RESEARCH ARTICLE

Development and Characterization of anti aging topical Gel: An approach towards Gerantology

Upendra Nagaich, Promila Sharan*, Rajeev Kumar, Spriya Sharan, Neha Gulati, Amit Chaudhary

Department of Pharmaceutics, School of Pharmacy, Bharat Institute of Technology, Partapur By-Pass Road, Meerut-250103 [U.P.] India

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ABSTRACT

Turning younger is on the priorities now days where caffeine is being used topically as one of the main ingredient in pharmaceutical products and at a glance in the world of cosmetics for various skin related problems like wrinkles, puffy eyes, dark circles etc.The present research work was carried out to develop caffeine loaded sustained release topical gel of Caffeine. For a suitable formulation Caffeine was used in varying concentration of two different polymers Carbopol 934 & HPMC K4M and three different formulations were prepared. Using dispersion method the gel was prepared and kept for 2h later glycerol as penetration enhancer, and Triethanolamine as cross-linking agent, NaOH to adjust pH up to 7 - 7.4, methyl para benzoate as preservative. Then the gel was evaluated for its pH, clarity, viscosity, spreadibility, drug content, *in vitro* release, drug release kinetics and stability studies. For the optimized formulation F2 the pH was in the range of 7.2 -7.4. The viscosity 65,000 to 76,000 cps, spreadibility 276.21gm.cm per 2.54 min for, drug content 99.00 % for F2, the *In-Vitro* Drug Release 96.89 % for F2. Higuchi release kinetics was applied and Quasi Fickian Diffusion and as per stability studies F2 found to more stable in case of appearance and drug content. From the conducted research we can conclude that Carbopol 934 & HPMC K4M in 1.5% and 0.5% concentration gives us an optimized Topical Gel.

Keywords: Caffeine, Carbopol Gel, Puffy Eyes, Anti Aging.

INTRODUCTION

The most accessible route of administration is topical route if the action to be observed is localized as patient can comply with it easily. Topical drug delivery system refers to application of a drug on the surface of the skin so as to treat dermal disorders [1].

Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid with in a three dimensional polymeric matrix in which cross linking plays a vital role. Topical gels are basically the dosage forms which are applied on to the skin and do not allows its penetration to the systemic circulation and shows localized action [2]. As skin is most accessible organ on human body therefore it becomes easy to administer. The topical formulation reduce GIT irritation and also it by-pass first pass metabolism, which enhance the bioavailability of the drug with a fast onset of action for treating the skin than any other drug delivery system [3]. These are less greasy then ointments hence can be easily removed from skin if any irritation is observed. The topical administration of drug is often opted in order to achieve optimal therapeutic effect as cutaneous and percutaneous drug delivery has recently gain an importance because of numerous advantages as they can avoid gastrointestinal irritability by gastrointestinal pH and enzymatic activity [4]. They can substitute for oral administration of medication when that route is unsuitable. To avoid the first pass effect, of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme. They are non-invasive and have patient compliance. They are less greasy and can be easily removed from the skin [5].

Caffeine which is having an anti aging property as it contains anti oxidants. It constricts small blood vessels and reduce redness in skin, reduce puffiness,

Address for correspondence

Ms. Promila Sharan
Dept. of Pharmaceutics,
School of Pharmacy, Bharat Institute of Technology,
Partapur By-Pass Road, Meerut-250103, India.
Email: promilasharan@gmail.com

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also it minimize the dark circles and this quality serves caffeine as an ingredient. Caffeine due to its dehydrating properties is used to draw out excess fluid from fat cells to improve skin's appearance. It is not absorbed by body tissues and is totally safe for human consumption. It is having bioavailability 99% then $t_{1/2}$ 5h and the excretion is 100% via urine [6]. Test for toxicological tolerance show that it does not have pronounced physiological action and is non toxic nature. Due to its stimulant action it provides relaxation and removes dark circles [7]. Drug products which are topically administered through skin fall into two general categories, one which are applied for local action and another for systemic effects. Local actions include where formulation acts at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis as shown in fig-I [3, 6, 7]. Carbopol polymers have demonstrated zero-order and near zero-order release kinetics [8]. These polymers are effective at low concentrations (less than 10%) and feature extremely rapid and efficient gelation characteristics under both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) test conditions. A penetration enhancement of drugs after topical application can be achieved by several compounds which are able to promote the transport of actives across the skin barrier for which alcoholic solution was used [9].

