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Research Article

FORMULATION AND DEVELOPMENT OF HYDROGEL BASED SYSTEM FOR EFFECTIVE DELIVERY OF RUTIN

HIMESH SONI[1*] AND AK SINGHAI[2]

[1]Suresh Gyan Vihar University, Jaipur-302025, India, [2]Lakshmi Narain College of Pharmacy, Raisen Road, Bhopal (M.P.)-462021, India.
Email: himeshsoni@rediffmail.com

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ABSTRACT

Hydrogels, the swellable polymeric materials, have been widely investigated as the carrier for drug delivery systems. The hydrogel can be defined as a cross-linked polymeric network which has the capacity to hold water within its porous structure. The water holding capacity of the hydrogels arise mainly due to the presence of hydrophilic groups, viz. amino, carboxyl and hydroxyl groups in the polymer chains. Hydrogels are cross-linked polymeric networks and hence provide a 3-dimensional polymeric network structure. Rutin is the rhamnoglucoside of the flavonoid quercetin. It is quercetin 3-rutinoside and found in many plants and used for treatment of various vascular diseases. The goal of this work was to formulate and optimized hydrogel systems containing rutin 0.025% (w/w) which can improve the therapeutic efficacy of poor water soluble drugs (rutin). Hydrogels were prepared using Carbopol 934 and HPMC in different concentrations ratio 2:1, 1:1 & 2:1 along with methanolic (co-solvent) dispersion of rutin. Choice of optimal concentrations of polymers is based on rheological properties of hydrogels. Hydrogels were characterized by means of pH measurement, determination of % entrapment, pH, viscosity, Spreadability. *In vitro* release behaviour of rutin from hydrogels was determined using Franz diffusion cell. Release profile of the rutin was also fit into various kinetic models to find out the mechanism of drug release and formulations were showing the release by zero order system. On the basis of these parameters, the formula was optimized.

Keywords: Hydrogel, Rutin, Carbopol 934, Topical delivery.

INTRODUCTION

Hydrophilic gels called hydrogels are cross-linked polymeric networks absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials [1]. The hydrophilic functional groups attached to the polymer backbone helps to absorb water. Water inside the hydrogel allows free diffusion of some solute molecules, while the polymer serves as a matrix to hold water together. Gels are used pharmaceutically as lubricants and as carriers for spermicidal agents [2] and other drugs for their local effects and percutaneous absorption [3]. Hydrogels have been used as drug delivery system due to following reasons:

- Hydrogels provide suitable semi-wet, three-dimensional environment for molecular-level biological interactions.
- Hydrogel's mechanical properties are highly tunable, for example elasticity can be tailored by modifying cross-link densities.

Hydrogels can be designed to change properties (e.g. swelling/ collapse or solution-to-gel transitions) in response to externally applied triggers, such as temperature, ionic strength, solvent polarity, electric/magnetic field, light, or small (bio) molecules [4]. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve. They are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements [5]. The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic e specifically that a depot formulation is created from which drugs slowly elute, maintaining a high local concentration of drug in the surrounding tissues over an extended period, although they can also be used for systemic delivery. Hydrogels are also generally highly biocompatible [6].

Classification of hydrogel

Hydrogels are broadly classified into two categories:

Permanent / chemical gel: they are called 'permanent' or 'chemical' gels when they are covalently cross-linked (replacing hydrogen bond by a stronger and stable covalent bonds) networks. They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density [7].

Reversible / physical gel: they are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements, and / or secondary forces including ionic, hydrogen bonding or hydrophobic interactions. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains. All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress [8]. Rutin is a flavonoid present in the plant kingdom as a secondary metabolite. Rutin is the rhamnoglucoside of the flavonoid quercetin and found in many plants and used for treatment of various vascular diseases [9]. It is quercetin-3-rutinoside or 3,3',4', 5,7-pentahydroxy flavones-3-rutinoside, and has a chemical formula $C_{27}H_{30}O_{16}$.

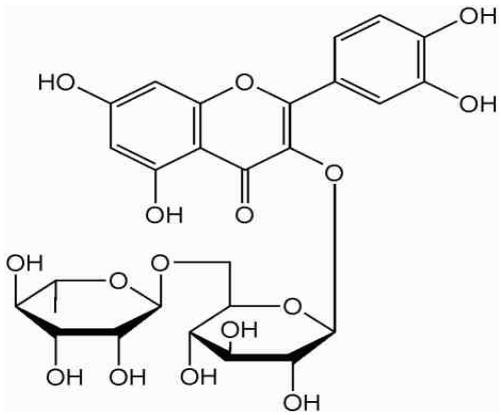

Fig. 1: Structure of Rutin

Rutin acts as antioxidant and exhibited several beneficial effects, such as anti-inflammatory, anti-allergic, antiviral as well as an anticancer activity. It is suggested that rutin play a protective role in liver diseases, cataract and cardiovascular diseases[10].The poor water solubility and low stability of rutin in aqueous alkaline

medium restricts its application in use. The objective of the present study was to formulate topical hydrogel of rutin which can be effectively used for various skin and other disorders.

MATERIAL AND METHODS

Rutin was isolated from *Annona squamosa* leaves & identified as well as characterized by various analytical techniques like HPLC, FT-IR. Carbopol 934 and HPMC were purchased from Hi-media laboratories Pvt. Ltd. All other chemicals and reagents used were of analytical grade.

