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FORMULATION AND EVALUATION OF LIQUORICE EMULGEL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Acne vulgaris, commonly called acne, is a skin condition affecting many individuals globally. The multifactorial onset of acne vulgaris manifests as pilosebaceous follicles. Open and closed comedones, as well as inflammatory lesions like papules, are indicative of this condition nodules and pustules. Phytoconstituents present in methanolic extracts of Camellia sinensis, Glycyrrhiza glabra and Calendula officinalis (COME) have antibacterial and antioxidant properties. Extracts loaded with carbopol® 934 were used for the preparation of herbal (F1-F8) and polyherbal gel (PHF), followed by evaluation for pH, viscosity, spreadability and in vitro drug release and FT-IR spectral analysis. Emulgel is the promising drug delivery system for the delivery of hydrophobic drugs. Preparation of emulgel is done by incorporation method. Higuchi's approach was followed by the optimized formulation, F3, which demonstrated a 93% drug release. The outcome demonstrated that the liquorice extract was homogeneous when placed into an oil-in-water emulsion, and the in vitro release analysis indicates that the F3 formulation exhibits the highest level of drug release. The conclusion that licorice extract of emulgel can be employed as an efficient topical dose form is that it combines the benefits of an emulsion and gel.

KEYWORDS: Acne vulgaris, Glycyrrhiza glabra, COME, PHF, Emulgel.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat the cutaneous disorder. When oral, sublingual, rectal, and parental medication administration routes are ineffective or in localized situations, the topical drug

delivery system is typically utilized similar to a fungal infection in the skin.[1] Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment.[2] The drug application to the topical surfaces evades the hepatic first pass metabolism, gastric pH variations and fluctuations in plasma levels, frequently encountered when a drug is administered through the oral route.[3] The other advantages associated with the topical drug delivery system include the following[4]

- Patient compliance and acceptance,
- Ease and convenience of application,
- Painless and non-invasive technique,
- Improvement in drug bioavailability,
- Better physiological and pharmacological response and
- Minimum systemic toxicity and exposure of drug to non-infectious tissue/sites.

The skin is the single largest human organ, with 2m² of surface and 3.6kg of weight in adults. It acts as a waterproof, insulating shield, protecting the body against environmental stresses. It also produces antimicrobial peptides that prevent infections, and hormones, neuropeptides, and cytokines that exert biological effects, not only locally on the skin but also systemically throughout the whole body.

Emulgel is an emerging topical drug formulation which is becoming increasingly popular due to its advantages over the conventional topical preparations. Emulsion and gel can be combined to create a mixture known as emulgel,[5] for lipophilic materials, use O/W emulsion and for hydrophilic materials, w/o components.[6] Emulgels without grease, without difficulty are thixotropic extensible, without difficulty detachable, moisturizing, non-toxic, biological cordial, clear additionally aesthetically acceptable.[7] In addition, their cutaneous extended shelf-life and penetration,[8-9] which together make emulgels are a beneficial topical medication delivery mechanism. In a gel, a colloid consisting primarily of water is held in place by surface tension between the colloid and a web of macromolecules formed from strands built from a very small amount of the gelating substance. Gels have several advantages, but one major disadvantage is that they cannot be used to give hydrophobic medicines.[10]

Acne vulgaris is a cutaneous disorder of multifactorial beginning that shows in the pilosebaceous follicle. It is described by open and closed comedones and inflammatory lesions such as papules, pustules, and nodules.[11] The primary causes of acne include excessive testosterone secretion, aberrant microorganism proliferation (Propionibacterium acnes, Staphylococcus, and Malassezia), excessive keratinization of the sebaceous duct of hair follicles, and skin hyper-immunity.[12] Clinically, acne is usually treated with drug therapy and physical therapy.[13] Drug therapy includes oral administration of antibiotics, retinoic acid, or topical application of fusidic acid cream. However, the drug treatment effect of acne is often poor due to poor tolerance, skin sensitivity, and other reasons in some patients.[14]

Four factors are important in the development of acne

1. Plugging of the hair follicle with abnormally cohesive desquamated cells.
2. Sebaceous gland hyperactivity.
3. Proliferation of bacteria (especially Propionibacterium acnes) within sebum.
4. Inflammation.

MATERIALS AND METHODS

Materials

Liquorice was purchased from BioNutriz Healthcare Pvt. Ltd, Bangaluru India. All other chemicals were Propylene glycol (Fischer Scientific, Mumbai), Span 20 (molychem; Mumbai), Tween 20 (Thermo fisher Scientific India Pvt. Ltd), Light Liquid Paraffin (Sisco Research Laboratories Pvt. Ltd.), Carbopol 934 (Lubrizol Advanced Materials, India), Propyl paraben (BRM Chemicals), methyl paraben (BRM Chemicals).

