Available online on 15.01.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Formulation and Evaluation of Capsaicin Transemulgel for the Treatment of Arthritis

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Article Info:

Article History:

Received 19 Oct 2024
Reviewed 30 Nov 2024
Accepted 28 Dec 2024
Published 15 Jan 2025

Cite this article as:

Manjanna KM, Veeran Gouda B, Tanusha AS, Ankita S, Anusha H, Arpita J, Formulation and Evaluation of Capsaicin Transemulgel for the Treatment of Arthritis, Journal of Drug Delivery and Therapeutics. 2025; 15(1):83-83 *DOI: http://dx.doi.org/10.22270/jddt.v15i1.6946*

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Abstract

Capsaicin (CAP)is a non-narcotic analgesic and anti-inflammatory drug used to relieve pain and inflammation associated with rheumatoid arthritis. Transemulgel is a new approach with combination emulsion and gel base having special characteristics dual controlled release for the treatment of various conditions arthritis. The present research work, a novel transemulgel with CAP (F1-F6) was formulated by using different concentration of gellan gum (GG) and xanthan gum (XG) as gelling agents with oil in water emulsion base. No significant drug-excipient interactions were observed in FT-IR studies. To evaluate various characterizations of transemulgel such as pH, spreadability, viscosity, gelation time, drug content, *Invitro* drug release of gel was examined in phosphate buffer pH-7.4 by Franz diffusion cell technique. The optimized transemulgel of (F5) showed pH of 5.8 ± 0.52 and viscosity of2840 ± 0.65cps. The percentage of drug content in the formulated transemulgel (F1-F6) was observed in the range of 84 to 96%w/w respectively. The optimal transemulgel spreadability was found to be 22.23 ± 0.25g·cm/s. The percentage of cumulative drug release from the formulations (F1-F3) were found to be in the range between 72.85 to 62.18% w/w and the batches (F4-F6) were observed in the range 76.85 to 70.66%w/w at the end of 6h.By considering all the investigated data while increase in concentration of GG and XG were influenced rheological properties, drug content efficiency, the *Invitro* drug release of transemulgel. The present investigate suggest that the CAP loaded transemulgel can be a promising topical delivery to relieve pain, inflammation and provided greater bioavailability to improve therapy.

Keywords: Topical delivery, Transemulgel, Capsaicin, Xanthan gum, Gellan gum, Emulsion, Arthritis

1. INTRODUCTION

The human skeleton and muscle help to make possible the peaceful gyration as well as more safe routine movements of everyday life. Natural glucosamine in the body which is involve to produces principal lubricating proteins in our cartilage, tendons, ligaments, synovial fluid and mucous membranes.[1] Imbalance in the regeneration process of these functional elements of the joint leads to friction, pain and inflammation.[2]. Arthritis is a term that includes a group of disorders that affect your joints and muscles cases certain symptoms include joint pain, inflammation and limited movement of joints[3]. Major types include osteoarthritis, rheumatoid arthritis, and gout.[4] Although many specific drugs for treatment of major inflammation and/or acute pain like steroidal anti-inflammatory agents or narcotic analgesics are available in the form of oral tablets, capsules and injectable solutions. The traditional conventional oral and injectable solution dosage forms having certain potential drug related adverse effects and poor patient compliance.[5]

In the past and present scenario, the treatment of various conditions of arthritis diseases has been accomplished by administration of active medicaments as dosage forms to human body via dermal route. Topical drug delivery system is a route of administration of specifically designed with active drug formulations to deliver across the skin and mucous membrane[6]. Skin is one of the crucial and important multifunctional organs of the human body that acts as semi-permeable membrane to deliver the drugs in to systemic circulation [7]. There are several conventional pharmaceutical products such as solutions liniments, creams, gels and aerosol sprays are applied on skin to relief pain at inflamed area of the body. These are having several drawbacks as inability to absorb through multilayer of the skin due to has a less residential time and poor penetrability. Skin penetration of drugs mainly depends directly on nature of epidermal layer as stratum cranium and the physiochemical properties drug in the formulation.[8]

Capsaicin (CAP) is a newly potent non-narcotic analgesic and anti-inflammatory drug used to relieve pain and

inflammation associated with rheumatoid arthritis, osteoarthritis post-therapeutic neuralgia.9. CAP is an BCS-II (Biopharmaceutics classification system) compound with poor aqueous solubility and low dissolution rate. CAP is unsuitable for oral administration due to its high first-pass metabolism and gastric irritation.[10] CAP based pharmaceutical products such as solutions, creams, dermal patches and aerosol sprays are used for topical delivery for the treatment of pain and inflammatory disorders. The lipophilic properties of CAP are a good candidate for formulation of topical products.[11] Gels as topical drug delivery systems contain a more significant amount of aqueous or hydro-alcoholic liquid in a network of colloidal solid polymeric materials The higher aqueous component permits greater dissolution of drugs, and permits easy migration of the drug as compared to the ointment or cream base products. The main disadvantage of gels are unsuccessful in delivering hydrophobic or lipophilic drugs.[12]Nowadays the pharmaceutical manufacturers are focusing for development of emulsion gel-based drug carriers are considered to be effective enough potential modification of skin permeability, safe delivery of both hydrophilic and lipophilic drugs.

Transemulgel is prepared both in oil-in-water and water-in-oil type emulsion mixed with gel. Oil-in-water type is used for lipophilic drugs and water-in-oil type is used for hydrophobic drugs delivery.[13] The Transemulgel have many advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf-life[14].

