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Formulation and Evaluation Studies of Acyclovir Topical Gels for Anti-Viral Activity

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ABSTRACT

The aim of the study is to formulate & evaluate of topical gel of acyclovir for treatment of viral disease. Acyclovir gels were formulated using different polymers like Carbopol 934, Carbopol 940, hydroxy propyl methyl cellulose and Sodium Carboxy methyl cellulose. Different concentrations of polymer were used in the formulation of gels. All the formulations were evaluated for the various parameters. Different formulations with use of different polymers were prepared. The amount and percentage of drug present in gel formulation using different polymers were estimated as per the procedure. Stability study for the best formulation was done as per the procedure. The gel was both physically and chemically stable at 4-5 °C, Room temperature and 37±5 °C. From this investigation, it was concluded that formulation A2 with 1% Carbopol-934 may be the best formulation having good in vitro release profile and stability. Based on this study, it can be concluded the solubility and permeability of acyclovir can be increased by formulating into gel.

Keywords: Acyclovir, Gel, In-vitro drug release, Antiviral Activity

INTRODUCTION

Acyclovir is a broad-spectrum anti-viral agent against Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV). (1) Two conditions like Chicken pox and Shingles caused by VZV, which infects mucous membrane, skin and neurons. Acyclovir is poorly water soluble and poor oral bioavailability; hence intravenous administration is necessary if high concentrations with fewer side-effects. Therapy for this disease is based on the application of anti-viral agents to inhibit virus growth. (2, 3) Topical semi-solid preparations are designed to produce local activity. Creams, gels, ointments and pastes are some of the topical semi-solids in use for many decades. These have evolved with little understanding or absorption mechanism. But now gels have gained more and more importance because the gel formulations have better percutaneous absorption than Creams and Ointments. (4, 5) Gels are gaining more popular due to ease of application, undetectable to eye and neither tacky nor greasy. (6) Hence a study on formulation and evaluation of Acyclovir gel was as a principal objective for anti-viral activity.

MATERIALS AND METHODS

Acyclovir was obtained as a gift sample from Macleods pharmaceuticals, Mumbai. Carbopol 935, 940, HPMC and SCMC were purchased from S. D. Fine Chem. Ltd., Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Formulation Of Gels: Acyclovir gels were formulated using different polymers like Carbopol 934, Carbopol 940, Hydroxy propyl methyl cellulose and Sodium Carboxy methyl cellulose. Different concentrations of polymer were used in the formulation of gels. The concentrations chose varied with the polymer used. After initial trials, the concentrations that gave products of good consistency were selected for the formulation. The concentration of drug taken in all the formulation remained constant. Table 1 to 4 gives the different concentrations of polymers used in the formulation. (7, 8, 9)

i) Preparation of Carbopol- 934 gels

- Accurately weighed quantity of Acyclovir was dispersed in purified water with constant stirring and the drug solution was heated to 50 °C.
- Methyl paraben was added as a preservative.
- The carbopol-934 was added to the solution under stirring while temperature Was maintained at 50 °C.
- The dispersion of gelling agent was neutralized by addition of triethanolamine solution to attain the neutral pH . Stirred slowly till a clear gel was obtained.

Table 1: Preparation of Carbopol- 934 gels

S. No.	Ingredients	Formula for 100gms		
		A1	A2	A3
1	Acyclovir	**1.0**	**1.0**	**1.0**
2	Carbopol-934	0.5	1.0	1.5
3	Triethanolamine	0.5	0.5	0.5
4	Purified water	98	97.5	97
5	Methyl paraben	0.002	0.002	0.002

ii) Preparation of Carbopol- 940 gels

1. Accurately weighed quantity of Acyclovir was dispersed in purified water with constant stirring and the drug solution was heated to 50 °C.

2. Methyl paraben was added as a preservative.

3. The carbopol-940 was added to the solution under stirring while temperature was maintained at 50 °C.

4. The dispersion of gelling agent was neutralized by addition of triethanolamine solution to attain the neutral pH. Stirred slowly till a clear gel was obtained.

