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FORMULATION AND EVALUATION STUDIES OF VALACYCLOVIR TOPICAL GEL FOR ANTIVIRAL ACTIVITY

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ABSTRACT: ***The present work describes a study on Formulation and Evaluation studies of Valacyclovir topical gels for Antiviral activity. Valacyclovir is a broad spectrum antiviral agent against Herpes Simplex Virus and Varicella Zoster Virus, which is specific to viral-infected cells with low toxicity and which is less toxic than earlier generation of antiviral agents and as such represents a major therapeutic advance. This drug was selected for the study because it has good percutaneous absorption and appears to be more active as antiviral activity and is well tolerated. The polymers namely Carbopol-934, Hydroxypropyl methyl cellulose studied for their drug release from the gel formulations. It is evidence from the IR spectrum that all the polymers used in the gel formulations were compatible with the drug Valacyclovir. Carbopol gels were transparent, non-greasy and smooth on application. Sodium CMC and HPMC gels were opaque, non-greasy and sticking on application. The gel was prepared using 1%Carbopol-934 has maximum drug content (101.72%) than the others.***
The pH of the formulations ranged from 6.8 to 7.2 and viscosity is from 36,000 to 51,000cps.
Extrudability of carbopol and HPMC gels were excellent than the Sodium CMC gel.
The spreadability data shown that the formulation with 1% Carbopol- 934 has the highest value (8cm), whereas the others have significant values.

KEYWORDS: ***Valacyclovir, Antiviral Activity, Topical Gel***

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INTRODUCTION

Intravenous infusion is recognised as a advanced mode of drug management not best to by using skip hepatic "first pass" metabolism, also to preserve consistent drug level in the body. This gives direct access of drug into the systemic flow however involves positive risks. Topical administration is employed to supply a drug right now on the point of utility, so sufficient capsules is absorbed into the systemic circulate to reason therapeutic consequences. To provide non-stop drug infusion via an intact pores and skin, several topical formulations are used one in all this is "Gels". Gels mainly used for the motive of topical dosage shape particularly that's to supply drug across a localized place of the pores and skin. (1)

The traumatic expectancies of topical consist of:

1. Formula of gel must have both physical and chemical balance.

2. Components that have one (or) extra components are non-sensitizing, non- irritating.

3. System must have acceptability of the patient.

4 System should have ability to launch healing tiers of drugs and numerous elements have an impact on the absorption the skin. Pores and skin

CHARACTERISTICS (2)

The purpose of topical dosage shape is to readily deliver drugs through out a localized location of the skin. medicines are carried out to the pores and skin within the shape of ointments, creams, gels and so forth. The absorption of materials from outside the skin,

Including entrances into the blood circulation is known as percutaneous absorption. it is necessary to recognize the skin traits to increase a really perfect topical dosage shape.

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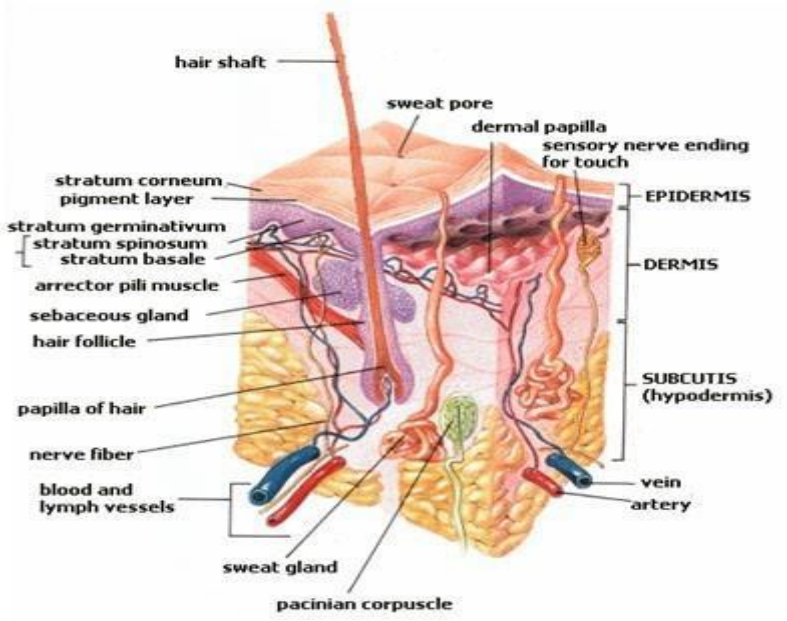
Skin

