SYNERGISTIC ANTIMICROBIAL EMULGEL FORMULATION OF QUERCETIN DIHYDRATE AND ZINC OXIDE: A POTENTIAL APPROACH FOR AZOLE-RESISTANT CANDIDIASIS TREATMENT

Dr .PRABHU R*[1] , VENKATESH BABU M [1] , NAVEENA N [2] , DHILIP S[2]

Abstract

This study investigated the synergistic effects of quercetin dihydrate and zinc oxide in an antimicrobial emulgel formulation. An emulgel, a combination of gel and emulsion, was investigated as an alternative to traditional gel formulations because of their hydrophobic properties. Different gelling agents and quercetin dihydrate and zinc oxide concentrations were used to prepare twelve antimicrobial emulgel formulations (F1-F12). The components did not interact chemically according to FTIR studies. In addition to color, homogeneity, consistency, phase separation, pH, viscosity, and spreadability, the prepared emulgels were evaluated for a number of parameters. Among the formulations tested, Formulation F4 with 1% Carbopol 940 and 5% zinc oxide showed the best results. After 8 hours, the drug permeated 42.2% (quercetin dihydrate). Furthermore, formulation F4 exhibited in vitro antimicrobial activity against Candida albicans, azole-resistant *Candida species, Staphylococcus aureus, and E. coli*. It appears that the developed antimicrobial emulgel, especially formulation F4, is potentially an effective treatment option for azole-resistant candidiasis, potentially improving patient compliance and treatment outcomes.

Keywords: Emulgel, topical drug delivery, quercetin, anti-microbial, anti-bacterial, *C. albicans*

Introduction

Different routes of administrations were used in past years to cure any illness, routes that were used were sublingual, oral, rectal, topical, parenteral, inhalation, etc. This route of administration has many years of history, but new methods and technologies are being investigated and developed for better patient compliance [1]. Drugs are applied topically to impact the application site or to have systemic effects. The topical route of administration is the best option for cutaneous purposes as the skin is the most accessible organ and facilitates the delivery of drugs with better efficacy when compared to the other routes of administration [2,3]. Ointments, creams, lotions, gels, etc., are few examples of topical dosage forms. These have many disadvantages like stickiness, stability problems, and less spreadability plus, it also causes allergic reactions, poor permeability, absorption, and causes irritation [4]. Gels have many advantages, but despite it, they have a major issue in the delivery of hydrophobic drugs [5]. Emulgel are prepared to overcome such gels limitations [6]. There are two types of emulgel; oil in water or water in oil, and these are gelled by the addition of a gelling agent [7]. There are many advantages due to emulgel is considered being used as topical delivery. The usage of transparent gels in cosmetics and medicinal preparations has increased due to all of these variables within the principal category of semisolid preparations. Despite the numerous benefits of gels, one significant drawback is the delivery of hydrophobic medicines. To address this constraint, an emulsion-based technique is being employed to effectively integrate and transport even a hydrophobic medicinal component via gels [8].

Quercetin is an important phytochemical, belonging to the flavonoid group of polyphenols. It possesses a variety of pharmacological activities. It has been shown to inhibit the growth of different Gram-positive and Gram-negative bacteria as well as fungi and viruses. And also, it shown to inhibit the growth of various drug-resistant microorganisms, thereby suggesting its use as a potent anti-microbial agent against drug-resistant strains. Furthermore, certain structural modifications of quercetin have sometimes been shown to enhance its anti-microbial activity compared to that of the parent molecule. Recently, quercetin has also achieved GRAS (Generally Recognized as Safe) status by the United States Food and Drug Organization. Quercetin shows antifungal activity against *C. albicans* by induced apoptosis with increase in intracellular magnesium along with mitochondrial dysfunction. ZnO NPs/MPs has a wide spectrum of anti-microbial activity against microorganisms including *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis,* and the M13 bacteriophage. Mechanisms of anti-microbial actions of ZnO materials has been explained in association with particular interaction based on their unique physicochemical properties of (a)

Zn2+ ion release, (b) adsorption, and (c) ROS generation, and the intracellular responses in microorganisms of (d) energy metabolism inhibition; (e) lipid peroxidation, and cell membrane damage; and (f) DNA replication disruption, and DNA break (Figure 1). Based on the fundamental mechanisms of action, ZnO NPs/MPs has a differential susceptibility against pathogenic microorganisms, affected by their physicochemical characteristics including morphology, particle size, and porosity

