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Original Article

Formulation and evaluation of topical nano emulgel of adapalene

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ABSTRACT

The aim of the present research work is to decrease the systemic side effects and to create a more pronounced effect of Nano emulgel of Adapalene with lower doses of the drug. Nano Emulgel emerged as one of the most interesting topical drug delivery system as it has dual release control system. Also the stability of emulsion is increased when it is incorporated into gel. The Nano emulgel was developed using polymers like carbopol 934 (1:1) of gel and emulsion. Drug-excipients interaction was characterized by FTIR studies. The Nano emulgel was prepared by preparing emulsion and gel separately and incorporation emulsion into the gel. The emulgel was evaluated for their physical appearance, pH evaluation, Spreadability, rheological study, drug content, in-vitro permeation study and accelerated stability study. After all evaluation it can be concluded that Adapalene emulgel could increase the drug permeability across the membrane and fast release of the drug could be achieved successfully.

KEY WORDS: Adapalene, nano emulgel, carbopol 934, Tween 80, Soyabean oil.

INTRODUCTION

Over the last decades of the treatment of illness have been accomplished by administrating drugs to the human body via various roots namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder or the cutaneous manifestations of the general disease (eg:-psoriasis) with the intent of containing the pharmacological and the effect of drug to the surface of the skin or within the skin semi-solid formulations in all their diversity dominate the system for topical delivery but foams, spray, medicated powders, solutions and even medicated adhesive systems are in use. Emulsions are two-phase preparations in which one phase (the dispersed or internal phase) is finely dispersed in the other (continuous or external phase). The dispersed phase can have either a hydrophobic-based (oil-in-water), or be aqueous based (water-in-oil). Because there are two incompatible phases in close conjunction, the physical stabilizing system. In most pharmaceutical emulsions and the stabilizing system comprises surfactant (ionic or nonionic), polymers (nonionic polymers, polyelectrolyte, or biopolymers), or mixtures of these. Nanoemulsions have attracted great attention in delivery of the therapeutically active agents since approximately 40% of new chemical entities are hydrophobic in nature and the delivery of these poor water soluble drugs is a challenge for delivery of drugs. The term "Nanoemulsion" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids. So, oil and water stabilized by an interfacial film of surfactant molecule. The emulsions and nanoemulsions differ mainly in size and shape of the particles dispersed in the continuous phase. The particle size in nanoemulsions is (10-200 nm) and those of conventional emulsions are (1-20 μm).Biocompatible gels having weak interaction with surfactants have already been explored to modify the rheological behavior of nanoemulsion. Variant gel matrices of carbomer 980, carbomer 940, carbomer 934, Xanthan gum and carrageen have been exploited to increase the viscosity of nanoemulsion for transdermal delivery. It is incorporation of nano emulsion into gel matrix can result in nanoemulgel which may be more relevant for transdermal application when compared to nanoemulsion. It promotes better stability of nanoemulsion by reducing the surface and interfacial tension and also enhancing viscosity of the aqueous phase for better administration

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topically. Besides that, drug delivered through nanoemulgel has larger concentration gradient towards the skin, hence influences better the skin penetration. It was gel based formulation of nanoemulgel. Formulation of gel using thickening agents, increase the consistency of any dosage form. Finally nanoemulgel will be produced by the incorporation of nanoemulsion into the gel base with in continuous stirring.[1,2]

MATERIALS AND METHODS: Adapalene was obtained as a gift sample from Zydus pharmaceutical ltd. Carbopol 934, Tween 80, Glycerine, Soyabean oil, Isopropyl alcohol was procured from orbit pharmaceutical ltd.

Emulgel preparation: Gelified emulsion of Adapalene was prepared in three steps. Step 1: Emulsion of Adapalene using Soyabean oil as the oil phase and water as the aqueous phase with span 80, Tween 20 and tween 80 as emulsifying agents, Isopropyl alcohol as the permeation enhancer. Glycerine used as humectant. Step 2: The gel formulation were prepared from with carbopol 934. But the optimum concentration for the emulgel with respect to consistency, Extrudability and Spreadability was found to be with carbopol 934 gel. Hence these concentrations were fixed as a standard for emulgel formulation. Step 3: The emulsion and gel formulation were mixed in the ratio of 1:1 as and homogenized to get an uniform emulgel of Adapalene. The different formulations with varied concentration of emulsifying agents and emulsion: gel combination ratios were prepared and evaluated.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Adapalene(gm)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Tween 80(gm)	2	2	2	6	6	6	10	10	10
Glycerine(gm)	8	8	8	8	8	8	8	8	8
Soyabean oil(gm)	6	10	14	6	10	14	6	10	14
Isopropyl	10	10	10	10	10	10	10	10	10
Water(gm)	73.90	69.90	65.90	69.90	65.90	61.90	65.90	61.90	57.90

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbopol 934	2	2	2	2	2	2	2	2	2
Water	98	98	98	98	98	98	98	98	98

Table no. 1: Nano Emulgel preparation

Evaluation parameter.[5,6,7]

1. Determination of globule size: The globule size analysis of the optimized formulations was the determined by Zetasizer. 0.5gm of adapalene is dissolved in water.

2. Physical appearance: The prepared emulgel formulations were inspected visually for their color, phase separation, homogenecity and consistency.

3. pH: pH evaluation is the very important criteria especially for the topical formulation. The pH of the emulgel should be between 6 to 7 to mimic the skin condition. The pH of the prepared emulgel is acidic or basic. It causes irritation to the patient.

pH of the prepared emulgel was measured using digital pH meter (Lab India) by dipping the glass electrode into the emulgel. In triplicate the measurement of the pH of each formulation was done and average values were calculated.

4. Rheological study: The viscosity of the gel during handling, transport and storage is the important criteria. The viscosity of different emulgel formulation was determined at 25^{o}C using the Brook field viscometer (Brookfield). The emulgels were rotated using spindle 1 at 10, 50 and 100 rpm and the viscosities were measured.

