IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2019 Vol.:16, Issue:2
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Formulation and Development of Topical Gel Containing Acyclovir for the Treatment of Herpes Simplex Virus Infection

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Submission: 23 August 2019
Accepted: 28 August 2019
Published: 30 September 2019

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Acyclovir, Carbopol 934, HPMC, Anti-viral Activity

ABSTRACT

The study was aimed to develop and evaluate antiviral gel containing Acyclovir as the chief constituent for the treatment of Herpex Simplex Infection. The objective of this study was to give a cooling effect and relief to the patient suffering from herpes infection. Acyclovir has a wide spectrum of antiviral activity against a various herpes virus, hence it is selected for the treatment of viral Infection. Acyclovir gel is formulated by using carbopol 934 & HPMC as a gelling agent, Acyclovir as a medicinal agent, DMSO IS used as drug solubilize & drug penetration enhancer, polyethylene glycol co-solvent, Methyl Paraben, and propyl Paraben as a preservative and needed an amount of water as vehicle. The prepared gel was evaluated for various properties such as viscosity, pH, spreadability, extrudability, drug content, stability study, etc. In-Vitro experiments demonstrated that the formulation F4 is a suitable dosage form for the treatment of Herpes Simplex Infection. Based on the result obtained in this present study, we conclude that the gel formulations of Acyclovir F4 showed good physicochemical properties as well as good drug content compared to other formulations.

INTRODUCTION

Infection with the herpes simplex virus is commonly known as herpes, can be due to herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2). HSV-1 is mainly transmitted by oral to oral contact to cause infection in or around the mouth (oral herpes). HSV-2 is almost exclusively sexually transmitted, causing infection in the genital area. However, HSV-1 can also be transmitted to the genital area through oral-genital contact to cause genital herpes infection. Both oral herpes infections and genital herpes infections are mostly asymptomatic but can cause painful blisters or ulcers at the site of infection.

Acyclovir (ACV), also known as acyclovir, is an antiviral medication.[3] It is primarily used for the treatment of herpes simplex virus infections, chickenpox, and shingles.[4] Other uses include prevention of cytomegalovirus infections following transplant and severe complications of Epstein-Barr virus infection.[4][5] It can be taken by mouth, applied as a cream, ointment or injected.[4]

Common aspect effects embody nausea and looseness of the bowels[4] Potentially serious side effects include kidney problems and low platelets.[4]Greater care is recommended in those with poor liver or kidney function.[4] It is generally thought to be used in a physiological state with no hurt having been discovered.[4][6] It appears to be safe during breastfeeding.[7][8] Acyclovir is a nucleic acid analog creat from guanosine.[4] It worked by less the production of the virus's DNA.[4]

The discovery of acyclovir was proclaimed in 1977.[9] It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.[10] It is on the market generic medication and is marketed beneath several whole names worldwide.[1] The wholesale cost as of 2014 to 2016 was between US$0.03 and US$0.12 for a typical dose by orally.[11][12] The cost of a typical course of treatment in the United States is less than US$25.[7]

Acyclovir is one such product exhibiting multiple benefits and has gained considerable importance in clinical research [4].

Since Acyclovir shows low intrinsic toxicity along with a wide spectrum of anti-viral actions against herpes simplex virus and varicella-zoster virus infection including Genital herpes simplex, Neonatal herpes simplex, Herpes simplex labialis, Acute chickenpox, Herpes

simplex encephalitis, Herpes of the eye. Its effectiveness in treating Epstein-Barr virus (EBV) infections is less clear [5].

The present study was aimed to formulate antiviral gel containing Acyclovir for the treatment of Herpes Simplex Infection and then evaluated for their physicochemical properties including drug content, spreadability, and extrude ability, viscosity, and stability study.

MATERIALS AND METHODS

MATERIALS:

Acyclovir is obtained as a gift sample from Torrent Pharmaceuticals Ltd. Methylparaben and propylparaben were procured from S.D. Fine chemicals Pvt. Ltd, Mumbai, India. All other excipients, Chemicals, and reagents from Sigma Aldrich Co.

