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Critical Parameters Characterization of Gel Dosage Form of "Novel Neutraceutical Drug Combination"

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ABSTRACT

Glucosamine is an amino monosaccharide and a natural component of glycoprotein found in connective tissue and gastrointestinal mucosal membranes. Each person naturally produces a certain amount of glucosamine within his or her body, but the amount might not be sufficient for healthy joint maintenance, especially as age increases. Chondroitin is considered a complex macromolecule. It is a natural polymer of α-disaccharide with an alternating sequence of D-glucose and N-acetyl-galactosamine-4-sulphate or 6-sulfate residues linked together through different bonds. It is a high molecular weight GAG with a molecular weight of 10000-50000 Da. Skin is one of the most readily accessible organs on the human body for topical administration and is the main route of the topical drug delivery system. The objective of formulating gel formulations is for better patient compliance and to reduce the dose of a drug and to avoid the side effects associated with the drugs when taken as oral dosage forms. A combination of Glucosamine and Chondroitin topical gel of carbopol based formulations were made. The formulation study was aimed to keep all other ingredients constant and only change in Carbopol 940 concentrations. Gel formulations were characterized for Physical Evaluation, pH, Spreadability, Extrudability, Gel Strength, Homogeneity and Grittiness, *in-vitro* drug release, and drug release kinetic study. The results were found satisfactory for all the parameters studied.

INTRODUCTION

Transdermal drug delivery gives many important advantages such as it is easy for application, protects the active compound from gastric and enzymatic degradation, simple to terminate the therapy if the undesired side effect occurs[1]. Skin is a natural barrier, and only a few drugs can penetrate through it easily in sufficient quantity[2].

There are various skin infections caused by fungus. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes.

The need for the development of new drug treatments for OA that could systemically relieve pain and potentially modify structural damage has emerged. Nutraceuticals such as glycosaminoglycans (GAGs) have recently been introduced as biological alternatives for drug treatment since there is a substantial interest in the chondroprotective effects of GAGs such as glucosamine sulfate and chondroitin sulfate. Both of these drugs have been approved as agents that modify the natural history of OA[3]. Glucosamine sulfate and chondroitin sulfate are natural nutraceutical compounds that are known as cartilage precursors. They are not only considered as symptomatic drugs for OA, but they also have a disease-modifying potential, hence, they have gained worldwide popularity over the last decades[4]. This review article focuses on those two compounds for the treatment of OA.

Commercially Glucosamine & Chondrotropin sulfate topical gel preparation is not available in the market, thus this formulation is made for better patient compliance and to reduce the doses of the drug, and to avoid the side effects. A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical route[5].

Various medicated products are applied to the skin. Such products are referred to as topical or dermatological products. There are various Hydrophilic polymers such as carbopol 940, hydroxyl propyl methylcellulose (HPMC), Sodium alginate that is used in topical gel delivery system[6]. Based on molecular fraction these polymers are used in concentration between 1-5 % in a topical formulation.

Brief Information on Gel:

Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removed, emollient, non-staining, compatible with several excipients, and water soluble or miscible[5-6]. The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing an interpenetrated by a liquid. The inorganic particles form a three dimensional structure. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into the continuous phase[7].

MATERIALS AND METHODS:

Glucosamine, Chondroitin, Carbopol 940, Benzyl alcohol, Oleic acid, Glycerine, Triethanolamine

Preparation of Gel Base:

Purified water was taken and Carbopol 940 was added and allowed to soak for 24 hours. To this, the required amount of drugs (500 mg & 500 mg each gm) was dispersed in water, and then carbopol 940 was then neutralized with a sufficient quantity of triethanolamine. Glycerine as a moistening agent and oleic acid as a penetration enhancer and benzyl alcohol as a preservative were added slowly under continuous stirring until the homogenous gel was formed. The formulation of various batches is shown in Table No. 1.

Table No. 1: Formulation Table for Glucosamine, Chondroitin gel preparation

Sr. No	Ingredients	GCF1	GCF2	GCF3
01	Glucosamine and Chondroitin Sulfate	1 gm	1 gm	1 gm
02	Carbopol 940	1 gm	2 gm	3 gm
03	Benzyl alcohol	2 mL	2mL	2 mL
04	Oleic acid	1 mL	1 mL	1 mL
05	Glycerine	20 mL	20 mL	20 mL
06	Triethanolamine	3 mL	3 mL	3 mL
07	Water	QS	QS	QS

Evaluation:

1) Physical Evaluation[9]: The gel formulations of Glucosamine and Chondroitin were evaluated for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability, etc.

