ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Evaluation of Semi Synthetic Guar Gum Derivative for The Development of Transdermal Patches of Aceclofenac.

Shankrayya M*, Shyanubhogara Basavaraj, and Sreenivasa GM.

S.C.S. College of Pharmacy, Harapanahalli, Karnataka. India

ABSTRACT

Transdermal patches of aceclofenac were prepared using semi-synthetic polymer of Sodium carboxy methyl hydroxyl propyl guar and synthetic polymers like HPMC, Sodium CMC, PVA and PVP by solvent evaporation method. The prepared patches were evaluated for various physicochemical characteristics like thickness, weight variation, folding endurance, % moisture absorption, % elongation, tensile strength, drug content and *in-vitro* release. On the basis of results obtained from the *in-vitro* release study and physical evaluation the patches containing 2% Sodium carboxy methyl hydroxy propyl guar has shown better sustained release up to 24 hrs compared to all other patches formulated by synthetic polymers.

Keywords: Aceclofenac, HPMC, Sodium CMC, PVA, PVP.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Developments of several drug delivery systems are based on natural polymers that do not change their chemical structure but these materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Moreover these modify, drug release to achieve the dosage forms to release the drug in a constant manner and maintain steady state plasma concentration for the entire period of treatment to reduce the dose related adverse effects. The recent rediscovery of polysaccharide based materials is also attributable to new synthetic routes for their chemical modification, with the aim of promoting new biological activities and/or to modify the final properties of the biomaterials for specific purposes [1]

Polymers have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose [2] but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible. Because of their wide diversity in structure and physical properties natural polysaccharides have found a wide range of applications in the food, pharmaceutical and other industries [3].

Guar gum is a naturally occurring galactomannan polysaccharide; consists of chiefly high molecular weight hydro colloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due to presence of microbial enzymes. It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Guar gum has a molecular weight of approximately one million, giving it a high viscosity in solution. The high viscosity of guar gum results from its high molecular weight and long chain structure.

Guar gum is most commonly used at concentration below 1% w/v. High viscosity products form thick dispersions and form gels at 3% w/v. Guar and guar derivatives are available in lower viscosity grades for special applications. Guar gum has been used in various pharmaceutical applications; however, its pharmaceutical application limits its use because of uncontrolled rate of hydration, drop in viscosity on storage, poor interaction coefficient and susceptibility to microbial contamination. Moreover, guar imparts color when used in extemporaneous preparations and produces translucent or turbid solution in liquid dosage form. Keeping this in view, an attempt is made to overcome such limitations by suitably derivatizing the guar Gum to Sodium Carboxy Methyl Hydroxy Propyl Guar [4]

Formulation of transdermal therapeutic system (TTS) involves optimization of several factors such as release rate, stability, safety, convenience of use, etc. The key component in a TTS, which monitors the release of an active ingredient, is the rate controlling polymeric membrane. The polymer should possess good film forming properties, should be non-irritating, inert, and stable.

Though several polymers are already in use, a constant research is on, to explore new polymers for the TTS utility. Such an approach towards establishing new polymers is necessary, as not all the existing polymers possess all the ideal qualities. One of the major disadvantages of transdermal drug-delivery system as compared to other controlled release formulations is its high cost. A major percentage of formulation cost is due to the utility of expensive synthetic polymers.

The gel forming abilities of the polymer (NaCMHPG) from guar gum was established by the earlier literature and this has made an attempt to test the possibility of its use in designing TDD systems [5]

Aceclofenac is a Non-steroidal anti-inflammatory drug (NSAID) used for relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Aceclofenac is a phenylaceticacid derivative and it is an inhibitor of prostaglandins synthesis. Unfortunately, the systemic administration of this drug, similar to other NSAIDs, presents gastrointestinal side effects that could be avoided by using a topical application [6, 7, 8 and 9].

