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Studies on Hydrotrope Potato Starch Gel as Topical Carrier for Rofecoxib

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ABSTRACT

The potential gastrointestinal disorders associated with oral administration of Rofecoxib can be avoided by delivering the drug to the inflammation site at a sustained, concentrated level over an extended period of time. The present research has been undertaken with the aim to develop a transdermal gel formulation of Rofecoxib, which would attenuate the gastrointestinal related toxicities associated with oral administration. Starches form an important class of gel forming material of natural origin obtained from various sources like potato, corn, maize, wheat, rice etc. Various batches of Hydrotrope-gelled potato starch were prepared using 3^2 factorial designs. Potato starch along with hydrotropic salts like sodium salicylate and sodium benzoate were used. The formulations were evaluated for various parameters such as physical appearance, homogencity, P^H, drug content uniformity, and rheological properties. In- vitro drug release of Rofecoxib from the formulations was studied using Keshary-Chein type diffusion cell. It was observed that hydrotropic salt sodium salicylate induced better gelling than sodium benzoate. Higher concentration of salts yielded more viscous gels. The gels prepared using sodium benzoate showed higher viscosity. In-vitro release data indicated that hydrotrope-gelled starch containing 1% Rofecoxib in formulation containing 15%w/w sodium salicylate and 5%w/w potato starch (W_{7SPD}) with a percent average release of 16.65% in 6 hrs while formulation containing 15%w/w sodium salicylate and 10%w/w potato starch (W_{8SPD}) showed a release of 16.39% in 6hrs. These formulations showed much higher release when compared to some marketed formulations whose percent release were between the ranges of 15.81% to 4.77% in 6hrs.

Key words-Potato Starch, Gel, Spreatability, Rofecoxib, Keshary-Chein type diffusion cell.

INTRODUCTION

Oral administration of Rofecoxib associated with gastrointestinal disturbances that can be avoided by delivering the drug to the inflammation site at a sustained, concentrated level over an extended period of time. [1]

Rofecoxib (ROX) is a commonly used as Anti-inflammatory, analgesic, antipyretic agent. Chemically it is 4–[4-Methyl sulfonyl) phenyl]–3–phenyl–2 (5H)–Furanone. [2, 3]

Now a days factorial design is most frequently used for preparation of various batches of pharmaceutical products. [4]

Hydrotropes are recognized as a class of compounds which, in fairly high concentrations, increase the solubility of a variety of poorly soluble drugs in water and the solubility of water in organic solvents. Another feature of hydrotropes, although less extensively investigated, is their effect on biocolloids. For instance, hydrotropic agents were shown to inhibit the gelling of gelatin solutions, denature haemoglobin, induce haemolysis in hypertonic solutions increase liposomal membrane permeability and considerably affect the properties of albumin in different systems. As far as starch is concerned, hydrotropic salts were reported to induce swelling and gelatinization of starch without the use of heat, i.e. decrease the gelatinization temperature, the effect being structure and concentration dependent. [5] As part of trials of explores new pharmaceutical applications of hydrotropy, the present work reports on some properties of hydrotrope-gelled starch, particularly release of solutes. This gel may be of pharmaceutical interest because of the high solubilizing capacity conferred by the hydrotropic gelling agent. The effect of sodium salicylate and sodium benzoate on the stability and dissolution rate of Rofecoxib was also studied.

MATERIALS AND METHODS

Materials

Model drug Rofecoxib was obtained from Aarti Drugs Limited, Mumbai, (MS) India. Sodium salicylate and sodium benzoate (Loba Chemie Pvt. Ltd., Mumbai), Potato starch (Sd Fine Chem Ltd., Boisar) were used in the study. All other chemicals and reagents used were of analytical reagent grade.

Preparation of hydrotope-gelled starch

Hydrotropic salts like Sodium Salicylate and Sodium Benzoate were used as the gelling agents. Preliminary trials were carried out using different concentrations of potato starch (5-15% w/w) and sodium salicylate (5-15% w/w) in order to determine the concentration of either ingredient required to obtain a satisfactory gel in terms of complete gelatinization with loss of birefringence of starch granules under the polarized-light microscope. Gels were prepared by adding the required amount of starch to sodium salicylate solution of predetermined concentration at ambient temperature with constant stirring until complete gelatinization was achieved. For the preparation of drug loaded gels, a model drug (Rofecoxib) was solubilized in the sodium salicylate solution prior to the addition of starch.

