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To Study and Formulate Aloe Vera Transdermal Gel Using Penetration Enhancer for Herpes Treatment

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Vivek Gupta[1], Shobha Rajpoot[2*]

1. *Director, Shri Rawatpura Sarkar Institute of Pharmacy Datia (M.P.) India.*
2. *M.Pharm Scholar, Shri Rawatpura Sarkar Institute of Pharmacy Datia (M.P.) India.*

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Keywords: Aloe Vera; Transdermal drug delivery system; Permeation; Penetration enhancer; Permeation enhancer.

ABSTRACT

Skin penetration enhancers are the foremost ordinarily used approach for enhancing drug penetration into the skin through a stratum drug delivery system or topical administration. These skin penetration enhancers are molecules that reversibly take away the barrier resistance of the horny layer and permit medication to penetrate additional without delay to the viable tissues and therefore enter the general circulation. the aim of this review was to gift penetration enhancing the potential of succulent Vera. A. Vera gel inflated the *in vitro* skin penetration of compounds looking on their mass, with a visible inverse correlation between sweetening quantitative relation and molecular weight of the compound. Some constituents of the A. Vera gel itself conjointly penetrated the skin and this was apparently addicted to the mass of the co-applied compounds. Therefore, the penetration sweetening result of the succulent gel was explained by a probable pull effect of complexes fashioned between the compound and therefore the enhancing agent among the aloe gel, however, it had been expressed that the planned mechanism of action needs to be investigated and confirmed.

INTRODUCTION

A transdermal drug delivery system is a convenient route for the delivery of drugs having a short biological half-life. Transdermal drug delivery is based on the absorption of drugs into the skin after topical application. Transdermal patches are pharmaceutical preparation of varying sizes containing one or more active ingredients that when applied to the skin delivers the drug directly into the systemic circulation after passing through the skin barrier[1].

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, though human skin provides an effective barrier to the permeation of most drugs in the form of stratum corneum. The success of the transdermal route depends on the ability of drugs to breach this barrier and permeate the skin at a rate sufficient to attain effective plasma concentration. There are many approaches that are employed to enhance the skin permeation rate of active moieties. However, the most convenient and widely implemented approach is the use of chemical penetration enhancers such as DMSO, DMF, azone, ionic surfactants, but their use is also associated with unpleasant and toxic side effects. In recent years there has been a search for natural compounds as permeation enhancers to improve drug permeation that also exhibits low toxicity while maintaining their enhancing activity[2].

