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Original Research Paper

NOVEL FORMULATION STRATEGY TO ENHANCE SOLUBILITY OF QUERCETIN

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ABSTRACT

The aim of present study to enhance the solubility of quercetin, a poorly water soluble drug, quercetin containing blends (keeping total concentration 40% w/v, constant) was fabricated by mixed-solvency approach. In this technique, blends of solubilizers (sodium acetate, sodium citrate, urea as hydrotropic agent, propylene glycol, glycerin, PEG 200, PEG 400, PEG 600 as co solvents, PEG 4000, PEG 6000 as water soluble solvents etc.) have been employed to increase the solubility. The significant enhancement in solubility of drug in mixed solvents was observed in A4 blends which contain 10% sodium citrate, 5% sodium acetate and 25% S co-solvents (25% S co-solvents contains PG, glycerin, PEG 200, PEG 400, PEG 600, PEG 4000, PEG 6000). After improvement of solubility of quercetin in selected blends that incorporated into topical dosage form (prepared gel) by utilizing Carbopol ETD 2020 as gelling agent. The prepared blends and gel were evaluated for pH, surface tension, specific gravity and viscosity and *in–vitro* diffusion study, skin irritation studies, spreadability respectively. The characterization of pure quercetin, blend, and gel was performed by differential scanning calorimetry (DSC); X-ray diffraction (XRD) etc. From experimental work it was found that the prepared formulation is safe, effective, non-irritant, non-toxic and stable with good spreadability. The results showed that mixed solvency has valuable and unique strategy to ameliorating the solubility of lipophilic herbal anticancer component, quercetin.

Keywords: Mixed solvency, Quercetin, Hydrotropes, Co-solvents, Carbopol ETD 2020, Permeation rate.

INTRODUCTION

About of 90% new discovered compounds screening out from pharmaceutical drug delivery pipeline are reported to poorly soluble in water (Reintjes, 2011). This causes various problems for the industry and for active pharmaceutical ingredient cannot reach to market even those molecules having high therapeutic value (Sharma, 2009; Reintjs, 2011). Solubility is one of the key physiochemical parameter of new chemical entities that needs to be addressed very early in drug discovery and drug candidate selection process (Sikarra *et al*., 2012; Stegmanna, 2007). Different solubilization technologies has been developed to resolve this issues by intensifying the solubility of such drug candidate are become most important to the pharmaceutical field by providing the multiple pathways to prepare effective and marketable from active molecule (Reintjes, 2011; Bajaj, 2011). In recent years, much attention has turned to mixed solvency with aim of increasing improving solubility and bioavailability of poorly water soluble drug (Maheshwari, 2006). This new term generally invented by Neubergs to describe the increase in solubility of solute by addition of fairly high concentration of alkali metal salts of various organic acids (Kapadiya *et al*., 2011; Sikarra,

2012). However the term has been used in literature to designate non- micelle forming substances, liquid or solid, organic or inorganic capable of solubilizing insoluble compounds (Maheshwari, 2008; Jain, 2010). Maheshwari have been stated that synergistic enhancement in solubility due to mixed solvency technique and this technique basically has been used for the analysis of poorly soluble drug, Rifampicin, spectrophotometrically (Maheshwari, 2012). Their research suggested that how mixed solvency approach applies efficiently in titrimetrically or spectrophotometrically for estimation of large poorly water- soluble drugs without using organic solvents (Maheshwari, 2006; Maheshwari, 2005). Mixed solvency process involves co-operative intermolecular interaction with several balancing molecular forces rather than either specific complexation event or process dominated by a medium effect, such as co-solvency or salting in (Ali, 2012; Mahashweri, 2007). This mixed solvency technique is based on the principle that instead of using one solubilizers in large concentration for desired level of a solubility, several solubilizers like hydrotrpoes (sodium citrate, sodium acetate, urea), co-solvents (propylene glycol, PEG200, 400,600) and water soluble solids (PEG 4000, PEG 6000, soluplus) in varying concentration may be used that may show additive or synergistic enhancement in solubility (Khan, 2013; Maheshwari, 2010). Utilization of this technique in the formulation of dosage forms made of water insoluble drugs can also reduce the concentration of individual hydrotropic agents, in order to minimize the side effects (in place of using a large concentration of one hydrotrope, a blend of several hydrotropes can be used in much smaller concentrations, diminishing their individual toxicities) (Maheshwari, 2010; Jain, 1997; Agrawal, 1990; Maheshwari, 2005).

Quercetin as selected drug belongs to large group of naturally occurring flavonoids having some healthy benefit properties, which are widely observed in terms of chemical as well as biological activity (Bokava, 2012). The antioxidant, antitumor and antibacterial activity of flavonoids is the main interested area of many researchers in pharmaceutical and medicinal chemistry (Naidu, 2012). However, quercetin is extremely lipophilic in nature, so there is need to enhance the solubility of Quercetin (Kakran, 2012). The main purpose of this present work was to expand the application of mixed solvency technique to influence the solubility of Quercetin. In this present investigation, we have objective that design and develop new suitable formulation with increasing solubility and bioavailability. Quercetin containing topical preparation has ability to inhabit oxidative stress and inflammation which is induced due to UVB exposure. Anticancer activity of quercetin is not preferable clinically due to low absorption when administered orally. To achieve targeted therapeutic level of quercetin in systemic circulation, high dose is required which is practically not beneficial (Sahu, 2013). So that we prepared topical preparation of drug to avoid first pass metabolism and thereby improving the permeation rate of formulation.