Instruments

Viscometer (Brookfield Rotational Viscometer), Franz diffusion cell type glass, UV spectrophotometer (Shimadzu 1700, Japan), Digital pH meter and FTIR (ATR Bruker, Germany) were used.

Preformulation Study

Organoleptic Characteristics

The drug (Rutin) was evaluated for its appearance, melting point, solubility studies and partition coefficient.

Solubility

The Rutin was found to be soluble in most of the organic solvents (methanol, ethanol etc.) and was poorly soluble in distilled water showing its hydrophobic nature.

Determination of λ_{max}

The isolated rutin was dissolved in methanol and their UV absorption spectrum was compared with standard rutin. Spectrophotometric analysis was carried out in Shimadzu 1700 UV spectrophotometer.

Calibration Curve

About 100µg/ml rutin stock solution was prepared in methanol. Different concentrations (2,4,6,8,10µg/ml) were made by serial dilution. The absorbance was recorded at 257nm & calibration curve was prepared.

Partition coefficient

About 50mg of rutin was dissolved in 50ml of distilled water and n-octanol separately and both the solution were mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 257nm by using UV spectrophotometer. The concentration of rutin was determined with the help of standard curve and partition coefficient was determined by following formula:

Partition coefficient = Concentration of drug in organic phase

Concentration of drug in aqueous phase

Selection of polymer

The polymers were selected on the basis of the drug excepient compatibility studies. In the present study, the drug excepient compatibility of the Rutin with Carbopol 934 & HPMC was determined by FT-IR (Brucker).

Preparation of Hydrogels

In a separate containers, the hydrogel forming polymers were dissolved in small amount of double distilled water in various proportions as shown in Table no.1 and then remaining ingredients i.e. glycerine and sodium benzoate were added. The, methanolic dispersion of rutin (1mg/ml) was added to it and the volume up to 100 ml. Then, sonicated (Lark probe sonicator) at 6φ frequency,20 sec at 28^{0}C. The above formulation was allowed to stand for 24 hrs at room temperature. The pH of this gel preparation was maintained 6±0.4 and stored in well closed container.

Table 1: Composition of various Hydrogel formulations

S. No.	Components	Quantity		
		H1(2:1)	H2(1:1)	H3(1:2)
1.	Carbopol 934	500 mg	500mg	250 mg
2.	HPMC	250 mg	500mg	500 mg
3.	Acaica	500mg	500mg	500mg
4.	Glycerine	2.ml	2.ml	2.ml
5.	Sodium benzoate	100mg	100mg	100mg
6.	Rutin	4mg	4mg	4mg
7.	Distilled water	q.s 25 ml	q.s 25 ml	q.s 25 ml

Evaluation of formulated Hydrogels

Appearance

The hydrogels formulated were observed for their Visual appearance, colour, texture, feel upon application such as grittiness, greasiness, stickiness, smoothness, stiffness and tackiness.

pH

The pH of the hydrogels was determined by immersing pH meter to a depth 0.5 cm in a beaker containing hydrogels. The determinations were carried out in triplicate and the average of three reading is recorded.

Viscosity

The viscosities of formulated hydrogels were determined using Brook-field viscometer (spindle number LV-61) in triplicate and the average of three reading is recorded

Spreadability

It was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides[11]. Spreadability was then calculated by using the formula:

S = M.L / T

Where,

S = Spreadability

M = Weight tide to upper slide

L = Length of glass slide

T = Time taken to separate the slide completely from each other

Unit =g.cm/sec

Drug content determination

Rutin was assayed in hydrogels by RP-HPLC. Approximately 3.0 g of formulation was placed in a 25 mL volumetric flask. Methanol was added and the flask was maintained under moderate stirring with ultrasound for 30 minutes. This sample was centrifuged, diluted with the mobile phase and then filtered through a sartorius filter and the HPLC analysis was carried out using a LC-100, Cyberlab TM, Salo Torrace, Millburry, MAO 1527, USA with LC-UV-100 UV detector. A CAPCELL (C-18) HPLC-packed column (4.6 mm I.D.X 250 mm), type MG 5 µm, number AKAD/05245 was used for the chromatographic separations. The mobile phase contain methanol: water (50:50) acidified with phosphoric acid (pH 4.0). The flow rate of 1.0 mL·min−1. About 20 µl sample was injected and the rutin was detected at 257 nm[12].

% Drug Entrapment efficiency

1ml of hydrogel was taken and volume was made up 10ml with distilled water and centrifuged at 15000rpm for 15min. The supernatant was collected and again 1ml of supernatant diluted with 9ml of distilled water. The supernatant was analysed spectrophotometrically for Rutin content at 257 nm. Now, from observed absorbance concentration was determined from standard curve. The amount of drug in supernatant (w) was then subtracted

from the total amount of drug added (W). The % entrapment was calculated from the formula:

$$\% \text{ Drug Entrapment} = \frac{W-w \times 100}{W}$$

Where; W = the weight of drug added to the system

w= the weight of drug in the supernatant

***In vitro* release study**

In vitro release studies were performed using modified Franz diffusion cell.