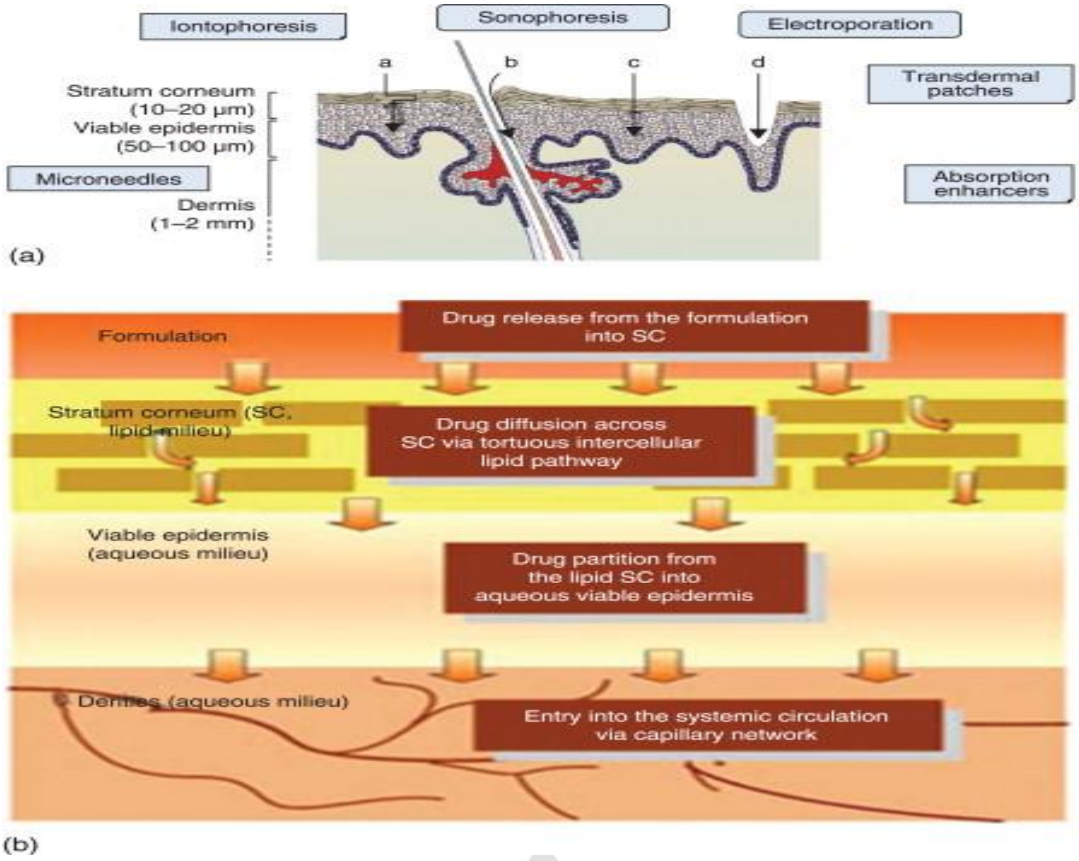

Fig. No 1:- Mechanism of Drug penetration through transdermal drug delivery

In particular, herbal penetration enhancers that have received much attention and an enhancement system based upon a product is 'Aloe Vera', which appears as an attractive prospect due to its purported skin-friendly and humectants properties[3].

The semi-tropical plant, Aloe Vera, has a long and illustrious history dating from biblical times. It has been mentioned throughout recorded history and given a high ranking as an all-purpose herbal plant. Aloe's thick, tapered, spiny leaves grow from a short stalk near ground level. It is not a cactus, but a member of the tree lily family. Aloe is related to other members of the Lily family such as the onion, garlic, and turnip families. Its relationship to the lily family is evident from the tubular yellow flowers produced annually in the spring that resemble those of the Easter lily. There are over 250 species of Aloe grown around the world. However, only two species are grown today commercially, with Aloe barbadensis Miller and Aloe arborescent. Aloe barbadensis Miller (Aloe Vera Linne) is the most widely used both commercially and for its therapeutic properties. This plant is having various medicinal, cosmetic, and nutraceutical purposes[4].

Fig. No. 2:- Aloe Vera

Aloe Vera Gel

Aloe (often called Aloe vera) produces two substances, gel, and latex, which are used for medicines. Aloe gel is the clear, jelly-like substance found in the inner part of the aloe plant leaf. Aloe latex comes from just under the plant's skin and is yellow in color. Aloe Vera Gel is the vicious, transparent, and colorless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of Aloe Vera. It is a succulent, almost sessile perennial herb; leaves 30–50 cm long and 10cm broad at the base; color pea-green (when young spotted with white); bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike; stamens frequently project beyond the perianth tube[5].

Major constituents

Aloe Vera Gel consists primarily of water and polysaccharides (pectin's, hemicelluloses, glucomannan, acemannan, and mannose derivatives). It also contains amino acids, lipids, sterols (lupeol, campesterol, and J-sitosterol), tannins, and enzymes. Mannose 6-phosphate is a major sugar component. At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended. Preparation of fresh gel: harvest leaves and washes them with water and a mild chlorine solution. Remove the outer layers of the leaf including the pericyclic cells, leaving a "fillet" of gel[6]. Care should be taken not to tear the green rind which can contaminate the fillet with leaf exudates. The gel may be stabilized by pasteurization at 75-80°C for less than 3 minutes. Higher temperatures held for longer times may alter the chemical composition of the gel[7].

Herpes Simplex Virus

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) cause prevalent, chronic infections that have serious outcomes in some individuals. Neonatal herpes may occur when the infant traverses the cervix during maternal genital herpes. Genital herpes is a major risk factor for human immunodeficiency virus type 1 transmission. Considerable efforts have been made to design and test vaccines for HSV, focusing on genital infection with HSV-2[8].

