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Design, Development and Formulation of Antiacne Dermatological Gel

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Abstract

In the present study, Adapalene gels were prepared using CMC Na, HPMC, HPC, Carbomer and combinations of cellulose derivatives; as base and PluronicPE-6200 as penetration enhancer for the treatment of Acne. The gels were evaluated for drug content, viscosity determination, in vitro permeation (Nylone-66) and stability studies. The drug content of the gels was found to range from 98-105.7 %. The viscosity of the gels ranged between 7100-83144 cps. . In-vitro diffusion profile of Adapalene gel (optimized formula F-22) obtained in ethanol with water (80:20) indicate that 40.33% drug release found within 6 hrs. while 35.22% of marketed preparation. Although the difference is insignificant, the percentage release of drug was found to increase in the following order of the polymer composition: Carbopol-980> Carbopol-940> Carbopol-934> HPC > SODIUM CMC> HPC+SODIUM CMC > METHYL CELLULOSE > HPMC > HPC+HPMC. Further the formulation F-22 was found to be stable at accelerated stability condition with respect to percent drug content, release characteristics, pH, transparency, feel and viscosity.

Keywords: CMC Na, HPMC, HPC, Carbomer; Adapalene; Pluronic-PE6200; Topical; Gels; Permeation enhancer

Introduction

Gels are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or

sometimes chemical) cross-linking has been introduced. Some of these systems are as clear as water in appearance, visually aesthetically pleasing as in gelatin deserts and other are turbid. The clarity range from clear to a whitish translucent. The polymers are used between 0.5-15% and in most of the cases they are usually at the concentration between 0.5-2%. Gels are usually clear transparent semisolid containing the solubilised active substances. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic particles form a three-dimensional "house of cards" structure. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains. Various topical application dosage forms like creams, ointments, liniments, lotions, gels and jellies have been in use for many decades. Gels and jellies are although age old formulations, they have now gained more and more importance and the extensive studies on their release properties have revealed that the active ingredients in gel based formulations are better percutaneous absorbed than from creams and ointment bases. Thus facts have clearly indicated that a formulation and development of a gel based topical dosage form for anti-acne drug will be proved to be worthwhile. Hence a study on formulation and evaluation of gels for a new anti-acne drug –"Adapalene" was selected as the principle object of this project work. Topical application of gels overcome the problems to be associates with other dosage forms are: Avoidance of first pass metabolism. Convenient and easy to apply. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc. Achievement of efficacy with lower total daily dosage of drug by continuous drug input. Avoids fluctuation in drug levels, inter- and intra-patient variations. Ability to easily terminate the medications, when needed. A relatively large area of application in comparison with buccal or nasal cavity Ability to deliver drug more selectively to a specific site. Avoidance of gastro-intestinal incompatibility. Providing utilization of drugs with short biological half-life, narrow therapeutic window. Improving physiological and pharmacological response. Improve patient compliance. Provide suitability for self-medication.

Materials and Methods

Adapalene is procured by Zhejiang Neo-Donkon, China, Carboxymethylcellulose Sodium, Hydroxypropylmethylcellulose, Hydroxypropylcellulose are gifted by Colorcon Asia Pvt.Mumbai, Methylcellulose is gifted by Signet chemical corp., Mumbai, Carbopol-934, Carbopol-940, Carbopol-980 are gifted by Noveon Inc.,Brussel, Propylene Glycol is procured by Merck, Pluronic PE-6200 is procured by BASF(Germany), Sodium Hydroxide, Benzoic Acid are procured by Central Drug House (P) Ltd., Delhi, Methylparaben, Propylparaben are procured by Clariant (Nipasol).

Preformulation Study

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre-formulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those

physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic-biopharmaceutical properties of the resulting product.

Organoleptic Characteristics: The colour and odor of the drug were characterized and recorded using descriptive terminology. It was found as White to Jasmine Crystalline Powder, with odorless.
Solubility: Practically insoluble in water, Soluble in DMSO (3 mg/mL) and DMF (6 mg/mL), (THF) and in ether. Slightly soluble Ethanol.

