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Formulation And Evaluation Studies Of Anti-Hiv Topical Gels

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Abstract

The present work describes that Acyclovir drug is selected for the study becauseit 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 forformulation of gels and studied for their drug release from the gel formulations. It is evidence from the IR spectrum that all the polymers used in the gel formulations were compatible with the drug Acyclovir. 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 onaddition 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.

Keywords: Acyclovir, Topical application, Skin, Polymer.

INTRODUCTION

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

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.

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

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

The demanding expectations of topical include:

1. Formulation of gel should have both physical and chemical stability
2. Formulation that have one (or) more components are non-sensitizing, non-irritating.
3. Formulation should have acceptability of the patient.

4. Formulation must have ability to release therapeutic levels of drugs andvarious

factors influence the absorption through the skin.

SKIN CHARACTERISTICS[2-3]

The purpose of topical dosage form is to conveniently deliver drugs across alocalized area of the skin. Medications are applied to the skin in the form of ointments, creams, gels etc. The absorption of substances from outside the skin,

including entrances into the blood stream is referred to as percutaneous absorption. Itis necessary to understand the skin characteristics to develop an ideal topical dosage form.

SKIN[4-8]

The skin is an organ because it consists of tissues structurally joined together to perform specific activities. It is one of the larger organs of the body in terms of surface area. For the average adult, the skin occupies a surface area of approximately2 sq.m (3000 sq.inches)

It is a common site of administration for dermatological drugs to achieve a localized pharmacological action. Here, the drug molecules diffuse to a target in the skin to produce its action before it is distributed to the blood circulation for elimination.

The skin also serves as a port of administration for a number of systemically active drugs whereby those drugs applied topically are first absorbed into the blood circulation and then transported to the target for elicitation of its therapeutic effect.

GELS AS TOPICAL APPLICATION[9-12]

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”. This network limits fluid flow by entrapment and immobilization of solvent molecules.

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.

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%).

The gels, are being used more frequently in therapeutic and cosmetic becauseof several properties such as

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 solubilityof the drug.

GEL CHARACTERISTICS

Ideally, gelling agents should be inert, safe and non-reactive to other formulation components. The gelling agent should provide a reasonable solid like nature during storage that can be broken easily when subjected to the shear forces generated by squeezing a tube or during topical application. The gel should exhibit little viscosity change under the temperature variations of normal use and storage. The gel characteristics should match the intended use. A topical gel should not be tacky.

FORMULATION CONSIDERATIONS[13-17]

In the formulation of gel, the efficiency is often dependent on the composition of the vehicle. The ability of a drug in gel formulation to penetrate the skin and exert its effect depends on two consecutive physical events. The drug must first diffuse out of the vehicle to the skin surface and then, it must penetrate the natural barrier to enter into the site of action. Many so called 'Vehicle effects' reported in the literature are the consequences of these two diffusional processes. These two processes are intimately related and are dependent upon physico - chemical properties of the drug, vehicle and the barrier.

FORMATION OF GEL

All polymer solutions are prone to settling to gels because the solute consists of long flexible chains of molecular thickness that find to become entangled, attract each other by secondary valence force. Cross linking of dissolved polymer molecule also causes their solutions to gel.

Gel often contract on standing and some of the interstitial liquid is squeezed out. This phenomenon called syneresis is due to crystallization or the formation of additional contact points between polymer segments on aging.

Pharmaceutical gels are random coil networks and hence further discussion or random coiled will be worthwhile. Random coil relation mechanisms are rooted in the polymer-polymer and polymer-solvent interactions with a given polymer the gel network increases in strength with increase in polymer concentration this result in a reduction of interparticle distances which subsequently leads to chain entanglement and further development of cross links. Continual addition of polymer strengthens the gel network and results in increased resistance and viscoelasticity.

Although the gel network is basically formed through polymeric interactions,the nature of the polymer-solvent affinity, actually determines the integrity of the gel. Classical theory is distinguished between three categories of solvents.

1. Free solvents that are very mobile
2. Solvent bound as a salvation layer usually through hydrogen bonding
3. Solvent entrapped within the network structure.

