Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 62 (2013) 17599-17603

ISSN: 2229-712X

Design, Development and formulation of Topical anti arthritic gel using different gelling agents

Pacharne Priyanka S, Patil Jayashri R, Chaudhari Shilpa P* and Ratnaparkhi M.P

Department of Pharmaceutics, Marathwada Mitra Mandal's College of Pharmacy, Thergaon, Pune-33.

ARTICLE INFO

Article history:

Received: 30 July 2013;

Received in revised form:

20 August 2013;

Accepted: 2 September 2013;

Keywords

Ibuprofen topical gel,

Diffusion,

Drug release.

ABSTRACT

The aim of this study was firstly to compare between different gelling agents for its drug release characteristics, and viscosity and Secondly, to investigate the effect of presence of PluronicF127 on drug release and viscosity of different gelling agents. Topical gel formulations of Ibuprofen were prepared by using Carbopol 934, Carbopol 940, HPMC, Sepineo, Sodium Carboxymethylcellulose (NaCMC) and Hydroxyethylcellulose (HEC) polymer as a gel-forming material that is biocompatible and biodegradable. The skin permeation enhancer used was Menthol. Permeation studies were carried out in-vitro using Cellophane Membrane. In-vitro diffusion study showed that diffusion studies of formulation F6 and marketed gel was comparable. The in-vitro study also reveals that addition of Pluronic F127 results in increase in viscosity of gel which further sustains the drug release. Results shows that as concentration of gelling agent increases viscosity increases and drug release decreases.

Introduction

Ibuprofen[2-(4-isobutylphenyl) propionic acid], a strong non-steroidal anti-inflammatory (NSAID) drug having excellent anti-inflammatory and analgesic effects frequently prescribed for the long term treatment of rheumatoid arthritis [1]. Oral dose of ibuprofen causes an increased risk of gastric mucosal damage bleeding and ulceration which could be lethal to human body. To avoid the adverse effect, alternate routes of administration have been tried by investigators [2]. The selection of an appropriate gelling agent is essential for formulation of an effective gel. Generally, various polymers in the concentration range of 0.5 to15% are used to provide the structural network for gel system. The selected polymer should show good swelling, syneresis and rheological properties suitable for solidifying stiffening the system[3]. Essential properties for gels include thixotropic, greaseless, easily spreadable, easily removed, good adhesion to mucous membrane, emollient, non-staining, compatible with several excipients and water soluble or miscible[4]. Delivery of drugs to the skin is an effective tool. However, poor permeability of ibuprofen is major problem for topical drug delivery. The permeability problems at the skin surface can be overcome by the use of drug penetration enhancers The physicochemical properties of the vehicle and the drug employed play important role for drug release[5]. Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The percutaneous absorption of drugs involves two consecutive processes: the release of the drug from the topical formulation, and its absorption into the skin at the site of application[6-8].Therefore the present study aims at studying the effect of various gelling agents with and without Pluronic F127 on the drug release keeping constant the type and concentration of penetration enhancer.

Materials:

Ibuprofen (Gift sample, Briocia pharma D P ltd), Carbopol-934, Carbopol 940, Hydroxypropyl methylcellulose(HPMCK100M), Hydroxyethylcellulose(HEC), Sodiumcarboxymethylcellulose (Na.CMC), Triethanolamine(TEA), Propylparaben, Sodium hydroxide, Potassium dihydrogen orthophosphate, isopropyl alcohol used were analytical grade. Pluronic F127 and Sepineo was obtained from Sigma Aldrich Banglore and Yasham Bio-science Pvt Ltd.Mumbai respectively.

Methods:

Procedure of gel preparation:

The composition of Ibuprofen topical gel formulae were shown in table 3. Gel formulations containing Polyacrylic acid polymer (carbopol 940 and carbopol 934) were prepared by dispersing the calculated amount of polymer in distilled water with the aid of constant stirring. The solid dispersion containing 1% drug was dissolved in IPA and this solution was transferred to the above gel and agitated for additional 20 min with continuous stirring. Solvent blend was transferred to carbopol container and agitated for additional 20 min. The dispersion was then allowed to hydrate and swell for 60 min. TEA was used as neutralizing agent to adjust the pH of formulations. For formulations with pluronicF127, it was added by cold technique at 4^0C.Preservatives propyl paraben was added finally and formulations were allowed to equilibrate for at least 24 hours at room temperature. Other gel formulations were prepared by dispersing HPMC, Na CMC, HEC and Sepineo in water with continuous agitation. To this gel, solid dispersion containing 1% drug was added and mix thoroughly with constant stirring.