The pores and skin is an organ as it consists of tissues structurally joined together to carry out unique sports. it is certainly one of the bigger organs of the body in terms of floor area. For the average person, the skin occupies a surface place of about 2 sq.m (3000 sq.inches)

The epidermis is composed of stratified squamous epithelium and consists of four wonderful styles of cells. they're 1) Keratinocytes 2) Melanocytes Non- pigmented granular dedtrocytes previously called three) Langerhans cells and four) Granstein cells. The keratinocytes of the epidermis are prepared into the following



Structure of skin underlying subcutaneous tissue

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1. Stratum basale
2. Stratum sponosum
3. Stratum granulosum
4. Stratumlucidum

MECHANISM OF DIFFUSION THE STRATUM CORNEUM

The stratum corneum is a multicellular membrane and the intercellular areas are filled with lipid wealthy amorphous material. in the dry membrane, the intercellular extent might also reach 5% of the whole volume. although molecules diffuse through intercellular areas, the available proof suggests that for water-soluble, non-electrolytes diffusion isn't in most cases intercellular.

The transcellular permeation is defined on the basis of fairly smaller diffusion coefficient. thus, molecules diffuse via intercellular direction and also penetrate by means of transcellular mechanism.

The stratum corneum has a finite thickness and so there is a duration of brief diffusion (lag time) after making use of the drug to the pores and skin, at some point of which the price of transfer via the pores and skin rises to attain a regular country. The lag time (t), is related thickness of the membrane (h), and the diffusion coefficient (D) of the drug, with the aid of the relationship, t=h2/6D.

The lag time has an immediate bearing at the rate of the onset of skin penetration by way of the drug. Generally it ranges from minutes to days for the transepidermal direction and from seconds to mins for the trans follicular path. Therefore an early pharmacological reaction might be dependent on a few drug penetration through manner of the transfollicular route. but, once the consistent state has been established, the contribution of the shunt to the general diffusion turns into negligible and bulk diffusion then occurs in large part thru the transepidermal route.

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Harm or destruction of the stratum corneum barrier by way of keratolytic agents, cracking of the skin and by way of bodily harm through accelerated absorption. as a result, the stratum corneum functions physiologically because the principle diffusion barrier. once molecules bypass the horny layer, they permeate rapidly via the dwelling tissues of the dermis and the dermis into the systemic. Dermis The second precept a part of the skin, is composed of connective tissue containing collagenous and elastic fibres. Several blood vessels, nerves, glands and hair follicles are embedded within the epidermis. The upper area of the dermis, about one 5th of the thickness of the whole layer is called the papillary region or layer. It consists of free connective tissue containing satisfactory elastic fibres. Its surface area is greatly elevated through small, finger like projection known as dermal papillae (pa-PIL-e)

AFFECTING TRANSDERMAL PERMEABILITY

The precept of transport mechanism throughout mammalian skin is via passive diffusion5 through by and large transepidermal course at constant state or through transappendegel course at nonsteady state. The elements influencing and inflicting in transdermal permeability can be categorized into 3 important categories: 1. Physico chemical houses of penetrants 2. Physico chemical houses of drug transport machine 3. Pathological & Physiological conditions of the skin. Various physico-chemical properties of the drug like partition co-green, concentration within the automobile, situations, molecular size and molecular weight play a crucial role in finding out the percutaneous absorption.

MECHANISM OF DIFFUSION via THE STRATUM CORNEUM

The stratum corneum is a multicellular membrane and the intercellular areas are filled with lipid wealthy amorphous material. in the dry membrane, the intercellular extent might also reach 5% of the whole volume. although molecules diffuse through intercellular areas, the available proof suggests that for water-soluble, non-electrolytes diffusion isn't in most cases intercellular. The

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II. MATERIALS AND METHODS

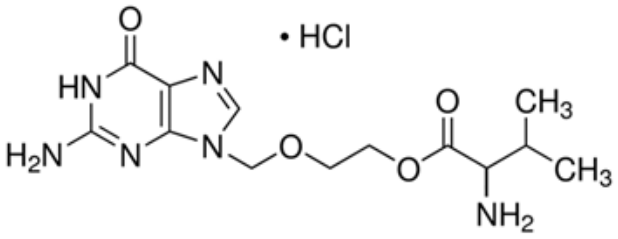
Valacyclovir raw material obtained from atom pharma, Surat was tested as per in house specification. All other solvent and reagent are used was of analytical grade.