5. Spreadability test: One of the criteria for the dermatological preparation is to meet the ideal qualities of that it should be possessed good Spreadability. Spreadability is the term expressed to denote to the extent of area to which the gel readily spreads on application to the skin and the affected area. The therapeutic efficiency to the formulation is depending on its Spreadability values. So determination of Spreadability is very important in evaluating nano emulgel characteristics. Spreadability is measured as:S = M×L/T. The Spreadability of the each sample was evaluated in triplicate using with fabricated Spreadability apparatus with consists of two glass plates. 0.5 gm of sample was placed on the lower plate and the upper plate was placed on the top of the sample. Force was applied by adding increasing weight slow at 1 min interval into the pan

connected to the upper plate. Sample was tested for three times the constant temperature and weight and the mean values of spread surface area on to the lower plate were calculated.

6. Extrudability: It is a usual empirical test to measure the force required to extrude from material tube. The method was applied for the determination of applied shear in the region of the rheogram corresponding to the shear rate exceeding to the yield value and exhibiting consequent for plug flow. The emulgels were filled into crimped, collapsible tubes and the Extrudability of the formulation from the packed material was tested.

7. Drug content determination: Drug concentration in emulsified gel was measured by HPLC. Adapalene content in the emulsified gel was measured by dissolving accurately weighed 5gm in 50ml of emulsified gel in solvent (purified water) by Sonication phosphate buffer pH 7.4. Heated for 5 min and Sonication for 15 min. The test was conducted into the triplicate and the average % drug content was calculated.

8. In-vitro drug permeation study: In-vitro permeation study was carried out by using Franz diffusion apparatus having capacity of 10 ml volume. Sigma dialysis Membrane was the isolated and used for the study. Preweighed (1g) emulgel was spread evenly on to the membrane. The sigma dialysis membrane was clamped between donor and receptor compartment. The receptor compartment was filled with 10 ml of purified water maintained at 37ºC and stirred by using magnetic stirrer. The sample (0.5ml) was collected at suitable time intervals and analyzed for drug content by HPLC after appropriate dilutions as discussed earlier.

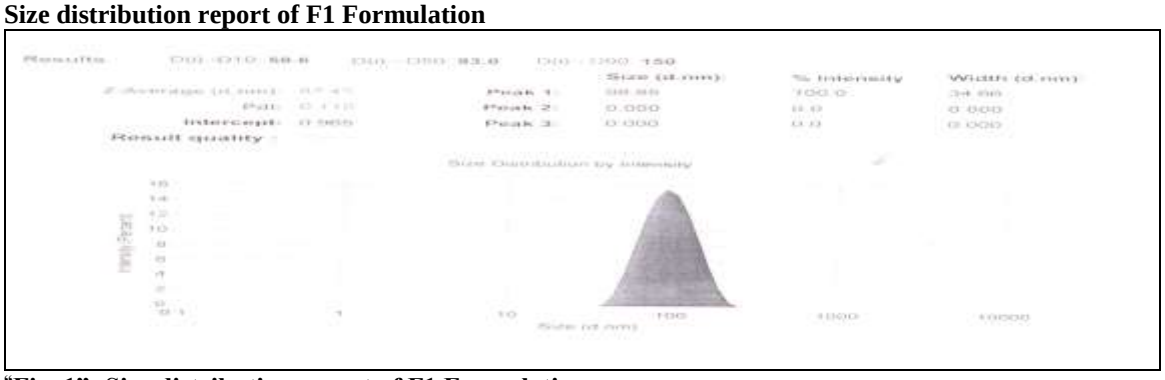
The same procedure was opted for Adapalene prepared by using carbopol 934.

9. Stability studies: Stability of a drug is defined as the ability of particular formulation in specific container to the remaining into its physical, toxicological, specification, chemical and therapeutic.

RESULT AND DISCUSSION:

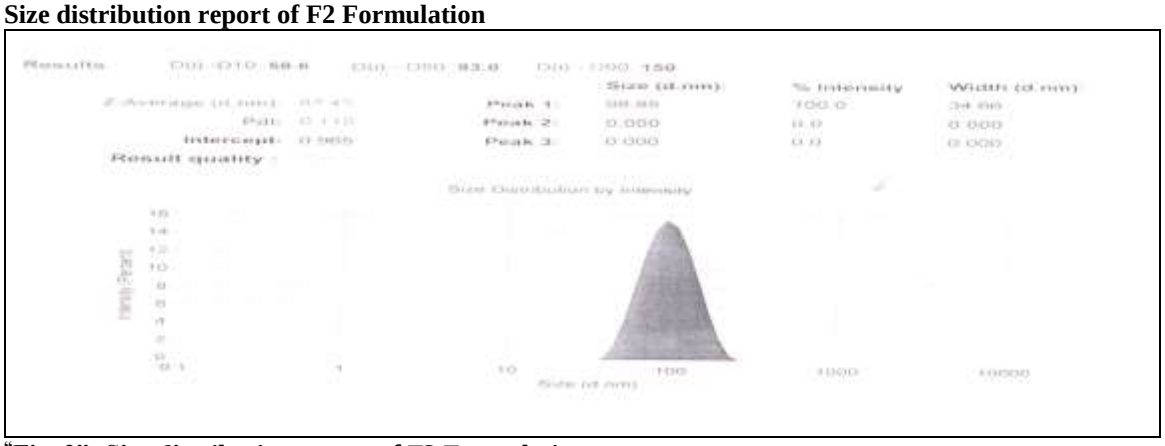
1. Determination of globule size: The globule size analysis of the optimized formulations was determined by Zetasizer. 0.5gm of adapalene is dissolved in water.

