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Original Article

DEVELOPMENT AND EVALUATION OF HYDROGEL OF AN ANTI-FUNGAL DRUG

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ABSTRACT

Objective: Topical gel preparations are used for application on skin or to certain mucosal surfaces for local action or for their emollient or protective action. Topical delivery of drugs can be achieved by incorporating drugs into the hydrogel matrix for effective delivery of drugs, thus avoiding first-pass metabolism and for increased local action in pain management and skin diseases.

Methods: Hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Miconazole nitrate (MN) is a broad-spectrum antifungal agent of the imidazole group. It has been selected as a model drug for the preparation of hydrogel. For the preparation of hydrogel, Carbopol of different grades like 934p, 971p, and 974p have been selected. Drug–polymer interaction has been carried out by FT-IR spectroscopy. Standard curve of miconazole nitrate was prepared in phosphate buffer pH 5.5 and 7.4. Physico-chemical characteristics of the hydrogel, like pH, viscosity and % swelling index, were studied. % cumulative drug permeation study through dialysis membrane was done in phosphate buffer pH 7.4.

Results: The results were found to be satisfactory. Carbopols have been used in different ratios to get a number of formulations. Out of these, nine formulations have been chosen by their satisfactory physicochemical characteristics and used for the study. The average pH, viscosity, % swelling index and drug content were found to be 7.36, 1.09 x 100 cps, 23.1 and 98.36 %, respectively. Drug permeation kinetics through the dialysis membrane has been done in a Franz diffusion cell at phosphate buffer pH-7.4. The permeation of Miconazole Nitrate through the dialysis membrane was maximum in F1 and minimum in F9. The drug permeation through the dialysis membrane followed zero-order kinetics.

Conclusion: A sharp correlation between the % swelling index and the Cumulative % of drug permeated through the dialysis membrane has been found. With the increase in the % swelling index over a period of 6 h the permeation decreased; thus, the swelling of the formulations is responsible to inhibit the permeation of Miconazole Nitrate through the skin.

Keywords: Hydrogel matrix, Antifungal, Topical gel

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INTRODUCTION

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers [1]. Hydrogels also possess a degree of flexibility very similar to natural tissue due to their significant water content. It possesses a degree of flexibility similar to natural tissue with low toxicity as well as time-dependent release with good transport also having biocompatible properties [2]. The cross-links between the different polymer chains result in viscoelastic and sometimes pure elastic behaviour and give a gel its structure (hardness), elasticity and contribute to stickiness [3, 4].

Permeability and water-holding capacity are two of the most important characteristics of a hydrogel [5]. The polar hydrophilic groups are the first to be hydrated upon contact with water, which leads to the formation of primary-bound water. As a result, the network swells and exposes the hydrophobic groups which also are capable of interacting with the water molecules [6]. The network will absorb additional water due to the osmotic driving force of the network chains towards infinite dilution. This extra swelling is opposed by the covalent or physical crosslinks, resulting in an elastic network retraction force [7]. Thus, the hydrogel will reach an equilibrium swelling level [8].

Biodegradable hydrogels, containing labile bonds, are therefore advantageous in applications like tissue engineering, wound healing and drug delivery [9, 10]. Biocompatibility is one of the most important characteristic properties required by the hydrogel. Biocompatibility entails compatibility with the immune system of the hydrogel and its degradation products formed, which also shouldn't be toxic [11]. Ideally, they ought to be metabolised into harmless products or can be excreted by the renal filtration process [12]. Generally, hydrogels possess decent biocompatibility since their hydrophilic surface has a low interfacial free energy when in contact with body fluids, which leads to a low tendency for proteins and cells to adhere to these surfaces [13, 14]. Moreover, the soft nature of hydrogels minimizes irritation to surrounding tissues [15].

The study aims at the development and evaluation of a hydrogel drug delivery system for the antifungal drug Miconazole nitrate for topical application.