MATERIALS AND METHODS

Materials

Quercetin (3, 3', 4'5 and 7pentahydroxyflavone) (Baghal, 2012) as model drug was purchased from Research Laboratories Ltd., Islampur, India. Propylene glycol and tri-sodium citrate dihydrtate were obtained from Loba Chemie, Mumbai, India. Sodium citrates, sodium acetate and urea, glycerin, PEG200, PEG 400, PEG 600, PEG 4000, PEG 6000 were obtained from Chime, Mumbai, India. Carbopol ETD 2020 was obtained from Lubrizol, Mumbai. All the chemicals and solvents used were of analytical /HPLC grade. Membrane filter (0.22µm) (Sartorius, Germany), aluminum seal, glass vials (5 ml) and rubber plugs (Modern Laboratories Nasik, India) were also employed in this study. A UV visible spectrophotometer (Model -UV 1600S) Shimadzu was used for quantitative analysis.

Preparation of Standard Stock Solution and Calibration Curve

Quercetin (10 mg) was accurately weighed and transferred to 100 ml volumetric flask. To this 90 ml of distilled water was added. The flask was shaken to dissolve the drug and volume was made

up to the mark with distilled water. The stock solution was further diluted with distilled water to obtain various dilutions containing between 0-20ug/ml. Absorbance was noted at 370 nm against regent blanks to get the calibration curve.

Preliminary Solubility Study Determination

The classic saturation shake flask method was employed for determination of equilibrium solubility at 37± 2 ^{0}C. Solubility of quercetin was determined by taking an excess amount of quercetin was added to 100mL of conical flask which contain 10ml of each solvent such as buffers of pH (1.2-7.4), solution of hydrotropic agent, and different concentration of solubilizers (Table 1,2 and 3). To diminish photochemical degradation flasks were covered with aluminum foil. The flasks were shaken mechanically for 12 hr at 37± 2 ^{0}C in orbital shaker (Khera Instrument Pvt. Mumbai, India). The solution were kept to equilibrate for next 24 hrs and then added to test tubes after that mixed properly in cyclone mixer (CM 101 cyclone mixer, Remi Instrument limited, Mumbai) and then centrifuged for 10 min at 1000 rpm (Remi Instruments Limited, Mumbai India). The supernatant solutions of each flask were filtered through what man filter paper no.41. An aliquot of each flask was adequately diluted with distilled water and that appropriate dilution analyzed by spectrophotometric method using a double beam UV-visible spectrophotometer (model-UV 1600 S Shimadzu) at 370 nm.

Enhancement ratio was determined by following formula: (Maheshwari, 2011)

$$\text{Enhacement ratio} = \text{Solubility of drug in} \frac{\text{solubilizers}}{\text{Solubility of drug in distilled water}}$$

Solubility Study Determination of Blends

To avoid toxicity and irritation, the higher concentration have been divided into smaller concentration as 15% and 25% and then prepared blends used for solubility determination of drug.

Characteristics and Evaluation of Blends

Various characteristics of solution such as pH, viscosity, specific gravity, surface tension were performed by using digital pH meter, Ostwald's viscometer, specific gravity bottle, Staglanometer respectively.

Drug Excipients Compatibility Study

Fourier Transform Infrared (FTIR) Study

IR spectra of the pure drug, blends, carbopol ETD 2020 were recorded by Eudragit film method by using FTIR spectrophotometer (FTIR-8400S Shimadzu). A background correction was done by using eudragit film and then spectrum of pure quercetin and blends were measured over the range 700-40000cm^{-1} with an individual spectrum average of 20 scan.

Differential Scanning Calorimetric (DSC) Study

Differential scanning calorimetric (DSC) measurement was performed by a **(**DSC- 60, Shimadzu**)** thermal analyzer. The samples of about 5mg were hermetically placed in aluminum sealed pans and scanned at heating rate of 5^{0}C/min over a temperature range of 30- 360^{0}C by using nitrogen gas as effluent gas. The thermal properties of pure quercetin, quercetin containing blend and gel were characterized.

X-Ray Diffraction Analysis

X-ray diffraction pattern of pure quercetin, quercetin containing blends was analyzed by using the Rigaka miniflex, Japan X-ray diffractometer with Cu kα radiation. All pattern scanned over range of 5-60^0 2θ/s with scanning rate at 10^0/min by applying voltage 30 kV and current 15 mA to observe the crystallinity of sample.

