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

Human Journals
Research Article
February 2021 Vol.:20, Issue:3

Formulation and Characterization of Gel Dosage Form of Novel Neutraceutical Drug Combination

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

Thejaswini HB*[1], Girish Nihalani[2], Mohammed Mubeen Ahmed[3]

[1]Research scholar OPJS University, Churu, Rajasthan, India

[2]Teva Pharmaceuticals USA Inc., FL, USA.

[3]Research Guide OPJS University, Churu, Rajasthan, India

Submitted: 10 January 2021
Revised: 30 January 2021
Accepted: 19 February 2021

Keywords: Glucosamine, Chondroitin, Carbopol 940, Gel, Gel Forming Agents, Spreadability, Extrudability, Topical delivery

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 (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 in gel formulations is for better patient compliance and to reduce the dose of 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, protect the active compound from gastric and enzymatic degradation, simple to terminate the therapy if an undesired side effect occurs[1]. Skin is a natural barrier, and only 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 sulphate and chondroitin sulphate. Both of these drugs have been approved as agents that modify the natural history of OA[3]. Glucosamine sulphate and chondroitin sulphate 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 sulphate topical gel preparation is not available in the market, thus this formulation is made for better patient compliance and to reduce the doses of 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 skincare. 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 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 micelle[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, 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 below table 1.

Table No. 1: Formulation Table for Glucosamine, Chondroitingel preparation

Sr. No.	Ingredients	GCF1	GCF2	GCF3
01	Glucosamine & Chondroitin Sulphate	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 & Chondroitin were evaluated for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability etc.

2) pH Determination: The pH of the gels was determined using digital pH meter[10](3310, Jenway, UK). The reported pH values are from the average of 3 times. Results are shown in table 2.

3) Spreadability

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5minutes where no more spreading was expected (De Martin and Cussler, 1975; Lucero *et al.*, 1994; Vennat*et al.*, 1994; Contreras and Sanchez, 2002). Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are an average of three determinations.

4) Extrudability Study[11 & 12]

The extrudability of gel formulations was determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel.

5) Homogeneity[13] **and Grittiness:**

The gel formulations of Glucosamine & Chondroitin were subjected to critical tests like Homogeneity and grittiness in the gel.

6) Gel Strength: An accurately weighed quantity of 30 g of gel was placed in a 50 mL graduated measuring cylinder and was allowed to form gel in a water bath at 37°C. By applying 50 g weight to the gel with the help of a cylinder, the time taken by the cylinder to sink 5 cm down through the gel was measured[14].

7) Drug Content:

A specific quantity of developed gel was taken and dissolved in 100 mL of phosphate buffer of pH 5.5. The volumetric flask containing gel solution was shaken for 2hr on a mechanical shaker to get complete solubility of drug. This solution was filtered using 0.45 µm filter.

After suitable dilution drug absorbance was recorded by using UV- visible spectrophotometer (UV – 1700, Shimadzu,) at λ_{max} 570 nm Yunqi Wu, et al (2005) (Wu Y. et al., 2005) for the measurement of Glucosamine & the diluted aliquots were measured for the drug absorbance was recorded using UV- visible spectrophotometer (UV – 1700, Shimadzu,) at λ_{max} 275 nm for the measurement of Chondroitin Sulphate nm using phosphate buffer (pH 6.8) as blank for both the drugs.

8) *In-vitro* Drug Release:

The *in-vitro* drug release from gel formulations was studied across cellophane membranes using modified KesheryChien diffusion cell[15]. The receptor compartment was filled with the mixture of phosphate buffer of pH 5.6 maintained at 37 ± 0.5°C with constant magnetic stirring. Accurately weighed quantity of gel was placed on the donor compartment. The samples (1mL) was collected from the receptor compartment at a predetermined time interval and replaced by equal volume of fresh receptor solution to maintain constant volume allowing sink condition throughout the experiment. The amounts of Glucosamine and Chondroitin in the sample were analyzed at 570 nm and 275 nm respectively against appropriate blank.