MATERIALS AND METHODS

Materials

The materials required for the present work were acquired from diverse sources. The drug (Miconazole Nitrate) was a gift sample from a pharmaceutical concern. The other ingredients used were of analytical grade and were used as required. Potassium Dihydrogen Phosphate and Sodium Hydroxide pellets from Emplura, India, Carbopol 934 p, Carbopol 971 p, Carbopol 974 p from Mylan Laboratories Ltd. Triethanolamine from Desh chemicals Pvt Ltd., India.

Methods

Preparation of phosphate buffer pH-5.5 (I. P)

Potassium Dihydrogen Phosphate and Sodium Hydroxide Pellets were taken as per I. P and mixed with 1000 ml of Distilled Water. The pH was adjusted to 5.5 by NaOH and checked by pH meter.

Preparation of phosphate buffer pH-7.4 (I. P)

Potassium Dihydrogen Phosphate and Sodium Hydroxide Pellets were mixed with 1000 ml of Distilled Water. The pH was adjusted to 7.4 by NaOH and checked by pH meter.

Determination of λmax

The drug Miconazole Nitrate in phosphate buffer pH-5.5 and pH-7.4. was scanned in the UV spectrophotometer at a range of 200-400 nm of wavelength to determine λmax.

Standard curve of miconazole nitrate in phosphate buffer pH-5.5 at 230 nm

The drug was accurately weighed in an electronic balance. The weighted amount of drug was placed in a 100 ml volumetric flask and mixed with phosphate buffer pH-5.5, which was indicated as stock solution. From the stock solution, different concentration of the sample was withdrawn. A solution of Miconazole nitrate was prepared in Phosphate Buffer and Methanol. UV spectrum was used in UV–visible spectrophotometer with 1 cm matched quartz cells (UV-1800 Shimadzu). Then the absorbance was recorded against the blank at 230 nm UV spectrophotometer (UV 1800 SHIMADZU). The means were taken to draw the standard curve. A graph of absorbance vs. concentration was plotted and was found to be linear over a range of 5 to 30 µg/ml, indicating its compliance with Beer's law [16].

FTIR study for drug-polymer compatibility

FTIR has been used to check drug-polymer compatibility. KBr pellets were prepared and scanned to get FTIR spectra of the drug polymers individually and of the mixture. This study was carried out using the FTIR spectrophotometer (Perkin Elmer, spectrum GX FTIR). The IR spectrum of miconazole nitrate was recorded with diffuse reflectance principle sample preparation involving mixing the sample with Potassium bromide (KBr), triturating in glass mortar and finally placing it in the sample holder. The spectrum was scanned over a frequency range 4000-400 cm-1. The infrared absorption spectra of pure drug and physical mixture of polymer and drug were obtained [17, 18].

Preparation of hydrogel

Carbopol has very good dispersion ability and forms gels rapidly. Carbopol (weight in grams) was dispersed in distilled water. In the meantime, the required amount of drug, Miconazole Nitrate was mixed to it. The mixture was stirred until thickening occurred and then neutralized by dropwise addition of 50% (w/w) triethanolamine until a transparent gel appeared. Quantity of triethanolamine was adjusted to achieve gel with the desired pH. Gels were stored for 24 h at room temperature to stabilize [19]. Various formulations were made by varying the amount of Carbopol 934p, 971p and 974p according to the formulations given in table 1.

Table 1: Formulation of hydrogels

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Miconazole Nitrate (mg)	5	5	5	5	5	5	5	5	5
Carbopol 934p (mg)	150		-	50	100	50	50	50	50
Carbopol 971p (mg)	-	150	-	-	50	100		-	50
Carbopol 974p (mg)	-	-	150	100		-	100	50	-
Distilled Water (ml)	15	15	15	15	15	15	15	15	15
Triethanolamine (drops)	2	2	2	2	2	2	2	2	2

Evaluation of topical miconazole nitrate hydrogel

The optimised hydrogels were evaluated for the following tests:

Physical appearance

The physical appearance and homogeneity of the prepared gels were tested by visual observations [20]. The marketed formulation was considered as a reference.

