ORIGINAL ARTICLE

STUDY OF HYDROXY PROPYL GUAR DERIVATIVE FOR ITS GELLING PROPERTY AND IT'S USE IN THE FORMULATION OF TENOXICAM GELS

NGN SWAMY, TS DHARMARAJAN AND KLK PARANJOTHI

Government College of Pharmacy, Bangalore-560 027, India

Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Sarjapur Road, Bangalore-560034, India

Department of Pharmaceutics, Al-Ameen College of Pharmacy, Hosur Road, Bangalore-27, India

ABSTRACT

Gels of tenoxicam 1% w/w were formulated using 2% w/w hydroxy propyl guar derivative and 3% w/w sodium carboxy methyl cellulose as gelling agents. A detailed rheological investigation was carried out to study the influence of preservative, drug and preservative, solvent system and the preservative, drug, solvent system and the preservative on the pseudoplastic behaviour of polymers. Hydroxy propyl guar derivative in 2% w/w strength resulted in gels with a higher pseudoplastic index value of 3.383 in contrast to an index value of 1.797 for a 3% w/w sodium carboxy methyl cellulose gels of a similar composition. The gels were stored at different temperatures and variations in pH values were recorded. Hydroxy propyl guar derivative based gels revealed variations in pH values over a narrow range in contrast to sodium carboxy methyl cellulose gels. The gels were subjected to short term stability studies by storing gels at refrigerated temperature, lab temperature, at 37°C and at 45°C. Gels based on hydroxy propyl guar derivative revealed better drug keeping qualities in contrast to sodium carboxy methyl cellulose stabilized gels. Release studies of tenoxicam from formulations across hairless albino mice skin revealed a zero order drug release pattern from both the formulations.

Keywords: Hydroxy propyl guar as a gel former, pseudoplasticity index, tenoxicam gels, rheological properties.

Corresponding author: E-mail: ngnswami@yahoo.co.in

INTRODUCTION

Gels (British Pharmacopoeia, 2000) consist of liquids gelled by means of suitable gelling agents. Gels comprise of homogeneous preparations intended to be applied to the skin or certain mucous membranes; gels may contain auxiliary substances such as antimicrobial preservatives, anti oxidants and stabilizers.

Tenoxicam (Rahman *et al.,* Year of Publication?) is a nonsteroidal anti-inflammatory and analgesic agent belonging to the chemical class of oxicams. Tenoxicam is indicated in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and rheumatic conditions and soft tissue injuries. The bioavailability of tenoxicam is 100% after oral administration and 80% after rectal administration. The major side effects are epigastric pain, nausea and vomiting. With a view to minimize the side effects following oral administration, development of gel formulation was undertaken. The objective of this study was to test the suitability of hydroxy propyl guar derivative (HPG) as a gelling agent for the topical administration of tenoxicam. The 2% w/w HPG based gels containing 1% w/w tenoxicam were compared and evaluated in respect to 3% w/w sodium carboxy methyl cellulose (NaCMC) gels of similar tenoxicam strength.

MATERIALS

Tenoxicam was obtained as a gift sample from M/s. Bangalore Pharmaceutical and Research Laboratories, 9th Block, Jayanagar, Bangalore-560011.

HPG (Swamy *et al.*) (DS 0.626) was prepared in our laboratory.

Propylene Glycol (Tehrani and Mohramizi, 2000) - Qualigens make.

Methyl paraben and propyl paraben – IP grade.

NaCMC – Loba-chemie, high viscosity grade.

Ethanol (Tehrani and Mohramizi, 2000) - 95% v/v.

METHOD

1 gm of tenoxicam was accurately weighed and transferred to a previously tared beaker and dissolved in about 75 gms. of water containing the preservatives, propylene glycol and ethanol with agitation till the tenoxicam dissolved completely. To one of the formulations, Gel-1, 3 gms of NaCMC was incorporated; while for the second formulation, Gel-2, 2 gms of HPG was incorporated. The agitation was effected by a slow moving propeller blade; enough distilled water was added in each case to adjust the weight to 100 gms. The agitation was continued for a further period of 6 hours to achieve homogeneity throughout the sample. Since tenoxicam is light sensitive, the preparation was carried out in subdued light. The gels were stored in airtight containers until subjected to evaluation tests. The composition of the gels namely, Gel-1 and Gel-2 is contained in table 1.