9) Drug Release Kinetic Study

The data obtained from the *in-vitro* release experiments were analyzed using the linear regression method according to the following equations:

a- Zero-order equation:

$$Q = k_o t$$

Where Q is the amount of drug released at time t, and k_0 is the zero-order release rate.

b- First – order equation:

$$\text{In } (100 - Q) = \text{In } 100 - k_1 t$$

Where Q is the percent of drug release at time t, and k_1 is the first-order release rate constant.

c- Higuchi's equation:

$$Q = k\, t^{1/2}$$

Where Q is the percent of drug release at time t, and k is the diffusion rate constant[16]

RESULTS AND CONCLUSION:

1) Physical Evaluation: All the three formulations of Glucosamine and Chondroitin were evaluated for organoleptic characteristics, Color, Odor, Phase separation, Occlusiveness, and Washability etc. and found acceptable with respect to the evaluated physical evaluation. The results are given in Table 2.

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

Sl. 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) Extrudability:

The results for extrudability showed that Carbopol based gels were in acceptable limits. The results of extrudability are shown in the below table No.3.

Table No. 3: The details of Extrudability of Glucosamine and Chondroitin Gel Formulations (++ very good, +good)

Sr. No.	Formulation Code	Extrudability
1	GCF1	++
2	GCF2	++
3	GCF3	+

3) Spreadability:

The spreadability results showed that the formulated gels of carbopol gels were most effective i.e. they showed the best results for spreadability. The results of spreadability are shown in the below table No.4.

Table No. 4: The details of Spreadability of Glucosamine and Chondroitin Gel Formulations

Sr. No.	Formulation Code	Diameter [cm]
1	GCF1	5.4
2	GCF2	5.3
3	GCF3	5.0

4) Homogeneity and Grittiness:

Almost all the formulations were found to be homogeneous and none of the formulations showed grittiness. The results of Homogeneity and Grittiness are shown in the below table No.5.

Table No. 5: The details of Homogeneity and Grittiness of Glucosamine and Chondroitin Gel Formulations

Sr. No.	Formulation Code	Homogeneity	Grittiness
1	GCF1	Yes	No
2	GCF2	Yes	No
3	GCF3	Yes	No

5) pH:

The pH values of all three formulations were in range 5.5-7 which is considered acceptable to avoid the risk of irritation upon application to the skin[17&18]. The results are tabulated in table No. 6.

Table No. 6: The pH details of Glucosamine and Chondroitin Gel Formulations

Sr. No.	Formulation Code	pH
1	GCF1	5.5
2	GCF2	6.6
3	GCF3	6.9

6) Drug Content:

The drug content in the gel formulations was evaluated to understand the active content present in the Gel system. The results for drug content for the all gel formulation revealed

that the drug content is satisfactory. All the formulations gave satisfying results for the percentage drug content. The % drug content is shown in the below table No. 7.

Table No. 7: The % drug content of Glucosamine and Chondroitin Gel Formulations

Sr. No.	Formulation Code	Drug Content
1	GCF1	97.2 (G)& 98.4 (C)
2	GCF2	98.8 (G) & 96.9 (C)
3	GCF3	99.8 (G) & 97.2 (C)

7) *In-vitro* Drug Release

The *in-vitro* drug release studies performed on dialysis membranes reveal that the drug Glucosamine and Chondroitin is released to a satisfactory extent. The results indicate that the higher the concentration of carbopol, the lesser is the release and the higher concentration of polymers might be retarding the release of the drug while the drug is released to a greater extent in the dialysis membrane. Formulation GCF1 was able to give good release over some time when tested in the dialysis membrane, the % drug release is shown in table 8 and also the graphical representation of % drugs release is shown in figure No. 1& figure No. 2 for Glucosamine & Chondroitin respectively.