Spread ability test

Spreadability can be determined by applying the gel over an even surface and observed for the gritty nature of the hydrogel if present [21].

pH determination

The pH of the gel formulations was determined by using a pH meter. For pH determination, 1% of hydrogel formulation in deionized water was prepared and pH was determined [22].

Drug content

For assay of the drug in gels, miconazole nitrate was extracted from 1 g of each gel formulation with 20 ml of phosphate buffer pH 5.5 and pH 7.4 for 30 min. The content was determined spectrophotometrically at 230 nm [23].

Viscosity measurement of hydrogel

The viscosity of the gel formulations was determined using a Brookfield viscometer with spindle no. 64 at 100 rpm at the temperature of 30 °C [24].

Swelling index

The extent of swelling was measured in terms of % of weight gained by hydrogel mass [25]. One gm. from each formulation was weighed and kept on a sieve placed on a petri dish containing 10 ml of pH 5.5 buffer solution. At the end of specified time intervals, a sieve containing hydrogel were withdrawn from Petridis and excess buffer blotted with tissue paper and weighed. The % of weight gained by the hydrogel was calculated by using following formula:

$$\% \text{ swelling index} = \frac{Mt - Mo}{Mo} \times 100$$

Where Mt = weight of formulation at time't';

Mo = Initial weight of formulation [26, 27].

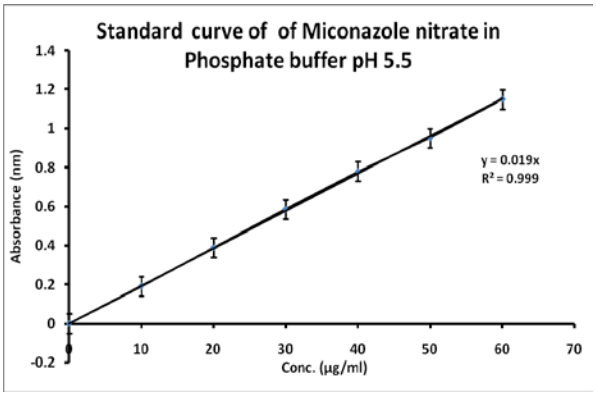

Fig. 1: Standard curve of miconazole nitrate in phosphate buffer pH 5.5, mean±SD

***In vitro* permeation study**

Franz diffusion cell of 60 ml capacity was used for the *in vitro* skin permeation study. 2 gm of hydrogel was spreaded on the dialysis membrane on the donor compartment. The donor compartment containing hydrogel spread on the skin was placed on the receptor compartment of the diffusion cell containing phosphate buffer pH

7.4 and maintained at room temperature. The phosphate buffer in the receptor compartment was continuously stirred using the magnetic beads during the experiments. 5 ml of the sample was withdrawn at the time interval and it was replaced with a 5 ml fresh phosphate buffer. Absorbance of the sample was measured in UV–a visible spectrophotometer at 230 nm against blank [28].

RESULTS

The absorbance of Miconazole nitrate in Phosphate buffer at pH 5.5 and 7.4 was observed in UV Vis Spectrophotometer at 230 nm wavelength. The graph of absorbance vs concentration was plotted and found to be linear. The standard curve at pH 5.5 shows R^2=0.999 and at pH 7.4 shows R^2=0.998.

FTIR study

The IR spectrum of miconazole nitrate showed a characteristic peak at 1587.36, 1474.1, 1408.89 and 822.9 cm^{-1} (fig. 3), which is in good agreement with the work done by Barillaro *et al.* who explained that the characteristic peak at 1587.36 cm^{-1} is related to stretching of C-C bond of dichloro-substituted benzene ring, while the peak at 1474.1 cm^{-1} is related to CH bending of the two dichlorobenzene groups and to the CH bending of the C6 and C17 [29, 30]. The peak at 822.9 cm-1 may represent the C-H group of the Meta di-substituted benzene ring.