FORMULATION OF GEL: -

Valacyclovir gels were formulated using different polymers like Carbopol 934, Sodium Carboxy methyl cellulose. Concentrations of polymers are used in the formulation of gels. The concentrations choose varied with the polymer used. After initial trials, the concentrations that gave products of good consistency for selected to the formulation. The concentration of drug taken in all the formulation remained constant

DRUG NAME: Valacyclovir Hcl

Structure:



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Molecular Formula: C13H20N6O4

Molecular weight: 324.34

IUPAC Name: 2-[(2-amino-6-oxo-1H-purin-9-yl)methoxy]ethyl (2S)-2-amino-3-methylbutanoate

Solubility: Crystalline solid, occurs as hydrate.

UV max (water): 252.8 nm (e 8530).

Solubility in water: 174 mg/mL

Category: Anti viral activities

Dose: The total daily dose may vary from 100 mg-350 mg taken orally.

Physical description: Solid Appearance White Crystal Powder

Melting point: 170-172 Log p : -0.3.

Mechanism of action: Valacyclovir is converted to Valacyclovir, which is converted to its triphosphate form, Valacyclovir triphosphate (ACV-TP). ACV-TP competitive inhibited viral DNA polymerases, incorporates into and terminate the growing viral DNA chain, and inactivated of the viral DNA polymerase.

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III. EXPERIMENT

METHOD OF PREPRATION

Preparation of Carbopol- 934 gels

PROCEDURE

1. Accurately weighed quantity of Valacyclovir and all Ingredients

2. Ingredients was dispersed in purified water with constant stirring and the drug solution was heated to 500C.

3. Methyl paraben was added as a preservative.

4. The carbopol-934 and Sodium carboxy cellulose was added to the solution under stirring while temperature Was maintained at 500 C.

5. The dispersion of gelling agent was neutralized by addition of triethanolamine solution to attain the neutral pH. Strried slow till a clear gel was obtained. 6.Evaluate The topical gel for antiviral activity pH all Activity.

Ingredients	**Formula for 100gms**				
	F1(gms)	F2(gms)	F3(gms)	F4	F5
Valacyclovir	1.0	1.0	1.0	1.0	1.0
Carbopol-934	1.5	1.0	2.0	2.5	0.5
Triethanolamine	0.5	0.5	0.5	0.5	0.5
Purified water (qs.)	97	97.5	98	98.5	99
Methyl paraben	0.002	0.002	0.002	0.002	0.002
Sodium Carboxy methyl Cellulose	2.0	3.0	4.0	5.0	6 .0

Formulations with varying Carbopol-concentrations

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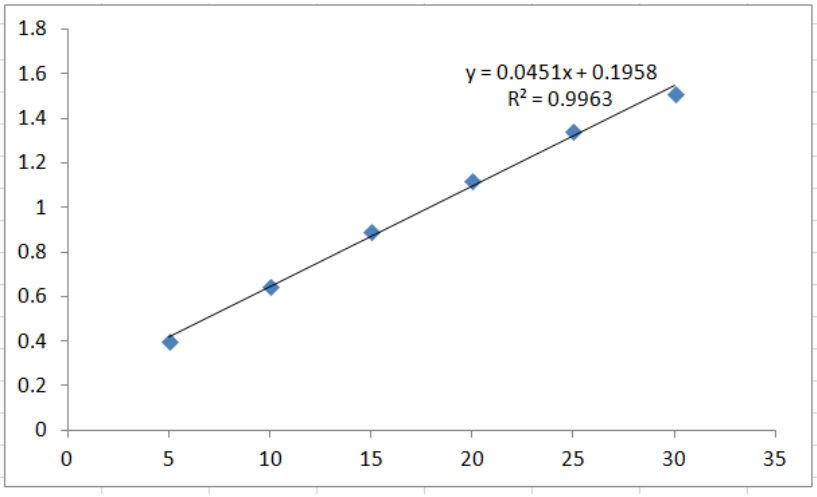
PREFORMULATION STUDIES