Table 2: Preparation of Carbopol- 940 gels

S. No.	Ingredients	Formula for 100gms		
		B1	B2	B3
1	Acyclovir	1.0	1.0	1.0
2	Carbopol-940	0.5	1.0	1.5
3	Triethanolamine	0.5	0.5	0.5
4	Purified water	98	97.5	97
5	Methyl paraben	0.002	0.002	0.002

iii) Preparation of Hydroxy propyl methyl cellulose gels

- Accurately weighed quantity of Acyclovir was dispersed in purified water with constant stirring and the drug solution was heated to 50 °C.
- The solution was maintained at 50 °C, HPMC was gradually added to the Solution under stirring until a thick viscous gel was formed.
- Methyl paraben was added finally to the preparation as a preservative.
- Formulation was allowed to settle down to room temperature.

Table 3: Hydroxy propyl methyl cellulose gels

S. No.	Ingredients	Formula for 100gms			
		C1	C2	C3	C4
1	Acyclovir	1.0	1.0	1.0	1.0
2	HPMC	1.0	1.5	3.0	4.0
3	Triethanolamine	0.5	0.5	0.5	0.5
4	Purified water	98	97.5	96	95
5	Methyl paraben	0.002	0.002	0.002	0.002

iv) Preparation of Sodium carboxy methyl cellulose gels

- Accurately weighed quantity of Acyclovir was dispersed in purified water with Constant stirring.
- Sodium Carboxy methyl cellulose was added under stirring to the above solution.
- Methyl paraben was added to the dispersion under stirring as a preservative.
- The dispersion was allowed to stand for complete hydration of Sodium CMC. Finally, the weight was adjusted to 100gm by adding purified water.

Table 4: Sodium carboxy methyl cellulose gels

S. No.	Ingredients	Formula for 100gms		
		D1	D2	D3
1	Acyclovir	1.0	1.0	1.0
2	SCMC	1.0	1.5	3.0
3	Triethanolamine	0.5	0.5	0.5
4	Purified water	98	97.5	96
5	Methyl paraben	0.002	0.002	0.002

EVALUATION OF GELS

The prepared gels were proposed to be evaluated for Drug content, pH, Viscosity, Extrudability, Spreadability, In vitro release characteristic and the selected gel formulation subjected for Stability. (10)

Standard curve of Acyclovir: 100 mg of accurately weighed Acyclovir was dissolved in little amount of 0.1M hydrochloric acid and made up to required volume 100 ml with 0.1M hydrochloric acid. So that each ml of stock solution required concentration of 5, 10, 15, 20, 25, 30, 35 and 40 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- spectrophotometer. The standard plot was made with concentration (µg /ml) on X axis and Absorbance on Y axis. (11, 12)

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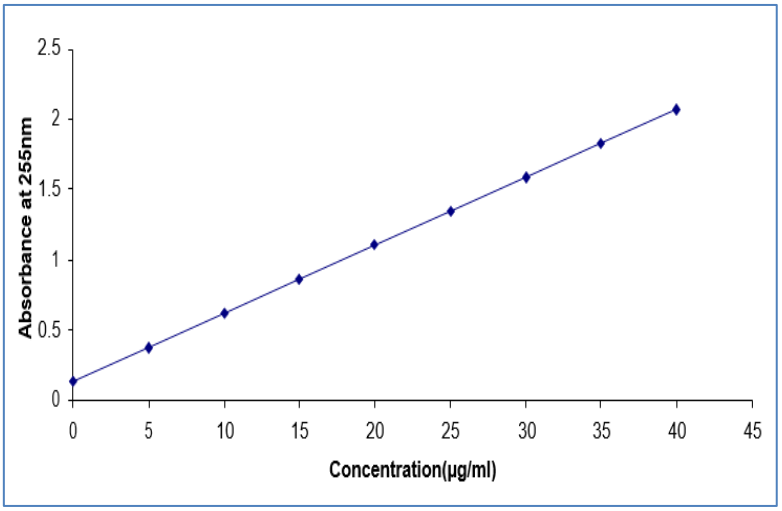