Table 1: Composition of tenoxicam gels

Ingredients	Gel-I	Gel-II
Tenoxicam	1gm	1 gm
Sodium CMC	3 gm	--------
HPG	--------	2 gm
Propylene glycol	10 gm	10 gm
Ethyl alcohol (95%)	5 gm	5 gm
Methyl paraben IP	0.18 gm	0.18 gm
Propyl paraben IP	0.02 gm	0.02 gm
Distilled water QS	100 gm	100 gm

EVALUATION OF GELS

1. *Rheological study:* The studies were conducted using Brook-field's Synchrolectric RVT model viscometer using spindle no.6. The studies were carried out on dispersions of (i) Polymer in preservative solution (ii) polymer and drug in preservative solution (iii) polymer and solvent system in preservative solution (iv) polymer, drug and solvent system in preservative solution. These studies were carried out to know the effect of drug, solvent system, drug and solvent system together on the pseudoplasticity behaviour of the polymer. Rheograms were constructed on 2% w/w HPG and 3% w/w NaCMC dispersions on systems as mentioned above. Subsequently log probability graphs were constructed to get the value for "N" – the index of pseudoplasticity by fitment to Martin and co-worker's equation (Martin *et al.,* 1983). Rheogram representations and log probability graphs for NaCMC gels and HPG gels are displayed in graph 1 and graph 2 respectively. Variations in "N" value with variations in the Gel composition is shown in table 2.

2. *Assay for drug content:* Tenoxicam reveals an absorption maxima at 360nm in methanol. The drug obeys Beer-Lambert's law in the concentration range of 1 to 8 mcg/ml. A calibration curve was constructed by using suitable dilutions of tenoxicam in methanol. The linear relationship revealed a slope value of 0.0424 and an intercept value of 0.0144. Assay for gels was carried out by extracting tenoxicam from gels with methanol, and effecting suitable dilutions and absorbances were measured. The drug contents were arrived mathematically by making use of the equation for straight line. Gel-1 revealed a drug content of 1.0413 whereas Gel-2 revealed a value of 1.0143 gms/100gms.

Table 2: Variations in N value (Pseudoplasticity index) with variations in the composition of gels viz Gel-1 and Gel-2

S. No.	Gel –1 (stabilizer 3%w/w NaCMC)	N (Values borrowed from respective graphs)	Gel – 2 (stabilizer 2% w/w HPG)	N (Values borrowed from respective graphs)
1.	Methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 1-1-A)	1.9439 (graph 1-1-B)	Methylparaben0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 2-1-A)	2.8614 (graph 2-1-B)
2.	Tenoxicam 1% w/w methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 1-2-A)	1.815 (graph 1-2-B)	Tenoxicam1% w/w methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 2-2-A)	3.3377 (graph 2-2-B)
3.	Propylene glycol 10%w/w ethyl alcohol 95% v/v – 5%w/w methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 1-3-A)	1.8078 (graph 1-3-B)	Propylene glycol 10%w/w Ethyl alcohol 95% v/v methyl paraben 0.18%w/w Propel paraben 0.02%w/w distilled water QS.100 grams (graph 2-3-A)	3.3051 (graph 2-3-B)
4.	Tenoxicam1% w/w Propylene glycol 10%w/w ethyl alcohol 95% v/v methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 1-4-A)	1.7978 (graph 1-4-B)	Tenoxicam1% w/w Propylene glycol 10%w/w Ethyl alcohol 95% v/v methyl paraben 0.18%w/w propyl paraben 0.02%w/w distilled water QS.100 grams (graph 2-4-A)	3.383 (graph 2-4-B)