The IR spectra of miconazole nitrate mixed with carbopol polymer mixture showed the same characteristic peaks of the drug at 1589.98 1409.4 and 821.95 cm^{-1} while the drug peak at 1474.1 cm^{-1} was slightly shifted to 1463.43 cm^{-1} as illustrated in fig. 4 and fig. 5.

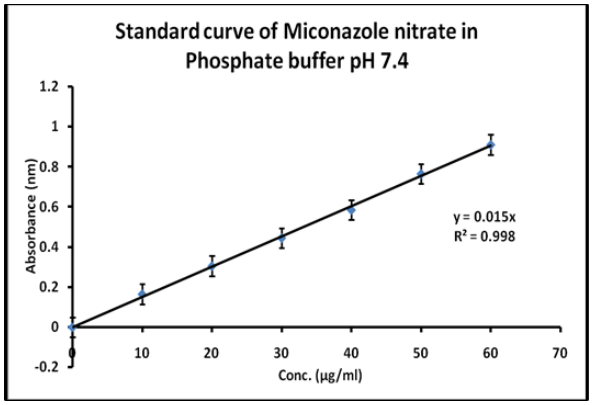

Fig. 2: Standard curve of miconazole nitrate in phosphate buffer pH 7.4: N=6, mean±SD

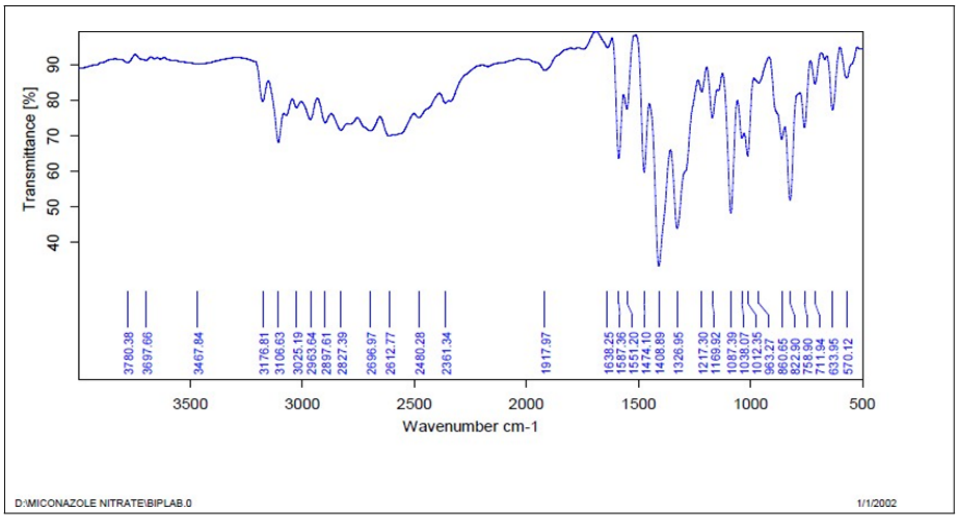

