J. Pharm. Biomed. Sci., 2(5)53-58, 2012

ISSN 2090 – 424X
Journal of Pharmaceutical and Biomedical Sciences
www.textroad.com

Characterization of Glycolic Acid Transdermal Gel: The Impact of Polymeric Base and Co-solvent on Release Pattern

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ABSTRACT

It is well known that proper skin care is essential for having beautiful skin. In order to make this occur there are many facial skin rejuvenation treatments and products. Thus, in this study, skin care gels containing 15% glycolic acid using Hydroxypropyl methycellulose (HPMC) or Hydroxyethylcellulose (HEC) or carbomer as gel forming agent were prepared. Also glycerin (in concentration 5, 10%) and propylene glycol (in concentration 5-30%) as co-solvent were used. Also Tween 80 in concentration 0.25 to 1% as surfactant was added to the formulation made of HPMC base and its release behaviour was investigated. To adjust pH of the product, buffer phosphate pH 6.8 was used and then the capacity of buffer was increased 4 folds. Finally triethanolamin (TEA) was added in concentration 1, 2, 5 and 10% as alkaline agent. The pH of product reached to 3.8 at the highest concentration (10%) of TEA. Data obtained from drug release study showed that the release pattern from formulations containing 10% propylene glycol in both gel forming agents (HPMC & HEC) improved significantly more than the other formulations. In this research stability studies showed that the formulation containing HEC using 10% propylene glycol found to be more stable (regarding chemical stability) compared to gels containing HPMC. The shelf life of 164 days was obtained for formulation containing HEC, whereas formulation containing HPMC had showed a 27 day shelf-life. Antimicrobial stability and efficacy of preservative was investigated according to USP experimentally and the effectiveness of methyl paraben was proved. At the end the formulation containing HEC was selected as the best formulation.

KEY WORDS: Hydroxypropyl methycellulose (HPMC), Hydroxyethylcellulose (HEC) ,Glycolic Acid(GA).

1- INTRODUCTION

Aging process begins from birth and continues during life time (1). Skin aging is the result of some reactions in dermis, epidermis, pigment cells, hair follicles, sebaceous glands, blood vessels and sensory organs (2).The process leads to increase in stratum corneum layer, the phenomenon which is responsible for skin scaling, wrinkling and roughness (3). Alphahydroxy acids (AHAs), also called fruit acids are among non-organic compounds used in treatment of skin aging (4, 5). AHAs interfere in metabolic pathways and basic cellular cycles, such as Krebs cycle, glycolysis and serin biosynthesis (6). They are used in the treatment of several dermal conditions such as acne, scar, pigmentation, skin dryness, wrinkling and also for reduction of adverse effects of UV radiation (5, 7). Glycolic acid (GA) is the smallest member of AHAs, extracted from sugar cone (5). Formulations containing GA are currently used topically, vaginally and rectally or as ophthalmic preparations for treatment of skin aging and sunlight induced hyperpigmentation (8-11). The objective of the present study was to formulate a dermal preparation of glycolic acid and to evaluate the effect of polymer nature and other formulation factors on the stability and release profile of the drug.

2- MATERIALS AND METHODS

Glycolic acid, hydroxypropylmethyl cellulose (HPMC), hydroxylethyl cellulose (HEC), carbomer 940, methyl paraben, glycerin and propylene glycol (PG) were obtained from Merck, Germany.

Formulation of Gels

Different amounts of HPMC were weighed and dissolved in 70% of total water volume. Deionized water was preserved by adding 0.2% methyl paraben. The solution was then stirred at high shear rates. After complete wetting, the remainder of deionized water was added to make gels with different (1, 2, and 3%) concentrations (12). The prepared formulations were then refrigerated for 24 hours to ensure complete hydration and

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deaeration. HEC based gels were prepared by adding 1, 2, 3, 4 and 5 (w/w) percent of the polymer to preserved deionized water and then warmed to 60-70 oC to acquire the proper viscosity (12). Carbomer was added to hot water. After complete dispersion, the remainder of cold water was added, and then 2-3 drops ethanolamine was added to clarify the gel. The final concentration of GA in each formulation was 15% (w/w). In case of presence of co-solvent, the drug was primarily dispersed in co-solvent (glycerin or PG), and then the other ingredients were added (13). The exact amount and the composition of different formulations are tabulated in tables 1 and 2.

