Original Article

ISSN Print 2231 – 3648
Online 2231 – 3656

EFFICIENT FORMULATION AND EVALUATION OF FLURBIPROFEN TRANSDERMAL GEL COMPARED WITH MARKETED GEL BY USING WATER SOLUBLE POLYACRYLAMIDE POLYMER.

*,1 Jeevaprakash Ganapathi, 2Dheivanai Laxmanan, 2Selva kumar S
*,1 S Chaavan College of Pharmacy, Nellore, Andhra Pradesh, India-524346.
2Jagan's College of Pharmacy, Nellore, Andhra pradesh, India-524346.

Abstract

High molecular weights water soluble homopolymer type of acrylamide was reported to obtain very high viscosity in low concentration, transparency, film forming properties and useful in formation of transdermal gel. The flurfibrofen gels were prepared by using different concentration of polyacrylamide for topical drug delivery with an aim to gradually increase transparency and spreadability. These preparations were further compared with marketed known flurbiprofen gel. Spreadability and consistency of polyacrylamide gel containing flurbiprofen gel (S9) were 6.5g.cm/sec and 5mm as compared to 5.5g.cm/sec and 10mm respectively of known marketed gel, indicating good spreadability nature and consistency of the prepared gel (S9). The transparency nature of prepared batch (S9) was good as compared to the known marketed gel. The percent drug release was 97.85 and 98.84 from S9 and known marketed gel respectively. No irritation was felt in the skin irritation test. Stability studies conducting under accelerated condition were shown satisfactory results. It can be concluded that polyacrylamide gel containing flurbiprofen gel showed good consistency, spreadability, homogeneity and stability and had wider prospect for topical preparations.

Keywords: Topical drug delivery, Water soluble polymer, flurbiprofen gel, Transdermal gel, Polyacrylamide.

Introduction

Transdermal gel preparations are intended for superficial skin application or to some mucosal surfacesfor local action or skin penetration of medicament or for their soothing or protective action.[1] Gels are typically formed from a liquid phase that has been thickened with other ingredients. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release might be equivalent to that from a simple solution.[2] NSAID's nonsteroidal anti-inflammatory drugs are having excellent anti-inflammatory and analgesic activity but NSAID produces GIT ulceration, liver and kidney trouble produced in case of oral administration.

Author for Correspondence:
Jeevaprakash Ganapathi,
S Chaavan College of Pharmacy,
Nellore, Andhra Pradesh, India-524346
Email: jeevaprakash.g@gmail.com

In view to reduce adverse drug reaction associated with oral formulations, we have prepared as transdermal gel.[3] Polyacrylamide is used as water soluble or hydrophilic polymers topically in gel drug delivery system.[4] A range of grades based on molecular fractions of these polymer are available, they are typically used at a concentration between 1 to 5% in topical gel formulation. Due to their non greasy properties, they can provide easily washable film on the skin.[5] Polyacrylamide polymer of high molecular weight do not penetrate the skin and are non toxic.[6] Human cutaneous tolerance tests performed to evaluate the irritation of 1-5% w/w polyacrylamide indicated that the polymer was well tolerated. Polyacrylamide polymers have the potential to be naturally broken down and biodegradable and do not persist or accumulate in the environment.[7]

Material and methods

Flurbiprofen was purchased from Indian Drug House (Hyderabad, India).Polyacrylamide homopolymer were purchased by Suyog Chemicals Ltd (Nagpur, India). Sodium metabisulphite AR grade was procured by Sigma Pvt. Ltd. (Mumbai, India). All other ingredients were of analytical grade. Brufengel was purchased from market.

Procedure of gel preparation

About 5g of flurbiprofen was weighed and dissolved in 5g of isopropyl alcohol, to this solution, specified quantity of glycerin or propylene glycol or cocodiethanolamide was added and dissolved (solution A). Weighed quantity of polyacrylamide was added to the 75g of distilled water containing 0.1g of sodium metabisulfide used as antioxidant and continuously stirred to dissolve the same (solution B). Solution A and B were mixed thoroughly and the final weight was made upto 100g. (Table 01)

Table 01
Composition and concentration of flurbiprofen gel.

Batch No	Polymer (g)	Polymer (g)	Isopropyl alcohol (g)	Sodium Metabisulphite(g)	Glycerin (g)	Propylene glycol (g)	Cocodiethanolamide (g)	Distilled water (g)
S1	5	3	5	0.1	1	---	---	Upto 100
S2	5	3	5	0.1	3	---	---	Upto 100
S3	5	3	5	0.1	9	--	---	Upto 100
S4	5	3	5	0.1	---	1	---	Upto 100
S5	5	3	5	0.1	---	3	--	Upto 100
S6	5	3	5	0.1	---	9	--	Upto 100
S7	5	3	5	0.1	---	--	0.1	Upto 100
S8	5	3	5	0.1	--	--	0.3	Upto 100
S9	5	3	5	0.1	--	--	0.9	Upto 100

Precipitation or turbidity occurs in some of the batches (S1, S2, S3, S4, S5 and S6) of polyacrylamide gel containing flurbiprofen which has been due to the incompatibility in the system due to presence of glycerin or propylene glycol. Hence, these batches were discarded finally and remaining batches (S7, S8 and S9) were considered for further study.