Estimation of Adapalene by HPLC method
Chromatographic conditions:
Column: Cosmolsil, C18, 250 x 4.5mm, 5 µ equivalent
Flow rate: 1.0mL/minute
Injection volume: 20 µL
Wavelength: 235 nm
Run Time: 15 minutes
Diluent: Mobile Phase

Standard solution: weigh accurately about 20.0 mg of Adapalene standard in to a 100.0 mL volumetric flask, and add 50.0 mL of tetrahydro furan, sonicate to dissolve, dilute to volume with tetrahydro furan.
Further dilute 5.0 mL of this solution to 50.0 mL with diluent and mix.
Procedure: Inject blank (diluents, 1 injection) and standard solution (5 injections) and check for system suitability parameters as follows-

- The RSD for Adapalene area response from 5 injection of standard solution should not be more than 2.0%.
- The tailing factor for Adapalene peak should not be more than 2.0
- The theoretical plates for Adapalene peak should not be more than 2000.
- If the system suitability parameter passes, inject sample solution (2 injections) and record the responses.

Calculation: Calculate the content of Adapalene, in % by following formula –

$$\frac{AS}{AT} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{LC} \times 100$$

Where:
AS: Average area of Adapalene Peak from sample solution.
AT: Average area of adapalene Peak from standard solution.
WS: Weight of sample in mg
DS: Dilution of sample solution
LC: Label claim of Adapalene in % w/w
P: Potency of Adapalene standard in % w/w on as is basis

$$\text{Adapalene in \% Label claim} = \frac{\text{Content of Adapalene, in \% x Adapalene Label claim in \%}}{100}$$

Table No.1 Composition of Formulation F1-F9

S.no.	Ingredients	F1	**F2**	F3	**F4**	F5	F6	F7	**F8**	F9	
		%	**%**	%	**%**	%	%	%	**%**	%	
1	Adapalene	0.1	**0.1**	0.1	**0.1**	0.1	0.1	0.1	**0.1**	0.1	
2	Propyleneglycol	15	**15**	15	**15**	15	15	15	**15**	15	
3	Methyl paraben	0.2	**0.2**	0.2	**0.2**	0.2	0.2	0.2	**0.2**	0.2	
4	Propyl paraben	0.02	**0.02**	0.02	**0.02**	0.02	0.02	0.02	**0.02**	0.02	
5	Pluronic pe-6200	0.2	**0.2**	0.2	**0.2**	0.2	0.2	0.2	**0.2**	0.2	
6	Purified water	80.98	**80.5**	79.98	**80.98**	80.5	79.98	80.98	**80.5**	79.98	
7	Sodium cmc	3.5	**4**	4.5							
8	Hpmc				**3.5**	4	4.5				
9	Methyl cellulose							3.5	**4**	4.5	

Table No2 Composition of Formulation F10-F18

S.NO.	INGREDIENTS	F10	F11	**F12**	**F13**	F14	F15	F16	**F17**	F18
		%	%	**%**	**%**	%	%	%	**%**	%
1	Adapalene	0.1	0.1	**0.1**	**0.1**	0.1	0.1	0.1	**0.1**	0.1
2	PropyleneGlycol	15	15	**15**	**15**	15	15	15	**15**	15
3	Benzoic acid	0.1	0.1	**0.1**	**0.1**	0.1	0.1	0.1	**0.1**	0.1
5	Pluronic PE-6200	0.2	0.2	**0.2**	**0.2**	0.2	0.2	0.2	**0.2**	0.2
6	Purified water	81.2	80.7	**80.2**	**76.1**	75.6	75.1	**76.1**	75.6	75.1
7	HPC	3.5	4	**4.5**						
8	HPC+SODIUM CMC				**6+2.5**	6+3	6+3.5			
9	HPC+HPMC							6+2.5	**6+3**	6+3.5