Formulation of Gel

The formulation and composition of quercetin gel are shown in Table 1.Firstely; slowly carobopol ETD 2020 added in the propylene glycol/water solution. A specific quantity of quercetin was dissolved in A4 blends and then carefully added to above solution with continuous stirring until uniformly dispersed. Then distilled water was added to this respective solution to adjust final weight. Final pH of prepared gel was adjusted by addition of triethanolamine.

Texture Profile Analysis (TPA)

Texture profile analysis was carried out by using a CT3 texture analyzer. TPA is method to determine mechanical properties of gel in which cylindrical analytical probe (35mm diameter) was inserted into sample (10gm) at particular rate (1mm/s) at defined depth (10mm). At least three samples were

performed at temperature 25^0C and 35^0C. From the resulting force-time graph, the hardness, compressibility and the adhesiveness were studied (Pande, 2013).

Spread Ability Test

Spreadability test was carried out by using CT3 Texture Analyzer in compression mode. A cone analytical probe (60^0) was inserted into samples at specific rate (1mm/s) and at specific depth (10mm). When apply a force of 10gm has been established, the probe move towards to penetrate into sample at test speed of 2mm/s to a depth 25mm. The probe removed from the sample at the post test, when specific penetration has been reached. The maximum force or peak is taken as measurement of firmness. The area which covered under the positive curve indicates the energy necessary to deform the sample at particular distance (hardness, work done). In general, the hardness work done and firmness is inversely proportional to the spreadability.

In-Vitro Drug Diffusion Study

Franz –type diffusion cell with diameter 1.5 cm with diffusion area 1.76cm^2 and receptor volume (5ml) and cellophane membrane as semipermeable membrane were employed to perform in- vitro drug diffusion study. The donor compartment was placed on the receptor compartment and temperature was maintained at 37± 0.5^0C. The selected receptor fluid (pH 6.8 phosphate buffers) was stirred continuously on magnetic stirrer at 300rpm. Prepared formulation (1%) was kept on donor compartment. Permeation study was performed upto 7hrs after application. Samples were taken out from the receiver compartment at specific time interval (60, 120, 180, 240, 300, and 360 min) and volume of media was maintained by replacing the equal volume of fresh receptor media. The amount of quercetin in the each samples were analyzed by UV visible spectrophotometer.

Drug Content

Drug content was determined by dissolving 1gm formulation in phosphate buffer pH 6.8 by using magnetic stirrer for 3 hrs. Then resultant mixture was transferred into 100ml volumetric flask and diluted suitably with phosphate buffer to adjust the final volume. The absorbance was recorded by UV visible spectrophotometer at 370nm (Mekkawy, 2013).

Skin Irritation Test

Skin irritation test was performed on 3 experimental rabbits to observe the irritancy of quercetin gel. Before application of formulation on rabbits were shaved carefully. Formulation was applied on the free hair less rabbits with uniform spreading. The skin surface can be observed for any change such as redness, inflammation, irritation after 24, 48 and 72hrs on formulation application. The numbers of scores were recorded depending upon erythema.

Stability Study

The prepared gel was stored at 4 ± 2^0C, 30 ± 2^0C/ 70 ± 5 relative humidity (RH), 40± 2^0C/70 ± 5 (RH), the conditions maintain according to ICH guideline. At Specific time interval (1, 2, 3 month) the sample collected from particular formulation and evaluated for physical, chemical stability (Vicentini, 2011).

RESULT AND DISCUSSION

Intrinsic Solubility Study

The solubility of quercetin in distilled water was found to be 0.1648mg/ml, which is indicating that the present drug having very poor solubility.

pH Dependent Study

Quercetin solubility was determined in various buffers of pH (1.2-7.4). The solubility of quercetin was increased with an increase in pH. The result showed that quercetin more soluble in alkaline medium than acidic medium. The effect of pH on solubility of quercetin is shown in figure 1, table 2.

Solubility Study in Various Solubilizers

The improvements in solubility of quercetin in all solution containing different solubilizers are shown in (Figure 2, Table 3&4). The greatest increase in solubility was observed in 40% w/v sodium citrate and sodium acetate and least in case of 40%w/v PEG 200 solution. Among those solubilizers, the hydrotropic agents are freely soluble organic compound formed stacky type of aggregation at sufficient concentration which

considerably responsible for enhancing the aqueous solubility of quercetin (Maheshwari, 2009).

Solubility Study in Blends

Figure 3 and Table 5 illustrates the advantages of making blends of solubilizers. More solubility enhancement was observed in A4 blend as compared with other blends. These result demonstrated that the principle of mixed solvency concept that water soluble substances whether that are hydrotrope, co-solvents and water soluble solids can combined randomly to give desired solubility for water insoluble drugs. But if we increase the concentration of solubilizers it not only increases the solubility of quercetin but also toxic effect of individual solubilizers. Therefore, in formulation of liquid dosage form blends of solubilizers can be employed in safe level concentration of individual's solubilizers to give concentrated solution as well as reducing the toxicity of solubilizers (Maheshwari, 2012)

Characterization and Evaluation of Blends

In the present study, there was no any more changes was observed in all blends. This study was performed to study the effect of co-solvents on surface tension of each blend. The results indicated that the increase or decrease in concentration causes some minor changes in specific gravity and surface tension. The viscosity of all solution gradually increased with increasing the concentration. The characterization of blends is shown in table 6.