Table 3: pH value for gels

S. No.	pH value			
	Freshly prepared sample	At the end of three months on samples stored at		
	(Lab temperature (25^0c)	Refrigerator temperature (5^oC)	37^oC	45^oC
Gel – I	6.78	7.47	7.64	7.45
Gel- II	6.81	6.94	6.96	6.86

Table 4: Short term stability data for tenoxicam gels

S. No.	Initial drug content	Drug content at the end of three months when stored at			
		5^oC	25^oC	37^oC	45^oC
Gel – I	0.954Gm	0.596 Gm	0.825Gm	0.718Gm	0.543Gm
Gel- II	1.008 Gm	0.869 Gm	0.901Gm	0.856Gm	0.575Gm

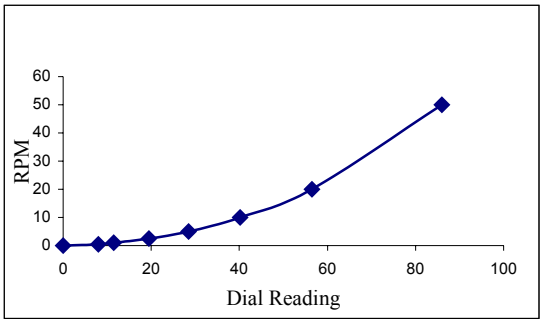
3. *pH measurement of gels* (Chi and Jun, 1991): The pH of the gels was measured using a calibrated pH meter for freshly formulated gels as also on gels stored at refrigerated temperatures, at 37^oC, 45^oC and at the end of 3 months. pH readings are recorded in table 3.

4. *Short term stability studies* (Paranjothi, 1994): The gels were stored at refrigerated temperature (5^oC), lab temperature (25^oC), at 37^oC and 45^oC and assayed after a period of 3 months. The data for drug retained in the formulations is contained in table 4.

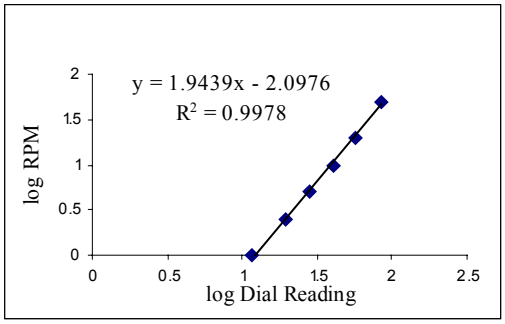
5. *Release of tenoxicam from gel formulations* (Sanghavi and Mahalaxmi 1991): The study was carried out by observing the permeation of tenoxicam across hairless albino mice skin. The skin was securely fastened to an inverted thistle funnel with the epidermis facing the inner bulb aspect of the funnel. About 0.5 gm of the tenoxicam gel was spread on the epidermis aspect of the skin before securing the skin to the funnel brim. The funnel brim was dipping in 100ml of the phosphate saline buffered to pH 5.8. Temperature was maintained at 37^oC with the help of electrically heated thermostatic magnetic stirrer.

4.5ml of the release medium was withdrawn at the end of 30 minutes and subsequently at hourly intervals. Each time the withdrawn sample was replaced by an equivalent amount of isotonic buffered solution. Tenoxicam in isotonic solution buffered to pH 5.8 revealed a shift in the absorption maxima from 360 to 374.8 nm. Accordingly, the calibration curve was reconstructed in isotonic solution buffered to pH 5.8 at 374.8 nm. The linear relation-

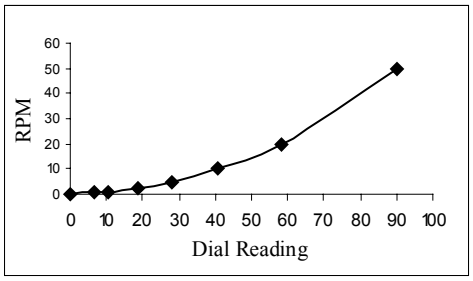
Graph 1: Rheograms for NaCMC gels



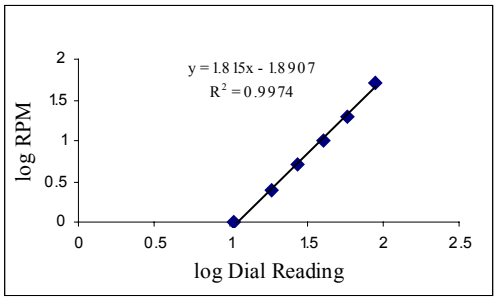
Graph 1-1-A: Rheogram for 3 % W/W Na CMC gels containing 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