Herpes simplex virus (HSV)is a ubiquitous, enveloped, and double-stranded DNA virus, belonging to the family of Herpes viridae transmitted across mucosal membranes and non-intact skin, that migrate to nerve tissues, where they persist in a latent state. HSV-1 predominates in facial lesions and is typically found in the trigeminal ganglia, whereas HSV-2 is most commonly found in the lumbosacral ganglia. Nevertheless, these viruses can infect facial areas and the genital tract. In some developed countries type, 1 has recently emerged as the prominent causative agent of genital lesions. Changes in sexual behaviors of young adults may partly explain its higher incidence. A first primary infection develops when a susceptible person (lacking pre-existing HSV-1 and HSV-2 antibodies) is exposed to HSV. Indeed, a first non-primary episode occurs when a person with pre-existing HSV antibodies (against type1 or 2) experiences a first episode with the opposite HSV type. Recurrent infection occurs in a person with preexisting antibodies against the same HSV type[9]. Infections during pregnancy may be transmitted to newborns: HSV-1 and HSV-2 may cause eye or skin lesions, meningoencephalitis, disseminated infections, or fetal malformations[10, 11, 12].

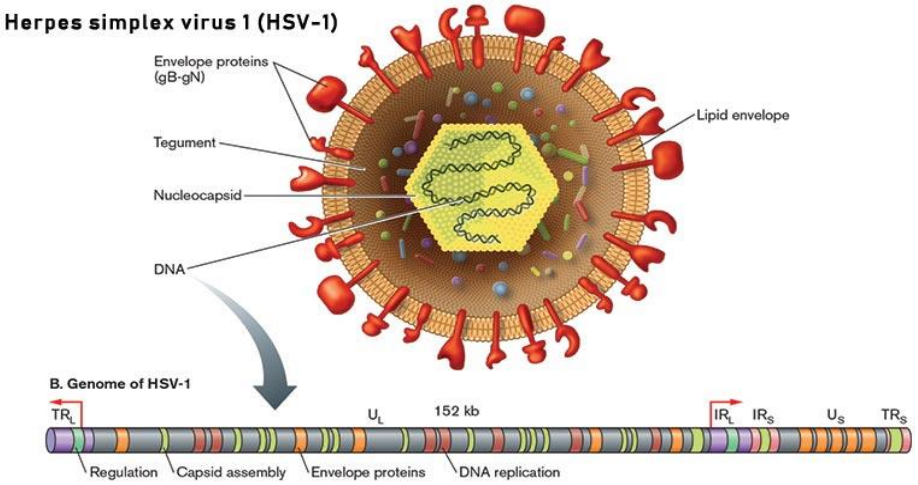

Fig. No. 3:- Herpes Simplex Virus

Pathogenesis of Disease

Viral inoculation occurs through inoculation micro-abrasions during oral, vaginal, or rectal sex with micro abrasions infected partner. Infection of epithelial cells occurs with rapid intranuclear viral replication. Changes include focal necrosis, ballooning, and degeneration of cells. Hallmark: multinucleated giant cell and Cowdry type A bodies = eosinophilicintra nuclear inclusion Multinucleated[13].

All members of this species establish latent infection in specific target cells. The infection latent infection persists despite the host immune response, often with recurrent disease. Re-infection can occasionally occur spite immunity[14].

DRUGPROFILE[15,16]

Name: Acyclovir

Synonyms: Acycloguanosine; Acyclovir

IUPAC Name: 9-[(2-Hydroxyethoxy) methyl] guanine; 2-Amino-1,9-dihydro-9-(2-hydroxyethoxymethyl)-6*H*-purin-6-one**.**

Molecular formula: $C_8H_{11}N_5O_3$

Molecular weight: 225.2

Structure:

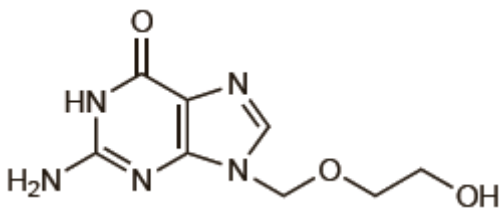

Fig. No. 4: Chemical structure of Acyclovir

MATERIALS AND METHODS

Acyclovir obtained from Cipla laboratories limited, Indore; Polysorbate 80 obtained from Oxford Lab, Mumbai; Aloe Vera Gel obtained from Patanjali Ayurvedic Pvt. Ltd, Haridwar; Methylparaben and propylparaben obtained from MCW Industries Indore.

