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Exploration of mixed hydrotropy strategy in formulation and development of etodolac injection

Abstract

Etodolac is a non-steroidal anti-inflammatory drug used in the treatment of mild to moderate pain, osteoarthritis or rheumatoid arthritis and it is basically available in the market only as tablet dosage form for human use. The present study was investigated with an intention to develop a stable and effective parenteral formulation, containing Etodolac for acute pain management. Etodolac is a Biopharmaceutical Classification System (BCS) class II drug and it is insoluble in water hence solubility and dissolution rate enhancement was carried out by using various hydrotropic blends.. Etodolac was blended in different proportion with various hydrotropic agents like sodium acetate, sodium benzoate, sodium citrate etc and other co-solvents. The drug was formulated in injectable dosage form using a optimized hydrotropic blend as solvent. The optimized batches of Etodolac injection formulation were subjected to various evaluation tests and accelerated stability study. Amongst all trial batches, formulation containing 15% sodium benzoate and 25% solvent system S (Blend C) and 10% sodium acetate, 5% sodium citrate and 25% solvent system S (Blend O) were found to be more stable and passed all tests satisfactorily.

Keywords: Etodolac, Parenteral formulation, Hydrotropy, Mixed hydrotropy

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1. Introduction

A key role in bioavailability is the solubility of the drug molecules. The aqueous solubility of BCS class II drug molecules in the gastrointestinal fluid often causes unsatisfactory bioavailability. High doses are often required to reach therapeutic plasma concentrations of such poorly water soluble drugs. Hydrotropy is the term originally coined by Neuburg .[1] The increase in the solubility of a solute by the addition of fairly high concentrations of high alkali metal salts of different organic acids was described as hydrotropy by Neuburg. A number of hydrotropes have been utilized for the solubility enhancement of various drugs. Hydrotropes are the compounds which are micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds.[2] The phenomenon by which the solubility of poorly water soluble drugs are increased in the blends of hydrotropic agents is known as mixed hydrotropy. The utilization of this synergistic enhanced solubility in the formulation of dosage form reduces the concentration of individual hydrotropic agent.[3]

Etodolac is a pyranocarboxylic acid and falls in the Non-Steroidal Anti-inflammatory Drugs (NSAIDs) category. It belongs to BCS class II type and is used as analgesics, anti-inflammatory and anti-pyretics.[4] The aim of the present research work was to explore the possibility of employing mixed hydrotropic solubilization technique for the development of an aqueous parenteral formulation of etodolac, so as to minimize the concentration of individual solubilizers in order to reduce the toxic effects of them. Etodolac is an NSAID and is targeted for acute pain management. In the present research work, the solubility of Etodolac was enhanced significantly in manifolds and further stable parenteral injectable formulation was prepared. The preparation was further investigated for physical and chemical stability.

2. Materials and methods

Materials

The gift sample of Etodolac was obtained from Glenmark, Nashik. All the other chemicals used were of all analytical grades.

Pre-formulation study

Calibration curve: The calibration curve was obtained by preparing standard stock solution by dissolving 0.01g of Etodolac sample in 10% methanolic water. The solutions of 2, 4, 6, 8, 10 ppm concentration were prepared and absorbance was recorded at observed λmax (281nm) of Etodolac (Table 1).

Table 1 Calibration of Etodolac

λmax: 281 nm, Y = 0.009x + 0.207, R2 = 0.988

Solubility studies of Etodolac in different solvents: Solubility study was performed by the Shake Flask Method.[5] The excess drug along with different solvents was taken in 10ml stoppered volumetric flasks. The flasks were subjected to shaking in an orbital shaker for 24 hours at 25°C and 60rpm speed and further equilibrated for next 24 hours. Then the solutions were centrifuged at 1000rpm for 10 minutes and filtered through Whatmann filter paper (0.45µm). The absorbances were recorded on Ultra Violate (UV) spectrophotometer of these filtered solutions after appropriate dilutions to determine the solubility using respective solvents as blank (Table 2).

Table 2 Solubility in different solvents and pH solutions.

The pH dependent solubility: All the samples of saturated solution of drug at different pH were shaken in an orbital shaker for 24 hours at 25◦C and 60rpm and further equilibrated for next 24 hours. After centrifugation and filtration the absorbances were recorded at 281nm using respective solutions as blank (Table 2).[6]

Solubility with different hydrotropes: Solubility of Etodolac in various solutions was determined by Shake Flask Method. Excess amount of drug was added to 10ml stoppered volumetric flasks. Various hydrotropes in 20% and 40% concentration solutions in distilled water were filled in the volumetric flasks. The flasks were shaken for 12 hours in orbital shaker at 25°Cand 60 rpm speed. The solutions were allowed to equilibrate for the next 24 hours. The solutions were then centrifuged for 10 min at 1000 rpm. Supernatants

of each sample were filtered through 0.45µm membrane filter and analyzed for drug content spectrophotometrically at 281nm after suitable dilutions (Table 3 & 4).[7]

Table 3 Solubility of Etodolac in various hydrotropic solutions.