Estimation of Liquorice by UV- visible spectrophotometer[15]

UV-visible spectrophotometer is generally used for structural information of various drugs to obtain specific information on the chromophoric part of the molecules in solution when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. The UV spectrum is generally recorded as a plot of absorbance versus wavelength. Double beam UV-visible spectrophotometer was used to know the λmax of drug. A 1000µg/mL solution of Celecoxib in methanol was scanned in the range of 200-400.

Solubility studies[16]

The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility.

For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned culture flasks containing 5 mL of different solvents (Methanol, Ethanol, Chloroform, pH 7.4 phosphate buffer saline, water) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 hrs. at room temperature. After 24 hrs, each sample was centrifuge for 15 minutes at 15,000 rpm and was suitably diluted and determined spectrophotometrically.

Liquorice extract emulgel formulation[17]

Using the generated formulation code, eight different drug formulations were created.

Table: Composition of different formulation Liquorice Emulgel with different polymers.

Ingredients % (w/w)	Formulation Batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Liquorice	1	1	1	1	1	1	1	1
Carbopol 934	1	1	1	1	1	1	1	1
Tween 20	0.5	1	1.5	1	0.5	1	0.5	1
Span 20	0.5	0.5	1	1	1.5	1.5	2	2
Liquid Paraffin	5	7.5	5	7.5	5	7.5	5	7.5
Methyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylene Glycol	5	5	5	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Method of preparation liquorice emulgel

Dissolving the oil-soluble components in the oil vehicle (Dissolving span 20 in liquid paraffin, for example) and the water-soluble components in the watery vehicle (Dissolving Tween 80 in filtered water) is the initial step in making an emulsion. The two phases were mixed in a turbulent mixing environment to ensure the dispersion of the two phases into droplets. Water-soluble substances, sometimes referred to as excipients, are first dissolved by mixing the aqueous vehicle with mechanical stirring. To keep the mixture from aggregating, the hydrophilic polymer is added gradually, and stirring is continued until the polymer dissolves and the pH remains within the desired range. At create emulgel, the gel and emulsion stages are combined at a 1:1 ratio.[18]

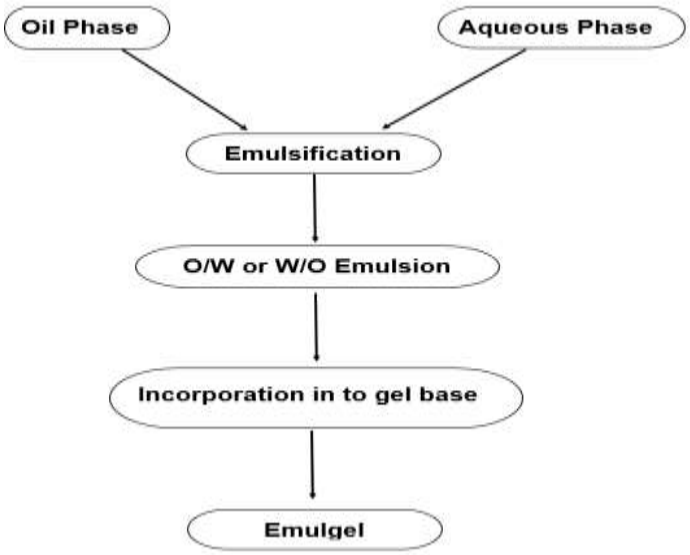


Figure: Schematic representation of emulgel preparation.

Evaluation studies

FTIR studies: Fourier transform infrared Spectroscopies of different compounds were performed for identification of that particular compound. FT-IR Spectroscopy of pure drugs was done using Liquorice Powder. Various peaks in FT-IR Spectrum were interpreted for identification of different group in the structure of pure drugs. FT-IR Spectroscopy can also be used to investigate and predict any physicochemical interactions between different components.[19]

TEM studies: The size and shape of emulgel were examined by transmission electron microscope (TEM) with the image software. The drug loaded emulsion was spread on firmware-coated copper grids and absorbed after complete air drying.[20]

Entrapment efficiency

1. The percentage drug content of the Liquorice in each prepared batch of the ibuprofen loaded lavender oil emulgel gel was determined by solubilizing the accurately weighed gel equivalent to 50mg of drug in beaker containing 10ml of the methanol solvent.
2. The solution was vortexed for 1 min. followed by sonicated for 5min.
3. The sample was centrifuged at 5000rpm for 10min. the supernatant was transferred to the 10ml volumetric flaks and suitable diluted with the methanol solvent.
4. The sample was scanned ranging 200-400nm using the UV spectrophotometer.

