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Research Article

FORMULATION AND EVALUATION OF DICLOFENAC SODIUM INJECTION USING 2-HYDROXY PROPYL BETA CYCLODEXTRIN

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ABSTRACT

The objective of the present research was formulation and development of safe and stable injectable formulation of Diclofenac sodium using 2-hydroxy propyl beta cyclodextrin. For improvement and enhancement of solubility and stability of Diclofenac sodium by making inclusion complex with 2-hydroxy propyl beta cyclodextrin were made. The concentration of 2-hydroxy propyl beta cyclodextrin was selected on the basis of the research article and literature survey. Here the concentration of the antioxidants was optimized. Among the various antioxidant study it was observed that N-acetyl-L-cysteine and Disodium EDTA in combination shown good stability profile as compared to other antioxidants.

Keywords: Diclofenac Sodium injection

INTRODUCTION

In the present work, Diclofenac sodium, a non-steroidal anti-inflammatory agent was selected as a model drug, which is BCS class II drug (low soluble & high permeable). This invention relates to a stable parenteral aqueous solutions comprising of an inclusion complex of diclofenac sodium and a cyclodextrin, which is suitable for intramuscular and intravenous administration. The solutions contain diclofenac sodium, cyclodextrin, and an antioxidant selected from a combination of ethylene diamine tetra-acetic acid and N-acetyl-cysteine.

Rationale for selection of drug and formulation

Conventionally formulated diclofenac sodium injections are limited to intramuscular administration. This limitation has arisen, not as a consequence of the intravenous safety profile, but principally due to the physico-chemical properties of the drug, summarized as follows:

Poor aqueous solubility of the sodium salt--Diclofenac has a particularly high tendency to crystallize from aqueous and organic solutions. Physically stable solutions containing at least 25 mg/ml of diclofenac sodium necessitates the use of potent solubilizing co solvents, such as macrogols and benzyl alcohol. These co solvents have an unfavorable intravenous safety profile and are associated with venous sequelae, high hemolytic and sensitizing.

Susceptibility to oxidation--Diclofenac's tendency to oxidize in solution necessitates formulation with antioxidants, for example sulphite salts. In the commercial European intramuscular product, antioxidants such as sodium metabisulphite or sodium disulphite are usually used. Sulphite salts have been implicated in serious hypersensitivity reactions causing, for example, broncho-constriction.

pH and Osmolality--The high pH of the marketed product (8.5) required rendering diclofenac sodium soluble and the hyperosmolar nature of the formulation contribute to the discomfort which is frequently experienced at the site of the injection when administered intramuscularly.

Injection Volume--Owing to poor solubility, the commercial product is formulated as 25 mg diclofenac sodium per ml. The recommended dosage is 75 mg and therefore the product is given as a 3 milliliter intramuscular injection. This is above the recommended volume of 2 milliliters for intramuscular injection accepted by the United States Food and Drug Administration.

MATERIALS AND METHOD

Materials

Diclofenac sodium salt was received from Schwit Biotech, Ahmedabad, Gujarat. Disodium EDTA was purchased from Finar Chemicals Ltd., Ahmedabad, Gujarat. HPLC grade acetonitrile was obtained from Samir Tech Chem Ltd, Vadodara, Gujarat. 2-Hydroxypropyl beta CD (molar substitution of 0.9) (HPBCD) was obtained from Shreji Chemicals Ltd., Ahmedabad, Gujarat. N-acetyl-L-cysteine was received from Sujata Chemicals, Ahmedabad, Gujarat. Sodium formaldehyde sulphoxilate (SFS) Merck Specialties Pvt Ltd, Mumbai. All other reagents and chemicals were obtained from Samir tech chem. Ltd, Vadodara, Gujarat.

Procedure for preparation of solution

Here WFI between 60% of the batch size having 75^{0}C temperature in a beaker was taken and kept the beaker on the magnetic starrier device. Providing continuous nitrogen purging for about 20 minutes. The water heated to 50^{0}C. Processing continues under a nitrogen blanket. Add gradually weighed quantity of 2-HPBCD to the WFI and mixing was allowed until dissolved. The solution is then allowed to cool to room temperature. The solution was pre filtered with 0.45µ filter, followed by the addition of NAC and Disodium EDTA. The solution was stirred until all the NAC and Disodium EDTA was dissolved. The pH was then adjusted near to 4.5. Then gradually weighed quantity of Diclofenac sodium added to the solution and stirred until dissolves and made up to 100% volume with WFI and then adjusts pH to 7.4, should it be required. The resultant Diclofenac sodium solutions were sterilized by filtration with 0.22µm filters and fill and sealed it in transparent glass vials. The prepared solution was evaluated for various physico-chemical parameters. For each parameter average values of 2 samples were considered.

NOTE: Do not provide force cooling after addition of 2-HPBCD is dissolved in hot water as it may results in precipitation of above materials.

Evaluation of formulation batches

1. Physical appearance

For the large scale of production, 10-liter batch size was considered on the tentative basis for further study. It takes almost 4-5 hrs for processing a batch. Therefore, prepared formulations were visually observed for their physical appearance at initially and after 4 weeks of time interval.