ISSN: 0975-8585

Hence, in the present study an attempt was made by utilizing guar gum derivative, as a polymer candidate for the formulation of transdermal films of aceclofenac. This was compared with other synthetic polymers such as HPMC, Sodium CMC, PVA and PVP.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained from Ronak laboratories, Ahmadabad. Sodium Carboxy Methyl Hydroxy Propyl Guar has been synthesized in our laboratory. HPMC, Sodium CMC, PVA and PVP from SD Fine chemicals, Mumbai and all other chemicals used were of analytical grade.

Method

Formulation of Drug Incorporated Transdermal Patches

The matrix-type transdermal patches containing aceclofenac were prepared using different ratios of NaCMHPG, HPMC, Sodium CMC, PVP and PVA as shown in table no: 1.The solutions were prepared by dissolving weighed quantities of polymers in water by heating on a water bath at 70^{o}C. The solutions were stirred for 20 minutes using magnetic stirrer and add calculated quantity of drug to the respective polymer solutions and stirred on the magnetic stirrer to obtain a uniform dispersion. Then the dispersion was poured in to the mould. The rate of evaporation of the solvent was controlled by inverting a cut funnel over the mould. Then the patches were cut into 1x1 cm^2 size. The patches were further subjected to various physical evaluations along with the *in-vitro* permeation studies [10]

Table 1: Formulation of Aceclofenac Transdermal Patches

Patches	NaCMHPG (mg)	HPMC (mg)	NaCMC (mg)	PVA:PVP (5:1) (mg)	Glycerine (ml)	Distilled Water (ml)
F1	100	-	-	-	0.1	10
F2	200	-	-	-	0.1	10
F3	-	100	-	-	0.1	10
F4	-	200	-	-	0.1	10
F5	-	-	100	-	0.1	10
F6	-	-	200	-	0.1	10
F7	-	-	-	100	0.1	10
F8	-	-	-	200	0.1	10

Drug excipient compatibility studies

Drug excipient compatibility studies were conducted using Fourier transform infrared (FTIR) spectroscopy for the drug alone, polymer alone and physical mixture of drug and polymer.

Evaluation of Films

Physicochemical properties such as thickness, weight variation, folding endurance, % moisture absorption, tensile strength, and drug content of prepared films were determined.

Physical Appearance: All the transdermal patches were visually inspected for their colour, flexibility, homogenous and smoothness [11, 12 and 13]

Thickness: The thickness of films (1×1cm^2) was measured by digital screw gauge (Mitotiyo. Japan). The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation [14]

Weight variation: Six films of same size (1 × 1cm^2) were weighed on electronic balance and average weight was calculated [15]

Folding endurance Studies. This study was determined by repeatedly folding a (4 × 4 cm^2) size films, at the same place, till it broke [16]

Moisture Absorption: The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. The average percentage moisture absorption of the films was calculated [16].

Tensile strength: Tensile strength of the films was determined by universal strength testing machine. It consists of two load cell grips, the lower one is fixed and upper one is movable. The test film of specific size (4× 1 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms [16]

Drug content: The patch of area (1 x 1cm^2) was cut in to small pieces and dissolved in small volume of methanol. Transferred in to a 100ml volumetric flask containing about 50ml phosphate buffer and remaining volume was made up to mark with phosphate buffer. The solution was filtered by using what man filter paper. The absorbance of the solution was measured at 274nm and the drug content was calculated [17]