Table No3. Composition of Formulation F19-F27

S.NO.	INGREDIENTS	**F19**	F20	F21	**F22**	F23	F24	F25	**F26**	F27
		%	%	%	**%**	%	%	%	**%**	%
1	Adapalene	**0.1**	0.1	0.1	**0.1**	0.1	0.1	0.1	**0.1**	0.1
2	PropyleneGlycol	**0.2**	0.2	0.2	**0.2**	0.2	0.2	0.2	**0.2**	0.2
3	Methyl Paraben	**0.02**	0.02	0.02	**0.02**	0.02	0.02	0.02	**0.02**	0.02
4	Pluronic PE-6200	**0.2**	0.2	0.2	**0.2**	0.2	0.2	0.2	**0.2**	0.2
5	NaoH	**0.2**	0.2	0.2	**0.2**	0.2	0.2	0.2	**0.2**	0.2
6	Purified water	**83.65**	85.6	85.12	**83.65**	85.6	85.12	83.65	**85.6**	85.12
7	CARBOPOL 940	**0.5**	1	1.5						
8	CARBOPOL 980				**0.5**	1	1.5			
9	CARBOPOL 934							0.5	**1**	1.5

Evaluation of formulated gel:

Appearance:

The Adapalene Gel formulated was observed for their Visual appearance, Colour, Tenture feel upon application such as grittiness, greasiness, stickiness, smoothness, stiffness and tackiness.

pH:

The pH of the gels, were found immersing pH meter to a depth 0.5 cm in a beaker containing gel. The determinations were carried out in triplicate and the average of three reading is recorded.

Viscosity:
The viscosity of formulated gel bases was determined. The viscosity determinations were carried out on Brook-field viscometer using spindle number S-06 and the determinations were carried out in triplicate and the average of three reading is recorded

Spreadibility:
The parallel plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations. The advantages of the method are simplicity and relative lack of expense. Also, the assemblies can be designed and fabricated according to individual requirements to type of data required. On other hand, the method is less precise and sensitive, and the data it generates must be manually interpreted and presented.

Later, Vennat et al. validated the spreading diameter measurements of hydro gels on the basis of cellulose derivatives and established the linearity of spreading diameter measurements. The linear relationship between viscosity and spreading diameter was independent of the derivative. The spreading capacity of the gel formulations was measured 48 h after preparation by measuring the spreading diameter of 1 g of the gel between two 20×20 cm glass plates after 1 min. the mass of the upper plate was standardized at 125 g. panigrahi et al. used a similar apparatus to asses the spreadibilty of gels. The following equation was used for the purpose:

$$S = m \times \frac{L}{T}$$

Where:
S, is the spreadibilty of gel formulations
M, is the weight (g) tied on the upper plate,
L, is the length (cm) of the glass plates, and
T, is the time taken for plates to slide the entire length.

Procedure: two glass slide of 20×20 cm were selected. The gel formulations whose Spreadibility had to be determined were placed over one of the slides. The other slide was placed upon the top of the gel such that the gel was sandwiched between the two slides in an area occupied by a distance of 60. cm along 100g weight was placed upon the upper slide so that the gel between the two slides was pressed uniformly to form a thin layer. The weight was removed and the excess of gels adhering to the slide was scrapped off. The two slides in positioned were fixed to a stand without slightest disturbance and in such a way that only the upper slide to slip off freely by the force of weight tied to it. A 20 g weight was tied to upper slide carefully. The time taken for the upper slide to travel the distance of 6 cm and separate away from the lower slide under the direction of weight was noted. The determinations were carried out in triplicate and the average of three reading is recorded.

Extrudability:
It is a useful empirical test to the measure the force required to extrude the material from a tube. Since the packing of gels have gained a considerable importance in delivery of desired quantity of gel from jar o extrusion of gel from collapsible tube, therefore measurement of extrudability becomes an important criteria for gels.
Procedure: the gel formulation were filled in standard caped collapsible lami-tube and sealed. The tube was weighed recorded. The tube was placed between two glass slides and was clamped.

A 500 g weight was placed over the glass slide and then cap was opened. The amount of gel extruded were collected and weighed. The % of gel extruded was calculated; and grades were allotted (+ + + + excellent, + + + Good, + + fair, + Poor).

Drug content uniformity:

To determine the drug content uniformity, the sample has taken from top, middle, and bottom from the container. And further assay is done to determine uniformity in label claim.

***In-vitro* drug diffusion study:**

Arrangement of assembly:

Six Franz Diffusion Cells are interconnected to each-other in crisscross motion, for maintaining the temperature 32 ^{o}C. The Franz Diffusion Cells are interconnected by nylon tube and the both ends of these tubes are connected to the chiller. The one end of the chiller provides water of 32 ^{o}C temperature to outer jacket of cell and another end recycles the water to the chiller.

