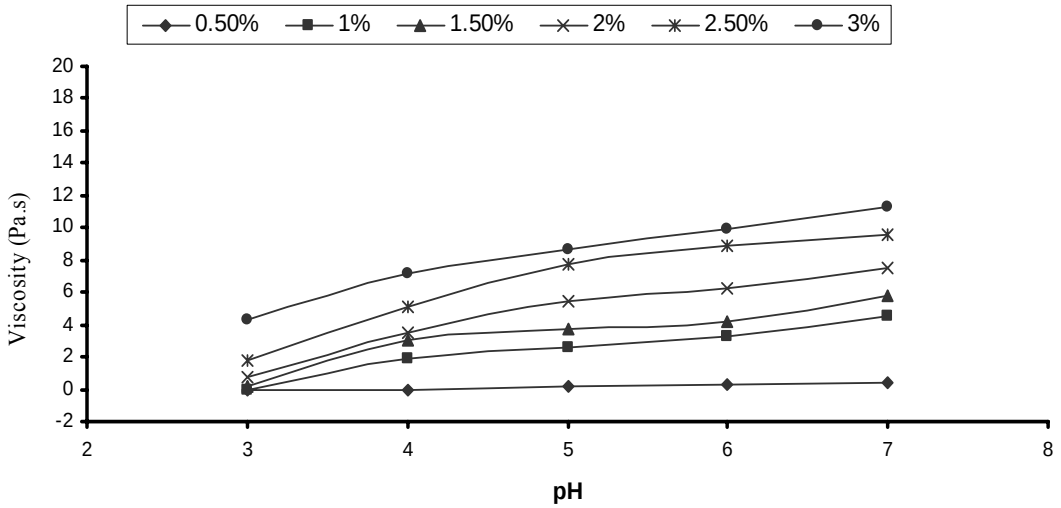

Fig. 5: Viscosity of various HPC gels at various pH at a shear rate 40.

The effect of Viscosity on the pH

Increasing concentrations of each polymeric component increased the hardness, compressibility, adhesiveness of the formulations. The effects on product hardness may be due to increased product viscosity and, hence, increased resistance to compression. The structures of these systems are predominantly built up by hydrogen bonds, which are easily breakable under shear stress (Fig. 6). When HPC is exposed to water, the polymer begins to uncoil, generating an increase in viscosity and gel formation (6).

Bioadhesion force

The bioadhesive force is an important physicochemical parameter for topical preparations (6). The addition of different concentrations from bioadhesive polymer to SA gel is shown in Fig. 7. The bioadhesive force has significantly increased as the concentration of bioadhesive polymers increased over the range of 0.5-3%.The maximum bioadhesive strength could be seen at 3% concentration of HPC. Furthermore, Ahuja et al. showed high molecular weight is important to maximize adhesion through entanglements and Van der Waals forces (18). The reinforcement of the bioadhesive forces of gel by the used polymer could be explained by the fact that secondary bond forming groups (e.g. hydroxyl, ether oxygen and amine) are the principle source of bioadhesion (19, 20).

Spreadability

The parallel-plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations. Parallel-plate instruments provide accurate, reproducible, and statistically relevant data. The advantages of the method are simplicity and relative lack of expense. The spreadability is an important factor in therapy and it is shown as index of ease of application (Table 2).

Each value is given as the mean of the three experiments. They were finally graded from fluid to very stiff on the basis of the value of Φ obtained. Product cohesiveness has been found to be significantly affected by its degree of polymeric concentration, and in nearly all cases increased polymer concentration has led to increased viscosity of the formulation. Therefore, the selection of polymer combinations and relative ratios play a very important role in formulation development and must be carefully considered to achieve the desired spreadability.

For hydroxylpropylmethyl cellulose (HPMC) gels, its strength or cohesiveness increased as the concentration of the polymer was increased (21). In quantitative evaluation of the changes of dynamic surface tension and therefore the spreading behavior of HPMC aqueous solutions, various concentrations of the same were tested against Avicel pH-101(FMC Corp., Philadelphia, PA) tablets. It was observed that by increasing the concentration of HPMC and thereby increasing the viscosity, the dynamic contact angle values also increased, thus, decreasing the spreading behavior of the polymer solution on the tablet surface. Ferrari et al. suggested that the gel strength of HPMC gels is related to the degree of cross-linking in the polymer network (21).