5. The UV spectrum of the sample was noted and absorbance of the ibuprofen was determined. The amount of the ibuprofen was determined using the standard calibration curve. The activity was performed in the triplicate manner

$$\text{Drug Entrapment Efficiency} = \frac{\text{Initial Drug Content} - \text{Final Drug Content}}{\text{Initial Drug Content}} * 100$$

pH evaluation: The pH of the gel was determined using calibrated pH meter. Determinations were carried out in triplicate and an average of these determinations was taken as the pH of the gel.[21]

Visual appearance: Colour, phase separation, consistency was found in emulgel formulation.[22]

Swelling index: 1g of prepared emulgel formulations was taken on porous aluminium foil and then placed in the petri dish containing 10 mL 0.1N Hcl. The samples were taken from the Petri dish at a different time interval and left undisturbed in a dry place for some time so that the external liquid is removed and weighed. Swelling index is then calculated by using below formula,

Swelling Index (SW) % = [(Wt. − Wo) / Wo] × 100 Where (SW) % = Equilibrium percent swelling, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time.[23]

Rheological research (Viscosity): Viscosity measurements of prepared topical Emulgel based gel were carried out by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity.[24]

Determination of drug content: By combining 1gm of the Emulgel with 100 mL of methanol, the drug concentration of each batch of Liquorice Emulgel formulation was assessed independently. To obtain clear solutions, the resultant solutions were filtered through a filter. Further were centrifuged 10000 rpm for 30 min. Using methanol as a blank, the drug content of these samples were analysed using UV-spectrophotometer scanning from 200- 400 nm.[25]

Zeta potential: The zeta potential of the chosen formulation was ascertained by laser diffraction analysis utilizing a particle size analyzer. The value of the zeta potential shows the

degree of electrostatic repulsion between neighboring, similarly charged particles in dispersion.[26]

In- vitro release study: Franz-diffusion cells were used to analyze the diffusion of emulgel compositions. The cellophane membrane was utilized in Franz-diffusion cell. The receptor compartment had a capacity of 20 millilitres and the cell was manufactured locally. For in-vitro release, phosphate buffer with a pH of 6.8 was utilized as the receptor media. After applying the emulgel sample to the membrane, the quality diffusion cell's donor and receptor compartments are fixed. In the receptor compartment, phosphate bufferpH6.8 was present. The diffusion medium was continuously swirled at a speed of 50 rpm using a magnetic stirrer, and the temperature was thermostatically maintained at 37 ± 0.5oC by surrounding water in a jacket. At hourly intervals, 1 ml aliquots were removed and replaced with an equivalent volume of receptor media for a duration of 12 hours.[27]

Ex- vivo drug release study[28]

- Zero order kinetics
- First order kinetics
- Higuchi's Model
- Korsmeyer-Peppas Model

Stability studies: Stability studies were conducted on an improved formulation with the maximum in-vitro drug release from the generated liquorice extract emulsion. As per ICH requirements, this investigation was conducted in a stability chamber with testing conducted at room temperature and humidity. The parameters that were employed for temperature and humidity were: 40°C ± 2°C at 75% ₊5%RH, 25°C ± 2°C at 75% ₊5%RH, and 5°C ± 3°C. During a three-month period, samples were taken out at 0 and 30day intervals, and their physical characteristics, pH, viscosity, and drug concentration were assessed.[29]

RESULT

Determination of λmax and construction of calibration curve in methanol: The liquorice was scanned by UV spectroscopy and λ max was found to be 254nm.

Table: Calibration curve of Liquorice in methanol (λ_{max}= 254 nm).