Preparation of media:

In a 500 ml volumetric flask ethanol: water is mixed in 80:20. After mixing, flask is shaken, to facilitate the uniform mixing of solvents.

Procedure:

- Before starting the study the cells are calibrated for their volume capacity.
- Media taken in 50 ml beaker, in which diffusion membranes (6) are poured and stand for few minutes.
- Membranes are removed out and dried in oven at 30-35 ^{o}C.
- The gel preparation to be evaluated is poured in 2 ml needle.
- Now membrane placed on butter paper and butter paper placed on weighing balance.
- 300 mg gel through needle; weigh on weighing balance. This is done for all six membranes and recorded as S1, S2, S3, S4, S5, and S6.
- Now cells are filled with media, and one magnetic bead. With the use of glass slide (to remove air bubbles) put the membrane over the cell.
- Now membrane is cover with cell cape and put the clamp.
- Starts the chiller and takes reading in interval of 30min, 1H, 2H, 4H, and 6H.

Comparison with marketed products:

Selected formulations (F22) were compared with marketed gels (Opalen), for different tests like appearance, pH, viscosity, spreadibilty, extrudability, and in-vitro diffusion study.

Stability studies of adapalene gels:

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists detoriation. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Detoriation of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

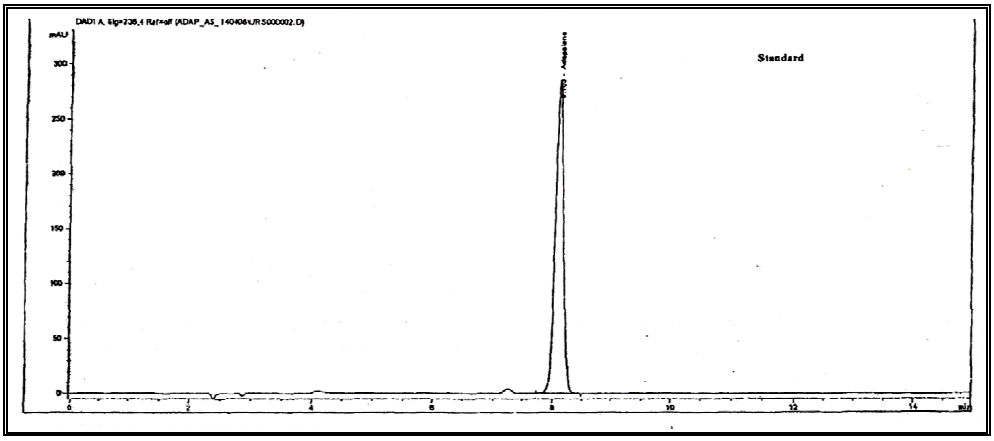

Figure:1 Standard Area for Adapalene

Accelerated Stability Testing:

Since the period of stability testing can be as long as two years, it is time consuming and expensive. Therefore it is essential to devise a method that will help rapid prediction of long-term stability of drug. The accelerated stability testing is defined as the validated method by which the product stability may be predicted by storage of the product under conditions that accelerate the change in defined and predictable manner. The stability studies of formulated gels were carried out at 40/75(^{o}C/RH) and at room temperature for one month. The effects of temperature, Humidity and time on the physical characteristics of the gels were evaluated for assessing the stability of the prepared formulations.

