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A study on Hydrotrope corn starch gelled as a carrier for topical drug delivery

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ABSTRACT

Starches form an important class of gel forming material of natural origin; hydrotropic salts not only induce swelling and gelatinisation of starch at reduced temperatures but at fairly high concentrations increase the solubility of poorly soluble drugs in water. The present research work mainly concern with to evaluate the potential of hydrotropic gelled corn starch as a suitable vehicle for topical drug delivery and to determine the effect of change in starch/ hydrotropic salt concentration on Rheology of the gel with Rofecoxibs invitro drug release study from the formulated gel. In this study the potential of hydrotrope-gelled starch as a carrier for topical delivery of model drug (Rofecoxib)is seen. Various batches of hydrotrope gelled starches were prepared using 3^2 factorial designs. Corn starch along with hydrotropic salts sodium salicylate and sodium benzoate were used. The formulations were evaluated for various parameters such as physical appearance, homogeneity, pH, drug content uniformity, and rheological properties. In- vitro drug release of model drug 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. The viscosity increased with an increase in the concentration of polymer. Higher concentration of salts yielded more viscous gels. The gels prepared using sodium benzoate showed higher viscosity. In-vitro release data shows that hydrotrope-gelled containing 1% Rofecoxib in 10%w/w corn starch and 15%w/w sodium salicylate (W_{8SCD}) showed highest percent drug release 23.53% 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. The release of Rofecoxib from hydrotrope-starch gel formulations was influenced by initial drug concentration in the vehicle, starch concentration and to a lesser extent the hydrotrope concentration. Thus different release rates may be achieved by controlling these factors.

Keywords-Corn starch, Gel, spreatability, Transdermal drug delivery, Hydrotropes

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INTRODUCTION

Corn starch has the potential to be a commodity starch because of its specific properties and its potential production from low-cost corns. [1]Systemic delivery of drugs via transdermal routes has generated considerable interest during the last decade. Transdermal drug delivery systems deliver drugs through the skin into the systemic circulation at a predetermined rate, thereby avoiding

metabolism in the GI tract and liver. Therefore, the amount of active ingredient required for transdermal delivery can be significantly less than that for oral systems. This system provides constant blood levels for 1 to 7 days and increased patient compliance. The efficacy of non-steroidal anti-inflammatory drugs is well known for treatment inflammatory disorders such as muscle pain, osteoarthritis and rheumatoid arthritis. These potential side effects may be overcome by the topical administration of the drug.[2]

Rofecoxib (ROX) is a commonly used as Anti-inflammatory, analgesic, antipyretic agent. One of the major problems with ROX is that, it is practically insoluble in water, chemically 4–[4-Methyl sulfonyl) phenyl]–3–phenyl–2 (5H)–Furanone[3,4].The oral bioavailabity of Rofecoxib is 93%.Rofecoxib is approved by USFDA for management of pain, inflammation in rheumatoid arthritis,osteoarthritis,musculosketel disorders.[5]

Hydrotropes are less extensively investigated category compounds which, in fairly high concentrations, in- crease the solubility of a variety of poorly soluble drugs in water and the solubility of water in organic solvents. 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.[6] The research 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.

In this research work by using corn starch as a vehicle we compare the effect of a hydrotropic salt, sodium salicylate, sodium benzoate on the effect of sodium salicylate and sodium benzoate on the stability and dissolution rate of Rofecoxib was also we studied topical gel containing corn starch as carrier along with drug this gel is evaluated for various parameters like, Physical Appearance And Homogeneity PH,' Drug Content Uniformity, Spread ability ' Viscosity .

MATERIALS AND METHODS

Pure drug Rofecoxib was obtained from Aarti Drugs Limited, Mumbai, (MS) India. Sodium salicylate and sodium benzoate (Loba Chemie Pvt. Ltd., Mumbai), corn 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

A typical hydrotropic salt, sodium salicylate, was used as the gelling agent. Preliminary trials were carried out using different concentrations of corn starch (2-30% w/v) and sodium salicylate (2 -30% w/v) 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 mod el drug (Rofecoxib) was solubilized in the sodium salicylate solution prior to the addition of starch.