Preparation of Standard curve :- 100 mg of accurately weighed Valacyclovir was dissolved in little amount of 0.1M hydrochloric acid and made up to required volume 100 ml with 0.1M hydrochloric acid41. So that each ml of stock solution required concentration of 5, 10, 15, 20, 25, 30 µg/ml was made up with 0.1M hydrochloric acid. The absorbance of the dilute sample was measured spectrophotometrically at 255nm using 0.1M hydrochloric acid in UV-spectrophotometer42. The standard calibration curve was made with concentration (µg /ml) on X axis and Absorbance on Y axis

Standard curve of Valacyclovir



pH Measurements

Gel pH measurements were made using a digital pH meter by completely immersing theglass electrode in the gel system to cover the electrode. **The results were 7.2**

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Determination of viscosity

The viscosity of the gel was measured using a Brookfield viscometer (model RVTP). Spindle type, RV7, 20 rpm 100 g of gel was placed in a beaker and the spindle was lowered therein and rotated for about 5 minutes before reading.

Formulation	Viscosity in cps
1	43,001
2	41,001
3	36,001
4	51,001

Determination of viscosity

Extrudability

This is a useful empirical test for measuring the force required to extrude material from a tube. The formulations were filled in a collapsible metal tubes with a nasal tip of 5mm opening tube extrudability was then determined by measuring the amount of gel, extruded the tip That a pressure was applied on tube gel. The extrudability of the formulation was checked and the results were tabulated.

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Formulation	Extrudability
1	+++
2	+++
3	+
4	++

+++Excellent, ++Good, +Not satisfactory

Table No 10 Extrudability

Determination of spreadability

One of the criteria for the ideal quality of a gel is good spreadability. About 1 g of the gel composition was weighed and placed in the center of a standard dimension (10×10 cm) glass plate, and another glass plate was carefully placed on top of the gel so that the gel was sandwiched between the two glass slides. A 2 kg weight was placed in the center of the plate (to prevent the plate from sliding).The diameter of the gel in cms, after 30 minutes was measured.

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Formulation	Time taken (minutes)	Spreadability (cm)
1	30	8.1
2	30	7.7
3	30	7.5
4	30	7.8

Spreadability of gel formulations

In vitro Drug release pattern of Valcyclovir gels

The In vitro release of Valacyclovir from the gel formulation was studied by open ended cylinder method. Diffusion cell apparatus consists a glass tube and an inner diameter of 2.5 cm, open at the both end. One end of the tube tied with Cellophane membrane, which serves as a donor compartment.

1 gm of Valacyclovir gel was taken in this compartment and placed in a beaker containing 200ml of 0.1M Hydrochloric acid stirring at moderate speed, maintaining the temperature at 37 ± 1^{0}C. Periodically, 5 ml of samples were taken and the diffusion medium was changed after each selection using 0.1 M hydrochloric acid to maintain flow throughout the experiment. Then the samples were assayed by spectrophotometrically at 254 nm in UV-Spectrophotometer using0.1M Hydrochloric acid as blank

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Drug release profile of Formulation Gel.

Time (minutes)	Percentage drug release* of different formulation			
0	F1	F2	F3	F4
30	2.0	2.02	1.04	1.90
60	9.28	9.33	7.21	10.67
90	14.10	14.18	10.65	13.87
120	15.60	15.72	12.60	16.0
150	19.5	19.7	15.07	18.62
180	21.02	22.17	16.27	20.60

Drug release profile of Formulation Gel

Drug release profile of Formulation Gel.