2) Rheological Studies:

The viscosity of the different gel formulae was determined at 25°C using rotational Brookfield viscometer of cone and plate structure with spindle CPE-41 and CP-52[10]. The apparent viscosity was determined at a shear rate of 40 sec^{-1}. The flow index was determined by linear regression of the logarithmic form of the following equation:

$$\tau = k\ \gamma\ n \text{.....Equation (1)}$$

Where "τ" is the shear stress, "γ" is the shear rate, k is the consistency index, and n is the flow index. When the flow is Newtonian n=1, if n>1 or n<1, shear thickening or shear thinning is indicated, respectively. The evaluation was conducted in triplicate.

3) Sensitivity Test:

A drop of diluted suspension of the tested gel (1:1) and another drop of saline (control) was put on two corresponding spots of the arms of three human volunteers. After ten minutes, the spot was investigated for any erythema, wheel, or allergic reaction.

4) Skin Irritation Test[11 & 12]:

As the formulation was intended for dermal application, skin irritancy should be tested. Skin irritation tests were conducted in rabbits to determine irritancy after a single application of Glucosamine and Chondroitin gel. The back of rabbits after depilation was used in this experiment. About 0.5 g of Chondroitin gel was applied on two different rabbits and then the applied area was covered with gauze and an adhesive bandage. The formulation was removed after 24 h and the exposed skin was graded for the formation of edema and erythema. Scoring was repeated 72 h later. Based on the scoring, the formulation was graded as 'nonirritant', 'irritant,' and 'highly irritant'.

The total scores for the irritation test were calculated using the following equation:

$$\text{Average irritation scores} = \frac{(\text{Erythema reaction scores} + \text{Edema reaction scores})}{\text{Time interval } (h)}$$

5) *Ex-Vivo* [*In-Vitro*] Diffusion Study[13]:

The abdominal skin of Albino mice, weighing 20 – 25 gm of 8 – 10 week old was shaved using a hand razor and clean the skin with hot water cotton swab. 5 gm of the gel was applied uniformly to the skin. The skin was mounted between the compartments of the Franz diffusion cell with the stratum corneum facing the donor compartment. The reservoir compartment was filled with 100 ml phosphate buffer of pH 6.8. The study was carried out at 37 ± 1°C and speed was adjusted until the vortex touches the skin and it was carried out for 4½ h. 5 ml of sample was withdrawn from the reservoir compartment at 30 min intervals and the drug content was measured. Each time the reservoir compartment was replenished with the 5 ml volume of phosphate buffer pH 6.8 solution to maintain a constant volume.

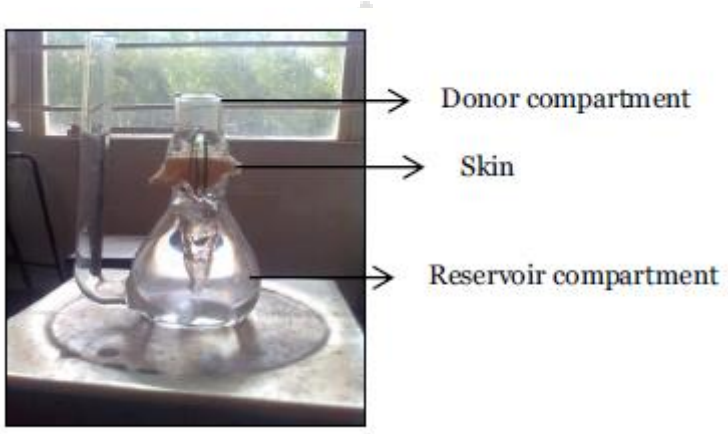

Figure No. 1: Franz diffusion cell with skin mounted between compartments

RESULTS AND DISCUSSION:

1) Physical Evaluation: All the three formulations of Glucosamine & Chondroitin gel were evaluated for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability, etc., and found acceptable with respect to the physical evaluation. The results are given in Table No. 2.

Table No. 2: Physical Evaluation of Glucosamine and Chondroitin Gel Formulations.

