Formulation And Evaluation of Famciclovirgel Microemulsions

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Abstract: **Microemulsions are characterized as the dispersion of at least two fluids that are not easily mixed, with the droplets being extremely minute in size (often in the range of nanometers, such as 20-200 nm). Transparent or translucent systems exhibit thermodynamic equilibrium between the components found in distinct phases. The gelling microemulsion drug delivery system is an innovative method for formulating pharmacological molecules for transdermal administration. This strategy amalgamates the benefits of both solutions, including the precision and ease of administration of the former, and the extended duration of the latter. Therefore, the gel-forming system extends the duration that the drug remains in the body and enhances the absorption of the drug through the skin. The main benefit of this formulation is the ability to deliver precise and consistent amounts with enhanced penetration. Microemulsion is a highly promising method for addressing the challenges associated with formulating hydrophobic/lipophilic medicines. Apreformulation study was conducted, which involved investigating the solubility of the medicine and studying the compatibility between the drug and excipients. The hydrogel was assessed for its viscosity, pH, in vitro drug release, spread ability, and diffusion research. The globule size of the microemulsion was assessed. Hydrogel samples from the final formulations F3&F6 were retained for a stability study lasting one month.**

***Index Terms*—Microemulsions, Gelling, Transdermal, Hydrogel**

I.INTRODUCTION

Transdermal delivery provides several advantages compared to traditional techniques. One major issue with transdermal administration is that it is challenging for most medications to penetrate the skin. However, drugs given topically by microemulsions offer various advantages.1.The product exhibits little skin irritation, possesses strong penetration capabilities, and has a large capacity for loading drugs.2.There are several methods by which microemulsion can boost permeation. These include an enhanced concentration gradient and thermodynamic activity to the skin, which promote permeation improvement.3. This can be achieved by incorporating hydrogel thickening agents such as Carbopol, hydroxypropyl methylcellulose, and xanthan gum into the formulation. Famciclovir is commercially accessible in cream and ointment forms. This makes it a appropriate candidate for the development of a hydrogel formulation of the medicine, which can be achieved by incorporating a penetration enhancer and a controlled release polymer.[1,2]

Hydrogels are polymer matrices that swell in water and have a high capacity for absorbing water. The particular properties of swell under physiological settings make it an exceptional material for biomedical applications. Hydrogels are classified based on the polymers used, the origin of these polymers, the process of crosslinking, their responsiveness to stimuli, and their ionic charge. The hydrogels consist of polymers that can be either natural, synthetic or a combination of both. The gels are designed to respond specifically to their stimuli. As the physical environment changes, the gels will exhibit the property of swelling and can be utilized in various conditions. Hydrogels are specifically created from both natural and synthetic polymers. Multiple procedures are employed to synthesize hydrogels. Hydrogels typically consist of ionic or covalent connections between polymeric chains that are chemically crosslinked.[3]

Hydrogels are widely employed in a variety of controlled release systems, including as systems that are swelling-controlled, chemically controlled, or

diffusion-controlled. We'll talk about drug release mechanisms in a variety of systems below.[1]

- Diffusion-controlled Delivery Systems
- Swelling-controlled Delivery Systems

Applications Of Hydrogels In Drug Delivery

- Peroral drug delivery
- Drug delivery in the oral cavity
- Drug delivery in the GI tract
- Rectal delivery
- Ocular delivery
- Transdermal delivery
- Subcutaneous delivery

A microemulsion can be defined as a stable liquid solution consisting of water, oil, and an amphiphile, which exhibits optical isotropy and thermodynamic stability. Microemulsions consisting of tiny droplets of either oil-in-water (o/w) or water-in-oil (w/o) dispersed in a size range of around 5−50 nm in a drop radius. The droplets of the dispersed phase are typically of considerable size, usually exceeding 0.1 μm, resulting in a cloudy, rather than clear, appearance. Microemulsions undergo spontaneous production provided the appropriate conditions are met. Regarding uncomplicated aquatic systems, the generation of microemulsions relies on the kind and structure of the surfactant. Microemulsions can only be generated when a surfactant with a single hydrocarbon chain, such as sodium dodecyl sulphate (SDS), is ionic. Additionally, the presence of a co-surfactant, such as a medium-sized aliphatic alcohol, and/or an electrolyte, such as 0.2 M NaCl, is necessary. Co-surfactant is not required when using double chain ionics (such as Aerosol-OT) and certain non-ionic surfactants. The primary function of the surfactant is to effectively decrease the energy needed to expand the surface area, thus facilitating the spontaneous dispersion of water or oil droplets and ensuring the system's thermodynamic stability. The generation of microemulsions is highly dependent on the system composition, with ultra-low tensions playing a vital role.[4,5]