Figure 1: Standard curve of Acyclovir

Estimation of Drug content: 1gm of Acyclovir gel was dissolved in sufficient quantity of 0.1M hydrochloric acid to get the clear solution, volume was made up to 100ml with 0.1M hydrochloric acid. 1ml of the solution was diluted to 10ml with 0.1M hydrochloric acid solution. Absorbance was measured at 255nm using UV spectrophotometer. The amount of Acyclovir was determined from the standard calibration curve and the percentage drug content in different formulations was calculated. Results were tabulated as follows:- (13)

Table 5: Drug content in the gel formulations

S. No.	Formulation	Drug content (mg)	Drug content (%)
1	A2	10. 172	101.72
2	B2	9.81	98.1
3	C3	9.78	97.8
4	D2	9.69	96.9

Average of three readings

pH Measurements: pH measurements of the gel were carried out using a digital pH meter by dipping the glass electrode completely into the gel system so as to cover the electrode. The results were tabulated as follows. (14)

Table 6: pH Measurements in the gel formulations

S. No.	Formulation	pH
1	A2	6.9
2	B2	7.2
3	C3	7.1
4	D2	6.8

Average of three readings

Determination of viscosity: Viscosities of the gels were determined by using Brookfield Viscometer (model- RVTP).Spindle type, RV-7 at 20 rpm. 100gm of the gel was taken in a beaker and the spindle was dipped in it and rotated for about 5 minutes and then reading was taken. (15)

Table 7: Viscosity of gel formulations

S. No.	Formulation	Viscosity in cps
1	A2	43,000
2	B2	41,000
3	C3	36,000
4	D2	51,000

Average of three readings

Extrudability: It is useful empirical test to measure the force required to extrude the material from the 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 when a pressure was applied on tube gel. The extrudability of the formulation was checked and the results were tabulated. (16)

Table 8: Extrudability of gel formulations

S. No.	Formulation	Viscosity in cps
1	A2	+++
2	B2	+++
3	C3	+
4	D2	++

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

Determination of spreadability: One of the criteria for a gel meet ideal quality is that it should possess good spreadability. About 1 gm of gel formulation was weighed and kept at the center of the glass plate of standard dimensions (10x10cm) and another glass plate placed over it carefully, that the gel was sandwiched between the two slides. 2 kg weight was placed at the center of the plate (avoid sliding of the plate). The diameter of the gel in cms, after 30 minutes was measured. (17)

Table 9: Extrudability of gel formulations

S. No.	Formulation	Time taken (minutes)	Spreadability (cm)
1	A2	30	8.0
2	B2	30	7.8
3	C3	30	7.4
4	D2	30	7.7

Average of three readings

In vitro Drug release pattern of Acyclovir gels: The In vitro release of Acyclovir from the gel formulation was studied by open ended cylinder method. This diffusion cell apparatus consists of a glass tube with an inner diameter of 2.5 cm, open at the both ends. One end of the tube tied with Cellophane membrane, which serves as a donar compartment. 1 gm of Acyclovir gel was taken in this compartment and placed in a beaker containing 200ml of 0.1M Hydrochloric acid stirring at moderate speed, maintain the temperature at 37±1 °C. Periodically 5ml of samples were withdrawn and after each withdrawal using 0.1M Hydrochloric acid was replaced into the diffusion medium to maintain the sink condition throughout the experimentation. Then the samples were assayed by spectrophotometrically at 255nm in UV-Spectrophotometer using 0.1M Hydrochloric acid as blank. (18, 19)