Table 1.Different formulations prepared

W_{1SC}	5% w/w sodium salicylate + 5% w/w corn starch
W_{2SC}	5% w/w sodium salicylate + 10% w/w corn starch
W_{3SC}	5% w/w sodium salicylate + 15% w/w corn starch
W_{4SC}	10% w/w sodium salicylate + 5% w/w corn starch
W_{5SC}	10% w/w sodium salicylate + 10% w/w corn starch
W_{6SC}	10% w/w sodium salicylate + 15% w/w corn starch
W_{7SC}	15% w/w sodium salicylate + 5% w/w corn starch
W_{8SC}	15% w/w sodium salicylate + 10% w/w corn starch
W_{9SC}	15% w/w sodium salicylate + 15% w/w corn starch
W_{1BC}	5% w/w sodium benzoate + 5% w/w corn starch
W_{2BC}	5% w/w sodium benzoate + 10% w/w corn starch
W_{3BC}	5% w/w sodium benzoate + 15% w/w corn starch
W_{4BC}	10% w/w sodium benzoate + 5% w/w corn starch
W_{5BC}	10% w/w sodium benzoate + 10% w/w corn starch
W_{6BC}	10% w/w sodium benzoate + 15% w/w corn starch
W_{7BC}	15% w/w sodium benzoate + 5% w/w corn starch
W_{8BC}	15% w/w sodium benzoate + 10% w/w corn starch
W_{9BC}	15% w/w sodium benzoate + 15% w/w corn starch
W_{SCD}	Sodium Salicylate + Corn Starch + Drug
W_{BCD}	Sodium Benzoate + Corn 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[7].

PH 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 [8].

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 (Pharmacia LKB Biochem Ultraspec III, Sweden). Then drug content was calculated. [9]

Rheological properties:
The following rheological properties of the formulations were determined:

Spreadability[10,11]:
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[12]:
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.[13]

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±2°C, 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).[14]

RESULT AND DISCUSSION

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

Table 2.Standardization of Corn Starch

Sr. No.	Characteristics(test performed)	I.P. Limit	Observation
1.	Solubility	Practically insoluble in cold water and ethanol	Complies
2.	Determination of loss on drying	Not more than 15%	7.4%
3.	Determination of oxidizing substances	No distinct brown or blue colour is observed	Complies
4.	Determination of sulphated ash	Not more than 0.6%	0.16%
5.	Determination of iron	Complies with the limit test for iron	Complies with the limit test for iron.

2. Identification of starch and model drug:
Infrared Spectrum: The marketed corn starch showed a significant shoulder above 3500 cm^{-1} to a broad band appearing from 3100 cm^{-1} to 3350 cm^{-1}. This significant shoulder above 3500 cm^{-1} is accountable for the presence of number of CH_2OH functionalities present in the starch molecule. The broad hump is due to the combinations of vibration of ν_{OH} functionalities present in the

starch moiety. The peaks due to the absorption of ν_{C-H} appeared around 2904 cm^{-1} as depicted. This data are concurrent with the structure of the starch moiety. Similarly identified model drug.

3.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-3. Physical Appearance & Homogeneity of Hydrotrope-Gelled Starch containing Rofecoxib

Sr. No.	Formulation Code	Physical Appearance	Homogeneity
1.	W_{8SCD}	White translucent	++
2.	W_{9SCD}	White translucent	++
3.	W_{8BCD}	White translucent	++
4.	W_{9BCD}	White translucent	++

++ = *Good*

4. PH measurement

The pH of the various formulations of hydrotrope-gelled starch without rofecoxib was determined. PH for corn starch and sodium salicylate gels were found to be between 4.16 to 6.43 and pH for corn starch and sodium benzoate gel was 7.23 to 7.87). Generally, it was observed that, formulation of sodium benzoate had a higher pH compared to formulations containing sodium salicylate.

Table-4. PH of Hydrotrope-gelled starch-containing Rofecoxib (corn starch & Sodium Salicylate)

Sr. No.	Formulation Code	pH
1.	$W_{8\ S\text{-}C\text{-}D}$	6.45
2.	$W_{9\ S\text{-}C\text{-}D}$	6.61

Table 5. PH of Hydrotrope-gelled starch-containing Rofecoxib (corn starch & Sodium Benzoate)

Sr. No.	Formulation Code	pH
1.	$W_{8\ B\text{-}C\text{-}D}$	7.55
2.	$W_{9\ B\text{-}C\text{-}D}$	7.56

5. Drug Content Uniformity

The drug content uniformity of the selected formulations was found to99.83%, the marketed topical gel formulations of ROX (mark-I) were found to have a percent drug content of 95.43%.

Table-6.Drug Content Uniformity

Sr. No.	Formulation Code	Absorbance	Drug Content in mg (mean)	S.D.	S.E.M.	% Drug Content
1.	$W_{8\ B\text{-}C\text{-}D}$	0.422	24.08	0.1351	±0.060	96.34
2.	$W_{8\ S\text{-}C\text{-}D}$	0.421	24.02	0.6773	±0.3029	96.11
3.	$W_{9\ B\text{-}C\text{-}D}$	0.408	23.28	0.3701	±0.1655	93.15
4.	$W_{9\ S\text{-}C\text{-}D}$	0.411	23.45	0.0333	±0.0148	99.83
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

6. Rheological properties

i) Spread ability 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 of W_{8SCD} was higher (165 gm-cm/sec). (By applying 30 gm (m) weight to the upper slide, Length of the glass slide (l) = 22cm).