***In-vitro* drug release studies**

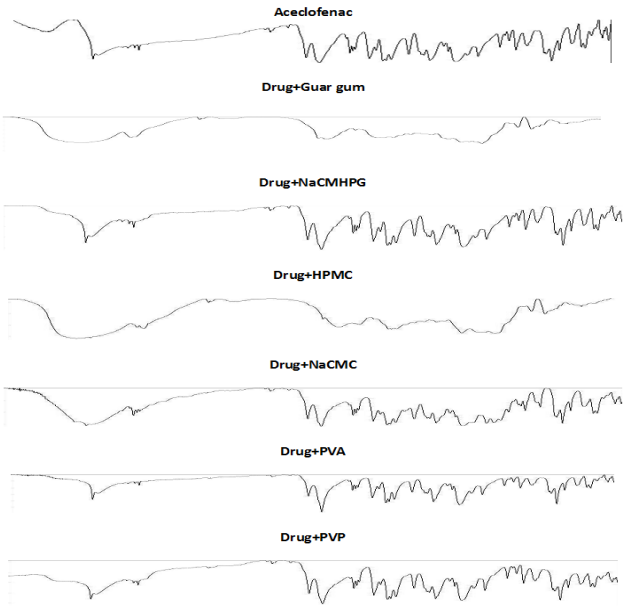
The *in-vitro* permeation studies of the patches were done using a modified Keshary-Chein diffusion cell designed and fabricated in our college laboratory. The cell consists of two compartments, the donor and the receptor compartment. The donor compartment (8 cm in length and 2 cm diameters) to which the cellophane membrane is tied. The receptor compartment contains 100ml of pH7.4 phosphate buffer solution and was stirred by a magnetic stirrer. Transdermal patches (1X1 cm^2) were placed in donor compartment and the donor cell was placed in to the receptor compartment such that the cellophane membrane is in contact with the buffer solution. The samples were withdrawn at interval of time up to 24 hours and equivalent volume of solution was replaced in to receptor compartment after each withdrawal [17].

Patches showing highest drug release with cellophane membrane were selected and used to carry out the further *in-vitro* permeation studies through the rat abdominal skin with same procedure as described above.

RESULT AND DISCUSSION

Drug excipients compatibility studies

Figure 1: FT-IR spectra's of drug, physical mixture of Drug and Polymers



This Preformulation study was carried out to study the compatibility of the pure drug aceclofenac with the polymers prior to the preparation of the transdermal patch. In IR spectra of aceclofenac major peaks of functional groups were found at the wavelength of 3318.89cm^{-1}, 1718.80cm^{-1}, 1344.30cm^{-1}, 1256.16cm^{-1} and 749.09 cm^{-1} All these peaks were also found into the drug-polymer mixture, spectra's indicates no interaction between the drug and polymers as shown in figure No.1.

Physicochemical evaluation of patches:

The results of the physicochemical evaluation of the patches were shown in table No. 2 and 3. The thickness ranged between 0.013 to 0.022±0.010 mm, which indicated that they were uniform in thickness. The weights ranged between 14.66 ± .169mg to 23.83 ±0.36 mg, which showed that different patches weights were relatively similar. Drug content uniformity among the various patches was observed and ranged from 60.74 ± 0.578 % to 92.91 ± 0.578 % which indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. The tensile strength ranged between 61 ± 0.152 to 239 ± 0.987 results showed that all the formulations had good mechanical strength along with flexibility. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. Moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduces bulkiness.

Table: 2: Physicochemical evaluation data of Aceclofenac Transdermal Patches

Patches	Polymer	Avg* Thickness (mm)	Avg* Weight (mg/cm^2)	Avg* Folding Endurance	Avg* % moisture Absorption
F1	2%NaCMHPG	0.018±0.003	18.11±0.120	94±0.132	1.84±0.067
F2	3%NaCMHPG	0.022±0.007	14.83±0.130	61±0.152	2.54±0.098
F3	2% HPMC	0.016±0.009	14.66±0.119	188±0.578	1.77±0.045
F4	3% HPMC	0.019±0.001	16.6±0.356	221±0.328	2.15±0.097
F5	2%NaCMC	0.021±0.005	20.16±0.321	63±0.362	3.67±0.099
F6	3%NaCMC	0.018±0.002	22.66±0.342	168±0.567	5.48±0.021
F7	2% PVA: PVP	0.020±0.004	23.83±0.362	239±0.987	2.96±0.064
F8	3% PVA: PVP	0.013±0.010	16.5±0.144	209±0.346	0.78±0.65