Thus, the objective of present research work was to formulate and evaluate anti aging topical gel of caffeine using Carbopol 934 and HPMC K4M as gel forming polymers and also to study the effect of varying the polymer concentration on in vitro drug release as well [10].

MATERIAL AND METHODS

Materials:

Caffeine anhydrous was received as gift sample from Hi Media Laboratories Pvt. Ltd, Mumbai, India. Carbopol-934 and HPMC K4M, Triethanolamine, glycerol, Methyl para benzoate were purchased from Central Drug House, New Delhi. All other chemicals used were of analytical grade and used without further modification.

Preparation of Caffeine Loaded Topical Gels:

Caffeine loaded topical gels were prepared by dispersion method using carbopol 934 and HPMC K4M [11]. All the accurately weighed ingredients were taken in quantity as shown in Table 1. Then, Carbopol-934 and HPMC K4M were dispersed in water and kept aside for 4 hours for proper swelling of polymer. Caffeine was dissolved in 10% v/v ethanol which acts as penetration enhancer [8, 11] and was added to gel with constant unidirectional mixing so as to avoid incorporation of air bubbles to it. The gel mixture was mixed with a magnetic stirrer and then sonicated to remove air bubbles. Triethanolamine was subsequently added to caffeine loaded polymeric mixture of carbopol 934 and HPMC K4M so as to enhance the cross linking between polymer which results in clear gel formation. Then, Glycerol was added to the gel to balance its viscosity and the pH was adjusted to skin pH with the help of 0.1N NaOH [12].

CHARACTERIZATION OF TOPICAL CARBOPOL GEL OF CAFFEINE

The basic physicochemical parameters were studied for the developed formulation.

Physical Appearance

The prepared gel formulations were inspected visually for their color, clarity, homogeneity and appearance. As shown in table 2 [5, 13].

Formulation pH

The pH values of 1% aqueous solutions of the prepared gels were measured by a pH meter (Systronics, 361-micro pH meter). 1 gm of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated, as shown in table 3, [5, 14].

Viscosity

To measure the viscosity, all the formulated gels were taken in beakers and placed beneath the spindle and the spindle was rotated at 10 rpm in Brook Field Viscometer was used fitted with RV-7 spindle and10 rpm speed As shown in table 3 [5, 15].

Spreadibility

The Spreadibility of the gel was evaluated by using slides method. 1gm of gel was kept between the two slides. The preweighted plate was kept above the gel and more weights were added on the plate until the gel stop spreading. Final cumulative weight and the total time taken by the gel to spread was measured and noted. Then total weight applied and mass of the gel were compared by the time as shown in table 3 [15].

Spreadibility= Mass x Length/ Time

Drug Content

To determine the drug content of gel, 10 mg of caffeine loaded gel was weighed and mixed to the phosphate buffer saline (PBS pH 7.4) and the concentration of caffeine was spectrophotometrically (UV 1601, Shimadzu, Japan) measured at 273 nm. The gel base containing the identical amount of ingredients without caffeine was used as a blank [14].

In-Vitro Drug Release Studies

The *in-vitro* drug release was evaluated with the help of Franz Diffusion cell. The 2.5 g of each gel was placed in a donor compartment. The receptor compartment was filled with 10 ml PBS (pH 7.4), thermo regulated at 37^{o}C and magnetically stirred at 400 rpm with a semi permeable membrane area of 1.8 cm^{2}. The 2 ml of receptor fluid was withdrawn at an interval of 0.5, 1, 2, 3, 4, 8 and 10 h. An equal volume of PBS was simultaneously added to the receptor compartment after each sampling to maintain sink conditions. Each sample was filtered through a 0.45 um polyamide membrane filter (Sartorius AG, Germany) and then determined for caffeine content by UV spectrophotometer [8, 9]. The concentrations of all the formulations were calculated and then the % drug content release was determined, as shown in Figure 1. [16].