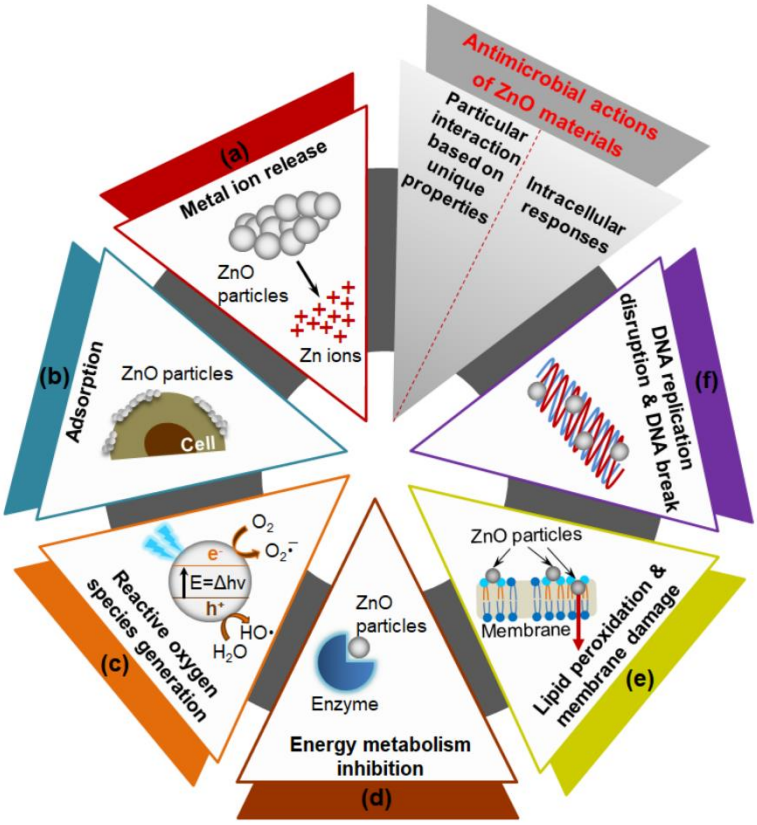


Figure.1 ZnO used in anti-microbial applications

Methodology

Chemical used

Quercetin Dihydrate, Zinc oxide, Carbolpol-934, Carbopol-940, HPMC K4, HPMC K15 received as gift sample from Freedom Biopharma Pvt Ltd, Liquid paraffin, span 20, Tween 20 and Triethanolamine procured from universal Scientific Appliances, Madurai.

Preformulation study

Organoleptic evaluation

By visual examination the Quercetin Dihydrate and Zinc Oxide was tested for its physical characters like colour, odour and appearance.

Solubility study

Quercetin dihydrate: Drug was taken in a test tube and solubility in DMSO, methanol, ethanol, distilled water, and Phosphate buffer pH 7.4 is tested [9].

Zinc oxide: Zinc oxide was taken in a test tube and solubility in various solvents such as DMSO, HCL, distilled water, Phosphate buffer pH 7.4, is tested [10].

UV spectroscopy determination

λmax determination

10 mg quercetin was dissolved in 25 ml absolute alcohol and 10 mg zinc oxide was dissolved in 25 ml DMSO separately. The volume made up to 50 ml with phosphate buffer solution pH 7.4. 5 ml of drug solution was taken into a 100 ml volumetric flask and made up the volume to 100 ml with phosphate buffer solution. From the stock solution, ultraviolet scan was taken between the wave lengths 200-400nm.

Standard calibration curve

Quercetin dihydrate and Zinc oxide in pH 7.4 phosphate buffer

10 mg of Quercetin Dihydrate was weighed accurately and dissolved in 25 ml of absolute alcohol in a volumetric flask and volume was made up to 50 ml with the phosphate buffer solution pH 7.4. 10 mg of Zinc oxide was weighed accurately and dissolved in 25 ml of DMSO in a volumetric flask and volume was made up to 50 ml with the phosphate buffer solution pH 7.4. Then 200 µg/ml stock solutions were prepared for both. 2.5 ml of this solution was diluted to 25 ml with phosphate buffer solution pH 7.4 to obtain a sub-stock solution of 20µg/ml. From this sub stock solution, aliquots of 1, 2, 3, 4, 5 ml were taken into 10 ml volumetric flask and volume was made up to 10 ml with phosphate buffer solution pH 7.4. The absorbance of these solutions was measured at 370 nm (quercetin) and 260 nm (Zinc oxide) against a blank phosphate buffer solution pH 7.4 by Spectrophotometric method using Shimadzu UV- 1800 Spectrophotometer. The calibration curve was plotted between concentration and absorbance.

Compatibility study

The drug-drug interaction studies were carried out by using FTIR Spectroscopic technique. The samples (pure drug quercetin dihydrate and zinc oxide) was dispersed in KBr and compressed into pellets. FTIR spectra of pure drugs and formulation were obtained. The pellets were placed in the light path and the spectrum was recorded in the wavelength region of 4000- 400cm-1[11,12].

Formulation of emulgel

Emulgel formulation was developed by taking into account various gelling agent [Carbopol 934, Carbopol 940, HPMC K4 and HPMC K15] in same concentration [1%] along with different concentration [5-15%] of zinc oxide (for antimicrobial synergistic activity) and same concentration [0.1%] of quercetin dihydrate. Optimization of formulation was done by preparing twelve different formulations. As seen from table no.1; Formulations F1-F3 were prepared by using gelling agent 1% of Carbopol 934 with 5-15% of zinc oxide. Formulations F4-F6 were prepared containing 1% of Carbopol 940 with 5-15% of zinc oxide. Further trials focused on another gelling agent 1% of HPMC K4 [F7-F9] and 1% of HPMC K15 [F10-F12] along with 5-15% of zinc oxide.

Table:1 Formulation of emulgel

Ingredients	Formulation (%w/w)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12

Quercetin Dihydrate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Zinc Oxide	5	10	15	5	10	15	5	10	15	5	10	15
Carbolpol-934	1	1	1	-	-	-	-	-	-	-	-	-
Carbopol-940	-	-	-	1	1	1	-	-	-	-	-	-
HPMC K4	-	-	-	-	-	-	1	1	1	-	-	-
HPMC K15	-	-	-	-	-	-	-	-	-	1	1	1
Span 20ml	1	1	1	1	1	1	1	1	1	1	1	1
Tween 20 ml	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Liquid paraffin (ml)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Triethanolamine (ml)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Evaluation of emulgel

Determination of emulgel physical properties

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, and phase separation [13].

pH evaluation

For pH determination, 1gram of product was taken and dissolve in 10ml of distilled water and pH measured with using digital pH meter [14].