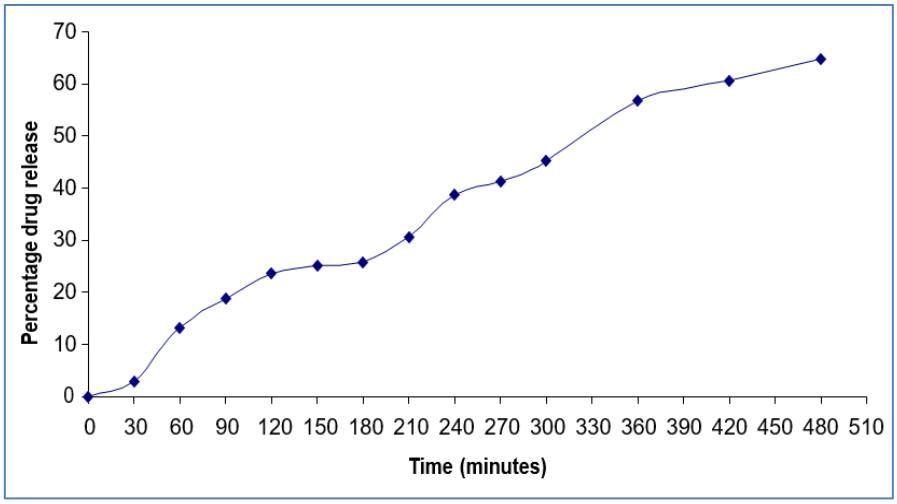

Figure 2: In vitro release profile of Acyclovir from 1% Carbopol – 934 gel

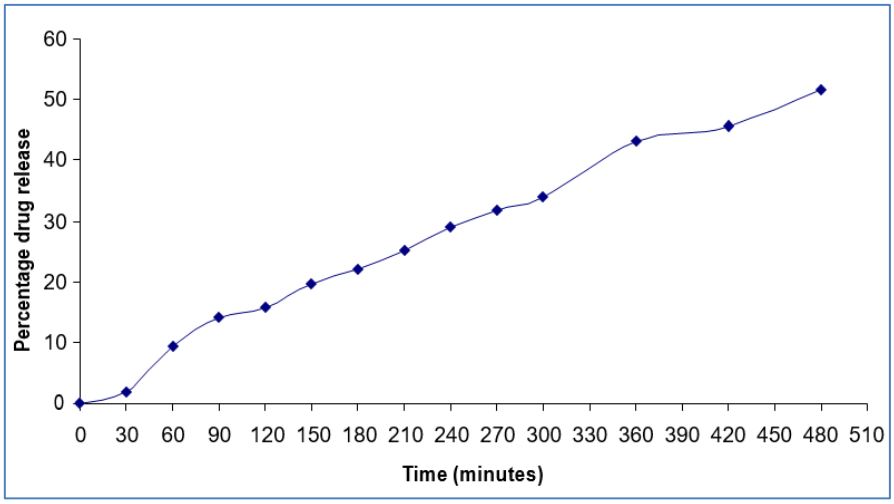

Figure 3: In vitro release profile of Acyclovir from 1% Carbopol – 940 gel

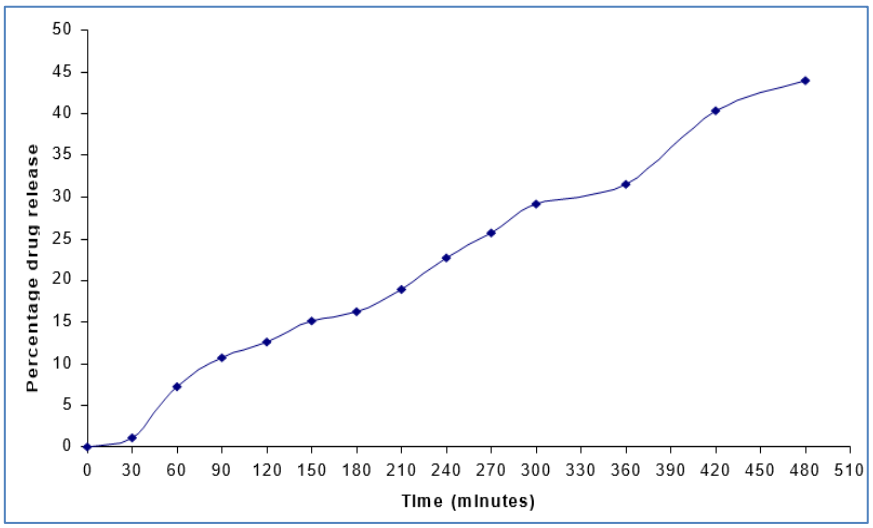

Figure 4: In vitro release profile of Acyclovir from 3% Hydroxy propyl methyl cellulose gel