Classification of microemulsions (Winsor)

- Type I: Oil-in-water (o/w) microemulsions occur and the surfactant is favorably solvable in water (Winsor I). Surfactants is only existing as monomers in modest concentrations in the oil phase, which coexists with the surfactant-rich water phase.
- Type II: water-in-oil (w/o) microemulsions develop when the surfactant is mostly in the oilphase. The aqueous phase (Winsor II) with low surfactant content coexists with the oil phase that is rich in surfactants.
- Type III is a three-phase system in which a middle-phase rich in surfactants coexists with phases that are deficient in surfactants and surplus water (Winsor III or middle-phase microemulsion).
- Type IV: Upon adding a suitable quantity of amphiphile (surfactant plus alcohol), a single-phase (isotropic) micellar solution is formed.

2.EXPERIMENTAL WORK

21.Preformulation Studies[6]

Bulk Density:

The mass of a powder divided by its bulk volume is known as bulk density, or apparent density. A 100 ml graduated cylinder containing the sample was filled after it had been precisely weighed and sifted through 18 #. Apparent volume (V0) is the level that was measured without any compacting.
D=M/V0, Where, M=Mass of powder taken. V0= Apparent untapped volume.

Tapped Density:
The limited density known as the "tapped density" is often obtained through "tapping down" in a mechanism that raises and lowers a volumetric measuring cylinder filled with powder from a certain distance. The Electrolab USP apparatus was used to measure the taped density.Sample was put into a 100 ml graduated cylinder after being precisely weighed and sorted through 18 #. By placing the cylinder on the tapped density tester and mechanically tapping it, the cylinder was able to fall under its weight, producing a set drop of 142 mm at a nominal rate of 300 drops per minute. Initially, the cylinder was tapped 500 times, and the tapped volume (V1) was calculated to the closest graded unit. The tapped

volume (V2) that was closest to the graded units was recorded after the tapping was done 750 more times.TD = M/V2,Where; M= Weight of powder,V2= Tapped volume (after 750+1000 taps)

Hausner'sratio :

The blend's flow can be estimated using Hausner's ratio. It is the proportion of bulk density to tapped density.

HR = Tapped density / Bulk density

Angle of Repose:

Irregular flow of powders from the hopper o compression machine results in tablets with non-uniform weights.

Tan ɵ = h/r,Where, h = height of pile,r =radius ofthe base ofpile ɵ = angle of repose

Using a clamp, a funnel was held such that its stem was 2 cm above the graph paper that was laid out on a horizontal surface. Once the powder had been weighed, five grammes of it was added to the funnel while blocking the funnel's opening. Once the obstruction was removed, the powder was allowed to flow until the conical pile's peak just touched the funnel's tip.

2.2Solubility

The BCS criteria for determining solubility were used to determine the drug's solubility. The solubility was examined in water and 250 cc of buffers with pH values between 2 and 8. After precisely weighing the maximum dosage, it was transferred to a separate volumetric flask with a variety of buffer solutions and sonicated for 30 minutes.

2.3.Identification Of Drug

2.3.1Melting Point Study:The capillary technique or differential scanning colorimetry (DSC) were used to conduct the melting point investigation.

Table No.1

Batchcode	Ingredients			
Trial -1	Carbopol-940	Water	Microemulsion	Triethanolamine
F1	1.5 g	20 g	100 g of batch A1	1 g
F2	1.5 g	20 g	100 g of batch A2	1 g
F3	1.5 g	20 g	100 g of batch A3	1 g
Trial -2	Xanthan Gum	Water	Microemulsion	Triethanolamine
F4	1.5 g	20 g	100 g of batch A1	1 g
F5	1.5 g	20 g	100 g of batch A2	1 g
F6	1.5 g	20 g	100 g of batch A3	1 g

2.1.2FTIR Absorption Spectroscopy Study: A Perkin Elmer Spectrum GX FTIR was used to record the infrared spectra of KBR Pellets throughout a wave number range of 4500- 450 cm.

