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Formulation And Evaluation Of Microemulsion Based Tablets Of Acyclovir For Better Patient Compliance

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Abstract: The aim of study was to develop a microemulsion based tablets to increase the solubility and the bioavailability of acyclovir. An Isopropyl myristate microemulsion formulation with Tween 80 as surfactant and Ethanol as cosurfactant were used. Phase behavior of the microemulsion system was characterized. A single bicontinous region was found in the pseudoternary phase diagrams of Isopropyl myristate: Tween 80: Ethanol in different ratios. The microemulsion system was characterized in terms of other characteristics, such as, particle size, viscosity and bioavailability. The limitations of microemulsion are poor palatability due to the lipid content leading to the poor patient compliance. Due to their water content, microemulsions cannot be encapsulated in soft gelatin or hard gelatin capsules. All these limitations may be overcome by converting microemulsion into solid dosage i.e tablet form by adsorbing onto the solid support i.e. adsorbent. In this study we are using colloidal silica as an adsorbent.

Acyclovir having poor solubility displayed high solubility in a microemulsion based tablet formulation using Isopropyl myristate (18 %), Tween 80 (45%), Ethanol (15%) and water (22%). The in vitro dissolution study of microemulsion based tablets revealed an increase % release (2 times) as compared with the commercially available tablets.

Keywords: Microemulsion, Non-Ionic surfactant, Interfacial tension, Particle size.

Introduction

Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analog is derived from guanine, is the most widely used antiviral agent. It is used in the treatment of in both herpes simplex virus HSV-1 and HSV-2, and varicella-zoster virus (VZC).[1] The bioavailability of acyclovir is very low 10% to 30%.[3] Approximately 80% of an oral dose is is excreted through the feces. The kidney is the main excretory organ for acyclovir. The pharmacokinetic parameters of acyclovir are highly variable after oral administration. Peak plasma values were found to be 0.49 to 0.89 or 0.79 to 1.41 µg/L after a single oral dose of 200 or 400 mg, respectively, [2] and have been generally obtained 1.4 to 2.6 hours after oral administration.[2, 3] The plasma half-life of acyclovir is 3.2 hours in adults with normal renal function.[4]

In this study the use of a microemulsion as tablet form was evaluated to improve the extent of absorption and the overall bioavailability. This novel drug delivery system has been reported to improve the rate and extent of absorption of poorly water soluble drug like Acyclovir.[5-9] Microemulsions are Clear, homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, in combination with a cosurfactant (typically a short-chain alcohol). Microemulsions having advantages, including high stability, and ease of preparation.

In the present study, a microemulsion was prepared using the non-ionic Tween 80 (as surfactant, hydrophile-lipophile balance HLB-15), Ethanol (as cosurfactant, HLB-8), IPM and water. Pseudoternary phase diagrams were prepared to find out the zone of microemulsion formation at different ratios of surfactant to cosurfactant in which microemulsion formed. (eg, 4:1 and 3:1).

The effect of formulation variables on different physicochemical characteristics such as globule size, and viscosity was studied. Then microemulsion is converted into solid tablets by using colloidal silica as an adsorbent. The administration of the microemulsion and in a form of a free solid dosage form offers significant advantages. [10]

- The solid dosage form presents a more robust and stable dosage.
- It is more patient acceptable and thus provides potential for better patient compliance.
- The more robust and easy solid dosage forms makes for easier production and packaging.
- It provides the use of various ingredients in combination with the dosage forms to enhance bioavailability and the rate of dissolution.[10]

An *in-vitro* dissolution studies were carried out in 0.1N HCl, it was found that the % release of tablets 2 times more than commercially available formulation (Acivir, Cipla, Mumbai, India).

Introduction and Experimental

Acyclovir, IPM (Propan-2-yl tetradecanoate), Tween 80 (Polyoxyethylene (20) sorbitan monooleate), Ethanol and Colloidal silica were obtained from NMIMS, Shirpur. All chemicals used were of analytical reagent grade. Double-distilled water was used throughout the study.

- **Preparation of Microemulsion**

Microemulsion was prepared by dissolving Acyclovir in IPM and Tween 80: Ethanol (3:1) were then added in acyclovir solution followed by titrating with distilled water. The monophasic microemulsion was formed spontaneously at room temperature.

- **Preparation of Phase Diagrams**

Pseudoternary phase diagrams were constructed to investigate the formation of microemulsion by using four components: oil, surfactant, cosurfactant, and aqueous phase system. The 4-component system consisted of (1) isopropyl myristate; (2) surfactant (Tween 80); (3) co-surfactant (ethanol); and (4) double-distilled water (aqueous phase). Pseudoternary phase diagrams were constructed keeping the ratio of Tween 80 and ethanol constant and varying water and oil components. The water was titrated along dilution lines drawn from the surfactant-cosurfactant apex (100% surfactant-cosurfactant) to the opposite oil side of the triangle. If turbidity appeared during preparation, followed by a phase separation, the samples were considered as biphasic. If clear and transparent mixtures were obtained after stirring, the samples were considered monophasic. The point was marked in the phase diagram. The area covered by these points was considered to be the microemulsion region [11]

- **Adsorption of Microemulsion onto Adsorbent**

The microemulsion can be adsorbed onto the solid particle adsorbent. The amount of microemulsion is kept low so that the mixture of adsorbent and microemulsion forms an easily compressible, free flowing powder.