METHOS:

Method of Preparation of gel:

The gels were prepared by soaking carbopol 934 and HPMC in water and by neutralizing with triethanolamine to pH 6.4. A weighed amount of methyl and propylparaben were added to the water before the addition of carbopol 934 [6]. In another beaker, the required quantity of DMSO and propylene glycol was taken in another test tube to which accurately measured the amount of Acyclovir corresponding to its MIC was incorporated and finally this mixture was added to the beaker containing carbopol and HPMC with stirring continuously till it forms a homogenous product [8]. The volume created with water and stirring was done smartly. All the ready gels were then subjected to analysis tests to pick the most effective formulation. The composition of different gel formulations is listed in Table No. 1.

Physicochemical characteristics of Acyclovir:

The Acyclovir was analyzed for physicochemical characteristics like color, odor, melting point, solubility as given in content of Table no.2.

Evaluation of gel formulation

Physical appearance:

- **Colour:** The color of the formulation was checked out against a white background.

- **Consistency:** The consistency was checked by applying on the skin.

- **Greasiness:** The greasiness has assisted by the applied on to the skin.

- **Odor:** The odor of the gels was check by mix the gel in water and takes the smell.

- **Determination of pH:** The pH of the gel was determined using a digital pH meter by dipping the glass electrode completely into the gel system [9].

- **Determination of viscosity**: Viscosities of the formulation gels was determined using Brooke field viscometer, spindle no. 7 and spindle speed 60rpm at 25◦C was used for gels, the corresponding dial reading on the viscometer was noted [10] in Table No. 3.

- **Determination of spreadability:**

Spreadability resolve by change picket block and glass slide equipment. The apparatus consisted of a wooden block with a fixed glass slide and a pulley [11]. A pan was attached to another glass slide (movable) with the help of a string [12-15]. For the determination of spreadability measured amount of gel was placed in the fixed glass slide, the movable glass slide with a pan attached to it, was placed on the fixed glass slide such that the gel was sandwiched between the two slides for 5 minutes. Now about 50 grams of weight was added to the pan [16-18]. Time taken for the slide to separate was noted down. Spread ability was determined using the following formula.

$$S = M.L/T$$

Where S is the spreadability in grams.cm/sec, M is the mass in grams; T is the time in seconds

- **Determination of extrudability:**

It was determined by employing a tube crammed with the gel, having a tip of 5mm opening and by measuring the amount of gel that extruded through the tip when the pressure was applied on the tube was noted.

- **Determination of homogeneity:**

All the developed gels were tested for homogeneity by visual inspection after the gels have been set in the container [19-20]. They were tested for his her look and presence of any aggregates.

- **Determination of drug content:**

The drug content of the gel formulations was determined by dissolving an accurately weighed amount one of gel in one hundred millimeters of solvent (a mixture of fermentation alcohol and phosphate buffer pH 6.8 for the formulation of Acyclovir). The solutions were kept for shaking for 4 hr and then kept for 6 hr for the complete dissolution of the formulations [21]. Then the solutions were filtered through 0.45 mm membrane filters and proper dilutions were made and solutions were subjected to the spectrophotometric analysis [22]. The drug content was calculated from the statistical regression equation.

- **Determination of pH:**

Weighed 50 g of each gel formulation were transferred in 10 ml of the beaker and measured it by using the digital pH meter. The pH of the topical gel formulation ought to should be between three – nine to treat the skin infections.

- **Skin irritation study:**

This study was distributed in healthy rats. The animals were divided into two group's i.e. control, Gel formulations F4. The back skin of area 5^2 cm was shaved before one day of starting the study. The study was carried out for 4 days. At the tip of the study, the animals were observed for any skin irritation like erythema or edema and score were given as per the irritation.

If the formulation produces a score of two or less, then it is considered to have no irritation.

