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Formulation and Evaluation of Topical Hydrogel Patch Containing Amide Type Local Anaesthetic Agent

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ABSTRACT

Hydrogel based drug delivery systems provides significant effect in designing sustained release topical dosage forms. Topical patch containing drug in hydrogel type polymer matrix provides not only targeted drug flux through the skin but also provides cooling effect on application site. Topical hydrogel patch containing lidocaine was prepared by using sodium poly acrylate as bioadhesive polymer. Effect of brij 30 and transcutol was also evaluated on topical flux of lidocaine base from hydrogel patch. Transcutol (10% w/w) provides sufficient drug release in contrast to brij 30(4%w/w) in prepared hydrogel patches. Maintenance of uniformity of weight is one of the critical task in preparation of hydrogel patch as polymers used are highly water absorbent. Excess amount of penetration enhancers leads to alter adhesive property of bioadhesive patch so formulation was optimized with Sodium polyacrylate (7%w/w) as the desired concentration for necessary bioadhesiveness and zinc oxide as cross linking agent.

KEYWORDS

Hydrogel, Topical patch, Lidocaine, Sodium polyacrylate, Brij 30, Transcutol.

INTRODUCTION

Lidocaine is a local anesthetic agent of the amide type. Local anesthetics reversibly block the initiation and conduction of nerve impulses by interfering with the flux of sodium ions though the neuronal membrane. Topical patch containing lidocaine has advantages of once a day application and controlled release of medicaments in topical area of skin and lesser side effects in comparison of oral dosing. Hydrogel patch is one of the ideal option for delivery of drugs for chronic pain treatment therapy. Hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium.[1,2]

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As the drug is used for pain relief, hydrogel type system will have advantage of patient compliance by providing cooling effect on the site of application. Pressure sensitive adhesive(PSA) based topical patch can not provide such advantage generally as water content will be lesser in such type of formulations. Hydrogels possess also a degree of flexibility very similar to natural tissue, due to their significant water content.[3] Furthermore, high degree of biocompatibility is exerted by hydrogel patch and overcomes problem of skin irritation on one day or more patch application.[4,5] Cellulose based polymers, polyacrylate polymers and natural gums can be used as hydrocolloids in topical patch formulation but maintenance of bioadhesiveness and providing sufficient drug flux is a major challenge in designing topical hydrogel patch.[6]

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MATERIAL AND METHOD

Lidocaine base and sodium polyacrylate solution (25%w/w) were obtained from Cadila Healthcare (Ahmedabad,India) and Astron chemicals (Ahmedbad, India) respectively. Gelatine, Poly vinyl acetate, Sodium Carboxy methyl cellulose (CMC Na) were purchased from Astron chemicals Ltd (Ahmedabad, India). Colloidal silicone dioxide (CSD) and bentonite were purchased from Sigma Aldrich (Mumbai, India). Polyethylene terepthalate release liner was purchased from Loparex ltd (Vapi,India) and Non woven polyester backing membrane was kindly supplied by Shakti pharmatech pvt. Ltd (Ahmedabad,India). Transcutol was obtained from Colorcon Asia Pvt. Ltd.(Mumbai, India) and Brij 30 was purchased through Angel tradelinks, (Rajkot,India). All other chemicals and solvents were of analytical grade.

Preparation of Hydrogel Patch

Accurately weighed Lidocaine was dissolved in Propylene glycole(PG)and Brij 30 and in a glass beaker by sonication till clear solution obtained as premix-1. Bentonite was added in gelatin solution to obtain uniform dispersion as premix-2. Uniform dispersion of CMC-Na, Zinc oxide and HPMC K4M was prepared in glycerin(or transcutol) as premix-3.Premix-2 and premix-1 was added in premix-3 simultaneously, followed by addition of sodium polyacrylate solution (25% w/v, pH 7.8) with constant high speed stirring. CSD was sprinkled over at the end and dispersion was stirred till uniformity of the blend is obtained. The film was prepared by casting the polymeric dispersion on release liner by using patch coating machine. Coated laminates were dried for 40 minutes at 70°C till dry matrix thickness remains 180-184µm to achieve 14gm/140cm^2 drug content per patch size. Concentrations of various excipients were studied as shown in table 1, in order to get optimal self adhesiveness and flux. Suitable sized Sample patches from various formulation batches are taken for further evaluation testing.

Physiochemical Characterization of Patches

Water Content

Water content of patch from each batch was determined by Karl Fischer instrument using small part of drug matrix after optimized drying time.

Adhesion Performance Testing

Achievement of bioadhesiveness in hydrogel patches preparation is one of the important task after sufficient drug flux achievement. In separate work, Placebo patches were prepared with variable concentration of Gelatine, SPA, CMC Na and PG in order to get sample patches of different adhesion parameters. In vitro adhesion testing was done by using adhesion testing instruments (Cheminstruments Inc, USA) and using standard parameters specified by PSTS-7(PRESSURE SENSITIVE TAPE COUNCIL,USA).In vivo testing was done by wearing placebo patches by human volunteers for 12 hrs duration. Best result for in vivo testing is 90% adherence(essentially no lift off of the skin).[7] Both results are correlated to get target in vitro adhesion testing values which were found to be 2.5 N/2.5mm as peel values, 1.4 N/1.5 cm^2 as tack values and 4.5 min as shear value. In vitro adhesion testing was done for each batch of formulation trials and compared with target values.