In Vitro Drug Release Kinetics

The various kinetics equations were then accorded to the obtained data from *in vitro* release. The kinetic models used were: Zero Order (cumulative amount of drug release vs. Time), First Order (log cumulative percentage of drug remaining vs time), Higuchi model (cumulative percentage of drug release vs. square root of time) and Korsmeyer and Peppas (log cumulative percent drug release *vs.* log of time) [11, 12].

Zero-Order Kinetics: $Qt = K_0t$ (1)

Where K_0 represents the zero-order rate constant expressed in units of concentration/time, t is the time in h, and Qt is the amount of drug release in time t; graph of concentration *vs.* time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

First-Order Kinetics: $\text{Log } Q = \text{Log } Q_0 - kt/2.303$ (2)

Where Qo is the initial concentration of drug, k is the first-order rate constant, and t is the time.

Higuchi Kinetics: $Q = kt1/2$ (3)

k is the release rate constant and t is the time in h. Hence, the drug release rate is proportional to the square root of time.

Korsmeyer and Peppas Model: [13, 14].

$Mt/M\infty = Ktn$ (4),

where Mt and $M\infty$ are the absolute cumulative amount of drug released at time t and infinite time, respectively, K is a constant incorporating structural and geometric characteristic of the device, and n is the diffusional exponent indicative of the release mechanism [14].

Stability Studies

The various stability studies were carried out for all the gel formulation by freeze - thaw cycling. In this syneresis was observed by subjecting the product to a temperature of 2- 4° C for 2 then at 30°C for 2 month , then at 45°C for 2 month. Clear (+), Slightly Turbid (++), Turbid(+++), Opaque (-). RT- Room Temperature - (30±5^{0}), FT- Freezing Temperature - (2-4±2°), AT- Accelerated Temperature – (45±5^{0}) [15, 16].

RESULTS

The F1 and F2 formulations were found transparent whereas the formulation F3 was found translucent in appearance. The pH for all the formulations was found to be in the range of 7.2 -7.4 i.e. near to the skin pH. The viscosity of the following formulation was found to be 78,000 to 98,000 for F1, 65,000 to 76,000 for F2 and for F3 formulation it was found to be 56,000 to 65,000. The spreadibility of the formulations was found to be 254.56 gm.cm per 2.54 min for F1 276.21gm.cm per 2.54 min for F2 201.34 gm.cm per 2.54 min for F3. The drug content of the following formulation was found to be 92.43% for F1, 99.00 % for F2 and for F3 formulation it was found to be 98.88%. The *In-Vitro* Drug Release of the following formulation was found to be 91.00% for F1, 96.89 % for F2 and for F3 formulation it was found to be 86.32%. For the caffeine loaded topical gels when the drug release kinetics was applied the value of r^2 for the formulation as per zero order was found to be maximum for F3 i.e. 0.968, for the first order the value of r^2 was found maximum for F2 i.e. 0.782, in case of Higuchi release kinetics highest value of r^2 was for F3 i.e. 0.983 and as per Korsmeyer Peppas the r^2 was found to be maximum for F3 i.e. 0.928. The value of n was found in the range of 0.245 – 0.284 respectively, as shown in table 3. At the three different temperatures the stability studies were conducted at freezing temperature i.e. 2-4°C room temperature i.e. 30-35^0 C and at accelerated temperature i.e. 45±5^0 C where two parameters were analysed for 2 months i.e. physical appearance and drug content respectively where F1, was found to be opaque at accelerated temperature but translucent at freezing temperature and room temperature found to and the drug content which was initially in the range of 92.43±21% but was later reduced to 91.78±12 at freezing temperature 91.98±25% at room temperature and 91.08±12% at accelerated temperature. As shown in table 5.

