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Formulation of Niosomal Gel of Diclofenac Sodium and its *In-Vitro* Characterization

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ABSTRACT

Niosome is a non- ionic surfactant vesicles which being formed by the self assembly of non-ionic surfactant that have potential application in the delivery of hydrophobic and hydrophilic drugs. Preparation of anti-inflammatory Niosomal gel of Diclofenac sodium is evaluated using physical parameters, pH determination, content uniformity, extrudability, spreadability, degree of deformability testing. Rheological studies carried out to determine gel behavior. *In-vitro* permeation of gel formulations was investigated using Franz diffusion cell. Each of the prepared Niosome significantly improved drug permeation. Niosomes prepared with Span 60 provided a higher permeation across the skin than that of Span 20 and Span20:Span 60 combination ratio. Changes in the cholesterol content affect the encapsulation efficiency and permeation of gel. The encapsulation (%) of Niosomes with Span 60 surfactant showed a very high value of ~100% due to its low surface energy decreases the size of vesicle and drug permeation increases. It can be reasonably concluded that Niosomal gel using Span 60 is better suited for controlled release of Diclofenac sodium.

INTRODUCTION

Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms. These carriers can act as drug reservoirs, and modification of their composition or surface can adjust the drug release rate and/or the affinity for the target site [1]. The niosome are non-ionic surfactant vesicles in aqueous media resulting in closed bilayer structures that can be used as carriers of amphiphilic and lipophilic drugs [2,3]. The bilayer is multilamellar or unilamellar which enclose aqueous solution of solutes and lipophilic components are in the bilayer itself. Niosomes are formed by hydration of non-ionic surfactant dried film resulting in imbibing or encapsulating the hydrating solution. Major component of niosome is non-ionic surfactant which gives it an advantage of being more stable when compared to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability[4]. Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively. The bilayers of niosomes have both inner and outer surfaces to be hydrophilic with sandwiched lipophilic area in between. Thus a large number of drugs and other materials can be delivered using niosomes [5]. From a technical point of view, niosomes are promising drug carriers as they possess greater stability and lack of many disadvantages associated with liposomes, such as high cost and the variable purity problems of phospholipids. Another advantage is the simple method for the routine and large-scale production of niosomes without the use of unacceptable solvents [6].

Diclofenac sodium is a non-steroidal agent with potent analgesic and moderate anti-inflammatory activity[7,8]. It works by blocking the action of cyclooxygenase. Cyclo-oxygenase is involved in the production of various chemicals in the body, some of which are known as prostaglandins. Prostaglandins are produced in response to injury or certain diseases and would otherwise go on to cause pain, swelling and inflammation. Diclofenac sodium is used to relieve pain and inflammation in arthritic conditions. All the drugs in this group reduce inflammation caused by the body's own immune system and are effective painkillers. But it has several drawbacks such as narrow therapeutic index, short biological half-life. These factors necessitated niosomal formulation for Diclofenac sodium [9]. As this dosage form would reduce the dosing frequency, hence better patient compliance. The drug is currently administered intramuscularly

and orally in divided multiple doses for short-term management of post-operative pain (30 mg q.i.d. by IM injection and 50 mg b.i.d. as oral tablets). This frequent dosing, which results in unacceptable patient compliance, is required due to the short half-life of the drug (2-4 h). Therefore, an alternative noninvasive mode of delivery of the drug is needed. Transdermal delivery certainly appears to be an attractive route of administration to maintain the drug blood levels of Diclofenac sodium for an extended period of time[10]. The present study was aimed with the formulation of niosomes of Diclofenac sodium followed by the evaluating parameters such as drug content, entrapment efficiency, particle size, shape, size distribution and *in-vitro* drug release.