Effective evaluation of polyacrylamide gel containing flurbiprofen and marketed gel

The above prepared polyacrylamide gel containing flurbiprofen and marketed gel were subjected to evaluation for the following parameters:

pH

The pH of the various gel preparations was determined by using digital pH meter. (Table2)

Spreadability

It was estimated by wooden block and glass slide apparatus. Weights about 20g were added to the sterile pan and the time was accurately noted for upper slide (movable) to separate completely from the fixed slides.[8] (Table 02)

Table 02: Each values of evaluation parameters of developed gel and marketed gel

Batch No	pH	Spreadability (g.cm/sec)	Consistency (60 sec)	Homogeneity	Skin irritation test	Drug content (%)
S 7	6.8	6.0	5mm	Good	nil	99.94
S8	6.8	6.5	5mm	Good	Nil	99.93
S9	6.8	7.0	5mm	Good	nil	99.98
Marketed Gel	6.8	5.5	10mm	Good	nil	99.90

Spreadability was calculated by the formula:

$S = M.L / T$

Where,

S = Spreadability

M = Weight tide to upper slide

L = Length of glass slide

T = Time taken to separate the slide completely from each other

Consistency

The estimation of consistency of the prepared gels was done by dropping a cone attached to a holding rod from a fixed distance of 10cm in other way that it should fall down on the centre of the glass cup was filled with the gel. The penetration by the cone was accurately measured from the surface of the gel to the tip of the cone inside of the gel. The distance traveled by cone in the period was noted down after 10sec.[9] (Table 02)

Homogeneity

All developed gels were properly tested for homogeneity by visual inspection after gels has been set in the container. These were tested for their appearance and presence of any aggregates. (Table 02)

Skin irritation test

Test for irritation was carefully performed as per guidelines after getting informed consent on human volunteers. For each gel, five volunteers were selected and 1.0g of formulated gel was applied on an area of 2 square inch to the back side of hand. The volunteers were examined for lesions or irritation. (Table 02)

Drug content

A specified quantity (100mg) of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for the period 2hr on mechanical shaker in order to get absolute solubility of drug. This solution was filtered and estimated spectrophotometrically at 276.0nm using phosphate buffer (pH 6.8) as blank.[10] (Table 02)

Accelerated stability studies

All the selected formulations were subjected to a stability testing for the period of three months as per ICH norms at a temperature of 40° ± 2°. All selected formulations were analyzed for the changes in appearance, pH or drug content by procedure stated earlier.[11] (Table 03)

Permeability studies[12-13]

Phosphate buffer of pH 6.8 was used for *in vitro* release as receptor medium. The pretreated skin of albino mice was used in fraz diffusion cell. The gel sample was applied on the skin of animal and then fixed in between donor and receptor compartment of quality diffusion cell. The receptor compartment contained phosphate buffer (100ml) of pH 6.8. The temperature of diffusion medium was thermostatically controlled at 37° ± 1° by surrounding water in jacket and the medium was continuously stirred by magnetic stirrer at speed of 500rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of freshly prepared fluid. The samples withdrawn were spectrophotometrically measured at 276nm against their blank. (Table 04 and Figure 01)

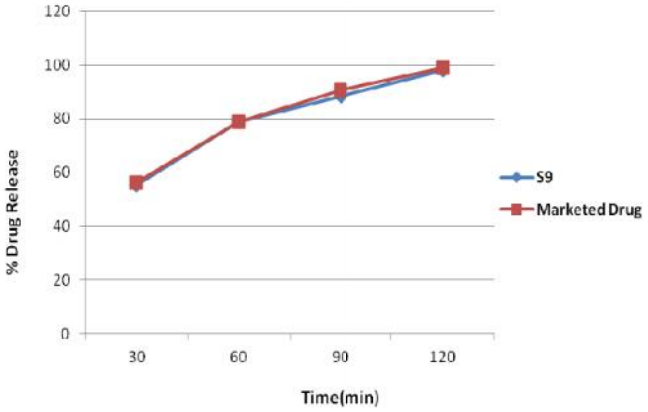
Table 03: Stability study of various kind prepared gel and marketed gel.

