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Development of an Innovative Nanotransdermal Formulation Utilizing an Optimal Combination of Acyclovir and Omeprazole to Improve Anti Viral Efficacy

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Abstract

The present study demonstrated that Acyclovir and Omeprazole nanogel were successfully developed by solvent diffusion method. pH was determined various formulation F1-F9 in that F9 have suitable for gel preparation. Drug content was determined by UV-spectroscopic method. The prepared nanogel was opaque, without any lumps, particle and aggregates. So, all the formulations are homo genous. Spreadability diameter study F9 shown the nanogel is having good Spreadability. Nanogel formulations shown viscosity range from 3268–3528 cps. It concluded that they are stable in nature. In-vitro dissolution study was performed and showed that F9 have good dissolution rate. The particle size, PDI and zeta potential to find out the F9 formulation. The particle size, PDI and zeta potential was found to be in 687.4, 0.842 and -43.7 respectively. TEM image was confirmed the shape of spherical and smooth surface of particles at range 650 nm. Comparing F9 nanogel formulation with acyclovir marketed formulation (MF) by in-vitro release study. According to result formulated Acyclovir and omeprazole nanogel is more efficient than the marketed acyclovir ointment. Hence from our study the acyclovir and omeprazole nanogel (F9) showed that sustain drug release than the marketed formulation, so it is evident that formulating into nanogel results increase the anti –viral activity.

Key words: Formulation, Nano Transdermal, Acyclovir, Omeprazole, Anti-Viral Activity

INTRODUCTION

Transdermal drug delivery is one of the least intrusive and patient-friendly ways for therapeutic agent administration. It can not only boost medication bioavailability by concentrating drug molecules in a particular skin region, but also limit the possibility of unforeseen adverse effects [1–3]. Therefore, transdermal drug delivery is an appealing option for oral administration and an alternative to hypodermic injection. In the 1970s, the Food and Drug Administration (FDA) first authorized the transdermal patch to administer scopolamine for the treatment of motion sickness [4]. Since then, various physical and chemical strategies of transdermal drug delivery systems (TDDs) have been developed with significant progress achieved. Physical methods include epidermal erosion, skin puncture devices using probes, high-frequency oscillating needle bundles, microneedle arrays, and high-velocity dry powder jets, whereas chemical methods include the use of penetration enhancers and prodrugs [5]. However, physical methods and chemical methods possess their own drawbacks. Physical methods such as iontophoresis may lead to

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pain, a burning sensation, blister formation, and skin necrosis with increasing current strength or if applied for a longer period [6] Slight itching, irritation, and a burning sensation have been reported with sonophoresis [7] Microneedles may cause skin irritation or allergy in sensitive skin. Topical formulations such as pastes, creams, gels, oils and ointments [8, 9] have been developed with significant progress achieved but have poor permeation through the stratum corneum (SC) and require a high dose and repeated applications in a day, which may cause severe side effects like skin rashes and itching that lead to poor patient compliance for long term therapy [10]. Moreover, the application of pro-drugs is another chemical technique to conquer the barrier function of the skin. The main disadvantage of this approach is that the pro-moiety is basically a redundant coarse stone, which, when released, may result in adverse effects. Thus, it is highly desired to develop new types of TDDs, improve drug penetration across the skin barrier and achieve therapeutically effective drug concentrations in the target cutaneous tissues.

Ever since the term "nanoparticles" was known to the scientific world from the 1970s, functional nano-systems have attracted great scientific interest and have always been the research hotspot in the dynamic interdisciplinary branch of science [11–13]. Functional nano-systems typically have diameters ranging from 10 to 1000 nm in at least one dimension and are composed of different biocompatible materials, including natural or synthetic polymers and lipids [14]. Due to their distinct characteristics, including small size and large specific surface area, high encapsulation capacity of both hydrophilic and lipophilic drugs and applicability for multiple administration routes, functional nano-systems can be used as superior drug delivery platforms, which can regulate the release rate, change the biodistribution and improve the bioavailability of the delivered drugs. As a result, functional nano-systems provide new concepts and opportunities for developing new TDDs. Recently, functional nano-systems have been attracted a great deal of interest for transdermal drug delivery, and plenty of research and significant achievements have been made. Various functional nano-systems, such as nanogels, polymeric nanoparticles, metallic nanoparticles, dendrimers, micelles, lipid nanoparticles and quantum dot nanocarriers, have been demonstrated to be an effective strategy to overcome the skin barrier, while causing no tissue harm and promoting transdermal drug delivery [15–20] Therefore, a comprehensive depiction of the whole scene on functional nano-systems for transdermal drug delivery, from fundamentals to evaluations and various advanced applications, is desired.

The aim of the research is to formulate novel nano transdermal using effective combination of acyclovir and omeprazole to enhanced anti-viral activity.

MATERIALS AND METHODS

METHODOLOGY

Preformualtion Studies

Preformulation studies involve physical, chemical and biological characterization of new drug substances in order to develop stable, safe and effective dosage form. Preformulation testing encompasses all studies enacted on a drug compound in order to produce useful information for subsequent formulation of a stable and bio-pharmaceutically suitable drug dosage form as seen in Table 1.

Table 1. List of materials used

S.N.	Ingredients	Vendor
1	Acyclovir	Mercury Medicare(gift sample)
2	Omeprazole	Enal drugs pvt. Ltd (gift sample)
3	Carbopol 940	Himedia laboratories pvt. ltd.

Physical Characteristics

By visual examination the drug was tested for its physical characters like colour, odour andtexture.