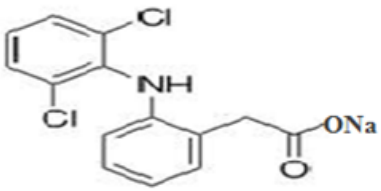
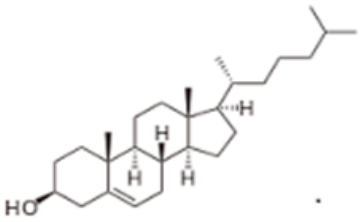


Figure 1: Structure of Diclofenac sodium



Cholesterol

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as a gift sample from Cipla Ltd. Goa, (India), Span 20 and Span 60, Research Lab (India), cholesterol, Carbopol 934, chloroform from Himedia Laboratories, Mumbai, (India), Ethanol, Potassium dihydrogen phosphate, Sodium hydroxide from Fisher scientific, Mumbai, (India). All other chemicals and solvents were of analytical grade.

Niosomal Gel of Diclofenac Sodium [11]

Preparation of Drug Loaded Niosome

Diclofenac sodium loaded niosomes were formulated by using thin film hydration technique and the different nonionic surfactants (Span 20 and Span 60) grades in different Drug: Surfactant: Cholesterol ratios as 1:1:1, 1:2:1, 1:1:2. Accurately weighted quantities of surfactant and Cholesterol were dissolved in 5 ml chloroform using a 100 ml round bottom flask. The lipid solution was evaporated by rotary shaker. The flask was rotated at 135 rpm until a smooth and

dry lipid film was obtained. The film was hydrated with 5 ml phosphate buffer saline (PBS) of pH 7.4 containing drug for 3 hours with gentle shaking. The niosomal suspension was further stabilized by keeping at 2-8ºC for 24 hours.

Preparation of Niosomal Gel

The preparation of niosomal gel using Carbopol 934, the gel base was prepared by dispersing 0.2% w/w Carbopol 934 in a mixture of water and glycerol (7:3), the dispersion is then neutralized and made viscous by addition of sufficient amount of triethanolamine.

The measured amount of selected niosomal formulations were centrifuged by using centrifuge apparatus for 30 min at 2500 rpm. The semisolid mass of niosomes was separated from the supernatant and mixed in the 0.2% Carbopol gel base by using electric homogenizer. The gel containing pure Diclofenac sodium was also formulated for making the comparison of parameters.

Table 1: Formulation and Composition of Niosomal gel

Formulation Code	Surfactant Used	Drug:Surfactant :Cholesterol Ratio	Solvent	Carbopol 934 (%)
F1	Span 20	1:1:1	Chloroform	0.2%
F2		1:2:1	Chloroform	0.2%
F3		1:1:2	Chloroform	0.2%
F4	Span 60	1:1:1	Chloroform	0.2%
F5		1:2:1	Chloroform	0.2%
F6		1:1:2	Chloroform	0.2%
F7	Span 20:Span 60	1:1:1	Chloroform	0.2%
F8		1:2:1	Chloroform	0.2%
F9		1:1:2	Chloroform	0.2%

Evaluation Parameters of Niosomal Gel

pH Determination:

The pH of each Niosomal gel was determined using pH meter. The electrode first calibrated with pH 4.0 and pH 7.0 solution then readings were recorded on pH meter [11].

Physical appearance:

The prepared Niosomal gel was characterized for their physical properties such as colour, odour by visual inspection [12].

Encapsulation efficiency:

Niosomal gel (100mg) was hydrated with 10 ml of phosphate buffer saline (pH7.4) solution. The aqueous niosomal dispersion was be sonicated in a bath sonicator for 10 min. The drug containing niosomal dispersion was separated from entrapped drug by centrifuging at 15000 rpm for 30 minutes. The clear supernatant was filtered off carefully to separate the unentrapped drug. Recovered supernatant is assayed by its analytical technique. The percentage of drug encapsulation was calculated by the following Equation [13].

$$EE\ (\%) = [(Ct-Cf)/Ct]\times 100$$

Where,

Ct is the concentration of total drug.

Cf is the concentration of free drug.

