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

Dr PRABHU R*[1] , VENKATESH BABU[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

In the past, various ways were used to treat illnesses, like taking medicine under the tongue, by mouth, through the rectum, applying it on the skin, injecting it, or inhaling it. Nowadays, researchers are exploring and creating new methods and technologies to make it easier for patients to follow their treatment plans [1]. Medications are applied to the skin's surface for two main reasons: treating the area where the medicine is applied or affecting the whole body. In treating skin issues, it is especially advantageous to use medicines on the skin since it is easy to reach, and it helps them work more effectively than other methods [2,3]. There are several types of topical medicines, including creams, lotions, and gels. They do, however, come with several disadvantages, including sticking, instability issues, difficulty spreading, causing allergies, poor absorption, and aggravating the skin [4]. The delivery of drugs that are not water-soluble poses a significant challenge when using gels [5]. These limitations of gels can be overcome with Emulgel [6]. In emulgels, an agent gels the oil in water or water in oil by adding oil to water [7]. There are several advantages to using emulgels topically. Various features within the semisolid category have made clear gels increasingly popular as cosmetics and medicines. In spite of gel's many benefits, hydrophobic drugs are a challenge to deliver through gels. Even hydrophobic medicinal ingredients can be seamlessly incorporated and transported through gels using an emulsion-based approach [8].

Quercetin is a significant phytochemical from the flavonoid group, exhibiting various pharmacological activities, including antimicrobial properties against a wide range of bacteria, fungi, and viruses. It's particularly effective against drug-resistant microorganisms. Some modifications to its structure can enhance its antimicrobial activity. Recently, it gained Generally Recognized as Safe (GRAS) status from the U.S. Food and Drug Administration.

Zinc oxide nanoparticles/microparticles (ZnO NPs/MPs) are also known for their broad-spectrum antimicrobial activity against various microorganisms. This action is attributed to their unique physical and chemical properties, including the release of Zn2+ ions, adsorption, and the generation of reactive oxygen species (ROS). They affect microorganisms by disrupting energy metabolism, causing lipid peroxidation, damaging cell membranes, interfering with DNA replication, and causing DNA breaks (Figure 1). The effectiveness of ZnO NPs/MPs varies depending on their characteristics such as shape, size, and porosity.