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Melting Point

The digital melting point apparatus was used to determine the melting point of drug. A capillary tube was taken and fused at one side with the help of a Bunsen burner. The drug acyclovirand omeprazole was introduced into the capillary tube through the unsealed end and then placed in a melting point viewer. Then the temperature at which drug starts melting was considered as themelting point of the drug

Solubility Test

Acyclovir and Omeorazole powder (about 1 mg) was taken in a test tube and solubility in ethanol, water, PH buffer 7.4 and methanol was tested

Determination of λ Max

10 mg of accurately weighed acyclovir and omeprazole was dissolved in 10 ml of 7.4 pH buffer in a 100 ml volumetric flask. It was made up to 100 ml by using distilled water to get a concentration of 100 µg/ml (Stock A). From the above stock solution A, concentration of 2 µg/mlwas prepared by pippeting 0.2 ml and made up to 10 ml using the medium. The solution was scanned by using double beam UV visible spectrophotometer between the wavelength ranges of 200 nm to 400 nm

Standard Curve

10 mg of accurately weighed acyclovir and omeprazole was separately dissolved in 10 mlof 7.4 pH buffer and distilled water in a 100 ml using phosphate buffer pH 7.4 to get a concentrationof 100 µg/ml (Stock A). From the above stock solution A, concentration ranges from 2 µg/ml to 10 µg/ml was prepared by pippeting 0.2 ml to 1 ml. It was made up to 10 ml using medium. The absorbance of each concentration was analyzed in the UV visible double beam Spectrophotometerat 252 nm and 305 nm respectively. The correlation coefficient (r^2) was determined from the graph. A calibration curve was plotted with concentration on the x-axis and absorbance on the Y-axis.

FT-IR Studies (Drug-Polymer Compatibility)

Drug polymer compatibility was determined by KBr pellet method using Fourier Transform Infrared Spectrophotometer. The samples were prepared by KBr pellet press method and it was scanned between 400–4000 cm^{-1}.

FORMULATION OF ACYCLOVIR AND OMEPRAZOLE NANOGEL

Preparation of Acyclovir and Omeprazole Nanogel

Acyclovir and omeprazole nanogel prepared by Nano solvent diffusion method Accuratelyweighed quantity of drug is dissolved in ethanol and propylene glycol with stirring (organic phase).In the second step aqueous phase is prepared by using Carbopol -940 dissolved in water with continuous stirring and heat for a 20 min in a magnetic stirring. And the drug phase is sonicated under ultrasonic bath Sonicator for 10 min. On next step drug phase is added drop by drop into aqueous phase during high speed homogenization for 30 min at 6000 rpm to from emulsion. The emulsion is converted into nanodroplet by homogenizer results in o/w emulsion formed. Then o/wemulsion is homogenized for 1 h at 8000 rpm and triethanolamine is added with continues stirringto from nanogel (using a combination of ultra-sonication and high speed homogenization). Carbopol and tracaganth were used as a gel forming polymer which were taken individually and in combination as seen in Table 2.

CHARACTERIZATION OF NANOGEL

pH

Direct measurements were made using a digital pH meter (MK-IV SYSTRONICS). Viscosity determination Viscosities were determined using cone and plate viscometer (Digital Rheometer model DV1, Brookfield) of the gels prepared. A spindle (no. 7) was rotated at 10 rpm.

Homogeneity Test

The formulations were tested for their homogeneity by visual appearance after the gels have beenset in the container. Also, a small quantity of each gel is pressed between the thumb and the index finger, and the consistency of the gel is noticed whether homogeneous or not.

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Table 2. Formulation table of nanogel.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	5	5	5	5	5	5	5	5	5
Omeprazole	160	160	160	160	160	160	160	160	160
Tracaganth	200	400	600	800	-	-	-	-	400
Carbopol	-	-	-	-	200	400	600	800	400
PPG	4	4	4	4	4	4	4	4	4
Triethanolamine	4	4	4	4	4	4	4	4	4
water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Spreadability

Spreadability was determined by applying weight to glass slides into which formulation was placed, and time in seconds required to separate the slides was noted. Spreadability of each formulation was reported in seconds. Spreadability was then calculated by using the formula: S =M.L/T (1) Where, S = Spreadability, M = weight tide to upper slide, L = length of glass slide, andT = time taken to separate the slide completely from each other.

Viscosity

The viscosity of the formulations (gel) was determined at 25°C by using Brookfield viscometer with spindle no. S-96 at 1 rpm and viscosity was measured in cps. The measurement of each formulation was done in triplicate and average values are calculated

Drug Content

Drug content was determined by ultra-centrifugation technique**.** Nanogel was dissolved incentrifuge tube containing 2 ml of distilled water. The solution was centrifuged at 12,000 rpm for 10 minutes. It was filtered and supernatant solution was analyzed using UV visiblespectrophotometer at 251 nm and 300 nm.

In-vitro Release Study

The *in vitro* drug release from gel formulations was studied across cellulose membranes (Sigma Aldrich) using Franz diffusion cells with effective diffusional surface area of 3.14 cm^2. The cellulose acetate membrane (cellophane membrane) having a pore size 33 mm was mounted between the donor and receptor compartment of the diffusion cell. The receiver compartment wasfilled with 15 ml of phosphate buffer pH 7.4 to ensure sink condition. The donor compartment ofthe cell was filled with 1 g vehicle containing the test drug. 0.5 ml sample was withdrawn at intervals of 1 hour for a period of 24 hours, and each time equal volume was replaced with drug-free receptor fluid. All samples were analyzed by UV spectrophotometer at 200 nm–400 nm. Theexperiment was carried out in triplicate, and the mean cumulative percentage releases from three batches were calculated.

EVALUATION OF OPTIMIZED NANOGEL

Particle Size and Polydispersity Index (PDI)

The average particle size and PDI of optimized Nanogel was determined using dynamic light scattering using Malvern Zetasizer (Nano ZS90, Malvern instruments) at 25°C. The samples werekept in polystyrene cuvette and the readings were measured at a fixed angle.

Zeta Potential

The zeta potential of optimized Nanogel was measured using Malvern Zetasizer (Nano ZS90, Malvern instruments) at 25°C. The samples were measured by zeta dip cell kept in polystyrene cuvette.

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TEM (Transmission Electron Microscope)

Transmission electron microscopy (TEM) is a microscopy technique in which a beam of electronsis transmitted through a specimen to form an image. The specimen is most often an ultrathin section less than 100 nm thick or a suspension on a grid.

In Vitro Drug Release Kinetics

The drug release kinetics of optimized formulation (F9) nanogel was determined by plotting the following kinetic models, using the data collected from in vitro release studies (zero order, firstorder and Higuchi equations). The mechanism of drug release was determined by using Korsmeyer-Peppas equations.

Zero-Order Kinetics

Cumulative amount of drug released was plotted against time.

$$C = K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the timein hours. A graph of concentration vs. time would yield a straight line with a slope equal to K0 andintercept the origin of the axis. This kinetics describes concentration independent drug release from the formulations.