Table 1.Different formulations prepared

W_{1SP}	5% w/w sodium salicylate + 5% w/w potato starch
W_{2SP}	5% w/w sodium salicylate + 10% w/w potato starch
W_{3SP}	5% w/w sodium salicylate + 15% w/w potato starch
W_{4SP}	10% w/w sodium salicylate + 5% w/w potato starch
W_{5SP}	10% w/w sodium salicylate + 10% w/w potato starch

W_{6SP}	10% w/w sodium salicylate + 15% w/w potato starch
W_{7SP}	15% w/w sodium salicylate + 5% w/w potato starch
W_{8SP}	15% w/w sodium salicylate + 10% w/w potato starch
W_{9SP}	15% w/w sodium salicylate + 15% w/w potato starch
W_{1BP}	5% w/w sodium benzoate + 5% w/w potato starch
W_{2BP}	5% w/w sodium benzoate + 10% w/w potato starch
W_{3BP}	5% w/w sodium benzoate + 15% w/w potato starch
W_{4BP}	10% w/w sodium benzoate + 5% w/w potato starch
W_{5BP}	10% w/w sodium benzoate + 10% w/w potato starch
W_{6BP}	10% w/w sodium benzoate + 15% w/w potato starch
W_{7BP}	15% w/w sodium benzoate + 5% w/w potato starch
W_{8BP}	15% w/w sodium benzoate + 10% w/w potato starch
W_{9BP}	15% w/w sodium benzoate + 15% w/w potato starch
W_{SPD}	Sodium Salicylate + Potato Starch + Drug
W_{BPD}	Sodium Benzoate + Potato Starch + Drug

Evaluation of formulations:

Physical Appearance and Homogeneity

The formulations containing Rofecoxib were visually inspected for clarity, color, presence of any particles and fibers and homogeneity. [6]

P^H Measurement

The electrode was inserted into the sample for 10 minutes, prior to taking the readings at room temperature. The pH of hydrotrope-gelled starch without drug and formulation containing Rofecoxib were determined by Digital Elico pH meter. [7]

Drug Content Uniformity

The Rofecoxib content in different formulations of Rofecoxib gels was determined. A gel equivalent to 25 mg of drug was weighed accurately and transferred into a 50ml beaker. Methanol (20 ml) was added to the beaker and covered with aluminium foil. Sonicated for 20 mins and then transferred into a 100 ml volumetric flask. Washed the beaker with 20-30 ml of 0.5M NaOH solution and transferred content into the 100 ml volumetric flask and finally make up the volume up to the mark with 0.5M NaOH solution. After that solution was filtered through Whatmann Filter paper No. 41. Filtrate (10 ml) was then transferred into another 100 ml volumetric flask and diluted up to the mark with 0.5M NaOH solution. The absorbance of the sample solution was recorded at 355nm by using UV-Visible Spectrophotometer. The drug content was calculated. [8]

Rheological Properties:

The following rheological properties of the formulations were determined:

Spreadability [9, 10]

Spreadability of the formulations was determined by an apparatus suggested by Mutimer et al, which was suitably modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on the block. An excess of gels (about 2g) under study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate having the dimensions of the fixed ground plate and provided with the hook. A 300g weight was placed on the top of two plates for five minutes to expel air and to provide a uniform film of the gel between the plates. Excess of the gel was scrapped off from the edges. The top plate was then subjected to a pull of

30g. With the help of a string attached to the hook and the time (in sec) required by the top plate to cover a distance of 10 cms be noted. A shorter the time interval indicates better spreadability.

The spreadability was determined by special apparatus and it was calculated using the formula:

$$S = \frac{ml}{t}$$

Where, S = Spreadability
m = weight tied to the upper slide,
l = length of the glass slide
t = time taken in sec.