Fig. 3: FTIR of miconazole nitrate

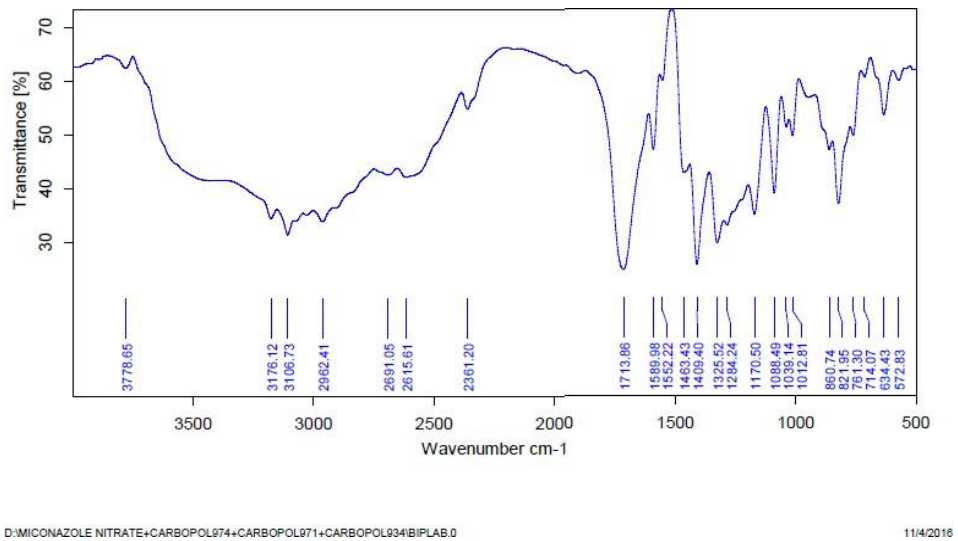

Fig. 4: FTIR of the mixture of miconazole nitrate and the polymers

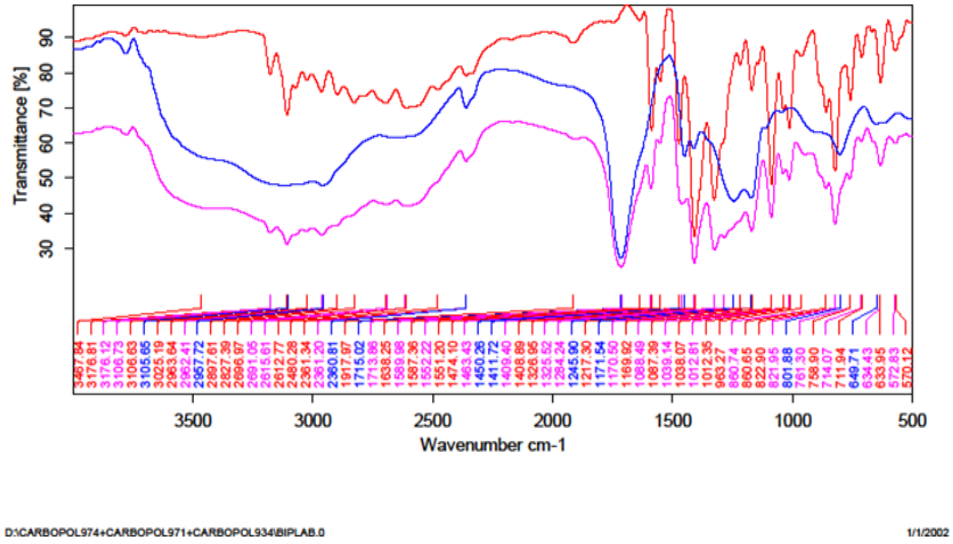

Fig. 5: FTIR of overlaid spectra of miconazole nitrate with all polymers

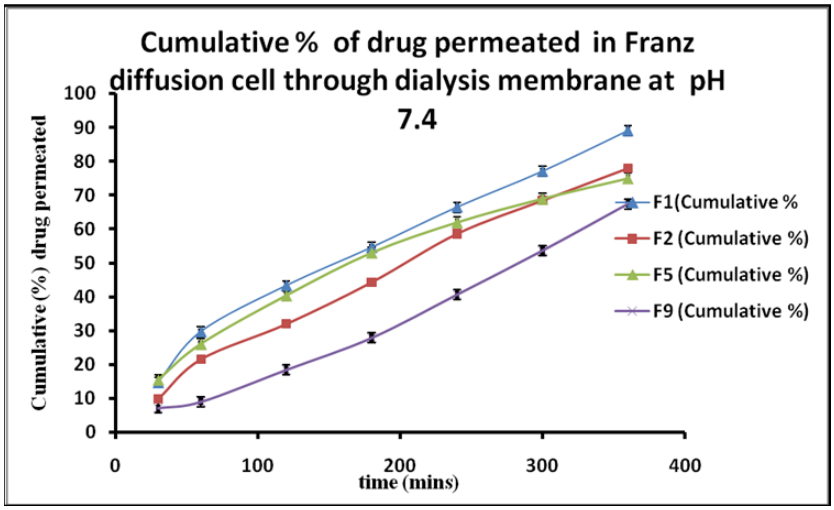

Fig. 6: Cumulative percentage of drug permeated in Franz diffusion cell through dialysis membrane at pH 7.4