METHOD OF PREPARATION

Aloe vera gel (50g) was taken in a pestle mortar, to this required amount of drug acyclovir (2.5g) dispersed in water. Polysorbate80 (3%) was added to the above mixture. Which is used as a penetration enhancer. After that methylparaben (0.15%) and propylparaben (0.05%) used as a preservative, were added slowly with continuous gentle trituration until the homogenous gel formed.

Table No. 1: Design of formulations

Formulation code	Acyclovir	Polysorbate80	Methylparaben	Propyl paraben	Aloe vera gel
S1	2.5g	1% w/w	0.15% w/w	0.05% w/w	q.s.50 g
S2	2.5g	2% w/w	0.15% w/w	0.05% w/w	q.s.50 g
S3	2.5g	3% w/w	0.15% w/w	0.05% w/w	q.s.50 g
S4	2.5g	4% w/w	0.15% w/w	0.05% w/w	q.s.50 g

EVALUATION PARAMETERS

Determination of *pH*[17]

pH was determined for each formulation by using a *pH* meter (*pH* meter Henna industries H198107) *pH* meter was calibrated before with buffer solutions of *pH* 4, 7, and 9.

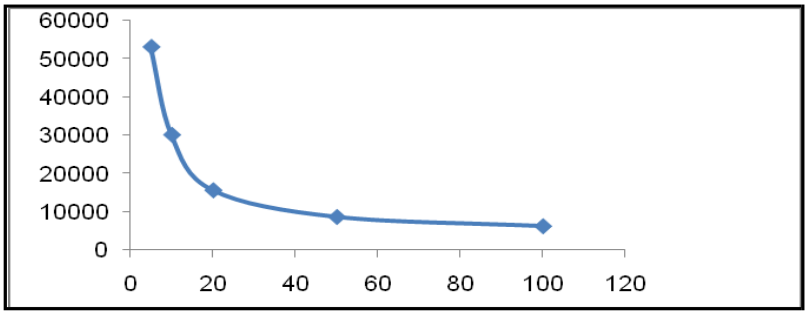

Figure No. 5: Plot of viscosity v/s rpm for S1

Table No. 2: *pH* of formulations

Sr. No.	Formulation code	*pH*
1.	S1	6.66
2.	S2	6.67
3.	S3	6.68
4.	S4	6.55

The *pH* of all formulations is found to be around 6 which is compatible with skin *pH*.

Determination of Viscosity[18]

Viscosity determined of each formulation by using Brookfield viscometer (Brookfield viscometer; type DV-E) with a spindle at room temperature and at 5, 10, 20, 50 and100 rpm.

Table No. 3: Viscosity of formulations

Rpm	Viscosity(cp)			
	S1	S2	S3	S4
5	53200	52770	58667	56687
10	30195	31545	30723	30616
20	15675	17865	19642	16545
50	8695	8350	8755	7688
100	6265	5320	6528	5515