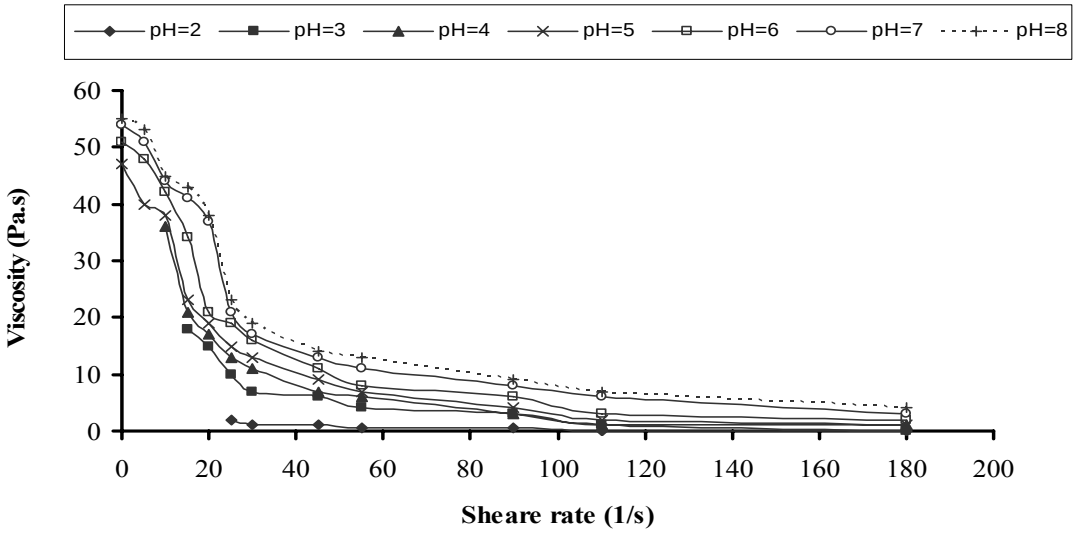

Fig. 6: Viscosity of HPC 1% gels at various pH.

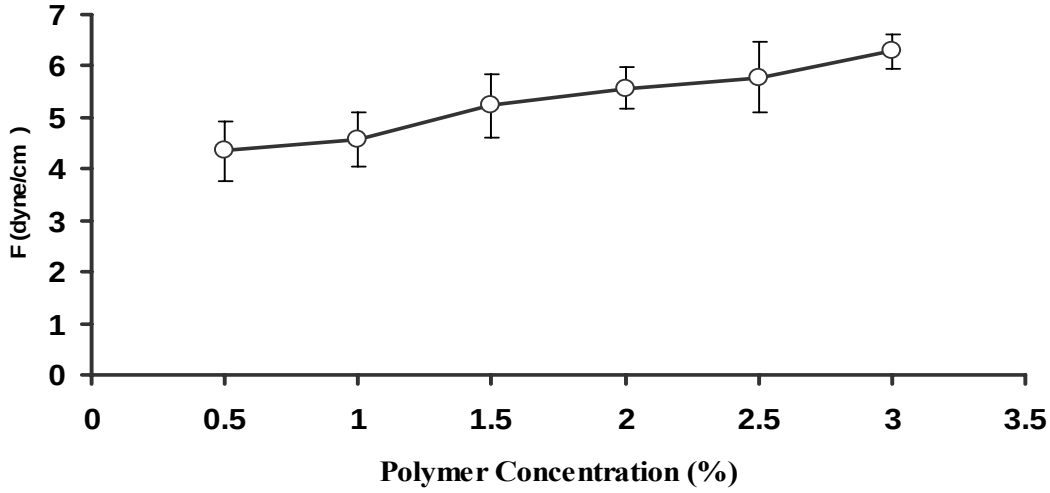

Fig. 7: Relationship between adhesive power (F) and polymer concentration in SA gels at 25°C.