First Order Kinetics

First order graph is plotted by log cumulative percentage of drug remaining vs. time. Thiskinetics describes concentration dependent drug release from the formulations.

$$\text{Log } C = \text{Log } Co + Kt/2.303$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi's Model:

Higuchi's model as cumulative percentage of drug released vs. square root of time.

$$Q = Kt1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. This model describes the release of drug on the basis of Fickian diffusion as a square root of timedependent process from swellable matrix.

Korsmeyer-Peppas Equations:

The mechanism of drug release, the first 60% of drug release were plotted in Korsmeyer et al's equation log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line,

$$Mt/M\infty = Ktn$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. This type of drug release is controlled by combination of polymer swelling, erosion and diffusion through hydrated matrix. The mechanism of diffusion is identified from thevalues of 'n'.

- The value of $n \leq 0.45$ indicating fickian diffusion (Case I)
- The value of n between 0.45 to 0.89($0.45<n<0.89$) indicating non fickian (anomalous) diffusion. Here release is controlled by combination of diffusion and polymer relaxation
- The value of n =0.89, indicating the zero order release or case 2 transport. Here the drugrelease rate is independent of time and involves polymer relaxation.
- The value of $n > 0.89$, indicating the super case 2 transport.

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Comparison Drug Release Data With Formulated Nanogel and Marketedformulation.

The *in vitro* release study was performed with comparison of optimized formulation andmarketed formulation.

RESULTS AND DISCUSSION

Preformulation Studies

Physical Characteristics

Acyclovir And Omeprazole was checked for its colour, odour and texture. Acyclovir AndOmeprazole is White colored powder in appearance, odourless and amorphous in nature.

Melting Point

Melting point of acyclovir was determined by capillary tube method and it was found to be 256℃ respectively, which confirms the purity of the drug.

Melting point of omeprazole was determined by capillary tube method and it was found to be 156℃ respectively, which confirms the purity of the drug.

Solubility Studies

The solubility of Acyclovir and omeprazole in various solvents like water, methanol, ethanol and pH 7.4 was done. The results shows that the Acyclovir drug is sparingly soluble in water, methanol and its highly soluble in buffer PH 7.4 and ethanol. Omeprazole is sparingly soluble inethanol and its highly soluble in water, methanol and buffer pH 7.4.

Determination of Standard Graph

Standard graph was constructed with concentration of 2 to 10 µg/ml. The absorbance was determined corresponding to their concentration were shown in Table 3. Correlation coefficient was found to be r^2= 0.9918 which shows standard graph was linear.

Table 3. Calibration data of Acyclovir

S.N.	Calibration data	Absorbance at 251 nm
1	2	0.050
2	4	0.118
3	6	0.202
4	8	0.247
5	10	0.307

Determination of Standard Graph

Standard graph was constructed with concentration of 2 to 10 µg/ml. The absorbance was determined corresponding to their concentration were shown in Table 4. Correlation coefficientwas found to be r^2 = 0.9872 which shows standard graph was linear as seen in Figure 1.

Excipient Compatibility Studies

FT IR Study

Drug excipients compatibility study was performed by FT IR. There is no incompatibilityobserved with the drug and excipients used in the formulation as seen in Figure 2 and Figure 3.

Acyclovir + Omeprazole Nanogel

Compatibility Study

The FTIR of the above compounds are studied for its compatibility. The Infrared Spectroscopy is used to study the functional group present. The Acyclovir API contain functional groups NH, OH,CH, C – O, C=O and C=N stretching at 3435.27 cm^{-1}, 3175.78 cm^{-1}, 2680.11 cm^{-1}, 1213.51 cm^{-1},1701.11 cm^{-1} and 1628.54 cm^{-1} peaks respectively. The peaks at 3278.18 cm^{-1}, 1637.30 cm^{-1} and 1410.26 cm^{-1} shows functional groups OH, C=N and C – O stretching respectively for Acyclovir GEL. The

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Omeprazole API contain S=O, NH, C– O and CN stretching functional group at 1410.65cm^{-1}, 1774.24 cm^{-1}, 1266.89 cm^{-1} and 2945.42 cm^{-1} peaks respectively. The absorption peak at 3324.56 cm^{-1}, 1700.59 cm^{-1} and 2940.23 cm^{-1} of Carbopol 940 shows functional groups OH, C=O and CH stretching respectively. The Tri ethanolamine shows functional group OH, C – N and CHstretching at 3308.32 cm^{-1}, 1405.33 cm^{-1} and 2945.60 cm^{-1} peaks respectively. The complex compound Acyclovir + Omeprazole GEL shows functional group OH, C=N and C – O stretchingat 3317.30 cm^{-1}, 1636.52 cm^{-1} and 1043.79 cm^{-1} respectively. The complex shows slight deviationin peaks but are compatible with the combined compounds, which can produce best combinationalformulation as seen in Table 5.

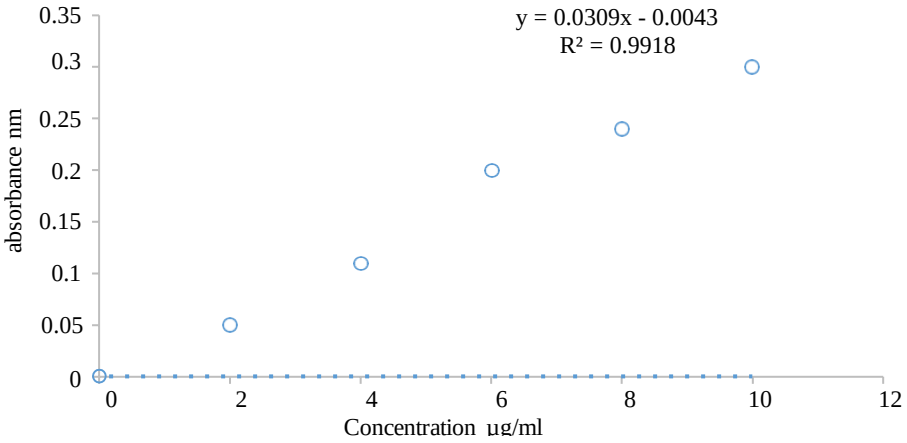

Figure 1. Standard graph curve of acyclovir.