Table: 3: Physicochemical evaluation data of Aceclofenac Transdermal Patches

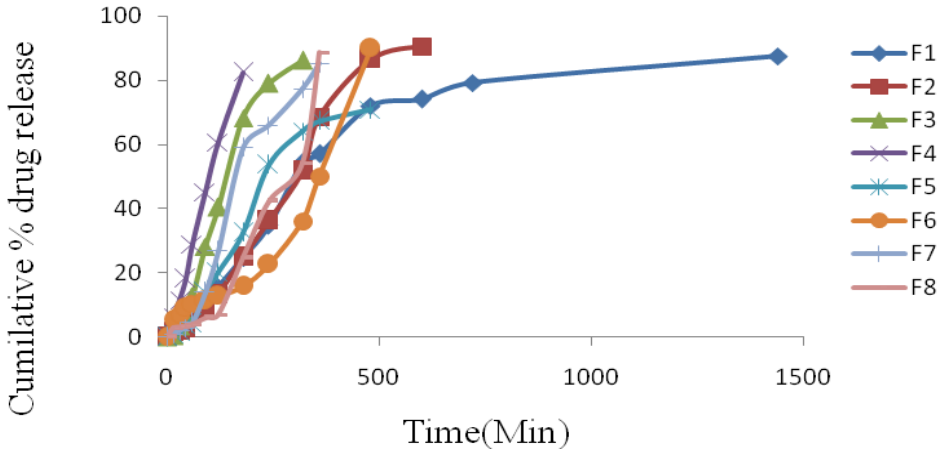
Patches	Polymer	Avg* Tensile Strength (mg/mm^2)	Avg* % Drug Content (mg/cm^2)
F1	2%NaCMHPG	2.318±0.289	91.00±0.437
F2	3%NaCMHPG	3.161±0.985	82.97±0.124
F3	2% HPMC	1.881±0.347	87.67±0.155
F4	3% HPMC	1.920±0.435	89.85±0.136
F5	2%NaCMC	1.350±0.345	80.41±0.799
F6	3%NaCMC	1.485±0.234	87.73±0.468
F7	2% PVA: PVP	1.508±0.231	92.91±0.578
F8	3% PVA: PVP	1.882±0.190	60.74±0.578

***In Vitro* Release Rate Study**

The *in vitro* release studies were carried out in a cellophane membrane to select the appropriate formulation, release profiles of the patches are given in Fig. 2.

ISSN: 0975-8585

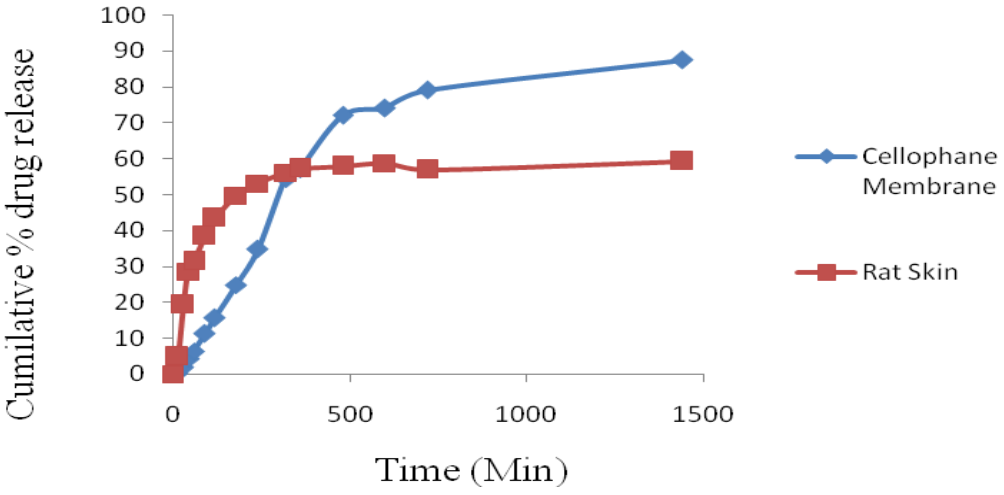
Figure: 2: Comparison of *In vitro* release profiles of Aceclofenac Transdermal patches (F1-F8)



The cumulative % drug release for formulations F2 to F8 was found to be 80.98%, 87.79%, 85.38%, 67.82%, 95.80% 66.12%, and 82.80%, respectively within 12 h and for F1 it was found 83.82% in 24 h. The formulation, F1 (2% NaCMHPG) is considered as a best formulation. From the formulations F3 to F8 it was concluded that the release pattern was not controlled by all synthetic polymers and there was a lower flux and lower diffusion rate through cellophane membrane for a period of 24 hours from formulation F1. Hence, this was selected to study the permeation/ diffusion through rat skin.