Sr. No.	Concentration (µg/ml)	Mean±SD
1	0	0
2	100	0.203±0.004

3	200	0.383±0.001
4	300	0.581±0.002
5	400	0.765±0.004
6	500	0.947±0.002

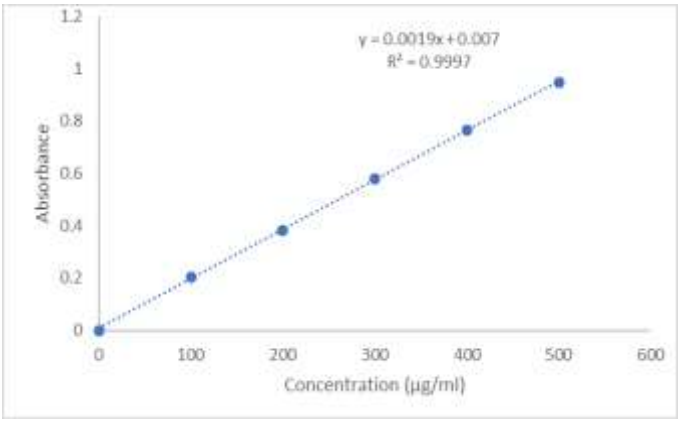


Figure 1: Calibration curve of liquorice in methanol.

Solubility studies: Liquorice solubility in various solvents: It was determined how soluble liquorice was in a variety of oils, surfactants, and co-surfactants. The following is the order in which liquorice dissolves in various oils: Light liquid paraffin <soybean oil<oleic acid< compoul PG-8< and triacetin. The following is the order in which liquorice dissolves in various surfactants and co-surfactants: Propylene glycol> IPA> Glycerol> Tween 20> span 80> tween 80> span 20.

Table 2: Liquorice solubility in various oils.

Oils	Solubility (mg/g)
Light liquid paraffin	3.31±0.01
Soyabean oil	2.99±0.01
Oleic acid	2.1±0.01
Triacetin	0.26±0.01
Compoul PG-8	0.24±0.01

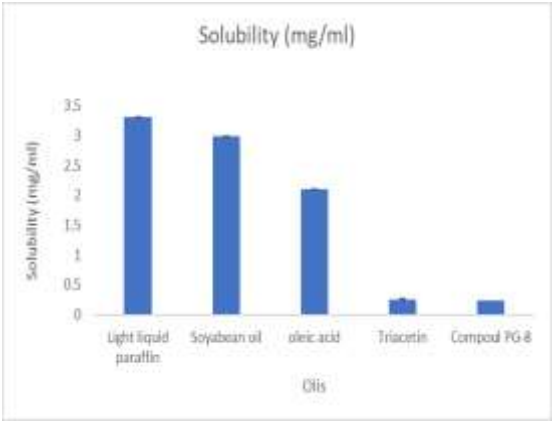


Figure 2: Solubilityof liquorice in various oils.

Table 3: Liquorice solubility in various surfactants and co- surfactanats.

Surfactants and co- surfactants	Solubility (mg/g)
Span 20	2.44±0.01
Tween 80	1.72±0.01
Span 80	1.18±0.01
Tween 20	0.82±0.01
Propylene glycol	1.26±0.01
Glycerol	0.76±0.01
IPA	0.66±0.01

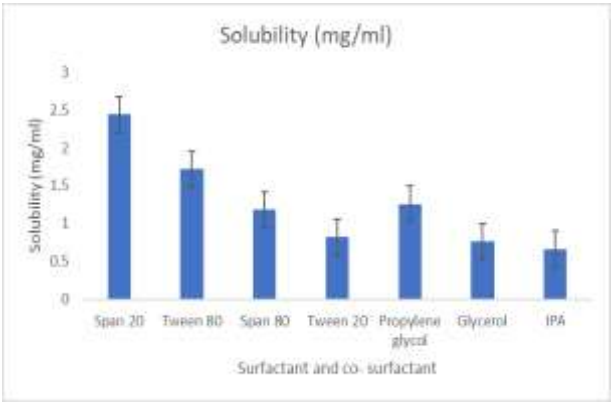
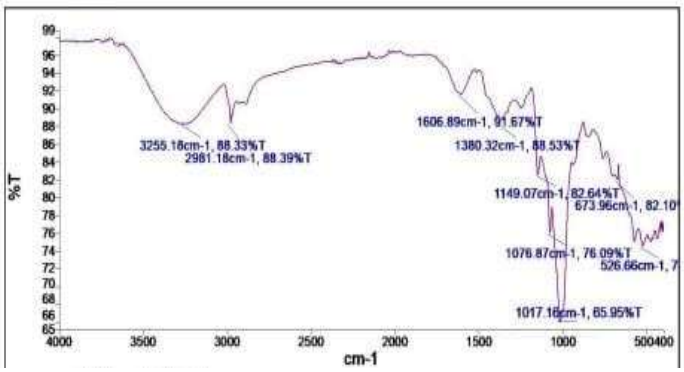


Figure 3 : Liquorice solubility in various surfactants and co- surfactants.