Table No. 8: The % drug released across the dialysis membrane for all 3 formulations

Sl. No.	Time Points [in Minutes]	Formulation Codes & % Drug Release					
		GCF1		GCF2		GCF3	
		G	C	G	C	G	C
1	30	25	28	17	20	15	17
2	60	38	41	31	33	27	31
3	90	54	58	46	49	34	38
4	120	68	72	60	62	50	55
5	150	81	85	74	78	58	65
6	180	90	92	83	86	70	74
7	210	95	97	86	88	76	80

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

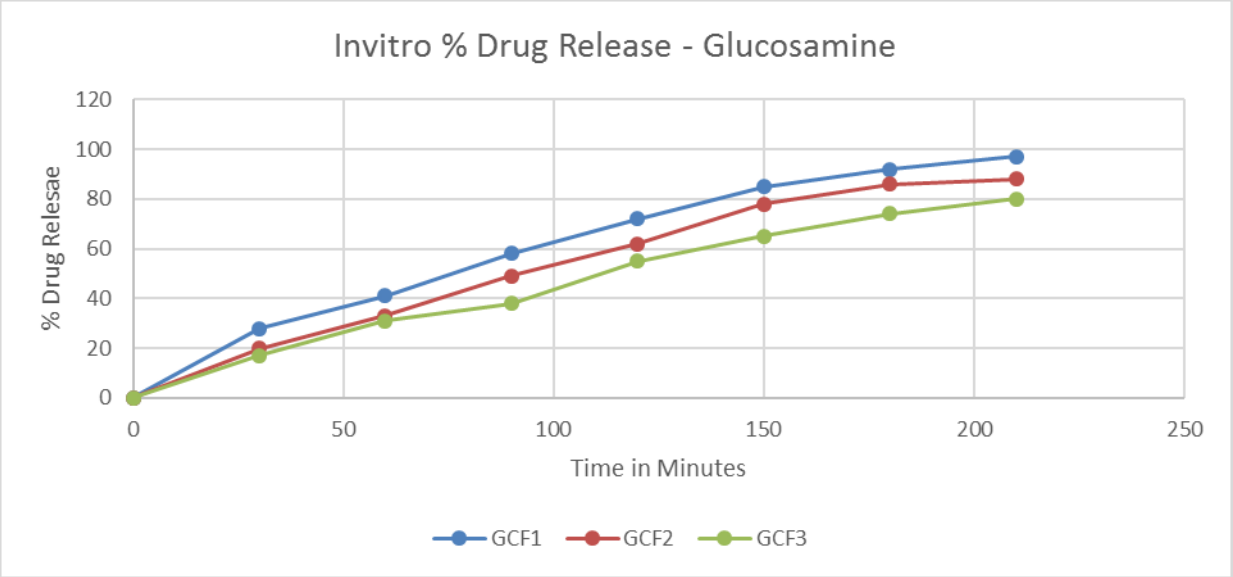

Figure No. 1: Graphical representation of in vitro drug release of Glucosaminefrom Glucosamine & Chondroitin Gel Formulations