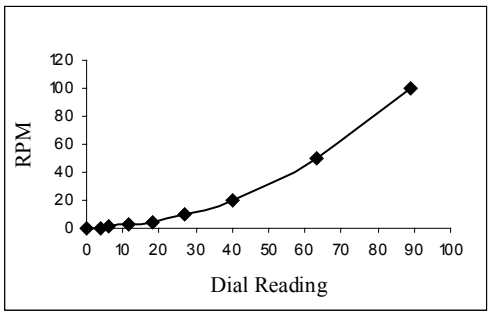
Graph 1-1-B: Log probability graph for 3 % W/W Na CMC gel containing 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



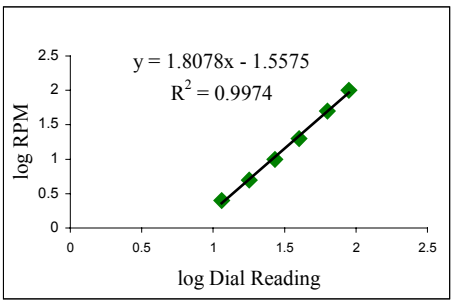
Graph 1-2-A: Rheogram for 3 % W/W Na CMC gels containing 0.1 % W/W tenoxicam, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



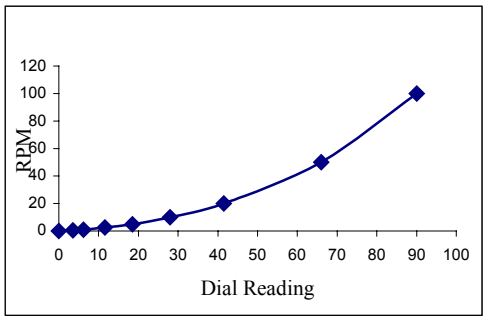
Graph 1-2-B: Log probability graph for 3 % W/W Na CMC gel containing 1 % W/W tenoxicam, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



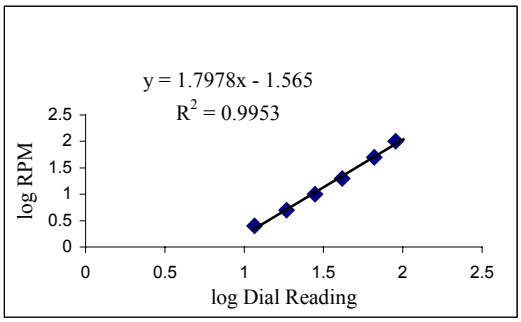
Graph 1-3-A: Rheogram for 3 % W/W Na CMC gel containing 10 % W/W propylene glycol, 5 % W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water



Graph 1-3-B: Log probability graph for 3 % W/W Na CMC gel conatining 10 % W/W propylene glycol, 5 % W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water

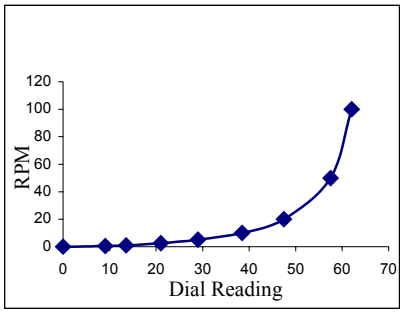


Graph 1-4-A: Rheogram for 3 % W/W Na CMC gel containing 1% W/W tenoxicam, 10% W/W propylene glycol, 5% W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water