Table 2: Physical properties of various formulations containing salicylic acid gels

Formulation code	Spreadability(Φ) (mm±SD)
F1	15.73±2.58
F2	13.34±1.99
F3	16.47±2.83
F4	18.53±3.45
F5	20.11±3.81

*Each value is given as the mean of three experiments.

The existence of a strong negative correlation between the spreadability of a formulation is inversely proportional to its cohesiveness because of strong cohesive forces within a formulation (22,23). Therefore, the cohesiveness of the selected ingredients must be considered during the development of topical and mucosal formulations (24). Increasing the viscosity of timolol eye drops by adding sodium carboxymethylcellulose increased the effect three-to nine fold as compared with that of non viscous drops. The ocular penetration increased as a result of longer corneal contact, and systemic absorption decreased as result of slower spreading of the solution on the nasal mucosa (25). Nyman-Pantelidis et al. showed the effect of viscosity on the retrograde spread of two enema formulations and found a statistically significant difference in the spread among the low-viscosity enemas spread over a larger area in the lower colon, mainly in the first 15 min following administration (26). In contrast, the enema with higher viscosity spread over a very small part of the rectum took a longer time to spread over the rectal mucosa. Also, the rate and extent of spreading was more variable with the latter formulations. The rapid evaporation of water from topical formulations influences the spreadability and results in an uneven topical dose within the treated area (26). The formulations also must be spread quickly and at multiple sites to ensure correct dosage.

Results of assay procedures

Results of assay of salicylic acid

Analytical parameters for the determination of SA by UV spectrophotometric method are given in Table 3.

Results of recovery studies

Recovery study results of SA gels are given in Table 4. Each dose contains 17 g of Salicylic acid. As it can be seen from Table 5 high percentage recovery shows that the method is free from the interferences of the excipients used in the formulation.

In vitro release studies

In different formulations of SA gel the drug release was studied. Different kinetic models (first-order release, Higuchi equation and zero order release) were employed to fit the data relating to the kinetics of the release of SA from gels. Increasing the concentrations of HPC increased viscosity and, additionally, the unique swelling significantly decreased the percent release of the original mass of salicylic acid, due to the properties of the formulations. The results of F_1, F_2, F_3 and F_4 formulations (disperse the hydroxypropyl cellulose in isopropyl alcohol) showed that the release kinetics on the basis of the highest r^2 and lower D% (ss) values best-fitted Peppas kinetic model (n> 0.5). The kinetic drug release was evaluated by using the well known exponential release equation (27, 28).

$$M_t/M_\infty = kt^n \quad (4)$$

In this equation, M_t/M_∞ is the fraction of drug released, k is the kinetic constant, t is the release time and n is the diffusion exponent that depends on the release mechanism and shape of swelling device tested. For formulations, values of n =0.5 indicate Fickian release (case-I transport), values of 0.5< n <1.0 indicate anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of n=1.0 indicate case-II or zero-

order release kinetics. Table 5 summaries the values of *n* for all the samples tested.

Comparing the mechanistic information obtained from different samples using this equation, the calculated exponent of Eq. (1) (Table 5) indicates that the release mechanism is anomalous for all cases which would be expected for swellable gels (29). A more reliable and informative analysis can be obtained by considering that drug release in swellable matrices depends on two processes: (i) drug diffusion into the swollen polymer, and (ii) matrix swelling due to the penetration. Calculation of the approximate contribution of the diffusion and relaxation mechanism to the anomalous release process is carried out by fitting the data to the heuristic model proposed by Peppas and Sahlin (29) for quantifying the two phenomena controlling the release from a swellable polymer. The equation of the model is;

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \qquad (5)$$

Where the first term of the right-hand side represents the Fickian contribution and the second term is the case-II relaxational contribution. In this model, drug release from swellable gels is described as the result of two transport mechanisms, i.e. diffusion across the gel layer and relaxation of the polymeric chains.