Determination of Viscosity [11]:
The viscosity of formulated gels was determined. The viscosity was determined using a Brookfield Viscometer. The sample holder taken for the viscosity measurement was filled with the sample and then inserted into a flow jacket mounted on the viscometer. The sample adaptor (spindle), rotated at an optimum speed was used to measure the viscosity of the preparation. The sample was allowed to settle for five minutes prior to taking the readings.

***In-vitro* drug release studies**
In vitro release studies of Rofecoxib from gel formulations were performed using a Keshary-Chein type diffusion cell. [12]

The cell consists of two chambers, the donor compartment which is open to air and the receptor compartment. Both the compartments are separated and clamped together using clips of strong grip. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37±2ºC, by using a thermostatic hot plate temperature control available on the magnetic stirrer as circulatory pump system. The content of the donor compartment (gel) and those of the receptor compartment (saline-phosphate buffer pH 5.4) were separated by cellophane membrane (previously soaked overnight in distilled water) sandwiched between two compartments. The magnetic needles stir the diffusion media to prevent the formation of concentrated drug solution layer below the cellophane membrane. At each sampling time the solution in the receiver compartment was completely withdrawn and replaced with saline-phosphate buffer pH 5.4.

Samples were taken from solvent side at intervals and assayed spectrophotometrically at 355nm.

The constants during the in-vitro drug release studies included:
1. Volume of Keshary-Chein receptor compartment = 13 ml.
2. Release medium = saline-phosphate buffer pH 5.4
3. Temperature of release medium = 37±2ºC.

Model Fitting for Release of Rofecoxib:
The different drug release profiles were analyzed using a preprogrammed computer package. The best fit models for the following release profiles were analyzed:
1) Zero order; 2) First order; 3) Matrix; 4) Peppas; 5) Hixon-Crowell.

Stability studies

The gels were filled in collapsible tubes (with epoxy lining or lacquered) and gross visual appearance was observed followed by the initial drug content determination by chemical analysis. The samples were divided into two batches and stored at 28±4ºC and 4±1^{0}C for 24 weeks (6 months) respectively. Samples were withdrawn for their stability analysis. At the end of 24th week, drug content determination, pH and viscosity measurement were carried out to assess the qualitative integrity of the drug and physical integrity of the formulation.

The stability analysis was carried out for the following parameters:

1. Chemical analysis (drug content)
2. PH of gel formulation: This was determined using the method mentioned under pH determination of gels.
3. Rheological evaluation (viscosity and spread ability). [13]

RESULTS AND DISCUSSION

Hydrotrope-gelled **POTATO** starch containing Rofecoxib (ROX):

1. Physical Appearance and Homogeneity

The physical appearance of hydrotrope-gelled starch containing ROX was found to be generally white opaque to white translucent with good homogeneity.

Table-2.Physical Appearance & Homogeneity of Hydrotrope-Gelled Starch containing Model drug

Sr. No.	Formulation Code	Physical Appearance	Homogeneity
1.	W_{7SpD}	White Opaque	++
2.	W_{8SpD}	White Opaque	++
3.	W_{7BpD}	White Opaque	++
4.	W_{8BpD}	White Opaque	++

++ = *Good*

2. P^H Measurement

The pH was found to be in the range between 6.56 to 6.81 for potato starch and sodium salicylate gels and for potato starch and sodium benzoate was observed in the range of 7.39 to 7.94.The pH of formulations containing Rofecoxib along with sodium benzoate was observed that (W_{7BPD}, W_{8BPD},) between 7.54 to 7.57, which were much higher than formulation containing Rofecoxib along with sodium salicylate (W_{7SPD}, w_{8SPD},) which ranged between pH 6.37 to 6.38.

Table-3.P^H of Hydrotrope-gelled starch-containing Rofecoxib (Potato Starch & Sodium Salicylate)

Sr. No.	Formulation Code	PH
1.	$W_{7\ S\text{-}P\text{-}D}$	6.37
2.	$W_{8\ S\text{-}P\text{-}D}$	6.38

Table4.pH of Hydrotrope-gelled starch-containing Rofecoxib (Potato starch & Sodium Benzoate)

Sr. No.	Formulation Code	PH
1.	$W_{7\ B\text{-}P\text{-}D}$	7.54
2.	$W_{8\ B\text{-}P\text{-}D}$	7.57

3. Drug Content Uniformity

The drug content uniformity of the selected formulations was found to be100.91%, where as the marketed topical gel formulations of ROX mark-I, mark-II, mark-III were found to have a percent drug content of 95.43%, 93.15%, 94.09%.