Vesicle size and shape:

Vesicle size and shape for each formulation was determined by optical microscope (Motic Image, Germany) each formulation was spread uniformly on glass slide and observed under optical microscope under 1gm of 45X optical lens for vesicular shape[14].

Scanning Electron Microscopy:

The SEM photographs of drug loaded vesicles of optimized formulation were obtained by scanning electron microscope (Jeol, JSM 6360 Aº) using platinum sputter technique [11].

Viscosity Determination:

Viscosities of the formulated niosomal gels were determined using rotational viscometer (Fungi lab) using L4 Spindle at 12 rpm [15].

Drug Content Uniformity:

Drug content uniformity is the degree of uniformity of the amount of active drug substance among containers, i.e., tubes containing multiple doses of the semisolid topical product. The uniformity of dosage is demonstrated by assay of top, middle, and bottom samples (typically 0.25–1.0 g) obtained from a tube cut open to withdraw respective samples for drug assay.

An accurately weighed 1 gm quantity of the gel was transferred into a 100 ml stopper volumetric flask and shaken vigorously with 100 ml methanol to extract the drug. The contents were filtered, volume was made up to the mark with methanol. From the above solution, 1 ml was pipetted out into a 10 ml volumetric flask and volume was made up to 10 ml with methanol. Finally, the UV absorbance of the resulting solution was measured at 284 nm against the blank solution of methanol [16].

Spreadability:

Spreadability of formulations was determined by an apparatus suggested by Multimer et al. which was fabricated in laboratory and used for study. The apparatus consist of a wooden block, with a fixed glass slide and movable glass slide with one end tied to weight pan, rolled on the pulley, which was in horizontal level with fixed slide.

Procedure

An excess of gel sample 1 gm was placed between two glass slides and a 1000g weight was placed on slides for 5 minutes to compress the sample to a uniform thickness. Weight (60g) was

added to the pan. The time (seconds) required to separate the two slides was taken as a measure of spreadability. It was calculated using the formula:

$$S = m.l/ t$$

Where,

S - Spreadability in g.cm / sec, m - Weight tied to upper slide

l - Length of glass slide, t - Time in seconds

Length of glass slide was 7.5 cm and weight tied to upper slide was (60g) throughout the experiment [16].

Extrudability:

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity of gel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude ribbon of study gel in 10 seconds. The measurement of extrudability of each formulation was in triplicate and the average values were presented [16].

Degree of Deformability:

In case of niosomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is done against the pure water as standard. Niosomes preparation is passed through a large number of pores of known size (through different microporous filters, with pore diameter between 50 nm and 450 nm, depending on the starting niosomes suspension). Particle size is noted after each pass by optical microscopy. The degree of deformability can be determined using the following formula.

$$E = J \times (rv/rp)^2$$

Where,

J= Amount of the suspension extruded during 5min,

rv = Size of the vesicle

rp = Pore size of the barrier[17].

***In-vitro* drug permeation:**

Permeation of Diclofenac sodium from different niosomal gel formulations was studied using a Franz glass diffusion cell. The effective permeation area of the diffusion cell and receptor cell volume was 1 cm^2 and 10 ml, respectively. The receptor compartment contained PBS (pH 7.4) and maintained at 37°C ± 1°C by magnetic stirrer. Egg membrane was mounted between the donor and receptor compartment.

The donor compartment was filled with the 1 gm niosomal gel formulation. 7.5 ml aliquot of 1: 99 (v: v) isopropanol: pH 7.4 phosphate buffer was used as receptor medium. At appropriate intervals, 0.5ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution to maintain a sink condition and analyzed by UV-Visible Spectrophotometer at 284nm[18].

Determination of Zeta-Potential:

The method involves the preparation of dispersion of niosomal gel in PBS (pH 7.4). Then this dispersion was filled in zeta cell and placed in the Zeta Sizer (Nano ZS, Malvern Instruments, UK) to determine the zeta-potential[11,18].

