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Formulation Development and Evaluation of Acyclovir Loaded Nanoemulsion

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Abstract

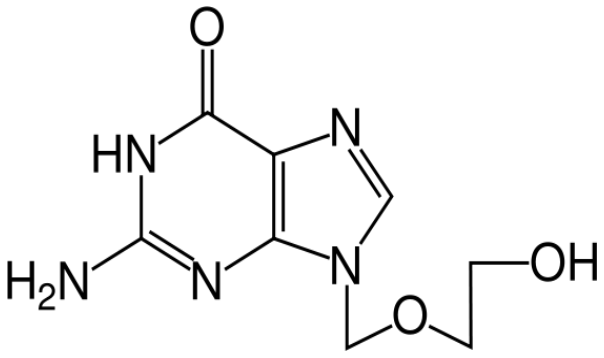
This work deals with the investigations carried out on the preparation and characterization of oil-in water nanoemulsion containing acyclovir with minimum surfactant concentration that could improve its solubility and oral bioavailability. On the basis of above study it was concluded that the solubility in the oils, surfactants and co surfactants like Span 40, Castor Oil, Oleic acid, PEG 400, Ethanol was found to be soluble and Tween 20, Tween 80 and Sunflower Oil was found to be Slightly soluble for the nanoemulsion preparation of acyclovir.

Key Words: Acyclovir, Nanoemulsion, Formulation

Introduction

Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean dropletdiameters ranging from 50 to 1000 nm. Usually, the average droplet size is between100 and 500 nm, terms sub-micron emulsion (SME) and mini-emulsion are used assynonyms. Since, the preparation of the first nanoemulsion in 1940s, it can be of three types such as oil-in-water (O/W), water-in-oil (W/O), and bi-continuous. Acyclovir, chemical name acycloguanosine, abbreviated as ACV, is a guanosine analogue antiviral drug, marketed under trade names such as Cyclovir, Herpex, Acivir, Acivirax, Zovirax, Zoral, Xovir and Imavir. One of the most commonly used antiviral drugs; it is primarily used for the treatment of herpes simplex virus infections, as well as in the treatment of varicella zoster (chickenpox) and herpes zoster (shingles).

Acyclovir has also been investigated for the treatment of herpes labialis applied using an iontophoretic device. Currently approved drugs for the treatment of herpes labialis (cold sores) exhibit low levels of efficacy due to the limited ability of the drugs to penetrate the skin to the site where the herpes virus is replicating. Iontophoresis uses electric current to enhance the delivery of drugs through the skin. [1-3]



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Experimental [4-7]

Characterization of drug:

Physiochemical Properties of Acyclovir

Physical evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor, feel of thedrug, etc.

Table 1: List of Sensory characters

S. No.	Sensory characters	Result
1.	Color	White off crystalline powder
2.	Odor	Odorless

Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N Hcl, 0.1N NaOH, Chloroform and 7.4 pH buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Table 2: Solubility of Acyclovir

Solvent used	Acyclovir
Distilled Water	Slightly soluble
0.1 N Hydrochloric acid	++++
Ethanol	++++
Methanol	++++
Chloroform	+++
0.1 N NaOH	+
Phosphate buffer pH 7.4	+++

Melting point

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Table 3: Melting point of the Acyclovir (British pharmacopoeia, 2015)

S. No.	Melting Point of Acyclovir	Average Melting Point of Acyclovir
1.	256-258°C	256-258°C
2.	256-258°C	
3.	257-259°C	

Determination of pH (1□ w/v solution in water):