Size distribution report of F1 Formulation



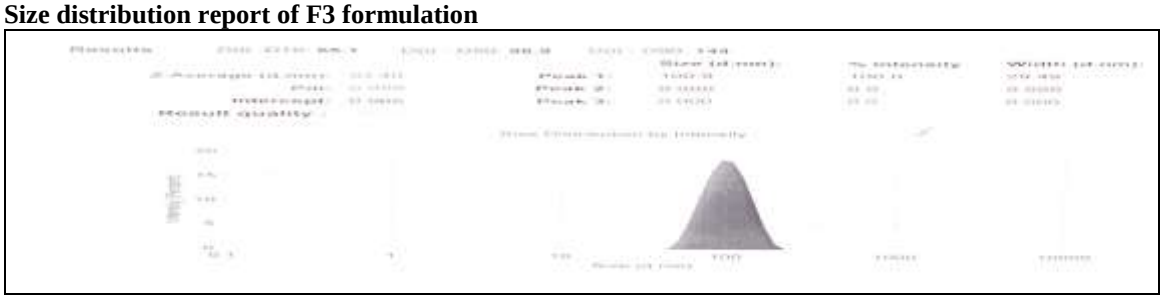
"Fig. 1": Size distribution report of F1 Formulation

Size distribution report of F2 Formulation



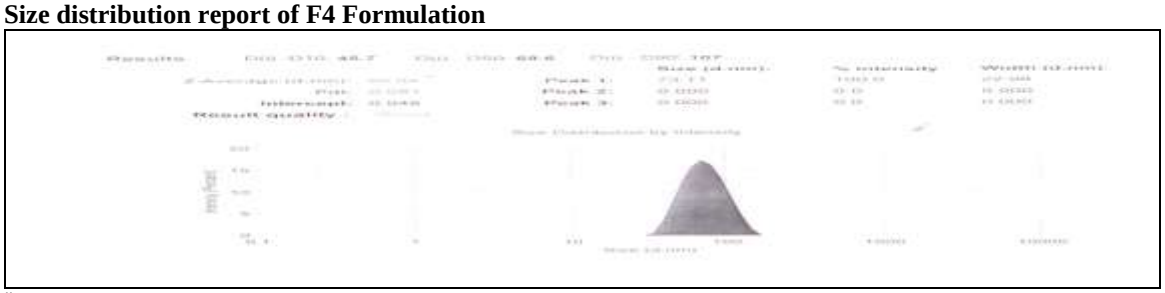
"Fig. 2": Size distribution report of F2 Formulation

Size distribution report of F3 formulation



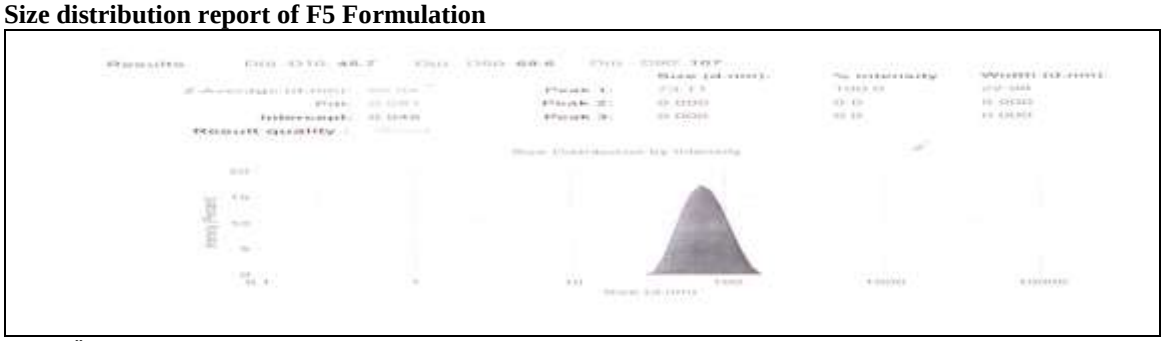
"Fig 3": Size distribution report of F3 Formulation

Size distribution report of F4 Formulation



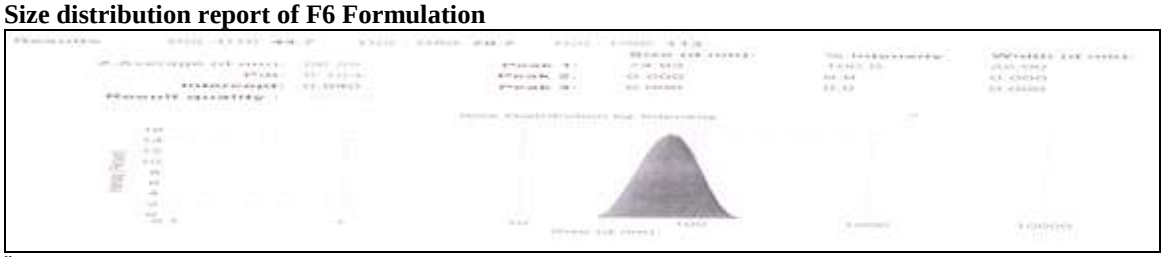
"Fig 4": Size distribution report of Tween 20

Size distribution report of F5 Formulation



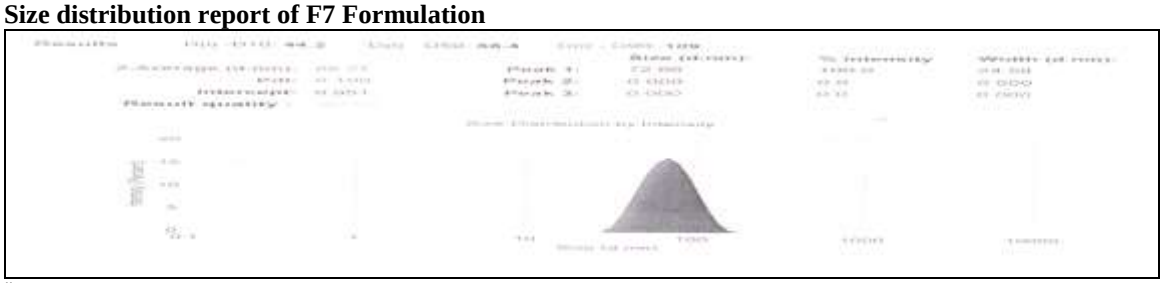
"Fig 5": Size distribution report of F5 Formulation