Table 4 Solubility of Etodolac in different co-solvents (20%).

Determination of additive/synergistic effect on solubility in hydrotropic blends: Shake flask method was employed. The total concentration of all solubilizers was 40% w/v (constant) in all aqueous mixed solvent systems (Table 5). The solubility of Etodolac was determined in these systems (Table 6).[8]

Table 5: Properties of optimized blends.

Table 6: Solubility of Etodolac in various hydrotropic blends. SB: Sodium Benzoate; SA: Sodium Acetate; U: Urea; SC: Sodium Citrate; S: Solvent System S &

Drug- excipients compatibility study

FTIR spectral studies: The Fourier Transform Infra Red (FTIR) spectra were obtained by means of a FTIR spectrophotometer (FTIR – 8300S, Shimadzu, Japan).[8] The samples were prepared by mixing of drug and all hydrotropic agents in 1:1 ratio and measurements were attempted over the range of 400–4000 cm^{-1} (Figure 1A-1D).

Figure 1A: FTIR spectra of pure Etodolac.

Figure 1B FTIR spectra of Etodolac + sodium acetate.

Figure 1C: FTIR spectra of Etodolac + sodium benzoate.

Figure 1D FTIR spectra of Etodolac + sodium citrate.

Selection of optimized formulation blend: The two hydrotropic blends which showed maximum solubility enhancement were selected for further investigation and formulation of aqueous injection.

Formulation Development: Attempts were made to develop a stable parenteral formulation using hydrotropic blends along with other excipients. The dose selected for formulation was 300 mg of Etodolac per 1ml solvent. The prepared formulations contained the following ingredients along with their concentrations are given in Table 7. The solvent system "S" comprises of Poly Ethylene Glycol (PEG) 200, PEG 400, PEG 600, glycerin and Propylene Glycol (PG) in equal concentrations. Thus prepared formulations were assayed for drug content respectively and some of these were placed at 5°C, room temperature (RT), 37°C, 40°C and 45°C for six weeks and observed for crystal growth, clarity, pH change, and drug content. Formula for the injection is given in Table 8.

Table 7: Effect of different temperature on crystal growth. RT: Room Temperature, +: Crystal growth, - :No crystal growth

Table 8 Formulation of injection.

Post formulation evaluations

Assay of Formulations

Reference Solution Preparation: The 100ml of stock reference solutions for each formulation was prepared. The composition of the reference stock solution was similar to that of the respective formulations excluding the drug and also they were diluted similarly as the formulations were diluted using water. This resulting solution is used as reference solution (blank) in comparison with the prepared formulations to measure the % drug content by measuring the absorbance using Shimadzu UV Visible spectrophotometer. The amount of Etodolac was determined from standard calibration curve (Table 9).[9,10]

Table 9 Assay of the formulations.

Sterility Study

Direct inoculation method: Aliquots of the sample were transferred aseptically into fluid thioglycolate medium (FTM) and soya casein digest medium (SCDM). The inoculated fluid thioglycolate medium was incubated at 32°C and soya casein digest medium at 22°C for 8 days. Likewise negative and positive controls are prepared (Figure 2) .[11]

Stability Studies: Stability of the prepared formulation is a very basic and important factor for any pharmaceutical dosage form to obtain a safe, effective and potent response of drug. The stability of a parenteral formulation can be accessed by the parameters like: Crystal growth, pH changes, Clarity and % Drug content (Table 7,10,11).[12,13]

Table 10: Effect of different temperature on clarity. +: Turbid, -: Clear

Figure 2 Sterility test (A: FTM and B: SCDM; before and after).

a. Crystal growth

The 10 ml of the each prepared formulations C, O were placed at refrigeration, room temperature, 37°C, 40°C and 45°C respectively for six weeks and observed for crystal growth. The data are given in Table 7.

b. pH changes

The 10 ml of the each prepared formulations C and O were kept at different temperatures/conditions such as refrigeration, room temperature, 37°C, 40°C and 45°C. At regular time intervals the samples were examined for pH changes for six weeks using a digital pH meter (Table 12).

c. Clarity

The 10ml of the formulations were placed at refrigeration, room temperature, 37°C, 40°C and 45°C for six weeks and observed for color change or turbidity (Table 11).

d. % Drug Content

The drug content of the formulations C and O were determined by following the same procedures as mentioned in assay. The estimates were done at intervals of two weeks up to six weeks. The data are given in (Table 13 & 14).