Viscosity determination

Viscosity of gel was carried out by using Brookfield Viscometer at 25^{o}C, with spindle speed at suitable rpm [15].

Spreadability studies:

Spreadability was determined by placing 1 g of each emulgel within an already pre-marked circle of 1 cm diameter on a glass slab. Another Preweighed glass slab was positioned on top and a weight that totalled to about 1 kg was put on the upper glass slab for 5 min. The resulting spread of the emulgel caused an increase in diameter which was measured using a Vernier Caliper [16]

Determination of drug content:

It was done by taking 1 g of emulgel, mix it in a 100 ml of freshly prepared phosphate buffer (pH 7.4). The solution was filtered with a Whatman filter paper to obtain a clear solution and 10ml of the filtrate was diluted to 50ml with the buffer solution. UV spectrophotometer was used to measure the absorbance and quantify the drug content [17].

***In vitro* Drug release study:**

These studies were conducted using a modified Franz diffusion (FD) cell. cellophane membrane was soaked in freshly prepared phosphate buffer (pH of 7.4) for at least 24 hrs before use. One gram of each emulgel formulation was placed and smeared on the surface of the cellophane membrane which was fixed between donor and receptor compartments of the modified FD cell that had a diffusion area of 6.2 cm^2. The receptor compartment was filled with phosphate buffer (pH7.4) which was the dissolution medium. A 10 ml sample was drawn at suitable time intervals and replaced with equal amount of fresh dissolution medium to maintain a constant volume. The aliquots were collected and analysed by UV-Vis spectroscopy and cumulative drug that permeated was calculated as a function of time for 8 hrs [18].

Selection of optimum formulation

The selection of best formulation among twelve prepared formulations [F1-F12] depends upon their comparison of their Physical characteristics and in-vitro drug permeation studies.

***In vitro* anti-fungal study (Azole resistant *Candida albicans* and azole resistant *Candida Species*):**

It was done by Kirby-Bauer disk diffusion susceptibility test method, in this test method the pathogenic organism that is azole resistant *Candida albicans* and azole resistant *Candida Species* was inoculated with Mueller-Hinton agar Medium at 37°C and allowed to set in a petri dish. Ketoconazole was used as standard against azole resistant *C. albicans* and *C. species*. Appropriate volume of formulations was added into petri dish. The plates were incubated at 37°C for 1 days. The diameter of inhibition zone was evaluated.

***In vitro* antibacterial study**:

It was done by Kirby-Bauer disk diffusion susceptibility test method, in this test method the pathogenic organism that is Staphylococcus aureus and *E. Coli* was inoculated with Mueller-Hinton agar Medium at 37 °C and allowed to set in a petri dish. Amikacin was used as standard against Staphylococcus aureus and *E. coli*. Appropriate volume of formulations was added into petri dish. The plates were incubated at 37°C for 1 days. The diameter of inhibition zone was evaluated.

Drug release kinetic profile

The cumulative amount of drug (quercetin dihydrate) released from the selected formulas at sequential time intervals are fitted to zero order, first order kinetics, Higuchi and Korsmeyer–Peppas models to characterize drug release kinetics and propose a mechanism of drug release [19].

Zero order kinetics

It describes the system in which the drug release rate was independent on its concentration i.e. a constant amount is released per unit time.

$$Qt = Qo - Ko\ t$$

Qt= remaining amount of drug

Qo= Total amount of drug

Ko= Zero order release constant

First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent i.e. a constant ratio is released per unit time.

$$logQt = logQo - k1\ t/\ 2.303$$

Q= Drug Release Fraction,

k1= First Order Release Rate Constant

t= Release Time.

Higuchi Model

It describes the fraction of drug release from a matrix was proportional to square root of time.

$$Qt\ /\ Q\infty\ =\ kH\ t1/2$$

Qt and Q∞= Cumulative quantity of drug release at time ‘t’ and infinite time

kH = Higuchi Dissolution Constant.

Korsmeyer- Peppas Model

The Korsmeyer-Peppas model law describes the drug release from the polymeric system in which the release deviates from fickian diffusion, as expressed in following equation.

$$Qt / Q\infty = KKP\ t\ n$$

$$log\ [Qt / Q\infty] = log\ KKP + n\ log\ t$$

Hixson crowel model

Hixson and crowel recognized that the particles regular area is proportional to the cube root of its volume. The equation describes the release form systems where there is a change in surface area and diameter of particles. They derived the equation:

$$\mathrm{Wo1/3 - W1/3 = KHC * t}$$

Results and discussion

Preformulation study

Organoleptic evaluation

Table:2 Organoleptic Characteristics of Quercetin dihydrate and Zinc Oxide

S.No	Characteristics	Observation	
		Quercetin dihydrate	Zinc Oxide
1	Colour	Yellow color	White color
2	Odour	Odourless	Odourless
3	State	Crystalline	Amorphous

Solubility study

Quercetin: The drug sample was freely soluble in DMSO, Methanol and Methanol: PBS pH 7.4 (10: 90), sparingly soluble in ethanol, slightly soluble in water.

Zinc oxide: The drug sample was freely soluble in HCL, DMSO and DMSO: PBS pH 7.4 (10: 90), insoluble in water.