Treatment of cellophane membrane

Cellophane membrane (7.069 cm^2), it was boiled for 1 hr in a beaker on water bath, for the removal of glycerol. The process was repeated by transferring the membrane in fresh distilled water for the complete removal of glycerol. Then the membrane was kept in ethanol for 24 hrs followed by washing with distilled water. For the removal of polysulphide from the membrane, it was treated with 0.3 % w/v solution of sodium sulphide for 1 min followed by washing with distilled water. The membrane was finally acidified using 0.2% v/v H_2SO_4 and then was washed with distilled water. The prepared membrane was stored in the saline phosphate buffer (pH 5.4).

Release studies

100 ml Phosphate buffer (pH 5.4) was used as acceptor phase to ensure sink conditions. The pH of the applied buffer approaches the natural pH value of human skin. Therefore, this kind of buffer is usually used as dissolution medium for the investigation of transdermal drug delivery. Hydrogel 0.50 gm was placed in the donor compartment prepared by closing the one side of a both open sided test-tube with the membrane. The effective diffusion surface area was 7.069 cm^2 (approx.). The receptor compartment was filled with phosphate buffer, pH 5.4(40 ml). During the experiments, the solution in receptor side was maintained at 37°C ± 0.5°C and stirred at 800 rpm with Teflon-coated magnetic stirring bars. At fixed time intervals (0.5, 1, 1.5,2,3,4,12 & 24 hrs) 5 ml sample was withdrawn from receptor compartment and analyzed by UV spectrophotometer.

Mechanism of drug release

Various mathematical models were evaluated considering the dissolution profiles of the samples[13].

In order to obtain the rate of release, the release data from the matrices were fitted to the following mathematical models: zero-order kinetic (Eq. 1), first-order kinetic (Eq. 2) and square-root of time equation (Higuchi equation, Eq. 3).

$Q = kt$ -------(1)

$\ln(100-Q) = \ln Q_0 - kt$ ----------(2)

$Q = Kt^{1/2}$ ----------(3)

In Eqs. (1)–(3), Q is the percent of drug released at time t and k is the coefficient of the equations. In Eq. (3) Q_0 equals 100.

RESULTS AND DISCUSSION

The overall objective of the present work was to develop a hydrogel dosage form containing rutin, as a potential dermatological formulation. The prepared formulation presented physicochemical properties compatible on its cutaneous administration, including the pH. The Rutin, yellow coloured, odourless and crystalline compound isolated from *Annona squamosa* leaves & identified as well as characterized by various analytical techniques like HPLC, FT-IR. Various organoleptic characteristics were tabulated in table 2. The partition coefficient of rutin was found 2.76, which confirm the lipophilicity of the drug.

Table 2: Organoleptic Characteristics

S. No.	Characteristics	Results
1.	Appearance	Pale yellow colour powdered
2.	Melting Point	196^{0}C
3.	Solubility	Soluble in methanol, ethanol, pyridine and poorly soluble in water,
4.	Partition coefficient	2.76

The absorbance maxia was found to be 257 nm by the UV Spectroscopy (Fig 2).

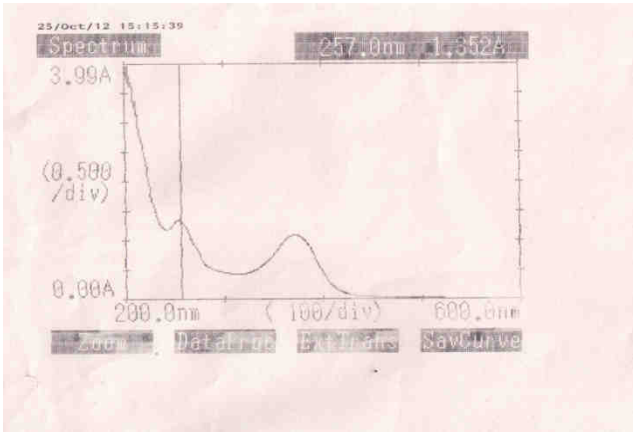

Fig. 2: UV λ_{max} of rutin

The calibration curve of rutin was prepared at 257nm(Fig 3).

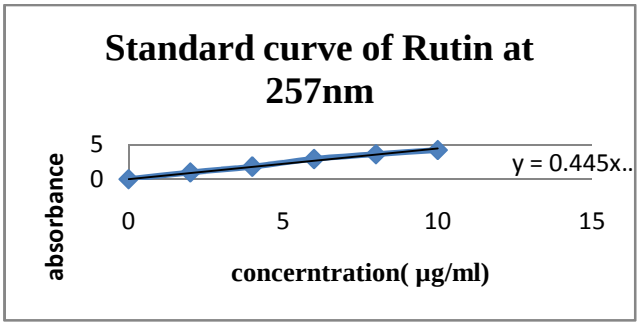

Fig. 3: Standard curve of Rutin at 257nm

The drug interaction studies of the drug and polymers were carried out by FT-IR spectroscopy. The presence of the peaks of the pure drug (table 3 & fig 7) belonging to different functional groups of the drug in the drug-polymer mixtures (Rutin, Carbopol 934 and HPMC) remains unaltered (Fig 6,7 & 8).