The present research work was to formulate and evaluate transemulgel by using different concentration of gellan gum (GG))) and xanthan gum (XG) as gelling agents with CAP incorporated into an oil-in-water emulsion base

2. MATERIALS AND METHODS

Capsaicin (CAP) was obtained as a gift sample from Naturita Agro products Ltd, Hyderabad. Xanthan gum and Gellan gum were gift sample from F.M.C. International biopolymers, Willington, Liquid paraffin, Tween80 and Span80 were purchased from Fine Chemicals, Bengaluru. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

2.1 Determination of melting point:

Melting point of capsaicin was determined by capillary method. Fine powder of capsaicin was filled in a glass capillary tube (previously sealed at one end). The capillary tube was tied to thermometer and placed in the Thieles tube. The melting point setup and temperature range at that the drug melted was recorded.

2.2. Development of absorption maxima (λ max) by UV – Visible spectroscopy

A stock solution of CAP was prepared by dissolving 10 (mg) of pure drug with pH 7.4 phosphate buffer in a 10 mL volumetric flask to obtain the concentration 1000 µg/mL. Accurately measured 1 mL of the above stock solution was further diluted up to 10 mL with pH 7.4 phosphate buffer to obtain a working standard solution containing 10 µg/mL were subjected to scanning between 200-400nm by using pH 7.4 phosphate buffer solution as blank in a UV-Visible spectrophotometer.[15] The absorption maxima of capsaicin were obtained at λmax 279nm.

2.3. Construction of calibration curve of capsaicin (pH 7.4 phosphate buffer):

The different aliquots of working standard solution were diluted serially by taking 1,2,3, 4 and 5ml from stock solution to diluted with 10ml of pH 7.4 phosphate buffer solution to get the concentration 10,20,30, 40 and 50µg/ml solution. The absorbance of these solution was measured against pH 7.4 phosphate buffer solution as blank. The solution was analysed at 279 nm by using UV spectrophotometer.[15] The standard calibration curve CAP plotted by taking concentration on x-axis and absorbance on y-axis to obtain a straight line. The certain parameters such as the slope, intercept, coefficient of correlation, standard deviation was calculated.

2.4. Saturation solubility studies:

The saturation solubility of CAP was determined by excess quantity of capsaicin (approx. 1G) was added individually to 10 mL of liquid paraffin, surfactants (Tween 80 and Span 80), and co-surfactants (triethanolamine and propylene glycol) in a 100 mL volumetric flask. Then, the mixture was kept in a shaking water bath at 37 ± 0.5 ◦C for 24 h at 100 rpm. The sample was then centrifuged at 3000 rpm for 15 min. After centrifugation, 1 mL of the supernatant fluid was withdrawn from each mixture, diluted with pH7.4 phosphate buffer and analysed at λ max 279 nm by UV-Visible spectrophotometer (Shimadzu 1800, Japan) [16]. The quantity of CAP present in the sample was calculated by using the equation of the standard curve.

2.5. Drug excipients compatibility study by using FTIR:

The drug polymer interactions were studied by using Fourier Transform Infrared (FT-IR) Spectrophotometer (Shimadzu 1700S). The samples were prepared by adopting KBr pellet technique and scanned from 4000 to 450 cm−1 taking air as the reference. The resultant spectra of pure drug, excipients and physical mixtures were compared for any possible changes their functional groups in the spectral region.

2.6. Preparation of CAP emulsion:

Three batches of CAP emulsion were prepared using a different concentration of span 80 and tween 80 as emulsifying agents. The selection of suitable emulsion

depends on parameters such as physical appearance, phase separation and formation of oil globule size at the time of emulsion formation. From considering these parameters, F3 containing emulsifying agent at a ratio (3:1.5) showed milkiness, longer phase separation and to form homogeneous stable emulsion.

Table 1: Composition of CAP Emulsion

Ingredients	F-1	F-2	F-3
Capsaicin(mg)	50	50	50
Liquid Paraffin(mL)	05	10	15
Tween 80(mL)	1.0	0.5	1.5
Span80(mL	1.0	1.5	3.0
Ethanol(mL)	5.0	5.0	5.0
Propylene glycol(mL)	5.0	5.0	5.0
Methyl paraben(mg)	0.05	0.05	0.05
Purified water up to mL	50	50	50

The oil phase of the emulsion was prepared by mixing span 80 in liquid paraffin stirred using magnetic stirrer at 50rpm until to form a homogenous mixture. While the aqueous phase was prepared by dissolving tween 80 in purified water. CAP was dissolved in ethanol, methyl paraben was dissolved in propylene glycol and added into the aqueous phase. Both the oily and aqueous phases were separately heated at 40–60°C, respectively, then the aqueous phase was added to the oily phase 1:1 ratio with continuous stirring until to cooled at room temperature. The composition of different CAP emulsion has been demonstrated in Table 1

2.7. Preparation of CAP Transemulgel:

The gel base was prepared by dispersing different concentration of gellan gum and xanthan gum as gelling agents in distilled water by stirring on the magnetic stirrer at 50rpm and maintains the temperature 55˚ C to form clear gel base, cooled at room temperature. The formulated stable emulsion was mixed with the gel base in the ratio 1:1 subjected to homogenization for 1 hours to get transparent transemulgel. The pH was adjusted to 6-7 using triethanolamine. The composition of different formulations has been demonstrated in Table 2.