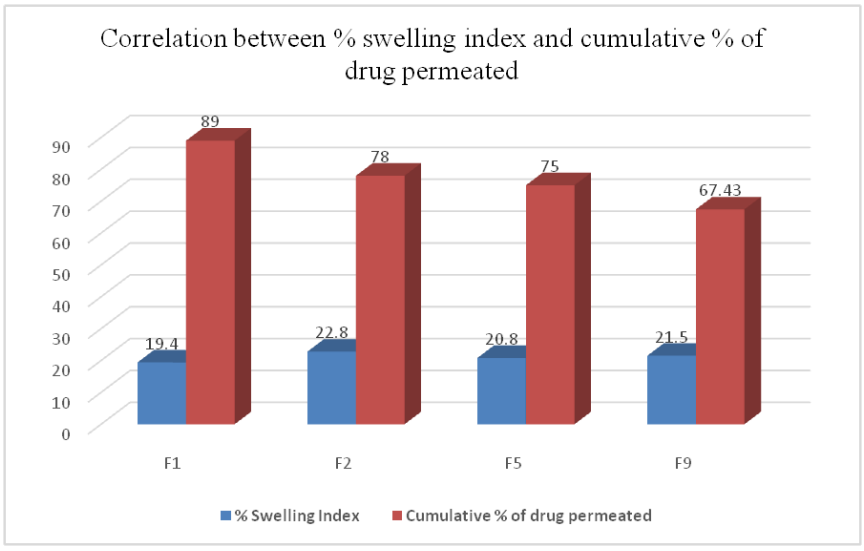

Fig. 7: Correlation between % swelling index and cumulative % of drug permeated from the hydrogel formulations

Table 2: Observation table of the pH, % swelling index and drug content of the hydrogel formulations

Formulation	pH	Viscosity (cps)	% Swelling Index	Drug content (%)
F1	7.32±0.12	1.12×100	19.4±0.41	98.23±0.94
F2	7.21±0.14	1.09×100	22.8±0.29	99.01±0.27
F3	7.42±0.15	1.06×100	25.8±0.21	97.21±0.92
F4	7.35±0.02	1.08×100	24.2±0.15	98.53±0.64
F5	7.36±0.20	1.18×100	20.8±0.34	98.78±0.82
F6	7.42±0.26	1.09×100	24.8±0.25	99.78±0.87
F7	7.40±0.25	1.05×100	25.8±0.21	97.16±0.73
F8	7.32±0.12	1.02×100	22.8±0.11	98.56±0.56
F9	7.40±0.26	1.16×100	21.5±0.04	98.01±0.45

Determination of the cumulative percentage of drug permeated through dialysis membrane in phosphate buffer pH-7.4. N=3, mean±SD