Table 3: IR Analysis of rutin

cm^{-1}	Functional Group
3330	OH (bonded)
2920	CH stretch
1660	C=O
1620	C=C
1600	Aromatic
1360	C-O-C

Different hydrogels were prepared by keeping the Carbopol: HPMC polymer ratio (2:1, 1:1 & 1:2) and hydrogels (H1, H2 & H3) were formulated. The composition of various ingredients used in formulations was tabulated in table1.The hydrogels were characterized by its appearance, pH, viscosity, spreadability & % entrapment (Table 4). On the basis of results of spreadability and % entrapment study the H2 formulation was found to be optimum which was more supported further by drug release study.

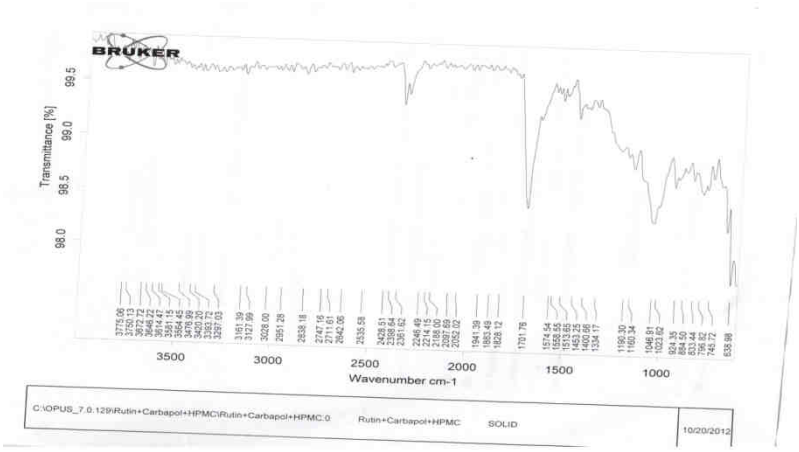

Fig. 6: IR spectra of Rutin + Carbopol 934 + HPMC mixture

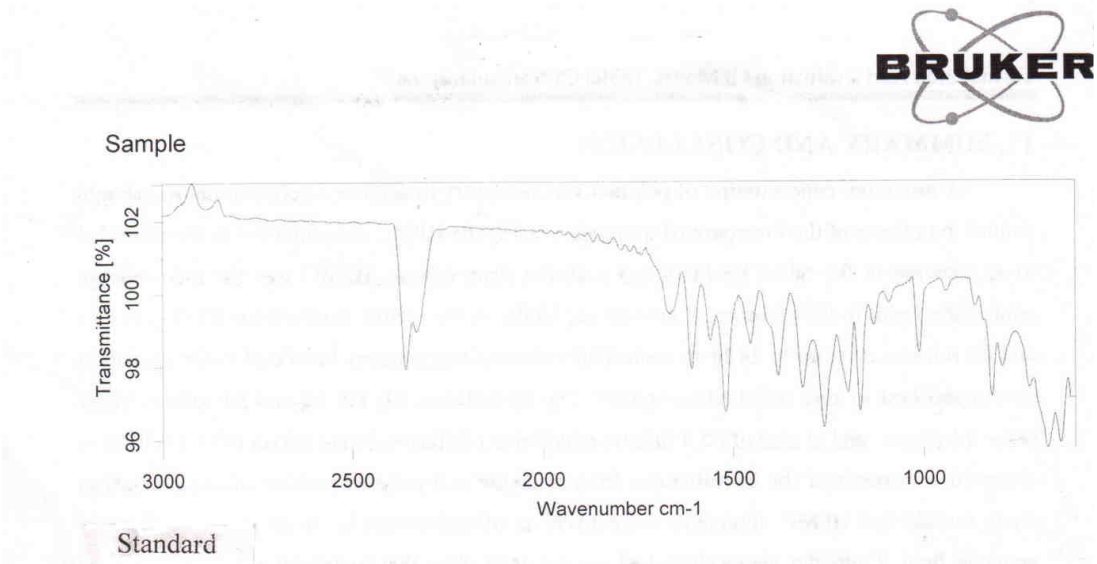

Fig. 7: IR spectra of standard Rutin

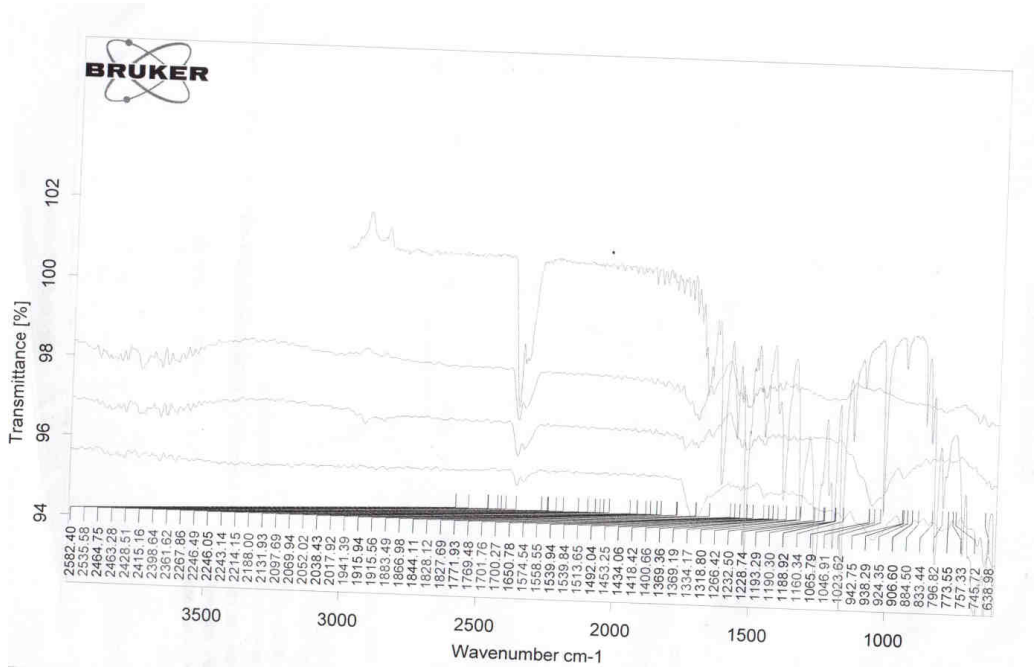

Fig. 8: Comparison of IR spectra of standard Rutin+ Carbopol 934+HPMC + Mixture

Table 4: Characterization of formulated Hydrogels

S. No.	Characteristics	Results		
		H1	**H2**	**H3**
1.	Appearance	glossy, pale-yellowish colour	glossy, pale-yellowish colour	glossy, pale-yellowish colour
2.	pH	5.5	5.7	5.7
3.	Viscosity	4200cps	4000cps	3600cps
4.	Spreadability	5.1 g.cm/sec	5.6 g.cm/sec	5.02 g.cm/sec
5.	% entrapment	97.2%	99.01 %	97.51%

Rutin content in hydrogels was also determined by HPLC analysis (Fig 4 & 5). The HPLC chromatogram of hydrogel (H2) containing rutin showed RT=5.70 min whereas standard rutin chromatogram showed RT=4.22 min.

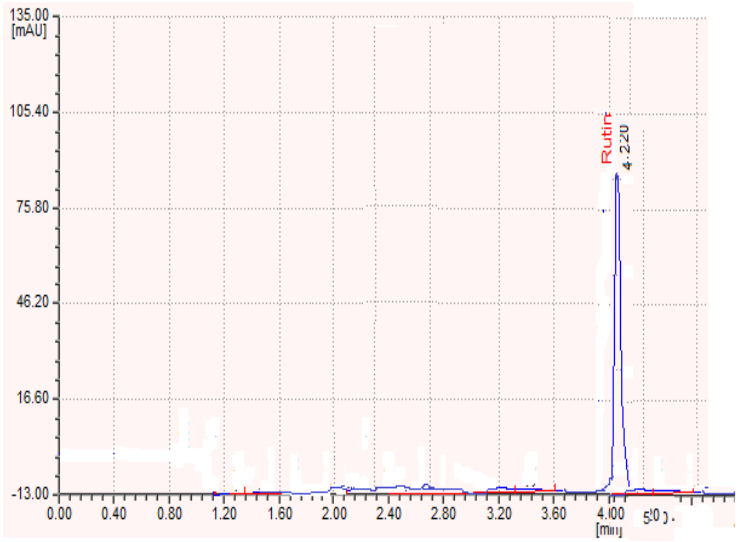

Fig. 4: HPLC chromatogram of standard rutin

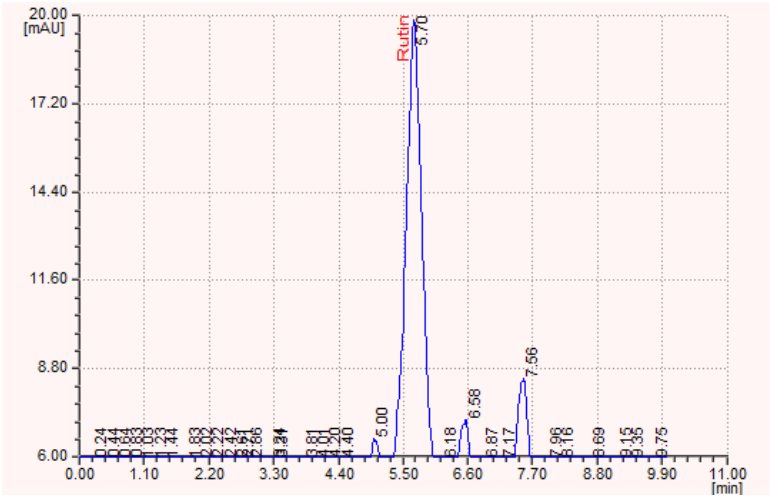

Fig. 5: HPLC chromatogram of Hydrogel containing rutin