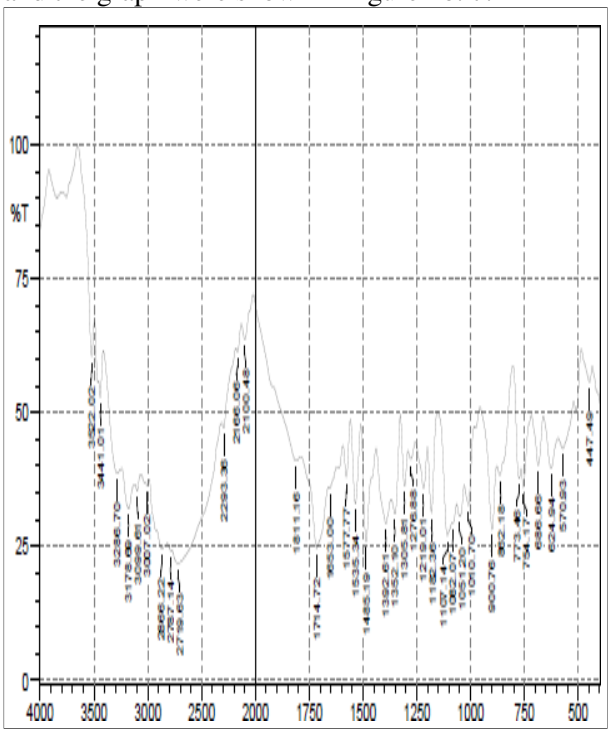
About 1gm of the Powder was taken and dissolved in 100ml of distilled water with sonication and filtered. The pH of the filtrate was checked with standard glass electrode.

Table 4: pH of the Acyclovir

S. No.	pH of the solution	Average pH of the solution
1.	7.2	7.2
2.	7.1	
3.	7.2	

FTIR pure Acyclovir

The IR spectrum of sample drug shows the peak values which arecharacteristics of the drug and the graph were shown in figure no. 7.1



Loss on drying

Loss on drying is directly measured by IR moisture balance. Firstly calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 15 minutes and constant reading set the knob and check % moisture.

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Table 6: Loss of drying of drug sample

S. No.	Initial weight	Final weight after 15 minutes	% loss of drying	Avg. % loss of drying
1.	5gm	4.92 gm	1.67 %	1.672 %
2.	5gm	4.91 gm	1.82 %	
3.	5gm	4.92 gm	1.67 %	

Table 7: Moisture content determination

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1	Acyclovir	0.565	0.13ml	0.07345

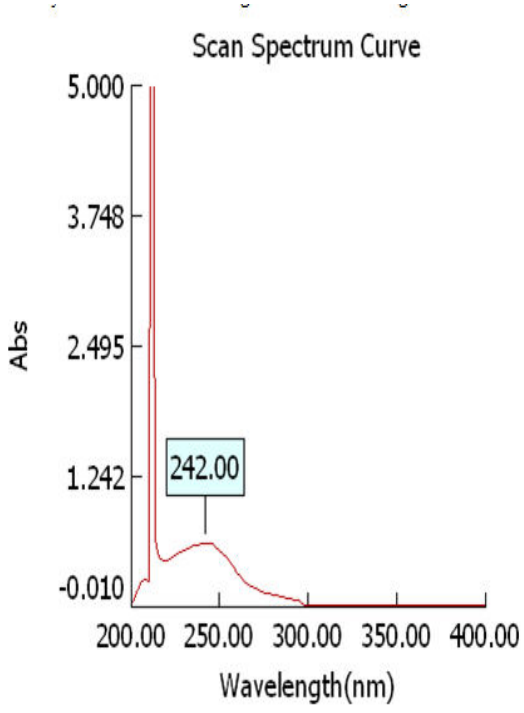

Figure 2: Wavelength maxima of Acyclovir in phosphate buffer pH 7.4

Preparation and characterization

Solubility determination in the various oils, surfactants and co-surfactants for formulating nanoemulsion drug delivery system the solubility of the drug in different oils is an essential step for the nanoemulsion formulation. So before starting the phase diagram one must have to select the oil, surfactant and co- surfactant in which the drug shows maximum solubility, to be in the desired solubility range, which is essential for the formulation of nanoemulsion drug delivery system.