Time (minutes)	Percentage drug release* of different formulation			
0	F1	F2	F3	F4
30	2.0	2.02	1.04	1.90
60	9.28	9.33	7.21	10.67
90	14.10	14.18	10.65	13.87
120	15.60	15.72	12.60	16.0
150	19.5	19.7	15.07	18.62
180	21.02	22.17	16.27	20.60

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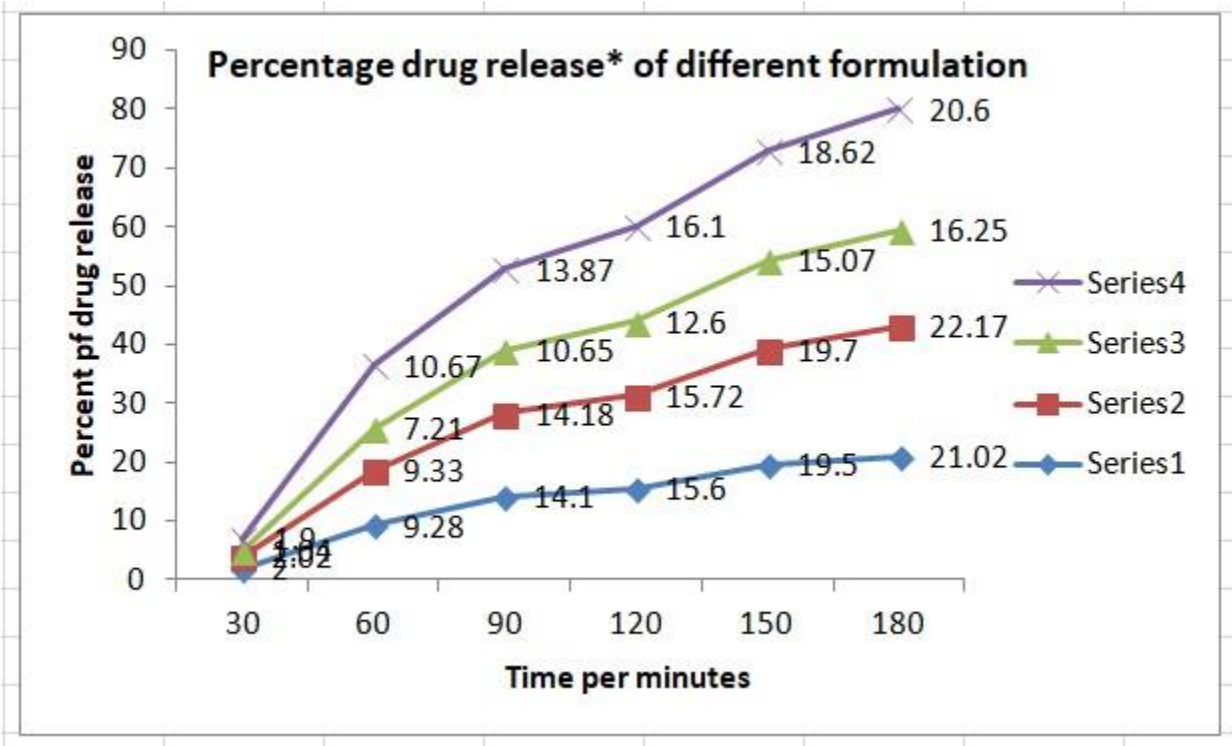
Drug release profile of Formulation Gel

Percentage of drug release Calibration curve



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Stability studies of the selected gel formulation

A procedure for evaluating the safety of a drug is the ability of the drug to retain its physical, chemical, and therapeutic properties. A common method for predicting stability is accelerated stability analysis, in which materials are exposed to high temperatures.

The gel is not applied because it melts at high temperatures. Therefore, the most commonly used temperatures are cooling (45°C), room temperature (2530°C) and 37±50°C. The samples were then checked regularly at intervals of 1, 2, and 3 months. The various parameters taken into account in the analysis include:

Physical parameters

1. Visual Appearance
2. pH
3. Viscosity
4. Extrudability
5. Phase separation
6. Leakage
7. Nature

Method

Pour the selected composition into an aluminum collapsible tube.

a. Room temperature

b. 37 ± 5^0C

c. $4\text{-}5^0$C

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The gel form was stored for 3 months. Samples were taken monthly for 3 months to assess drug content. At the end of third month they were evaluated for physical parameter and integrity of the product.

1. **Physical evaluation of Gel**

   Physical parameters considered for evaluation included appearance, product properties, pH, viscosity, leakage, phase separation and extrudability.