- **Stability studies:**

Stability testing of drug product is as a section of drug discovery and ends with the business product, to assess the drug and formulation stability, stability studies were done. The stability study was distributed for the foremost satisfactory formulation. The most satisfactory formulation was sealed during a glass bottle and unbroken at thirty ± 2°C and forty ± 2°C at

R.H 65 ± 5 and 75 ± 5 RH for 2 months. At the end of 1 and 2 months, the samples were analyzed for the drug content and in vitro diffusion study.

RESULTS AND DISCUSSION:

RESULTS:

Table No.1: Composition of Acyclovir Gel Formulation

Ingredients	F1	F2	F3	F4	F5
Acyclovir (ml)	2%	2%	2%	2%	2%
Carbopol 934(g)	0.2	0.3	0.4	0.5	0.6
HPMC(g)	0.5	0.4	0.3	0.2	0.1
DMSO (ml)	1	1	1	1	1
Polyethyleneglycol 400 (ml)	10	10	10	10	10
Glycerine (ml)	5	5	5	5	5
Methylparaben(g)	0.18	0.18	0.18	0.18	0.18
Propylparaben(g)	0.02	0.02	0.02	0.02	0.02
Distilled water (ml)	qs	qs	qs	qs	qs

Table No. 2: Physicochemical characteristics of Acyclovir

Sr. No.	Parameter	Acyclovir (Ref)	Acyclovir (Std)
1	Colour	White	White
2	Odor	Strong	Strong
3	Texture	Smooth	Smooth
4	Appearance	White Transparent	White Transparent
5	Solubility In DMSO	Freely Soluble	Freely Soluble
6	Melting Point	256°C	256°C
7	pH	6.4	6.7
8	Viscosity	1291.84 CP	1289.83CP

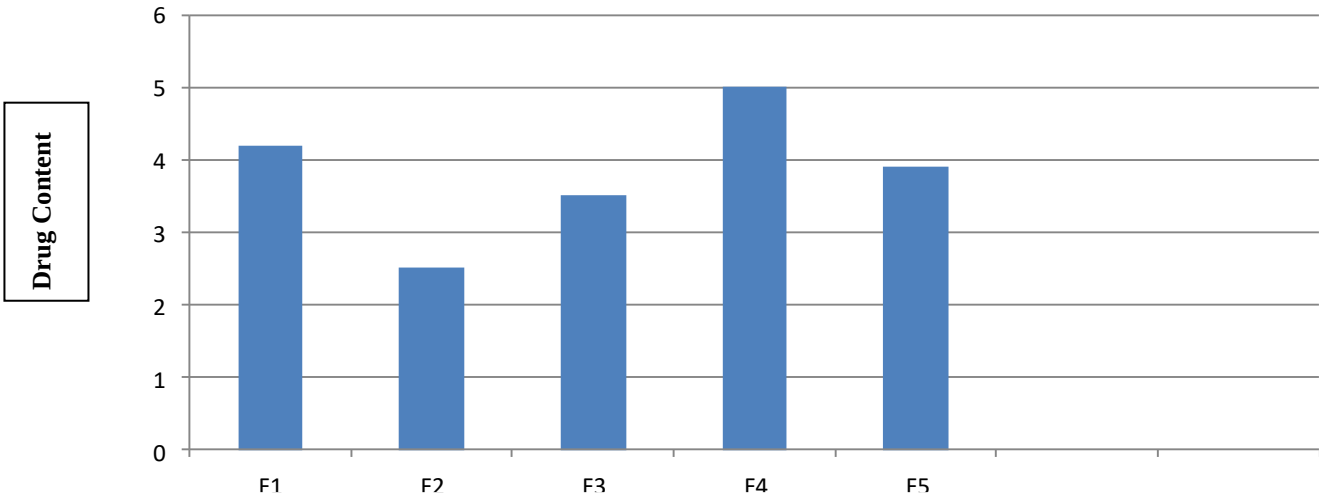

Figure No. 1: Drug Content of Acyclovir Gel Formulation

Table No. 3: Characteristics of Gel Formulation

Formulations	Appearance	pH	Spreadability (g-cm/sec)	Extrudability%	Homogeneity	Drug% content
F1	White	6.6	18.20	92.14	Good	95.00
F2	White	6.7	18.14	93.15	Good	95.20
F3	White	6.6	16.72	90.23	Good	93.62
F4	White	6.7	17.49	94.10	Very Good	95.40
F5	White	6.4	15.59	89.10	Good	89.80