UV-Spectroscopical study

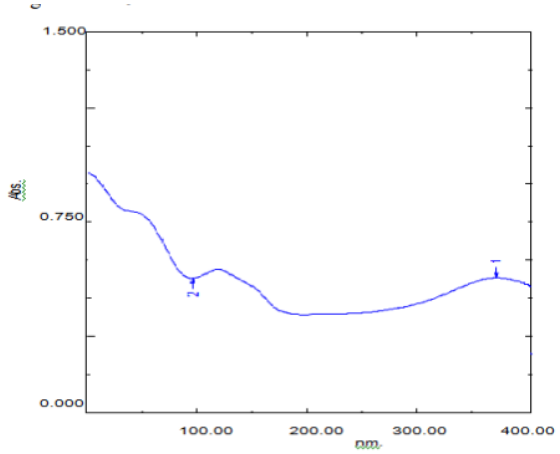


Figure:2 UV spectrum of Quercetin dihydrate

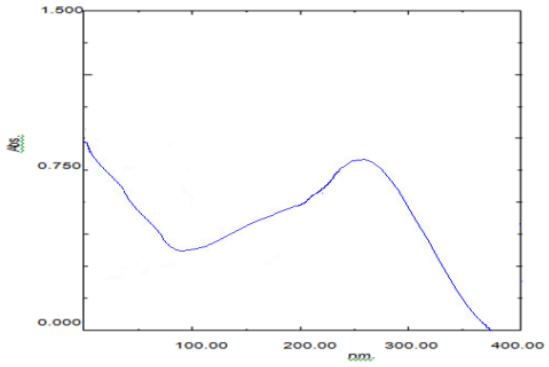


Figure:3 UV spectrum of Zinc oxide

Compatibility profile

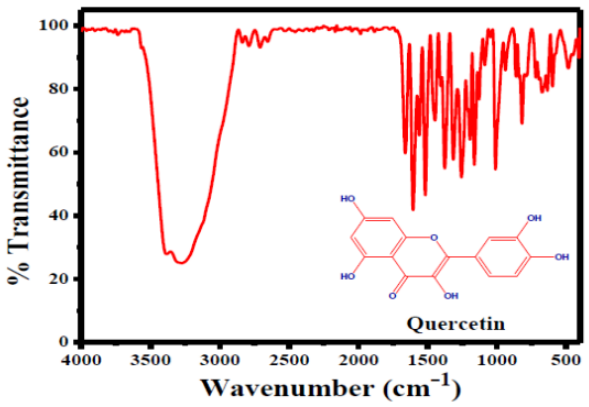


Figure: 4 FTIR Spectrum of Quercetin dihydrate

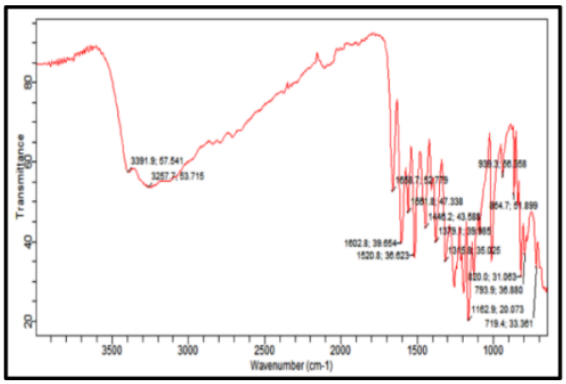


Figure: 4 FTIR Spectrum of Pure Quercetin dihydrate (Reference 20)

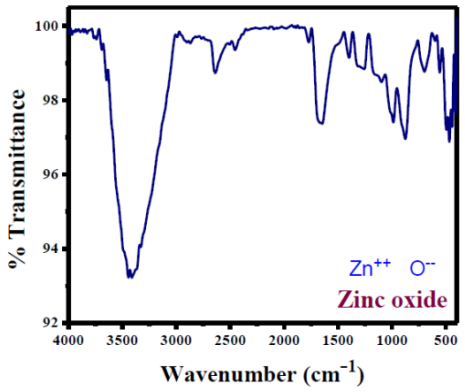


Figure: 6 FTIR Spectrum of Zinc oxide

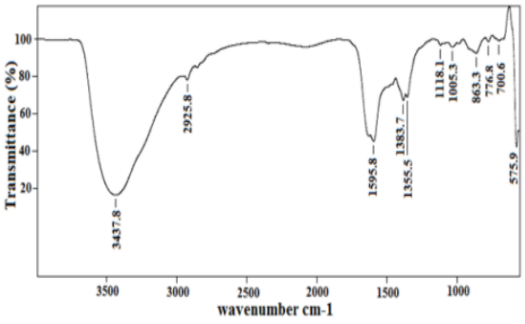


Figure: 7 FTIR Spectrum of Pure Zinc oxide (Reference21)

