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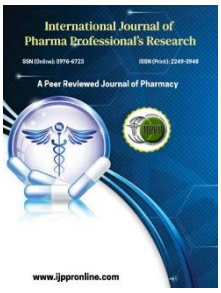


# Preparation and Characterization of an Antiviral Gel

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**ABSTRACT:** The study was to develop an antiviral gel for topical application. The topical application of drug has many advantages over the intravenous and oral administration. It prevents metabolism of drug from liver and avoid the risk of gastrointestinal disorder and inconvenience of intravenous therapy pain. When the drug is applied topically it can penetrate deeper into the skin hence show better absorption and bioavailability. The wide varieties of pharmaceutical dosage form are available for topical drug delivery system. The most used one is gel, ointment and cream. Herpes Simplex Virus (HSV) is widely spread that cause infections. There are two types of this virus, one is HSV-1 usually causes sore around the lip or inside the mouth that are sometime called fever blisters or cold sore and the second is HSV-2, it causes sore on the genitals. Acyclovir is a selective and effective antiviral agent.

Acyclovir remains the gold standard in the treatment of Herpes Simplex Virus infections, mainly due to emerging new drug delivery systems which are improving the bioavailability and fewer side effects. The gel was prepared in different batches or formulation by using different types of polymers in varying concentration viz. Carbopol-934, Carbopol-940, HPMC, and Na-CMC. The gel formulations were evaluated for physical and chemical characterization like visual appearance, drug content, pH, viscosity, extrudability, spread ability etc. and the results was compared.

**Introduction**: Parenteral route of administration is used to avoid the first pass effect/metabolism and also to sustain the constant level of drug into the body. The drug reaches into the systemic

circulation directly but it has certain disadvantages. One of the disadvantages of parenteral administration is invasive nature which can be overcome with topical route of administration. The topical route of administration is noninvasive drug delivery at the point of application, so adequate amount of drug is absorbed into the systemic circulation to provide remedial action One of the disadvantages of parenteral administration is invasive nature which can be overcome with topical route of administration. The topical route of administration is noninvasive drug delivery at the point of application, so adequate amount of drug is absorbed into the systemic circulation to provide remedial action. To give continuous drug mixture through unbroken skin, there are many topical preparations are used like "Gel".[1]

The ideal characteristics of topical application include:

a) Formation of gel should have both physical and chemical strength.
b) Formulation should have patient acceptability.
c) Formulation consisting one or more components should be non-sensitizing and non-irritating.
d) Formulation must have ability to release therapeutic agents within therapeutic window.

**1.1 Skin Characteristics:** The purpose of topical application of dosage form is to suitably delivery of drug across the localize area of the skin. Drug or medication are applied to the skin in a many pharmaceutical dosage forms like ointment, cream, gel, etc. the absorption occurs outside the skin including entry into the blood flow is known as the percutaneous absorption. It's necessary to determine skin characteristic to develop a perfect topical dosage form.[2]

**1.2 Skin Structure:** The skin is largest surface area of the body and structure is shown in figure 1. The average of adult it occupied a surface area approximately 2 sq. m. (3000 sq inches). Structurally, the skin composed of mainly two layers. The outer most layer is thinner portion it consists of epithelium, is called as epidermis. It contains five layers stratum corneum, s. granulation, s. lucidum, s. spinosum, and basal layer. The epidermis is cemented on the inner thicker layer (Connective tissue) called dermis. Beneath the dermis connected with subcutaneous layer it is also known as a superficial fascia or hypodermis, consist of areolar and adipose tissues.[3]