Size distribution report of F6 Formulation



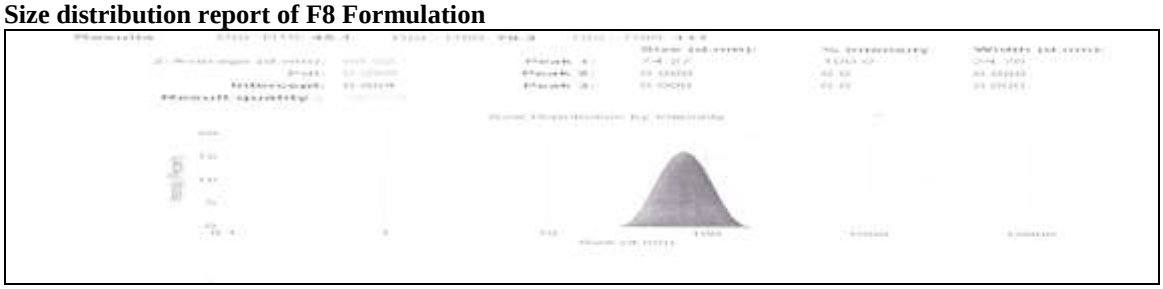
"Figure no 6": Size distribution report of F6 Formulation

Size distribution report of F7 Formulation



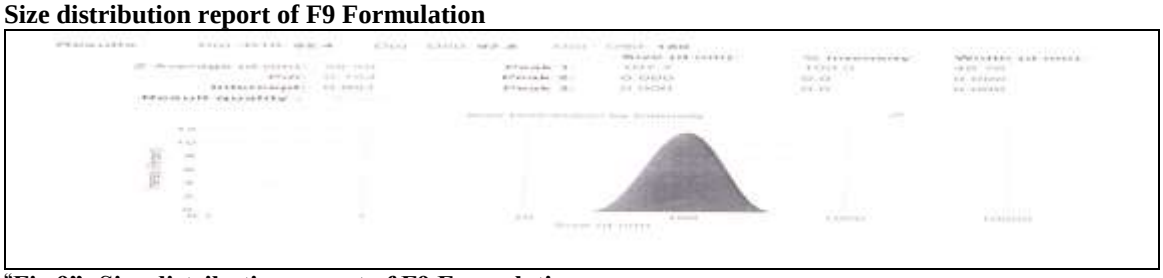
"Fig 7": Size distribution report of Tween 20

Size distribution report of F8 Formulation



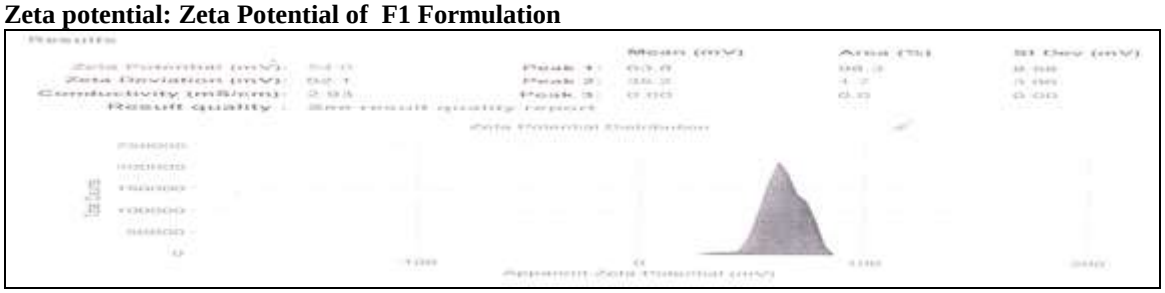
"Fig 8": Size distribution report of F8 Formulation

Size distribution report of F9 Formulation



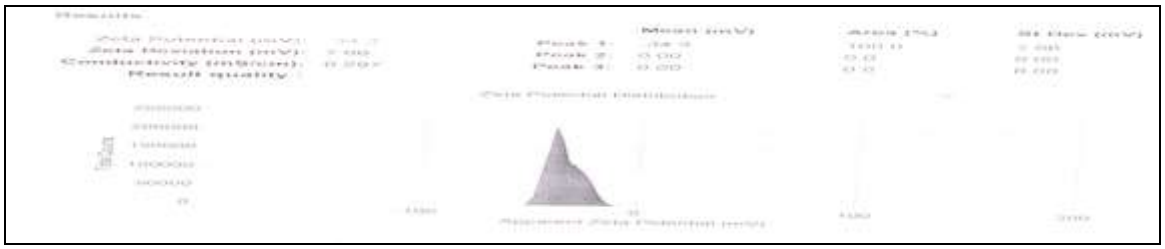
"Fig 9": Size distribution report of F9 Formulation

Zeta potential: Zeta Potential of F1 Formulation



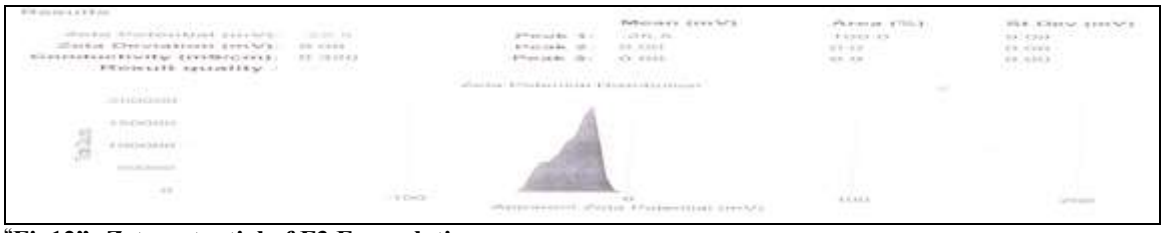
"Fig 10": Zeta potential of F1 Formulation