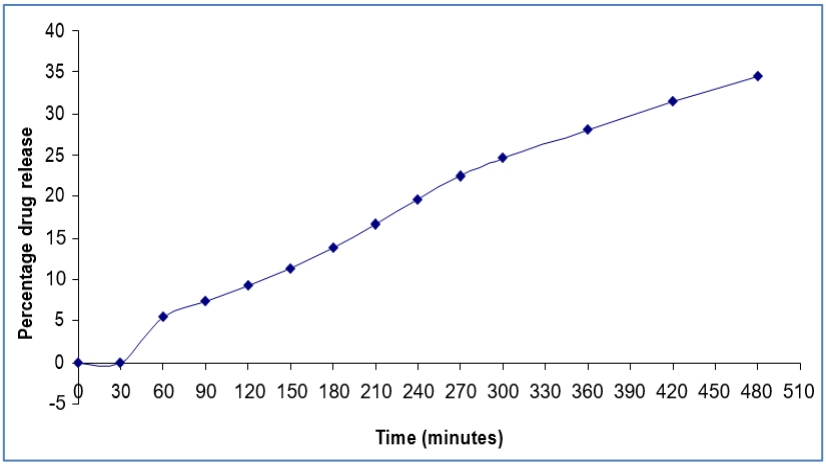

Figure 5: In vitro release profile of Acyclovir from 3% Sodium carboxy methyl cellulose gel

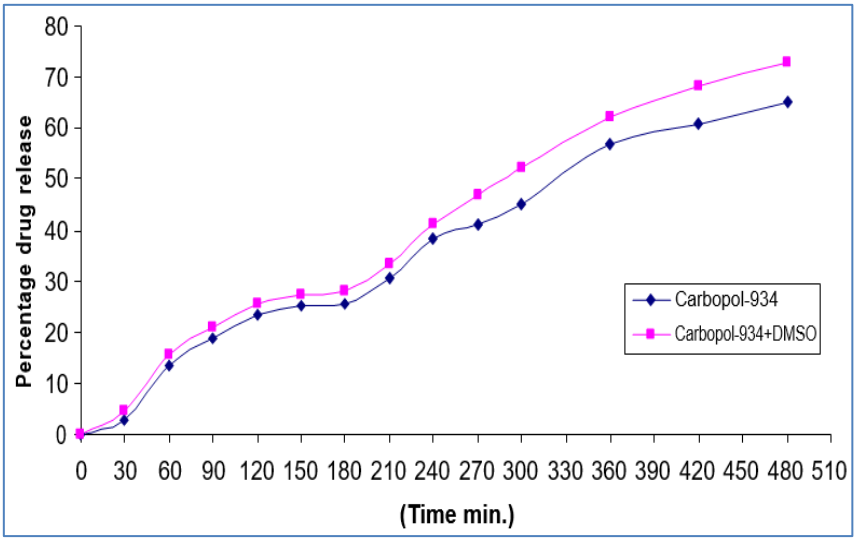

Figure 6: Comparative in vitro release profile of Acyclovir from 1% Carbopol -934 gel formulation with permeation enhancer

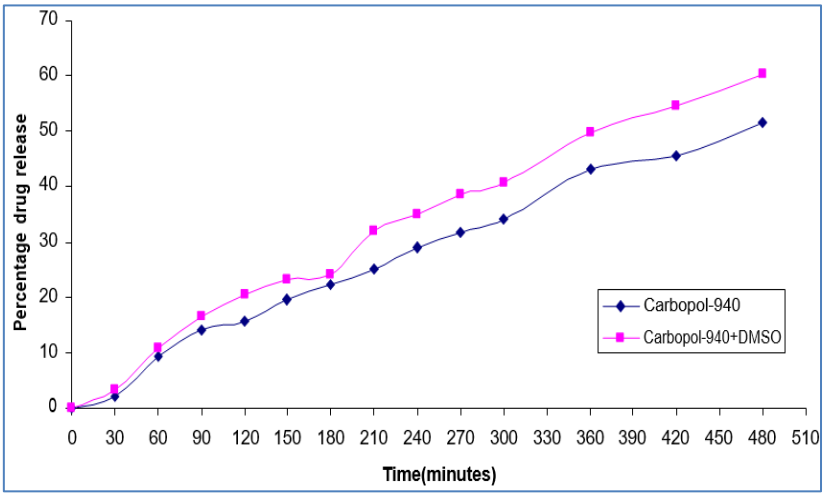

Figure 7: Comparative in vitro release profile of Acyclovir from 1% Carbopol -940 gel formulation with permeation enhancer