Table 4. Calibration data of Omeprazole

S.N.	Calibration data (µg/ml)	Absorbance at 305 nm
1	2	0.116
2	4	0.312
3	6	0.452
4	8	0.647
5	10	0.870

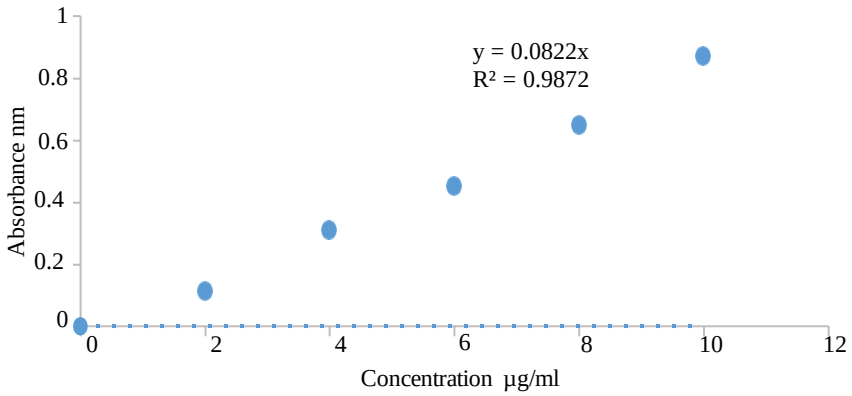

Figure 2. Standard graph of omeprazole.

FORMULATION OF NANOGEL

Selection of polymers for the formulation of Acyclovir and Omeprazole by emulsion solvent diffusion method was based on the trial batches carried out by using different polymers such as carbopol, triethanolamine, PPG in Table Drug: polymer ratio was selected based on the literature.The results indicated that F9 was found to be suitable for the formulation of Acyclovir and Omeprazole as seen in Table 6.

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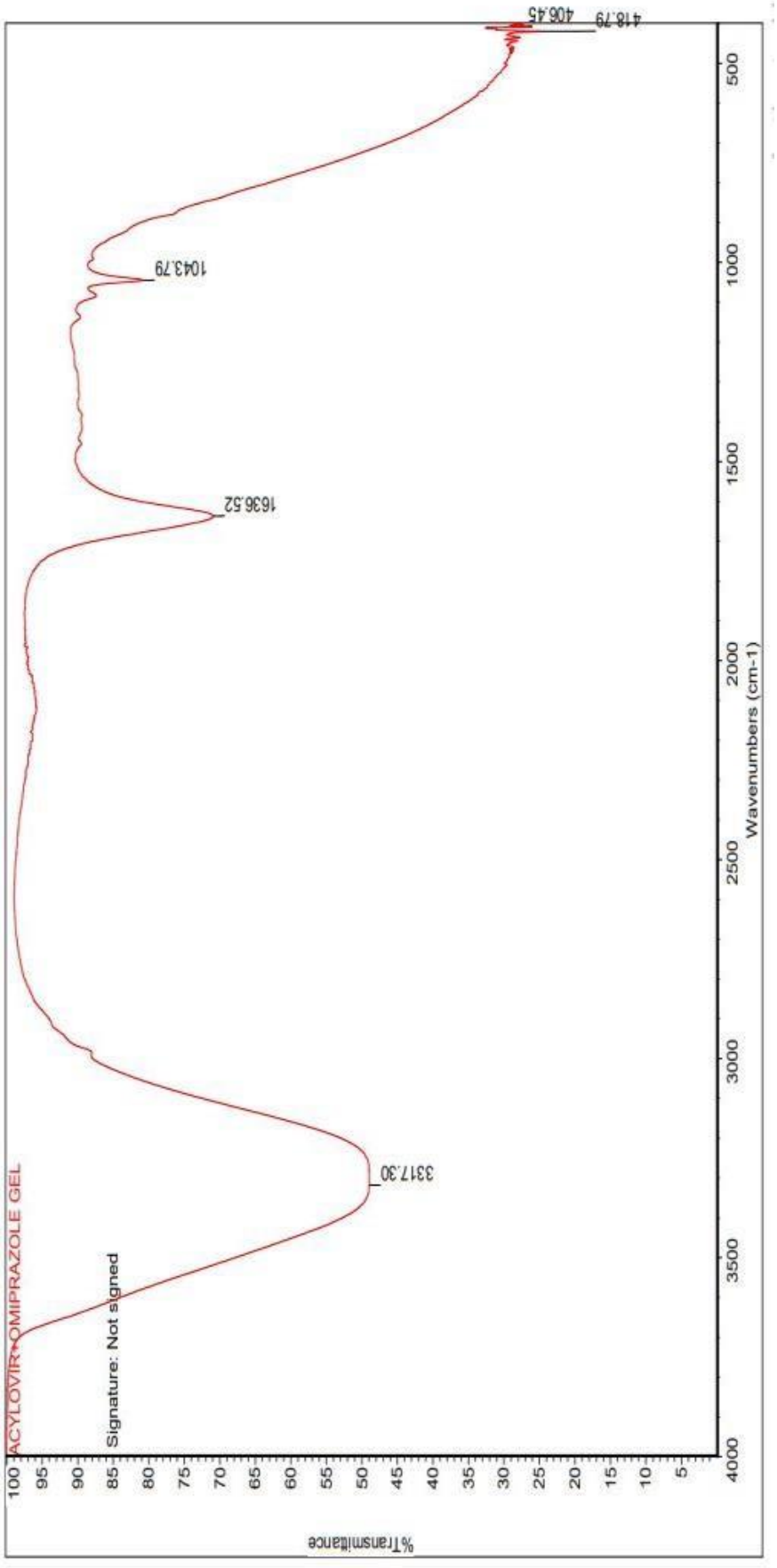

Figure 3. FT-IR of acyclovir and omeprazole nanogel.

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Table 5. FT-IR of acyclovir and omeprazole nanogel.

S.N.	Wave number cm^{-1}	Assignment
1	3317.30	OH stretching
2	1636.52	C=N stretching

Table 6. Trial batches for formulation of acyclovir and omeprazole.

Drug	Formulation code	Observed
Acyclovir and Omeprazole nanogel	F1	Light yellow
	F2	Solid in nature
	F3	Brown
	F4	Liquid in nature
	F5	Pale yellow
	F6	Pale orange
	F7	Semiliquid
	F8	Hard gel
	F9	transparent gel

CHARACTERISATION OF ACYCLOVIR AND OMEPRAZOLE NANOGEL

Determination of pH

The pH of different formulation from F1 to F9. The pH varies from one formulation to another according to their polymer ratios with drug.