Table 2: Composition of CAP Transemulgel

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6
Capsaicin(mg)	50	50	50	50	50	50
Liquid Paraffin(mL)	10	10	10	10	10	10
Gellan gum(gm)	0.5	1.0	1.5			
Xanthan gum(gm)	-	-	-	0.5	1.0	1.5
Tween 80(mL)	1.5	1.5	1.5	1.5	1.5	1.5
Span80(mL	3.0	3.0	3.0	3.0	3.0	3.0
Methanol(mL)	5.0	5.0	5.0	5.0	5.0	5.0
Propylene glycol(mL)	5.0	5.0	5.0	5.0	5.0	5.0
Methyl paraben(mg)	0.05	0.05	0.05	0.05	0.05	0.05
Purified water(mL) upto	q. s	q. s	q. s	q. s	q. s	q. s
Triethanolamine	To adjust pH					

3. Characterization and evaluation of CAP Transemulgel gel

3.1. Physical appearance:

All the batches of formulated transemulgel were inspected visually for physical appearance, colour, clarity, homogeneity, consistency, grittiness, and phase separation.

3.2. Determination of pH:

The formulated transemulgel was subjected to determine the pH meter (Systronics VL-808) at room temperature. This pH meter was three-point calibrated (pH 4, pH 7, and pH 10) with standard buffer solutions to ensure instrument validity. Weighed 1 gm of gel formulation was dissolved with 100mL of distilled water and estimation of pH in the range 4 to 9 was carried out in triplicates. The results were declared as average value ± standard deviation.

3.3. Measurement of rheology:

The viscosity of the formulated batches was measured by using Brookfield rotational viscometer (DV-II). The formulated transemulgel was taken in a beaker, allowed to settle down for 30 min at room temperature. Adjust the spindle in that way that does not touch the bottom of the jar. The viscosity of the sample was recorded by using spindle RV- 4 at speed of 6,12,30 and 60rpm for 10

minutes.[17]All measurements were carried out in triplicates, the results were represented as average value ± standard deviation.

3.4. Measurement of Spreadability:

For the determination of spreadability, 1gm of sample was applied between two glass slides and was compressed to uniform thickness by placing 1000gm weight on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. The top plate is then subjected to tying with the help of string attached to hook; the dispensing balance pan is fixed. The weights are placed on the pan and note the time (seconds) in which upper glass slide moves over the lower plate at constant distance. A shorter time to reach standard distance shows a better spreadability.[18] Each experiment was carried out in triplicate. The measurement of spreadability was calculated by using the formula,

$$S=M\times L/T$$

Where; S=Spreadability, M=Weight tied to upper slide, L=Length moved on the glass slide, T= Time (seconds) taken to separate the slides completely

3.5. Swelling Index:

Swelling behaviour of formulated transemulgel was determined by taking 1G gel on porous aluminium foil and then placed separately in a petri plate containing 10 ml of pH7.4 phosphate buffer. Then samples were removed from petri plate at different time intervals and reweighed. Each experiment was carried out in triplicate. The percentage of swelling index is calculated as follows:

$$\text{Swelling Index (SW)\%} = [(Wt. - Wo) / Wo] \times 100$$

Where, (SW) % = swelling index, Wo = Initial weight of transemulgel at zero-time, Wt. = Final weight of transemulgel after time t.

3.6. Extrudability:

All the batches 10G of formulated transemulgel were filled in standard capped collapsible aluminium tubes and sealed by crimping to the end. The tubes were placed between two glass slides and tying with thread or clamp. Known weight(500G) was placed over the slides, and then open the cap of the tube. Based on the weight required to easy extrude gel from the collapsible tube at particular time and area(cm). Measured the area (cm2), the amount of the extruded gel was collected and weighed. Each experiment was carried out in triplicate. The percentage of extrudability was calculated by using the following formula:

Extrudability = Weight to extrude transemulgel from tube (gm.)/Area (in cm 2)

3.7. Gelation time:

Weighed (2g) of the formulation was taken in a glass test tube and was placed in a water bath which is maintained at 37±2° C. The gelation time was noted when there was no flow of gel when the test tube was inverted. All measurements were carried out in triplicates, the results were represented as average value ± standard deviation.

3.8. Drug content:

Weighed 10Gof each gel formulation was transferred to 250 mL volumetric flask containing 20 mL of pH 7.4 phosphate buffer and was stirred on magnetic stirrer at 50rpm for 30min. The volume was made up to 100 mL and filtered through vacuum filter. One mL of the filtrates was further diluted with 10mL of pH 7.4 phosphate buffer and the absorbance was measured by using spectrophotometry[19] (Shimadzu 1201, Japan) at 279nm. The CAP amount present in each formulation was calculated using calibration curve by using following formula. Each experiment was carried out in triplicate

$$\text{Drug content} = \frac{(k \times \text{Absorbance} \pm B) \times \text{bath volume} \times \text{dilution factor}}{1000}$$

[where, k = Slope and B = intercept]

3.9. *Invitro* diffusion studies

The drug release from formulated CAP loaded transemulgel was performed by using Franz diffusion cell (Dolphin instruments, Mumbai). A suitable thickness of pre-treated cellophane membrane was fixed between donor and receptor compartment of the diffusion cell. The required quantity of gel (equivalent to 50mgof CAP) was kept in donor compartment. The entire surface of membrane was in contact with the receptor compartment containing 25 mL pH7.4 of phosphate-buffer with a rotation speed of 50 rpm for 3h and the temperature was maintained at 37±1°C. At the defined times (0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 h), the 5ml sample was withdrawn and replaced with same volume of fresh medium. The withdrawn samples were filtered through a 0.45 µm membrane filter and after appropriate dilution, the concentration of drug in releasing medium at each of these times were measured at 279 nm spectrophotometrically (Shimadzu 1800, Japan).[20] The percentage drug release vs time of each formulation was represented graphically.