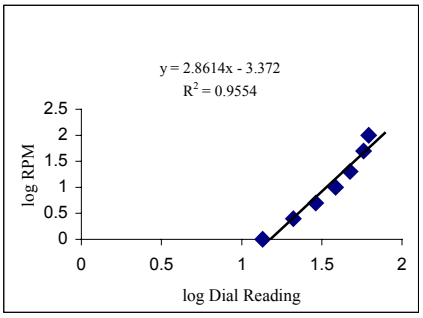


Graph 1-4-B: Log probability graph for 3 % W/W Na CMC gel containing 1 % W/W tenoxicam, 10 % W/W propylene glycol, 5 % W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water

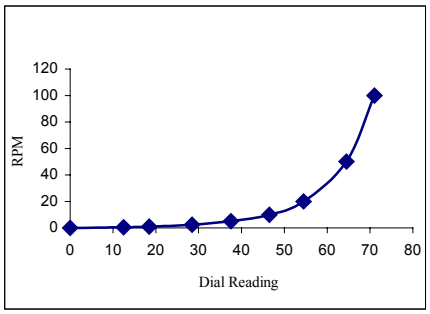
Graph-2: Rheograms for HPG gels



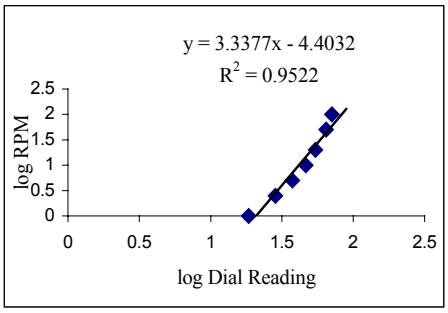
Graph 2-1-A: Rheogram for 2% W/W HPG gel containing 0.18% W/W methyl paraben and 0.02% W/W propyl paraben in distilled water.



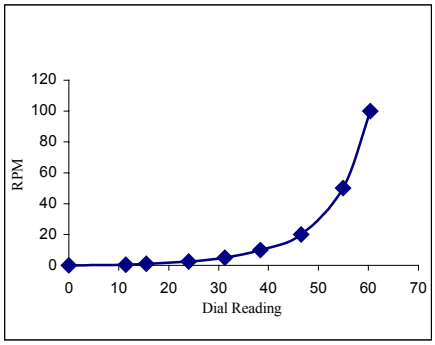
Graph 2-1-B: Log probability for 2% W/W HPG gel containing 0.18% W/W methyl paraben and 0.02% W/W propyl paraben in distilled water.



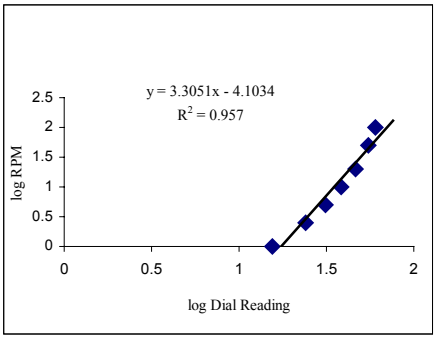
Graph 2-2-A: Rheogram for 2% W/W HPG gel conataining 1% W/W tenoxicam, 0.18% W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



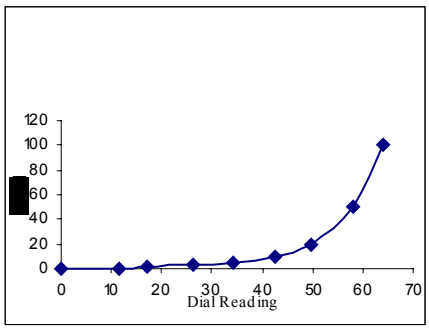
Graph 2-2-B: Log probability graph for 2% W/W HPG gel containing 1% W/W tenoxicam, 0.18% W/W methyl paraben and 0.02 % W/w propyl paraben in distilled water.



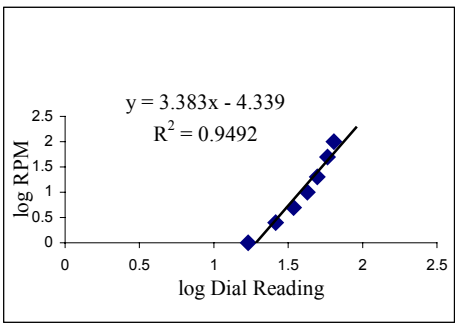
Graph 2-3-A: Rheogram for 2% W/W HPG gel containing 10% W/W propylene glycol, 5% W/W ethanol, 0.18% W/W methyl paraben and 0.02% W/W propyl paraben in distilled water.