Optimization design: Full factorial design 2FI

Full factorial design using three factors, one factor at six levels and other two at two levels was employed for optimization study. This gives 24 runs and hence in this design 3 factors were evaluated at all 24 possible combinations. The

Tele:

E-mail addresses: shilpapchaudhari78@yahoo.com

variables and their different levels studied are summarized in Table 1 and Table 2. The formulation layout for the optimization batches (F1-F24) is shown in Table 3. Depending upon these ranges all formulations were formulated as per Full factorial design.

Evaluation of gel containing ibuprofen gel:

The prepared ibuprofen gels were inspected for following parameters.

Appearance:

The prepared gel bases were inspected visually for clarity, colour and presence of any particles.

pH:

The pH of the various gel formulations was determined by using digital pH meter, which was calibrated before each use with standard buffer solutions at pH 4, 7, 9. The electrode was inserted into the sample 10 min priors to taking the reading at room temperature.

Homogeneity[9] :

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Grittiness [9]:

All the formulations were evaluated microscopically for the presence of particles if any no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Spreadability[9] :

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load, lesser the time taken for separation of two slides, better the spreadability.

It is calculated by using the formula: $S = M. L / T$

Where M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Viscosity measurements [10]:

A viscometer (Brookfield digital viscometer DV II+Pro) was used to measure the Viscosities (in cPs) of the gels. Samples of the gels were to settle over 30 min at the assay temperature (25±/1°C) before the measurements were taken.

Assay of gel formulations [11]:

Gel equivalent to 5mg of drug was dissolved in 100 ml of phosphate buffer (pH 7.4) .The volumetric flasks were kept for shaking for 15 min. Subsequently, the solution was filtered using the Whatmann filter paper no.42. Appropriate dilutions were done and the drug content was measured spectrophotometrically against placebo gel at 221 nm.

Diffusion studies: (diffusion cell)[12]:

Phosphate buffer of pH 6.8 was used for in vitro release as a receptor medium. The pretreated cellophane membrane was used in diffusion cell. The gel sample was applied on the cellophane membrane and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 6.8. The temperature of diffusion medium was thermostatically controlled at 37° ± 1° by surrounding water in jacket and the medium was stirred by magnetic stirrer. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 221nm against their respective blank.

Result And Discussion

In-Vitro Drug Release:

The in-vitro drug release for all gel formulations were studied as per full factorial design 2FI model. The in-vitro drug release was studied for Dependent variables Y, drug release at the end of 2 hours.

Data fitting to the model:

A three-factor, one at six levels and other two at two levels as per full factorial design provides 24 runs. All batches showed the drug release at 2hour (Y) in the range between 15.77% - 98.46% All the responses observed for 24 formulations were fitted into 2FI model when using Design Expert (State ease – Ver. 8.0.7.1) and the comparative values of R^2 and standard deviation are given in Table.along with the regression equation generated for each response. Only statistically significant ($p < 0.05$) coefficients are included in the equations. 3D Graphs showing effect of independent variables on drug release were shown in figure1.