Table 8: Solubility of Aciclovir in different oil, surfactants and co surfactants

S. No.	Component	Solubility
1	Span 40	Soluble
2	Tween 20	Slightly soluble
3	Tween 80	Slightly Soluble
4	Castor Oil	Soluble
5	Sunflower Oil	Slightly soluble
6	Oleic acid	Soluble
7	PEG 400	Soluble
8	Ethanol	Soluble

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Table 9: Formulation of nanoemulsion

Oil: Smix	Formulation code	Oil (mg)	Surfactant(mg)	Co-surfactants(mg)
0.5:1:1	F1	0.5	1	1
1:1:2	F2	1	1	2
2:1:3	F3	2	1	3
3:1:4	F4	3	1	4
3:4:1	F5	3	4	1
2:3:1	F6	2	3	1
1:2:1	F7	1	2	1
0.25:1:1	F8	0.25	1	1

Evaluation of Formulations

pH Determination

The pH of each formulation was found before and after dilution by using pH meter.

Table 10: Results of pH of Acyclovir loaded nanoemusion

S. No.	Formulation code	pH*
1	F1	6.81±0.02
2	F2	6.92± 0.01
3	F3	7.03±0.02
4	F4	7.04±0.01
5	F5	6.84±0.02
6	F6	6.95±0.03
7	F7	6.98±0.02
8	F8	6.95±0.01

***Average of three determination**

Centrifugation

This parameter characterized to check the physical stability of formulation. The nanoemulsion system was centrifuged at 5000 rpm for 10 minutes to determine whether the system shows signs of creaming or phase separation. The system was observed visually for appearance.

Determination of % Drug Content in nanoemulsion

The mixture (Nanoemulsion) was centrifuged at 1000 rpm for 15 min, 0.2 ml of supernatant was taken and diluted with 0.1 N HCL. Absorbance was measured at 242nm by UV Spectrophotometer. Concentration of acyclovir was determined using standard curve equation and % drug content was calculated.

Table 11: Results of Centrifugation and % Drug Content in nanoemulsion

Formulation Code	Centrifugation	% Drug Content in nanoemulsion*
F1	Transparent	78.23±0.23
F2	Transparent	75.58±0.15

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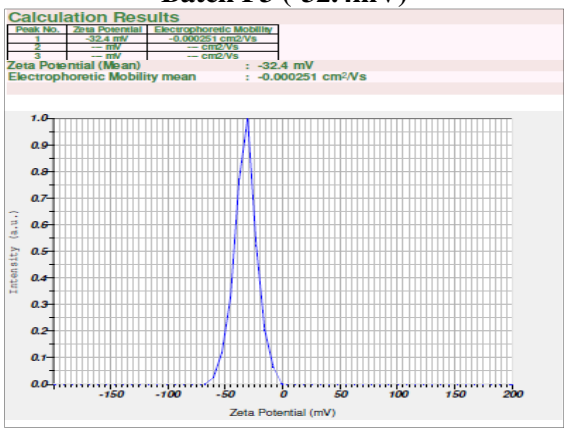
F3	Transparent	89.98±0.25
F4	Transparent	82.25±0.25
F5	Transparent	70.15±0.65
F6	Transparent	65.56±0.32
F7	Transparent	62.25±0.21
F8	Transparent	65.56±0.28

Average of three determination

Zeta Potential and Vesicle size Measurement of Optimized Batch F3

Zeta Potential of samples was measured by Zetasizer. Samples were placed in clear disposable zeta cells and results were recorded.

Figure 3: Result of Zeta Potential of Optimized Batch F3 (-32.4mV)



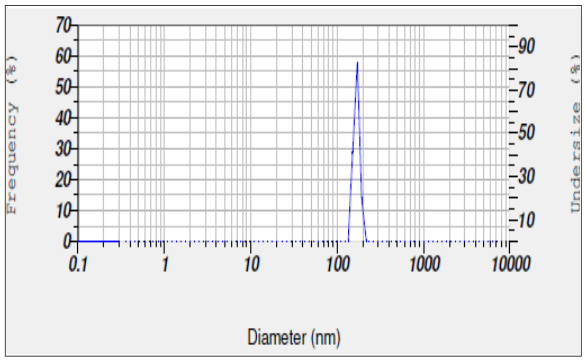


Figure 4: Result of Vesicle size of Optimized Batch

Formulation development of nanoemulsion loaded gel

Preparation of Gels

Preparation of carbopol gel base: 0.5 g Carbopol 934 was weighed and dispersed in water with mild stirring and allowed to swell for 24 hours to obtain 0.5% gel. Later 2 ml of glycerin was added to for gel consistency. Similarly 1 and 2% carbopol gels were prepared.