Calibration curve of Quercetin and Zinc oxide

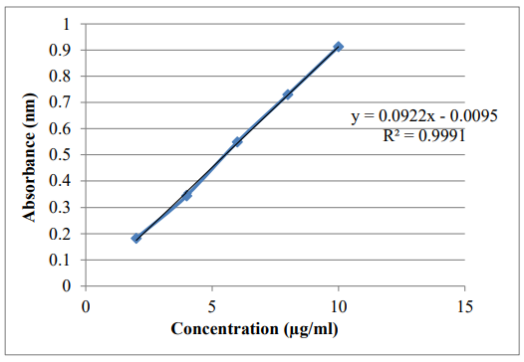


Figure: 8 Quercetin calibration curve

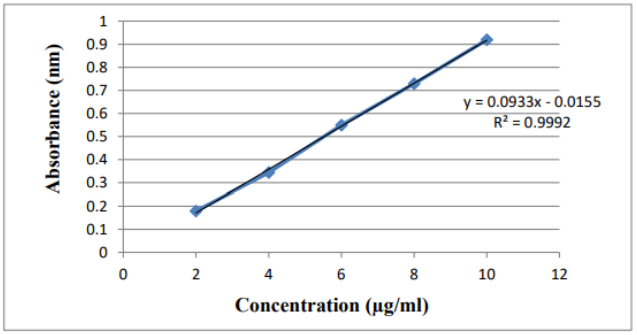


Figure: 9 Zinc oxide calibration curve

FTIR spectrum of Quercetin dihydrate and zinc oxide (Physical mixture)

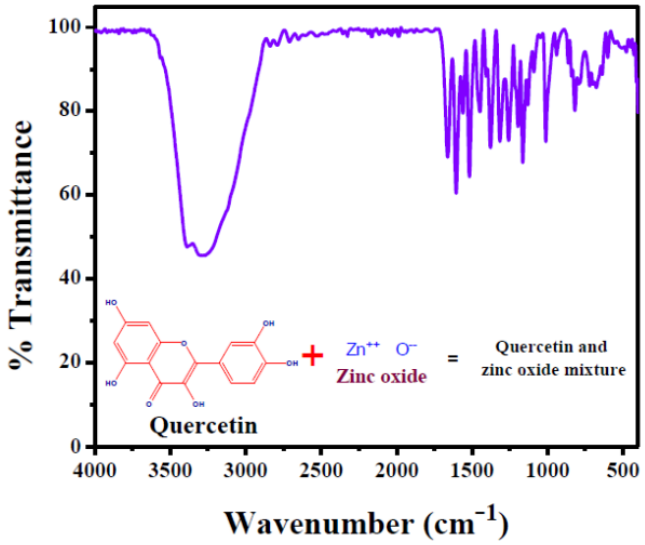


Figure: 10 FTIR spectrum of Quercetin dihydrate and zinc oxide (Physical mixture)

Evaluation of formulated emulgel

Physical Properties

The prepared quercetin and zinc oxide emulgel were inspected visually for their colour, homogeneity, Consistency and phase separation shown in table 3.

Table: 3 Physical properties of formulation (F1-F12)

Formulation	Color	Homogeneity	Consistency	Phase separation
F1	Yellow	Good	Good	None
F2	Yellow	Good	Good	None
F3	Yellow	Good	Good	None
F4	**Yellow**	**Excellent**	**Excellent**	**None**
F5	Yellow	Good	Excellent	None
F6	Yellow	Good	Good	None
F7	Yellow	Satisfactory	Satisfactory	None
F8	Yellow	Satisfactory	Satisfactory	None
F9	Yellow	Satisfactory	Satisfactory	None
F10	Yellow	Satisfactory	Satisfactory	None
F11	Yellow	Satisfactory	Satisfactory	None
F12	Yellow	Satisfactory	Satisfactory	None

pH Evaluation

The pH of all developed formulations is summarized in table 4

Table: 4 pH evaluation

Formulation code	pH
F1	5.6
F2	5.7
F3	6.1
F4	5.8
F5	5.8
F6	6.0
F7	5.7
F8	5.8
F9	6.1
F10	5.5
F11	5.7
F12	5.9

Viscosity determination

The viscosity of all developed formulations is summarized in the figure 11.

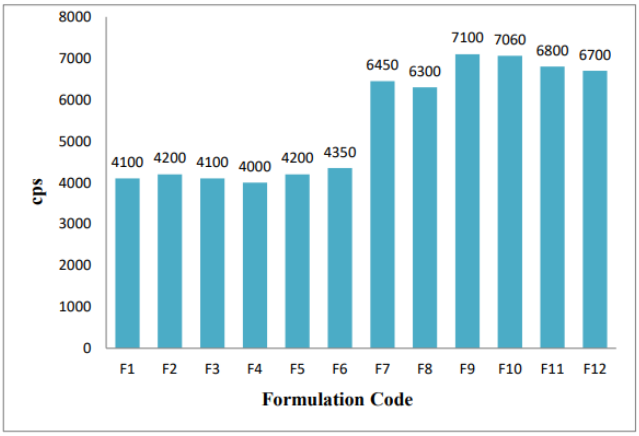


Figure: 11 Viscosity evaluation (F1-F12)

Spreadability study

The spreadability of all developed formulations are summarized in the figure 12

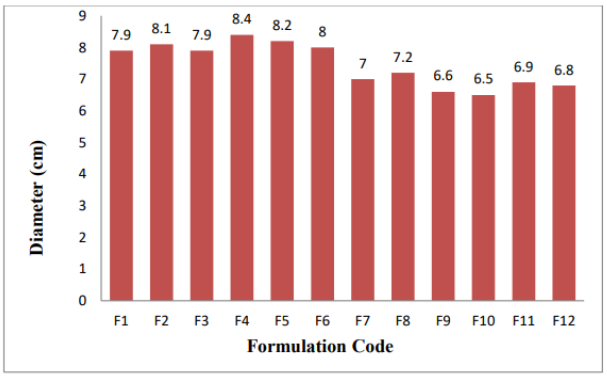


Figure: 12 Spreadability profile (F1-F12)