Compatibility Study

FT-IR Spectrophotometer

FT- IR study is useful tool to check the compatibility of drug in the mixed blends. The spectra obtained from IR studies at wavelength from 700 to 4000cm^{-1} showed slight shifting in peaks in case of blends. The result of FTIR spectral analysis demonstrated all solubilizers shows somewhat less peak intensity as compared to drug. Our data indicates that the drug and prepared blends, formulation is compatible to each other. The FT-IR spectra of drug, drug with blends and gel is represented in figure 4.

DSC Study

DSC studies were performed to observe the thermal properties and intermolecular reaction between quercetin, quercetin containing blends and prepared gel. In general, the physical state of drug mainly effects on the dissolution rate and bioavailability, so there is needed to study the physicochemical characteristics of drug with preparation. Pure quercetin shows sharp endothermic peak at 318 ^{0}C which corresponds to its melting point. The presence of sharp endothermic peak primarily indicates the crystalline nature of drug. The observed peak of quercetin with blends was slightly getting shifted and shows broadened peak at 357 ^{0}C with less intensity. Apart from that the heat of fusion of the crude quercetin powder, blends and formulation was found to be -11.5 KJ/S, -4.5 KJ/S, -3.9 KJ/S respectively. This data mightily indicate that the drug get totally solubilize in blends and dissolves at faster rate due to decreasing crystal particle within the blends. DSC thermogram of pure drug, blends and gel are depicted in figure 5.

X-Ray Diffraction Analysis

X-ray diffraction study was carried out to check the crystalline nature of quercetin samples. Figure5 shows the x ray diffraction pattern of the quercetin powder and the quercetin mixture with solubilizers. The X-ray pattern of quercetin showed the presence of distinct peaks 5.68^{o}, 10.42^{o}, 11.64^{o}, 15.28^{o}, 17.38^{o}, 23.25^{o}, 27.71^{o}, 31.56^{o}, 38.62^{o}, 42.14^{o}, 52.47^{o}, which suggest that the drug was having crystalline nature. The quercetin prepared blends showed peaks at 5.12^{o}, 10.06^{o}, 14.98^{o}, 17.10^{o}, 23.01^{o}, and 27.52^{o}. The intensity of peak of drug containing blends is get reduced due to drug slightly change from crystalline to amorphous. The amorphous forms always more acceptable due to that possess higher energy and higher surface area which gives higher solubility.

Texture Profile Analysis (TPA)

In this method, cylindrical analytical probe is 2 times penetrate into respective sample at specific time at definite depth, permeating a predefined necessary period between the end of first and the starting of second compression cycle shows in figure 6. The peak or maximum force is gives as

recording of firmness, higher the value the thicker is the consistency of sample. The negative region of plot created on probe return is the result of the weight of the sample is lifted firstly on the upper part of disc on return, and hence gives as demonstration of consistency. The maximum negative force is representation of stickiness/cohesiveness of sample. If negative values are more than more stuffing of the samples occurs.

Spreadability Test

The spreadability of formulation is basically related to viscosity of sample. If the viscosity is more than time required for spreading will be longer. Upon application of gel on skin area it is expected that will spread easily on that particular area. The spreadability of gel is shown in figure 7.

In-Vitro diffusion Study

The amount of drug diffused through the skin was drastically increases as time is increased. In the presence of blend the drug release rate greatly enhanced compared with without blends formulation. The permeated amount of quercetin in 7 hrs through the skin was 62% as compared with without blends preparation 44% Therefore, use of mixed-solvency is pivotal approach to the disturb barrier function of skin and enhance the permeation rate of drug through the skin. The In-vitro diffusion of drug is shown in figure.

Drug content

The percentage of drug content of respective formulation was determined from calibration curve of quercetin in water. The drug content of the formulation was observed as 98 %.

Skin Irritation Test

The irritation potential of quercetin gel was observed after application of formulation which not showing any irritation and redness, inflammation mark of formation. Irritation score of formulation was zero, which illustrated its safety; efficacy and acceptability for topical administration. The skin irritation result is depicted in table 7.

Stability Study

The developed formulations subjected at particular storage condition were found to be no any change has been observed in color, pH and dug content. But the formulation shows slight degradation in case of room temperature. So our study recommends that the prepared formulation should be stored at 4^0C.

CONCLUSION

The main finding that emerges out from the present study is the demonstration that mixed solvency approach exhibits significant enhancement effect on solubility of quercetin in case of A4 blends. The formulated gel had not only good physical appearance and spreadability but also safe, effective, non- chromogenic. The prepared gel formulation also shows increasing permeation rate with increase time. But it needs special storage condition for maintaining the stability. The present study indicated that the use of mixed solvency solubilization phenomenon is an effective strategy in improvement of solubility of hydrophobic drugs and optimization of this technique will prove boon for pharmaceutical industries to launch the new formulation of lipophilic drugs in the market. This approach has unique ability to solubilize non –polar compounds in polar media. Therefore, this technique can be successfully utilized as an alternative method for enhancing the solubility of poorly water soluble drugs.