Table No. 4: Stability study of Optimized formulation

Parameters	0 day	30 day	60 day	90 day
Appearance	No clog present	No clog present	No clog present	No clog present
Homogeneity	+++	+++	+++	+++
pH	6.5	6.5	6.5	6.4
% Drug Content	96%	96%	95.7%	95.40%

DISCUSSION

The procured Acyclovir was characterized for the following parameters:

The formulations were developed by using Acyclovir of same concentration and carbopol 934 and HPMC at different concentrations. Formulation composition is given in Table-1. All five batches of formulations were evaluated for physical properties. All the formulations were White in color and transparent. The pH of all formulations ranged from 6.4-6.7, which was well within the normal pH range of skin 6-7, which substantiates that the prepared gels will be irritation-free. Acyclovir was slightly soluble in an aqueous medium as compared to organic solvents. Acyclovir shows highest solubility in DMSO than other organic solvents. Acyclovir is already marketed in various dosage forms against infection of Herpes virus-like tablet, cream, ointment so it was effective against the Herpes virus and shows antiviral activity. Stability study of the developed formulation was performed according to International Conference on Harmonization (ICH) guideline and stability data of F4 indicate that optimized formulation exhibit good stability behavior regarding pH 6.4, appearance (no-clog present), homogeneity (+++) and Percentage drug content (95.40 %).

CONCLUSION

The Acyclovir gel formulation was assessed for its macroscopic characteristics and qualities such as Colour, Odour, Aroma, and Spreadability. The Acyclovir gel has a smooth texture and white color transparent with homogeneity. So according to this study, it was concluded that Acyclovir was successfully incorporated into carbopol 934 to obtain the gel. Therefore it was concluded that the formulation could be a very promising alternative for the topical application on the treatment of Herpes Simplex infection. However, some long term stability studies should be required.

ACKNOWLEDGMENT

Deep gratitude and appreciation of the Faculty of Pharmaceutical Quality Assurance, Dr. D. Y. Patil College of Pharmacy for the great help and valuable constructive co-operation in this work.