Further, *in-vitro* release studies were carried out by using modified Franz diffusion cell. In order to obtain the rate of release, the release study showed that the rutin was released in sustained manner due to the presence of the sustained release polymer Carbopol and HPMC. The drug release of formulation H1 was found to be 45.49 % due to presence of large concentration of Carbopol 934, on the other hand formulation H2 and H3 shown the release of 85.34% and 86.01% respectively. The increase in the % rutin release was due to increase in HPMC concentration in the formulation which is more hydrophilic in nature. On the basis of drug release study it was found that the formulation H2 was found to be optimised preparation. The release data from the matrices were fitted to the following mathematical models: zero-order kinetics, first-order kinetics and square-root of time equation [Higuchi equation] (table 5, 6 & 7) for H1, H2 &H3 formulations. As shown in Fig. 9-17 plots drawn according to various kinetic models, were giving linear relationship (table 8). The best linearity in H1, H2 & H3 were found in zero order plot (fig. 10, 13 & 16) (r^2= 0.9831*) indicating that release rate of drug from hydrogel system is independent on concentration of the drug present in the system. In above formulations zero order kinetics revealed that, the rate of molecule release depends on the swelling rate of polymer networks[14].The % release rate of rutin from different formulation (H1, H2 & H3) in different time intervals were shown in fig 18.The cumulative amount of rutin from hydrogel (H1, H2 & H3) permeated at the end of 24 h were found to be 0.69147, 1.29716 &1.30735 mg/cm^2 respectively.