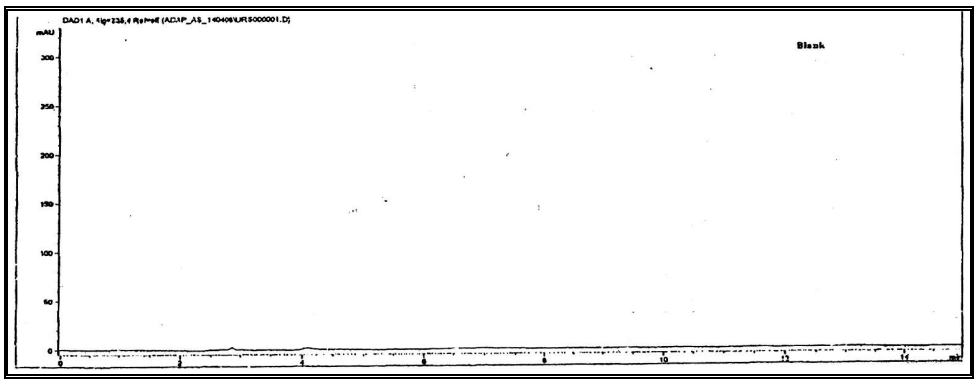

Figure:2 Blank for Adapalene gel

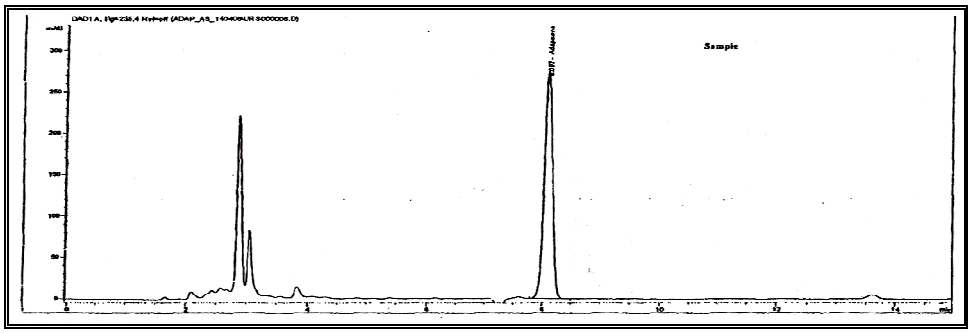

Figure: 3 Area for Sample Gel Formulation

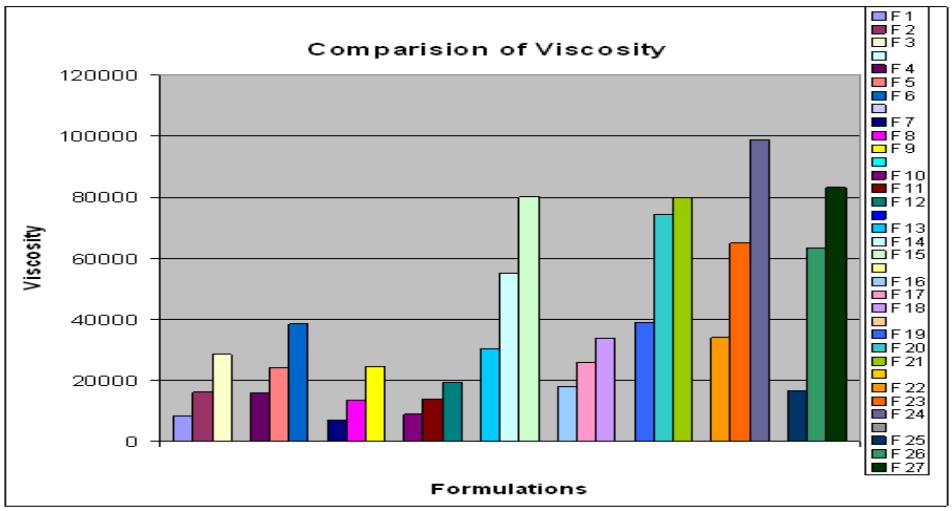

Figure No. 4 Comparison of Viscosity

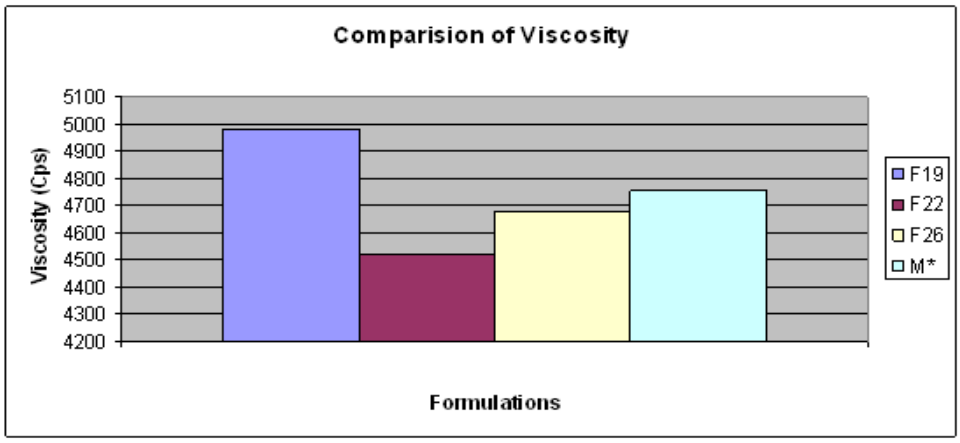

Figure No. 5 Comparison of Viscosity

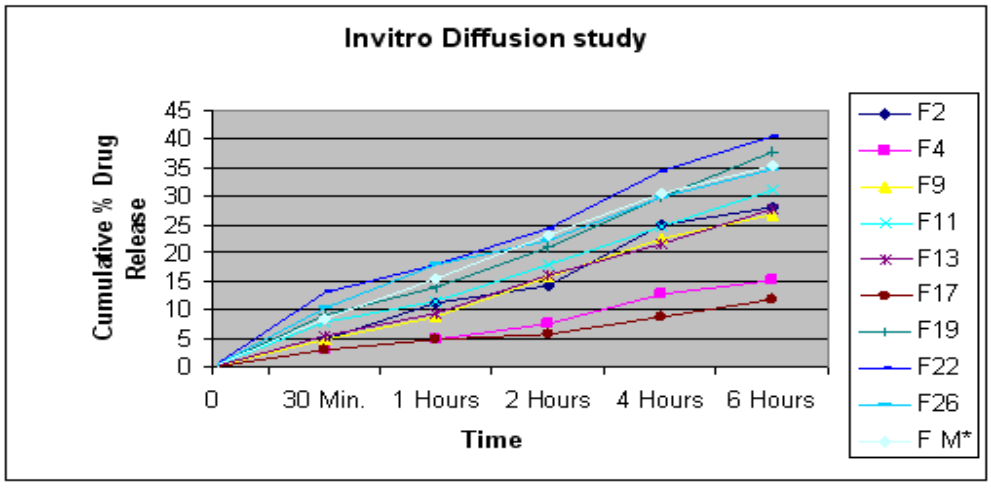

Figure No.6 Invitro diffusion Study of Formulations

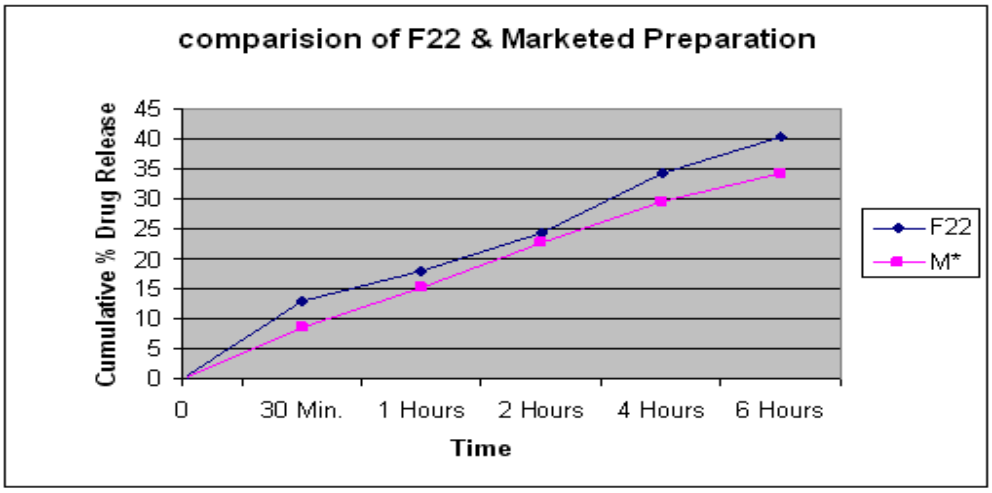

Figure No.7 Comparison of F 22 & Marketed Preparation

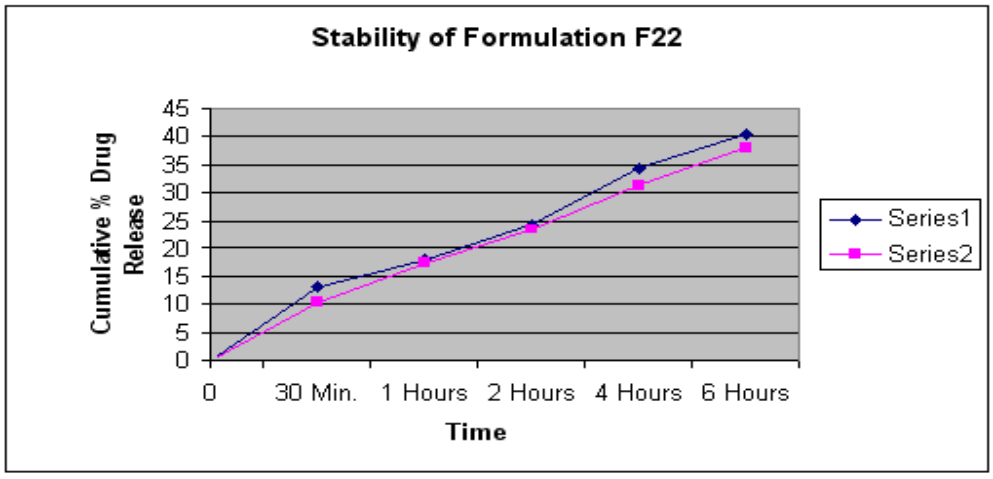

Figure No.8 Stability Study of In-vitro diffusion, for Formulation F22.

Table No.4Results of Organoleptic properties

Properties	**Results**
Description	Crystalline
Odor	Odor less
Colure	Off white Jasmine

Table No. 5 Results of the physical observation

Batch no.	Initial	40°c/75%RH			