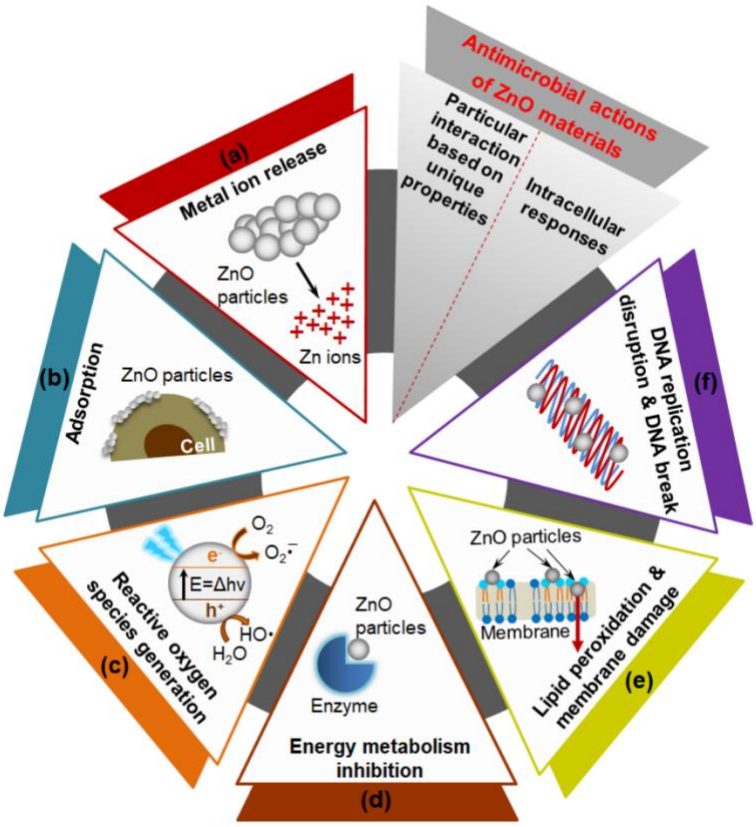


Figure.1 ZnO used in anti-microbial applications

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

To prepare the solution, 10 mg of quercetin was dissolved in 25 ml of absolute alcohol, and 10 mg of zinc oxide was dissolved in 25 ml of DMSO separately. The total volume was adjusted to 50 ml using a pH 7.4 phosphate buffer solution. Then, 5 ml of the drug solution was transferred to a 100 ml volumetric flask, and the volume was adjusted to 100 ml with the phosphate buffer solution. An ultraviolet scan was conducted within the wavelength range of 200-400 nm using this stock solution.

Standard calibration curve

Quercetin dihydrate and Zinc oxide in pH 7.4 phosphate buffer

Accurately weighing 10 mg of Quercetin Dihydrate, it was dissolved in 25 ml of absolute alcohol within a volumetric flask, and then the volume was adjusted to 50 ml using a phosphate buffer solution at pH 7.4. In a similar manner, 10 mg of Zinc oxide was accurately weighed and dissolved in 25 ml of DMSO in a volumetric flask, with the volume adjusted to 50 ml using the same phosphate buffer solution at pH 7.4. Subsequently, 200 µg/ml stock solutions were prepared for both substances. To create sub-stock solutions at 20 µg/ml, 2.5 ml of the stock solutions were diluted to 25 ml with the phosphate buffer solution at pH 7.4. From these sub-stock solutions, aliquots of 1, 2, 3, 4, and 5 ml were taken into 10 ml volumetric flasks, and the volume was adjusted to 10 ml using the same phosphate buffer solution at pH 7.4. The absorbance of these solutions was measured at 370 nm for quercetin and 260 nm for Zinc oxide, using a Shimadzu UV-1800 Spectrophotometer. A calibration curve was generated by plotting the relationship between concentration and absorbance, with a blank solution of phosphate buffer at pH 7.4 as the reference.

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)**

	I	II	III	IV	V	VI	VII	VIII	XI	X	XI	XII
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:

To assess spreadability, 1 g of each emulgel was placed within a pre-marked circle measuring 1 cm in diameter on a glass slab. Another glass slab, pre-weighed, was then placed on top of the emulgel. A weight of approximately 1 kg was placed on the upper glass slab for a duration of 5 minutes. This pressure caused the emulgel to spread, resulting in an increase in the diameter of the circular area, which was subsequently 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:**

The experiments were carried out using a customized Franz diffusion (FD) cell. A cellophane membrane was soaked in freshly prepared phosphate buffer with a pH of 7.4 for a minimum of 24 hours before use. In the modified FD cell, a gram of each emulgel formulation was applied and spread on the surface of the cellophane membrane, which was securely positioned between the donor and receptor compartments of the cell. The diffusion area measured 6.2 cm^2.The receptor compartment was filled with phosphate buffer at pH 7.4, which served as the dissolution medium. At specific time intervals, 10 ml samples were withdrawn, and an equal volume of fresh dissolution medium was added to maintain a constant volume. These collected samples were then analyzed using UV-Vis spectroscopy, and the cumulative amount of drug that permeated through the membrane was calculated as a function of time over an 8-hour period. [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

To understand the drug release patterns and propose a mechanism, we analyzed the cumulative release of quercetin dihydrate from the chosen formulations at different time intervals. We applied zero-order, first-order kinetics, Higuchi, and Korsmeyer-Peppas models to characterize the drug release kinetics [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 Crowell observed that the surface area of particles is directly related to the cube root of their volume. They formulated an equation to describe release mechanisms in systems where changes in the surface area and particle diameter occur.

