ejpmr, 2016,3(2), 181-185

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

SOLUBILITY ENHANCEMENT OF NEPAFENAC USING DIFFERENT SOLUBILIZERS

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Article Received on 23/11/2015 **Article Revised on 14/12/2015** **Article Accepted on 05/01/2016**

ABSTRACT

Aim of the present work is to investigate the effect of Sulfo butyl ether-β-cyclodextrin (SBE-β-CD) and different solubilizers on the solubility of Nepafenac. Apart from SBE-β-CD the three different solubilizers were used for the purpose, Polyethylene glycol 400 (PEG 400), Cremophor RH and Polysorbate 80. By physical observation it was observed that the solubility of Nepafenac was increased significantly with SBE-β-CD and the effect of different concentration of SBE-β-CD on the solubility of the drug was studied which was further investigated and confirmed by phase solubility study with the help of UV spectroscopy. From the phase solubility diagram, the increase in solubility of Nepafenac with 1 M, 1.5M, 2 M, 3 M was found to be 2.38 times, 2.725 times, 4.401 times and 5.857 times respectively. The drug solubility was increased linearly up to 3 M of SBE-β-CD. From the above result, the optimum concentration of SBE-β-CD was selected i.e. 3M and it was concluded that SBE-β-CD is the best solubilizer among all selected.

KEYWORDS: Solubility, Nepafenac, Solubilizer, Sulpho butyl ether-β-Cyclodextrin.

INTRODUCTION

Poorly water soluble drugs present significant challenges during the development of formulation of drugs due to their inadequate solubilization in digestive fluids and hence it is of paramount importance to enhance the solubility of poorly water soluble drug thereby improving the bioavailability. Nepafenac, a recent product of the NSAID class approved for topical opthalmic use is a prodrug of Amfenac used for the treatment of post-operative inflammation after cataract surgery. Prodrug nature of Nepafenac makes it a target specific NSAID.[2-4] Nepafenac is described chemically as 2-amino-3-benzoylbenzeneacetamide and is preferred over the other NSAID drugs as is having an excellent ability to penetrate corneal epithelium but its use is limited because of its poor aqueous solubility.[2-4]

It is now possible to increase the solubility of drug with the help of various techniques as mentioned

Solubility enhancement methods[5-9]

Some of the approaches to improve the solubility of the drug are

- Physical Modifications
- Particle size reduction: a. Micronization b. Nanosuspension
- Modification of the crystal habit: a. Polymorphs b. Pseudopolymorphs
- Drug dispersion in carriers: a. Eutectic mixtures b. Solid dispersions c. Solid solutions
- Complexation: a. Use of complexing agents
- Solubilization by surfactants or solubilizing agents a. Microemulsions b. Self microemulsifying drug delivery system
- Chemical Modifications
- Prodrug
- Salt Formation
- Other techniques to improve the solubility are Co-crystallization, Cosolvency, and Hydrotrophy.

Among the various methods the approaches, complexation (by using complexing agent like cyclodextrin) and solubilization by using surfactants or different solubilizers are of particular interest owing to their simplicity and effectiveness.

Complexation [8][12][13][15]

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. The most commonly used host molecules are cyclodextrins. Cyclodextrins are cyclic (α-1, 4) linked oligosaccharides of α-D glycopyranose, containing relatively hydrophobic central cavity and hydrophilic outer surface.[16] When cyclodextrin are used to solubilize water insoluble drugs, it is generally assumed that the solubilization proceeds through inclusion complex formation.[14-15] Solid inclusion complexes are prepared by various methods such as kneading method co-precipitation, neutralization, co-grinding, spray drying method, and microwave

irradiation method[5][6] Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. This ability to form inclusion complexes alter the chemical and physical properties of guest (drug) molecules, and results in improved water solubility, prolonged in vivo stability, reduced toxicity and irritancy, and improved bioavailability. Cyclodextrins can also be used to prevent drug-drug and drug additive interactions, convert liquid drugs into microcrystalline powder, decrease volatility, modify gastrointestinal or ocular irritation and mask of objectionable taste or odour of drugs.[14]

Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies. Cyclodextrin derivatives of pharmaceutical interest include the hydroxy propyl derivatives of β- and γ cyclodextrin, the randomly methylated β Cyclodextrin, sulfobutyl ether β Cyclodextrin. As modified β cyclodextrins like HP-β-CD and SBE-β-CD exhibits increased solubility in water than the parent β cyclodextrin.

Sulfobutylether beta cyclodextrin (SBE- β-CD)

Sulfobutylether beta cyclodextrin (SBE- β-CD) is an anionic β-cyclodextrin derivative with a sodium sulfonate salt separated from the hydrophobic cavity by a butyl spacer group. SBE-β-CD is a uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize interaction to improve the solubility, stability, bioavailability or lessen volatility, irritation, smell or taste in oral solid dosage forms. SBE-β-CD is not a single chemical species, but comprised of a multitude of polymeric structures of varying degrees of substitution and positional/regional isomers dictated and controlled to a uniform pattern by a patented manufacturing process consistently practiced and improved to control impurities. SBE-β-CD can form non-covalent complexes with many types of compounds including small organic molecules, peptides and proteins.