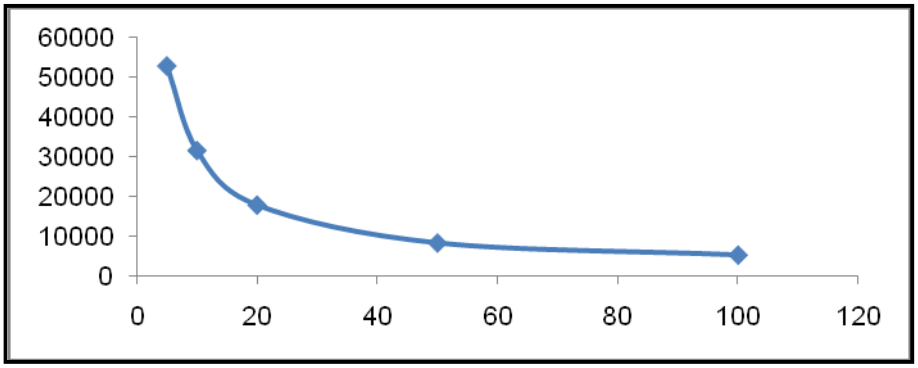

Figure No. 6: Plot of viscosity v/s rpm for S2

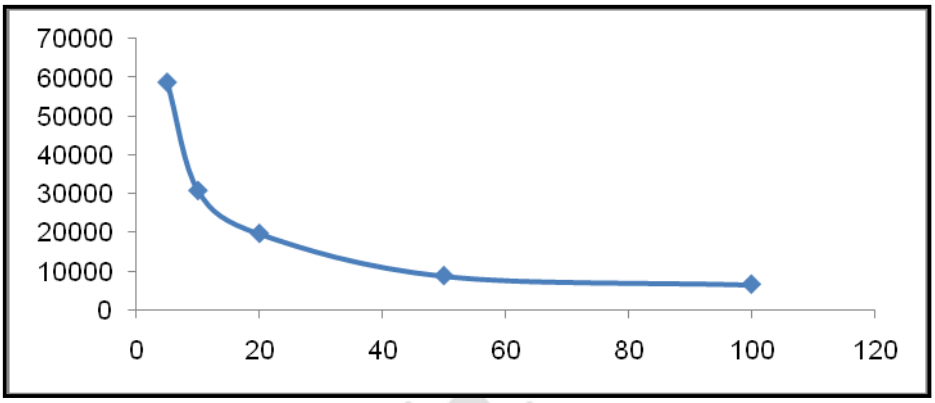

Figure No. 7: Plot of viscosity v/s rpm for S3

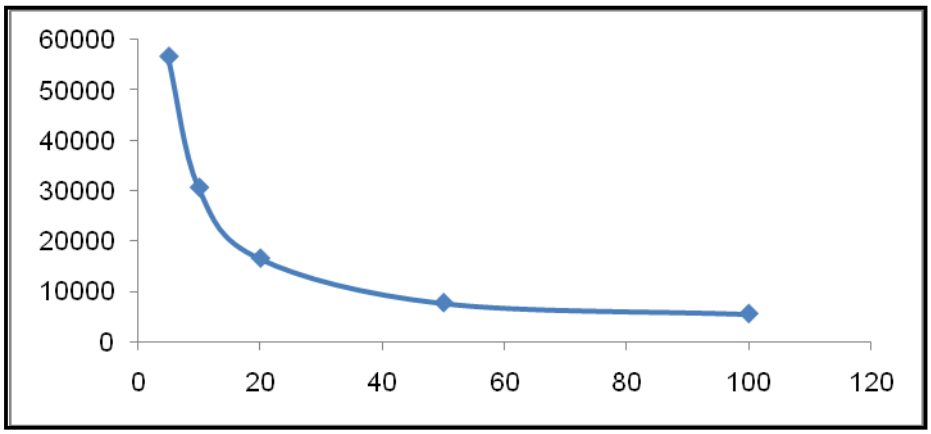

Figure No. 8: Plot of viscosity v/s rpm for S4

The term viscosity is defined as a measure of a fluid's resistance to flow. Viscosity describes the internal resistance or friction of moving fluids. A fluid with large viscosity resists motion because its molecular makeup gives it a lot of internalresistance[19].

Viscosity is an expression of the resistance of the fluid to flow; the higher the viscosity, the greater the resistance[20].

It is observed that the viscosity of the formulations goes on decreasing as the rpm increases i.e. an inverse relationship exists between the viscosity and the shear rate. From the figures, it can be said that the formulations follow pseudo plasticbehavior[21].

Drug Content[22-25]

1.0 gm of the gel formulation was taken in100ml volumetric flask which contains 20 ml of phosphate buffer *pH* 7.4 and stirred for 30 minutes. Volume was made up to 100 ml. 1ml of the above solution was further diluted to 10 ml by using a phosphate buffer of *pH* 7.4. The resultant solution was subjected to UV spectrophotometric analysis at 251.3nm and the absorbance was noted down.

UV spectrum of Acyclovir in presence of Aloe vera gel

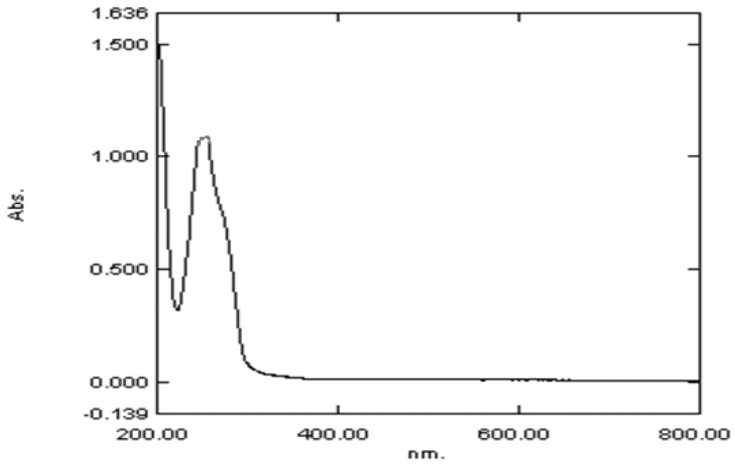

Fig. No. 9: UV spectrum of Acyclovir in presence of Aloe vera gel in phosphate buffer *pH* 7.4