Table 5: *In-vitro* drug release studied of H1 formulation

S. No.	Time(hrs)	Amount (mg)	$t^{1/2}$	% drug release	Cumulative % drug release	% C drug to be released	log% C drug to be released
1.	00	00	00	00	00	100	02
2.	0.5	0.0003	0.707	0.02	0.02	99.98	1.9999
3.	1	0.00063	1	0.042	0.062	99.938	1.9997
4.	1.5	0.00136	1.22	0.09	0.152	99.848	1.9993
5.	2	0.0182	1.41	1.2	1.352	98.648	1.9940
6.	3	0.0469	1.73	3.09	5.252	94.748	1.9765
7.	4	0.0755	2	4.97	10.22	89.78	1.9531
8.	12	0.1925	3.46	12.67	22.892	77.108	1.8870
9.	24	0.3435	4.89	22.6	45.492	54.508	1.7364

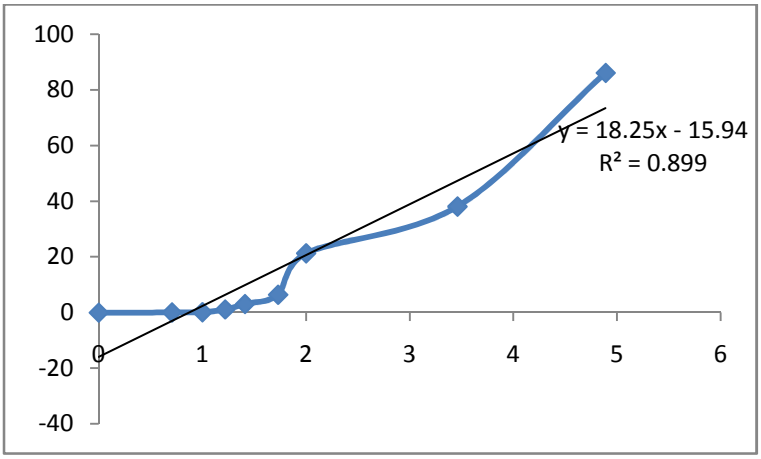

Fig. 9: Graph plot between cumulative % drug release vs $t^{1/2}$(Higuchi model kinetics)

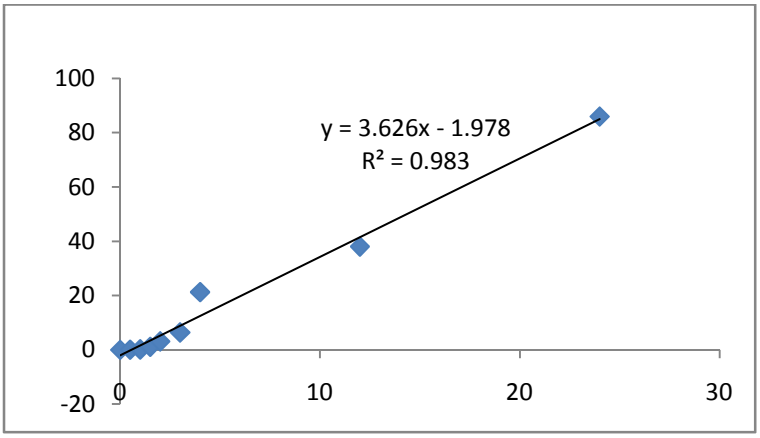

Fig. 10: Graph plot between cumulative % drug release vs time(Zero order kinetics)

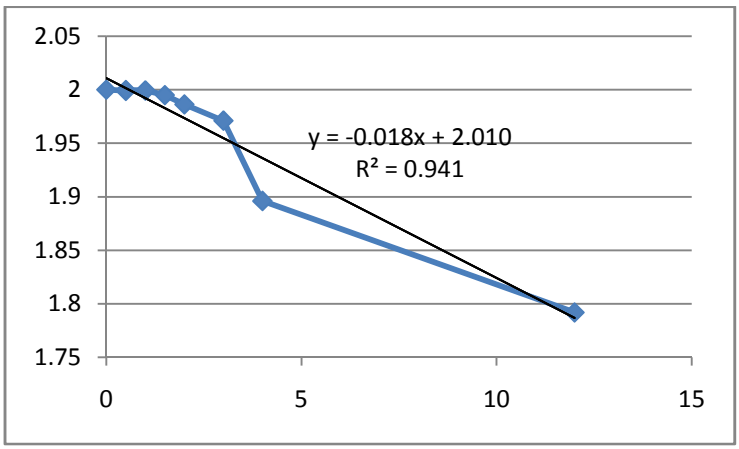

Fig. 11: Graph plot between time vs log% cumulative drug remaining to be released (First order kinetics)