Homogeneity

All the gel formulations (F1-F9) showed good homogeneity with absence of lumps. Gels were found to be transparent and were free from presence of particles, uniformity of gel, aggregates, foreign matter and phase separation.

Spreadability

Spreadability diameter for different formulations F1-F9 showed good spreadability i.e. gel is easily spreadable.

Viscosity

All the formulations of Nanogel were subjected to Brookfield viscometer used to measure the viscosity (in cps) by dropping a cone attached to a holding rod from distance of 10 cm in such a way that, it should fall on center of the glass cup filled with Nanogel.

Percentage Yield Analysis

The percentage yield was minimum for formulation F2 (32%) and maximum for formulation F9 (96.02%). From the results we can conclude that as the F9 has the highest percentage yield as seen in Figure 4.

Drug Content

The Drug content was found to be highest for F9 formulation which is 92.65% and the lowest entrapment of drug was found for F2 formulation. The prepared nanogel possess high drug entrapment efficiency and were found as seen in Tables 7–9.

IN VITRO DRUG RELEASE STUDIES

In vitro drug release study of the prepared Acyclovir and Omeprazole Nanogel was carried out using cellophane memberane by frantz diffusion cell. Amount of drug released in different time intervals were observed as seen in Figures 5–7.

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Table 7. Evaluation of formulated batches of nanogel.

Formulation code	pH	Homogeneity	Spreadibility	Viscosity
F1	6.1	Homogenous	2.5	3459
F2	6.3	Homogenous	3.5	3356
F3	6.2	Homogenous	2.9	3268
F4	6.5	Homogenous	3.4	3498
F5	6.2	Homogenous	2.6	3295
F6	6.3	Homogenous	2.9	3501
F7	5.9	Homogenous	3.2	3340
F8	6.4	Homogenous	2.8	3351
F9	6.9	Homogenous	3.5	3528

Table 8. Percentage yield of acyclovir and omeprazole nanogel.

S.N.	Formulation code	Percentage yield (%)
1	F1	65.76
2	F2	32.55
3	F3	34.14
4	F4	44.56
5	F5	68.89
6	F6	71.18
7	F7	86.80
8	F8	78.25
9	F9	96.02

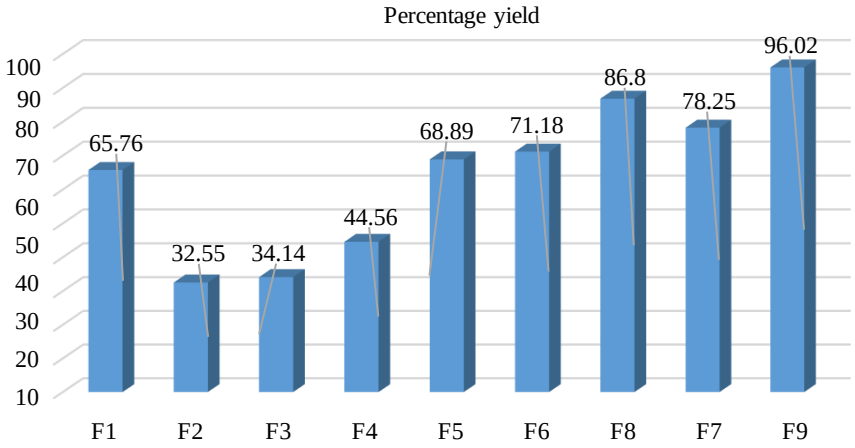

Figure 4. Percentage yield of acyclovir and omeprazole nanogel.

Table 9. Drug content of acyclovir and omeprazole nanogel.

S.N.	Formulation code	Drug content (%)
1	F1	60.54
2	F2	29.00
3	F3	30.84
4	F4	40.55
5	F5	61.45
6	F6	65.78
7	F7	85.11
8	F8	75.24
9	F9	92.65

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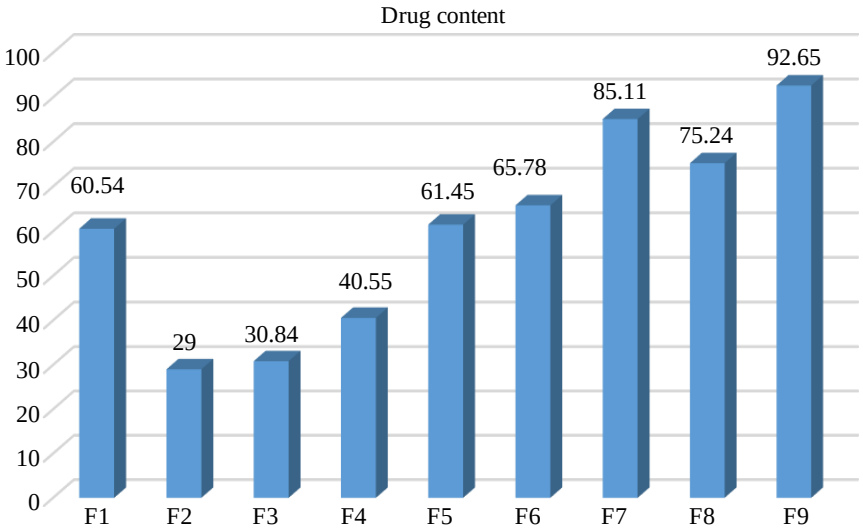

Figure 5. Drug content of acyclovir and omeprazole nanogel.

Table 10. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F1-F3).