$$Wo1/3 - W1/3 = KHC * t$$

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

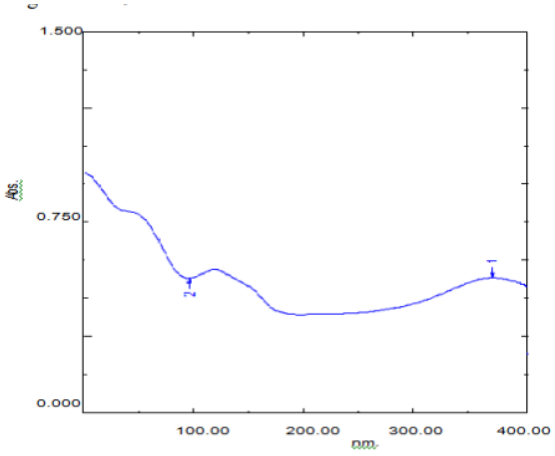


Figure:2 UV spectrum of Quercetin dihydrate

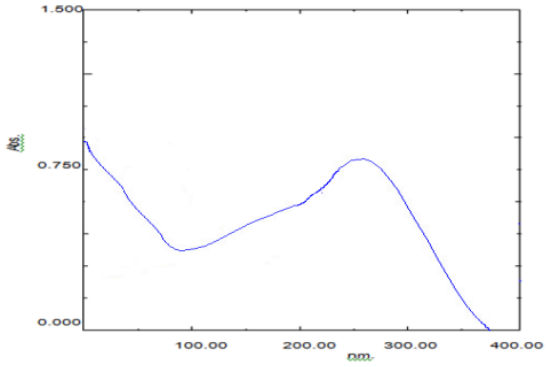


Figure:3 UV spectrum of Zinc oxide

Compatibility profile

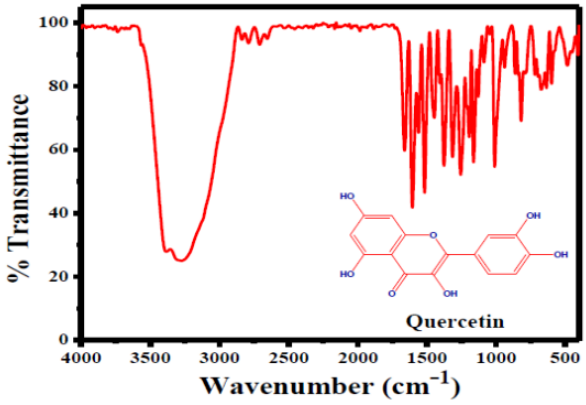


Figure: 4 FTIR Spectrum of Quercetin dihydrate

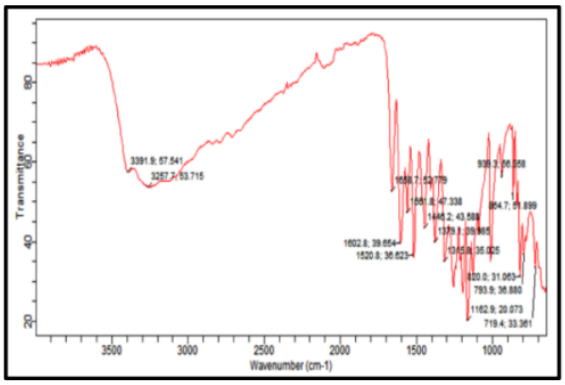


Figure: 4 FTIR Spectrum of Pure Quercetin dihydrate (Reference 20)