Drug content determination (%):

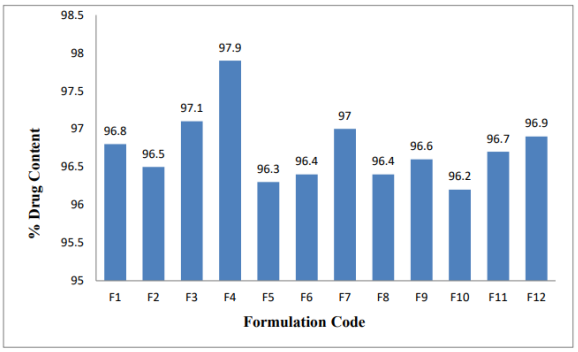


Figure: 13 % drug content (F1-F12)

In vitro drug permeation study

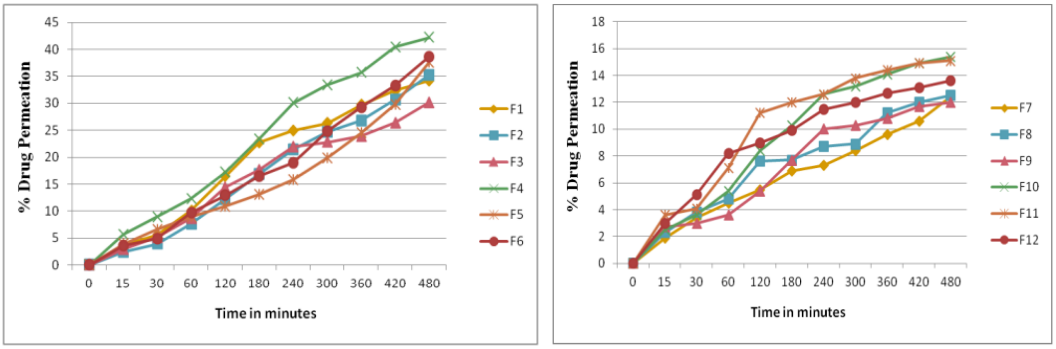


Figure 14 *In vitro* drug permeation

Selection of optimized formulation among (F1-F12) emulgel

On the basis of the drug permeation studies among the twelve formulations [F1-F12], F4 was considered as the best one due to its optimum drug release for 8 hrs. It has been concluded that the formulation F4 containing 1% Carbopol 940 and 5% zinc oxide is the best one in terms of all parameters of emulgel.

Anti-microbial study (among formulation F4, F5 and F6)

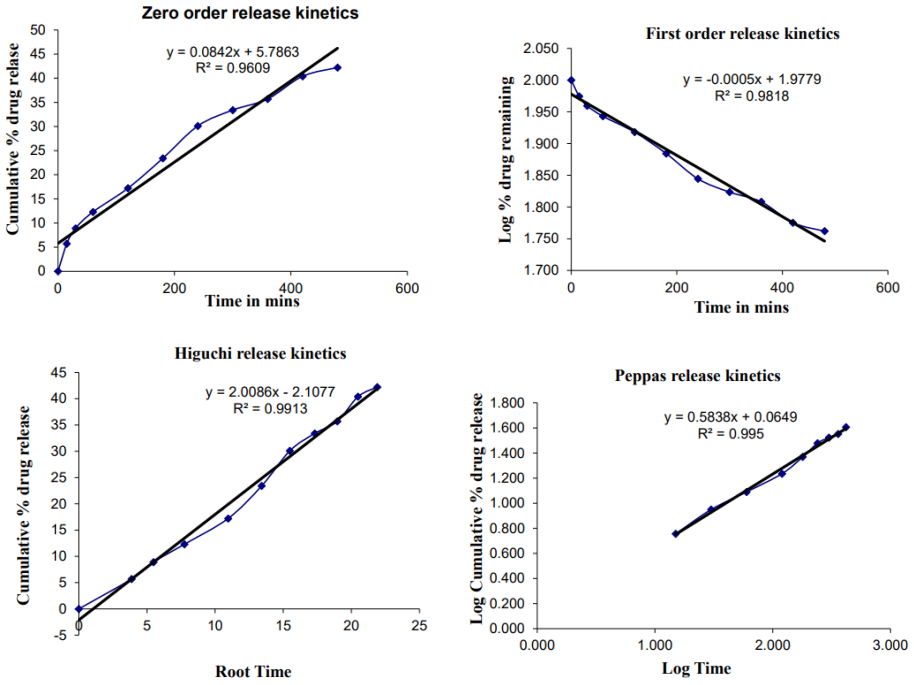
Table: 5 Anti-fungal zone of inhibition of quercetin and zinc oxide (F4, F5 and F6)

Antifungal Study (Azole resistant *C. albicans and C. species)*						
			Zone of Inhibition			
			API			
Microorganisms	**Standard**	**Standard Disc**	**Quercetin dihydrate**	**Zinc Oxide**	**Formulations**	
Azole resistant C. Species	Ketoconazole	Ketoconazole - Resistant	18mm	20mm	**F4**	**23mm**
					F5	22mm
					F6	19mm
Azole resistant *C.albicans*	Ketoconazloe	Ketoconazloe - Resistant	17mm	18mm	**F4**	**21mm**
					F5	20mm
					F6	**21mm**

Table: 6 Antibacterial Study (*Staphylococcus Aureus* and *E.Coli*)