Zeta Potential of F2 Formulation



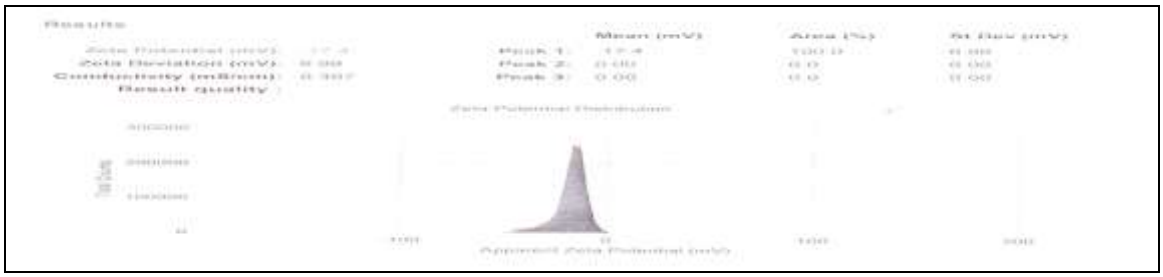
"Fig 11": Zeta potential of F2 Formulation

Zeta Potential of F3 Formulation



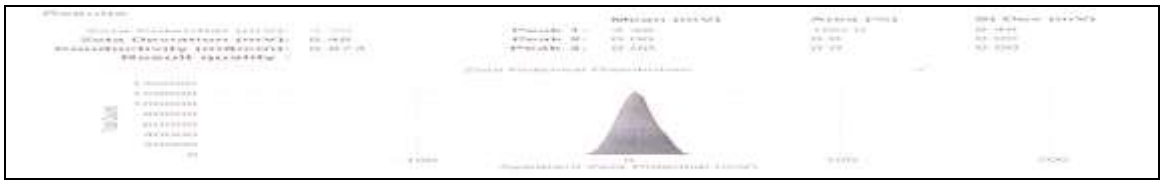
"Fig12": Zeta potential of F3 Formulation

Zeta Potential of F4 Formulation



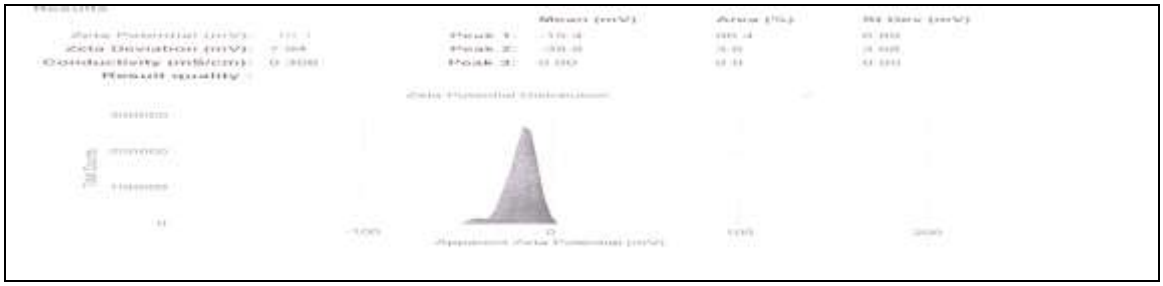
"Fig13": Zeta potential of F4 Formulation

Zeta Potential of F5 Formulation



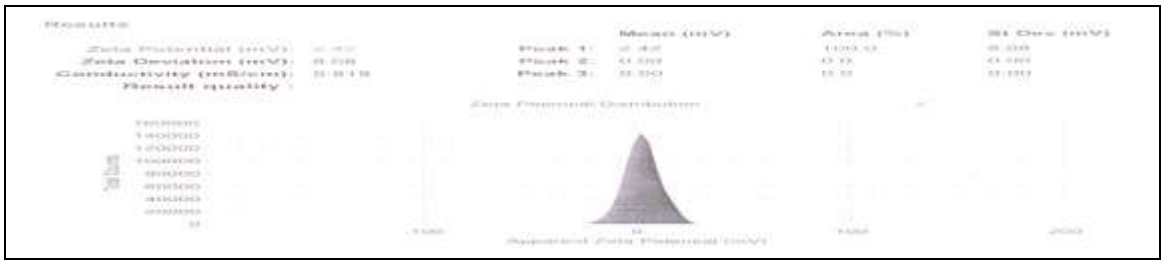
"Fig 14": Zeta potential of F5 Formulation

Zeta Potential of F6 Formulation



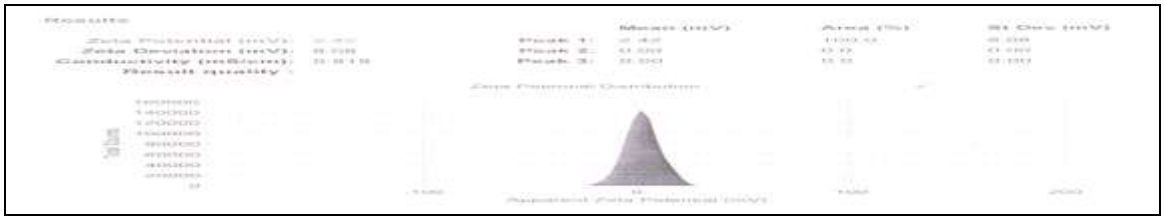
"Fig. 15": Zeta potential of F6 Formulation

Zeta Potential F7 Formulation



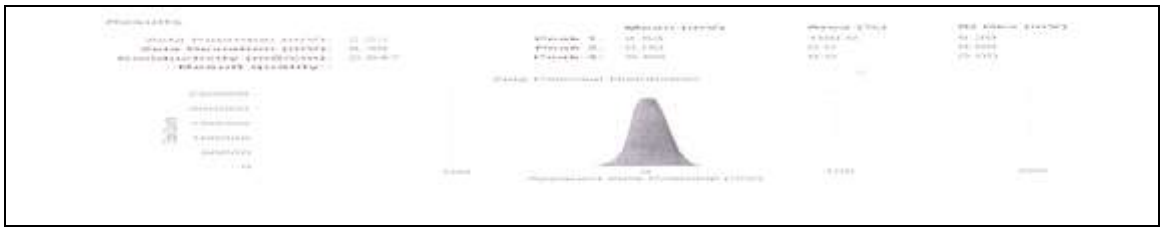
"Fig 16": Zeta potential of F7 Formulation