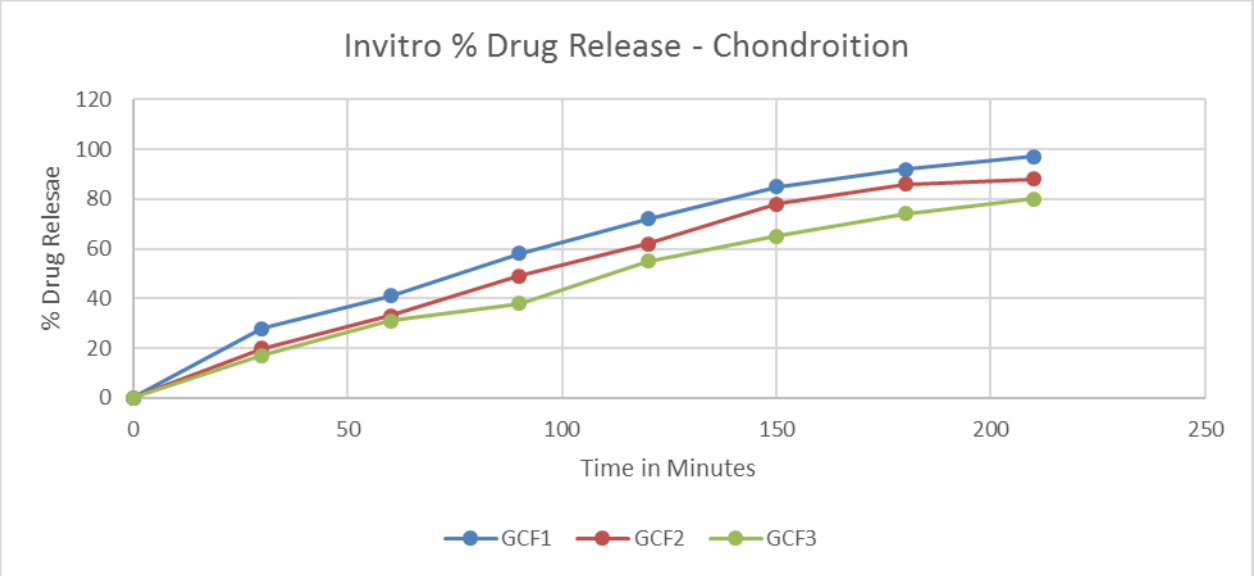

Figure No. 2: Graphical representation of in vitro drug release of Chondroitionfrom Glucosamine & Chondroitin Gel Formulations

8) Gel Strength:

It has been observed that gel strength increased with the increase in the concentration of carbopol polymer in the formulation. If the comparison is made among the formulations, GCF3 formulation showed higher gel strength than GCF1. The reason can be attributed to the higher concentration of carbopol present in GCF3 formulation as it tends to increase the gel

strength. The results obtained for strength test of all the formulations are mentioned in Table No. 9.

Table No. 9: Details of the Gel Strength of Glucosamine and Chondroitin Gel Formulations

Sl. No.	Formulation Code	Gel Strength
1	GCF1	88.6 ± 0.58
2	GCF2	94.8 ± 0.72
3	GCF3	102.8 ± 1.27

9) Kinetics of Drug Release:

The release data analysis was carried out using the various kinetic models i.e using cumulative % drug release vs. time (zero-order kinetic model); log cumulative % drug remaining vs. time (first order kinetic model) and cumulative % drug release vs. square root of time (Higuchi model) [19-21]. The R^2 values are tabulated in table No.; 10. All formulae showed best fitting to Higuchi model kinetics.

Table No. 10: Details of the Kinetics of drug release of Glucosamine and Chondroitin Gel Formulations

Sl. No.	Formulation Code	Correlation Coefficient [R^2]		
		Zero Order	First Order	Diffusion
1	GCF1	0.968	0.9978	0.9972
2	GCF2	0.889	0.972	0.9892
3	GCF3	0.874	0.965	0.9891

CONCLUSION:

The physical evaluation of all the formulated gels was successfully studied. All three formulations were easily spreadable. The color of formulations was found white and transparent. The pH of all the formulations was found between 5.5 to 7.0. All three formulations were found homogeneous and none of the formulations showed grittiness. The results for extrudability and spreadability showed that Carbopol gels were in acceptable limits. The results for both drug contents of all the three formulations were acceptable. The in vitro release studies of the formulations also gave satisfactory results. Thus, the objective of

the present work of formulation and evaluation of Glucosamine and Chondroitin topical gel was achieved with overall satisfactory results for the test parameters evaluated. Among the three gel formulations, 3%Carbapol 940P showed decreasing order of drug release against 2% and 1% Carbopol concentration. The reason for the decreased drug release could be attributed to an increase in the carbopol concentration. Since polymer concentration increases, the viscosity of gel formulations also tends to increase as the gel concentration and viscosity is directly proportional. All gel formulations containing penetration enhancer (Oleic acid) was used. From the above results, it can be concluded that the 1% carpool gel was suitable for topical application.