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Graphical Abstract

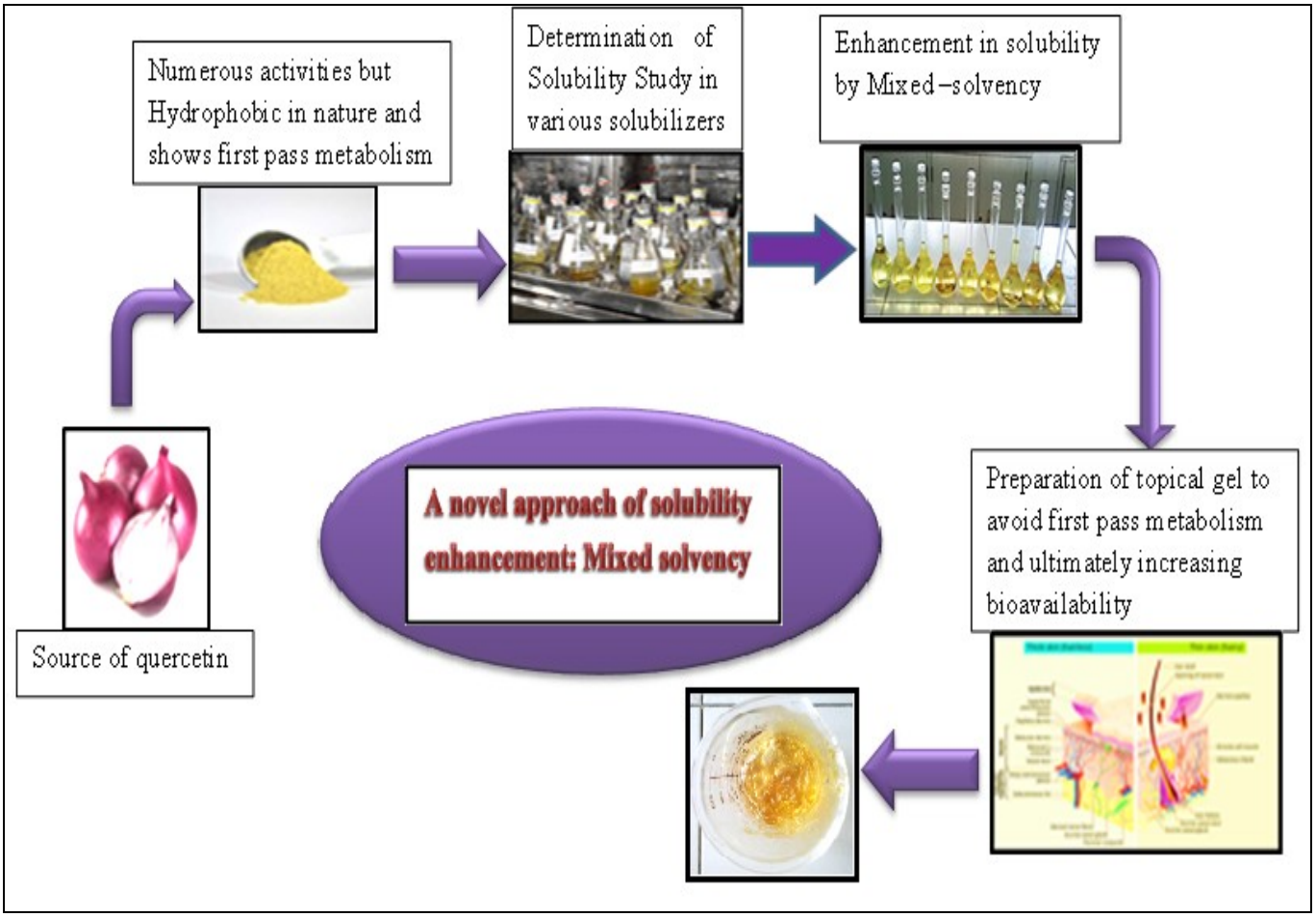


Table 1: Composition of gel

Composition	Quantity (%w/v)
Quercetin	0.5
Blends	40
Carobopol ETD 2020	1
Triethanolamine	q.s
Distilled water	q.s.

Table 2: pH dependent solubility of quercetin at 37± 2^0C

Buffer solutions	Solubility(mg/ml)[a]
Distilled water	0.1648± 0.00141
Hydrochloric acid buffer pH 1.2	0.1718±0.0018
Hydrochloric acid buffer pH 2.2	0.1835 ±0.00518
Acid phthalate buffer pH 4	0.3748± 0.00361
Phosphate buffer pH 6.8	0.6611 ± 0.0036
Phosphate buffer pH 7.4	0.9740± 0.004406

All values are expressed as means ± SD, n=3

Table 3: Solubility enhancement ratio of querectin in different solubilizers at 37±2^{0}C