		1st week	2nd week	3rd week	4th week
A	Off-White	+	+	+	+
B	Off-White	+	+	+	+
C	Off-White	+	+	+	+
D	Off-White	+	+	+	+
E	Off-White	+	+	+	+

Where: + indicates the there is no change in coloure or lumps formation

Table No.6 Physical evaluations of gel formulations

Formulations	Appearance	Feel on Application	pH	Gelling
F1	WT	Smooth	7.14	++
F2	WT	Smooth	7.23	++
F3	WT	Smooth	7.28	+
F4	WT	Smooth	4.58	+++
F5	WT	Smooth	4.2	+++
F6	WT	Smooth	4.17	++
F7	WT	Smooth	4.20	+
F8	WT	Smooth	4.12	+++
F9	WT	Smooth	4.15	++
F10	WT	Smooth	7.14	+
F11	WT	Smooth	7.23	+++
F12	WT	Smooth	7.28	++
F13	WT	Smooth	5.56	+++
F14	WT	Smooth	5.55	+++
F15	WT	Smooth	5.58	++
F16	WT	Smooth	4.2	+
F17	WT	Smooth	4.12	+++
F18	WT	Smooth	4.15	++
F19	WT	Smooth	5.72	+++
F20	WT	Smooth	4.95	+++
F21	WT	Smooth	4.32	+++
F22	WT	Smooth	5.21	+++
F23	WT	Smooth	4.99	+++
F24	WT	Smooth	4.83	++