2.1.3Uv Spectrum Analysis: To determine the maximum wave length and acquire the UV spectrum, the solution was scanned between 200 and 400 nm.

2.1.4Preparation of standard solution: Phosphate buffer with a pH of 7.4 was used to dissolve 100 mg of the medication, which was precisely weighed into a 100 ml volumetric flask. To produce a concentration of 1000 µg/ml (SS-I), the volume was made up using phosphate buffer at 7.4 pH. Ten millilitres (SS-1) are pipetted into one hundred millilitre volumetric flasks and the volume was adjusted with phosphate buffer 7.4 pH to achieve a concentration of one hundred and twenty-one parts per millilitre (SS-II). This led to the preparation of functional standard solutions.

2.1.5Preparation of working standard solutions:In volumetric flasks, aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 ml were diluted to 10 ml in order to get concentration ranges of 5–50 µg/ml from Standard II. A measurement was made at 252 nm for each concentration's absorbance.

3.FORMULATION OF HYDROGEL

A 5% w/w solution of famciclovir was dissolved in a eutectic combination of menthol and camphor in equal parts. Next, a mixture of co-surfactant and surfactant was added to the Famciclovir solution. Ultimately, to create a microemulsion, a suitable volume of water was gradually added drop by drop to the Famciclovir solution mixture.[7]

3.1Preparation of carbopol-940 hydrogel:

Carbopol Hydrogel with different concentrations of Eutectic mixture (15-35% w/w) with the blend of surfactant to co-surfactant (2:1) with different concentrations of (50-30) was prepared. Carbopol (1.5g) solutions were prepared in 20 g of double distilled water and samples were stirred by a magnetic stirrer (25 rpm for 40 min). A clear, viscous solution was obtained by gradually adding 100g of the previously prepared microemulsion while stirring continuously. A magnetic stirrer running at 25 rpm for 30 minutes was used to agitate the samples. Lastly, distinct hydrogel- thickened microemulsions were obtained by adding a predetermined quantity of triethanolamine. The hydrogels were made and their pH was adjusted to 7.4 ± 0.05.[8,9]

3.2Preparation of xanthan gum hydrogel:

Xanthan Gum Hydrogel with different concentrations of Eutectic mixture (15-35% w/w) with the mixture of surfactant to co-surfactant (2:1) with different concentrations of (50-30) was prepared according to table no. 4.2 . Xanthan Gum (1.5g) solutions were prepared in 20 g of doubled distilled water and samples were stirred by a magnetic stirrer (25 rpm for 40 min). A clear, viscous solution was obtained by gradually adding 100g of the previously prepared microemulsion while stirring continuously. Using a magnetic stirrer set at 25 rpm for 30 minutes, samples were stirred. To obtain various hydrogel-thickened microemulsions, a predetermined amount of triethanolamine was added at the end. The hydrogels were produced with a pH value of 7.4 ± 0.05.[8,9]

4.EVALUATIONS

4.1Globule size determination(microemulsion):

Photon correlation spectroscopy was used to measure the globule size of the chosen microemulsion. The experiment was carried out with four attenuators and a clear disposable zeta cell at 25 degrees and 210.6 kcps count rate speed for 70 seconds.[10,11,12]

4.2Physical Appearance AndPh

The clarity and solution type of all the hydrogels generated from Famciclovir-based polymer batches were examined. The pH of each solution of the Famciclovir polymer-based hydrogel was determined at 25°C using a calibrated digital pH meter.[13]