Stability study:

Stability study was carried out by storing the optimized formulation at various temperature conditions like refrigeration temperature (2°C±2°C), room temperature (25°C ± 2°C) and elevated temperature (45ºC±2ºC) for a period of one month. Encapsulation efficiency and variation in the average vesicle diameter were determined before and after completion of one month [19, 20].

RESULTS AND DISCUSSION

Preformulation studies showed that absorption maxima for Diclofenac sodium was found to be at 284 nm and the developed Spectrophotometric method obeyed beer's law with linearity range of

10 -50 µg/ml (Figure 2). Drug along with the ingredients showed no change in any characteristic peak in preliminary compatibility studies revealed that there no interaction between Diclofenac sodium and excipients which was as evidence from FTIR spectral studies.

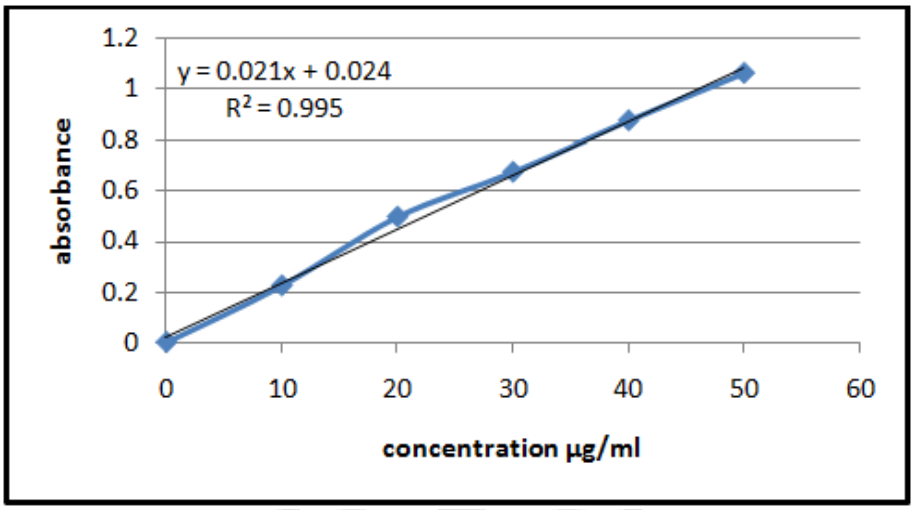


Figure 2: Calibration curve of Diclofenac sodium

Niosomal gels were prepared by thin film hydration method. The formulations were studied for physical characteristics like determination of pH, Vesicle size, Viscosity and Encapsulation efficiency and were found to be within the acceptable limits shown in Table 2.

Encapsulation efficiency and vesicle size of various Niosome formulations Niosomes prepared with non-ionic surfactants of alkyl ester including Span (sorbitan esters) were utilized to determine the encapsulation of associated Diclofenac sodium and vesicle size. As shown in Table 2, encapsulation efficiency of Niosomes formed from S20 and S60 Niosome gel exhibits a very high value of ≈100%. Most of the surfactants used to make non-ionic surfactant vesicles have a low aqueous solubility.

Table 2. Physicochemical characterization studies of Diclofenac sodium niosomal gel

Sr. No.	Formulation Code	pH	Vesicle size	Encapsulation Efficiency (%)	Viscosity (cps)
1	F1	6.8 ± 0.15	5.32 ± 1.56	77.95±1.96	12500 ± 0.28
2	F2	6.74 ± 0.177	4.67 ± 1.22	80.12±2.11	12503.33± 2.08
3	F3	6.54 ± 0.09	6.65 ± 1.56	75.26±2.39	10708 ± 162
4	F4	7.10 ± 0.0355	1.86 ± 0.79	86.27±1.92	12800± 0.48
5	F5	7.26 ± 0.35	1.33±0.58	89.55±3.90	13500±0.18
6	F6	7.21 ± 0.04	2.66 ± 0.42	84.02±2.23	11409 ± 1.85
7	F7	6.71 ± 0.13	3.32 ± 2.05	82.26±1.89	12700.42 ± 1.07
8	F8	6.99 ± 0.580	2.03 ± 0.24	84.67±0.27	13800 ±0.78
9	F9	7.4 ± 0.27	3.74 ± 1.56	81.14±2.11	10238 ± 1.06