The ratio of the three solvent types in a given gel, are dependent on the polymer concentration and the solvent affinity for the polymer. Solvent affinity governs the extension of this random coil. The greater the solvent affinities the more coil expands and entangles with adjacent coils to form cross-links.

In a good solvent, solvent molecules interpenetrate the polymer

chains and the salvation layer is enhanced, which facilitates random expansion and network formation. In a poor solvent, the polymer chain contract to minimize solvent contact reducing the effective number of cross-links and weakens the gel network structure.

Gelation theory can be readily applied when formulating gel products and some of the desirable attributes of gel formulations are in the following order. For optimum consumer appeal the gel should have good optical clarity and sparkling appearance. To preserve product integrity, the gel should maintain its viscosity at all temperatures.

Experimental work

Formulations with varying Carbopol-940 concentrations

Procedure

1. Accurately weighed quantity of Acyclovir was dispersed in purified waterwith 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 wasmaintained at 50^0 C.
4. The dispersion of gelling agent was neutralized by addition of triethanolaminesolution to attain the neutral pH. Stirred slowly till a clear gel was obtained.

Preparation of Hydroxy propyl methyl cellulose gels

Ingredients	Formula for 100gms			
	C_1(gms)	C_2(gms)	C_3(gms)	C_4(gms)
Acyclovir	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

Table 1: Formulations with varying Hydroxy propyl methyl celluloseconcentrations

Procedure

1. Accurately weighed quantity of Acyclovir was dispersed in purified water withconstant stirring and the drug solution was heated to 50^0 C.
2. The solution was maintained at 50^0 C, HPMC was gradually added to theSolution 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

Ingredients	Formula for 100gms		
	D_1(gms)	D_2(gms)	D_3(gms)
Acyclovir	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

Table No 2: Formulations with varying Sodium carboxy methyl cellulose concentrations

Procedure

1. Accurately weighed quantity of Acyclovir was dispersed in purified water withConstant stirring.

2. Sodium Carboxy methyl cellulose was added under stirring to the abovesolution.

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.

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 and In-vivo study by using Albino Rabbits.

Standard curve of Acyclovir

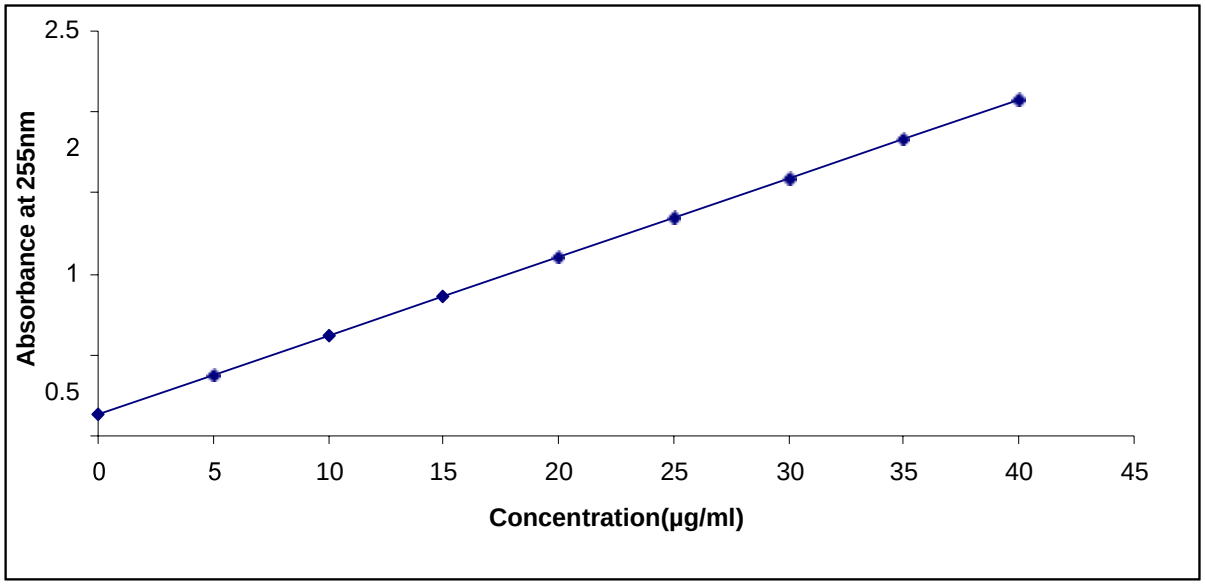
100 mg of accurately weighed Acyclovir was dissolved in little amount of 0.1M hydrochloric acid and made up to required volume 100 ml with 0.1M hydrochloric acid[41]. So that each ml of stock solution required concentration of 5, 10,15, 20, 25, 30, 35 and 40 µg/ml was made up with 0.1M hydrochloric acid. 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.