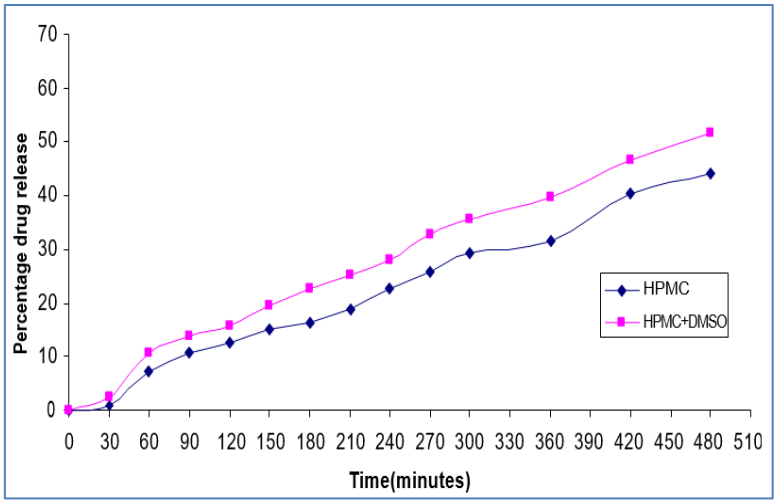

Figure 8: Comparative in vitro release profile of Acyclovir from 3% Hydroxy propyl methyl cellulose gel formulation with permeation enhancer

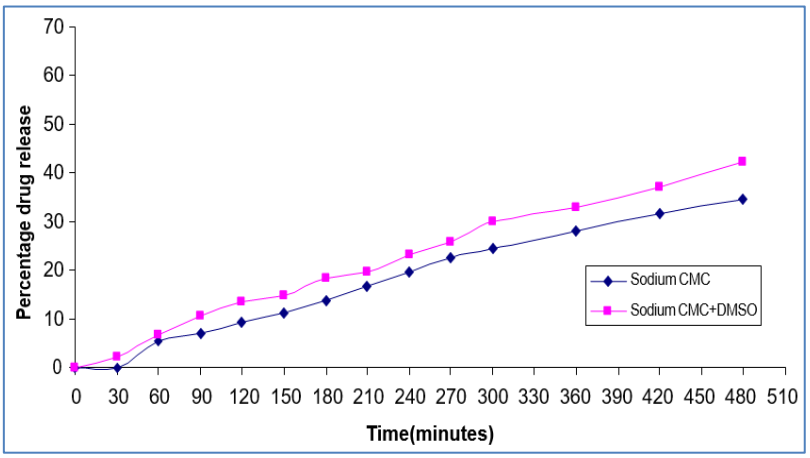

Figure 9: Comparative in vitro release profile of Acyclovir from 3% sodium carboxy methyl cellulose formulation with permeation enhancer