Content Uniformity Determination

A 7.94 cm^2 patch was cut into small pieces, after weighing a small piece was put into a 100-ml buffer (pH 4.5), and shaken continuously for 12 hours. Then the whole solution was ultrasonicated for 15 minutes. After filtration by mocropore® filter, the solution was injected to HPLC which includes a HPLC system (Cyberlab, USA) with c18 250 x 4.6 mm analytical column and UV detector set to 210 nm. The Mobile phase was mixture of 35%v/v methanol and 65%v/v 0.1 M phosphate buffer (pH 3.0) with 0.1%v/v triethanolamine at Flow rate of 1.2 ml/min.

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Table 1: Formulation Trials Starting from FD1 (FD1 based on Preformulation Studies)

FORMULATION CODE ----> / INGREDIENTS (% W/W)↓	F D 1	F D 2	F D3	F D 4	F D 5	F D 6	F D7	F D 8	F D 9	FD10
Lidocaine	5%	0%	5%	5%	5%	5%	5%	5%	5%	5%
Gelatin	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
PVA	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	-	-	-
CMC-Na	5%	5%	5%	5%	5%	5%	-	-	2%	2%
HPMC K4M	-	-	-	-	-	-	5%	5%	3%	3%
SPA	5%	5%	7%	7%	7%	7%	7%	9%	7%	7%
PG	5%	10%	20%	10%	10%	10%	15%	15%	20%	25%
Glycerol	20%	15%	10%	15%	15%	10%	-	-	-	-
Brij 30	-	-	-	-	-	4%				
Transcutol	-	-	-	-	-	-	10%	10%	10%	10%
Sorbitol	15%	15%	10%	15%	15%	15%	15%	15%	10%	10%
Zinc Oxide	0.5%	0.5%	0.5%	0.5%	0.5%	0.7%	0.7%	0.7%	0.7%	0.7%
CSD	-	-	-	-	-	0.5%	0.5%	0.5%	0.5%	0.5%
Bentonite	1%	1%	1%	1%	1%	0.5%	0.5%	0.5%	0.5%	1%
Purified water	**q.s. to make 100 gm**									

Retention time used was 9 min with 10 µl injection volume.[8] The test was done for ten random samples of each batch.

In vitro Skin Permeation

The in vitro permeation of lidocaine through defatted human cadaver skin was performed using modified franz diffusion cells. The active permeation area was 2 cm^2. Heat stripped skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin after removing the release liner. 20% propylene glycol in distilled water solution of 10 ml was added to the receptor site of the diffusion cell to initiate the skin permeation study. [9] The temperature of receptor solution was maintained in slow stirring condition at 37°C. The cumulative amount of lidocaine in the receptor compartment as a result of skin permeation calculation by assay using HPLC system and conditions mentioned earlier.

RESULTS AND DISCUSSION

Physiochemical Tests

Water Content Determination

Water content determination of hydrogel patch is important water because it has major contribution in the drug permeability from the skin and maintenance of drug concentration in specific area of patch after drying.[10] On the basis of water content shown in table 2, thickness of patch can be optimized. Here formulations contains Propylene glycol and Urea, which two ingredients only having skin penetration

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enhancing property and contributes in modification of stratum corneum of the skin for drug permeability. Effect of Sodium polyacrylate concentration as absorbent on water content was clearly seen. High water content significantly affects flux results that can be observed from flux results.

SPA potentiate anti adhesion effect of cellulose derivative generally. [11] In present study, from adhesion study it is revealed that there is lesser anti adhesion effect exerted on HPMC that on CMC Na by SPA.

Table 2: Physiochemical testing results of prepared patches

Analytical Methods	FD 1	FD 2	FD 3	FD 4	FD 5	FD 6	FD 7	FD 8	FD 9	FD 10
% Water content	10	10.5	15	18	18	20	24	24	29.4	30
Peel value N/25mm	0.0	00	1.1	1.3	1.7	1.7	2.0	2.5	2.54	2.53
Tack value N/sq cm	0.4	0.42	0.6	0.65	0.86	1.1	1.2	1.40	1.42	1.1
Shear value min	00	1.0	1.6	2.0	2.6	3.5	4.3	4.3	4.4	4.1
%Content Uniformity	100 ± 2.2	98.0 ± 2.3	97.5 ± 0.35	99.0 ± 1.2	100.1 ± 1.02	96.2 ± 1.5	98.01± 2.4	98.0 ± 1.3	97.5 ± 0.35	98.0 ± 1.2

Adhesion Performance Testing

Adhesion performance of the patch shows specific effect of Sodium polyacrylate as bioadhesive and co solvent propylene glycol (which was also acting as a plasticizer in the formulation). This was because of higher amount of SPA making patch of higher water content. The higher water content and more amounts of hydrophilic polymers are strongly making hydrogen bonding with Stainless steel plate surface leads to high peel resistance in the test. The residues of matrix remains on the surface of stainless steel plate when patches prepared from FD 5 batch are tested for adhesion testing. Which was the indication of poor matrix strength and the problem was eliminated by increasing concentration of Zinc oxide as crosslinker and CSD as matrix filler.