Suitable nontoxic adsorbent may be used. Preferably fine particulate adsorbents are used.We can use kaolin, bentonite, silicon dioxide, magnesium trisilicate, aluminium hydroxide, magnesium hydroxide, magnesium oxide or talc. We are using colloidal silica.

The resulting product should be a free flowing, compressible powder. When microemulsion is adsorbed onto the solid support, the powder should remains a completely dry powder and the powder should be a free flowing. It is more easily achieved with a o/w microemulsion because the water in the external phase evaporates during the incorporation process. When the microemulsion is adsorbed onto adsorbent it is appeared as slightly “damp”. Hence the proportions of microemulsion to solid support will important for the powder remains free flowing and dry. [10]

- **Formulation of Microemulsion based tablets**

Weigh and screen all materials in a blender for 30 minutes then weigh according to tablet weigh and compress tablets. [10]

- **Physicochemical Evaluation**

Particle Size Measurements: The droplet size of the microemulsion was determined by Motic Microscope.

- **Viscosity**

The viscosity of the microemulsion was evaluated by a Brookfield Viscometer at 30 °C using a CPE 62 spindle at 5 rpm. Experiments were performed for sample, and results were

presented as average ± standard deviation.

➢ **In-vitro Dissolution Studies of Tablets:**

The dissolution technique for testing of the drug release of Tablet is as follows –

- Apparatus : Apparatus II (Paddles)
- Medium : 0.1 N HCl
- Speed :50 rpm
- Volume: 900 ml
- Time points :10, 20, 30, 40, 50 and 60 minutes

In vitro dissolution kinetics of Acyclovir tablet was carried out in United States Pharmacopeia (USP) Type-II dissolution test apparatus. The dissolution medium used was 900 ml of 0.1 N HCl and maintained at 37.5 ± 0.5 °C. The paddle speed was kept constant at 50 rpm. Samples of 5 ml were withdrawn at specific time interval. The withdrawn samples were analyzed by UV spectroscopy at the wavelength maxima of 254 nm. The same amount of fresh 0.1 N HCl was used to replace at each time as amount withdrawn for respective dissolution media and assayed for drug release spectrophotometrically.

Results and Discussion

➢ Phase Diagram Study

A pseudoternary phase diagram of the quaternary system of IPM/ Tween 80/ Ethanol Water is given in Figure 1. Formation of microemulsion systems (the shaded area) was investigated at room temperature. Phase behavior study revealed the suitable approach to determine the water and oil phase, surfactant concentration, and cosurfactant concentration with which the transparent.

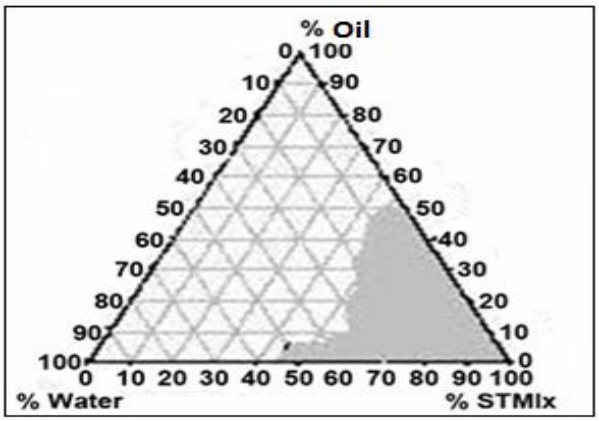

Figure 1: Pseudoternary phase diagram of ipm, tween 80, ethanol and water. Surfactant to cosurfactant ratio (3:1); stmix indicates surfactant + cosurfactant.

To obtain a clear microemulsion the surfactant-to-cosurfactant ratio was 3:1 in this case the maximum proportion of oil was incorporated in microemulsion systems. The increased oil content may provide a greater opportunity for the solubilization of acyclovir. When the composition (% wt/wt) of surfactant and co-surfactant mixture (Smix) in a microemulsion preparation was 40%, the formulation was less viscous. The optimized formula of microemulsion was Isopropyl myristate (18 %), Tween 80 (45%), Ethanol (15%) and water (22%)

➢ **Preformulation Studies:**

- Melting Point:

SPECIFICATION	RESULT
256.5–257 ˚C	255 ˚C

The melting point of Acyclovir was found to be 255 ˚C.