Table 3: Standard curve of Acyclovir

S.No	Concentration (µg/ml)	Absorbance at 255nm
1	5	0.399
2	10	0.647
3	15	0.896
4	20	1.119
5	25	1.347
6	30	1.513
7	35	1.726
8	40	1.947

r=0.9932 **a=0.1366** **b=0.0486**

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 curveand the percentage drug content in different formulations was calculated. Results were tabulated as follows

Formulation	**Drug content (mg)**	**Drug content (%)**
A_2	10.172	101.72
B_2	9.81	98.1
C_3	9.78	97.8
D_2	9.69	96.9

Table 4: Drug content in the gel formulations

Results and discussion

Table 5: Drug release profile of Formulation A_2 (1% Carbopol-934)

Time (minutes)	Absorbance at 255nm	Concentration (µg/ml)	Amount of drug release(mg)	Percentage drug release*
30	0.205	1.407	0.281	2.81
60	0.461	6.674	1.334	13.34
90	0.592	9.370	1.874	18.74
120	0.705	11.695	2.339	23.39
150	0.747	12.559	2.511	25.11
180	0.763	12.880	2.577	25.77
210	0.884	15.378	3.075	30.75
240	1.074	19.286	3.857	38.57
270	1.143	20.707	4.141	41.41
300	1.237	22.641	4.528	45.28
360	1.516	28.382	5.672	56.72
420	1.610	30.316	6.063	60.63
480	1.714	32.456	6.491	64.91

*Average of three readings

Table 6: Drug release profile of Formulation B_2 (1% Carbopol-940)

Time (minutes)	Absorbance at 255nm	Concentration (µg/ml)	Amount of drug release (mg)	Percentage drug release*
30	0.186	1.016	0.203	2.03
60	0.365	4.699	0.934	9.34
90	0.481	7.086	1.417	14.17
120	0.520	7.888	1.577	15.77
150	0.617	9.884	1.976	19.76
180	0.676	11.098	2.219	22.19
210	0.747	12.559	2.511	25.11
240	0.843	14.534	2.906	29.06
270	0.906	15.831	3.166	31.66
300	0.963	17.004	3.400	34.00
360	1.184	21.551	4.310	43.10
420	1.243	22.765	4.553	45.53
480	1.394	25.872	5.147	51.47

*Average of three readings

Table 7: Drug release profile of Formulation D_2 with Dimethyl sulfoxide

Time (minutes)	Absorbance at255nm	Concentration(µg/ml)	Amount of drug release (mg)	Percentage drug release*
30	0.194	1.181	0.236	2.36
60	0.304	3.444	0.688	6.88
90	0.396	5.337	1.067	10.67
120	0.464	6.736	1.347	13.47
150	0.497	7.415	1.483	14.83
180	0.583	9.185	1.837	18.37
210	0.612	9.781	1.956	19.56
240	0.698	11.551	2.310	23.10
270	0.761	12.847	2.569	25.69
300	0.864	14.967	2.993	29.93
360	0.938	16.489	3.297	32.97
420	1.042	18.629	3.725	37.25
480	1.163	21.119	4.223	42.23

*Average of three Readings

Table 8 Compare the percentage release of Acyclovir from gel formulations withand without Dimethyl sulfoxide (DMSO).