3.10. Kinetics of Drug Release:

In order to understand the mechanism and kinetics of drug release and the best fit model for the formulations was used by PCP-Disso-V2 software. The drug release data of the in vitro diffusion study was subjected to analysed with various kinetic equations like zero-order (% Release v/s Time), first-order (Log % retained v/s time), and Korsmeyer and Peppas equations ($Mt/M\infty = Ktn$). Where Mt is the amount of drug released at time t, $M\infty$ is the amount of drug released at infinite time, K is the kinetic constant incorporating the structural and geometric characteristics of the gel, and n is the diffusional exponent indicative of the release mechanism[21]. Where n= 0.5 represents Fickian diffusion, < = 1.0 case-II transport, and n > 1.0 super case-II transport. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

3.11. Accelerated stability studies:

The stability studieswere performed by filling the optimized batch (F5) transemulgel in a collapsible tube and stored at 30 °C/65% relative humidity (RH) and 40 °C/75% RH in the humidity chamber for 30 days. Sample was collected at 10, 15, 30 days interval of storage and assessed for physical appearance and drug content.

4. RESULTS

4.1. Determination of melting point of CAP

The melting point (MP), a fundamental physical property that specifies the transition temperature between solid and liquid phases during the manufacturing process is widely applied in pharmaceutical science. The observed value of M.P of CAP is 58^{0}C

4.2. Determination of absorption maxima (λmax):

For accurate analytical work it is important to determine the absorption maxima of the substance under study. Scanning of CAP stock solution (10µg/ml) in pH7.4 at 200–400 nm by using UV Visible spectrophotometer (ShimazduUV-1800) by using pH 7.4 PBS as blank The maximum absorbance was found to be 279 nm, which is similar to standard references. The obtained absorption spectra were depicted in Fig.1

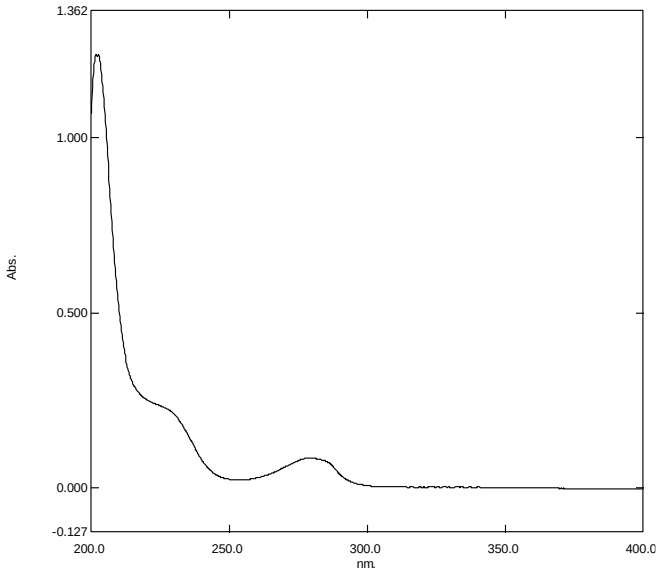

Figure 1: Absorption maxima (λ max) of CAP at 200-400nm

4.3. Construction of standard calibration curve:

Fig. 2 shows the calibration curve CAP in pH 7.4 phosphate buffer a straight line was obtained by plotting the absorbance versus concentration. This indicates that the calibration curve within this range of concentration obeys Beer-Lamberts law at λmax279 nm. A linear graph of absorbance vs. standard concentration (µg/ml) showed correlation coefficient (R2) value was 0.995 with regression equation Y= 0.0115x -0.312. The plot as shown in Fig.2

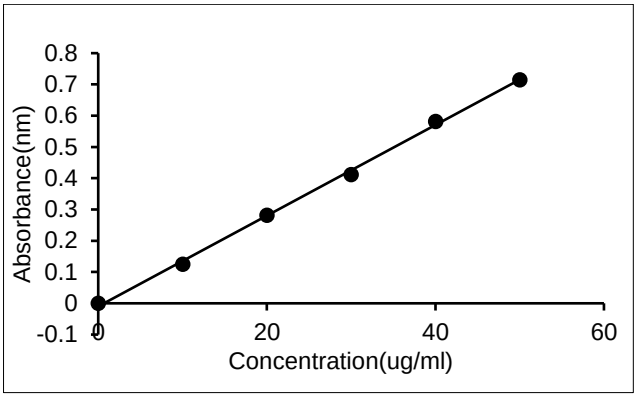

Figure 2: Standard calibration curve of CAP in pH PBS by UV – Visible spectroscopy

4.4. Saturation solubility studies:

CAP is belongs to a BCS-II drug with poor aqueous solubility and low dissolution rate. The solubility of CAP was determined in various vehicles, mentioned in Table 3.

Table 3: Saturation solubility of CAP in different vehicles.

Vehicles	Solubility of CAP (mg/mL)
Distilled water	024.55 ± 05
Methanol	105.55 ± 23
Liquid paraffin	085.50 ± 06
Clove oil	080.85 ± 10
Tween80	110.35 ± 25
Span80	135.87 ± 35
Propylene glycol	138.30 ± 15
Triethanolamine	141.25 ± 05
pH1.2 buffer solution	056.52 ± 07
pH4.8 buffer solution	108.65 ± 22
pH7.4 buffer solution	155.25 ± 50

Data are the mean ± S.D. n=3

4.5. Drug excipients compatibility study by using FTIR:

The molecular interactions of CAP, Gellan gum (GG) and xanthan gum (XG) in the transemulgel were investigated using FTIR spectroscopy. The characteristic absorption peaks of pure CAP were obtained 3276.5, 2858.5, 1348.3, 1179.6 and 949.4cm^{-1}corresponding to N-H and O-H stretching, C=O stretching, C-N bonds stretching, C-H bends respectively. (Fig.1a) In FTIR spectrum of GG (Fig. 1b), the bands appearing at 1627.81 and 1409.87 cm^{-1} are due to asymmetric and symmetric stretching of carboxyl group. The band at 2927.74 cm^{-1} is due to the stretching vibrations of –CH2 group, while those appearing at 1153.35 and 1024.13 cm^{-1}is due to

ethereal and hydroxylic C-O stretching. Bending vibration of C-H appeared at 891.05 cm–1. The band at 3427 cm–1 is due to the presence of OH– group of glucopyranose ring.