Table No. 4: Concentration and Absorbance values for Acyclovir in presence of aloe vera gel in phosphate buffer of *pH* 7.4(λmax251.3nm)

Sr. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	4	0.222
3.	8	0.567
4.	12	0.859
5.	16	1.085
6.	20	1.192

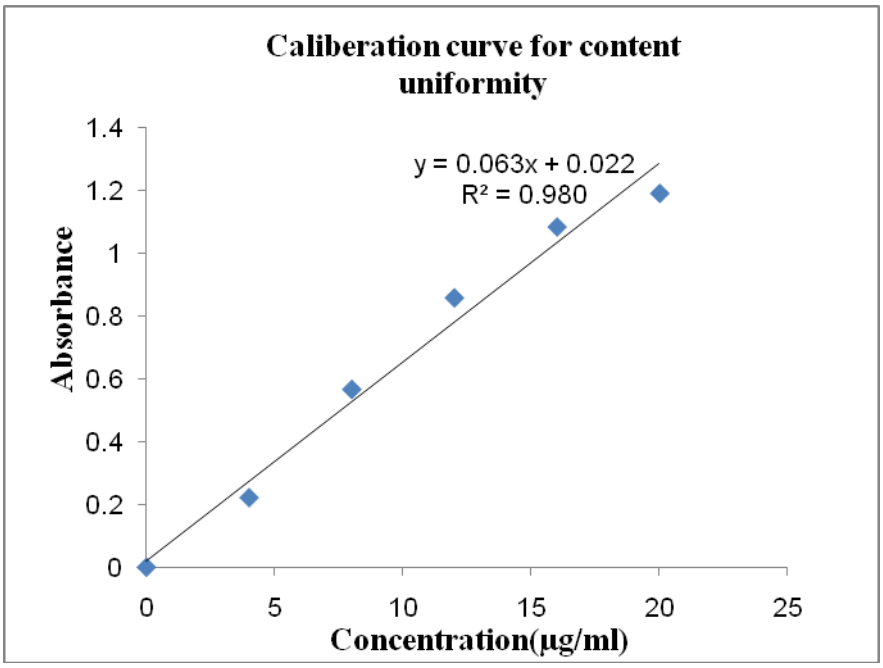

Fig. No. 10: Calibration curve of Acyclovir in presence of gel in phosphate buffer of *pH* 7.4

Calibration curve of Acyclovir in presence of Aloe vera gel was performed in phosphate buffer of *pH* 7.4. The calibration curve was found to be linear in the concentration range of 4-20 µg/ml having a coefficient of regression value r^2 = 0.980 and line equation, y=0.063x+0.022.

Table No. 5: Percent drug content of formulations

Sr. No.	Formulation code	Drug content (%)
1.	S1	96.27 ±1.2
2.	S2	97.53 ±1.3
3.	S3	98.12 ±1.1
4.	S4	99.23 ±1.6

The percent drug content was found to be within the range of 98 to 99 %.

SPREADABILITY[26-28]

Spreadability determined of the gel formulations, two glass slides of known standard dimensions are selected. Formulation whose spreadability was to be determined was placed on one slide and another slide. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two sides were placed onto a stand such that only the lower slide is held firm by the one opposite fangs of the clamp clips and allow the upper slide to slip freely over it by the force of weight tied Tie the 20 gm weight to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted. The spreadability was calculated by using the following formula.

Spreadability=

Values are spreadability, m is the weight tied to the upper slides, list h is the length of a glass slide, and t is the time taken.

Table No. 6: Spreadability of formulations

Sr.No.	Formulation code	Spreadibility (gm.cm/sec)
1.	S1	12.56
2.	S2	11.75
3.	S3	11.43
4.	S4	12.23

Spreadability of formulations is found to be in the range of 11.43 to12.56gm.cm/sec.