4.3.In Vitro Drug Release Studies

Using a Franz diffusion cell fitted with cellophane paper, the drug release studies were carried out in vitro. With a total capacity of 25 cc, the recipient chamber was outfitted with a water jacket. One arm was used for sampling, and the other held the thermometer. The internal diameter of the donor chamber was 2 cm. The receptor compartment's diffusion medium was directly in contact with the donor compartment. The receptor compartment was filled with a 7.4 pH phosphate buffer solution that was maintained at 37°C ± 1°C. The membrane was equilibrated before the application of the hydrogel containing 10 mg of medicine onto the donor side. At regular intervals, 3 ml of samples were taken from the receptor compartment and replaced with an equal amount of fresh PBS solution. These samples were then analyzed using a spectrophotometer at a wavelength of 252 nm.[14,15,16,17]

5.RESULT&OBSERVATION

5.1Identification Of Drug

Table No: 5.1. Melting Point Study by DSC

Stage	Temperature
Onset	102.2 °C
Peak	98.37 °C
End set	104 °C

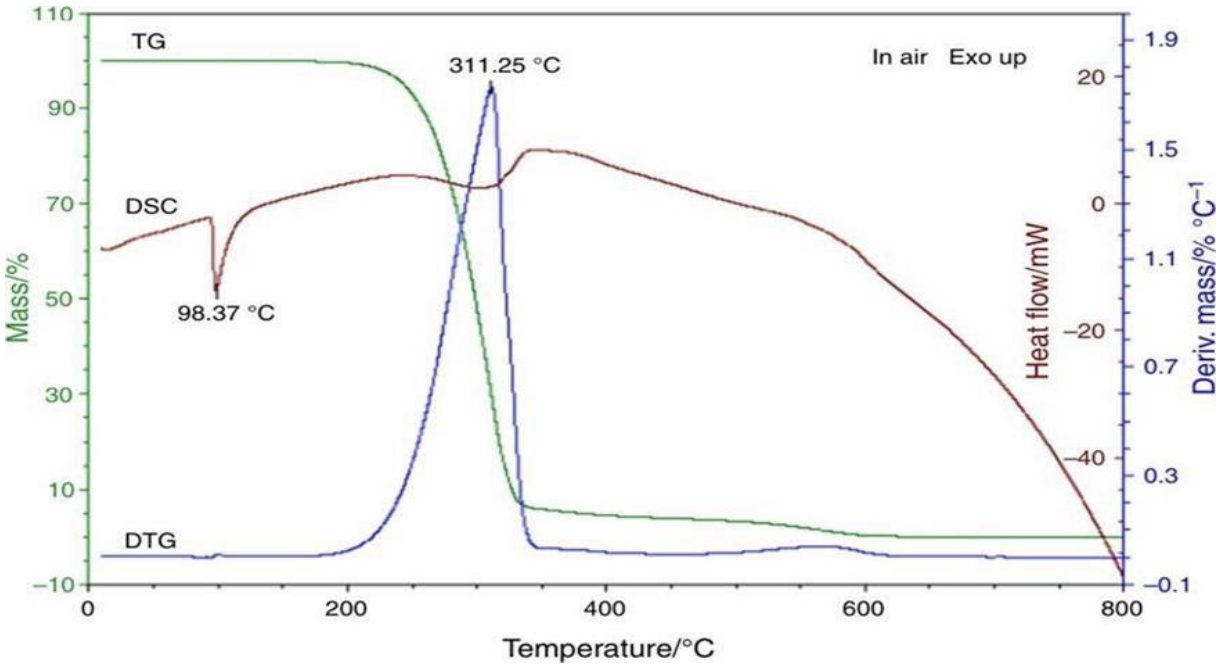

Figure 1 : DSC graph of pure Drug

5.2Absorption Spectroscopy Study BY FTIR

By spreading the medication throughout a KBR disc, the infrared spectra of famciclovir were obtained. The table below shows the major band obtained.