Antibacterial Study (*Staphylococcus aureus and E.coli)*								
		Zone of Inhibition		Zone of Inhibition		Formulations		
						Zone of Inhibition		
Microorganisms	**Standard**	**Standard Disc Amikacin**	**Quercetin dihydrate**	**Standard Disc Amikacin**	**Zinc Oxide**		**Standard Disc Amikacin**	
Staphylococcus Aureus	Amikacin	20mm	17mm	17mm	15mm	**F4**	**16mm**	**21mm**
						F5	16mm	19mm
						F6	**17mm**	**21mm**
E.coli	Amikacin	15mm	13mm	19mm	24mm	**F4**	**17mm**	**23mm**
						F5	17mm	21mm
						F6	18mm	22mm

Invitro drug release kinetics



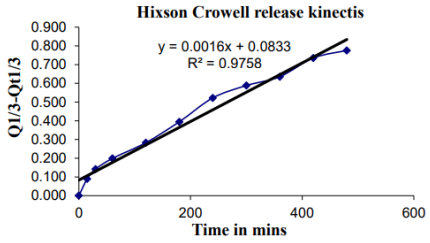


Figure: 15 Drug release kinetics

Discussion

The colour, odour and appearance of the drug were characterized and recorded, the results are shown in table 2. The quercetin dihydrate drug molecule of FT-IR spectra are shown in Figure 4. The absorption bands at 3384 and 3272 cm^{-1} represent the phenolic O-H present in the quercetin molecule. The bands at 1661 and 1604 cm^{-1} reveals that C=O stretching and 1516 cm^{-1} suggested the aromatic stretching, the band at 1447 and 1376 cm^{-1} presence of C-H stretching in the quercetin molecule. The band at 1315 and 1162 cm^{-1} which confirmed the C-O-C stretching in this drug molecule [22]. The absorption bands at 1087 and 599 cm^{-1} represents the out- of plane bending vibrations of aromatic C-H groups [23]. The characteristics peaks of given drug sample were found to be similar to the characteristics peaks Quercetin dihydrate (Reference), which shows that the given drug is Quercetin dihydrate. FT-IR spectra of Zinc oxide are shown in Figure 6. The absorption peak at 3443.28, 2911.21, 2454.94, 1646.91, 1398.14, 1258.32, 1098.26, 876.48, 699.06 and 599.75 cm–1 represent the meal oxygen of ZnO stretching vibration [23]. The characteristics peaks of given drug sample were found to be similar to the characteristics peaks Zinc oxide (Reference), which shows that the given sample is Zinc oxide. The regression equation obtained was y = 0.0923x - 0.0095. The mean correlation coefficient (R^2) was 0.9991 (Quercetin). The regression equation obtained was y = 0.0933x - 0.0155. The mean correlation coefficient (R^2) was 0.9992 (Zinc oxide). The characteristic peaks observed in the FT-IR spectrum of quercetin dihydrate and Zinc oxide, Physical mixture of Quercetin dihydrate and zinc oxide showed no shift and no disappearance of characteristic peaks of quercetin dihydrate and Zinc oxide. This suggests that there was no interaction between Quercetin dihydrate and zinc oxide. The absorption bands are position at 3388.32, 3284.18, 2837.74, 2710.46, 2650.68, 1662.34, 1605.45, 1560.13, 1517.70, 1448.28, 1405.85, 1377.89, 1316.18, 1130.08, 1090.55, 11011.40, 818.63, 794.52, 721.24, 600.71, 551.54 and 477 cm^{-1} are observed. These peaks are resemblance the quercetin dihydrate and Zinc oxide drugs molecule. After mechanical mixing the absorption bands are without changing in pristine drug molecule which has the confirmed the no interaction takes place between the both drugs molecule. Spreadability was found to be dependent on gelling agent concentration and viscosity. As gelling agent concentration increased in the formulations, viscosity increased and consequently spreadability reduced. Largest % of drug contents was obtained to be 97.90 % (F4) and the smallest % of drug content was 96.20%. Based on cumulative drug permeation after 1 h and after 8 h formulation F4 which contained 1% w/w Carbopol 940 and 5% w/w Zinc oxide had the highest drug permeation of 42.2% after 8 h. Formulation F9 on the other hand had the lowest drug permeation of 12% after 8 h and it contained 1% w/w HPMC K4 and 10% w/w Zinc oxide. Based on zone of inhibition mentioned in table 3 which indicating that the best formulation [F4] was sensitive to the azole resistant *C. species* and *C. albicans* microorganism. Based on zone of inhibition mentioned in table 4 which indicating that the best formulation [F4] was sensitive to the microorganism *S.aureus* and *E.coli.* The in-vitro release profile of the drug quercetin dihydrate from formulation F4 could be expressed by Korsmeyer-Peppas, as the plots shows high linearity (R^2= 0.9929) in comparison to zero order (R^2=0.9609), first order (R^2= 0.9818), Higuchi (R^2= 0.9913) and Hixson Crowell (R^2= 0.9758). To confirm release mechanism the data were fitted into Korsmeyer- Peppas model. The diffusion exponent value (n) of best formulation F4 containing quercetin dihydrate was found to be 0.59. Hence it shows the optimized formulation followed non-fickian diffusion release mechanism.