F2 was found to be translucent at freezing, room and accelerated temperature and at freezing and room temperature found to be translucent and the drug content initially was 99.00 ±12% which was reduced to 98.38±12 at freezing temperature 98.21±12% at room temperature and 98.03±12% at accelerated temperature. As shown in table 6

Lastly, F3 at was found to be translucent at freezing, room temperature but opaque at accelerated temperature and the drug content initially was 91.78 ±12% which was later reduced to 91.98±25 at freezing temperature 91.08±12% at room temperature and 98.03±12% at accelerated temperature respectively. As shown in table 7.

DISCUSSION

All the caffeine loaded gel formulations (F1 and F2) were found to be clear and transparent except F3 which was found to be slightly translucent. This may be attributed to the optimized ratio of concentrations of both polymers i.e. carbopol 934 and HPMC K4M that undergoes uniform swelling to form gel without any air bubble entrapment. The gels were homogeneous in nature. The pH of all the caffeine loaded gel formulations was found to be in the range of 7.2-7.4. This clearly indicates that the gel could mimic the pH of the skin and will not contribute to the irritation of skin [9, 11]. The viscosity of all the three formulations was in the range of 56000 to 98000 centipoises (cps). Viscosity differs according to the concentration of polymers. As the concentration of polymer increases, the viscosity of formulations also increases. The optimized viscosity was found in the range of 65,000 to 76,000 cps. The value of spreadibility was found to be in the range of 201.34 to 276.56 gm.cm per 2.54 min. the highest spreadibility value was observed for formulation F2 i.e. 276.21 gm.cm in 2.54 min. This clearly implies that the formulation will easily get spread on application to skin. Additionally, 10% v/v ethanol exerts its main role in spreadibility. It was used as penetration enhancer to enhance the penetration of caffeine via skin, as caffeine has poor penetration power through the skin [12, 14]. Glycerol created a stimulus for

barrier repair and improves the stratum corneum hydration. The drug content was found in the range of 92.54% to 99.9% which indicates uniform drug distribution in the gel formulation. Formulation F2 gave the optimized and promising results where Carbopol 934 as 1.5% and HPMCK4M was 0.5% this implies that the Carbopol 934 have a good release retarding tendency along with which Triethanolamine acted as the potent cross linking agent. The effect of polymer level on the release of caffeine from the topical gel preparation was studied. Formulations F1, F2, F3 were able to sustain the drug release for around 0, 2, 4, 6, 8, 10 hours respectively (Figure- 2). For formulation F1, 91.0 % of the drug was released, for F2 96.43 % after 5% for F3 86.32% after 10 hours. On increasing the concentration of Carbopol 934 up to 1.5 %, the release of the drug was retarded till 10 hours. Among all the formulations, F2 showed better dissolution profile in 10 hours, so it was selected to be the optimized formulation. [11]

The regression coefficient (R^2) was used as an indicator of the best fitting for each of the models considered as shown in Table 4. The kinetic data of all the formulations reached higher coefficient of regression (R^2 =0.949) for Higuchi followed by zero and first order. From the value of release exponent (n) in the Korsmeyer-Peppas model, it follows quasi Fickian diffusion i.e. swelling with diffusion are main mechanism of drug release via gels [14].

On the basis of the performed stability studies at 3 different temperature and humidity conditions, it was found that all the formulations shows variations in clarity. Slight opacity was observed in F1 and F3 but the F2 was still found transparent and without any other change in appearance. In case of drug content, a slight difference was observed as shown in Table 5, Table 6 and Table 7 for the formulations F1, F2 and F3 respectively [19].

CONCLUSION

There is an increased need for topical forms of caffeine gel, which can manifest in patients taking oral forms of the drug, since topical drug delivery system bypasses the Gastro Intestinal system, and first pass metabolism topical application of gels on the skin or body is one of the most compliable methods and people can easily use it on their own. Caffeine is believed to reduce wrinkles due to constriction of dilated capillaries. However, it was found that the cooling effect of the hydrophilic gels provided more effect on reduction of aging than the vasoconstriction of caffeine. Glycerol is a better alternative for the Improvement of the solubility and penetration through the skin. The ease and safety of topical drug delivery of caffeine makes it an ideal drug delivery system.