IN-VITRO DRUG RELEASE STUDY[29-30]

The *in vitro* release of acyclovir from gel formulation (S3) and the amount of drug that is permeated through cellophane membrane using the diffusion apparatus. The donor cell was filled with 300 mg of gel formulation. The receptor compartment was filled with phosphate buffer *pH* 7.4. The temperature of the receptor compartment was maintained at 37 ± 0.5ºC by hot water using a water bath. The samples were removed at predetermined intervals at 0.5, 1, 2, 4, 6 hours and replaced immediately with an equal volume of receptor solution to maintain sink conditions. The removed samples were analyzed at 251.3 nm on a UV spectrophotometer.

Table No. 7: Cumulative amount of drug released (Q) /cm^2 at different time intervals across cellophane membrane.

Time (hr)	Q(µg/cm^2)				
	S1	S2	S3	S4	Marketed
0.5	171.3□4.3	195.49□3.4	260.55□4.6	265.02□6.0	244.01□7.6
1	324.24□8.1	345.25□6.0	376.01□6.6	382.03□8.6	336.89□9.5
2	585.68□14.6	635.89□11.1	693.40□12.1	703.04□15.8	647.75□14.0
4	854.69□21.4	1007.0□17.6	1163.15□20.4	1172.00□26.4	999.00□19.3
6	1072.75□26.8	1165.07□20.4	1285.05□22.5	1290.82□29.0	1195.05□24.2

RESULTS AND DISCUSSION

The aloe-Vera-based transdermal gel was successfully prepared by the trituration method in the presence of PE (Penetration enhancer) polysorbate 80. In this formulation, the aloe vera concentration, polysorbate 80 concentration, was optimized to obtain the transdermal gel**.**

The use of penetration enhancers is a capable approach to enhance the permeation of drugs which having low permeability. Incorporation of penetration enhancer (polysorbate80) showed modified or improved *in-vitro* permeability and enhancement of the drug. In the

formulation greatest permeation is achieved at a 3 % concentration of penetration enhancer (polysorbate80) and hence S3 can be termed as the best formulation among those that are developed. No significant change in *in-vitro* drug release was obtained when taken the 4%penetration enhancer[31].

In the formulation, *pH* was determined the *pH* meter. In the formulations *pH* is found to be around 6.66 to 6.43 so *pH* is found in the range of 6 which is compatible with the skin. In case the range of *pH* of the formulation is found in the above range of *pH* 6 so it is not compatible with skin and causes irritation with skin.

Rheological properties showed that viscosity is inversely proportional to the rate of shear and thus the system shows pseudoplastic characteristics or behavior. It is observed that the viscosity of the formulations goes on decreasing as the rpm increases an inverse relationship exists between the viscosity and the shear rate. Viscosity is found in the range of 45770 to 4538 cp. Drug content was found within the range of 98 to 99 % for all the formulations. The spreadability of the formulations is found within the range of 11.43 to12.56 gm. cm/sec[32].

Drug release study of the formulation is found in the range of 1290.82(µg/cm^2) it is shown better result compared to the marketed formulation (1195µg/cm^2). Stability studies had shown that the formulation is stable at 40^{o}C at 75% RH for one month of period time. The result of the present study proved that the drug easily penetrated the dermis. The result clearly suggests that antiviral drug incorporated gel formulation couldbeutilizeforthe herpes virus infectious disease[33].

SUMMARY AND CONCLUSION

The Result obtained from all the experimental analyses as a part of project work suggested that it is possible to prepare an optimized formulation of transdermal gel preparation. In this method we have used of penetration enhancer is a capable approach to enhance the permeation of drugs which having low permeability. The incorporation of penetration enhancer (polysorbate80) showed modified or improved *in-vitro* permeability enhancement of the drug. In the formulation, the greatest permeation is achieved at a 4 %concentration of penetration enhancer (polysorbate80) and hence S4 can be termed as the best formulation among those that are developed[34].

In the formulation use of aloe vera gel as absorption base it possesses soothing, moisturizing,

and healing properties, aloe vera gel contains lignins, that allow for penetrative properties. Lignin's action is associated with excellent penetration abilities of aloe into the human skin so the aloe vera gel-based formulation is advantageous in delivering the entire drug safely to the skin.

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