Table 5. Drug Content Uniformity

Sr. No.	Formulation Code	Absorbance	Drug Content in mg (mean)	S.D.	S.E.M.	% Drug Content
1.	$W_{7\ B\text{-}P\text{-}D}$	0.442	25.22	0.3024	±0.1352	100.91
2.	$W_{7\ S\text{-}P\text{-}D}$	0.440	25.11	0.1489	±0.0665	100.45
3.	$W_{8\ B\text{-}P\text{-}D}$	0.423	24.11	0.0654	±0.0292	96.57
4.	$W_{8\ S\text{-}P\text{-}D}$	0.422	24.08	0.2708	±0.1211	96.34
5.	Mark-I	0.418	23.85	0.1966	±0.0879	95.43
6.	Mark-II	0.408	23.28	0.1907	±0.0852	93.15
7.	Mark –III	0.412	23.51	0.0512	±0.0292	94.09

Rheological properties

i) Spreadability of Hydrotrope-Gelled starch containing Rofecoxib

The hydrotrope-gelled starch formulation containing Rofecoxib were found to show better spreadability in comparison to marketed preparations. The spreadability was higherW_{7SPD} (110 gm-cm/sec) and $W_{7\ B\text{-}P\text{-}D}$ (82.5 gm-cm/sec) (By applying 30 gm (m) weight to the upper slide, Length of the glass slide (l) = 22cm).

Table-6.Spreadability of Hydrotrope-Gelled POTATO Starch containing Rofecoxib

Sr. No.	Formulation Code	Time taken to travel the distance of 10 cm (sec.)	Spreadability gm.cm/sec.
1.	$W_{7\ S\text{-}P\text{-}D}$	06	110.00
2.	$W_{8\ S\text{-}P\text{-}D}$	14	47.14
3.	$W_{7\ B\text{-}P\text{-}D}$	08	82.50
4.	$W_{8\ B\text{-}P\text{-}D}$	123	5.36
5.	Mark –I	150	4.40
6.	Mark –II	300	2.20
7.	Mark-III	242	2.72

$W_{7\ B\text{-}P\text{-}D}$: formulations containing sod. Benzoate and ROX.
$W_{8\ S\text{-}P\text{-}D}$: formulations containing sod. Salicylate and ROX.

ii) Determination of Viscosity

a) Viscosity of Hydrotrope-Gelled Starch (Potato Starch)

The viscosity of hydrotrope-gelled starch containing potato starch sodium salicylate and sodium benzoate for various formulations it can be observed that as percent w/w of potato starch

increases, there was an increase in viscosity. Hydrotrope-gelled starch containing 15% sodium salicylate and sodium benzoate showed greater viscosity as compared to 10% sodium salicylate and sodium benzoate. With 5% sodium salicylate and sodium benzoate, produce the least viscous gel. Thus, a concentration of sodium salicylate and sodium benzoate increases the viscosity of the gel is also increases.

Therefore, increment in the viscosity of gels is maximum by sodium benzoate than that of sodium salicylate.

Table-7.Viscosity of Hydrotrope-Gelled Starch (Potato Starch)

Sr. No.	Viscosity of Hydrotrope-Gelled Potato Starch in cp_s			
	Formulation Code	Sodium Salicylate	Formulation Code	Sodium Benzoate
1.	W_{1S-P}	17.2	W_{1B-P}	18.4
2.	$W_{2\,S-P}$	68.2	$W_{2\,B-P}$	77.3
3.	$W_{3\,S-P}$	492.5	$W_{3\,B-P}$	567.5
4.	$W_{4\,S-P}$	1012	$W_{4\,B-P}$	1044
5.	$W_{5\,S-P}$	1502	$W_{5\,B-P}$	2327
6.	$W_{6\,S-P}$	1712	$W_{6\,B-P}$	2961
7.	$W_{7\,S-P}$	1995	$W_{7\,B-P}$	3251
8.	$W_{8\,S-P}$	11554	$W_{8\,B-P}$	22387
9.	$W_{9\,S-P}$	17396	$W_{9\,B-P}$	29544