REFERENCES:

1. Ranade VV. Drug delivery systems transdermal drug delivery. J Clin Pharmacol1991;31:401-18.
2. Bruton LL, Laza JS, Parker KL. Goodman Gilman's; The Pharmacological Basis of Therapeutics. New York: McGraw Hill Medical Publishing Division; 2006. p. 801-10.
3. Lorza C, Altman R. Chondrotection in osteoarthritis. Bull Rheum Dis 1997;46:5-7.
4. Theodosakis J, Adderly B, Fox B. The Arthritis Cure. New York, NY: St Martin's Press; 1997.
5. Magdy I. Mohamed; Optimization of chlorphenesinemulgel formulation. AAPS J. 2004;6 (3) : 81-87.
6. Klich CM. Jels and Jellies.In: Swarbrick J, Boyan JC, eds. Encyclopedia of Pharmaceutical Technology. Vol (6);1992 Marcel Dekker Inc.:New York, USA.p.415-439.
7. J.R. Robinson and Lee, H.L.Vincent, Controlled Drug Delivery, Marcel Dekker, Inc., Madison Avenue, New York, 2nd Edn. Vol. 29, 524-526.
8. Sudhir Bharadwaj, G.D Gupta and V.K. Sharma (2012). Topical gel a novel approach for drug delivery, Journal of Chemical, Biological and Physical sciences, 2(2):856-867.
9. Sakurai. K., Maegawa. T., Takahashi. T.; Glass transition temperature of chitosan and miscibility of chitosan/poly (Nvinylpyrrolidone) blends. Polymer, 41(2000) 7051–7056
10. Shivhare U.D., Jain K.B., Mathur V.B., Bhusari K.P., Roy A.A. and Sharad. Formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer. Digest J. Nanomat.Biostruct., 2009;4: 285-290.
11. Panigrahi, John T, Sharif A, Shobha Rani and Hiremath R. Formulation and evaluation of lincomycin HCl gels. Indian Journal of Pharmaceutical Sciences. 1992 Nov-Dec. P.330-332.
12. Sanjay, Bidkar Devendra Jain, Amol Padsaly, Krishna Patel and Vinod Mokale. Formulation, development and evaluation of Fluconazole gel in various polymers bases. Asian Journal of Pharmaceutics. 2007 Apr-Jun; 1(1): P.63-68.
13. A Gupta1, AK Mishra, AK Singh, V Gupta, P Bansal "Formulation and evaluation of topical gel of diclofenac sodium using different polymers" Drug Invention Today 2010; 2(5), 250-253.
14 C. S. Yong, J. S. Choi, Q.-Z. Quan et al., "Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of poloxamer gels containing diclofenac sodium," *International Journal of Pharmaceutics*, vol. 226, no. 1-2,pp. 195– 205, 2001.
15. Keshary PR, Chien YW, Drug Develop. Ind. Pharm. 10, 1663 (1984).
16. Patel RP, Patel G, Baria A, Formulation and evaluation of transdermal patch of aceclofenac, Int. J. Drug Del., 2009;1: 41-51.
17. Clearly GW. Transdermal controlled release system. In: Langer RS, Wise DS, eds. Medical Applications of Controlled Release. Vol1. Boca Raton, FL:CRC Press;1984;204-251.
18. Lucero MJ, Vigo J, Leon MJ.:A Study of shear and compression deformations on hydrophilic gels of tretinoin. Int J Pharm. 1994;106;125-133.

19. Vuebaa, M.L.,deCarvalhob, L.A., Veigaa, F., Sousaa, J.J. and Pinaa, M.E., Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets, Eur.J. Pharm. Biopharm., 2004;58;51
20. Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension, Ibid, 1961; 50,874.
21. Higuchi, T., Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J.Pharm.Sci.,1963;52;1145.