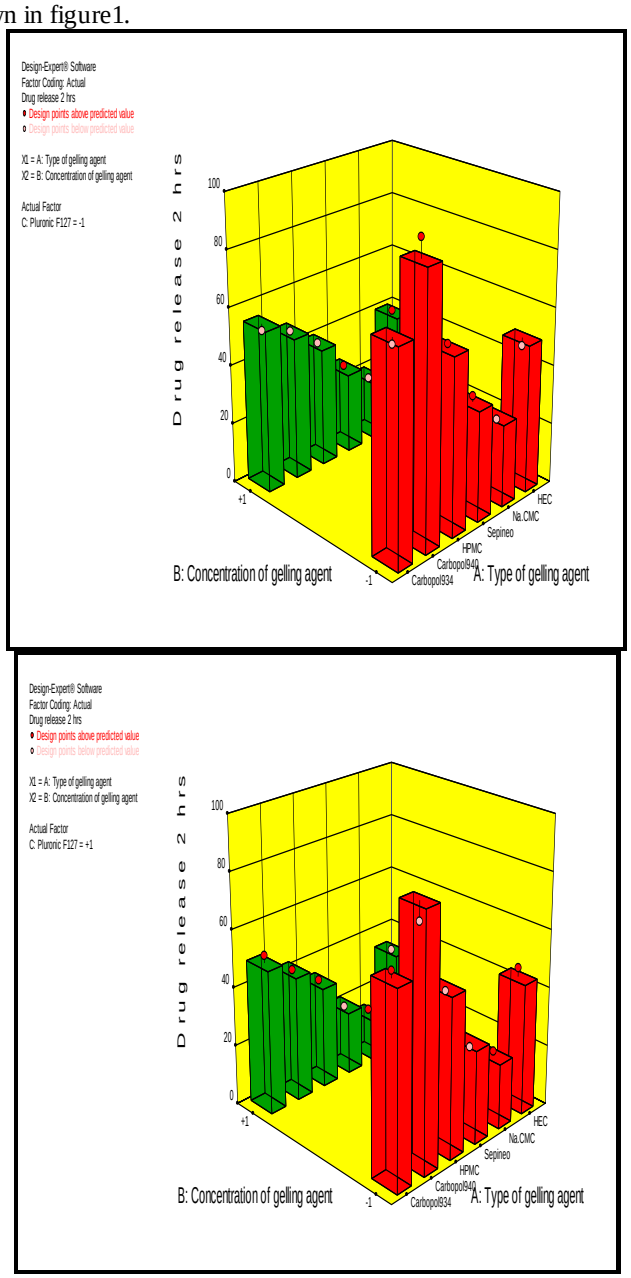

Figure 1. 3D graphs showing effect of independent variables on drug release from gel.(a)without Pluronic F127 (b) with Pluronic F127

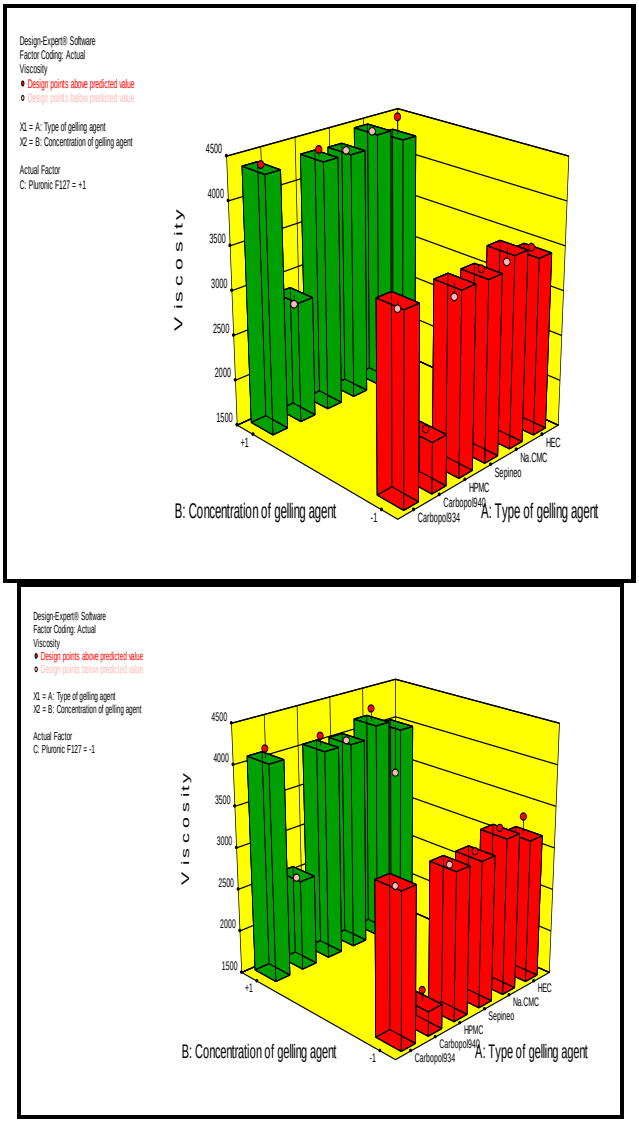

Figure 2. 3D Graphs Showing Effect of Independent Variables on Viscosity of Gel. (a) with Pluronic F127 (b) without Pluronic F127