FTIR spectrophotometer: No obvious distinctive absorption peaks are present in pure liquorice. The intense bands at the optimal wavelength displayed in (figure 4) are indicative of the emulgel spectrum.



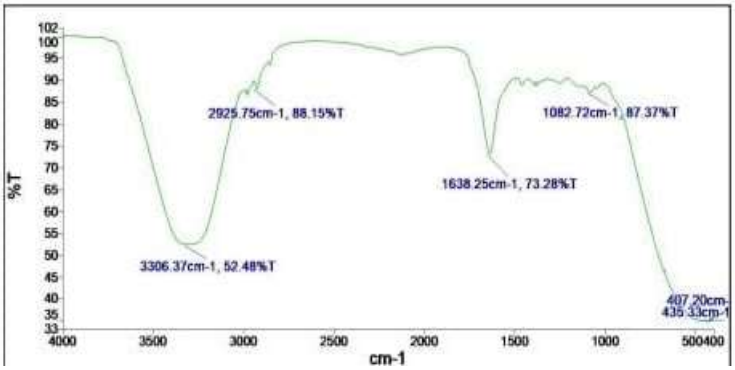


Figure 4: IR spectroscopy of (A) pure Liquorice & (B) Liquorice emulgel.

TEM study: TEM study of Liquorice Emulgel is given below:

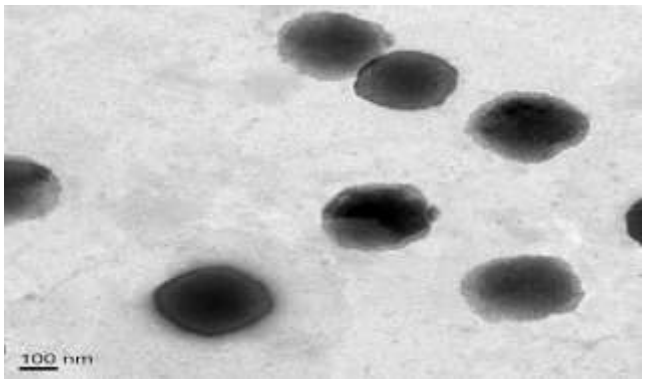


Figure 4: TEM study of liquorice emulgel.

Discussion: TEM was utilized to surface morphology of formulation. From above image, evaluated that globules are spherical and uniform in shape.

Percentage drug entrapment: Percentage yield and drug entrapment of Emulgel were given a table 4.

Table 4: Percentage drug entrapment of different liquorice emulgel.

Formulation code	Percentage drug entrapment
F2	84±0.8
F3	93±0.8
F5	81.2±0.8
F6	88.9±0.5
F7	69.5±0.5

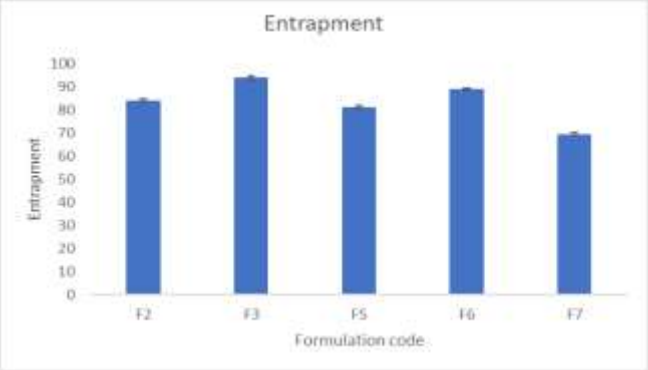


Figure 5: Percentage drug entrapment.

Discussion: The drug content of formulations was found to be 91.05± 0.74 and 99.65± 0.80%, respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the method adopted for formulations was found to be suitable.

Organoleptic Characteristics and Globule size: Freshly prepared emulsions were investigated. Organoleptically for homogeneity, colour, and phase separation. All the emulsions were found to be homogenous, creamy yellowish brown; no phase separation was observed. Globule size for F1 emulsion was up to 50 µ and F2 emulsion was up to 80 µ.

Table 5: Physical appearance data.

Emulsion	Homogeneity	Colour	Phase separation	Globule size
F1	Heterogenous	Yellowish brown	Separated	Up to 50µ
F2	Homogenous	Turbid	None	Up to 80µ
F3	Homogenous	Yellowish brown	None	Up to 80µ
F4	Heterogenous	Turbid	Separated	Up to 80µ
F5	Homogenous	Less Turbid	None	Up to 80µ
F6	Homogenous	Yellowish brown	None	Up to 80µ
F7	Homogenous	Yellowish brown	None	Up to 80µ
F8	Heterogenous	Less Turbid	Separated	Up to 80µ

Discussion: From the above result It was determine that F1, F4, F8 shown phase separation. These two formulations did not proceed further evaluation. F2, F3, F5, F6, F7, was evaluated further.