In the Niosomal gel formulations (F1 to F9) containing Span-60 (F4-F6) showed high encapsulation efficiency than formulations containing surfactants in different order (F1-F3 and F7-F9). Because the Span 60 having the highest phase transition temperature, low HLB value, higher lipophilicity and longer alkyl chain length provide the system that is less leaky and has highest entrapment. Incorporation of cholesterol was to know to influence vesicle stability, permeability and entrapment efficiency. Increasing the cholesterol content resulted in a more intact and ordered lipid bilayer as a barrier for drug release helps as a controlled release polymer also decreases drug leakage by improving the fluidity of the bilayer membrane and reducing its permeability, which led to lower drug elution from the vesicles. In niosomes formulation, the cholesterol is added in increasing order (F3, F6, F9), as concentration get increased the encapsulation efficiency also get reduced. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bilayer structure leading to loss of drug entrapment.

The mean vesicle sizes of niosomes formed from Diclofenac sodium niosome formulations are presented in Table 2. The differences in vesicle size among the niosomes prepared with Span 60 were not significant. On the other hand, niosomes prepared with Span 20 were significantly larger than those prepared with Span 60.

Vesicle Size Determination

Figure 3: Optimized formulation (F5) of Diclofenac sodium niosomal gel under Optical microscope with uniform size

Span 60 hydrophobicity has been attributed to the decrease in surface energy with increasing hydrophobicity resulting in the smaller vesicles and span 60 have low HLB = 4.3 among the all tested formulations. As for vesicle size, increasing hydrophobicity of the surfactant monomer led to smaller vesicles; a result which might be anticipated since surface free energy decreases with increasing hydrophobicity. It was observed that as concentration of Span increases in hydrophobicity results in decrease in the vesicle size.

SEM Analysis

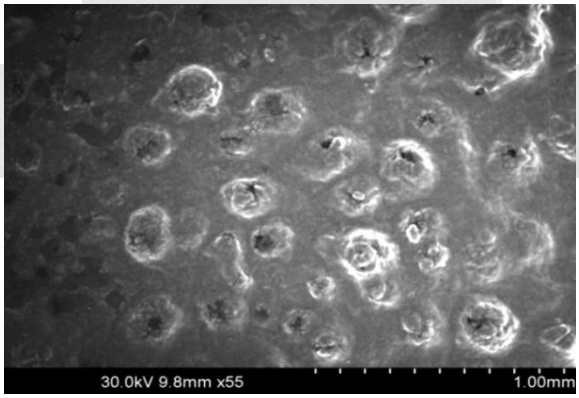


Figure 4: Scanning Electron microscopy for F5 Formulation

The drug content of the Niosomal gel was found to be within range by UV spectrophotometer to in range between to 89.76 ± 98.12 of the theoretical value for formulation (F1- F9).

Table No. 3. Drug content, Spreadability, Degree of Deformability studies of Diclofenac sodium niosomal gel

Sr. No.	Formulation Code	Drug content (%)	Spreadability (gm.cm/sec)	Degree of Deformability
1	F1	91.53±1.17	19. 08 ± 0.79	17.08 ±0.30
2	F2	92.22± 0.81	18.97 ± 0.46	21.88±0.59
3	F3	89.76 ±1.18	13.78 ± 0.135	10.19 ± 0.63
4	F4	96.51±1.01	20.2 ± 1.34	30.47 ± 0.45
5	F5	98.12±0.68	20.56 ± 0.89	33.21 ±0.19
6	F6	95.99± 4.45	17.21 ± 0.350	27.57 ± 0.54
7	F7	95.01± 0.88	19.56 ± 0.9	25.26 ± 0.42
8	F8	97.38±1.54	20.09 ± 0.99	29.42 ± 0.89
9	F9	94.49 ± 1.25	15.77 ± 0.87	26.05 ± 0.32