F_1, F_2, F_3 and F_4 exhibit values of the exponent *n* (0.75-0.85) which indicates that anomalous transport is very close to case-II transport (Table 5). Release was affected both by relaxation of the polymeric chains and diffusion of drug. This might reflect increased resistance of drug diffusion by the hydrated layers of the gel. The increased resistance could be due to the decreased diffusivity of the drug or the increased swelling of the gel. For F_5, *n* is very low (n=0.64), indicating that drug release is almost diffusive.

Therefore, gel containing low HPC is more swellable and less erodable than gel containing more HPC. As the amount of HPC increased, release rate of drug from the gels decreased (Fig. 8).This can be explained by the fact that diffusion may be the most important factor controlling the rate of drug release from the system diffusion (30). Catellani et al. reported that the amount of swellable polymer is inversely related to the initial release rate (29).

Table 3: Analytical parametersfor the assay of SA

Parameter	Result
Linearity range (µg/ml)	0.1-2
Slope	2.0919
Intercept	0.0186
Determination coefficient (r^2)	0.9992
LOD[a] (µg/ml)	0.01
LOQ[b] (µg/ml)	0.10

[a]LOD= limit of detection
[b]LOQ= limit of quantitation

Table 4: Recovery study results for SA gels

Theoretical value (g)	Practical value (g)	Recovery (%)	Mean recovery ±SD
17	16.95	99.70	99.61± 0.086
17	16.92	99.53	
17	16.93	99.59	

Colombo et al. (31) have demonstrated that the release of drug from swelling systems is directly related to the increase in surface area during swelling. When the amount of polymer increased in gels, the penetration rate of solvent into the gels was reduced. This reduction in solvent penetration was probably due to increased entanglement of the polymer. Since the swelling rate of the gels was initially slower, the SA present at the surface of the gel was rapidly released (15). The release of the drug from gel formulations are shown in Fig. 8. In all graphs, a linear relationship between Q (the cumulative amount of drug penetrated through the unit surface area of the membrane) and time was obtained after 30 min (see r^2 values in Table 6). Slopes of the linear portion of release profiles were calculated. These slopes represented the rate of release or Flux of SA from different formulations (Table 6). Table 6 shows the rate of release of SA or flux (μg/cm^2 min) is a function of drug release and it depends on the effects of composition of gel formulations. Analysis of Tukey showed that these correlations are statistically significant ($p<0.05$). Flux and Q_{150} (Table 6) for F_2 formulation were lower than other formulations. For example the Flux and Q_{150} (Table 6) for F_1 formulation were 8.270, and 1245.5 μg/cm^{2}min, respectively. When comparing formulations F_1, F_2, the results showed that increasing the HPC concentration at F_2, decreased the Flux and Q_{150} than F_1 (9,10) whereas increasing in the HPC concentration resulted in a decrease in release rate but also it caused an increase in pH. The results demonstrate that the flux of SA increased with decreased pH, because at low pH solutions may undergo acid hydrolysis, which causes chain scission and hence a decrease in solution viscosity (6).

Table 5: Analysis of release data from different formulations using Eq. (1)

Formulation Code	Kinetic constant k ×10^{-2} (m^{-n})	Diffusion exponent (±SD)
F_1	0.18	0.84±0.065
F_2	0.9	0.76±0.029
F_3	0.21	0.83±0.045
F_4	0.64	0.82±0.15
F_5	1.52	0.64±0.02

Table 6: The release characteristics of SA from different formulations of gel in vitro release studies

Formulation code	Flux[a] (μg/cm^{2}min)	Intercept (μg/cm^2)	r^2	Q^b_{150} (μg/cm^2)
F1	8.270±0.332	87.132±23.322	0.978±0.0016	1245.5±18.597
F2	6.753±0.456	76.426±2.357	0.9816±0.0051	1027.2±8.768
F3	7.395±0.434	251.55±63.424	0.9659±0.0177	1239.367±32.462
F4	7.899±0.551	68.236±15.352	0.9842±0.0006	1181.3±142.341
F5	8.054±0.186	127.223±21.26	0.9646±0.0018	1242.33±66.672

[a] Flux was obtained from regression analysis between the amount of drug release per unit surface area and time.

[b] Q_{150} is the amount of drug release per unit surface area after 150 min.