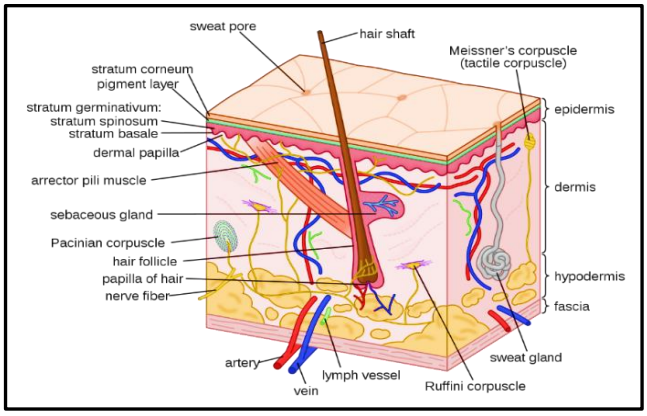


**Figure 1.** Structure of skin

Gels are "semisolid dosage form, in this system liquid phase trapped within 3D polymer matrix in which a high degree of chemical and physical cross linking is present" this matrix network create a resistance to flow of fluid due to the entrapment and immobilization of solvent molecules.[4]

**1.3 Factors Affect the Transdermal Permeation:[5]**

The main principal of transport mechanism through skin is passive diffusion. The factors influencing can be classified into three major categories.

a) Physicochemical properties of drug delivery system.
b) Pathological and physiological condition of skin.
c) Physicochemical properties of penetrates.

There are many other factors also affect the penetration of drug and the physicochemical

properties of drug like partition co-efficient, concentration of vehicle, molecular size and molecular weight etc.[6]

**1.4 Drug Diffusion Mechanism Through the Stratum Corneum:** Stratum corneum contains many intercellular membranes and the intercellular regions are filled with lipid rich amorphous material. In case of dry membrane, the intercellular volume is about 5% of total volume. Although molecules diffuse through intercellular region, the available evidence indicate that for polar or non-electrolyte, water soluble drug not diffuse primarily through intercellular. The transcellular permeation is explained on the basis of relatively smaller diffusion constant. Molecule also penetrates through transcellular mechanism.[7]

Stratum corneum has a finite thickness and there is a period of transient diffusion (lag time) after applying drug on the skin, rate of drug transfer through skin increase to reach a steady state. Lag time (t), is related to the thickness of the membrane (h), and the diffusion constant (D) of the drug, by relationship, $t=h^2/6D$. Physical destruction or damage of the stratum corneum barrier or cracking of the skin, increase the absorption. Stratum corneum is a main physical diffusion barrier.

**1.5 Gel Characteristics:** Ideally gelling agent are safe, inert, and non- reactive to other excipients. It provides reasonable solid like nature during storage that can be broken easily by applying shear stress generated by squeezing a tube or during topical application of medication. The gel should exhibit little viscous change under the temperature difference of normal use or during storage. The characteristic of gel should match to intended use. It should not be tacky.[8]

**1.6 Formulation Considerations:** In the formation of gel, the efficiency of gel is dependent on the composition of the vehicles. It must have ability to penetrate through skin barriers and exert their effect into the site of action. It called "vehicle effects" the consequences of these two diffusional processes. These two processes are closely related and are dependent upon physicochemical properties of the drug, vehicle, and the barriers.[9]

**2. Scope and Plan of Work:** Acyclovir is a broad spectrum anti-viral agent use against Varicella Zoster Virus (VZV) and Herpes Simplex Virus (HSV). This virus infects the mucous membrane, neurons and skin, two conditions like chicken pox and shingles caused by VZV. Acyclovir has low aqueous solubility and poor oral bioavailability there for intravenous or topical application are necessary for inhibition of virus growth, topical semi-solid dosage form is prepared to produce local activity. Gels, creams, ointment and pastes are some examples of semi-solid use for many years.[10]

Gels have better absorption than other formulation of semi solid dosage form. Consequently, a study on formulation and evaluation of acyclovir gel was as a main objective for their anti-viral action. It is well tolerated. It prevents the spread of the HSV into the body. So, the aim of this study to develop gel preparation containing acyclovir.[11] The main consideration of research work objectives is following: -

a) Compatibility study of drug with different polymers like Hydroxypropyl methyl cellulose, Carbopol and Sodium carboxy methyl cellulose.
b) Optimization of the formula to attain all gel characteristics.
c) Designing the trial formula for different concentration of each polymer
d) Selection of suitable formula from each polymer and preparation of gel formulations
e) Evaluation of the prepared gels for
   - PH
   - Drug content
   - Spreadability
   - Extrudability
   - viscosity
f) In-vitro drug release for each gel formulation, study the effect of permeation enhancer for

each formulation. From this the best formulation is considered for further studies.