F25	WT	Smooth	6.39	+
F26	WT	Smooth	5.1	+++
F27	WT	Smooth	4.8	++

Where: WT means whitish Translucent, + Good, ++ V. Good, +++ Excellent

Table no. 7 Results of viscosity, Extrudability and Spreadibility.

Formulations	Viscosity (Cps)	Extrudability	Spreadibility
F1	8400	+++	3.92
F2	**16200**	**+**	**4.95**
F3	28640	+	1.99
F4	**15920**	**++**	**2.62**
F5	24200	+	1.998
F6	38480	+	1.9913
F7	7100	+++	10.95
F8	13500	++	10.36
F9	**24500**	**+**	**6.78**
F10	8900	+++	10.49
F11	**14000**	**++**	**5.61**
F12	19500	+	3.8
F13	**30400**	**++**	**8.4**
F14	55100	+	4.48
F15	80156	+	2.31
F16	18000	+++	16.92
F17	26000	++	11.63
F18	33900	+	4.94
F19	**39000**	**++**	**4.97**
F20	74500	+++	1.99
F21	80000	+	1.9926
F22	**34000**	**+++**	**10.61**
F23	65000	++	1.99
F24	98700	+	0.99
F25	16600	+++	21.3
F26	**63500**	**+**	**2.21**
F27	83144	+	2.12