S.N.	Time (h)	Cumulative percentage drug release (%)					
		F1		*F2*		*F3*	
		A	*O*	*A*	*O*	*A*	*O*
1	0	0	0	0	0	0	0
2	1	3.4	0.5	1.2	1.1	1.5	1.5
3	2	12.5	9.5	8.8	7.2	10.6	8.8
4	4	25.2	20.8	24.5	15.4	18.7	17.3
5	6	43.8	35.1	40.5	27.9	29.3	23.9
6	8	53.6	50.5	50.9	43.5	35.6	39.6
7	12	60.4	55.7	55.3	51.4	42.1	46.4
8	16	65.5	60.8	60.4	69.6	56.6	52.5
9	20	79.9	70.0	62.9	72.3	65.2	65.7
10	24	80.1	75.9	70.4	75.7	72.7	69.1

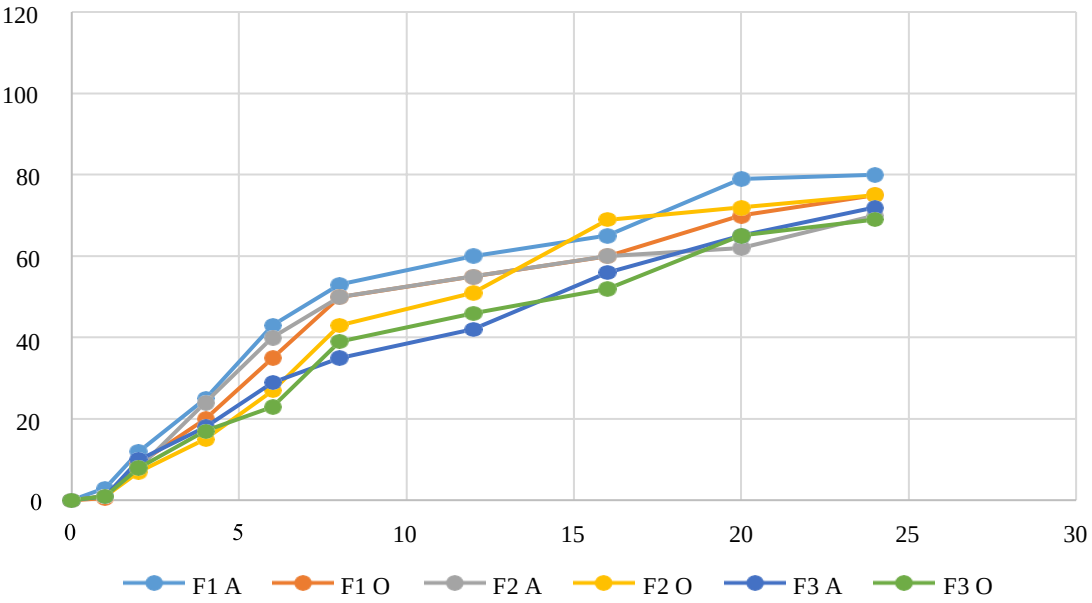

Figure 6. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F1-F3).

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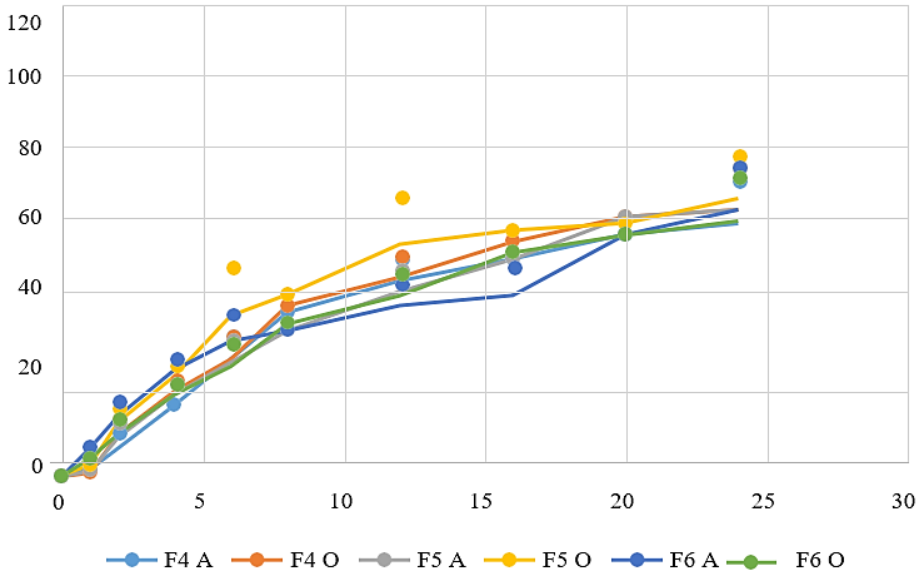

Figure 7. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F4-F6).

From the in vitro release data it was found that formulations F9 showed the best release of 99%and 97.5% respectively at the end of 24 hrs among all the nine formulations of Acyclovir andOmeprazole Nanogel as seen in Figure 8.

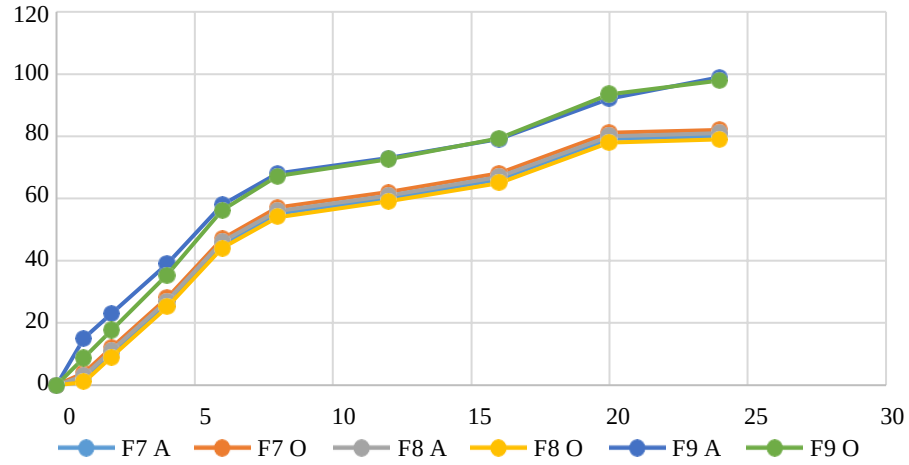

Figure 8. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F7-F9).

OPTIMIZATION OF ACYCLOVIR AND OMEPRAZOLE NANOGEL BY CHARACTERISATION:

According to characterization of acyclovir and omeprazole nanogel have good drug release properties in F9 formulation as seen in Tables 10–13.

EVALUATION OF OPTIMIZED FORMULATED F9:

Particle size and Zeta Potential:

The particle size is one of the most important parameter for the characterization of nanogel. The average particle sizes of the prepared F9 nanogel measured using Malvern zeta sizer.

Particle size analysis showed that the average particle size of Acyclovir and omeprazole nanogel formulated using (F9) was found to be 678.4 nm with polydispersity index (PDI) value 0.842 andwith intercept 0.857 as seen in Table 14.

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Table 11. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F4-F6).