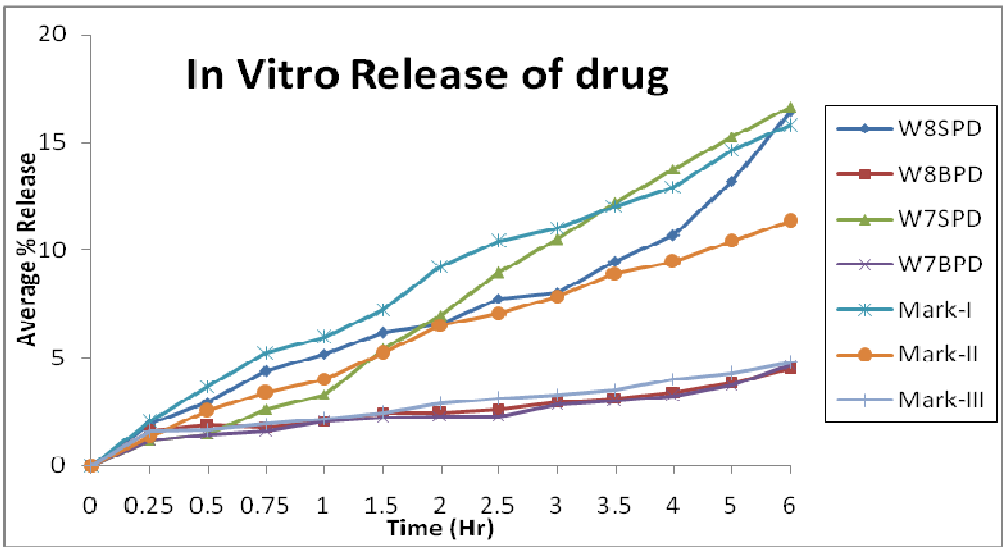

Fig.1.In vitro release of Drug and marketed product

Table-8. Viscosity of Hydrotrope-Gelled potato Starch containing Rofecoxib

Sr. No.	Formulation Code	Viscosity in cp_s
1.	W_{7S-P-D}	2015
2.	$W_{8\,S-P-D}$	11489
3.	$W_{7\,B-P-D}$	3222
4.	$W_{8\,B-P-D}$	22378

$W_{7\,B-P-D}$: formulations containing sod. Benzoate and ROX.
$W_{8\,S-P-D}$: formulations containing sod. Salicylate and ROX.

5. *In-vitro* drug release studies

It was observed that hydrotope gelled starch conatinig sodium benzoate showed less release of rofecoxib than gel containing sodim salicylate this may be attributed to higher viscosity of gels containing sodium benzoate than that of sodium salicylate.

6. Stability studies

Hydrotrope-gelled starch optimized formulations containing Rofecoxib were found to be stable even after stability study.