Statistical analysis: The polynomial equation for 2F1model as given below:

Y=A0+A1X1+A2X2+A3X3+A12X1X2+A13X1X3+A23X 2X3+A11X12+A22X22+A33X32

Y=45.10+(15.80)X1a+22.50X1b+(2.66)X1c+(-15.21)X1d+(-23.63)X1e+(-8.83)X2a+(-2.97)X3+0.88X1aX2+(-12.48)X1bX2+(-0.73)X1cX2+3.84X1dX2+4.92X1eX2

In-vitro drug release of ibuprofen gels containing different concentration of Carbopol 934, Carbopol 940, HPMC, Na CMC, Sepineo and HEC are shown in figure1. The results of diffusion study reveal that drug release was inversely proportional to the concentration of gelling agent. Among all the gel formulations, carbopol940 showed superior drug release then followed by Carbopol 934,HPMC, Sepineo, Na CMC and HEC. The results shows that carbopol was good

gelling agent as compare to other gelling agents for preparations of gel formulations. The structure of C940 comprises linear acrylic acid chains that are cross-linked with allyl pentaethyritol to produce a fishnet-type arrangement which results more open structure and hence the fast drug release. For formulations containing pluronic F127 the results of diffusion study shows that incorporation of Pluronic F127 results in a sustaining the drug release. This is because the PluronicF127 is surface-active agent, and it forms micelles in solution at the elevated temperatures and these micelles come into contact with one another and results in formation of aggregates. The resulting structure of micelles was continuing growing in both size and number, which leads to a more rigid gel structure. Consequently, the release of the drug is retarded the drug release also depends on the viscosity of gel, more the viscosity is, lesser the drug release and the viscosity of gel was directly proportional to the concentration of gelling agent. Also In vitro Diffusion study showed that diffusion of formulation F6 and marketed gel were comparable.

Physicochemical characteristics of ibuprofen gel formulations:

Appearance: All formulations of gel showed good homogeneity with absence of lumps and grittiness. The clarity and transparency of prepared gels were also good.

PH: pH values for all formulations were found to be in between 6-8 these values are acceptable to avoid skin irritation.

Spreadability: with increasing the concentration of the gelling agents the spreadability decreased.

Viscosity: As polymer concentration increases viscosity increased from 1918.68centipoise to 4683.49 centipoise. Viscosity is negatively related to the release of active substance from formulations and its penetration through the diffusion barriers. The decrease in the drug release could be attributed to increased microviscosity of the gel by increasing polymer concentration. addition of pluronicF127 further influences gel viscosity and sustains drug release. 3D Graphs showing effect of independent variables on viscosity of gel were shown in figure2.

Conclusion:

On the basis of the above findings we can concluded that ibuprofen was successfully incorporated into the different topical gel preparations. From among all the developed formulation the formulation F6 containing carbopol 940 shows good spreadability, viscosity, drug release and comparable with marketed gel. Presence of Pluronic F127 decresed the drug release and increased the viscosity of the formulation.

References:

1.Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Tarada K. Formulation design of a novel fast- disintegrating tablet, Int J Pharm. 2005; 306: 83- 90.

2. Fitz GG, Patrono C. The coxibs selective inhibitors of cyclooxygenase-2. N Engl J Med. 2001; 345: 433–42

3. Cordero JA, Alarcon L, Escribano E, Obach R, Domenech J.A comparative study of the transdermal penetration of a series of nonsteroidal antiinflammatory drugs. J Pharm Sci.1997; 86(4):503-8

4. Klich CM. Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology. Jels and Jellies. New York, NY: Marcel Dekker Inc; 1992; 6: 415-39.

5. Suhonen MT, Bouwstra JA, Urtti A. Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations. J Control Release 1999; 59: 149-61.

6. Green PG, Flanagan M, Shroot B, Guy RH. Walters KA., Handgraft J.Pharmaceutical skin penetration enhancement, Ionotophoretic drug delivery. New York, NY: Marcel Dekker. 1993, 311-333.