3- RELEASE STUDY

In vitro release measurement was performed using a vertical Franz diffusion cell, in which the diffusion area was 3.46 cm2 and dialysis membrane (cellulose, 12KD) was used as semi-permeable layer. Prior to the experiment, the membrane was immersed in deionized water for 24 hrs and then it was placed between the chambers. Donor chamber was containing formulated gels and the receptor compartment was filled with 0.1% HCl solution. The temperature was maintained at 32±0.50C. While stirring at 600 rpm, 5 ml samples were drawn at definite intervals and subjected to titration. To maintain the sink condition, it was replaced by 5 ml of the receptor phase (14,15,16). The results were plotted as the release percent vs. time (or log time). Comparing the R2, SE and F, the release model was detected.

4- STATISTICS

All in vitro experiments were carried out in triplicate and presented as mean±standard error (SE). Statistical analyses of the data were performed using ANOVA and students t- test with the level of significance set at $p < 0.05$.

5- RESULTS

The results of drug release from different formulations are shown in table 3. The parameters included in the table are t50, t15, SS, k, n and R2. Comparing the release parameters (F1 to F4), F2 showed the best release parameters and therefore it was selected for the study of the effect of surfactants (F5 to F7). In F8, triethanolamine (TEA) was added to maintain the gel pH at optimum value (4.5-6). The release profile of GA from gels containing 2% HPMC in combination with different concentrations of PG are shown in figure 1. The effect of addition of TEA is plotted in Figures 3 and 4. The efficacy of preservatives which was determined according to USP method showed no fungal growth during the first month of storage, assayed at 1 week intervals. Results of stability study showed that the shelf-life of the HPMC and HEC based gels at 25oC were 27 and 164 days, respectively. Also, there was no significant change in pH during and after storage at different temperatures ($p>0.05$). The viscosity of all of the formulations decreased when temperature rose to 50oC. In such a temperature, the HPMC based formulation showed phase separation phenomenon. In addition, regarding the odor and color characteristics, all of the formulations showed no significant change.

Formulation	Polymer	%
F1	HPMC	2
F2		3
F3		4
F4	HEC	1
F5		2
F6		3
F7		4
F8		5
F9	Carbomer	0.5
F10		1

Table 1. The composition and concentration of ingredients in primary formulations of gel base.

Formulation	Polymer	PG (%)	TEA	Tween 80 (%)
F11	HPMC 2%	0	-	-
F12		10	-	-
F13		15	-	-
F14		20	-	-
F15		10	-	0.25
F16		10	-	0.5
F17		10	-	1
F18		10	10	-
F19	HEC 5%	0	-	-
F20		10	-	-
F21		20	-	-
F22		30	-	-
F23		5	10	-

Formulation	Polymer	n	k	ss	t15 (min)	t50 (min)	R2
F11	HPMC 2%	0.634	2.94	1.23	15.0	84	0.9989
F12		0.681	2.59	13.50	3.8	85	0.9939
F13		0.724	1.98	13.60	19.0	81	0.9964
F14		0.750	1.82	34.10	20.0	77.5	0.9943
F15		0.697	2.38	32.00	16.9	74	0.9922
F16		0.710	2.37	15.60	16.3	68.3	0.9940
F17		0.730	2.02	16.50	8.3	85.9	0.9992
F18		0.797	1.60	0.77	12.9	80.3	0.9964
F19	HEC 5%	0.674	2.89	53.30	15.5	65	0.9957
F20		0.525	6.11	21.50	6.0	53.5	0.9944
F21		0.696	2.43	46.60	16.5	71.5	0.9962
F22		0.671	2.63	11.10	15.5	75.5	0.9990
F23		0.641	3.23	25.80	14.0	68.9	0.9974

Table 2. The composition and concentration of ingredients in final formulations of Glycolic acid gel.

Table 2. Release parameters (n, k and ss), regression coefficient (R^2), time needed for 15% release and the time needed for 50% release of Glycolic Acid from final formulations of Glycolic acid gel.

Finally, the release profile of selected HPMC and HEC based formulations is shown in figure 5. It can be seen that the release profiles does not differ significantly in the first 150 minutes of the study ($p>0.5$), while there was a significant increase in drug release for HPMC based gels after 3 hours.