Further, characteristic IR peaks of XG show around 3408.18cm-1which are due to O-H deformation, 2800-2950.84 -CH stretching, 1628.19, 1503.56cm-1 are due to C=O and COO- stretching and 718.81 cm^{-1}C-O of carboxyl group (Fig.1c). The physical mixture formulation batch (F3) characteristic peaks were obtained at 2820.28, 1591.72, 1384.91, 1102.03 and 766.4cm^{-1} (Fig.1d) and physical mixture of formulation batch (F5) characteristic peaks were observed at 30556.97, 2940.01, 1708.99, 1509.35 and 761.24 cm^{-1}(Fig. 1e).

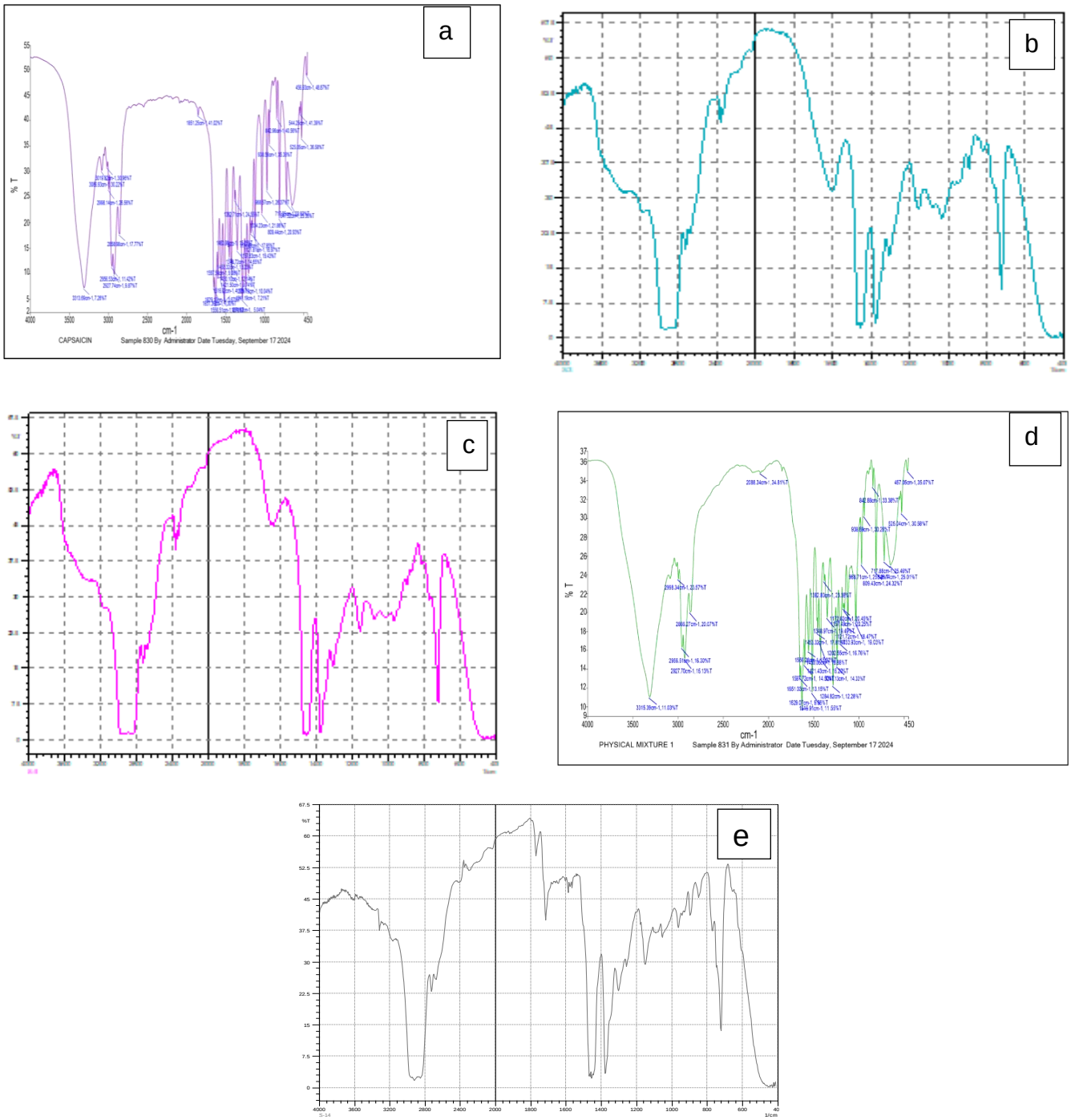

Figure 3: FT-IR Spectra a) Pure capsaicin b) Gellan gum c) Xanthan gum d) Physical mixture of formulation F3 e) Physical mixture of formulation F5

4.6. Evaluation of CAP loaded transemulgel:

All the batches of formulated transemulgel were subjected to evaluate the physical characteristics such as pH, extrudability, viscosity, spreadability, gelation time and drug content. The determined values are depicted in Table 4. The swelling behavior of the transemulgel in pH7.4 at different time intervals were investigate and represent graphically in Fig.4.