Sr. No.	Formulation Code	Color	Odor	Phase Separation	Washability	Occlusiveness
1	GCF1	White to off white	Odorless	No	Washable	No
2	GCF2	White to off white	Odorless	No	Washable	No
3	GCF3	White to off white	Odorless	No	Washable	No

2) Rheological Studies: The rheological behavior of the prepared formulae showed shear-thinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains. The different rheological parameters are given in Table No. 3.

Table No. 3: Details of the Rheological Properties of Glucosamine and Chondroitin Topical Gels

Sr. No.	Formulation Codes	Coefficient of determination (R^2)	Flow Index (n)	Viscosity (centipoise)(η)	Flow Behavior
1	GCF1	0.9285	0.2346	1927	Shear Thinning
2	GCF2	0.9321	0.2178	2178	Shear Thinning
3	GCF3	0.9498	0.1342	2487	Shear Thinning

3) Sensitivity Test:

The formulated Glucosamine and Chondroitin gel formulations of all three caused no irritation or sensitivity to the skin when subjected to a sensitivity test.

4) Skin Irritancy Study: This test is one of the important test parameters which needs to be evaluated for the topical application dosage form. Average response scores of skin irritation for a single application. The results indicate that all the gel formulations have low skin irritation. The details of the index are shown in Table No. 4.

Table No. 4: The Skin irritation Index of Glucosamine and Chondroitin Formulated Gels.

Formulation	Primary Irritation Index		
	24 hrs.	**48 hrs.**	**72 hrs.**
GCF1	0.058	0.0981	0.093
GCF1	0.046	0.0931	0.089
GCF2	0.055	0.0955	0.099

5) *Ex-Vivo* [*In-Vitro*] Diffusion Study:

The release studies reveal that the drug Glucosamine and Chondroitin are released to a lesser extent from the animal skin [mice] when compared to the cell membrane. The results indicated that the higher the concentration of carbopol, the lesser is the release and the higher concentration of polymers likely causing the release retard of both the drugs while the drug is released to a greater extent in the cell membrane. Though the GCF1 was able to give a satisfactory release over some time when tested in the cell membrane, however, the same showed lesser release because of skin thickness and also the polymer concentration. The % drug diffusion is shown in Table No. 5 and also the graphical representation of % drug release is shown in Figures No. 2 and 3 for Glucosamine and Chondroitin respectively.

Table No. 5: The % drug diffused across the mice skin for all 3 formulations

Sr. No.	Time Points [in Minutes]	Formulation Codes and % Drug Diffused					
		GCF1		GCF2		GCF3	
		G	C	G	C	G	C
1	30	16	17	08	11	07	09
2	60	24	25	16	18	15	17
3	90	36	35	24	26	25	27
4	120	47	45	37	40	36	35
5	150	56	61	42	51	43	44
6	180	68	70	49	60	47	52
7	210	74	75	56	68	55	57
8	240	81	84	63	74	60	62

G represents % drug release of Glucosamine. C represents % drug release of Chondroitin.