Table 6: *In-vitro* drug release studied of H2 formulation

S. No.	Time(hrs)	Amount (mg)	*$t^{1/2}$	%drug release	Cumulative %drug release	% C. drug to be released	log% C. drug to be released
1.	00	00	00	00	00	100	02
2.	0.5	0.395	0.707	2.6	2.6	97.4	1.9885
3.	1	0.0440	1	2.9	5.5	94.5	1.9754
4.	1.5	0.0457	1.22	3.01	8.51	91.49	1.9613
5.	2	0.046	1.41	3.03	11.54	88.46	1.9467
6.	3	0.0942	1.73	6.2	17.74	82.26	1.9151
7.	4	0.191	2	12.6	30.34	69.66	1.8429
8.	12	0.3784	3.46	24.9	55.24	44.76	1.6508
9.	24	0.4575	4.89	30.1	85.34	14.66	1.1661

* $t^{1/2}$ = square root of time

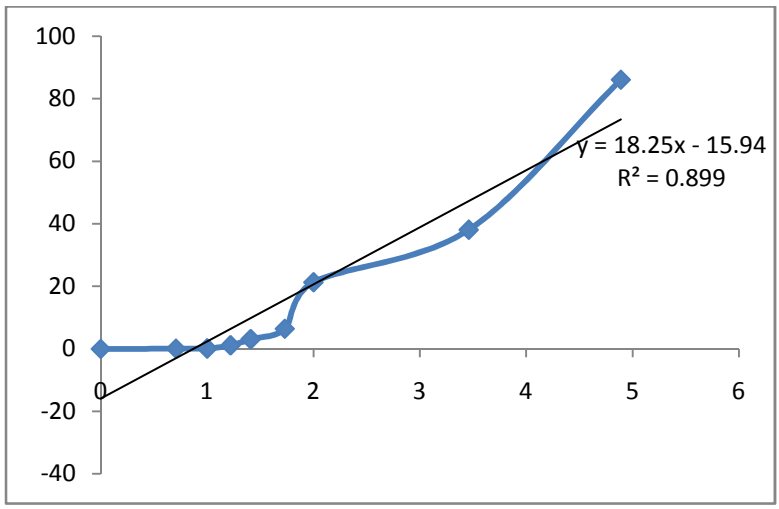

Fig. 12: Graph plot between cumulative % drug release vs $t^{1/2}$(Higuchi model kinetics)

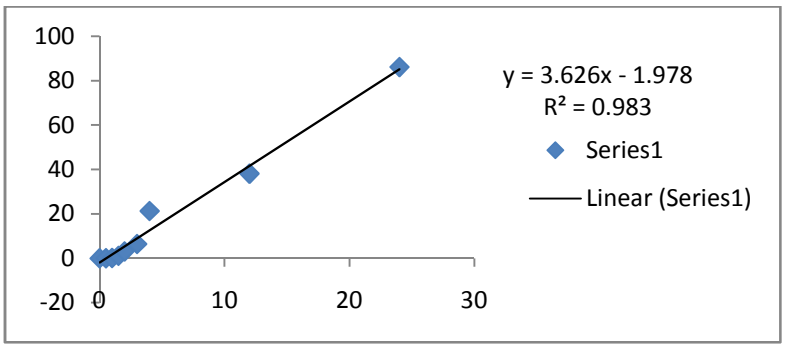

Fig. 13: Graph plot between cumulative % drug release vs time(Zero order kinetics)

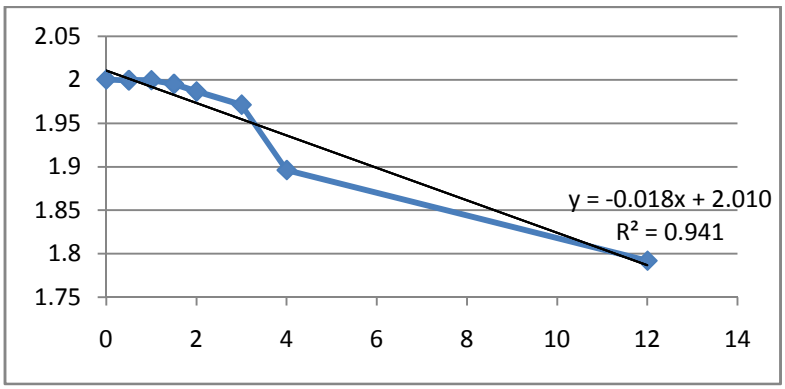

Fig. 14: Graph plot between time vs log% cumulative drug remaining to be released (First order kinetics)

Table 7: *In-vitro* drug release studies of H3 formulation

S. No.	Time(hrs)	Amount (mg)	$t^{1/2}$	%drug release	Cumulative %drug release	% C drug to be released	log% C drug to be released
1.	00	00	00	00	00	100	02
2.	0.5	0.00104	0.707	0.069	0.069	99.931	1.9997
3.	1	0.00118	1	0.078	0.147	99.853	1.9993
4.	1.5	0.01495	1.22	0.984	1.131	98.869	1.9950
5.	2	0.0299	1.41	1.97	3.101	96.899	1.9863
6.	3	0.05047	1.73	3.321	6.422	93.578	1.9711
7.	4	0.2259	2	14.864	21.286	78.714	1.8960
8.	12	0.2552	3.46	16.79	38.076	61.924	1.7918
9.	24	0.7285	4.89	47.934	86.01	13.99	1.1458