Zeta Potential of F8 Formulation



"Fig 17": Zeta potential of F8 Formulation

Zeta Potential of F9 Formulation



"Fig 18": Zeta potential of F9 Formulation

2. pH: pH evaluation is the important criteria especially for the topical formulation. The pH of the emulgel should be between 6-7 to mimic the skin condition. If the pH of the prepared emulgel is acidic or basic, it may cause irritation to the patient. pH of the prepared emulgel was measured using digital pH meter (Lab India) by dipping the glass electrode into an emulgel. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Sr. No	Formulation code	pH
1	F1	6.64
2	F2	6.50
3	F3	6.83
4	F4	6.95
5	F5	6.72
6	F6	6.77
7	F7	6.56
8	F8	6.60
9	F9	6.56

Table no.2:pH of F1-F9.

3. Rheological study: The viscosity of the gel during handling, transport and storage is an important criteria. The viscosity of different emulgel formulation was determined at 25ºC using a Brook field viscometer (Brookfield). The emulgels was rotated using spindle 1 at 10, 50 and 100 rpm and the viscosities were measured.

Formulation	10 RPM	50 RPM	100 RPM
F1	49,244	38,345	26,540
F2	48,679	39,200	27,168
F3	47,218	38,910	26,331
F4	49,866	39,540	25,018
F5	50,030	38,645	26,770
F6	50,554	41,230	27,902
F7	49,661	39,900	24,212
F8	47,410	41,148	27,445
F9	51,008	38,322	24,080

Table :3 Rheological study

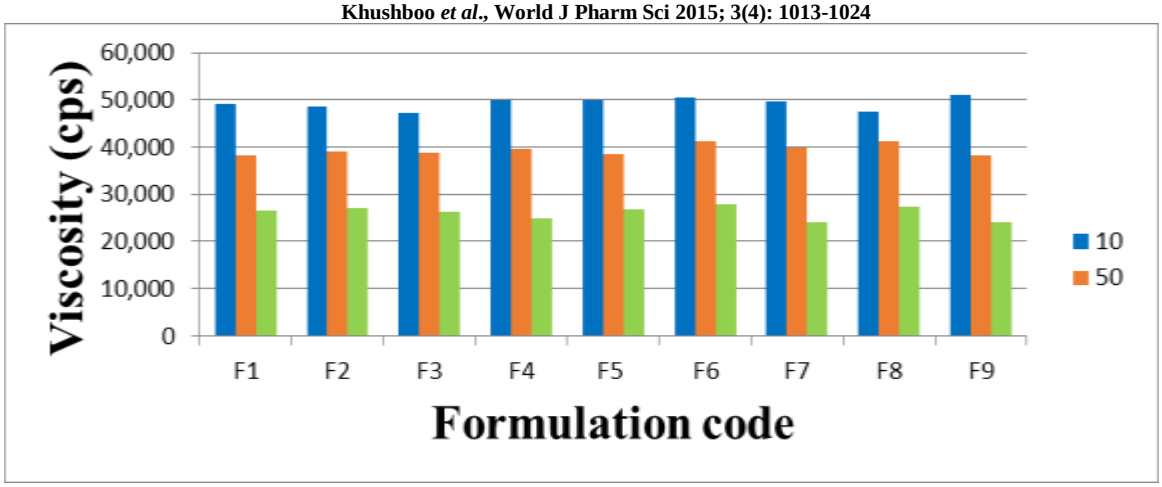


Figure 19: Rheogram for F1-F9

4. Spreadability test: One of the criteria for a dermatological preparation is to meet the ideal qualities is that it should possess good Spreadability. Spreadability is the term expressed to denote the extent of area to the gel readily spreads on application to skin or the affected area. The therapeutic efficiency of the formulation also depends on its Spreadability values. So, determination of Spreadability is important in evaluating gel characteristics. Spreadability is measured as: S= M×L/T**.** The Spreadability of each sample was evaluated in triplicate by using fabricated Spreadability apparatus which consists of two glass plates. 0.5 g of sample was placed on the lower plate and the upper plate was placed on the top of the sample. Force was generated by adding increasing weight slowly at 1 min interval into the pan connected to the upper plate. Each sample was tested at least three times at constant temperature and exerted weight and the mean values of spread surface area on the lower plate were calculated.

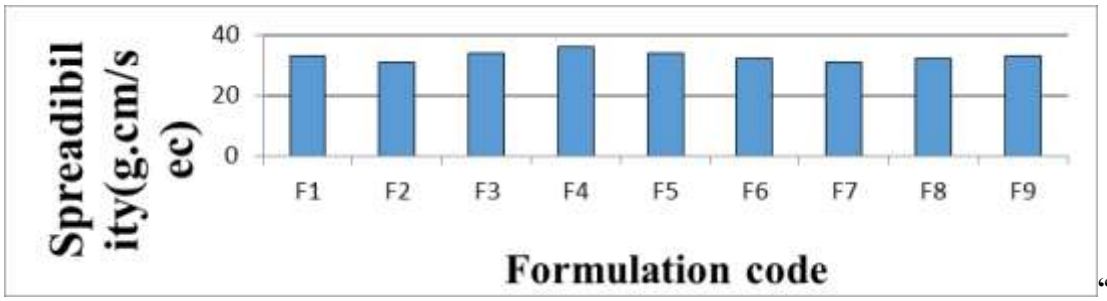


Fig 20": Graph of spreadability of F1-F9

Sr. No.	Formulation code	Spreadability g.cm/sec
1	F1	33.22
2	F2	31.82
3	F3	34.90
4	F4	36.96
5	F5	34.62
6	F6	32.12
7	F7	31.00
8	F8	32.26
9	F9	33.14

Table 4: Data for Spreadability studies of formulation F1-F9 :

5. Extrudability: It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of the applied shear in the region of the rheogram corresponding to the shear rate exceeding the yield value and exhibiting consequent plug flow. The

emulgels was filled into collapsible tubes, crimped and the Extrudability of the formulation from the packed material was tested.