Thermodynamic stability studies

Emulsions when subjected for centrifugation and followed by freeze thaw were found to be stable.

Table 6: Thermodynamic stability studies.

Emulsion	Centrifugation test (3500rpm for 30min)	Freeze-thaw test (2cycles NLT 48hrs)
F2	Passed	Passed
F3	Passed	Passed
F5	Passed	Passed
F6	Passed	Passed
F7	Passed	Passed

Robustness to dilution

Emulsions when subjected to dilution with water and 7.4 pH phosphate buffer were found to be stable.

Table 7: Robustness to dilution.

Emulsion	Distilled Water		6.8 pH phosphate buffer	
	10mL	100mL	10mL	100mL
F2	Stable	Stable	Stable	Stable
F3	Stable	Stable	Stable	Stable
F5	Stable	Stable	Stable	Stable
F6	Stable	Stable	Stable	Stable
F7	Stable	Stable	Stable	Stable

pH of Emulgel of Liquorice: The pH of emulgel of Liquorice was shown in table 6:

Table 8: pH of emulgel of Liquorice.

Sr. no.	Formulation Code	pH
1	F2	6.5±0.2
2	F3	7.5±0.1
3	F5	7.2±0.1
4	F6	7.1±0.2
5	F7	6.6±0.1

Value is expressed as mean ± SD; n=3

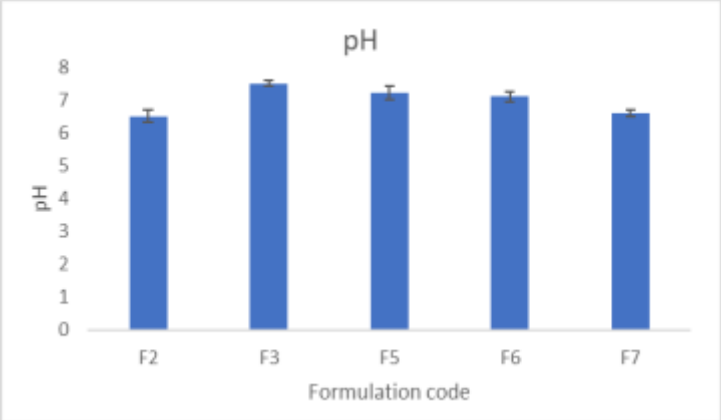


Figure 6: pH of emulgel of liquorice.

Discussion: From the Table 7.22 & fig.7.15, it was found that pH of all formulation was found to be in a range 6.5±0.2 to 7.5±0.1.

Viscosity: The viscosity of emulgel of Liquorice was shown in table 7.

Table 9: Viscosity of emulgel of liquorice.

Sr. No.	Formulation code	Viscosity(cPs)
1	F2	1264±8
2	F3	5555±9
3	F5	3264±9.2
4	F6	4372±15.3
5	F7	5350±4.1

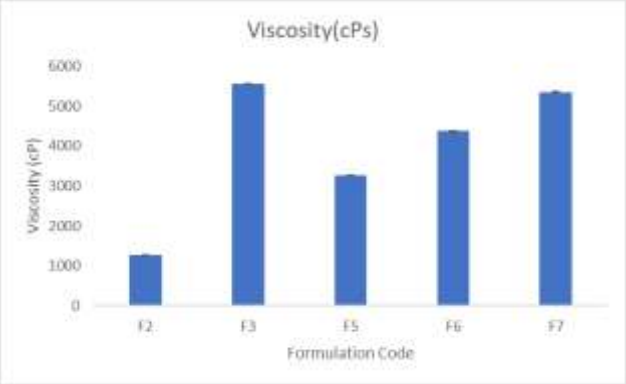


Figure 7: Viscosity of emulgel of liquorice.

Discussion: The Viscosity of the gel at different formulation was found to be in the range from 1264±8 to 5555±9.

Swelling index: The swelling index of Liquorice emulgel shown in Table 9.

Table 10: Swelling index of emulgel of liquorice.