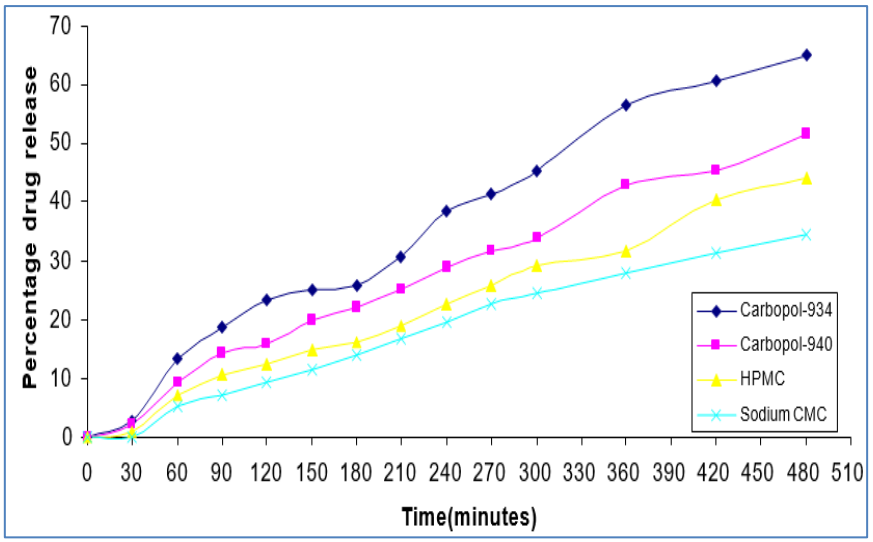

Figure 10: Comparative in vitro release profile of Acyclovir from different gel formulations

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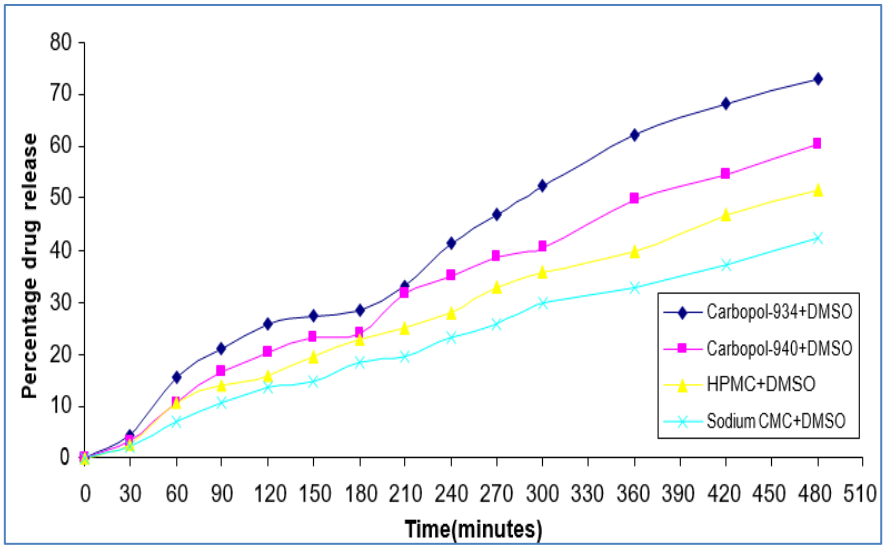

Figure 11: Comparative in vitro release profile of Acyclovir from different gel formulations with permeation enhancer

Stability studies of the selected gel formulation: The assessment procedure for the stability of a pharmaceutical product lies in the capability of a formulation to retain its physical, chemical and therapeutic specifications. A general methodology for predicting the stability is accelerated stability analysis in which the materials are subjected to elevated temperatures. This does not hold good for gels, as they melt at higher temperature conditions. Thus, the most commonly applied temperatures are refrigeration (4-5 °C), room temperature (25-30 °C) and 37±5 °C. Then the samples were checked at the regular intervals of 1, 2 and 3 months. Different parameters considered for analysis are shown below. (20, 21)

Table 10: Physical evaluation of formulation A2 (1% Carbopol-934)

Parameters	**Room Temperature**	**37±5 °C**	**4-5 °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	+++	+++	+++
Phase separation	Not found	Not found	Not found
Leakage	Not found	Not found	Not found
Nature			
Initial	Smooth	Smooth	Smooth
Final	Smooth	Smooth	Smooth

+++Excellent.

Chemical evaluation

The drug content of the formulation was estimated over a period of 3 months. The results were tabulated as follows.

Table 11: Drug content of formulation A2 (1% Carbopol-934)

Storage condition	Withdrawal period (monthly)			
	0	1	2	3
4-5 °C	101.72	101.54	100.04	99.36
Room Temperature	101.72	100.86	99.48	98.93
37±50C	101.72	100.55	99.08	98.24

Each reading represents the average of three determinations.