Sr. No.	Formulation code	Extrudability
1	F1	Easily extrudable
2	F2	Easily extrudable
3	F3	Easily extrudable
4	F4	Easily extrudable
5	F5	Easily extrudable
6	F6	Easily extrudable
7	F7	Easily extrudable
8	F8	Easily extrudable
9	F9	Easily extrudable

Table 5: Data of Extrudability for F-1 to F-9

6. Drug content determination [8,9]: Drug concentration in emulsified gel was measured by HPLC. Adapalene content in emulsified gel was measured by dissolving accurately weighed 5gm in 50ml of emulsified gel in solvent (purified water) by Sonication phosphate buffer pH 7.4. Heated for 5 min Sonication for 15 min. The test was conducted in triplicate and the average % drug content was determined.

Table :6 Drug content for F1-F9

Sr. No.	Formulation code	Mean % ± SD
1	F1	96.0 ± 2.0
2	F2	95.5 ± 4.2
3	F3	98.4 ± 3.6
4	F4	100.2 ± 2.3
5	F5	97.9 ± 3.3
6	F6	96.2 ± 2.9
7	F7	102.0 ± 2.6
8	F8	97.3 ± 1.6
9	F9	98± 2.3

7. In-vitro drug permeation study[10] :In-vitro permeation study was carried out using Franz diffusion apparatus having capacity of 10 ml volume. Sigma dialysis Membrane was isolated and used for the study. Preweighed (1g) emulgel was spread evenly on to the membrane. The sigma dialysis membrane was clamped between donor and receptor compartment. The receptor compartment was filled with 10 ml of purified water maintained at 37ºC and stirred by using magnetic stirrer. The sample (0.5ml) was collected at suitable time intervals and analyzed for drug content by HPLC after appropriate dilutions as discussed earlier. The same procedure was opted for Adapalene prepared by using carbopol 934.

	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	18.32±0.05	19.70±0.64	21.43±0.88	27.56±0.05	30.19±0.05	29.34±0.05	30.19±0.07	32.58±0.86	29.00±0.17
1	32.20±0.44	30.99±0.45	32.46±0.32	39.81±0.10	42.00±0.65	41.62±0.88	49.45±0.88	48.32±0.95	47.22±0.24
2	47.14±0.29	45.26±0.50	50.70±0.11	58.22±0.03	60.71±0.04	62.35±0.95	68.70±0.64	70.47±0.95	72.85±0.32
3	69.1900.03	65.42±0.99	66.93±0.11	70.44±0.03	78.83±0.20	75.80±0.04	79.85±0.95	82.88±0.25	85.98±0.89
4	72.8600.36	70.56±0.28	75.11±0.47	79.10±0.65	82.50±0.33	84.05±0.25	88.29±0.37	90.72±0.25	92.20±0.48
6	84.44±0.06	79.30±0.28	82.25±0.47	85.53±0.08	89.72±0.33	90.62±0.78	92.47±0.65	94.29±0.22	98.37±0.65
8	87.25±0.12	86.61±0.64	88.83±0.95	90.60±0.75	96.00±0.007	94.33±0.03	98.03±0.15	98.00±0.46	98.23±0.29