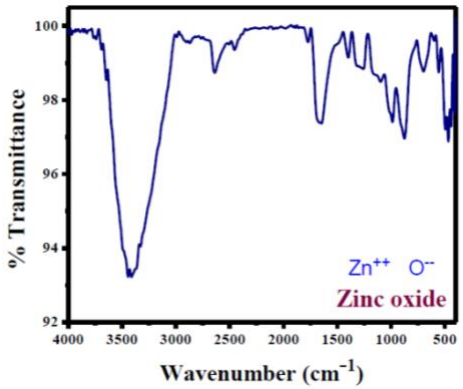


Figure: 6 FTIR Spectrum of Zinc oxide

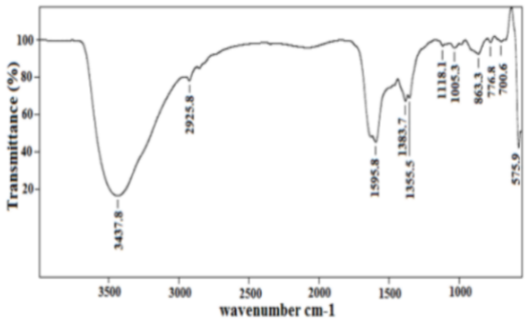
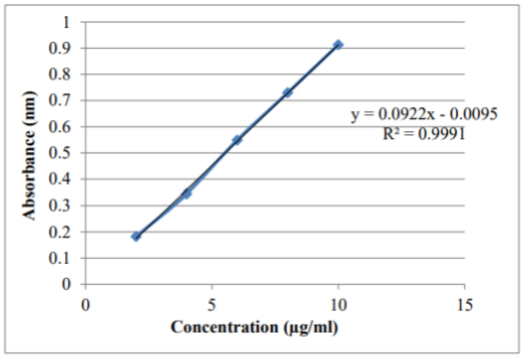


Figure: 7 FTIR Spectrum of Pure Zinc oxide (Reference21)

Calibration curve of Quercetin and Zinc oxide



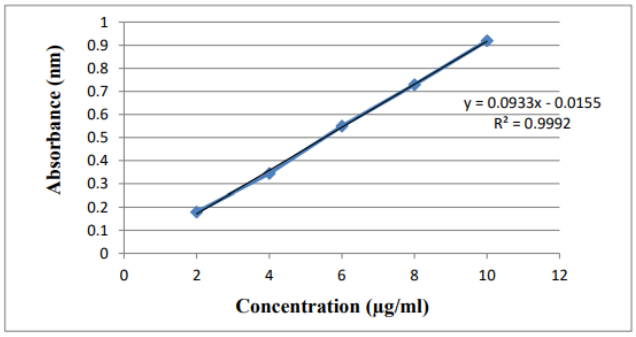


Figure: 8 Quercetin calibration curve **Figure: 9 Zinc oxide calibration curve**

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

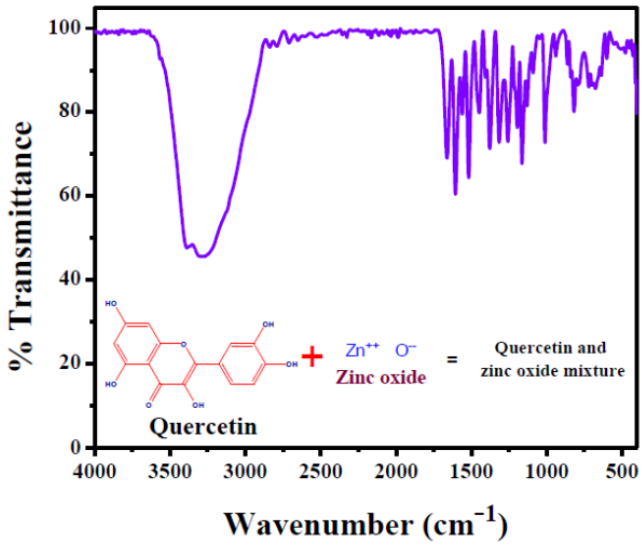


Figure: 10 FTIR spectrum of Quercetin dihydrate and zinc oxide (Physical mixture)

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.