Conclusion

Accordingly, the researchers developed an antimicrobial emulgel formulation with Zinc oxide for a synergistic therapeutic effect. The formulation was able to achieve sustained drug release over 8 hours with gelling agents like carbopol 940, making it suitable for once-daily use. It was found that F4 exhibited the greatest potential, exhibiting excellent characteristics. As a result of this study, the developed antimicrobial emulgel has the potential to be a valuable alternative for treating ketoconazole-resistant candidiasis, potentially enhancing patient compliance and satisfaction.

References

1. **Naga Sravan Kumar Varma V, Maheshwari PV, Navya M, et al.** Calcipotriol delivery into the skin as emulgel for effective permeation. Saudi Pharm J. 2014;22(6):591–599.

2. **Rathbone M, Hadgraft J, Roberts M, et al.** Dermal and transdermal drug delivery. Modified–release drug delivery technology. London: Informa Healthcare; 2002.

3. **Pednekar A, Dandagi P, Gadad A, et al.** Formulation and characterization of meloxicamloaded emulgel for topical application. Int J Pharm Pharm Sci. 2015; 7:216–222.

4. **Baibhav J, Vikas S, Gurpreet S.** Emulgel: a comprehensive review on the recent advancesin topical drug delivery. Int Res J Pharmacy. 2011;2(11):66–70.

5. **Ansel H, Allen J, Popovich NG.** Pharmaceutical dosage forms and drug delivery systems. New York, NY: Lippincott; 1999.

6. **Panwar AS, Upadhyay N.** Emulgel: a review. Asian J Pharmacy Life Sci. 2011;1(3):333– 343.

7. **Manli W, Liang F.** Percutaneous absorption of diclofenac acid and its salts from emulgel. Asian J Pharm Sci. 2008; 3(3):131–141.

8. **Kumar D, Singh J, Antil M, Kumar V.** Emulgel novel topical drug delivery system-a comprehensive review. Int J Pharm Sci Res, 2016; 7(12): 4733-4742.

9. **Abraham, Michael H., and William E. Acree Jr.** "On the solubility ofquercetin." Journal of Molecular Liquids 197 (2014): 157-159.

10. **Kothawade, Sagar, et al**. "Formulation development of antimicrobial zinc oxide nanoparticle loaded trans dermal patch by using 2 3 factorial design." Indo Am. J. Pharm.Res 9 (2019): 483-493.

11. **Rajendran, Sorna Prema, and Kandasamy Sengodan**. "Synthesis and characterization of zinc oxide and iron oxide nanoparticles using Sesbania grandiflora leaf extract as reducing agent." Journal of Nanoscience 2017 (2017).

12. **Jat, Ram Chandra, Suman Jain, and Kanika Arora**. "Preparation and evaluation of quercetin microsphere as antidotes of Sulphur mustard to overcome the poor bioavailability and frequent administration of the drug." World J. Pharmaceut. Res. 4

(2014): 574-603.

13. **Mohamed, Magdy I.** "Optimization of chlorphenesin emulgel formulation." The AAPS journal 6.3 (2004): 81-87.

14. **Varma, V. Naga Sravan Kumar, et al.** "Calcipotriol delivery into the skin as emulgel foreffective permeation." Saudi Pharmaceutical Journal 22.6 (2014): 591-599.

15. **Wood, John H., Gregory Catacalos, and S. V. Lieberman**. "Adaptation of commercialviscometers for special applications in pharmaceutical rheology I: the brookfield viscometer." Journal of Pharmaceutical Sciences 52.3 (1963): 296-298.

16. **Singh, D., Bedi, N., 2016**. Microemulsion Based Hydrogel of Tacrolimus for theTreatment of Atopic Dermatitis. Pharm. Nanotechnol. 4, 136–154.

17. **Singla, V., et al.** "Development and evaluation of topical emulgel of lornoxicam usingdifferent." Int Pharm Sci 2 (2012): 38-44.

18. **Mohamed, M.I., Abdelbary, A.A., Kandil, S.M., Mahmoud, T.M., 2019.** Preparationand evaluation of optimized zolmitriptan niosomal emulgel. Drug Dev. Ind. Pharm. 45, 1157– 1167.

19. **Costa, Paulo, and Jose Manuel Sousa Lobo.** "Modeling and comparison of dissolutionprofiles." European journal of pharmaceutical sciences 13.2 (2001): 123-133.

20. **Jawanjar SR, Chandewar SA, Biyani DM, Umekar MJ.** Preparation and Characterization of Mucoadhesive Nanoparticles (NPs) Containing Quercetin and Eudragit® RS 100 for Nasal Drug Delivery. Sch Acad J Pharm 2020; 09:58–67. doi:10.36347/sajp. 2020.v09i02.002.

21. **Tomečková V, Reháková M, Mojžišová G, Magura J, Wadsten T, Zelenáková K**.Modified natural clinoptilolite with quercetin and quercetin dihydrate and the study oftheir anticancer activity. Microporous Mesoporous Mater 2012; 147:59–67. doi: 10.1016/j.micromeso.2011.05.031.

22. **Jayarambabu, N., Kumari, B. S., Rao, K. V., & Prabhu YT**. Germination and growthcharacteristics of mungbean seeds (Vigna radiata L.) affected by synthesized zinc oxide nanoparticles. International Journal of Current Engineering and Technology, Int J Curr Eng Technol 2014;4:2347–5161.

23. **Abraham SA, Yashavanth G, Deveswaran R, Bharath S, Azamathulla M, Shanmuganathan S. Honey** based hydrogel as delivery system for wound healing.2021; 49:1709–18. doi: 10.1016/j.matpr.2021.07.488.

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