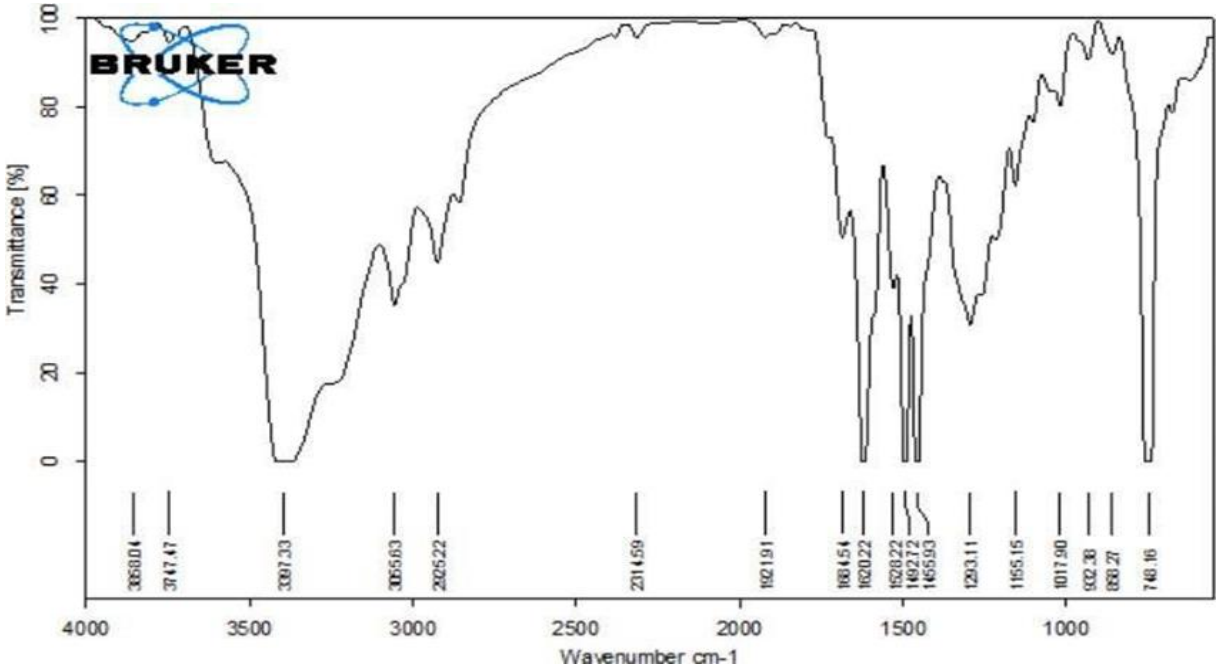

Figure 2 : IR graph of pure drug

The given API was identified as Famciclovir based on the value and the superimposition of spectra on the standard spectra of the drug, as demonstrated by the DSC and the above graph.