g) In-vitro evaluation of the selected formulation to perform by using Albino Rabbits and comparison with marketed acyclovir topical preparation.

h) Stability study of selected formulation to perform on them in different storage condition.[12]

**2.1 Formulation of Gel:** Acyclovir gels are prepared by using different polymers like Carbopol 934, carbapol940, Hydroxy propyl methyl cellulose, etc. different concentration of polymer used in preparation of gels.[13,14]

**2.2 Preparation of Carbapol-934 Gels**:

**Procedure:**

a) Accurately weigh the quantity of acyclovir is mixed in purified water with constant stirring and heat it at $50^0$C.

b) Add methyl paraben as preservative.

c) Add carbapol-934 to solution with continuous stirring at $50^0$C temperature.

d) Then add triethanolamine to the solution to maintain pH, stir until a clear gel was obtained.

| **Ingredients** | **Formula for 100 gms** | | |
|---|---|---|---|
| | **$P_1$ (gm)** | **$P_2$ (gm)** | **$P_3$ (gm)** |
| Acyclovir | 1.0 | 1.0 | 1.0 |
| Carbopol-934 | 0.4 | 1.1 | 1.6 |
| Triethanolamine | 0.5 | 0.5 | 0.5 |
| Purified water | 98 | 97.5 | 97 |
| Methyl paraben | 0.001 | 0.003 | 0.002 |

**Table 1.** Formulations with different carbapol-934 concentrations

**2.3 Preparation of carbapol-940 gels:** Repeat the same procedure and same amounts for carbapol-940 gel preparation.

| **Ingredients** | **Formula for 100 gms** | | |
|---|---|---|---|
| | **$P_1$ (gm)** | **$P_2$ (gm)** | **$P_3$ (gm)** |
| Acyclovir | 1.0 | 1.0 | 1.0 |
| Carbopol-940 | 0.4 | 1.1 | 1.6 |
| Triethanolamine | 0.5 | 0.5 | 0.5 |
| Purified water | 98 | 97.5 | 97 |
| Methyl paraben | 0.001 | 0.003 | 0.002 |

**Table 2.** Formulation with varying Carbapol-940

**2.4 Preparation of Sodium Carboxymethyl Cellulose Gel:**

**Procedure:**

**a)** Accurately weighed quantity of acyclovir was dispersed in purified water with constant stirring

**b)** Na-CMC was added in solution with continuous stirring. Add methyl paraben is used as preservatives by stirring.

**c)** Stand it for complete hydration of Na-CMC. Adjust weight to 10gm by adding purified water.

| **Ingredients** | **Formula for 100gms** | | |
|---|---|---|---|
| | **$A_1$** (gm) | | **$A_1$** (gm) |
| Acyclovir | 1.0 | Acyclovir | 1.0 |
| Sodium carboxy methyl | 2.5 | Sodium carboxy methyl | 2.5 |
| Purified water | 98 | Purified water | 98 |
| Methyl paraben | 0.004 | Methyl paraben | 0.004 |

**Table 3.** Formulation with varying Na-CMC concentrations

**3. Evaluation Parameter of Gel:** The gels were evaluated for the following parameters such as drug content, pH, viscosity, extrudability, spreadability and In-vitro release of drug by using Albino Rabbit.

**3.1 Determination of Drug content**: 1gm of Acyclovir gel was dissolved in 0.1M HCl and volume make up to 100ml. 1ml of solution is dilute with 10ml of 0.1M HCl solution. Absorbance was measured in a form of standard calibration curve at 255nm by using UV spectrophotometer.

| Formulation | Drug content (mg) | Drug content (%) |
|---|---|---|
| $P_1$ | 10.173 | 101.73 |
| $P_2$ | 9.82 | 98.2 |
| $P_3$ | 9.68 | 96.8 |