The results showed that SA permeation conformed to the pH partition hypothesis and polymer concentration. The presence of the inflection erodible gel delivery was explained as a combination of diffusion and erosion mechanism (32). In summary, the early time delivery rate of drug proved to be directly related to drug solubility. The results indicated that increase of alcohol could increase the release rate (comparing formulations F_1, F_3 and F_4 in Table 6, $p<0.05$). Table 6 also shows that when the amount of HPC was decreased the release rate increased (comparing F_4 and F_5, $p<0.05$). Isopropyl alcohol is a solvent for SA and when the alcohol volume increases drug release is faster from solvent and it penetrates more to skin surface. Therefore, the results indicated that increasing of HPC and water percent could reduce the release rate (F_2 formulation). Also, the results indicated that, an increase in the ratio of collodion: drug (2:1) and decrease in the ratio of isopropyl alcohol: drug (less than 3:1) resulted in a decrease of transparency of gel and the release rate.

Conclusion

The results showed that SA permeation conformed to the pH partition hypothesis and polymer concentration. HPC with different concentrations showed different bioadhesive release characteristics. In the gel containing SA, the drug was mainly released by erosion (33). Gel formulation of SA with bioadhesive properties and upper rate release is promising for prolonging skin residence time and thereby higher absorption. The release rate of a drug increases with decreasing viscosity of HPC and hence decreases the release rate of a drug. The results were demonstrated that the flux of SA decreased with increased pH. The results showed that increasing HPC concentration caused a reduction of SA release rate from gels and increasing HPC was related to an increased viscosity of formulation. Also, an increase in the ratio of collodion: drug (2:1) and a decrease in the ratio of isopropyl alcohol: drug (less than 3:1) caused a decrease in transparency of gel and the release rate. The results showed that diffusion of SA gel followed Peppas model.

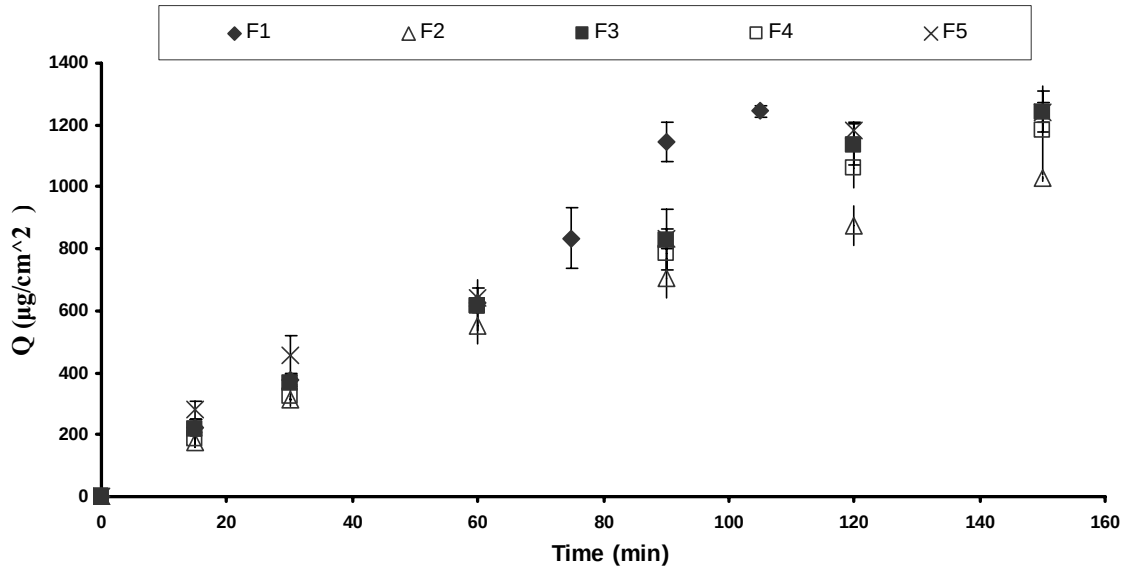

Fig. 8: The release rate of salicylic acid from gel formulations containing 17% drug.

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