Sr. No.	Formulation Code	At 10 min	At 20 min	AT 30 min
1	F2	45±0.1	77±0.1	96±0.1
2	F3	58±0.1	92±0.1	120±0.1
3	F5	54±0.1	87±0.1	104±0.1
4	F6	58±0.1	92±0.1	115±0.1
5	F7	62±0.1	91±0.1	98±0.1

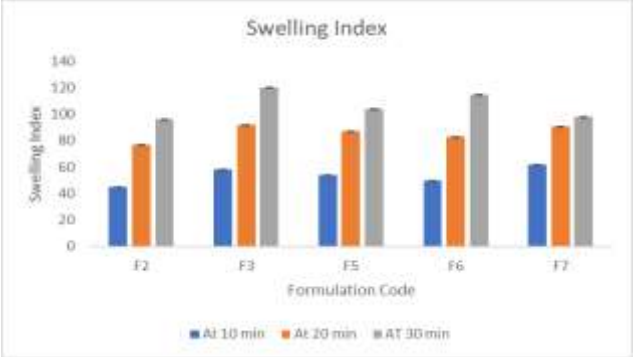


Figure 8: Swelling index of emulgel liquorice.

Percentage drug content of emulgel of liquorice: The percentage drug content of emulgel of Liquorice was shown in table 10.

Table 11: % Drug content of emulgel of liquorice.

Sr. No.	Formulation code	% Drug content
1	F2	92.63±0.53
2	F3	99.65±0.80
3	F5	95.09±0.80
4	F6	98.77±0.30
5	F7	91.05±0.74

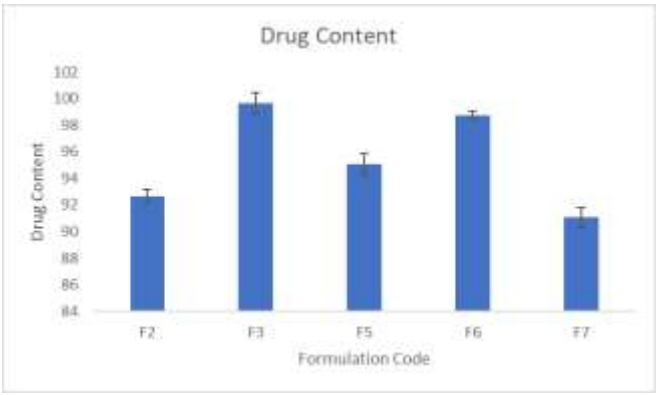


Figure 9: % Drug content of emulgel of liquorice.

Discussion: The drug content of formulations was found to be 91.05± 0.74 and 99.65± 0.80%, respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the method adopted for formulations was found to be suitable.

Zeta potential: Zeta potential of Liquorice emulgel was -21.4mV shown in figure 10.

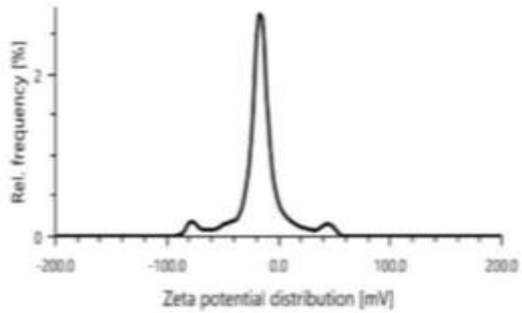


Figure 10: Zeta potential of liquorice emulgel.

Discussion: Zeta potential indicates the degree electrostatic repulsion between similar charge particles in a dispersion. High zeta potential value (positive or negative) suggest that particle will repel each other preventing aggregation and thus maintaining stability. It indicates -21.4 good stability.

In- vitro release study: The pure Liquorice results 93.47±0.14 of release in 8 h and then stopped the release. Whereas for formulated emulgel showed the initial burst release of 94.26±0.47 and then showed drug release in a controlled manner for 24 hours as shown in (figure 11).

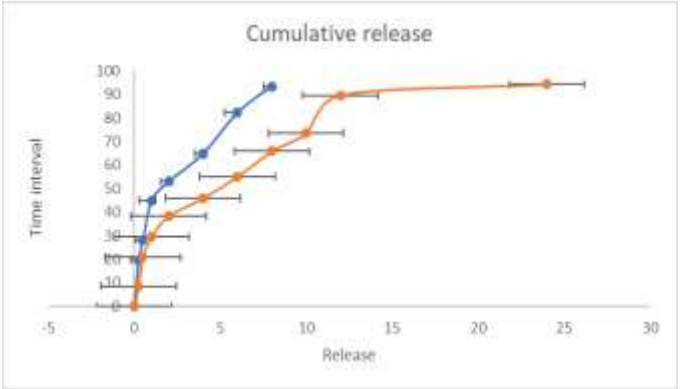


Figure 11: In- vitro release study of emulgel liquorice.