**Table 4.** Drug content in the gel formulation

**3.2 pH Measurements:** This is done by using digital pH meter as per procedure.

| Formulation | pH |
|---|---|
| $P_1$ | 6.8 |
| $P_2$ | 7.3 |
| $P_3$ | 6.9 |

**Table 5.** pH of gel formulations

**3.3 Estimation of viscosity:** The viscosity of gel is determined by using Brookfield Viscometer (model-RVTP).

| Formulation | Viscosity in cps |
|---|---|
| $P_1$ | 43,500 |
| $P_2$ | 41,400 |
| $P_3$ | 51,600 |

**Table 6.** Viscosity of gel preparations

**3.4 Extrudability:** It is a test to measure the force to extrude the material from a tube.

| Formulation | Extrudability |
|---|---|
| $P_1$ | ++++ |
| $P_2$ | ++ |
| $P_3$ | +++ |

++++Estimation, +++Good, +Not satisfactory

**Table 7.** Extrudability of gel

**3.5 Determination of Spreadability:** The ideal quality of gel should possess good spreadability. Take about 1gm of gel formulation and kept it on a center of glass plate [standard dimensions (10x10cm)] and another glass plate place over it carefully, and put 2kg weight at center of glass plate (avoid sliding of plate). The diameter is measured after 30 minutes in cm.

| Formulation | Time taken (minutes) | Spreadability (cm) |
|---|---|---|
| $P_1$ | 30 | 8.2 |
| $P_2$ | 30 | 7.9 |
| $P_3$ | 30 | 7.6 |

**Table 8.** Determination of spreadability

**4. Result and Discussion**:

**4.1 Compatibility Study**: The Acyclovir drug was compatible with all the polymers namely Hydroxypropyl methyl cellulose, Carbopol, Sodium carboxy methyl cellulose was used in the gel formulation and also used as a gelling agent.

**4.2 Evaluation of Acyclovir Gels:** Prepared gel undergoes to evaluation studies

**4.3 Estimation of Drug Content:** The drug content in gel formulation 1% carbapol-934($A_2$) showed the maximum drug content (101.73%) as compare to another formulations result shown in table 4.

**4.4 pH Measurements:** The pH measurement of gel is done by using Digital pH meter. The pH range of the formulations was from 6.8 to 7.3, the result shown in table 5.

**4.5 Determine the Viscosity of Gel:** Viscosity is measure by using Brookfield Viscometer. The viscosity of the gels was ranged from 41,400 to 51,600cps and the result shown in table 6.

**4.6 Extrudability:** The extrudability of gel was determined according to procedure. Extrudability of carbopol and HPMC gels were excellent than Na-CMC the result is shown in table 7.

**4.7 Spreadability:** The spreadability of gel was determined as per the procedure. The spreadability data of the formulation with 1% Carbopol-934 showed maximum (8.2cm), then other formulation was showed in table 8.

**4.8 *In-vitro* study:** *In-vitro* drug release of gel formulation was carried out as per procedure. Every formulation has different percentage of drug release and it determined at end of 8hr. 1% Carbopol-934 shows maximum release (64.91%). DMSO used as permeation enhancer in gel formulation. 1% Carbopol-940 shows release was lesser (51.47%). In case of HPMC and Na-CMC gels shows lesser release than Carbopol gels.

**5. Conclusion:** This study demonstrates that a gel formulation can be used to improve the solubility, permeability, bioavailability of acyclovir and it overcome the difficulties arises with its use in the clinic. On the bases of analysis different polymers Carbapol-934, Carbpol-940, HPMC and Na-CMC are used in the gel formulation. The prepared formulations exhibit all properties of gel. The selected formulation was evaluated for stability, viscosity, spreadability, drug content, and the pH study. The result suggest that the optimised formulation was stable at different temperature and the study shows that the prepared formulation is one of the formulations which has higher permeability, solubility and the bioavailability. The present work aimed to developing a successful Gel formulation for the topical treatment of Herpes Simplex Virus infections. In this study we got success in development and evaluation of gel. The study shows a successful development of gel formulation by using varying type of polymer (Carbapol-934, Carbpol-940, Na-CMC and HPMC). The gel containing Carbapol-934 shows higher drug content, stability and shows better properties than other polymer containing formulations.

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