EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 9
514-517
Year: 2022

FORMULATION OF ACYCLOGUANOSIN BASED TOPICAL GELS FOR ANTI-VIRAL ACTIVITY

Piyush Dwivedi[1]*, Priyanka Rathore[2] and Dr. R. B. Goswami[3]

[1]Research Scholar, M.Pharm (Pharmaceutics), SIRTS-Pharmacy, Bhopal.
[2]Assistant Professor, Department of Pharmaceutics, SIRTS-Pharmacy, Bhopal.
[3]Director, SIRTS-Pharmacy, Bhopal.

***Corresponding Author: Piyush Dwivedi**
Research Scholar, M.Pharm (Pharmaceutics), SIRTS-Pharmacy, Bhopal.

Article Received on 21/07/2022 **Article Revised on 11/08/2022** **Article Accepted on 01/09/2022**

ABSTRACT
Acycloguanosin 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, carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose were used for formulation of gels and studied for their drug release from the gel formulations. 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 A_2 (1%carbopol-934) and on the addition of DMSO as a permeation enhancer the drug release was improved. The formulation b_2, c_3 and d_2 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 A_2 was chosen as the best formulation. Stability studies were carried out by placing the gels in collapsible tube at 4- 5^0c, Room temperature and 37±5^0c for 3 months and also analyzed for various physical and chemical parameters. The result indicates that the prepared gel was both stable physically and chemically at all storage conditions.

INTRODUCTION
Continuous intravenous infusion is recognised[1] as a superior mode of drug administration not only to by pass hepatic "first pass" metabolism, but also to maintain constant drug level in the body. This provides direct entry of drug into the systemic circulation but entails certain risks.[2]

Recently, the benefits of I.V. drug infusion can be duplicated without its hazards by using skin as the port of drug administration to provide continuous transversal drug infusion into the systemic circulation.[3]

Topical administration is employed to deliver a drug immediately at the point of application, so enough drugs is absorbed into the systemic circulation to cause therapeutic effects.[4] To provide continuous drug infusion through an intact skin, several topical formulations are used one of this is "Gels".[5]

Gels mainly used for the purpose of topical dosage form especially which is to deliver drug across a localized area of the skin.[6]

Gels are "Semisolid system in which liquid phase constrained within three dimensional polymeric matrix in which a high degree of physical or chemical cross liking has been introduced".[7] This network limits fluid flow by entrapment and immobilization of solvent molecules.[8]

This network structure is also responsible for a gel resistance to deformation and clear as water in appearance and visually aesthetically pleasing as in gelatin deserts, their clarity ranges from clear to whitish translucent.[9]

Preservatives may be incorporated into the gels especially for those prepared from natural sources. Appropriate preservatives depending upon the use and the gelling agent include the parabens (0.2%), benzoic acid (0.2%) and chlorcresol (0.1%).[10]

The gels, are being used more frequently in therapeutic and cosmetic because of several properties such as[11]

1. Semisolid state
2. High degree of clarity
3. Ease of application
4. Ease of removal and use.

The gels provide a faster release of drug substances, independent of water solubility of the drug.

MATERIALS AND METHOD

S.NO	Materials	Source
1	Acycloguanosin	Microlabs, Hosur
2	Carbopol-934	Kemphasol, Mumbai
3	Carbopol-940	Kemphasol, Mumbai
4	Hydroxy propyl methyl cellulose	Himedia LЬS, Mumbai
5	carboxy methyl cellulose- sodium	Kemphasol, Mumbai
6	Propyl paraben	NATIONAL Chemicals
7	Methyl paraben	NATIONAL Chemicals
8	Dimethyl sulfoxide	Suvidhinath LABSS, ьaroda
9	Triethanolamine	Reachem LABS, chennai
10	0.1M Hydrochloric acid	--------
11	Cellophane membrane	--------

FORMULATION OF GELS

Acycloguanosin 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.

Preparation of carbopol- 934 gels

Ingredients	Formula for 100gms		
	A_1(gms)	A_2(gms)	A_3(gms)
Acycloguanosin	1.0	1.0	1.0
carbopol-934	0.5	1.0	1.5
Triethanolamine	0.5	0.5	0.5
Purified water	98	97.5	97
Methyl paraben	0.002	0.002	0.002

Formulations with varying carbopol-934 concentrations
Procedure

1. Accurately weighed quantity of Acycloguanosin was dispersed in purified water with constant stirring and the drug solution was heated to 50^0c.
2. Methyl paraben was added as a preservative.
3. The carbopol-934 was added to the solution under stirring while
4. temperature Was maintained at 50^0c.
5. 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.

Preparation of carbopol- 940 gels

Ingredients	Formula for 100gms		
	b_1(gms)	b_2(gms)	b_3(gms)
Acycloguanosin	1.0	1.0	1.0
carbopol-940	0.5	1.0	1.5
Triethanolamine	0.5	0.5	0.5
Purified water	98	97.5	97
Methyl paraben	0.002	0.002	0.002

Formulations with varying carbopol-940 concentrations
Procedure

1. Accurately weighed quantity of Acycloguanosin was dispersed in purified water with constant stirring and the drug solution was heated to 50^0 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 50^0 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.