2. **Chemical evaluation**

   The drug content of the formulation was estimated by withdrawing samples from different corners of the tube. The samples were mixed together and 1gm was taken for the assay. Theestimation of drug content was carried out as per the procedure.

Physical evaluation of formulation.

Parameters	Room Temperature	37±5^{0}C	4-5^{0}C
Visual appearance			
Initial	Transparent	Transparent	Transparent
Final	Transparent	Transparent	Transparent
pH			
Initial	6.9	6.9	6.9
Final	7.1	7.0	6.9
Viscosity (cps)			
Initial	43,000	43,000	43,000
Final	43,000	43,500	43,000
Extrudability			
Initial	+++	+++	+++
Final	+++	+++	+++

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Phase separation	Not found	Not found	Not found
Leakage	Not found	Not found	Not found
Nature Initial Final	 Smooth Smooth	 Smooth Smooth	 Smooth Smooth

Table No 13 Physical evaluation of formulation.

RESULTS AND DISCUSSION

Compatibility Study

With reference to the IR-spectrum, the drug Valacyclovir was compatible with all the Ingredients namely Carbopol, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose were used in the gel formulation.

Formulation of Valacyclovir topical gels using gelling agents

Gel formulations of Valacyclovir were prepared using polymers namely, Carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose as per the procedure.

Carbopol-940 as a gelling agent

Formulations with formula f_1 (0.5%Carbopol-940), f_2 (1.0%Carbopol-940) f 3 (1.0%Carbopol-940) and f_3 (1.5%Carbopol-940) were prepared. f_1 showed low consistency and f_3 showed very high viscosity. The gel formulation f_2 (1.0% carbopol-940) exhibited desired consistency. Gel Formulations of Valacyclovir were prepared using different polymers

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namely Carbopol-940, as per the procedure.

Formulations with formula f_1 (0.5%Carbopol-940), f_2 (1.0%Carbopol-940) and f_3 (1.5%Carbopol-940) f4 (1.5%Carbopol-940) were prepared. F_1 showed low consistency and f_3 showed very high viscosity. The gel formulation f_2 (1.0% carbopol-940) exhibited desired consistency.

Evaluation of Valacyclovir gels

All the optimized gel formulations were subjected to evaluation studies

Estimation of drug content

Carbopol 940 polymers were used to evaluate the amount and percentage of drug presentin the gel composition according to the procedure. The prepared gel using 1% carbopol- 934(A_2) showed maximum drug content (101.72%) compared to other formulations, The results were shown in the Table

pH Measurements

The pH measurements of all the gel formulations were carried out by using digital pH meter. The pH of the formulations were ranged from 6.8 to 7.2 and the results were shown in Table 17

Determination of viscosity

The viscosity of the gels was determine using Brookfield Viscometer. The viscosity of the formulations were ranged from 36,000 to 51,000cps and the results were shown in Table 18

Extrudability

The extrudability of the gel formulations were checked as per the

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procedure. Extrudability of carbopol and HPMC gels were excellent than sodiumCMC gel and the results were shown inTable 19.

Determination of Spreadability

The spreadability of the gel was determined according to the method.From spreadability data is observed that the formulation with 1.0% carbopol-934 showed maximum (8cm), where as the formulations with 1%carbopol-940, 3%, HPMC and SodiumCMC 3% were showed significant spreadability. The results were tabulated in Table 20

In vitro drug release of gel formulations

In vitro drug release of gel formulations were carried out as per the procedure. The percentage release of drug from different gel formulations at the end of 8hrs was determined.

1.0 % carbopol-934 shows maximum release (64.91%). Addition of DMSO as a penetration enhancer enhances drug release from the gel formulation.

Based on the drug release A2 (1.0 % carbopol-934) was the best formulation and the percentage release was found to be 64.91% . The percentage release of drug from different gel formulations was shown in Table 21 - 29 and Figure 16 -25.

Stability studies for the formulation A2 (1.0 % carbopol-934)

Stability study for the best formulation was done as per the procedure. The gel was both physically and chemically stable at 4-5^{0}c, Room temperature and 37±5^{0}c. The results were tabulated in Table 30 & 31.

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