Table 12: The pH changes of formulation C and O at different temperatures/conditions on ageing. No considerable change in pH of both C and O formulation was observed during study period at exposure temperature of 37°C, 40°C and 45°C; indicating the stability of both formulations.

Table 13 Percent drug content of formulation C at different temperatures/conditions on ageing. Each value is an average of 3 determinations.

Table 14 Percent drug content of formulation O at different temperatures/conditions on ageing. Each value is an average of 3 determinations

Dilution study

Precipitation of drug often occurs upon injecting a formulation into body fluids. The amount of precipitation can be correlated with the rate at which the drug is injected. Method for determination of such effect is dilution study. The serial dilutions of formulations were

prepared in ratio of 20:50 to 20:500 and stored at room temperature and examined visually for the appearance of crystals and turbidity up to 24 hours (Table 15).

Table 15: Dilution study. **+:** Crystals, -: Clear

1. Results

Solubility of Etodolac in different solvents and pH solutions, hydrotropic solutions, co-solvents and hydrotropic blends was carried out. As Etodolac is BCS Class II drug; least solubility (0.489 mg/ml) was found in distilled water. Various hydrotropic solutions in 20% and 40% concentration and co-solvents in 20% concentration were used to determine solubility of Etodolac. Sodium acetate and sodium benzoate have shown remarkable improvement (31.5 and 72.5 fold respectively) in Etodolac solubility. After this study; solubility in different hydrotrophic blends (Table 6) was carried out. Sample C and Sample O shown highest improvement in solubility i.e. 275.6 and 274.5 fold respectively. These two samples were used for development of injection dosage form.

FTIR Studies

According to the FTIR data obtained none of the excipients has interaction with the drug and hence proceeded for further investigation.

Experimental blends C and O were evaluated for parameters like pH, viscosity, surface tension and specific gravity. Both the blends have shown satisfactory properties. The pH of blend C and O was found to be 7.46 and 7.42 respectively. The viscosity of blend C and O was found to be 3.553 and 3.487 respectively. Surface tension and specific gravity of blend C and O were found to be 58.74 dyne/cm, 58.36 dyne/cm; 1.087 and 1.073 respectively.

Formulation development

A stable parenteral formulation of Etodolac was formulated after performing trials with various hydrotropic blends. Hydrotrophic substances sodium acetate, sodium benzoate and sodium citrate and co-solvent system (S) was employed for formulation of Etodolac injection along with water soluble preservatives sodium methyl papaben and sodium propyl paraben. Then prepared formulations (Table 8) were subjected for various tests and results are discussed in the following section.

Post-formulation studies

Scale up studies

a. Sterility testing: None of the formulations showed turbidity or signs of microbial growth (except the positive control) at the end of incubation period, indicating all the formulations were sterile.

b. Assay of formulations

The drug content within two formulations 'C' and 'O' found to be 104.45% and 99.71% respectively.

c. Stability evaluation

The stability study on formulations 'C' and 'O' was carried out using parameters like crystal growth, effect of temperature and light on clarity and color change. In the formulations C and O, no crystals were developed after two weeks. Both formulations C and O remained clear after two weeks. No color change was observed under during study period; suggesting that the both the formulations are sable under given conditions (Table 16).

Table 16: Dilution study. **+:** Crystals, -: Clear

Stability of both formulations C and O was tested by dilution study using normal saline solution and 5% dextrose solution. Dilutions from 10:25 to 10:250 were used for this study. Even at lowest and highest dilutions both preparations remained stable showing no sign of crystal growth.

Accelerated stability studies

a. pH change

No considerable change in pH of both C and O formulation was observed during study period at exposure temperature of 37°C, 40°C and 45°C; indicating the stability of both formulations.

b. Crystal growth

No crystal growth was observed in the formulations at different temperatures/conditions (Table 17).

c. Clarity studies

All the formulations were clear at different temperatures/conditions (Table 18).

d. Drug contents

The drug content in both formulations C and O remained almost similar during study period at exposure conditions.

Table 17 Crystal growth of formulation C, O at different temperatures/conditions on ageing. +: crystal growth, _: no crystal growth

1. Conclusion

The concept of parenteral formulations containing Etodolac offers a suitable, practical approach to achieve desired stable parenteral preparation with significantly enhanced solubility of drug in suitable solvent composition. In present work, parenteral formulation of Etodolac was prepared successfully by using different concentrations and combinations of hydrotropic agents. These formulations were expected to be stable for sufficiently long time. The conclusion derived from the above results indicates that the parenteral formulation containing Etodolac developed was found to be complying satisfactorily with all the evaluation tests performed as per official compendia and was stable for longer duration of time.

2. Acknowledgment

None.

3. Conflict of interest

None.

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