RESULTS AND DISCUSSION

Compatibility Study: With reference to the IR-spectrum, the drug Acyclovir was compatible with all the polymers namely Carbopol, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose were used in the gel formulation.

Formulation of Acyclovir topical gels using various gelling agents: Gel formulations of acyclovir were prepared using different polymers namely Carbopol-934, Carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose as per the procedure.

Carbopol-934 as a gelling agent: Formulations with formula A1 (0.5%Carbopol-934), A2 (1.0%Carbopol-934) and A3 (1.5%Carbopol-934) were prepared. A1 showed low consistency and A3 showed very high viscosity. The gel formulation A2 (1.0% carbopol-934) exhibited desired consistency.

Carbopol-940 as a gelling agent: Formulations with formula B1 (0.5%Carbopol-940), B2 (1.0%Carbopol-940) and B3 (1.5%Carbopol-940) were prepared. B1 showed low consistency and B3 showed very high viscosity. The gel formulation B2 (1.0% carbopol-940) exhibited desired consistency.

Hydroxypropyl methyl cellulose as a gelling agent: Formulations with formula C1 (1.0%HPMC), C2 (1.5%HPMC), C3 (3.0%HPMC) and C4 (4.0%HPMC) were prepared. C1 and C2 showed low consistency and C4 was highly viscous. The formulation C3 (3.0%HPMC) exhibited desired consistency.

Sodium Carboxy methyl cellulose as a gelling agent: Formulations with formula D1 (2.0%SodiumCMC), D2 (3.0%SodiumCMC) and D3 (4.0% Sodium CMC) were prepared. D1 showed low consistency and D3 showed very high viscosity. The gel formulation D2 (3.0%SodiumCMC) exhibited desired consistency.

Evaluation of Acyclovir gels: All the optimized gel formulations were subjected to evaluation studies.

Estimation of drug content: The amount and percentage of drug present in gel formulation using different polymers were estimated as per the procedure. The prepared gel using 1% Carbopol- 934(A2) showed maximum drug content (101.72%) compared to other formulations.

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.

Determination of viscosity: The viscosity of the gels were determined using Brookfield Viscometer. The viscosity of the formulations were ranged from 36,000 to 51,000cps.

Extrudability: The extrudability of the gel formulations were checked as per the procedure. Extrudability of carbopol and HPMC gels were excellent than sodium CMC gel.

Determination of Spreadability: The spreadability of gels was determined as per the procedure. 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 Sodium CMC 3% were showed significant spreadability.

In vitro drug release of gel formulations:

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

- % Carbopol-934 shows maximum release (64.91%). The addition of DMSO as permeation enhancer improves the drug release from gel formulation.

- 1.0% carbopol-940 also showed a similar release pattern, but the release was lesser (51.47%). The addition of DMSO as permeation enhancer improves the drug release from gel formulation.

- In case of HPMC and Sodium CMC gels the release was much lesser than Carbopol gels. The addition of DMSO as permeation enhancer drug release was improved.

- Based on the drug release A2 (1.0 % carbopol-934) was the best formulation and the percentage release was found to be 64.91%. So, stability and In vivo studies were carried out for A2 formulation.

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 °C, Room temperature and 37±5 °C.

CONCLUSION

The present work describes a study on "Formulation and Evaluation studies of Acyclovir topical gels for Antiviral activity". Different formulations of Acyclovir were prepared by using Carbopol-934, Carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose in varying proportions. 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. In vitro release studies of the formulations were carried out across the cellophane membrane using a diffusion cell. The release was highest for the formulation A2 (1%Carbopol-934) and on the addition of DMSO as a permeation enhancer the drug release was improved. The formulation B2, C3 and D2 also have significant percentage release and on addition of DMSO as a permeation enhancer the drug release from gel formulation was improved. Hence based on the above results, out of 13 formulations A2 was chosen as the best formulation. Stability studies were carried out by placing the gels in collapsible tube at 4-5 °C, Room temperature and 37±5 °C for 3 months and also analysed for various physical and chemical parameters. The result indicates that the prepared gel was both stable physically and chemically at all storage conditions.

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