Table-7.Spreadability of Hydrotrope-Gelled Corn Starch containing Rofecoxib

Sr. No.	Formulation Code	Time taken to travel the distance of 10 cm (sec.)	Spreadability gm.cm/sec.
1.	$W_{8\ S\text{-}C\text{-}D}$	04	165.00
2.	$W_{8\ B\text{-}C\text{-}D}$	13	50.76
3.	$W_{9\ S\text{-}C\text{-}D}$	45	14.66
4.	$W_{9\ B\text{-}C\text{-}D}$	190	3.47
5.	Mark –I	150	4.40
6.	Mark –II	300	2.20
7.	Mark-III	242	2.72

Weight tied to the upper slide (m) = 30 gm
Length of the glass slide (l) = 22 cm.
$W_{7\ B\text{-}c\text{-}D}$: formulations containing sod. Benzoate and ROX.
$W_{8\ S\text{-}c\text{-}D}$: formulations containing sod. Salicylate and ROX.

ii) Determination of Viscosity:

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

The viscosity of hydrotrope-gelled starch containing Corn starch sodium salicylate and sodium benzoate for various formulations is shown in table- 8, it can be observed that as percent w/w of Corn 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-8.Viscosity of Hydrotrope-Gelled Starch (Corn Starch)

Sr. No.	Viscosity of Hydrotrope-Gelled Corn Starch in cp_s			
	Formulation Code	Sodium Salicylate	Formulation Code	Sodium Benzoate
1.	$W_{1\ S\text{-}C}$	2.76	$W_{1\ B\text{-}C}$	5.5
2.	$W_{2\ S\ –C}$	5.34	$W_{2\ B\ –C}$	9.4
3.	$W_{3\ S\text{-}C}$	23.6	$W_{3\ B\text{-}C}$	40.6
4.	$W_{4\ S\text{-}C}$	30.7	$W_{4\ B\text{-}C}$	52.3
5.	$W_{5\ S\text{-}C}$	82.36	$W_{5\ B\text{-}C}$	112.5
6.	$W_{6\ S\text{-}C}$	218.7	$W_{6\ B\text{-}C}$	274.1
7.	$W_{7\ S\text{-}C}$	262.4	$W_{7\ B\text{-}C}$	475.6
8.	$W_{8\ S\text{-}C}$	2832	$W_{8\ B\text{-}C}$	4191
9.	$W_{9\ S\text{-}C}$	10153	$W_{9\ B\text{-}C}$	15031

Table-9.Viscosity of Hydrotrope-Gelled Corn Starch containing Rofecoxib

Sr. No.	Formulation Code	Viscosity in cp_s
1.	$W_{8\ S\text{-}C\text{-}D}$	2310
2.	$W_{9\ S\text{-}C\text{-}D}$	10908
3.	$W_{8\ B\text{-}C\text{-}D}$	3728
4.	$W_{9\ B\text{-}C\text{-}D}$	14251

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

8. *In-vitro* drug release studies:

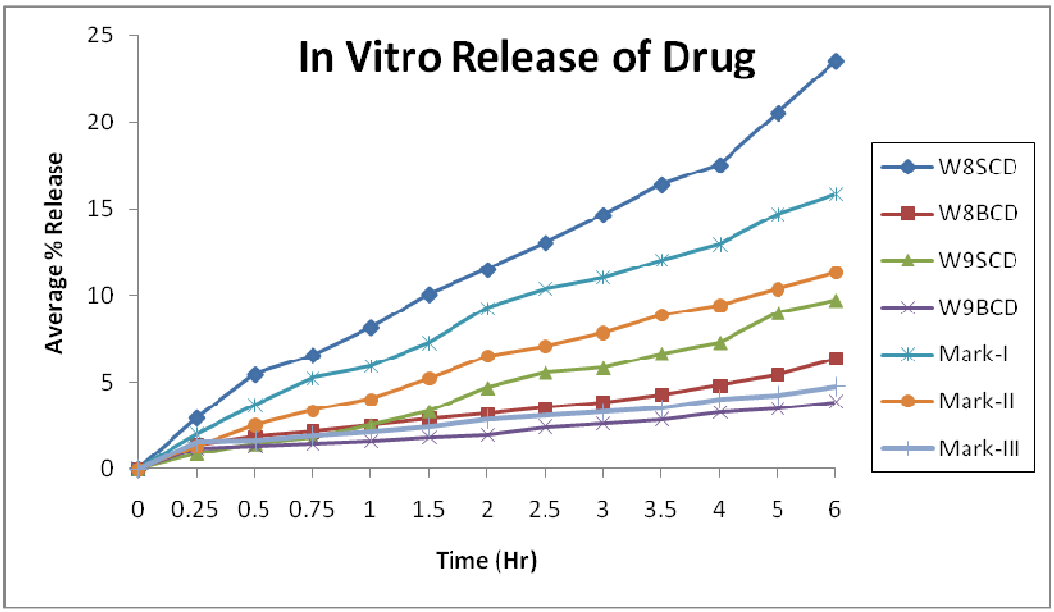

Fig.1.In vitro release of Drug and marketed brands

In-vitro release data indicated that hydrotrope-gelled starch containing 1% rofecoxib in 10%w/w corn starch and 15%w/w sodium salicylate (W_{8SCD}) showed highest percent drug release 23.53% 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.

7. Stability studies

Hydrotrope-gelled starch formulations containing Rofecoxib were found to be stable at the temperatures and parameters tested .Stability studies shows that no change in properties of optimized batches of corn starch along with drug.

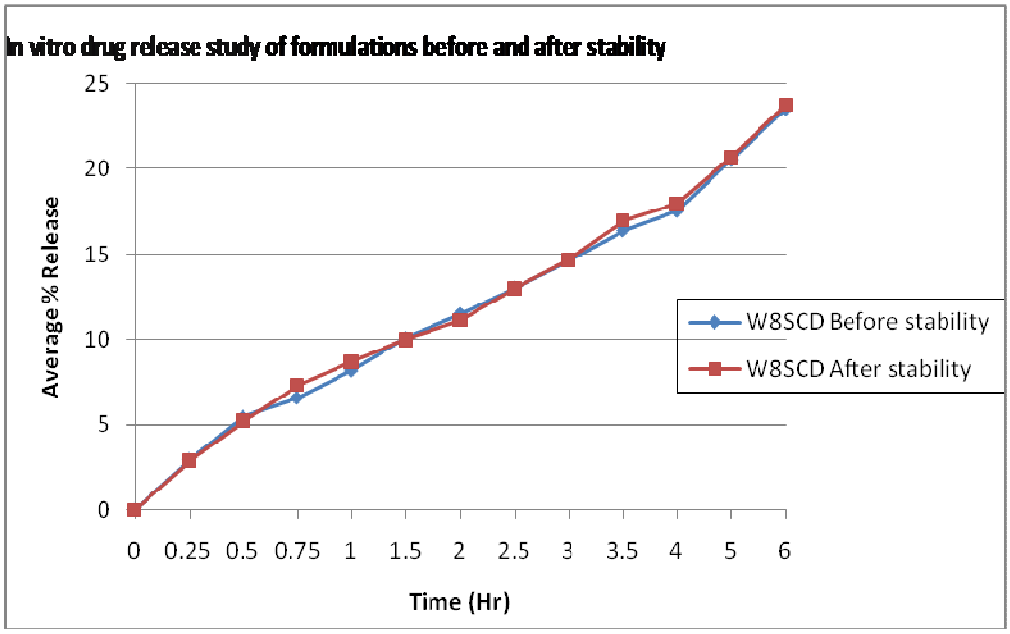

Fig.2.Stabibility study of optimized batch

Table- 10: Stability Studies of Hydrotrope-Gelled Corn Starch containing Rofecoxib

Sr. No.	Formulation code	Storage Temp. (ºC)	Spread-ability (gm cm/sec)	pH	Viscosity (cps)	Drug Content (mg)
1.	$W_{8\,S\text{-}C\text{-}D}$	Room Temp.	165.00	6.45	2310	24.02
2.	$W_{9\,S\text{-}C\text{-}D}$		14.66	6.61	10908	23.45
3.	$W_{8\,B\text{-}C\text{-}D}$		50.76	7.55	3728	24.08
4.	$W_{9\,B\text{-}C\text{-}D}$		3.47	7.56	14250	23.28
5.	$W_{8\,S\text{-}C\text{-}D}$	Stored in Refrigerator (4±1ºC)	163.00	6.45	2328	24.02
6.	$W_{9\,S\text{-}C\text{-}D}$		14.06	6.61	10919	23.45
7.	$W_{8\,B\text{-}C\text{-}D}$		50.16	7.55	3740	24.08
8.	$W_{9\,B\text{-}C\text{-}D}$		3.02	7.57	14256	23.28

CONCLUSION

In-vitro release data indicated that hydrotrope-gelled starch containing 1% Rofecoxib in 10%w/w corn starch and 15%w/w sodium salicylate (W_{8SCD}) showed highest percent drug release 23.53% in 6hrs .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.corn 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 corn gelled starch offers good potential as vehicle for topical delivery of various drugs.

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