Table 1: Formulation Table for Caffeine Loaded Topical Gel

S. No.	Ingredients	F1	F2	F3
1.	Caffeine	5%	5%	5%
2	Carbopol 934	1%	1.5%	0.5%
3.	HPMC K4 M	1%	0.5%	1.5%
4.	Glycerol	5ml	5ml	5ml
5.	Methyl Para Benzoate	2%	2%	2%
6.	Triethanolamine	2.5ml	2.5ml	2.5ml
7.	0.1 N NaOH	2.5ml	2.5ml	2.5ml
8.	Ethanol	10%	10%	10%
9.	Purified Water	25ml	25ml	25ml

Table 2: Characterization of Topical Carbopol Gel of Caffeine

S. No	Parameters	F1	F2	F3
1	Color	Transparent	Transparent	Translucent
2	Clarity	Clear	Clear	Clear
3	Homogeneity	Achieved	Achieved	Achieved

Table 3: Table for Evaluated Parameters

S No.	Formula Code	pH	Spreadibility (gm.cm/min)	Viscosity (cps)	Drug Content %	*In vitro* drug Release%
1.	F1	7.2-7.3	254.56/2.54	78,000-98,000	92.43	91.00
2.	F2	7.2-7.4	276.21/2.54	65,000-76,000	99.00	96.89
3.	F3	7.3-7.4	201.34/2.54	56,000-65,000	98.88	86.32

Table 4: Drug Release Kinetics Data for Caffeine Gel

Formulation	Zero order release		First order release		Higuchi Release		Korsmeyer Peppas	
	R^2	K	R^2	K	R^2	K	R^2	n
F1	0.936	9.619	0.777	0.478	0.949	0.009	0.917	0.245
F2	0.952	9.644	0.782	0.492	0.956	0.109	0.924	0.25
F3	0.968	9.781	0.765	0.495	0.983	0.118	0.928	0.284

Table 5: Drug Stability Study Data for Caffeine Gel

Days	F1					
	Physical appearance			Drug content (%)		
	RT	FT	AT	RT	FT	AT
0	+	+	+	92.43±21	92.43±21	92.43±21
7	+	+	+	92.39±23	92.39±13	92.39±23
14	+	+	++	92.33±42	92.31±22	92.36±42
28	++	+	++	92.28±32	92.27±41	91.88±32
35	++	++	+++	92.18±12	92.21±12	91.48±12
45	++	++	+++	91.93±23	92.13±17	91.23±23
60	+++	+++	-	91.78±12	91.98±25	91.08±12

Table 6: Drug Stability Study Data for Caffeine Gel

Days	F2					
	Physical appearance			Drug content (%)		
	RT	FT	AT	RT	FT	AT
0	+	+	+	99.00±12	99.00±12	99.00±12
7	+	+	+	98.97±23	98.98±23	98.87±23
14	+	+	+	98.94±42	98.87±42	98.76±42
28	+	+	+	98.88±32	98.85±32	98.65±32
35	+	+	+	98.78±12	98.75±12	98.59±12
45	++	+	++	98.53±23	98.32±23	98.21±23
60	++	++	++	98.38±12	98.21±12	98.03±12

Table 7: Drug Stability Study Data for Caffeine Gel

Days	F3					
	Physical appearance			Drug content (%)		
	RT	FT	AT	RT	FT	AT
0	+	+	+	98.88±13	98.88±13	98.88±13
7	+	+	+	98.78±12	98.81±67	98.82±40
14	+	+	++	98.53±23	98.79±32	98.78±12
28	++	+	++	98.38±12	98.58±43	98.64±42
35	+++	++	+++	98.18±37	98.33±25	98.41±12
45	+++	+++	+++	98.08±20	98.05±12	98.29±12
60	-	-	-	97.9±19	97.81±34	97.91±23