Graph 2-3-B: Log probability for 2% W/W HPG gel containing 10% W/W propylene glycol, 5% W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water.



Graph 2-4-A: Rheogram for 2 % W/W HPG gel containing 1 % W/W tenoxicam, 10 % W/W propylene glycol, 5 % W/W ethanol, 0.18 % W/W methyl paraben and 0.02 % W/W propyl paraben in distilled water



Graph 2-4-B: Log probability graph for 2 % W/W HPG gel containing 1 % tenoxicam, 10 % W/W propylene glycol, 5% W/W ethanol, 0.18% W/W methyl paraben and 0.02% W/W propyl paraben in distilled water

Table 5: Cumulative drug release data for tenoxicam from Gel-I and Gel –II across hairless albino mice skin

S. No.	Time in hours	Gel-I		Gel-II	
		%CDR	% drug retained in the Gel	%CDR	% drug retained in the Gel
1	0.5	3.66	96.34	5.26	94.74
2	1.5	5.33	94.67	6.30	93.70
3	2.5	7.03	92.97	6.62	93.38
4	3.5	9.37	90.63	7.03	92.97
5	4.5	10.69	89.31	7.88	92.12
6	5.5	12.29	87.71	9.45	90.55
7	6.5	12.78	87.22	10.75	89.25
8	7.5	13.31	86.69	12.29	87.71

ship revealed a slope value of 0.0407 and an intercept value of 0.0169. Data for determination of order of release of tenoxicam from Gel-1 and Gel-2 is contained in table 5 and graphical representation for drug release is contained in graph 3.

6. *T.L.C. study*: The study was carried out to rule out any interaction between the polymer and the drug. Silica gel plates "Kiesel gel" 60F–254, 20x10 cms (E. Merck Dermstadt) were used for T.L.C. study. Solvent system consisted of equal volumes of methanol and 5.61 pH buffer, maintained with disodium hydrogen phosphate and pH adjusted to 5.61 by phosphoric acid addition. The spots were allowed to fluoresce under U.V. and photograph. The Rf value for Gel-1, Gel-2 and that of pure tenoxicam was 0.85.

RESULTS AND DISCUSSION

A 1% w/w dispersion of tenoxicam, stabilized with 2% w/w HPG resulted in a gel having a higher viscosity in contrast to a 1% w/w tenoxicam dispersion stabilized with 3% w/w NaCMC. From the rheological studies, it is observed that HPG stabilized gels revealed a "N" value of 3.383 in contrast to a "N" value of 1.798 in case of NaCMC gels. Short term stability studies have shown a higher decline of drug content in Gel-1 in contrast to Gel-2 when stored at 0°C, 25°C, 37°C and 45°C. Fairly reproducible pH values were observed in case of Gel-1 upon storage where as in case of Gel-2, the pH changed towards alkalinity.

T.L.C. studies yielded a Rf value of 0.85 for Gel-1, Gel-2, and for that of the pure drug,thereby indicating the absence of any interaction between the drug and the polymer. A CDR of 13.31% was observed from Gel-1 across hairless albino mice skin in contrast to a CDR of 12.29% in case of Gel-2 at the end of 7.5 hours. The release of tenoxicam from both Gel-1 and Gel-2 followed zero-order kinetics.

To conclude, it can be said that a 2%w/w HPG gel has in comparison to a 3% w/w NaCMC gel, revealed superior pseudoplastic behaviour, superior drug keeping qualities on storage at 5°C, 25°C, and 37°C, comparable drug release pattern across hairless albino mice skin; both polymers have revealed compatibility with tenoxicam. Since HPG is used at a lesser strength, it can be claimed that HPG is superior to NaCMC as a gelling agent.

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2. Principal, Govt. College of Pharmacy, Bangalore – 560027, India.

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