DISCUSSION

The major objectives of the current study were to prepare Miconazole Nitrate-loaded hydrogel and to study the effect of the ratio of Carbopol of different grades used in the formulation on the basic properties (Spreadability, Viscosity, Swelling, etc.) of hydrogel and correlations of viscosity and swelling of hydrogel preparations with permeability coefficient of the drug. Miconazole nitrate (MN) is a broad-spectrum antifungal agent of the imidazole group. It acts by means of a combination of two mechanisms: ergosterol biosynthesis inhibition, which causes lysis of fungal cell membranes because of the changes in both membrane integrity and fluidity and direct membrane damage of the fungal cells. Miconazole Nitrate is primarily used as a topical treatment for cutaneous mycoses; poor dissolution and lack of absorption make it a poor candidate for oral administration [31]. It is used in the treatment of Superficial Candidiasis, Dermatophytosis and Pityriasis versicolor. The limited solubility of miconazole nitrate and the drug-intensive hepatic transformation that results in poor oral drug bioavailability of the drug and hinders its use for systemic treatment via the gastrointestinal tract. After the experiments with different combinations of polymers and evaluating the different physico-chemical parameters, the best polymeric compositions achieved have been reported here. The hydrogel was developed with different polymers (Carbopol 934p, Carbopol 971p, Carbopol 974p). Twelve combinations of hydrogel preparations were taken into considerations as given in table 1. Drug-excipient interaction is a very important study prior to the development of a new formulation [32]. Among the various methodologies available to study the drug-excipient interaction, common approaches are FTIR-spectroscopy UV Spectrophotometer. Standard Curve of Miconazole nitrate in Phosphate buffer pH 5.5 (fig. 1) and Phosphate buffer pH 7.4 (fig. 2) were done using UV-Vis Spectrophotometer. FTIR-spectroscopy shows the interaction between the molecules at the level of functional groups. Here drug excipient interaction was studied using FTIR-spectroscopy (fig. 3, 4, 5). It is suggested by the FTIR spectra that there may be some physical interactions. Mixtures of polymers can change the rate of diffusion of drug molecules by changing entanglement in the polymeric network. Blend of polymers is known to change the rate of diffusion of drug molecules by varying the entanglement in the polymeric network; leading to the change of tortuosity of diffusion pathways [33].

Thus, the interaction might be helpful in controlling the release of drug molecules from the experimental formulations. From the results it is evident that all gel formulations showed uniform homogeneity and spreadability. The physical appearance of the gel formulations was white translucent in nature. It is seen that viscosity changes as the concentration of polymers changes among the hydrogel preparations [34] as seen in table 2.

The pH of the hydrogel formulations was determined as shown in table 2. The swelling test for the various formulations were done to determine the percentage swelling index and the results were recorded as seen table 2. To investigate the drug permeation kinetics through the dialysis membrane, these membranes was fixed on the Franz diffusion cell. The experiment was thus conducted with 2 gm of drug-loaded hydrogel spread over the dialysis membrane within the donor chamber 60 ml of phosphate buffer pH 7.4 within the receiver chamber, at room temperature and on a magnetic stirring device. Samples were taken after 30 m, 1 h, 2 h, 3h, and 4 h and up to 6 h, replaced by fresh buffer. The absorbance of the sample was measured spectrophotometrically at 230 nm. The amount of the drug crossed the dialysis membrane could be easily calculated. It has been found that permeation of Miconazole Nitrate through the dialysis membrane was maximum in F1 and minimum in F9. Depending on the cumulative % of drug permeation, the formulations can be assigned in the following order F1>F2>F5>F9 as shown in fig. 6. The result clearly indicates that the presence of the polymeric combination of carbopol increase the drug permeation through skin. The drug permeation might be described by zero-order kinetics during the time of study. There is a correlation between % swelling index and Cumulative % of drug permeated through the dialysis membrane, as shown in fig. 7. With an increase in % swelling index over a period of 6 h the permeation decreased; thus, the swelling of the formulations is responsible to inhibit the permeation of Miconazole Nitrate through skin.

CONCLUSION

Miconazole Nitrate-loaded hydrogel with varying ratio of Carbopol of different grades and have a significant effect on the basic properties (Spreadability, Viscosity, Swelling, etc) of hydrogel. Depending on the cumulative % of drug permeation the formulations can be assigned in the following order F1>F2>F5>F9. Hence it can be stated that among the best combinations of Carbopol, Carbopol 934p offers best drug permeation through the dialysis membrane. There are significant correlations between % swelling index and the Cumulative % of drug permeated through the dialysis membrane. With an increase in % swelling index over a period of 6 h the permeation decreased; thus, the swelling of the formulations is responsible to inhibit the permeation of Miconazole Nitrate through skin.

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Nil

AUTHORS CONTRIBUTIONS

SAYANTAN BHATTACHARYA and BIPLAB PAUL performed the experimental work. SAYANTAN BHATTACHARYA and GOPA ROY BISWAS wrote the manuscript and analysed the data. All authors contributed accordingly and approved the final manuscript.

CONFLICT OF INTERESTS

Declared none

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