REFERENCES

1. Prorost C. Transparent oil-water gels. A review.Int J. Cosmet Sci. 1986: 8(3): 233-247.

2. Gupta A, Mishra AK, Singh AK, Gupta V, Bansal P. Formulation and analysis of topical gel of Voltaren diclofenac sodium using various polymers. Drug invention today 2010: 2(5):250-253.
3. Medscape Reference. WebMD. Archived from the original on 19 Feb 2014. Retrieved 5 Feb 2014.
4. De C, Erik F, Hugh J. Antiviral drug – the event of successful prodrug strategies for antiviral chemotherapy. British J. of Pharmacology. Jan 2006: 147 (1): 181-195.
5. Rashmi MS. Topical gel. A review. 2008: 6(3):244- 249.
6. The American Society of Health-System Pharmacists.Acyclovir. Archived from the original on Jan 5, 2015. Retrieved Jan 1, 2015.
7. Shivhare UD, Jain KB, Mathur VB, Bhusari KP, Roy AA. Formulation development and analysis of diclofenac sodium gel using water-soluble polyacrylamide polymer. Digest J Nanomet and Biostruct. 2009:4(2):285-290.
8. Rafailidis PI, Mavros MN, Kapaskelis A, Falagas ME. Antiviral treatment for severe herpes infection infections in apparently immunocompetent patients. J. of Clinic Medic: the Official Publication of the Pan American Society for Clinical Virology. 49 (3):151–157.
9. Golinkin HS. Process for fracturing well formulation using aqueous gels 1979; US patent no.US 4137182.
10. Prescribing medicines in pregnancy database. Australian Government. 3 March 2014.
11. Skin anatomy and physiology. (Online). 2009 Dec 16; obtain from: URL:http://www.essentialdayspa.com/epidermis-c 17.httm.
12. Hamilton, Richart. Tarascon Pocket Pharmacopoeia 2015. Deluxe Lab-Coat Edition. Jones & Bartlett Learning. 59.
13. Noreen H. Anatomy and physiology of the skin. DermatolNurs 2005: 17(1):62.
14. Stanely S. Transdermal drug delivery. MolInterv 2004: 4(6):308-12.
15. Clercq, edited by Erik De (2013). Anti-viral agents. San Diego, CA: Academic Press. p. 5. ISBN 9780124055377.
16. Girish C. Transdermal drug delivery systems. A review. (Online). 2006 Jan 12 (cited 2009 Jan 12); Obtain from: URL:http://www.pharmainfo.net/reviews/transder mal-drug-delivery-system-review.
17. International Drug Price Indicator Guide. Archived from the original on 5 March 2017. Retrieved 6 September 2015.
18. Gerry Fink and the Fink lab. How antifungal drug kill fungi and cure illness. (Online). 2005 Feb 9 (cited 2005 Feb 9);Obtain from: URL:http://www.medscape.com/viewprogram/296 3-pn.
19. Demuria D, Forrest A, Rich J. Pharmacokinetic and bioavailability of fluconazole in patients with AIDS. Antimicrob AgentChemother. 1993:37(10): 2187- 92.
20. Pappas PG, Rex JH, Sobel JD. Guidelines for treatment of candidiasis.Clin Infect Dis. 2004:346(4):161-89.
21. Baddley JW, Patel M, Bhavnani SM. Association of fluconazole pharmacodynamics with mortality in patients with candidemia. J Antimicrob Chemother. 2008:52(9):3022-8.
22. Sohrab E, Sahar K. Preparation of a fluconazole potentiometric sensor and its application to pharmaceutical analysis and drug recovery from biological fluids.Int J ElectrochemSci. 2009:4(2):1100-1108.
23. Marciniec B, Dettlaff K, Joroszkiewicz E, Bafeltowska J. Radiochemical stability of fluconazole in the solid-state. J Pharm Biomed Anal 2007:43(5):1879-1880.
24. Bennets JE, Blanton LL, Lazo JS, Parker KL, Goodman, Gilman. The pharmacological basis of, Ther J Chromatogr. 2006;12(5):1225-1227.
25. Koks CHW, Meen horst PL, Hillebrand MJX, Bult A, Beijnen. Pharmacokinetics of fluconazole in saliva and plasma when the administration of an oral suspension and capsules. J Antimicrobial Chemother. 1996:9(5):1935-1937.
26. Rathore RPS, Nema RK, Dulawat MS. Influence of the concentration of ketoprofen. J Global PharmaTechnol. 1999:6(5):135-139.
27. Willam GA. Randomized trial examination fluconazole with clotrimazole touches for the hindrance of flora infections in patients with advanced human immunological disorder viral infection. England J Medicine 1992:2(4):195-197.
28. David WD. Echinocandin antifungal drugs. The Lancet. Vol 362.Oct 4: 2003.
29. Abdelkader HB. Antimicrobial activity of rphapoticumacaule and scorzonera undulate growing wild in Tunisia. African J Microbio Res 2010:4(19):1954-1958.
30. Abdel EM. Chromatographic determination of clotrimazole, ketoconazole and fluconazole in pharmaceuticals formulation. IL formaco. 2002:57(7) 981-938.
31. Abdul RA. Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. N Eng J Med. 2002:346(12):211-213.
32. Sanjay D, Bhaskar M, Patel JR. Enhanced transdermal porosity of medicament DMSO from topical gel formulation. Int J Pharm Sci and Drug Res. 2009:1(1):13-18.