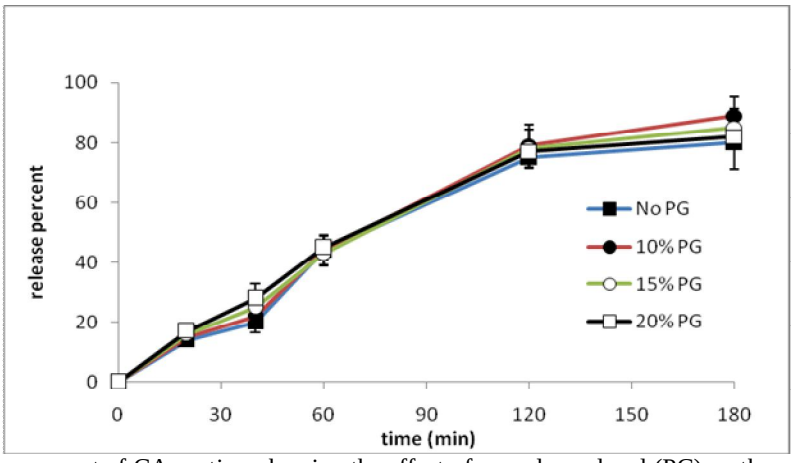

Figure 1. Release percent of GA *vs.* time showing the effect of propylene glycol (PG) on the release pattern of HPMC based gels.

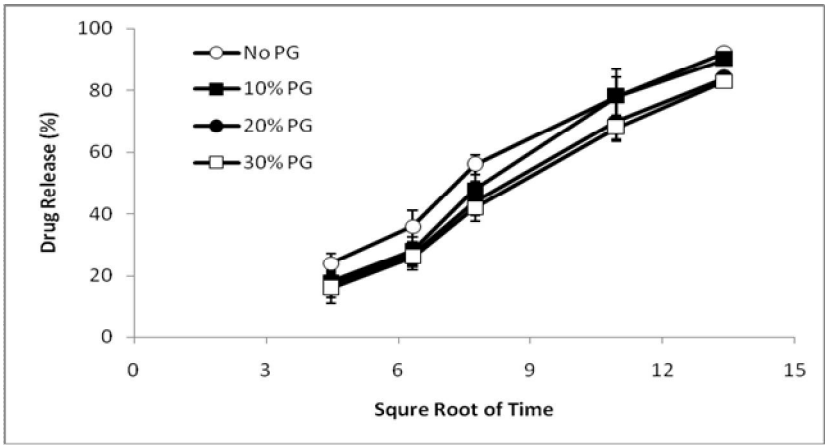

Figure 2. Release percent of GA *vs.* square root of time showing the effect of propylene glycol (PG) on the release pattern of HEC based gels.

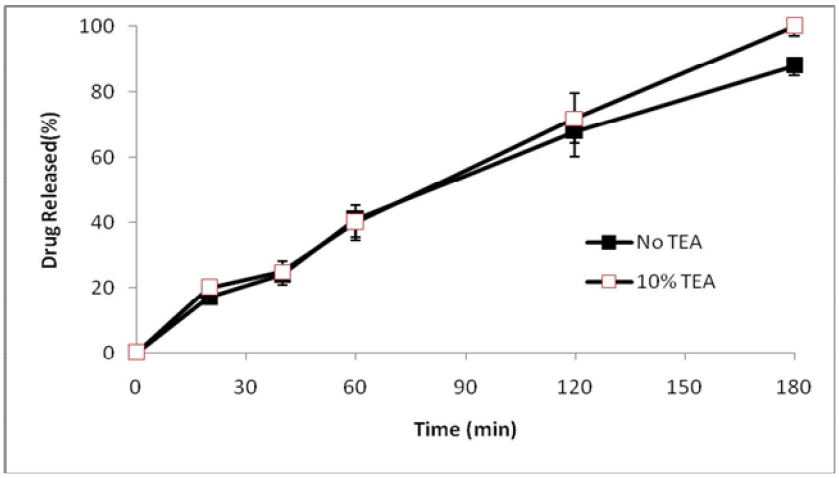

Figure 3. Release percent of GA *vs.* time showing the effect of triethanolamine (TEA) on the release pattern.