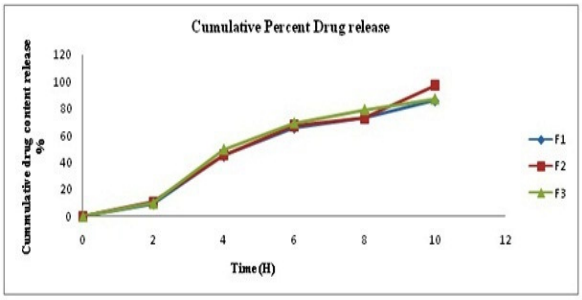

Fig 1: Occlusion Indicating Local Therapy via Topical Gel Formulation

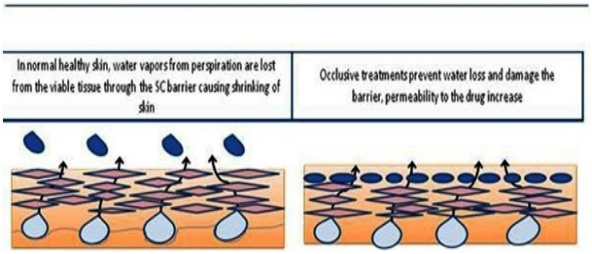

Figure 2: Cumulative Percent Drug Release of All Caffeine Loaded Gel Formulations

REFERENCE

1. Anuaikit T, Maneeuan D. Evaluation of Caffeine Gels on Physicochemical Characteristics and In Vivo Efficacy in Reducing Puffy Eyes. JAPS. 2011; 01 (02):56-59.
2. Amnuaikit T., Ingkatawornwong S., Maneenuan D., Worachotekamjorn K. Caffeine topical gel formulation. Isan J Pharm Sci. 2008; 4(1): 16 – 24
3. Trommer H, Neubert H. Overcoming the Stratum Corneum. The Modulation of Skin Penetration Skin Pharmacol Physiol. 2006; 19:106–121.
4. Rashmi, Garg R, Kumar S. Topical Gel. A Review Pharmainfo.net. 2008; 6(3).
5. Caffeine reduces Puffiness [internet], Eye Cream& Gels caffeine reduces: http://www.eyecreamsandgels.com (cited 2013 Jan 20).
6. Anti-Aging Skin Care for the Eyes [internet], hubpages.com/hub/Skin-Care-for-the-Eyes (cited 2013 Jan 20).
7. Banker G. S. and Rhodes C. T. Modern Pharmaceutics. Marcel Dekker. Inc. Madison Avenue. 2nd ed. Vol. 40. New York: 1990; 263-264.
8. Lachman, L. and Lieberman, H. A., The Theory and Practice of Industrial Pharmacy, 3rd ed., Varghese Publishing House. 1990;534
9. Patel Rakesh P, Patel Hardik H. Formulation and Evaluation of Carbopol Gel Containing Liposomes of Ketoconazole. International Journal of Drug Delivery Technology.2009;1(2):42-45.
10. Chavanpatil M, Jain P, Chaudhary S, Shear R, Vavia PR., Development of sustained release gastroretentive drug delivery system for ofloxacin. In vitro and in vivo evaluation. Int. J. Pharm. 2005; 304:178-184.
11. Norlen L, Skin barrier structure and function: The single gel phase model. J Invest Dermatol 2001; 117: 830–836.
12. Lorence AT, Jani P. Novel oral drug formulations. Their potential in modulating adverse-effects. Drug Saf. 1994;410(3):233-266.
13. Jain N, Kumar D, Gulati N, Nagaich U. Design Development and *in-vitro* evaluation of caffeine loaded natural gum matrix tablet. Indonesian J. Pharm. 2013;24(1): 30 – 34.

14. Kumar D, Jain N, Gulati N, Nagaich U. Nanoparticle laden in-situ gelling system for ocular drug targeting. J Adv Pharm Technol Res 2013; 4: 9-16.
15. Senthil V, Kumar RS, Nagaraju CV, Jawahar N, Design and Development of hydrogel nanoparticles for mercaptopurine. J Adv Pharm Technol Res 2010; 1:334-7.

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