Ingredients	Formula for 100gms		
	d_1(gms)	d_2(gms)	d_3(gms)
Acycloguanosin	1.0	1.0	1.0
Sodium carboxy methyl cellulose	2.0	3.0	4.0
Purified water	97	96	95
Methyl paraben	0.002	0.002	0.002

Preparation of Hydroxy propyl methyl cellulose gels

Ingredients	Formula for 100gms			
	c_1(gms)	c_2(gms)	c_3(gms)	c_4(gms)
Acycloguanosin	1.0	1.0	1.0	1.0
Hydroxy propyl methyl cellulose	1.0	1.5	3.0	4.0
Purified water	98	97.5	96	95
Methyl paraben	0.002	0.002	0.002	0.002

Formulations with varying Hydroxy propyl methyl cellulose concentrations

Procedure

1. Accurately weighed quantity of Acycloguanosin was dispersed in purified water with constant stirring and the drug solution was heated to 50^0c.
2. The solution was maintained at 50^0c, HPMc was gradually added to the Solution under stirring until a thick viscous gel was formed.
3. Methyl paraben was added finally to the preparation as a preservative.
4. Formulation was allowed to settle down to room temperature

Preparation of Sodium carboxy methyl cellulose gels

Formulations with varying Sodium carboxy methyl cellulose concentrations

Procedure

1. Accurately weighed quantity of Acycloguanosin was dispersed in purified water with constant stirring.
2. Sodium carboxy methyl cellulose was added under stirring to the above solution.
3. Methyl paraben was added to the dispersion under stirring as a preservative.
4. The dispersion was allowed to stand for complete hydration of Sodium cMc. Finally the weight was adjusted to 100gm by adding purified water.

RESULT AND OBSERVATION

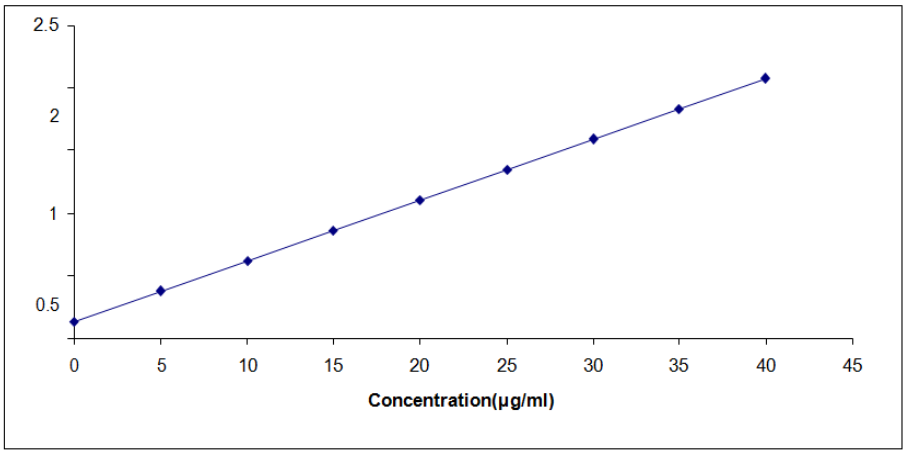
Standard curve of Acycloguanosin

100 mg of accurately weighed Acycloguanosin was dissolved in little amount of 0.1M hydrochloric acid and made up to required volume 100 ml with 0.1M hydrochloric acid.[41] 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.[42] The standard plot was made with concentration (µg /ml) on X axis and Absorbance on Y axis.

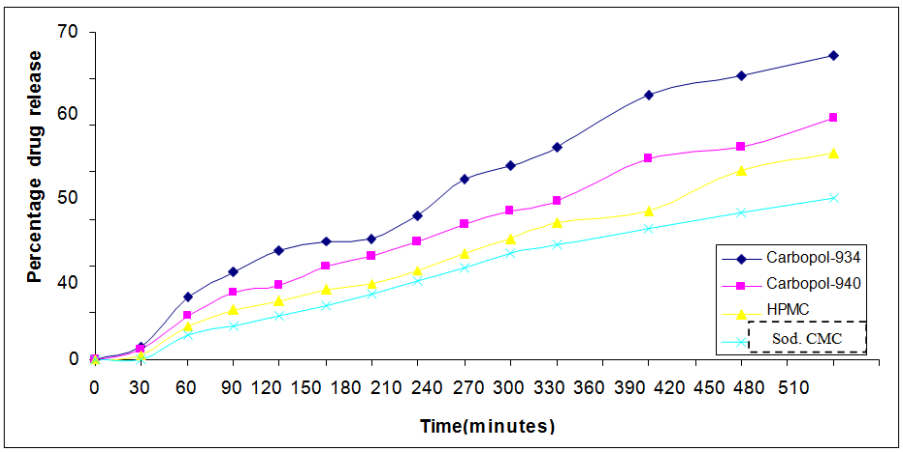
S.No	concentration (µg/ml)	Absorbance at 255nm
1	5	0.398
2	10	0.646
3	15	0.8978
4	20	1.119
5	25	1.346
6	30	1.514
7	35	1.725
8	40	1.948

r=0.9932 a=0.1366 b=0.0486

Standard curve of Acycloguanosin



Comparative in vitro release profile of Acycloguanosin from different gel formulations



CONCLUSION

Acycloguanosin 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, carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose were used for formulation of gels and studied for their drug release from the gel formulations. different formulations of Acycloguanosin 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. SodiumcMc 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 SodiumcMc gel.

The spreadability data shown that the formulation with 1% carbopol- 934 has the highest value (8cm), where as 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 A_2 (1%carbopol-934) and on the addition of dMSO as a permeation enhancer the drug release was improved. The formulation b_2, c_3 and d_2 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 A_2 was chosen as the best formulation.

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