The formulations F1-F9 in which F1, F2, F3, F6, F9 showed good extrudability and formulations F4, F5, F7 and F8 showed excellent extrudability. Deformability index of various Niosome formulations were found to vary significantly with surfactant and cholesterol concentration. It was observed that deformability index first increased significantly with increase in cholesterol concentration. However, deformability index was found to decrease on further increase in cholesterol concentration. One possible reason for this result could be the rigidization effect of cholesterol on higher concentrations. On the other hand, deformability was found to increase with surfactant concentration suggesting the major role of the surfactant in vesicle elasticity is shown in table 3.

In-vitro permeation studies of niosomal gel of Span 60 (F5) have high release profile than other tested surfactant formulations because niosomes prepared with span 20 were significantly larger than those prepared with Span 60. This would also explain the large vesicle size of niosomes prepared with span 20 which has a much lower hydrophobicity than that of Span 60. Hydrophobicity is also high (HLB = 4.3) so lipophilic drug can be easily penetrated through the skin. Vesicles with smaller diameter are believed to better permeate through the skin as smaller vesicles tend to fuse readily. The greater amount of span 60 are used in F5 formulation shows

greater permeability than from other formulation because niosomes of Span 60 were smaller in size, demonstrated higher hydrophobicity and higher surface area due to low vesicle size so better permeability of drug also occurs (Table 4 and Figure 5). Span 60 have high phase transition temperature and above the phase transition temperature cholesterol made the membrane more ordered and abolishes the gel to liquid phase transition of niosome system hence during formulation the temperature is maintained at 65º±3ºC so that membrane made more abolish during formulation. The drug permeation was low for F3, F6 and F9 formulation i.e. Cholesterol content are more than all tested formulation (F1-F9) as shown in Table 3. Increasing the cholesterol content contributed an increase in the hydrophobicity; which results retard in the permeation.

Table 4: *In-vitro* drug permeation of Niosomal gel formulation F1-F9

Formulation	Time (hr)	% drug permeation	Formulation	Time (hr)	% drug permeation
F1	12	90.82 ± 0.91	F6	12	90.987± 0.11
F2	12	91.543 ± 0.5	F7	12	93.47 ± 0.43
F3	11	89.925 ± 0.65	F8	12	96.56 ± 1.49
F4	12	95.231 ± 0.9	F9	11	90.382± 0.34
F5	12	97.58±0.774			

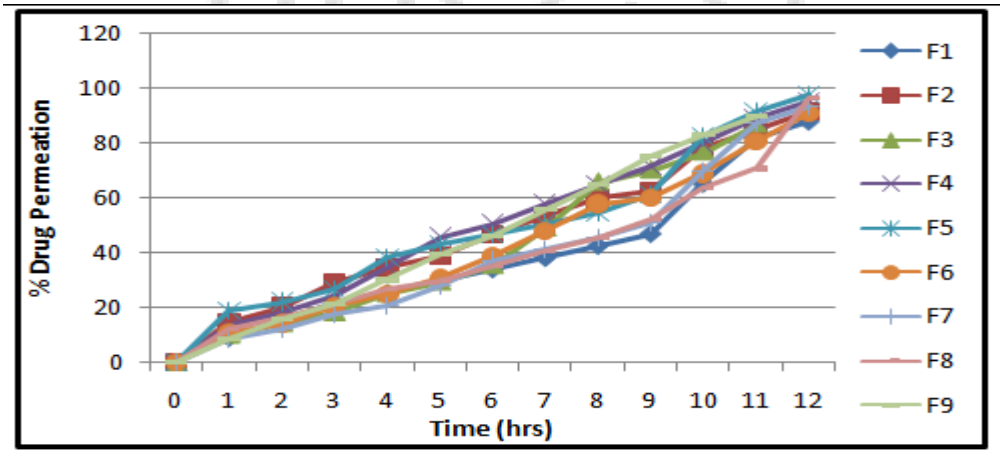


Figure 5: *In- vitro* drug permeation of Diclofenac sodium from various niosomal gel formulations

The optimized formulation (F5) was found to be stable for period of one month; it can be observed that the niosomal gel formulation showed no major alteration in relation to encapsulation efficiency and vesicle size (Table 5).