Solvents	Solubility(mg/ml)*	Solubility enhancement ratio
40%w/v Sodium citrate	38.24 ± 0.001	232.08
40%w/v Sodium acetate	37.66 ± 0.00070	228.53
40%w/v Urea	14.223 ±0.0030	86.18
40% w/v Propylene glycol	5.867 ± 0.0014	35.60
40% w/v Glycerin	5.923 ± 0.0010	35.94
40%w/v PEG 200	2.362 ± 0.00182	14.35
40%w/VPEG 400	2.503 ± 0.0012	15.18
40%w/v PEG 600	3.5144 ± 0.0026	21.32
40%w/v PEG 4000	2.826 ± 0.0045	17.14
40% /V PEG 6000	5.57 ± 0.00083	33.82

* All values are expressed as means ± SD, *n*=3

Table 4: Solubility enhancement ratio of querectin in different solubilizers at 37± 2^{0}C

Solvents	Solubility(mg/ml)*	Solubility enhancement ratio
20% w/v Sodium citrate	19.12 ± 0.0173	116.04
20%w/v Sodium acetate	18.83 ± 0.00793	114.25
20%w/v urea	13.70 ± 0.0036	83.15
20% w/v Propylene glycol	2.683 ± 0.002642	16.28
20%w/v Glycerin	2.828 ± 0.0083	35.60
20%w/v PEG 200	0.658 ± 0.0033	3.99
20%w/v PEG 400	1.558 ± 0.00141	9.58
20%w/v PEG 600	2.226 ± 0.0020	13.50
20% w/v PEG 4000	1.845 ± 0.0058	11.19
20%w/v PEG 6000	3.226 ± 0.0078	19.58

*All values are expressed as means ± SD, *n*=3

Table 5: Solubility enhancement ratio of querectin in different blends

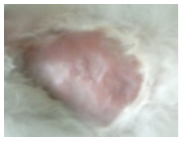
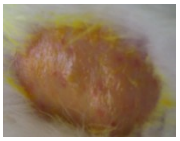
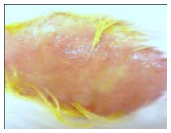
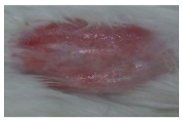
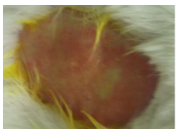
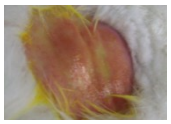
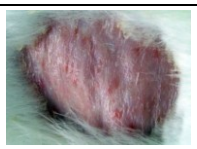
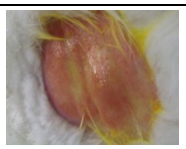
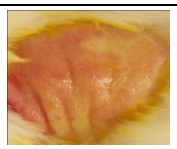
Blends	Solvents code	Solubility (mg/ml)	Solubility enhancement ratio
A1	15%S.C + 25%S	40.30 ± 0.0898	244.54
A2	15%S.A + 25% S	36.27 ± 0.00380	220.13
A3	15% Urea + 25% S	31.17 ± 0.00212	189.19
A4	10% S.C + 5%S.A + 25%S	62.43 ± 0.00210	378.86
A5	10%S.C + 5% Urea + 25%S	61.41 ± 0.00264	372.63
A6	10% S.A + 5% S.C +25%S	46.41 ± 0.00884	281.64
A7	10% S.A + 5% Urea + 25%S	45.82 ± 0.00316	278.04
A8	10% Urea + 5% S.A+25%S	43.96 ± 0.06031	266.76
A9	10% Urea + 5%S.C +25%S	44.98 ± 0.00353	272.98

[a]All values are expressed as means ± SD, *n*=3

Table 6: Characterization and evaluation of various blends

Blends pH	Specific gravity	Surface tension (dynes/cm)	Viscosity (cps)
A1 7.10	1.051	54.38	6.23
A2 7.15	1.041	53.55	6.16
A3 7.19	1.048	54.18	6.196
A4 7.16	1.035	52.13	6.114
A5 7.12	1.041	53.74	6.190
A6 7.14	1.026	52.05	6.110
A7 7.18	1.020	51.41	6.10
A8 7.24	1.017	51.20	6.06
A9 7.12	1.034	52.48	6.130

Table 7: Skin irritation test with blends and without blend

Time interval	No formulation	Formulation without blends	Formulation with blends
24 hrs			
48hrs			
72hrs			