- **Solubility studies:**

The solubility of Acyclovir in various components (oils, surfactants, and cosurfactants) was determined by using shake flask method. The concentration of Acyclovir in the filtrate was determined at 256 nm by UV Spectrophotometric method.

a) Solubility of Acyclovir in different Oil Phase:

Table 1: Acyclovir Solubility in Different Oils

SR NO.	OIL PHASE	SOLUBILITY (mg/ml)
1	Oleic Acid	4.6 ± 0.2
2	Castor Oil	13 ± 0.5
3	Soyabean Oil	15 ± 0.5
4	Olive Oil	3.0 ± 0.1
5	Sunflower Oil	9.3 ± 0.3
6	Isopropyl Myristate	1.95 ±0.05

b) Solubility of Acyclovir in different Surfactants:

Table 2: Acyclovir Solubility in Different Surfactants

SR NO.	SURFACTANTS	SOLUBILITY (mg/ml)
1	Tween 20	21 ± 1.2
2	Tween 60	15 ± 0.3
3	Tween 80	28 ± 1.1
4	Span 80	18 ± 0.5

c) Solubility of Acyclovir in different Co-Surfactants:

Table 3: Acyclovir Solubility In Different Co-Surfactants

SR NO.	CO-SURFACTANTS	SOLUBILITY (mg/ml)
1	Ethanol	92.32 ± 6.20
2	PEG 200	19 ± 1
3	Propylene Glycol	21 ± 3
4	Glycerin	25 ± 1.5

By performing the solubility of Acyclovir in different oil phase, surfactants and cosurfactants. Acyclovir maximum solubility were found in Tween 80, Ethanol. So, these compounds were shortlisted for the further screening.

- **Physicochemical Characterization of Microemulsion**

The physicochemical characteristics of the developed microemulsion showed in Table 4. It was clear that the developed system had low viscosity (~25.56 cP). From that we can conclude that the system is of the o/w type.

Table 4: Physicochemical Parameters Of The Developed Microemulsion

PARAMETER	VALUE
Particle size (nm)	40.2 ± 2.3
Viscosity (cP)	25.56

- Powder Evaluation

Table 5: Physical Property Of Powder

Bulk Density	0.67 g/ml
Tapped Density	0.80 g/ml
Carr's Index	15 %
Hausner Ratio	1.17
Angle of Repose (θ) degrees	32.43

Discussion:

API complies as per the specification. Based on the above data it was concluded that the API has good flow property.

- Tablet Evaluation:

Table 6: Evaluations Parameters Of Acyclovir Tablets

TABLET PARAMETERS	
Avg Wt. (gm) n= 10	2.14 ± 0.47
Hardness(kp) n= 3	2.28 ± 0.31
Thickness (mm) n= 10	5.40 ± 0.24
DT (min) n=3	1. 22 ± 0.49
Friability (%)	0.07

Dissolution Result

Apparatus	USP II (Paddles), Speed: 50 rpm.
Media & volume	0.1N HCl, 900ml

Table 7: Dissolution Study Of Innovator And Test Product

TIME (IN MIN.)	INNOVATOR %w/w DRUG RELEASE (MEAN ± S.D.)	TEST %w/w DRUG RELEASE (MEAN ± S.D.)
10	5.06 ± 0.11	14.63 ± 0.08
20	13.52 ± 0.25	21.25 ± 0.22
30	16.40 ± 0.22	31.92 ± 0.37
40	27.04 ± 0.13	53.52 ± 0.88
50	29.45 ± 0.18	66.21 ± 0.70
60	31.45 ± 0.08	70.43 ± 0.77
Sample Size n=3		

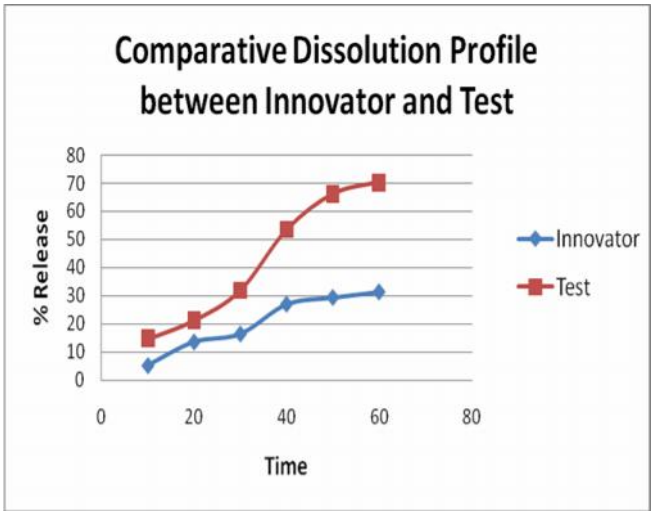

Figure 2: Comparative Dissolution Profile Between Innovator And Test

The % release of drug was found to be 70.43 % compared to 31.45 % of Innovator's Product at the end of 60 minutes which was two times higher than innovator's product.

Conclusion

The study demonstrates that the microemulsion composition (Isopropyl myristate, Tween 80, Ethanol and water) in the form of free flowing, compressible powder contains: a mixture of Acyclovir containing microemulsion and a solid adsorbent on which microemulsion got adsorbed and forms a free flowing and compressible powder which has having Carr's index 15 % and Hausner Ratio 1.17 indicated that powder has good flow property. Dissolution study showed that % release of test formulation was found to be 70.43% at 60 minutes which was two times higher than innovator's product. The dissolution study revealed that % release of test formulation was found to be 2 times higher than that of commercially available tablets (Acivir).

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