Table 12: Composition of different gel base

Formulation	Carbopol (%)
F1	0.5
F2	1.0
F3	2.0

Preparation of niosomes gels: Equivalent to 1g of nanoemulsion formulation was dissolved in 10ml of ethanol and centrifuged at 6000 rpm for 20 minutes to remove the unentrapped drug. The supernant was decanted and sediment was incorporated into the gel vehicle.

The incorporation of the nanoemulsion into gels was achieved by slow mechanical mixing at 25 rpm for 10 minutes. The optimized formulation was incorporated into three different gel concentration 0.5, 1 and 2% w/w.

Evaluation of Gels

The prepared gel was evaluated and results are presented below:

Table 13: Results of nanoemulsion gel formulations

Code	Drug content (%)	pH	Spreadability (Gm.cm/sec.)	Viscosity (cps)
F1	98.89± 0.021	7.0±0.021	20.75±0.075	6231±32
F2	98.68 ± 0.021	7.2±0.040	21.08±0.042	6525±24
F3	99.25 ±0.027	7.0±0.060	21.75±0.059	6758±25

Table 14: *In-vitro* drug release data for formulation F1

Time(h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % DrugRelease	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	13.560	1.132	86.440	1.937
1	1.000	0.000	32.560	1.513	67.440	1.829
2	1.414	0.301	65.560	1.817	34.440	1.537
4	2.000	0.602	75.580	1.878	24.420	1.388
6	2.449	0.778	76.200	1.882	23.800	1.377
8	2.828	0.903	76.210	1.882	23.790	1.376

Table 15: *In-vitro* drug release data for formulation F2

Time(h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % DrugRelease	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	20.250	1.306	79.750	1.902
1	1.000	0.000	45.580	1.659	54.420	1.736
2	1.414	0.301	68.890	1.838	31.110	1.493
4	2.000	0.602	73.250	1.865	26.750	1.427
6	2.449	0.778	73.560	1.867	26.440	1.422
8	2.828	0.903	74.150	1.870	25.850	1.412

Table 16: *In-vitro* drug release data for formulation F3

Time(h)	SquareRoot of Time(h)1/2	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	18.890	1.276	81.110	1.909
1	1.000	0.000	38.890	1.590	61.110	1.786
2	1.414	0.301	42.560	1.629	57.440	1.759
4	2.000	0.602	54.650	1.738	45.350	1.657
6	2.449	0.778	69.980	1.845	30.020	1.477
8	2.828	0.903	87.980	1.944	12.020	1.080