The release of drug from formulation F1 through rat skin was carried out. Cumulative % drug release from optimized formulation was shown in the figure No: 3 comparison of drug release from cellophane membrane with rat skin was been carried out, from the results it was evident that, there was lower flux and lower diffusion rate through rat skin was observed.

Figur 3: *Ex-vivo* drug release profile of Aceclofenac (F1) form cellophane membrane and skin



To study the drug release kinetics and mechanism, the results were subjected to zero order, first order, Higuchi's and Korsmeyer- peppas equation. The data and regression value was found to be in the range (0.691 to 0.979) which confirms first order release pattern. Further investigation was carried out to know whether diffusion was involved in the drug release by subjecting the data to Higuchi's equation. The lines obtained were comparatively linear (0.737 to 0.914) guiding the release of the drug through diffusion process.

CONCLUSION

The experiments on NaCMHPG have shown that the polymer wss a candidate of consideration for the formulation of transdermal drug-delivery systems. The polymer exhibited good film forming ability and could

be formulated into films possessing desired properties by varying the composition of the casting solution. The polymer is non-sensitizing and safe. *In vitro* and *ex vivo* permeation of aceclofenac shows that patch prepared by NaCMHPG was suitable when compared to patches prepared by other synthetic polymers. The result of the study shows that aceclofanac could be administered transdermal over period of 24 hours through the matrix type of TDDS.

ACKNOWLEDGEMENTS

The authors are highly indebted to President, Secretary, TMAE Society, and Principal, S. C. S. College of Pharmacy, Harapanahalli, Karnataka, India for providing necessary facilities to carry out the study.

REFERENCES

[1] Tommasina Coviello and Pietro Matricardi. J Contr Rele 2007; 119: 5-24.
[2] Guo JGW, Skinner WW, Harcum, and Barnum PE. PSTT 1998; 1254-261.
[3] Varshosaz JN, Tavakoli and Eram SA. Drug Deliv 2006; *13*:113-119.
[4] Mazhar Pasha and Swamy NGN. J Pharm Sci 2008; 21(1): 40-44.
[5] Swamy NGN, Mazhar Pasha and Zaheer Abbas. Indian J Pharm Edu Res 2010; 44(4). 310-314.
[6] Gowda DVB, Girish HG, Shivakumar and Afrasin Moin. Indian J Pharm Edu Res 2008; 42: 329 -36.
[7] Burkhard Heinz, Thomas Rau and Daniel Werner. Clin Pharmacol Ther 2003; 74: 22-27.
[8] Jaehwi Lee, Yoonjin Lee, Jongseok Kim, Mikyeong and Young Wook Choi. Arch Pharm Res 2005; 28: 197-02.
[9] Srinivas Mutalik. Int J Pharm 2008; 350: 279 -290.
[10] Saxena MS, Mutalik and Reddy MS. Indian Drugs 2006; 43(9): 740-5.
[11] Kusum D. and Paranjothy KLK. The Eastern Pharmacist 1998; 42 (485): 97-100.
[12] Raghuraman G and Velrajan. Indian J Pharm Sci 2002; 32-33.
[13] Panigrahi and Ghosny SK. Indian J Pharm Sci 2002; 79-82.
[14] Mohammed Gulzar,. Narayana Charyulu AR, Harish NM and Prabhakar Prabhu. Asian J Pharma 2009; 113-119.
[15] Venkateshwari YR., Jayachandra Babu, Sampath Kumar D and Mittal Neelam Pandit JKM. Indian Drugs 1995; 32 (5): 205**.**
[16] Prabhushankar GL, Gopalkrishna B, Manjunatha K M and Girisha CH. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(1):162-166.
[17] Prashant MS, Satturwar V, Fulzele K and Avinash Dorle. AAPS Pharm Sci Tech 2005; 6(4): 48-53.