Time (Mins)	Gel Formulations				Gel Formulations with DMSO			
	A_2	B_2	C_3	D_2	A_2	B_2	C_3	D_2
30	2.81	2.03	1.04	-----	4.50	3.18	2.65	2.36
60	13.34	9.34	7.21	5.44	15.53	10.75	10.67	6.888
90	18.74	14.17	10.67	7.25	20.96	16.64	13.888	10.67
120	23.39	15.77	12.60	9.23	25.69	20.46	15.90	13.47
150	25.111	19.76	15.07	11.41	27.46	23.30	19.64	14.83
180	25.77	22.19	16.27	13.88	28.24	24.04	22.85	18.37
210	30.75	25.111	18.98	16.72	33.34	31.86	25.07	19.56
24	38.	29.0	22.6	19.6	41.3	34.8	27.9	23.1

0	57	6	5	0	3	7	5	0
270	41.41	31.66	25.77	22.60	46.88	38.53	32.73	25.69
300	45.28	34.00	29.19	24.58	52.22	40.63	35.65	29.93
360	56.72	43.10	31.58	27.95	62.32	49.64	39.81	32.97
420	60.63	45.53	40.30	31.53	68.37	54.50	46.68	37.25
480	64.91	51.47	44.04	34.54	72.85	60.42	51.74	42.23

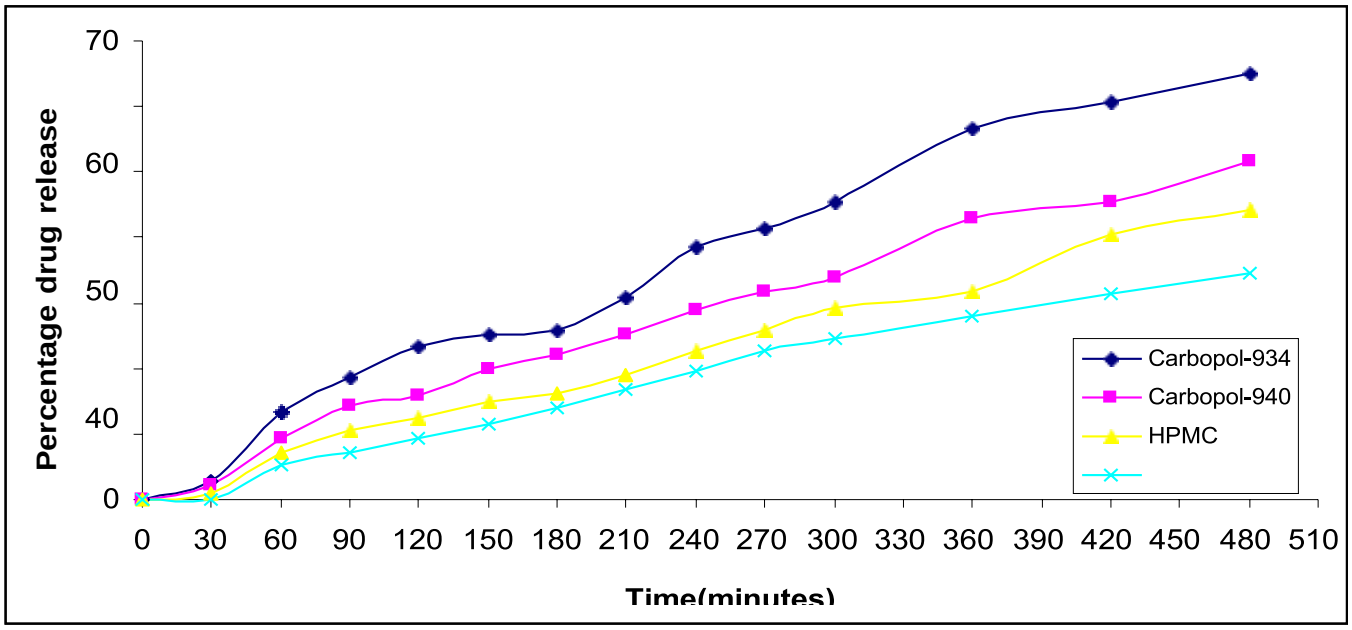


Figure 2: Comparative in vitro release profile of Acyclovir from different gel formulations

Conclusion

Different formulations of Acyclovir were prepared by using Carbopol-934, Carbopol-940, Hydroxypropyl methyl cellulose and Sodium carboxy methylcellulose 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 from36,000 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 hasthe 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 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 onaddition 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 bothstable physically and chemically at all storage conditions.

From the skin irritation test it was observed that the formulation A_2 wasfound to be safer for topical use.

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