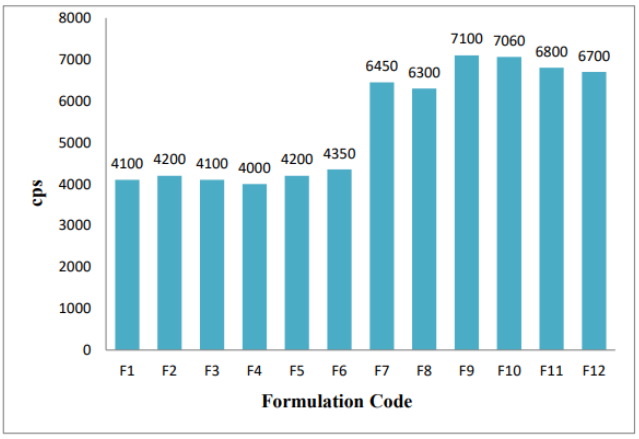


Figure: 11 Viscosity evaluation (F1-F12)

Spreadability study

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

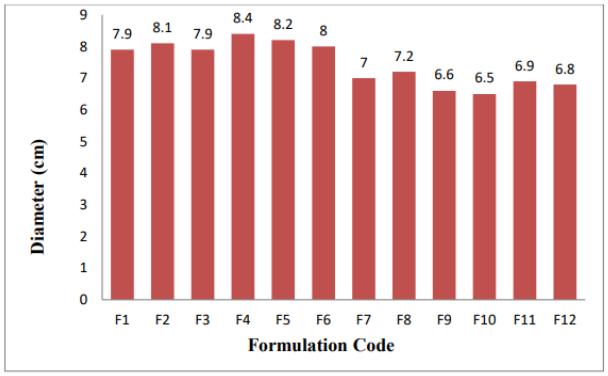


Figure: 12 Spreadability profile (F1-F12)

Drug content determination (%):

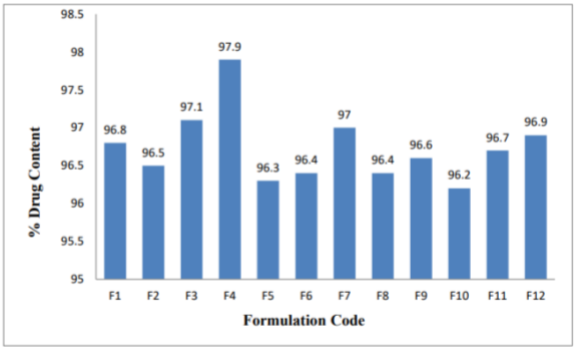


Figure: 13 % drug content (F1-F12)