S.N.	Time (h)	Cumulative percentage drug release (%)					
		F4		***F5***		***F6***	
		A	***O***	***A***	***O***	***A***	***O***
1	0	0	0	0	0	0	0
2	1	2.2	1.5	1.5	3.8	8.1	5.2
3	2	8.6	12.4	11.1	15.5	17.6	12.2
4	4	20.8	24.1	23.3	28.9	30.2	23.8
5	6	33.5	33.8	32.9	45.2	38.8	31.3
6	8	46.5	48.9	41.5	51.1	41.5	43.8
7	12	55.2	56.1	52.7	65.8	48.2	51.1
8	16	61.9	66.6	61.2	69.7	51.8	63.8
9	20	68.8	73.4	73.8	71.3	68.3	68.2
10	24	71.5	75.2	75.4	78.8	75.4	72.8

Table 12. *In vitro* drug release profile of acyclovir and omeprazole nanogel (F7-F9).

S.N.	Time (h)	Cumulative percentage drug release (%)					
		F7		***F8***		***F9***	
		A	*O*	*A*	*O*	*A*	*O*
1	0	0	0	0	0	0	0
2	1	2.4	4.7	3.7	1.4	15.2	8.8
3	2	10.2	12.5	11.5	9.5	23.5	17.6
4	4	26.5	28.1	27.6	25.4	39.2	35.2
5	6	45.3	47.8	46.4	44.6	48.8	45.5
6	8	55.8	57.4	56.1	54.7	61.5	58.2
7	12	60.5	62.7	61.8	59.3	73.1	72.6
8	16	66.5	68.2	67.1	65.5	81.6	83.2
9	20	79.9	81.9	80.4	78.8	92.4	93.5
10	24	80.2	82.2	81.9	79.5	98.1	97.9

Table 13. Optimization of acyclovir and omeprazole nanogel by characterization.

S.N.	Methods	Observed	Result
1	pH	6.9	F9
2	Homogeneity	Homogenous	F9
3	Spreadability	3.5	F9
4	Viscosity	3528	F9
5	Percentage yield	96.02%	F9
6	Drug content	92.65%	F9
7	In-vitro dissolution study	99 (A)and 97.2(O)	F9

Table 14. Zeta potential of formulation F9.

S.N.	Formulation Code	Particle size	PDI	Zeta Potential
1.	F9	678.4	0.842	-43.7

Determination of Zeta Potential

Zeta Potential was determined using Malvern zeta-sizer instrument. Zeta potential analysis is carried out to find the surface charge of the particles to know its stability during storage. The magnitude of zeta

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potential is predictive of the colloidal stability. Nanoparticles with zeta potentialvalue greater than +25 mV or less than -25 mV typically have high degrees of stability. If all the particles in suspension have a large negative or positive zeta potential then they will tend to repeleach other and there will be no tendency for the particles to come together. However, if the particles have low zeta potential values then there will be no force to prevent the particles comingtogether and flocculating.

For Acyclovir and omeprazole nanogel using zeta potential was found to be -43.7 mV with peakarea of 100% intensity. These values indicate that the formulated Acyclovir and omeprazole nanogel (F9) are stable as seen in Figure 9 and Figure 10.

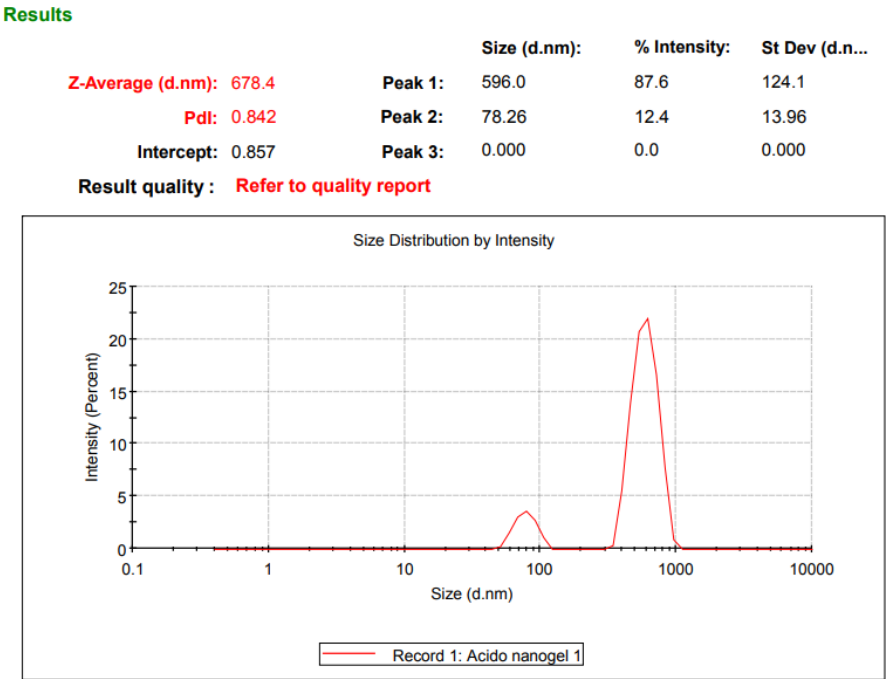

Figure 9. Particle size and PDI of the formulation F9.