Discussion: Drug release graphs for pure drug & formulation F3(G2) was shown in Figure were significantly different from the profile of pure drug. In the pure drug 44.94% was released within 1hr. On the other hand, the release of formulation D14(G2) was release up to AR.34% within 24 hr. followed by sustained manner.

In- vitro kinetic release study: Several kinetic equations of zero order, first order, the Higuchi model, the Korsemeyer Peppas model, and the improved formulation F3 were fitted using the data from the in-vitro drug release.

Figure 12: Zero- order drug release plot of formulation F3.

Figure 13: First- order drug release plot of formulation F3.

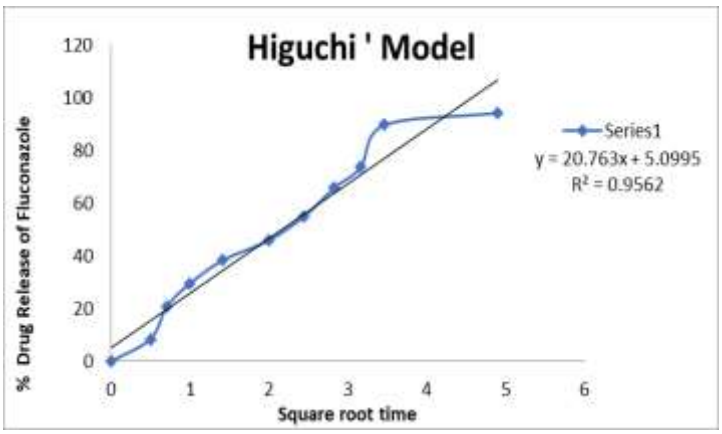


Figure 14: Higuchi-release model of formulation F3.

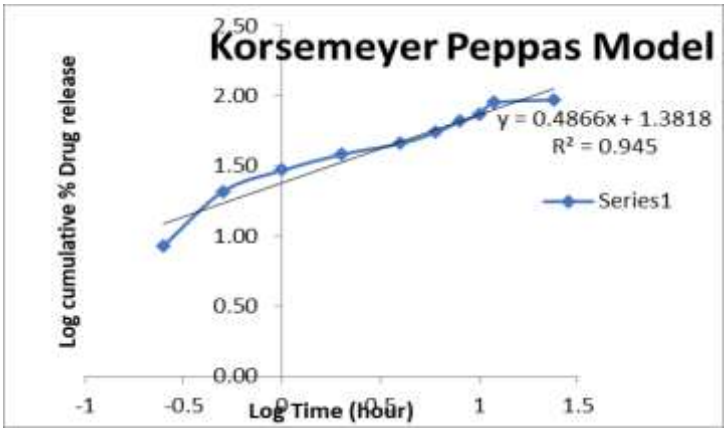


Figure 15: Korsemeyer peppas release model of formulation F3.

Table 12: Drug release kinetics of optimized formulation F3.

Formulation code	Zero order		First order		Higuchi		K. Peppas	
	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2
F11	3.8567	0.7846	-0.0522	0.9329	20.763	0.9562	0.4866	0.945

CONCLUSION

Emulgels will proliferate as a drug delivery method due to their advantages in extrusion, adhesion, viscosity, and spreadability. Topical medicine administration devices are commonly utilized due to their increased patient compliance rates. It was used to load hydrophobic medications onto gel bases that dissolve in water.

Using liquid paraffin as the oil phase, span 20 as the surfactant, PEG as the co-surfactant, and water as the aqueous phase, liquorice extract emulsion was effectively created. The formulation F3 were evaluated for pH determination reported as7.5±0.1, rheological studies reported as 5555±9, spreading coefficient studies reported as 7.5±0.3, swelling index reported as at 10min 58±0.1, At 20 min 92±0.1, At 30 min 120±0.1, in vitro drug release reported as 94.27±0.47%, and zeta potential was -21.4. They have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf-life bio-friendly, transparent and pleasing appearance. The formulation F3 was found to be explained by Higuchi's model, Korsemeyer Peppas release model, zero-order drug release, and first order drug release based on the results of the kinetic experiments. -

It may be concluded that liquorice emulgel extract can be utilized as an efficient topical dose form since it combines the benefits of an emulsion and a gel.

Conflict of interest

The authors have no conflicts of interest regarding this investigation**.**

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