Table 7 : In-vitro drug permeability study by using Franz diffusion cell

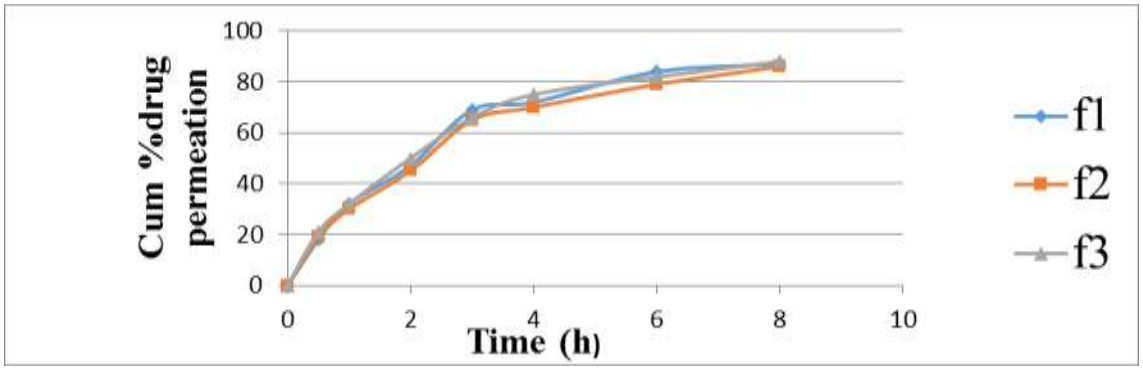


Figure 21: Drug permeation profile for formulation F1-F3

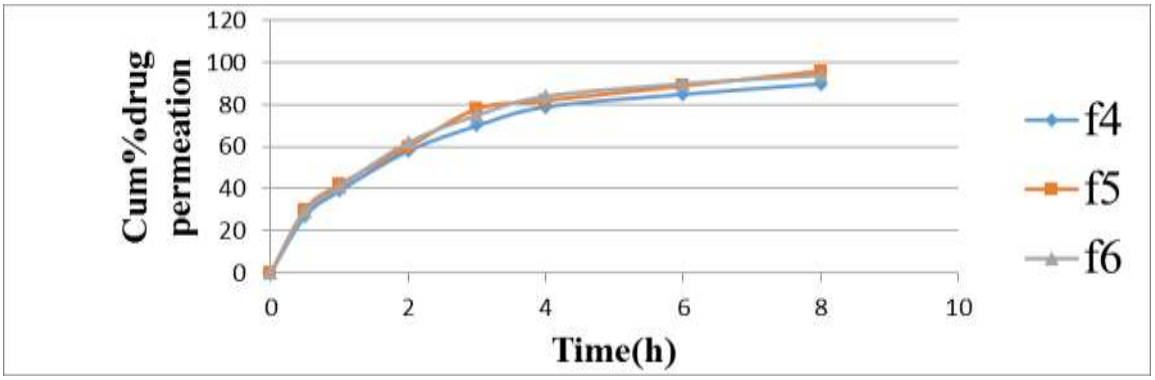


Figure 22: Drug permeation profile for formulation F4-F6

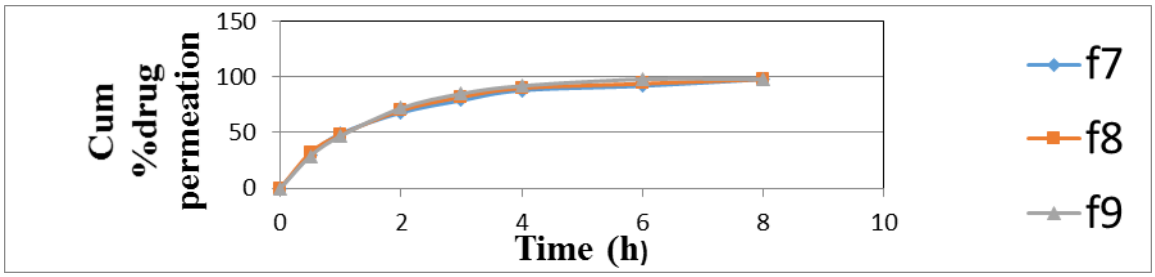


Figure 23 : Drug permeation profile for formulation F7-F9

8. Stability studies

Time (day)	Physical appearance	pH	Drug content%
0	+++	6.95	100
30	++	6.95	99.98

Table 8:Data of stability studies of the optimized formulation F-4

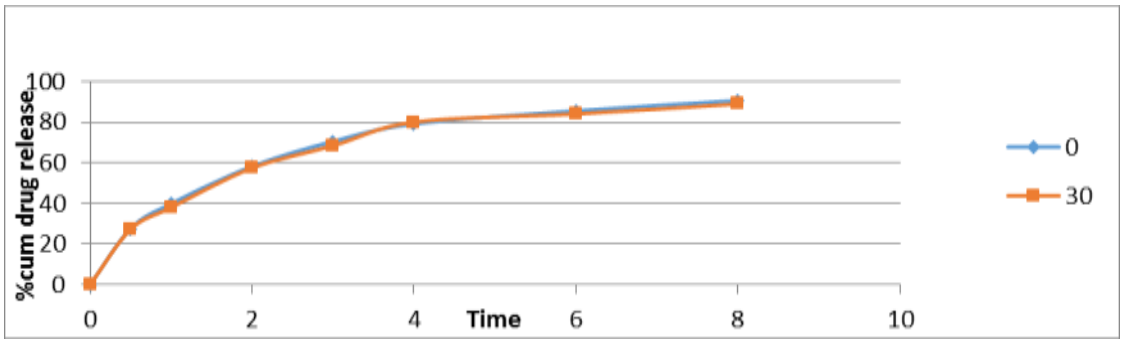


Figure 24 : Permeation studies of the optimized formulation F4

Time	Marketed (Adaferine 0.1%)	Invitro permeation 0 day(F4)	Invitro permeation 30 day(F4)
0	0	0	0
0.5	5	27.56	27.20
1	9	39.81	38
2	16	58.22	57.42
3	24	70.44	68.40
4	38	79.10	79.98
6	54	85.53	83.67
8	69	90.60	89.50

Table 9: Comparision with marketed product of Adaferine 0.1%

CONCLUSION

Adapalene is categorized as anti-acne drug and is successfully used in the treatment of acne. Adapalene is having low bioavailability. Hence, to overcome the above drawback it is required to administer the drug by topical route which is more beneficial over oral route of administration. Adapalene was done by using UV Spectrophotometry by comparing test with the standard using polymer solvent system. Nanoemulsion was tried with different concentration of Surfactant and oil. All the formulations were evaluated for stability and gelling was done using carbopol 934.Preliminary data shows that good stable emulsion can be successfully achieved using high pressure homogenized converting globule size into nanometer. Initial preliminary trial show that 1% carbopol gives good gelling shows same concentration was used for all the batches and was evaluated using design of experiment. On the basis of priliminary work we found that carbopol 934 with concentration in1:1 ratio with shows better homogeneous gel like semisolid consistency, with good gelly like appearance, viscosity which is suitable for making emulgel containing drug as compared to other priliminary batches of different concentration of gelling agent. The optimized formulations showed a shear thinning with thixotropic property with better Spreadability and *in-vitro* permeability compared to other formulations. In the study, it was observed that concentration of span 80 tween 20 and tween 80 had positive effect on evaluation parameters like consistency, Spreadability, viscosity and *in-vitro* permeability. Amount of hydrogel mixed with the emulsion was also having the effect on drug permeation from the formulation showing direct drug retardant release from the formulations.Adapalene emulgel which could increase the drug permeability across the membrane and fast release of the drug could be successfully achieved. When compared with the market preparation nanoemulgel formulation shows better inviro permeation with confirm that nanoemulgel can help in better penetration of this found of drug which are highly insoluble. On the

basis of quality of emulgel produced, nine formulations namely F1, F2, F3, F4, F5, F6, F7, F8, F9 were produced. They were evaluated for physical appearance, pH evaluation, rheological study, Spreadability study, drug content and *in-vitro* permeation study. In the study, it was observed that concentration of span 80 and tween 80 had positive effect on evaluation parameters like consistency, Spreadability, viscosity and *in-vitro* permeability. Amount of gel mixed with the emulsion was also having the effect on drug permeation from the formulation showing direct drug retardant release from the formulations. Batch showed the 100% drug release at the end of 8 hours and F-4 showed the 100% drug release at the end of 6 hours.

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