Table 4: Physical characterization of formulated CAP Transemulgel

Batch code	pH	Extrudability (cm2)	Viscosity (cps)	Spreadability (g.cm/sec)	Gelation time(sec)	Drug content (%w/w)
F-1	5.64 ± 0.55	18.62 ± 0.22	2410 ± 0.81	13.12 ± 0.23	62 ± 1.2	84 ± 0.2
F-2	5.55 ± 0.82	15.35 ± 0.51	2630 ± 1.12	16.10 ± 0.52	80 ± 1.3	90 ± 0.3
F-3	5.45 ± 0.21	16.75 ± 1.12	3840 ± 0.52	28.46 ± 0.11	102 ± 0.5	94 ± 0.5
F-4	5.75 ± 0.35	20.65 ± 0.53	2620 ± 0.54	11.56 ± 0.42	69 ± 0.8	87 ± 0.6
F-5	5.80 ± 0.26	19.35 ± 0.23	2840 ± 0.65	22.23 ± 0.25	87 ± 0.6	92 ± 0.1
F-6	5.60 ± 0.12	17.87 ± 0.05	3896 ± 1.23	26.65 ± 0.36	120 ± 0.2	95 ± 0.2

Data are the mean ± S.D. n=3

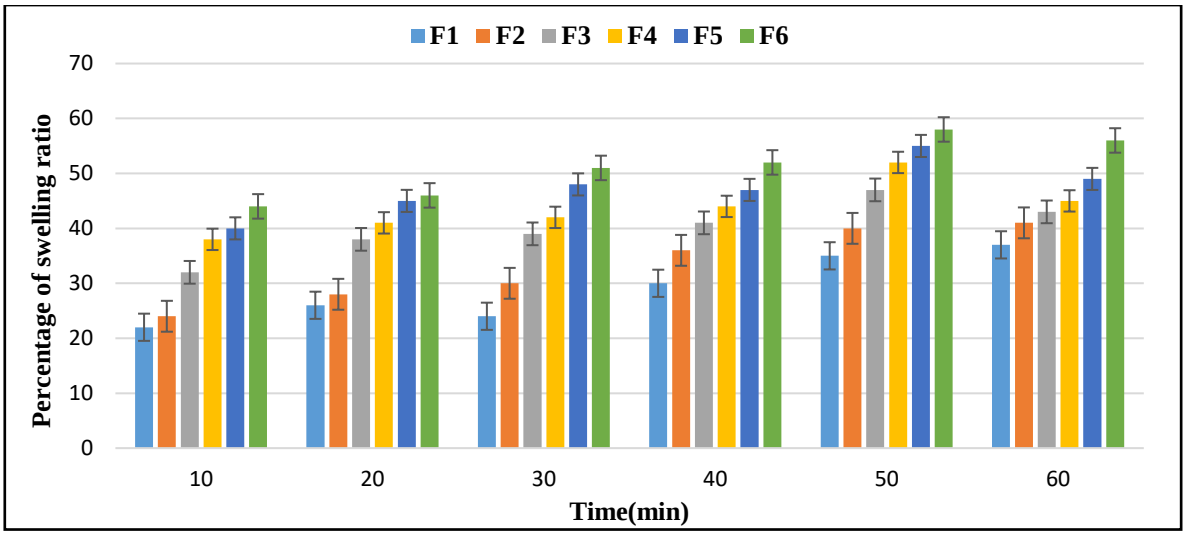

Figure 4: Swelling behaviour of transemulgel formulations in pH7.4PBS at the end 60min

4.7. *Invitro* diffusion studies:

The formulated capsaicin loaded transemulgel was subjected to In-vitro diffusion studies by using Franz diffusion cell fixed with cellophane membrane at different time intervals up to 6h. The percentage of cumulative drug release from the formulations (F1-F3) were found to be in the range between 72.85 to 62.18% w/w and the formulation batch(F4-F6) were observed in the range 76.85 to 70.66%w/w at the end of6h. The release profiles are depicted in Fig.5,6

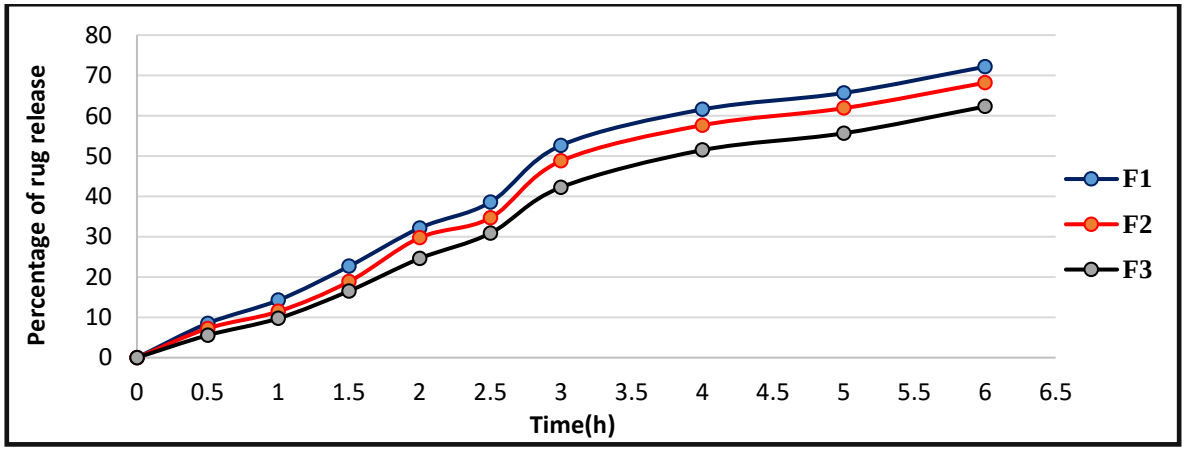

Figure 5: In vitro drug release profile from transemulgel formulations at pH7.4PBS