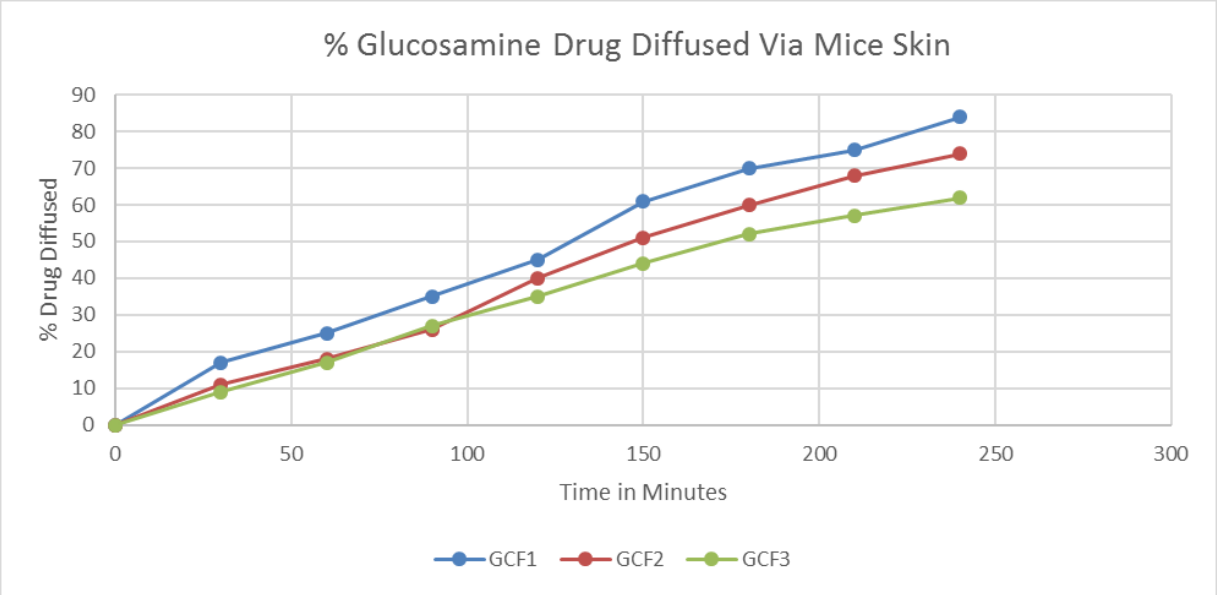

Figure No. 2: Graphical representation of % Glucosamine diffused of all 3 formulations across mice skin.

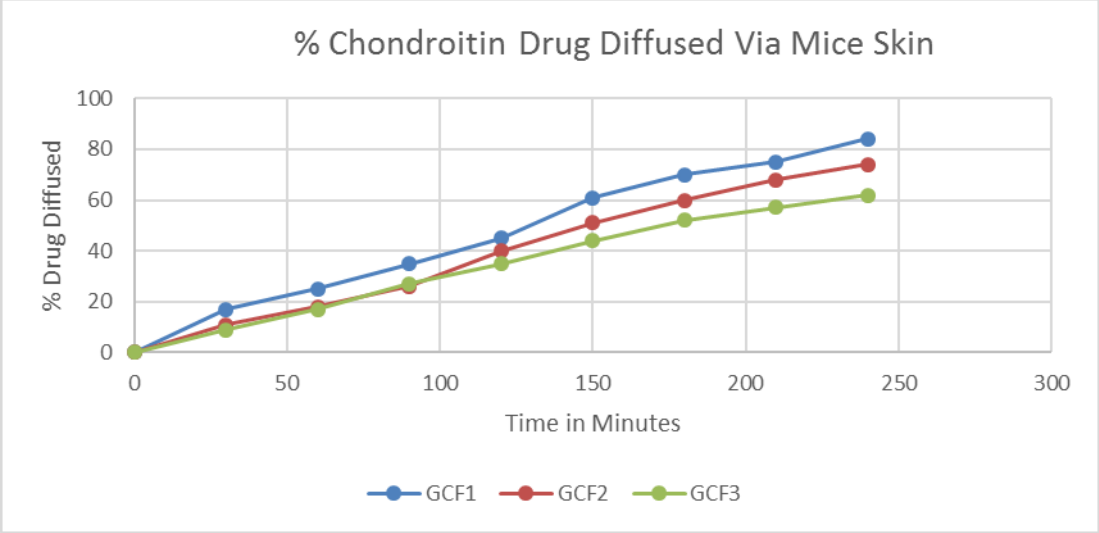

Figure No. 3: Graphical representation of % Chondroitin Sulfate diffused of all 3 formulations across mice skin

CONCLUSION:

The physical evaluation of all three gel formulations was carried out. All the three studied formulations were found easily spreadable. The color of formulations was white transparent

to off white. None of the gel formulations showed sensitivity and skin irritation. The rheological properties were found satisfactory. The viscosities of Carbopol gels ranged from 1900 to 2500 centipoises (n). It can be concluded that gel formulations showed acceptable physical properties and drug diffusion study. Among all the three gel formulations, Carbopol 940P having 1 % concentration showed promising results for % drug diffused. GCF1 formulation showed satisfactory % drug diffusion results. Further, in the carbopol gel formulations, the % drug diffusion was decreased with an increase in carbopol concentration which is attributed due to polymer concentration. Due to higher polymer concentration presence, the viscosity increases. From the above results, it can be concluded that the Glucosamine and ChondroitinGel formulation GCF1 was suitable for topical application.

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