5.3Spectrometric Analysis of Famciclovir by UV

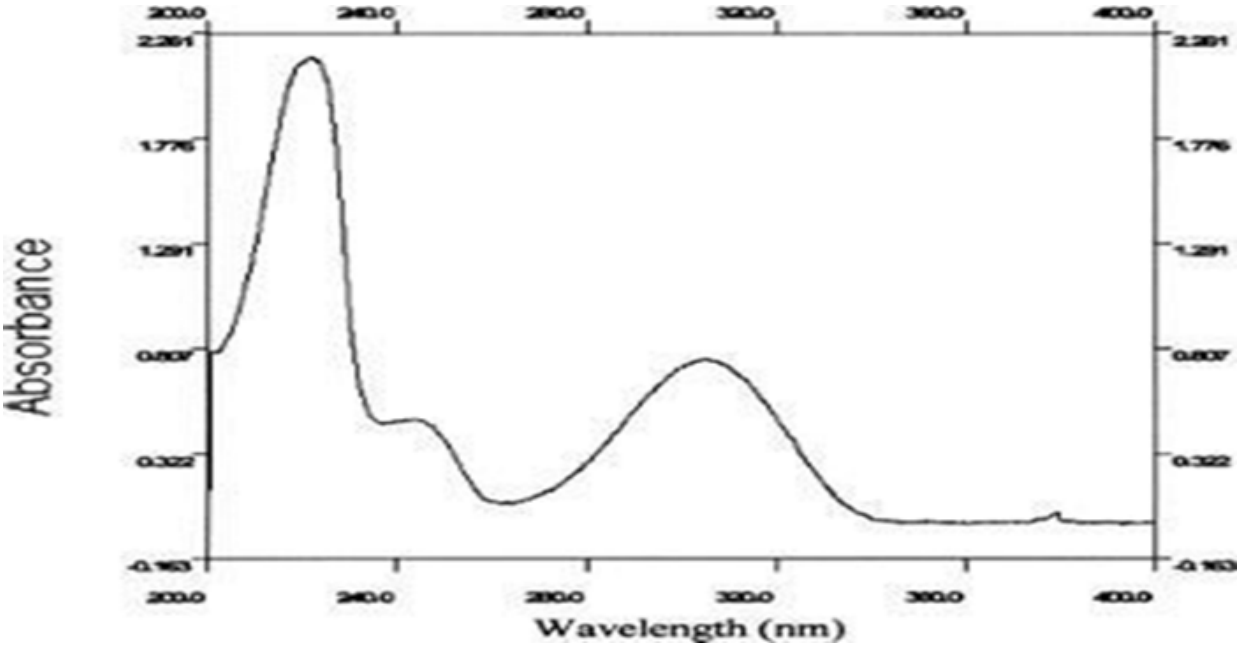

Figure 3 : UV spectrum of Famciclovir in 7.4 pH

One peak was found at 221 nm when the Famciclovir solution in 7.4 pH phosphate buffer was scanned from 200 nm to 400 nm, as illustrated in Figure 6. Famciclovir's claimed UV spectrumserved as confirmation of this.

5.4Physical Properties of Famciclovir
Table no.5.1

Drug	Bulk density	Tapped density	Carr's index	Hausner ration	Angle of repose(degree)
FAMCICLOVIR	0.67 g/ml	0.80 g/ml	15%	1.17	32.43°

5.4Calibration curve of Famciclovir in DMSO: Methanol (2:1)
The R^2 value was found 0.997. The method obeys Beer's Law in the concentration range of 2 to16 µg/ml.
Table 5.2Calibration curve of Famciclovir in DMSO: Methanol (2:1)

Concentration	Absorbance
2	0.109
4	0.241
6	0.33
8	0.455
10	0.533
12	0.663
14	0.789
16	0.901

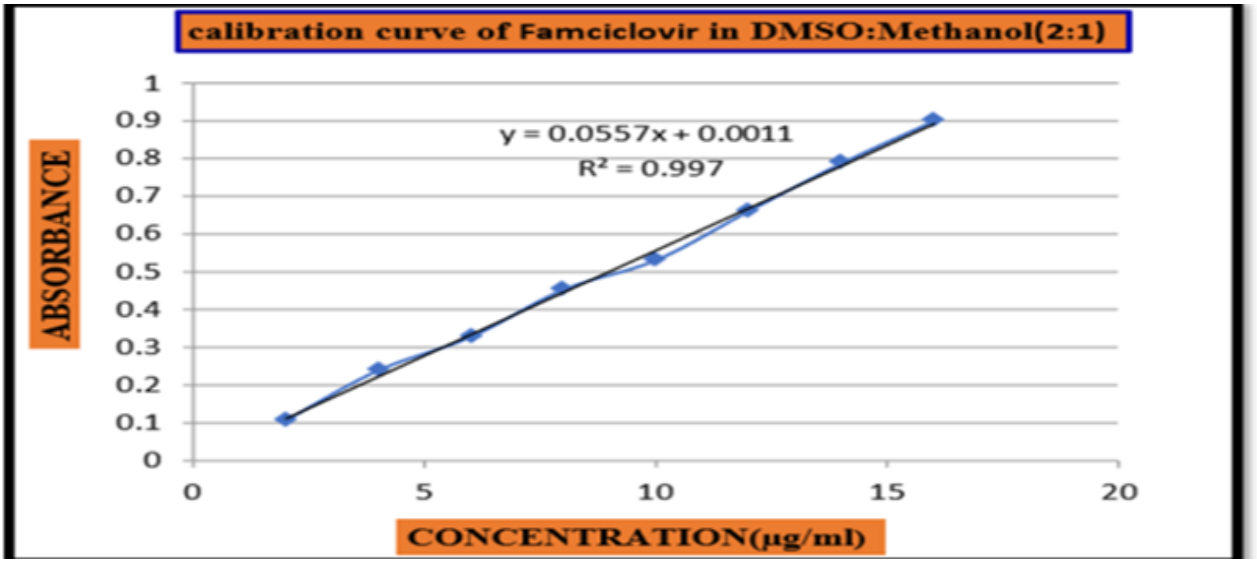

Figure 3: Famciclovir Calibration curve in DMSO: Methanol (2:1)