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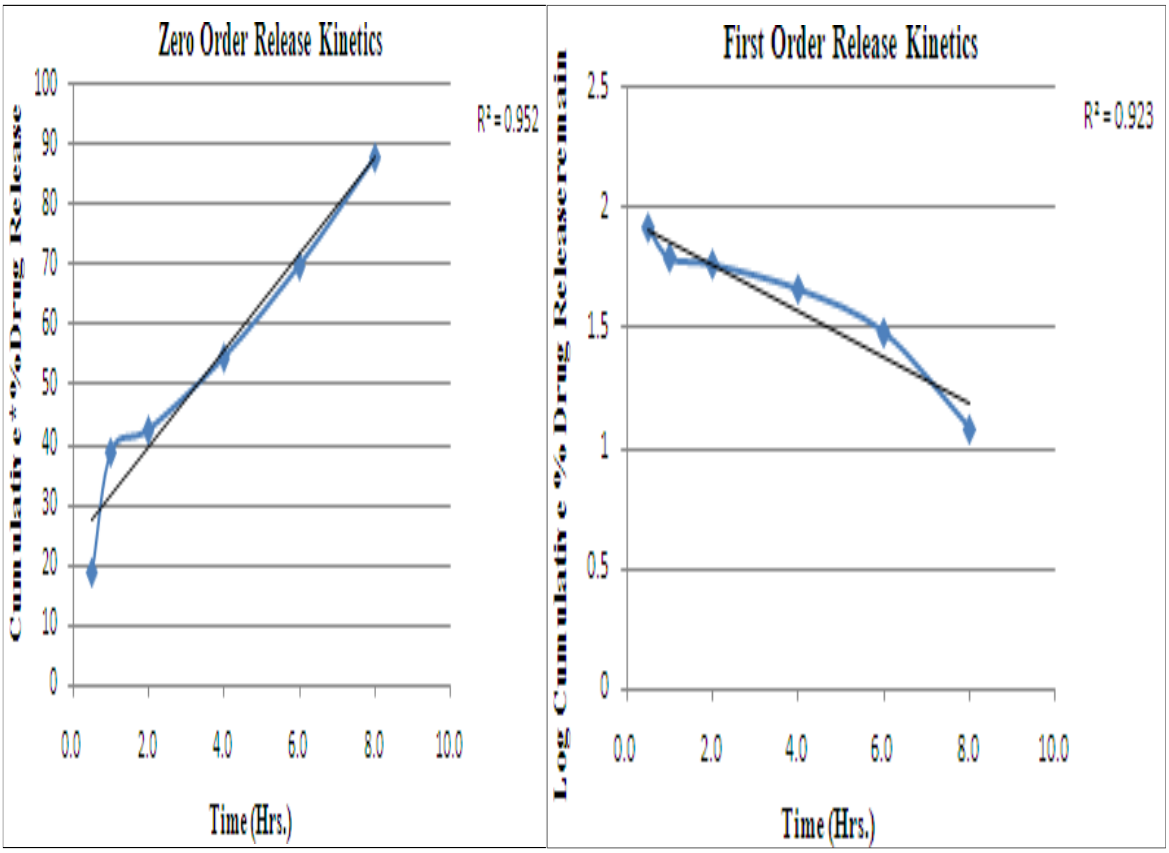

Release Kinetics of Optimized Formulation F3

Table 17: Regression analysis data of optimized formulation

Batch	Zero Order	First Order
	R^2	R^2
F3	0.952	0.923

Conclusion

On the basis of above study it was concluded that the solubility in the oils, surfactants and co surfactants like Span 40, Castor Oil, Oleic acid, PEG 400, Ethanol was found to be soluble and Tween 20, Tween 80 and Sunflower Oil was found to be Slightly soluble (Table 7.1) for the nanoemulsion preparation of acyclovir.

Different physicochemical properties of the selected oils were studied and were found to be favourable for oral nanoemulsion drug delivery system. The selected oils come under the GRAS (Generally regarded as safe) category and frequently used forthe many food products.

The Vesicle size analysis of the optimized formulation F3 was done using particle size analyzer (Horiba).The mean Vesicle size was found to be 41.6nm. The particle size distribution of optimized formulation F3 is shown in fig 7.2. Zeta potential of the optimized formulation F3 was determined using particle size analyzer (Horiba). Zeta potential of optimized formulation was found to be -32.4mV. The zeta potentialof the optimized formulation (F3) is shown in fig 7.1.

Drug content is most important in nanoemulsion formulation and the data found are satisfactory. It was found to be 97.5 to 98.25% which shows the good capacity of formulation to hold the drug.

Three Different carbopol gel base prepared for optimization (0.5%,1.0% and 1.5%) and evaluated for pH, Spreadibility, Viscosity measurements and *in vitro* drug release studies.

In transdermal drug delivery system pH plays an important role, the result of formulations shows that all the formulations are suitable for skin

delivery. The pH values of the prepared gels were within acceptable limits of 6-7

A modified apparatus was used for determining spreadability. The spreadability was measured on the basis of slip and drag characteristics of the gels and was in the range of 20.75 – 21.75gms. cm. /sec. The gels should have optimum spreadability because very high and very low spreadability values indicate that the application of the gel to the site is difficult.

The results show that the viscosity of the gels increased with an increase in polymer concentration. The increase in viscosity with the polymer concentration may be due to increase in bonds between the polymer molecules which lead to formation of a hard and dense compact mass.

In vitro drug release study of Optimized formulation was carried out using modified franz Diffusion cell. The optimized formulation F3 showed the maximum 87.980% drug release in 8 hrs.

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