Sr No	Batches	Months	Appearance	pH	Drug Content (%)
01	F7	0	Clear	6.8	99.45
		1	Clear	6.6	97.74
		2	Clear	6.7	98.86
		3	Clear	6.6	96.62
02	F8	0	Clear	6.7	97.48
		1	Clear	6.8	98.64
		2	Clear	6.6	96.48
		3	Clear	6.6	99.46
03	F9	0	Clear	6.7	96.98
		1	Clear	6.8	98.26
		2	Clear	6.6	97.28
		3	Clear	6.7	99.97
04	Marketed gel	0	Clear	6.6	98.40
		1	Clear	6.5	99.89
		2	Clear	6.8	95.60
		3	Clear	6.7	96.48

Table 04: Permeability studies of S9 and marketed gel

Sr. No	Time Interval	Medium pH	%Drug release (min)	
			Batch S9	Marketed preparation
1	30	6.8	55.42	56.24
2	60	6.8	78.68	78.92
3	90	6.8	88.46	90.57
4	120	6.8	97.85	98.84

Figure 01: Drug permeability release profile of flurbiprofen gel formulation and S9



Results and discussion

The pH values of all formulated (S6, S7, S8 and S9) and marketed gel was 6.8.The values of measured spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of marketed gel was 5.5g.cm/sec while S9 was 6.5g.cm/sec, indicating spreadability of polyacrylamide containing flurbiprofen gel was good as compared to the marketed gel. The consistency reflects the capacity of the gel, this has been get ejected in uniform and desired quantity when the tube is squeezed. Consistency in shake of distance traveled by cone was 5mm of all developed batches when compared to 10mm of marketed gel. Consistency is inversely proportional to the distance traveled by falling cone. Though, the consistencies of polyacrylamide gel containing flurbiprofen were better as compared with marketed gel. All formulated and marketed gel showed good homogeneity with absence of lumps. The formulated preparations showed much clear and transparent when compared to marketed gel. The skin irritation studies of prepared transdermal gel were carried out on human volunteers and that confirmed the absence of any irritation on the applied surface. During the stability studies the visible appearance was clear and no significant variation in pH which was observed. Considering the accelerated stability studies and physiochemical parameters, batch S9 was selected for *in vitro* permeability release studies as well as compared with the marketed gel. *In vitro* Permeability study shown that permeation studies of F9 and marketed gel were comparable. It was concluded that polyacrylamide gel containing flurbiprofen (batch S9) produced better spreadability nature and consistency when compared to marketed flurbiprofen gel. The prepared S9 gel showed good homogeneity, no skin irritation, good stability and *in vitro* permeability was comparable with known marketed gel. The polyacrylamide form completely water washable gel due to its water solubility and has wider prospects to be used as a transdermal drug delivery system.

Conclusion

The prepared polymer being macromolecules of very high molecular weight remain unabsorbed on the skin and from our studies it can be concluded that polyacrylamide can be used for various topical dosage form for external application. It has been proved that optimized batch produces the gel with good consistency, homogeneity, spreadabiltity and stability. Hence, the polymer is water soluble; consequently, it forms water washable gel and has been wider prospects to be used as a transdermal drug delivery dosage form.

Acknowledgement

Authors are thankful to Management of both S.Chaavan College of Pharmacy and Jagan's College of Pharmacy (Nellore, Andhrapradesh, India) for providing necessary facilities to carry out this research work.

References

1. G.J.Narin, Encyclopedia of Pharmaceutical Technology. Marcel Decker, New Work. (1997).
2. British Pharmacopoeia, International Publication. Vol II. (1993).
3. A.C.Williams, Topical and Transdermal Formulation. Pharmaceuticals Press Published, New York. (2003).
4. H.S.Golinkin, Process for fracturing well formations using aqueous gels. US Patent No. US 4137182, (1979).
5. J.R.Fried , Polymer Science and Technology. Prentice-Hall, New Jersey. (1998).
6. D.J.King, R.R.Noss, Toxicity of polyacrylamide and acrylamide polymers. Environ Toxi Chem. 16, 1-4, (1989).
7. C.D.Rowland, J.R. Burton. A review on toxicity of various hydrophilic polymers. Environ Toxi Chem., 19, 2136-2139, (1999).
8. G.D.Gupta, R.S. Gound , Release rate of nimesulide from different gellants. Indian J Pharm Sci. 61: 229-234(1999).
9. L.William, Remington: The Science and Practice of Pharmacy. 20th edition. Mack Publishing Company. Easton, PA, (2000).
10. U.V.Sera, M.V.Ramana, *In vitro* skin absorption and drug release – a comparison of four commercial hydrophilic gel preparations for topical use. The Indian Pharmacist, 73, 356-360 (2006).
11. ICH Harmonized Tripartite Guidelines. Stability Testing of New Drug Substances and Products. ICH Committee, 8, (2003).
12. S.K.Sahoo, A.R.Samal, Estimation and evaluation of secnidazole The Indian Pharmacist.5(46), 73 (2006).
13. U. D. Shivhare, K. B. Jain, formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer, Digest Journal of Nanomaterials and Biostructures, 285 – 290 (2009).