5.5 Table 5.3, Globule Size Determination of Microemulsion

Formulation code	Globule size (nm)
A1	19.72
A2	19.01
A3	20.47

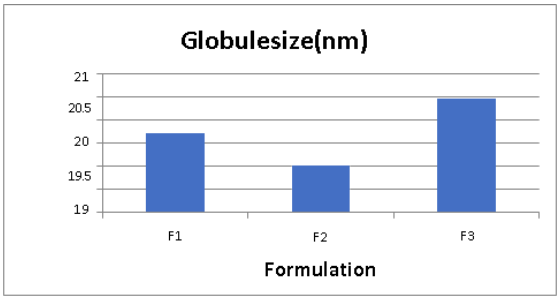

Fig No 4 : Globule size Determination of microemulsion with Malven Apparatus

5.6.CALCULATION OF IN VITRO DRUG RELEASE STUDIES

Table no. 5.4. In Vitro drug release from cellophane membrane for F1

Time in Hour s	Absorbance	Conc in µgm/ 3 ml	Error	Conc in µgm/45 ml	CDR µgm	CDR µgm/cm^2/hr	% CDR
1	0.238	12.61	---	189.16	189.16	41.46	17.59
2	0.246	13.05	12.61	195.83	208.44	45.69	19.39
3	0.268	14.27	25.66	214.16	239.83	52.57	22.31
4	0.294	15.72	39.94	235.83	275.77	60.45	25.65
5	0.309	16.55	55.66	248.33	304	66.63	28.27
6	0.315	16.88	72.22	253.33	325.55	71.36	30.28
7	0.325	17.44	89.11	261.66	350.77	76.89	32.63
8	0.359	19.33	106.55	290	396.55	86.92	36.88
9.	0.367	19.77	125.88	296.66	422.55	92.62	39.30
10.	0.385	20.77	145.66	311.66	457.33	100.24	42.54
11.	0.401	21.66	166.44	325	491.44	107.72	45.71
12.	0.419	22.66	188.11	340	528.11	115.76	49.12