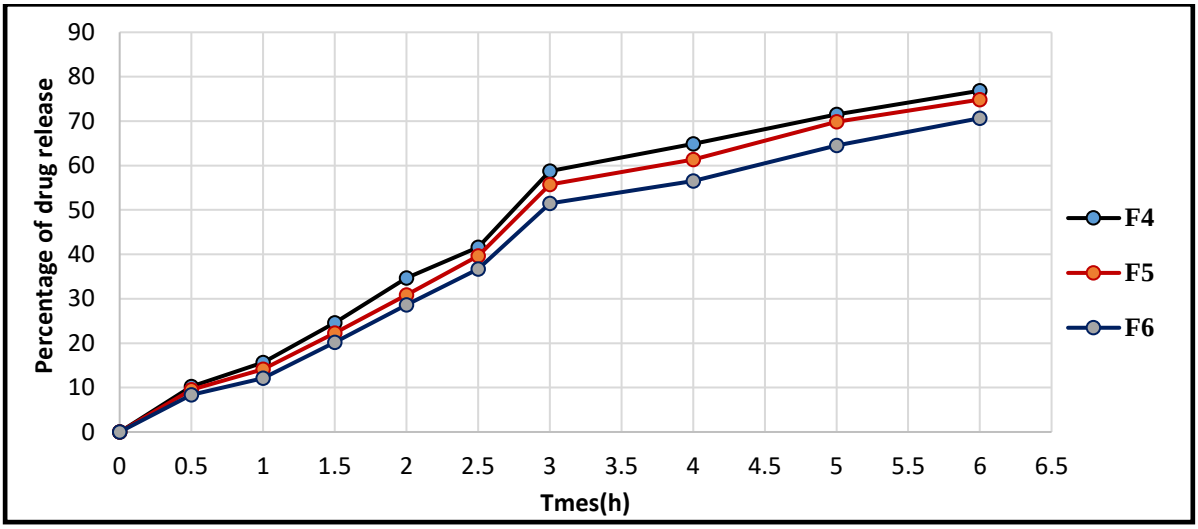

Figure 6: In vitro drug release profile from transemulgel formulations at pH7.4 PBS

4.8. Kinetics of Drug Release:

The data obtained from the *in-vitro* dissolution studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software. The optimized batch (F5) transemulgel *Invitro* dissolution data were analysed by different kinetic models in order to find out the n-value, which describes the drug release mechanism. The results depicted in Table 5.

Table 5: Kinetic drug release of optimized formulation F-5 transemulgel

Kinetic models	R2 Values	n-Values
Zero-order	0.9698	
First order	0.9430	-
Hugachi Matrix	0.9109	-
Korsemeyer-Peppas	0.9982	1.5140

4.9. Stability studies:

The optimum batches of formulated transemulgel were subjected to stability studies at 30 ^{0}C/65% relative humidity (RH) and 40 ^{o}C/75% RH for 30 days. The physical characteristics such as color, odor, texture and drug content were determined at 10, 15, 30 days interval. The results depicted in Table 6.

Table 6: Stability data of Formulation FG-3

Parameter	**Day 0**	**Day 10**	**Day 15**	**Day 30**
Color	No changes	No changes	No changes	No changes
Odor	No changes	No changes	No changes	No changes
pH	5.80	5.80	5.75	5.63
Drug content	92 ± 0.1	92 ± 1.25	91 ± 0.15	90 ± 0.65

5. DISCUSSION:

Capsaicin (CAP) is a newly potent non-narcotic analgesic and anti-inflammatory drug used to relieve pain and inflammation associated with rheumatoid arthritis, osteoarthritis post-therapeutic neuralgia. The CAP belongs to BCS-II have poor water soluble and dissolution rate and short biological half-life can lead to a low concentration of the drug reaching to the plasma as result shows sub-therapeutic response. Moreover, for dermal application of CAP in the form of conventional liniments or creams can be causes more irritation and sensitization on the skin surface. Therefore, the efforts of many researchers have to develop lipid-based gel that

was increases the adhesiveness to the skin epidermis layer to create a concentration gradient which is ultimately to improve bioavailability and minimizes the drug related disorders.[22]In this paper a novel technique used to prepare transemulgel and investigated the potential utility of the natural materials such as gellan gum and xanthan gum as gelling agents with oil in water emulsion base to reduce the dosing frequency, eliminate the dose related adverse effects and ultimately improve the compliance in the pharmacotherapy of arthritis, inflammation and pain.

The batches F1-F3 using GG gum as gelling agents shows light yellow color and the formulated batches F4-F6 using XG shows white off color. By manual observing under the luminous light all the formulations were viscous, creamy preparation with a smooth, homogeneous texture, glossy appearance. The grittiness of the gel was observed under light microscope, found free from any extraneous matter or aggregates.

The analysis of MP is one of the tools for examination of the purity of materials. The MP of CAP (58^0C) as compare to IP grade specifications suggest that the absence of impure substances and no heat transition during manufacturing process. Therefore, the CAP is suitable candidate for formulation of transemulgel.

The absorption maxima of capsaicin were subjected to scanning in the range of 200-400nm using double beam UV-Visible spectrophotometer (ShimazduUV-1800). The characteristic sharp absorption peak capsaicin was obtained at 279nm. Thus, regression analysis for the linearity showed very good correlation between absorbance and concentration at 279nm.