In vitro Skin Permeation

Flux results of different formulations are graphically summarized in following chart.Systems containing PG and fatty acid based penetration enhancers were more effective in drug diffusion in comparision to either PG or other enhancers alone.[12-14] Similar results were observed in present studies where increased concentration of PG provides better flux results. Transcutol provides sufficient flux 5.5 mcg/cm.sq in 14 hrs applications in comparison of topical patch containing brij 30 which provides 3.9 mcg/cm.sq. As told previously in results of water content determination, the water content of prepared patch was also showing effect on drug release.

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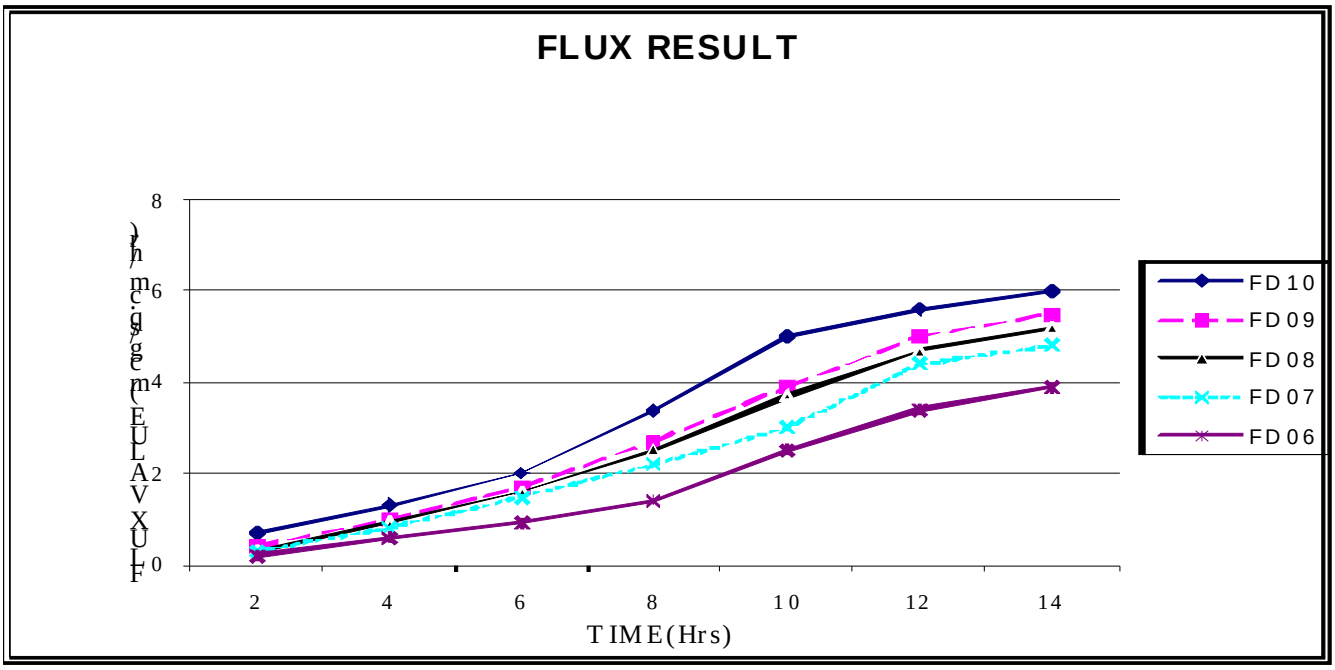

From the graph of drug release it is clearly observed that drug release was swelling controlled. The drug release profile is not linear but showed a slow initial permeation, followed by increase in flux and in the late times, the flux value decreased. The change in polymer content in the finished product can, in principle, modify swelling and/or diffusive mobility as well. So lidocaine in this transdermal patch is conditioned to the hydration of the polymeric components by water of skin and environment. Formulations with lesser SPA and higher CMC-Na were showing lesser flux than the formulations containing HPMC and higher amount of SPA.

CONCLUSION

Topical hydrogel patch containing lidocaine base with 10% transcutol provides sufficient drug flux. Sodium poly acrylate solution (7% w/w) provides excellent bioadhesion of topical patch and elastic behaviors of hydrocolloidal blend can be controlled by using low viscosity grade cellulose polymers like HPMCK4M. From the optimized formulation, it is possible to delivery lidocaine topically with effective therapeutic concentration for 12 to 14 hours duration.

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