Table 5: Stability study of optimized formulation (F5)

Sr. No.	Temp.	Initial		After 1 months	
		Encapsulation Efficiency	Vesicle size	Encapsulation Efficiency	Vesicle size
1	2°C	89.55±3.90	1.33±0.58	89.38 ± 0.34	1.45±0.64
2	25°C	89.47±3.59	1.48±0.63	89.23 ± 1.04	1.87±0.78
3	45°C	89.38±2.89	1.96±0.79	88.98 ± 0.88	2.1 ± 0.56

Zeta potential of the Diclofenac sodium loaded Niosomes prepared by Span 60 (F5)1:2:1 ratio showed higher stability and zeta potential of optimized formulation was found to be -17.8 Mv is shown in Figure 6.

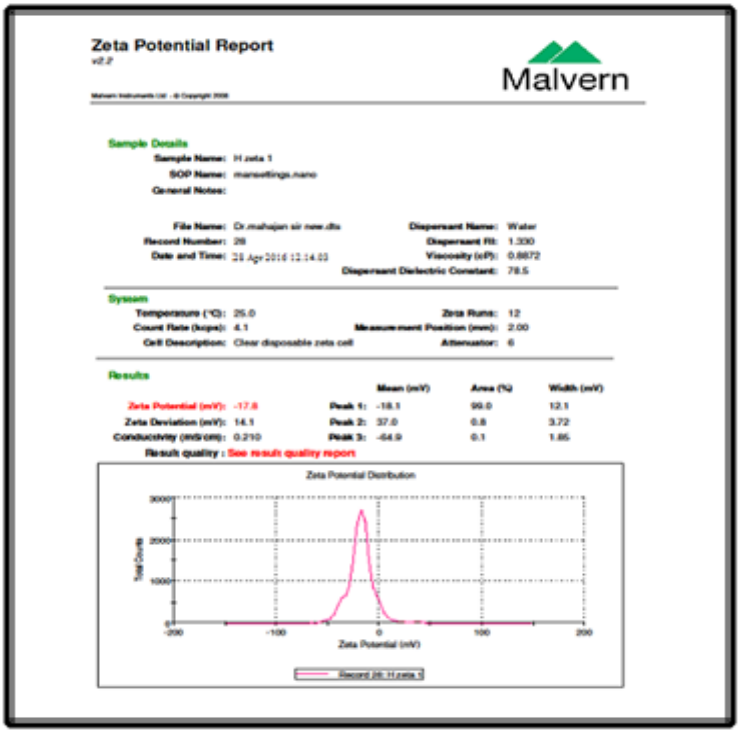


Figure 6: Zeta potential of optimized formulation (F5)

CONCLUSION

The *in- vitro* permeation of Diclofenac sodium from niosomes of various compositions and types of nonionic surfactants have been studied and evaluated. Diclofenac sodium was successfully entrapped within the lipid bilayers of the vesicles with high efficiency. Niosome formulated with span 60 have shown the best entrapment efficiency as compared with niosomes prepared with other grades like Span 20. This may be due to low HLB value, higher lipophilicity, higher phase transition temperature and longer alkyl chain length of Span 60. The vesicle size and drug permeation was greater for Span 60 (F5) due to its low surface energy which decreases the size of vesicle and increases drug permeation. Incorporation of cholesterol was known to influence vesicle stability, permeability and entrapment efficiency. The Drug permeation retards by increasing the concentration of cholesterol (F3, F6 & F9) due to increase in hydrophobicity. The results of *in- vitro* anti-inflammatory study also revealed that the gel formulation having span 60 niosomes showed the best inhibition of inflammation and sustained the drug release for a period of 12 h.

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