2. pH measurement

The pH of the prepared formulations was measured using Thermo Scientific pH meter at 25 ±1ºC.

3. Particulate matter

The particulate matter can be determined by the visual inspection by naked eye under direct light beam.

4. Assay content for Diclofenac sodium

Carried out by the method for liquid chromatography (HPLC) using the following solution. Solution (1) Take injection and make dilution of injection which contains 0.005% w/v of Diclofenac sodium in mobile phase. Solution (2) contains 0.005% w/v of Diclofenac sodium RS in the mobile phase. Mobile phase: A mixture of 60 volumes of methanol and 40 volumes of 0.1 M sodium acetate solution. Column: Stainless steel column 12.5 cm X 4.6 cm packed with octylsilica. Flow rate: 1 ml/min Spectrophotometer set at 254 nm. A 10µl loop injector. Inject alternately the test solution and the reference solution and record the chromatograms for 2.5 times the retention time of the principal peak. If necessary adjust concentration of methanol in the mobile phase to obtain the resolution of the peak due to Diclofenac sodium.

Table 1: Composition trial batches (Batch size of each is 100 ml)

Ingredients	Batch code					
	T1	T2	T3	T4	T5	T6
Diclofenac Sodium (75mg/2ml)	3.75 gm	3.75 gm	3.75 gm	3.75 gm	3.75 gm	3.75 gm
2-Hydroxypropyl-Beat-cyclodextrin	33.30 gm	33.30 gm	33.30 gm	33.30 gm	33.30 gm	33.30 gm
N-acetyl-L-cysteine	--	--	0.1% w/v	0.1% w/v	--	--
Disodium EDTA	--	0.05%w/v	--	0.05% w/v	--	0.05% w/v
SFS	--	--	--	--	0.1% w/v	0.1% w/v
NaOH (10%)	Quantity sufficient for pH 6.0-6.4 adjustment					
WFI	Up to 100 ml					

RESULTS AND DISCUSSION

Physical appearance

Physical appearance (color, transparency, precipitation, etc.) of prepared formulations was studied. Batch T3, T4 appeared colorless and clear initially as well as after 4 week of time interval at 25°C/60%RH and 40°C/75%RH.

pH Measurement

The pH of all the formulations was set initially in the range of 6.5-8.1. pH of the prepared solution initially and after 4 week of time interval was measured which are shown in table.

Particulate matter

Batch T4 shows good stability after 4th week.

Table 2: Observation for physical appearance

Batch Code	Time Point	Storage Condition	
		25°C	40°C
T1	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Discoloration	Discoloration
T2	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Discoloration	Discoloration
T3	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Clear, colorless solution	Clear, colorless solution
T4	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Clear, colorless solution	Clear, colorless solution
T5	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Discoloration	Discoloration
T6	Initial	Clear, colorless solution	Clear, colorless solution
	4th week	Clear, straw color	Clear, straw color

Table 3: Results of pH measurement

Batch Code	Time Point	Storage Condition	
		25°C	40°C
T1	Initial	7.41	7.41
	4th week	7.86	8.12
T2	Initial	7.43	7.43
	4th week	7.76	8.06
T3	Initial	7.40	7.40
	4th week	7.55	7.99
T4	Initial	7.41	7.41
	4th week	7.46	7.51
T5	Initial	7.40	7.40
	4th week	7.89	8.22
T6	Initial	7.39	7.39
	4th week	7.89	8.06

Table 4: Results of particulate matter

Batch Code	Time Point	Storage Condition	
		25°C	40°C
T1	Initial	-	-
	4th week	++	+++
T2	Initial	-	-
	4th week	++	+++
T3	Initial	-	-
	4th week	+	++
T4	Initial	-	-
	4th week	-	-
T5	Initial	-	-
	4th week	++	++
T6	Initial	-	-
	4th week	++	++

Key: (-) = Absent

(+) = Very few colloidal particulates, fibers or filling artifacts

(++) = Evidence of physical instability under light

(+++) = Physical instability readily observable with the naked eye

Assay content for Diclofenac sodium

Table 5: Results of assay content of Diclofenac sodium

Batch Code	Time Point	Storage Condition	
		25^{0}C	**40^{0}C**
T1	Initial	99.3%	99.3%
	4th week	98.1%	97.7%
T2	Initial	99.8%	99.8%
	4th week	98.5%	97.6%
T3	Initial	100.9%	100.9%
	4th week	100.2%	99.8%
T4	Initial	101.2%	101.2%
	4th week	101.1%	100.7%
T5	Initial	100.9%	100.9%
	4th week	100.1%	99.8%
T6	Initial	98.9%	98.9%
	4th week	98.1%	97.1%

CONCLUSION

From the various antioxidant studied, it was found that N-acetyl-L-cysteine (0.1% w/v) and Disodium EDTA (0.05% w/v) in combination provides an excellent antioxidants for preparation of intravenous dosage form of Diclofenac sodium.

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