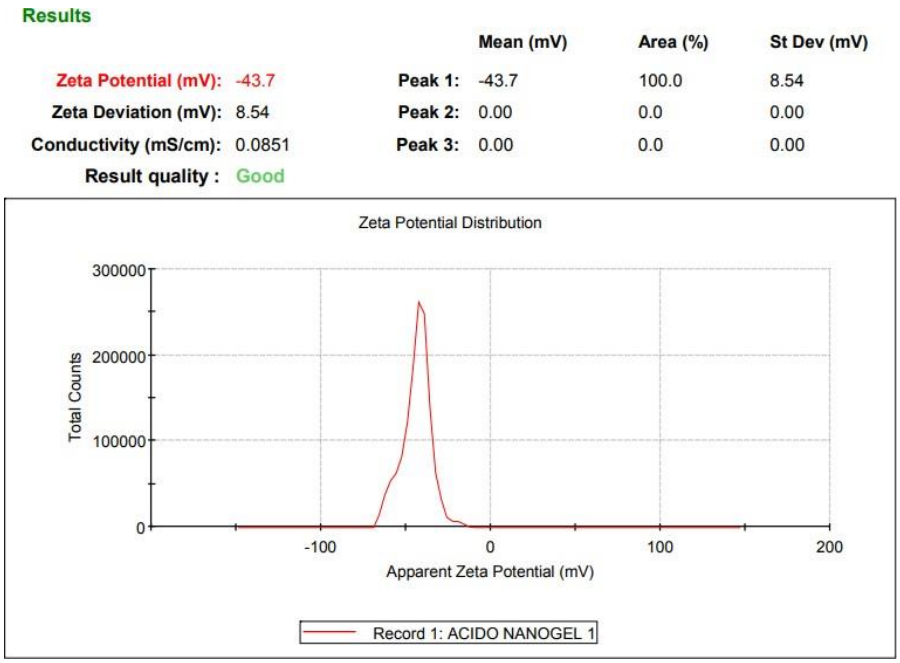

Figure 10. Zeta potential of formulation F9.

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TEM (Transmission Electron Microscope)

Transmission electron microscopy (TEM) is a microscopy technique in which a beam of electrons is transmitted through a specimen to form an image. The specimen is most often an ultrathin section less than 100 nm thick or a suspension on a grid.

***IN-VITRO* DRUG RELEASE KINETICS**

The data obtained from the *in vitro* release study was used to fit into kinetic models. This was doneto find out the mechanism of drug release from Acyclovir and omeprazole nanogel F9. In order todetermine the release model, the *in vitro* release data were analyzed according to zero order kinetics. The preference of a certain mechanism was based on the coefficient of determination (r^2) for the parameters studied, where the highest coefficient of determination is preferred for the selection of the order of release. The kinetic parameters of Acyclovir and omeprazole nanogel F9. Since the r^2 value is higher for zero order, it is selected as the best fitted model. This was confirmedby plotting percentage cumulative drug release and square root of time and r^2 value ranges between0.928 and 0.921. However, in many experimental situations, the mechanism of drug diffusion deviates from the Fickian equation and follows a non-Fickian (anomalous) behaviour. In these cases, the Korsemeyer–Peppas model was used to analyse the release kinetics. It is observed that formulation F9 followed Fick's law of diffusion and rest showed an anomalous behavior as seen in Figure 11.

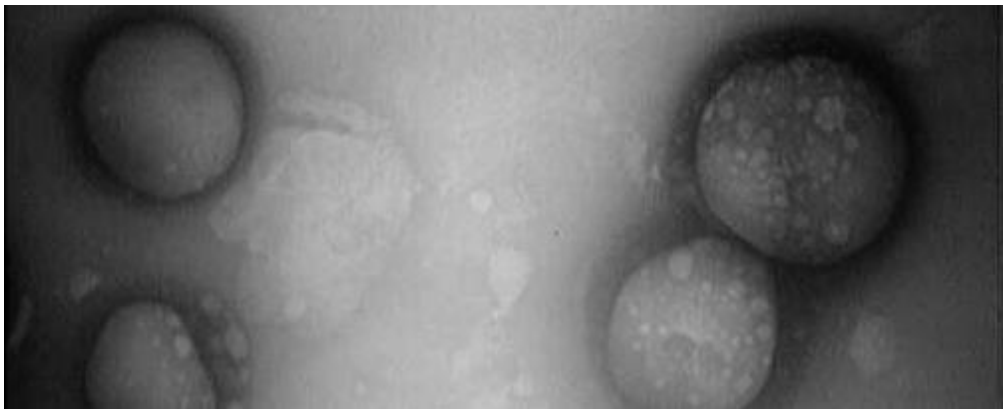

Figure 11. TEM image.

SUMMARY

- The λmax Acyclovir and Omeprazole were confirmed by UV spectrometer at range 251nm and 305 nm.
- Standard graph was determined by various concentration of Acyclovir and Omeprazole
- The present study demonstrated that Acyclovir and Omeprazole nanogel were successfully developed by solvent diffusion method.
- pH was determined various formulation F1-F9 in that F9 have suitable for gel preparation.
- Drug content was determined by UV-spectroscopic method.
- The prepared nanogel was opaque, without any lumps, particle and aggregates. So, all the formulations are homogenous.
- Spreadability diameter study F9 shown the nanogel is having good Spreadability. Nanogel formulations shown viscosity range from 3268–3528 cps. It concluded that they are stablein nature.
- *In-vitro* dissolution study was performed and showed that F9 have good dissolution rate.
- The particle size, PDI and zeta potential to find out the F9 formulation.
- The particle size, PDI and zeta potential was found to be in 687.4, 0.842 and -43.7 respectively.
- TEM image was confirmed the shape of spherical and smooth surface of particles at range650 nm.

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- Comparing F9 nanogel formulation with acyclovir marketed formulation (MF) by *in-vitro* release study.
- According to result formulated Acyclovir and omeprazole nanogel is more efficient than the marketed acyclovir ointment.
- Hence from our study the acyclovir and omeprazole nanogel (F9) showed that sustain drug release than the marketed formulation, so it is evident that formulating into nanogel results increase the anti –viral activity.

CONCLUSION

It can be concluded that the experimental study carried out that the formulation of a Nanogel containing anti-viral drug and anti-ulcer drug yields a formulation with spherical and smooth surface, nano in size range. The prepared nanogel was opaque, without any lumps, particle and aggregates. So, all the formulations are homogenous. Based on all the factors the nanogel drug delivery system F9 shows good drug content compare to other. The particle size of the nanogel formulation is optimum and it is less than 1000 nm. So, it concluded that the particles are in tiny and nano in size range. All nanogel formulations shows pH in the range of 6.1 to 6.9. Formulation F9 shows highest pH of 6.9. Because the pH range of nanogel were 1 to 7 pH. Based on the Spreadability diameter study it shown the nanogel is having good Spreadability. Nanogel formulations shown viscosity range from 3268–3528 cps. It concluded that they are stable in nature. Formulation F9 shows highest percentage of drug release compare to other formulations. In-vitro diffusion studies show F9 formulation shows controlled release pattern of drug from the formulation. The formulation was found to be stable in short term stability studies. Here we have selected F9 has an optimized formulation which shown good morphological features, drug content efficiency and controlled drug release. Hence the F9 formulation is efficient than the marketed formulation of acyclovir ointment (ACIVIR).

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