The available data on solubility profile of CAP indicated that the drug is freely soluble in methanol; acetone and practically insoluble in water, partially soluble in different oils. The saturation solubility of CAP in different vehicles were investigated by using UV-Visible spectroscopy (Table 1). Saturation solubility of CAP in different medium increased with an increase in buffer pH as well as with an increase in surfactant and co-surfactant concentration. Lipophilic property of CAP is favourable for solubility with oil medium.

The compatibility of CAP with other excipients used in the formulation were investigated by FTIR studies. The spectral functional groups of the drug and combination of excipients mixture were compared with the pure drug and individual polymer showed no shift and no disappearance of characteristic functional groups suggesting that confirms the drug was molecularly dispersed in the oil phase and gel base of the formulation without any interaction.

The maintenance and the protection of the normal physiological skin pH is very important that could be contribute to skin health and therapeutic action of the dosage regimen. The investigation of pH is one of the crucial parameters for topical products which are close to the physiological range between pH 4.5- 7.0 to avoid the irritation of skin. The pH values of all the batches F1 to F6 were found to be in the acceptable range as 5.39-5.64 (Table.4) indicates no risk of irritation upon application to the skin. The ability of the gel easy to extrude from a collapsible tube can be measured in terms of extrudability and was obtained in the range 15.35 ± 0.51to 19.35 ± 0.23cm^2 (Table.4).The concentration of gelling agent used in the formulation may influences the consistency of the gel. Low viscous gel extrudes quickly and higher consistency gel was extruding slowly when apply to more external pressure.

Table.4. All the formulated formulations (F1-F6) were found optimum viscosity and gives in the range between of2410 ± 0.81 to 3896 ± 1.23cps. Viscosity is a significant rheological parameter to measure the thickness of a gel to flow that is related to the mechanical and physical properties, such as spreadability, consistency, extrudability, easy to apply and removal and diffusion of the drug. The concentration of gelling agent used in the formulation was significantly influences the viscosity. Therefore, the concentration of gelling agent increases the viscosity can be predominately in an increasing manner which affects the consistency.

The spreadability is the ability of a topical transemulgel easy to spread on the surface skin and also plays a major role in the penetration of drug through different layer of skin. The spreadability of the formulated batches (F1-F3) by using GG as gelling agent were obtained in range of 13.12 ± 0.23to 28.46 ± 0.11 g.cm/sec, batches (F4-F6) by adding XG as gelling agent were observed in the range of 11.56 ± 0.42 to 26.65 ± 0.36 g.cm/sec, (Table 4). The batches showed highest spreadability, due to the low concentration of gelling agent, lowest spreadability may be due the formation of high gelling network structure gel. Moreover, the highest spreadability of a gel create a larger surface area for the drug to increases permeation which can enhance the drug diffusion.

The drug content uniformity is necessary for semi-solid preparation to ensure molecular dispersion of active medicament in the entire formulation. UV -Visible spectrometer was used to determine the CAP content in the formulated transemulgel and was observed in the range of 84 ± 0.2 to 95 ± 0.2% w/w (Table 4). The results reveal that the percentage of drug content increase progressively with the concentration of gelling agent due to more quantity of drug entrapped in dense matrix of the gel. The loss of the drug during formulation processes was insignificant

The batches of transemulgel (F1-F3) were formulated by using different concentration of GG (0.5, 1.0, 1.5g) as gelling agent, percentage cumulative drug release obtained in the range of72.15, 68.18, 68.28 w/w up to 6h (Fig.5). Further, percentage cumulative drug release obtained in the range of 76.85, 74.55 w/w up to 6h from the batches of transemulgel (F4-F6) were formulated by using different concentration of XG (0.5, 1.0, 1.5g) as gelling agent (Fig.6).The obtained results suggest that the concentration of gelling agent was increased that will significantly decreases the drug release due to more

viscosity followed by decreasing of drug diffusion and penetration as a result the release of drug slowly in a sustained manner for extended period of time.

The*in vitro* dissolution data were analyzed by different kinetic models in order to find out the n-value, which describes the drug release mechanism (Table 5). The *Invitro* drug release from the optimized formulation (F5) containing 1%w/w of XG was found to zero-order kinetics followed to best fit with Korsmeyer–Peppas model. The values of diffusion coefficient obtained in the range of n = 1.5140 indicating the drug release from the gel followed case-II transport controlled by diffusion of gel matrix in dissolution medium.

The results of stability studies did not show any significant change in the physical appearance and drug content. Therefore, the formulated transemulgel was stable at 30 ^{0}C/65% RH and 40 ^{o}C/75% RH for 30 days. (Table 6)

6. CONCLUSION

Capsaicin (CAP) is a newly potent non-narcotic analgesic and anti-inflammatory drug used to relieve pain and inflammation associated with rheumatoid arthritis, osteoarthritis post-therapeutic neuralgia. The CAP belongs to BCS-II have poor water soluble and dissolution rate and short biological half-life can lead to a low concentration of the drug reaching to the plasma as result shows sub-therapeutic response. Thus, incorporation of capsaicin into o/w emulsion and then into formulation of gel increased the solubility. The present research work a novel transemulgel with CAP (F1-F6) was formulated by using different concentration of gellan gum (GG) and xanthan gum (XG) as gelling agents with oil in water emulsion base. Based on present investigated results the transemulgel formulated by using 1%w/w xanthan gum (F5) as gelling agent showed acceptable pH, viscosity, better spreadability, permeation, minimizes irritation to skin and release the optimum drug. Therefore, overall, the results showed that transemulgel can be a promising formulation for the application of capsaicin to relieve pain and inflammation.

Acknowledgement: The authors thank to the principal, chairman of T. V. M College of Pharmacy, Ballari, Karnataka for giving the permission to conduct the research work with providing necessary facilities

Conflict of interest: The authors declare that they have no conflict of interest.

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