In vitro drug permeation study

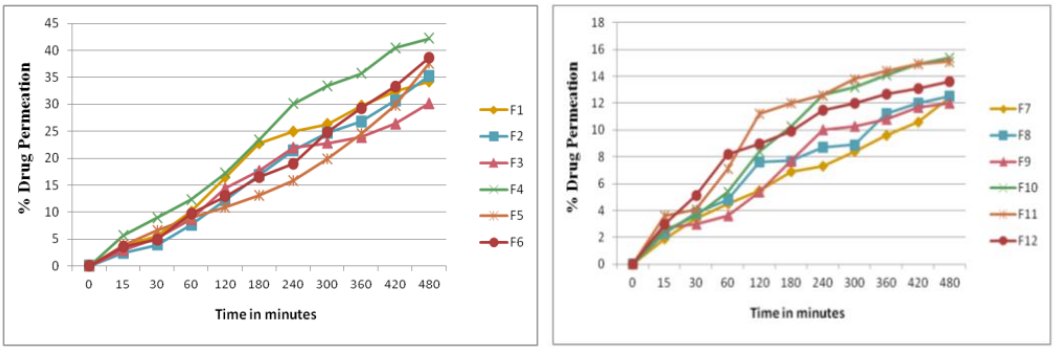


Figure 14 *In vitro* drug permeation

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

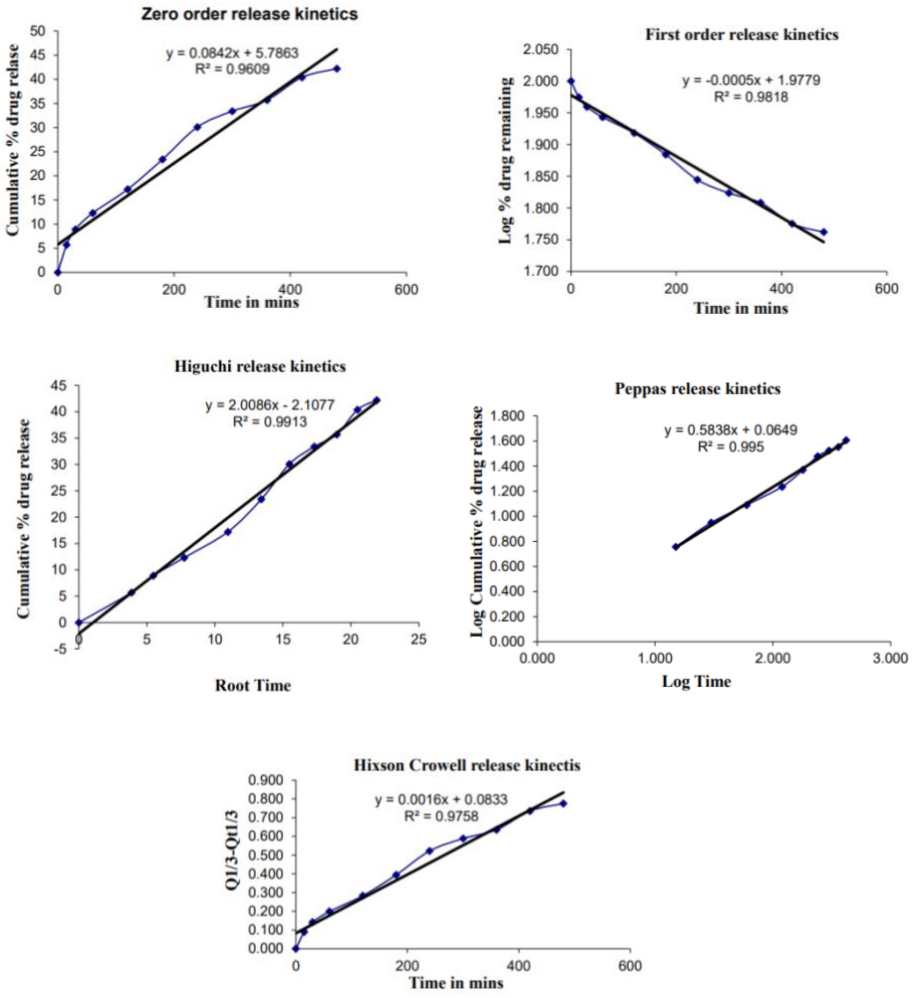


Figure: 15 Drug release kinetics

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 emulgelforeffective 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 lornoxicamusingdifferent." 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 Quercetinand 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, ZelenákováK**.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 andTechnology, 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.

ORIGINALITY REPORT

30%	28%	17%	10%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	erepository.uonbi.ac.ke Internet Source	5%
2	storage.googleapis.com Internet Source	4%
3	uomustansiriyah.edu.iq Internet Source	2%
4	www.ncbi.nlm.nih.gov Internet Source	2%
5	jpsr.pharmainfo.in Internet Source	1%
6	innovareacademics.in Internet Source	1%
7	fulltext.scholarena.co Internet Source	1%
8	nepjol.info Internet Source	1%
9	Submitted to Bundelkhand University Student Paper	1%
10	ijpsr.com Internet Source	1%
11	www.researchgate.net Internet Source	1%
12	saspublishers.com Internet Source	1%
13	tud.qucosa.de Internet Source	1%
14	Handbook of Bioceramics and Biocomposites,	1%