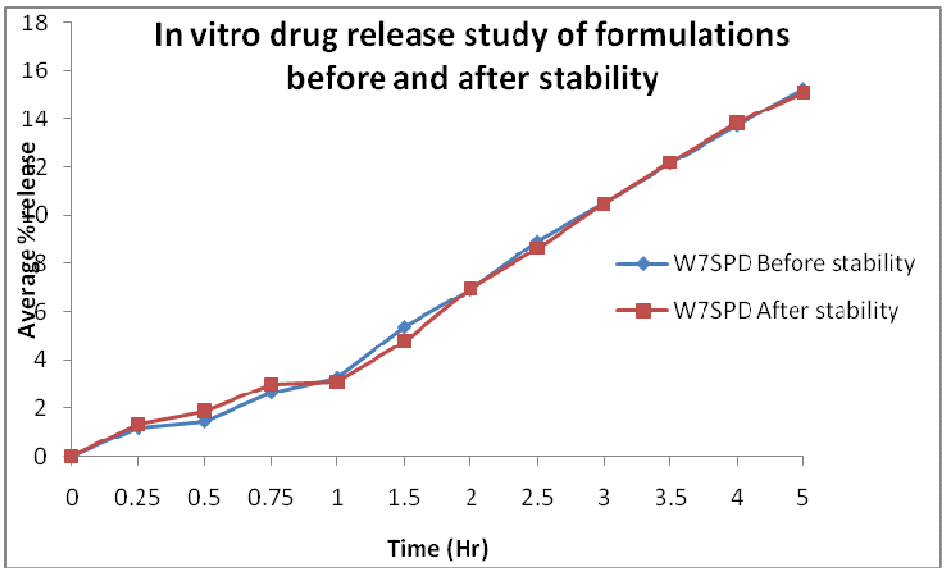

Fig.2.Stabibility study of optimized batch

Table- 9. Stability Studies of Hydrotrope-Gelled potato Starch containing Rofecoxib

Sr. No.	Formulation code	Storage Temp. (°C)	Spreadability (gm cm/sec)	pH	Viscosity (cps)	Drug Content (mg)
1.	$W_{7\,S\text{-}P\text{-}D}$	Room Temp.	110.00	6.38	2015	25.11
2.	$W_{8\,S\text{-}P\text{-}D}$		47.14	6.37	11489	24.08
3.	$W_{7\,B\text{-}P\text{-}D}$		82.50	7.54	3222	25.22
4.	$W_{8\,B\text{-}P\text{-}D}$		5.36	7.57	22379	24.11
5.	$W_{7\,S\text{-}P\text{-}D}$	Stored in Refrigerator (4±1°C)	108.00	6.38	2020	25.11
6.	$W_{8\,S\text{-}P\text{-}D}$		47.11	6.37	11494	24.08
7.	$W_{7\,B\text{-}P\text{-}D}$		81.80	7.54	3221	25.22
8.	$W_{8\,B\text{-}P\text{-}D}$		5.28	7.57	22389	24.11

CONCLUSION

It was observed that hydrotropic salt sodium salicylate induced better gelling than sodium benzoate. The viscosity increased with an increase in the concentration of polymer i.e., potato starch. Higher concentration of salts yielded more viscous gels. The gels prepared using sodium benzoate showed higher viscosity as compare to sodium salicylate. It was conclude that hydrotrope potato gelled starch offers good potential as vehicle for topical delivery of Rofecoxib.

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REFERENCES

[1] Malay k. das and abdul b. ahmed, *Acta Poloniae Pharmaceutica n Drug Research*, Vol. 63 No. 5 pp. 461n467, **2007.**
[2] Matheson AJ, Figitt DP, *Drugs*, **2001**; 61(6): 833-865.
[3] RofibaxTM Gel, Ranbaxy, Manufactures Data Sheet, Information compiled in June **2001**.
[4] Bolton S, Pharmaceutical Statistics, Practical and clinical applications, 2nd Edition, Marcel Dekker Inc., **1990;** 308-316.
[5] El-Khordagui L.K., *International Journal of Pharmaceutics*, **1991** Aug.; 74 (2): 25-32.
[6] Panigrahi L, John T, Shariff A and Shobha Rani R. Hiremath, *Indian Journal of Pharmaceutical Sciences*, **1997** Nov.-Dec; 330-332.
[7] Ahmed M, El-Gendy, Sun HW and Alaa A, Kassem, *Drug Development and Industrial Pharmacy*, **2002;** 28(7): 823-831.
[8] Swati Rawat and Jain SK, *Indian Journal of Pharmaceutical Sciences*, **2002** Sept.-Oct; 500-501.
[9] Panigrahi L, John T, Shariff A and Shobha Rani R. Hiremath, *Indian Journal of Pharmaceutical Sciences*, **1997** Nov.-Dec; 330-332.
[10] Margaret N Mutimer, Charles Riffkin, John A, Hill, Murray E Glickman and Gilman Ncyr, *J. Am. Pharm. Assoc. Sci*., Ed., **1946**; 45: 212.
[11] Ahmed M, El-Gendy, Sun HW and Alaa A, Kassem, *Drug Development and Industrial Pharmacy*, **2002;** 28(7): 823-831.
[12] Keshary PR, Chein YW, *Drug Development and Industrial Pharmacy*, **1984**; 10(6): 883-912.
[13] http://www.ich.org.