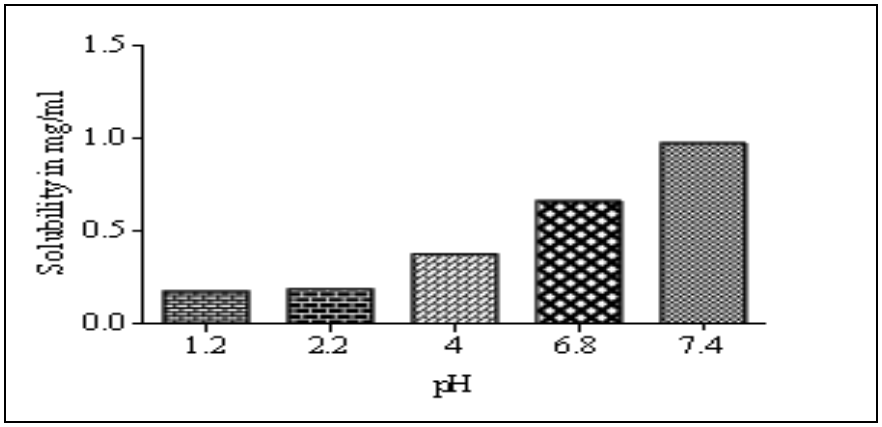


Figure 1: pH dependent solubility of drug

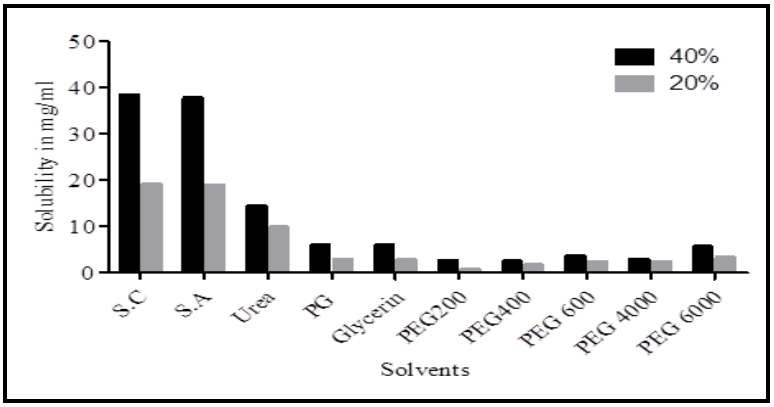


Figure 2: Comparison of solubility of drug in 40% and 20% concentration

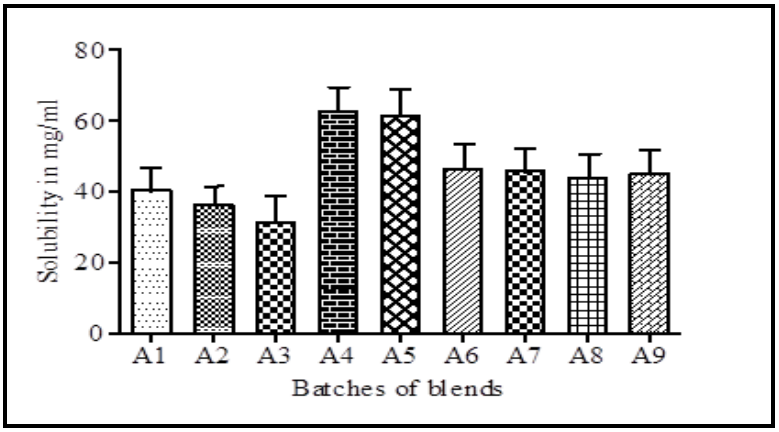


Figure 3: Solubility of drug in various blends

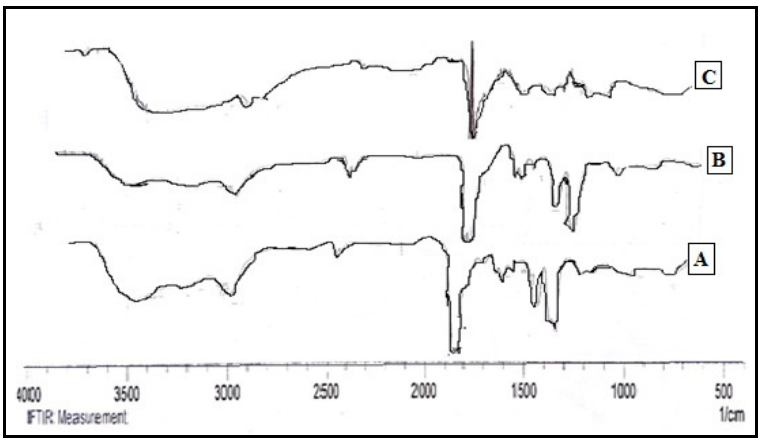


Figure 4: FTIR spectra of (A) Quercetin, (B) Quecretin with blends (C) Quercetin with carbopol ETD 2020

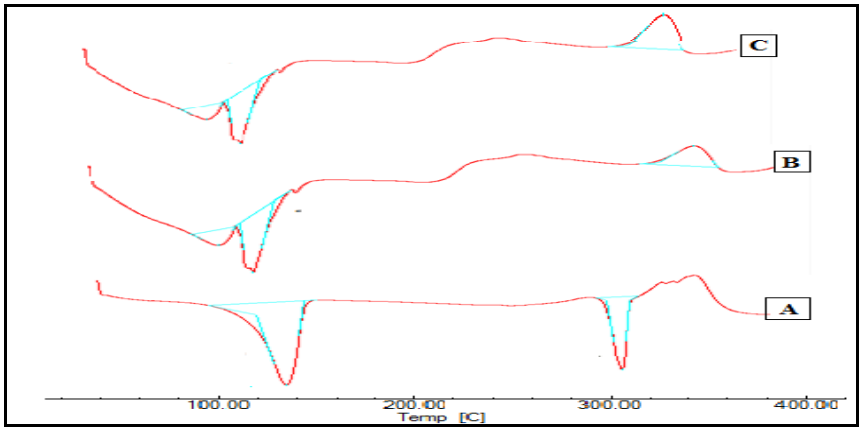


Figure 5: DSC thermogram of (A) quercetin, (B) quercetin with blends, (C) Quercetin with carbopol ETD 2020