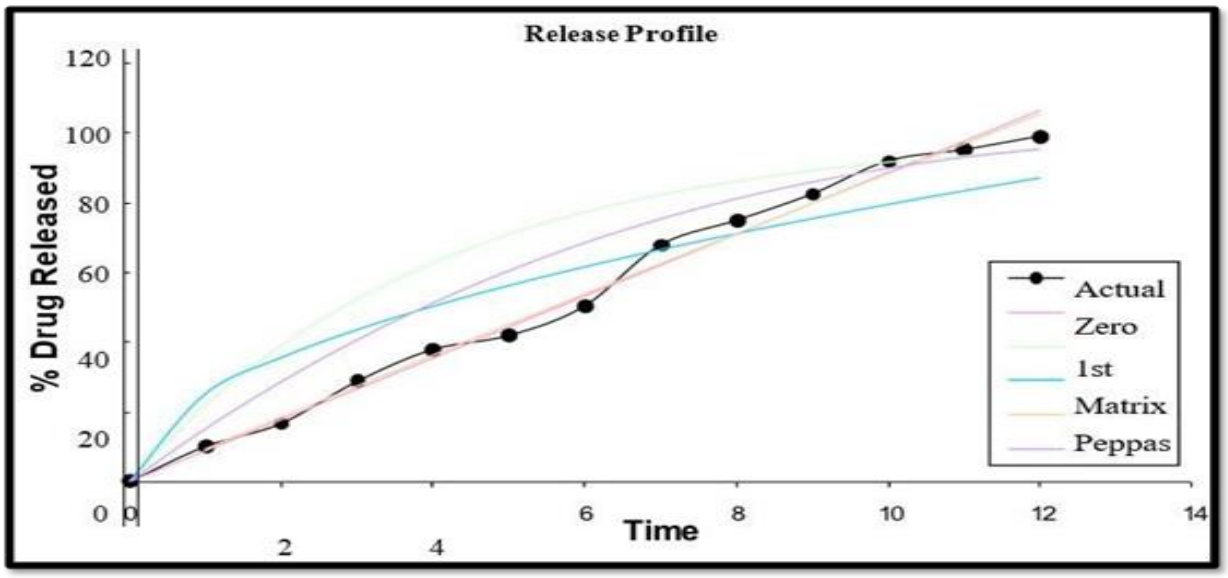

Figure No 5 : Cumulative percent drug release for formulation F1

6.CONCLUSION

It is anticipated that the effective formulation of Famciclovir in gel microemulsion form will augment its therapeutic efficacy in comparison to either plain drug solution. This may result from increased drug penetration from the microemulsion due to the presence of cosurfactants and surfactants, which increase membrane permeability and boost drug uptake. Consequently, the danger of adverse effects can be reduced and the need for frequent administration can be addressed. Moreover, this microemulsion's gelling polymer content is anticipated to extend its time on the skin.

REFERENCES

[1] Ganji F, Vasheghani-Farahani E. Hydrogels in controlled drug delivery systems. Iranian Polymer Journal. 2009;18(1):63-88.

[2] Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000;50(1):27-46.

[3] Pierard G, Arrese J, Pierard-Franchimont C. Treatment and prophylaxis of tinea infections. Drugs. 1996;52(2):209-24.

[4] Huabing C, Xueling C, Danrong D, Jin L, Huibi X, Xiangliang Y. Microemulsion- based hydrogel formulation of ibuprofen for topical delivery. Int J Pharm. 2000;315:52- 58.

[5] Tenjarla S. Microemulsions: An overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16:461-521.

[6] Peltola S, Saarinen-Savolainen P, Kiesvaara J, Suhonen T, Urtti A. Microemulsions for topical delivery of estradiol. Int J Pharm. 2003;254:99-107.

[7] Dongsheng M, Huabing C, Danrong D, Chengwen M, Jiangling W, Huibi X, Xiangliang Y. Hydrogel thickened nanoemulsion system for topical delivery of lipophilic drugs. Int J Pharm. 2008;353:270-76.

[8] Yano T, Nakagawa A, Tsuji M, Noda K. Skin permeability of various non-steroidal anti-inflammatory drugs. Life Sci. 1986;39:1043-50.

[9] Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, Rossi C. Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Rel. 2004;99:73-82.

[10] Irevolino M, Cappello B, Raghavan S, Hadgraft J. Penetration enhancement of ibuprofen from supersaturated solutions through human skin. Int J Pharm. 2001;212:131-41.

[11] Heard C, Gallagher S, Harwood J, Maguire P. The in vitro delivery of NSAIDs across skin was in proportion to the delivery of essential fatty acids in the vehicle-evidence that solutes permeate skin associated with their solvation cages. Int J Pharm. 2003;261:165-69.

[12] Yun-Seok R, Jung-Gyo C, Eun-Seok P, Sang-Cheol C. Transdermal delivery of ketoprofen using microemulsions. Int J Pharm. 2001;228:161-70.
[13] Chen H, Chang X, Weng T, Zhao X, Gao Z, Yang Y, Xu H, Yang X. A study of microemulsion systems for transdermal delivery of triptolide. J Control Rel. 2004;98:427-36.
[14] Bamba M, Puisieux F, Marty J, Carstensen J. Release mechanism in gel forming sustained release formulation. Int J Pharm. 1979;2:307-15.
[15] Gohel M, Parikh R, Padshala M, Sarvaiya K, Jena D. Formulation and optimization of directly compressible isoniazid modified release matrix tablet. Indian J Pharm Sci. 2007;69:640-45.
[16] Vinod S, Yi T, Pradeep S, Jen-Pei L. In vitro drug dissolution profile comparison- Statistics and analysis of the similarity factor, f2. Pharm Res. 1998;15:889-96.
[17] Khan M. Bioavailability of vitamin B12 using a small volume nebulizer ophthalmic drug delivery system. ClinExpOphthalmol. 2005;33:402-07.