7. Patel J, Patel B, Banwait H. Formulation and evaluation of topical aceclofenac gel using different gelling agent. Int. J. of Drug Dev & Res. 2011, 3: 156-164.

8. Dey S, Mazumdar B, Patel JR. Enhance percutaneous permeability of acyclovir by DMSO from topical gel formulation. Int. J. of Pharma. Sci and drug Res. 2009, 1: 13-18.

Table 1. Variables in Optimization Study

Parameter	Variables
Type of gelling agent	Independent variable(X1)
Concentration of gelling agent	Independent variable (X2)
% drug after 2hours	Dependent variable(Y1)

Table 2. Independent variables levels for ibuprofen gel formulation.

Independent variables	Levels
Factor X1(A) (Type of gelling agent)	6 levels (Carbopol 934, Carbopol 940, HPMC,Sepineo, Na.CMC, HEC)
FactorX2(B)(Concentration/Levels of gelling agent)	+1(2gm), -1(1gm)
FactorX_3(C) Presence of Pluronic F127	+1 (with) , -1(without)

Table 3. Full Factorial design Layout for Ibuprofen gel formulation

Formulation No.	X1	X2	X_3	Formulation No.	X1	X2	X_3
F1	Carbopol 934	-1	+1	F13	Sepineo	-1	+1
F2	Carbopol 934	-1	-1	F14	Sepineo	-1	-1
F3	Carbopol 934	+1	+1	F15	Sepineo	+1	+1
F4	Carbopol 934	+1	-1	F16	Sepineo	+1	-1
F5	Carbopol 940	-1	+1	F17	Na.CMC	-1	+1
F6	Carbopol 940	-1	-1	F18	Na.CMC	-1	-1
F7	Carbopol 940	+1	+1	F19	Na.CMC	+1	+1
F8	Carbopol 940	+1	-1	F20	Na.CMC	+1	-1
F9	HPMC	-1	+1	F21	HEC	-1	+1
F10	HPMC	-1	-1	F22	HEC	-1	-1
F11	HPMC	+1	+1	F23	HEC	+1	+1
F12	HPMC	+1	-1	F24	HEC	+1	-1

Table 4. Physicochemical characteristics of Ibuprofen gels formulations

Formulation No.	Spreadability (gm x cm/sec)	pH	Drug content(%)
F1	25.78	6.34	98.71
F2	26.27.	6.67	99.44
F3	19.11	6.56	97.86
F4	17.46	6.81	97.16
F5	30.87	6.98	96.17
F6	33.60	7.14	98.90
F7	26.14	6.43	99.34
F8	28.13	6.12	97.57
F9	26.97	7.12	98.87
F10	24.14	7.19	99.13
F11	18.98	6.13	99.76
F12	20.18	6.44	97.86
F13	23.44	7.23	98.58
F14	24.57	7.68	97.98
F15	19.32	7.56	101.24
F16	21.65	6.67	99.54
F17	22.19	6.64	98.69
F18	24.58	7.34	97.34
F19	20.76	7.29	98.97
F20	21.56	7.64	96.44
F21	19.45	6.98	96.75
F22	23.75	7.46	101.25
F23	17.64	6.49	99.37
F24	18.20	6.79	97.37

Table 5. Summary of Result of Regression Analysis for Response Y

Model	R^2	Adjusted R^2	Predicted R^2	S.D.	Remarks
2F1	0.9844	0.9674	0.9258	3.63	Suggested

9.Kaur LP, Garg R, Gupta GD. Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia. Int. J. Pharmacy and Pharm. Sci. 2010, 2: 43-47.

10.Gendy AME, Jun HW, Kassem AA. In vitro release studies of flurbiprofen from different topical formulations, Marcel Dekker, New York, Drug Dev Ind Pharm 2002;48:823-31.

11. Kane R, Naik S, Bumrela S, Kuchekar B. Preparation, physicochemical characterization, dissolution and formulate studies of irbesartan cyclodextrin inclusion complexes: Comparison between β-CD & HPβCD, Journal of Pharmaceutical Research, 2009; 2(8), p1359-1364.

12. Bregni C, Chiappetta D, Faiden N, Carlucci A, Garcia R, Pasquali R. Release study of diclofenac from new carbomers gels. Pak. J. Pharm. Sci.2008 ,21:12-16.