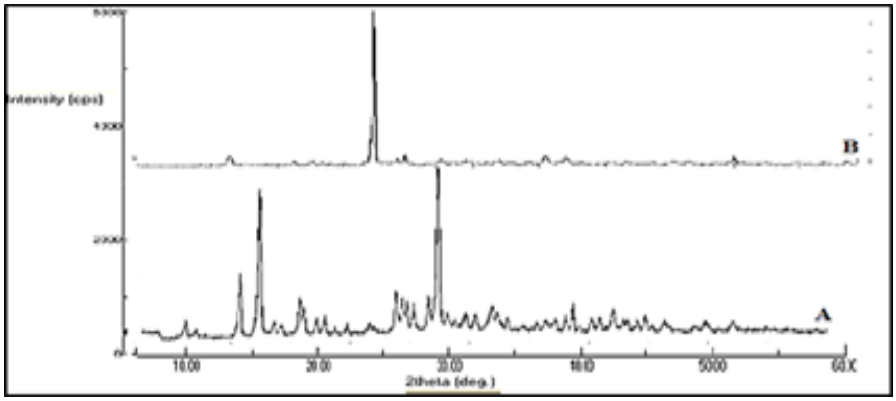


Figure 6: X- ray diffractgrams of (A) Quercetin and (B) Physical mixture (Blends)

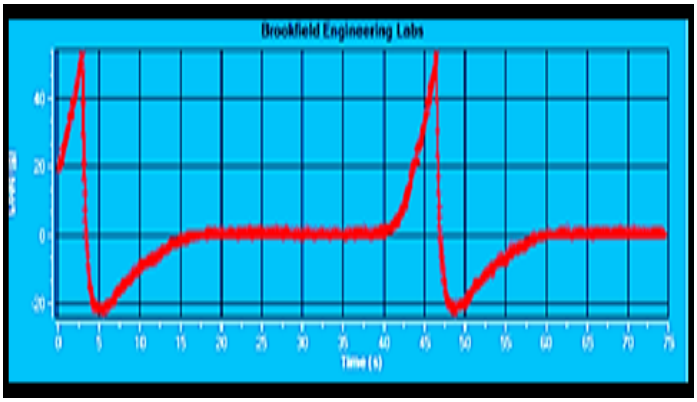


Figure 7: Texture profile analysis of quercetin gel

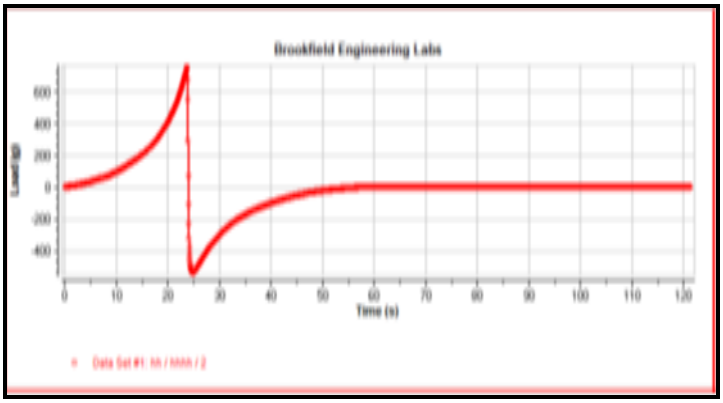


Figure 8: Spreadability pattern of quercetin gel

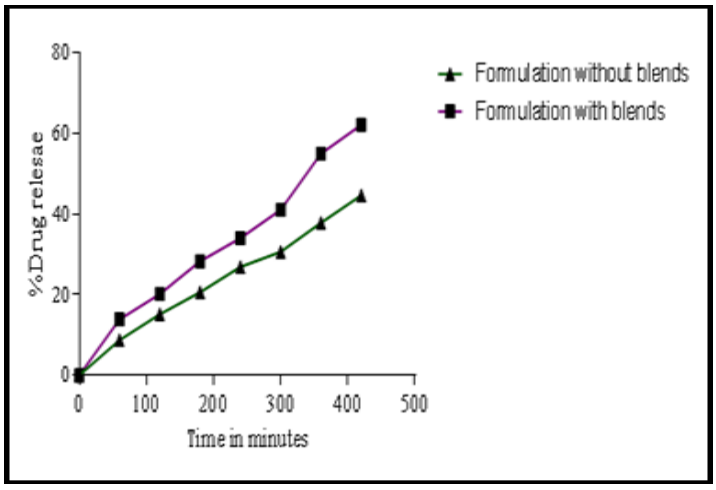


Figure 8: In-vitro diffusion of quercetin

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