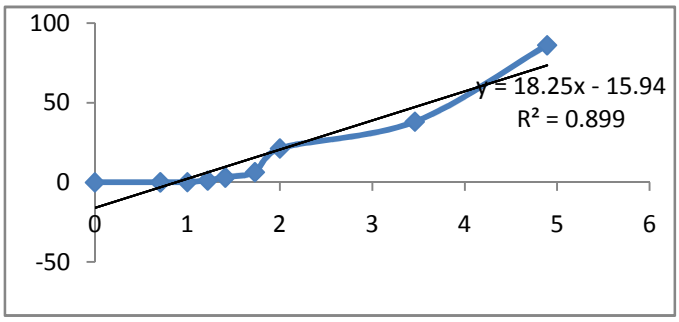

Fig. 15: Graph plot between cumulative % drug release vs $t^{1/2}$(Higuchi model kinetics)

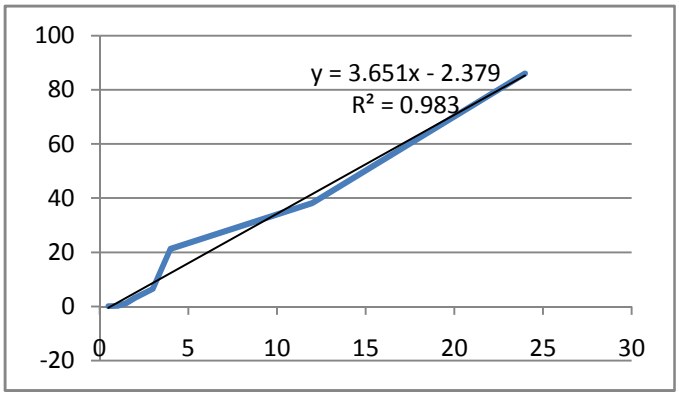

Fig. 16: Graph plot between cumulative % drug release vs time(Zero order kinetics)

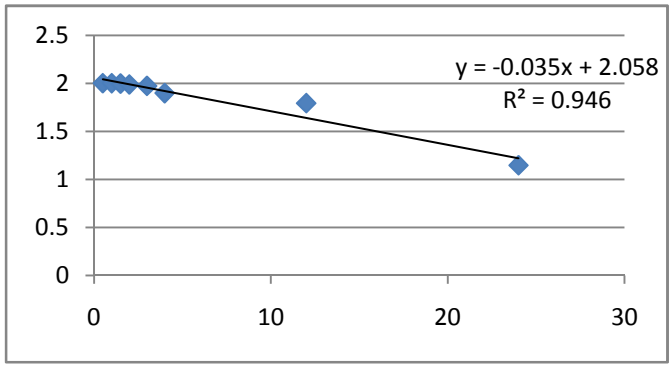

Fig. 17: Graph plot between time vs log% cumulative drug remaining to be released (First order kinetics)

Table 8: Pharmacokinetic release of formulations

S. No.	Formulations	Models	Equation	R^2
1.	H1	Zero order	y = 3.6261x - 1.9789	0.9831*
2.	H1	First order	y = -0.0186x + 2.010	0.9412
3.	H1	Higuchi	y = 18.259x - 15.947	0.8991
4.	H2	Zero order	y = 3.6261x - 1.9789	0.9831*
5.	H2	First order	y = -0.0186x +2.0106	0.9412
6.	H2	Higuchi	y = 18.259x - 15.947	0.8991
7.	H3	Zero order	y = 3.6516x - 2.3796	0.983*
8.	H3	First order	y=-0.035x+2.058	0.9467
9.	H3	Higuchi	y = 18.259x - 15.947	0.8991

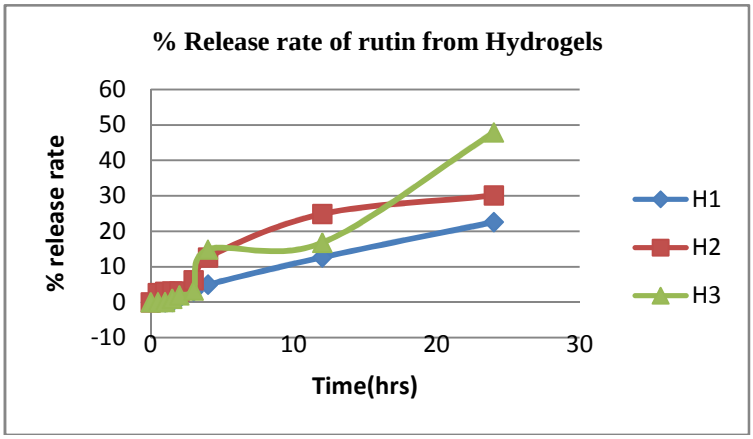

Fig. 18: % release rate of rutin from hydrogels

CONCLUSION

The topical application of Rutin had been suggested in many articles. The present study confirms that the hydrogel can improve the therapeutic efficacy of poorly water soluble drugs like rutin. Hydrogel can sustain the release for 24 hours. The slow release of the rutin revealed that drug remains localized for a longer period of time, thus enabling drug targeting to the skin and feasibility of using a dermatological formulation to improve skin wound healing, inflammation and prevent microbial infection.

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