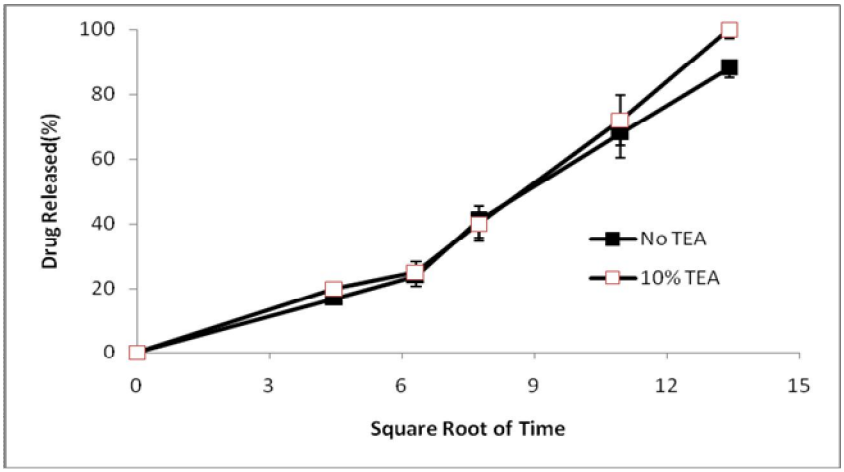

Figure 4. Release percent of GA vs. square root of time showing the effect of triethanolamine (TEA) on the release pattern.

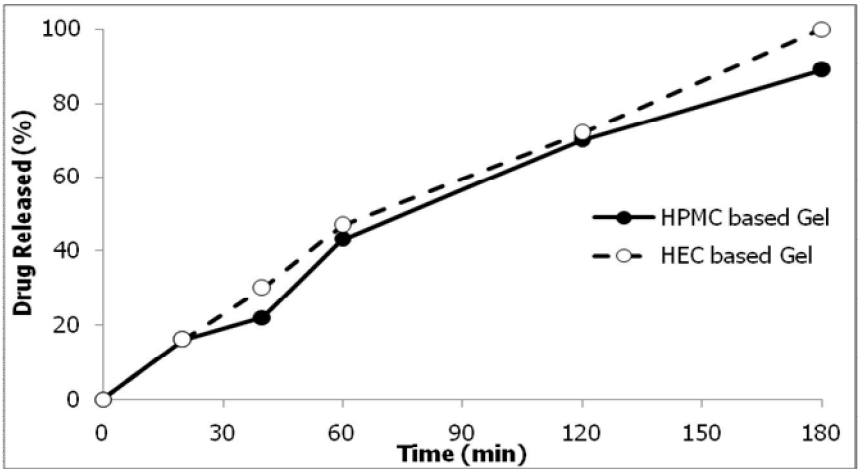

Figure 5. Release percent of GA versus time, showing the effect of polymer (HEC and HPMC) on the release pattern.

6- DISCUSSION

Several studies have shown the effectiveness of GA in the treatment of skin conditions. Evaluation of different formulations, containing 8% GA or lactic acid significantly showed the effectiveness of both compounds in the healing of dermal disorders when compared to placebo (17). Results of another study showed that application of alph-hydroxy acids in cosmetic preparations, in addition to proper hydration of skin, may heal sunshine induced wrinkles and lesions. It was suggested that the decrease in dermal fatty component of skin layers may be responsible for such effects (18). The effect of GA in skin peeling has been reviewed previously. They claimed that the presence of trichloroacetic acid improves the effect of GA in skin peeling and healing of wrinkles. They suggested that their formulation may be applied for peeling in body surfaces except for facial area (19). According to our results, the viscosity of gel base increased significantly with increasing of carbomer, HPMC and HEC concentration, while there was no significant change in transparency of the gels. Comparing different polymers regarding their physicochemical and rheological characteristics, 1% carbomer showed a better ability and effectiveness in gel forming phenomenon. After addition of GA, there was an intensive decrease in viscosity of carbomer based gels. The incompatibility of carbomer with acidic media has been previously reported by several authors (13, 20, 21). It is suggested that due to the acidic nature of GA, it completely depolymerize carbomer and the viscosity falls significantly. Therefore, carbomer was completely omitted from the study. In the next step, it was tried to increase the transparency of HEC and HPMC based gels by adding a co-solvent. Glycerin (5-10%) did not affect the turbidity of gels, while PG in concentrations of 5, 10 and 20 % significantly improved the properties of the HPMC containing gels. The study of release behavior showed the effect of PG on the release pattern of HPMC based gels. The results demonstrated that except for the formulation containing 10% PG which showed a zero order release, the release behavior of the other formulations follows Higuchi model. To improve the release pattern of the formulations, Tween 80 was added to gels. Although there was no increase in n factor for all of the formulations, the values were not statistically significant ($p>0.05$).

In conclusion, regarding physical stability and appearance, and also release profiles of different formulations, the 15% GA gel containing 2% HPMC, 10% TEA and methyl paraben was selected as the final preparation.

7- Acknowledgement

The paper is issued from Pharm.D. Thesis of Bahareh Rezaee and financially supported by Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

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