Where: +Good, ++ V. Good, +++ Excellent

Table No.8 comparison of Viscosity

Formulation	Viscosity (Cps)
F19	4980
F22	4523
F26	4682
M*	4756

Table No. 9Assay of different of formulations

Formulations	F2	F4	F9	F11	F13	F17	F19	F22	F26	M*
Assay	104	105.7	103.2	98	103.6	103.3	104.4	102.1	98	103.2

Where M* is marketed formulation (Opalen Gel), RLD_MP/2001282/01

Table No. 10 Percentage Drug Content Uniformity of Formulations

Assay	F2	F4	F9	F11	F13	F17	F19	F22	F26
TOP	104.4	104	101.88	98.77	105.4	107.1	100.3	101.7	98
MIDDLE	102.1	105.7	100.41	99.46	99.6	103.6	96.8	101.5	99
BOTTOM	98	103.2	103.82	99.29	104.2	103.3	96.4	106.8	98

Table No. 11 Cumulative % drug release of Formulations

Time	F2	F4	F9	F11	F13	F17	F19	F22	F26	M*
30 Min.	5	2.9	4.88	7.8	5.5	2.96	9.12	12.97	10.32	8.45
1 Hours	11.4	4.82	8.95	11.51	9.52	4.82	13.9	17.82	17.91	15.58
2 Hours	14.3	7.49	15.78	17.95	16.07	5.88	21.01	24.27	22.12	23.16
4 Hours	25.06	12.65	22.62	24.65	21.63	8.93	29.78	34.24	29.83	30.53
6 Hours	28.06	15.19	26.78	30.98	27.74	11.84	37.59	40.33	34.69	35.22

Where M* is marketed formulation (Opalen Gel), RLD_MP/2001282/01

Table No.12 Comparison of F 22 & Marketed Preparation

Time	F22	M *
0	0	0
30 min	12.97	8.45
1 Hours	17.82	15.24
2 Hours	24.27	22.56
4 Hours	34.24	29.63
6 Hours	40.33	35.22

Where M* is marketed formulation (Opalen Gel), RLD_MP/2001282/01

Table No :13 Stability parameters of formulation F-22

Parameters	Controlled	After one months 40/75(^{o}c/rh)
Appearance	Whitis transluscent	Whitis transluscent
Feel on application	Smooth	Smooth
Ph	5.21	5.43
Viscosity	4523	4611
Drug content (%)	102.1	98.77

Table No :14 Stability study of in-vitro diffusion for formulation F-22

TIME (MIN)	CUMULATIVE % DRUG RELEASE	
	Controlled	After one months
0	0	0
30 Min.	12.97	10.33
1 Hours	17.82	17.43
2 Hours	24.27	23.35
4 Hours	34.24	31.19
6 Hours	40.33	37.87

Conclusion

The Present study was undertaken with an aim to formulate and evaluate gel formulation of Adapalene using different polymers with the addition of wetting agent Pluronic PE-6200. Preformulation study was carried out initially and results directed for the further course of formulation based on the Preformulation studies different batches with polymer addition were prepared using selected excipients.Permeation enhancement of Adapalene was done by addition of poloxamer (Pluronic PE-6200) .The Adapalene gel formulation was optimized on the basis of different physical parameters and mainly with the comparision of formulations on the basis of in-vitro diffusion study and found to be 40.33 % release within 6 hours in media ethanol: water (80:20).Various formulation of Adapalene gels were formulated by using various polymers – CMC Na, HPMC, HPC, CARBOPOL-940, CARBOPOL-980, CARBOPOL-934. Results of all the batches shown that all the formulation comply with the pharmacopeial and/or standard references.

Results of all the physical and in-vitro dissolution data concluded that formulation F-22 was the most promising formulation. A comparision was done with the marketed Formulation in which drug is as such and result were found that F22 shown 40.33% release and marketed formulation shown 35.22 % release in 6 hours, The results were revealed that F 22 shown better release as compared to the marketed formulation.Stability study was conducted for optimized batch F-22 Stored at 40°c/75%RH for one month. Gels were evaluated for appearance; feel on application, pH, viscosity, and assay and in-vitro drug release profile after one month. It concluded that Formulation F-22 was stable.

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