Solubilization by surfactant/solubilizing agent[5][12]

Surfactants are molecules with distinct polar and nonpolar regions. The polar group can be anionic, cationic, zwitter ionic or non-ionic. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.[5] Surfactants like Spans, Polyglycolized glyceride, Tweens, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc have been successfully used to improve solubility and as carrier for dissolution enhancement.[6]

Solubilizing agents[12]

The solubility of poorly soluble drug can be improved by various solubilizing materials. In this study the different solubilizers are used. They are PEG 400, Cremophor RH and Polysorbate 80. PEG 400 is a commonly used solubilizer as is compatible with many of the drugs and shows complete solubility in water. It is a clear, colourless, viscous liquid. soluble in acetone, benzene, glycerine, density 1.110-1.140. Due in part to its low toxicity, PEG 400 is widely used in pharmaceutical and cosmetic industry.[12] Cremophor RH is Poly Oxyl Hydrogenated Castor oil. It is a non ionic solubilizer for hydrophobic APIs and fat soluble vitamins and also is an emulsifying agent. It forms nearly clear solution in water, ethanol and isopropanol and in essential oils. It has advantage of a very little taste or odour but it shows little tendency to foaming. Another solubilizer used in the study was Polysorbate 80. It is an excellent solubilizer for essential oils and has a good function as wetting agent, viscosity modifier, anti static agent stabilizer and dispersing agent.

In this study, investigations were performed on the possibility of solubilization by different solubilizers and complexation of Nepafenac with SBE-β-CD for improving the solubility and in turn to increase the bioavailability and therapeutic efficacy of Nepafenac.

MATERIALS AND METHODS

Nepafenac was kindly received as a gift sample from Manus Aktteva Biopharma LLP India. PEG 400 and Polysorbate 80 were procured from Croda chemical and SBE-β-Cyclodextrin from Captisol and Cremophor RH were procured from BASF.

Procedure

I. Determination of solubility of Nepafenac using different solubilizers

1. The solubilizer (surfactant or complexing agent) was first dissolved in water followed by the addition of drug i.e. Nepafenac so as to produce solutions in molar ratios of Drug: Solubilizer as 1:1, 1:1.5, 1:2.0 and 1:3.0. (for each solubilizer)
2. The mixtures were labelled as 1M:1M, 1M:1.5M, 1M:2.0M and 1M:3.0M to denote the drug: solubilizer in molar ratios of 1:1, 1:1.5, 1:2.0 and 1:3.0 respectively.
3. Drug solution in different combinations of solubilizers in water was sonicated.
4. Physical observation and time required for Sonication for each mixture was noted.

Observation

Sr no.	Drug: PEG 400		Physical Observation-Turbidity	Sonication time(hr)
	In moles ratio	In grams		
With PEG 400				
1.	1M :1 M	0.1:0.157	↑↑↑	>2.5
2.	1M:1.5M	0.1:0.235	↑↑	>2
3.	1M:2.0M	0.1:0.314	↑	>1.5
4.	1M:3.0M	0.1:0.471	↓	>1
With Poly Oxyl Hydrogenated Castor oil (Cremophor RH)				
5.	1M :1 M	0.1:0.983	↑↑	>2.5
6.	1M:1.5M	0.1:1.47	↑	>2
7.	1M:2.0M	0.1:1.96	↑	>1.5
8.	1M:3.0M	0.1:2.94	↓	>1
With Polysorbate 80				
9.	1M :1 M	0.1:0.515	↑↑	>2.5
10.	1M:1.5M	0.1:0.772	↑	>2
11.	1M:2.0M	0.1:1.030	↑	>1.5
12.	1M:3.0M	0.1:1.545	↓	>1
With SBE-β-Cyclodextrin				
13.	1M :1 M	0.1: 0.865	↑↑	>2.5
14.	1M:1.5M	0.1: 1.298	↑	>2
15.	1M:2.0M	0.1: 1.730	↓	>1.5
16.	1M:3.0M	0.1: 2.595	No turbidity, Clear yellow solution.	>1

So, by physical observation the most clear solution of the drug was observed with SBE-β-CD (in the ratio-1M:3.0M) and was then further investigated by phase solubility analysis.

II.Solubility determination by using UV-Visible Spectrophotometry

A. Determination of maximum wavelength of Nepafenac

Nepafenac 50 mg was dissolved in 50 ml distilled water. 1 ml from this solution was further diluted up to10 ml water. The concentration of the resulting solution was 100µg/ml and this stock solution was diluted further with distilled water to get 6µg/ml. The absorbance of the resulting solution was measured using UV-Visible spectrophotometer in the wavelength range of 200-400 nm using distilled water as a blank.

B. Standard graph of Nepafenac in distilled water

Nepafenac, 10 mg was accurately weighed and it was dissolved in 10 ml distilled water. 1 ml from this is diluted to 10 ml (100µg/ml).The above solution served as stock solution. From the stock solution, dilutions are prepared giving the concentration of each solution ranging from 4-12µg/ml. Absorbance of the resulting solutions is determined at 238 nm using UV-Visible Spectrophotometer against distilled water as a blank.

C. Effect of SBE-β-CD on aqueous solubility of Nepafenac

Nepafenac, 10 mg was accurately weighed and it was dissolved in 10 ml distilled water, to which accurately weighed 0.2594 g of SBE-β-CD was added. The solution was then sonicated for near about 1 hour. Then 1 ml from this is diluted to 10 ml (100µg/ml).The above solution served as stock solution. From the stock solution, dilutions are prepared giving the concentration of each solution ranging from 6-14µg/ml. Absorbance of the resulting solutions is determined at 238 nm using UV-Visible Spectrophotometer against distilled water containing same concentration of SBE-β-CD devoid of drug as a blank and calibration curve of drug with SBE-β-CD was plotted.

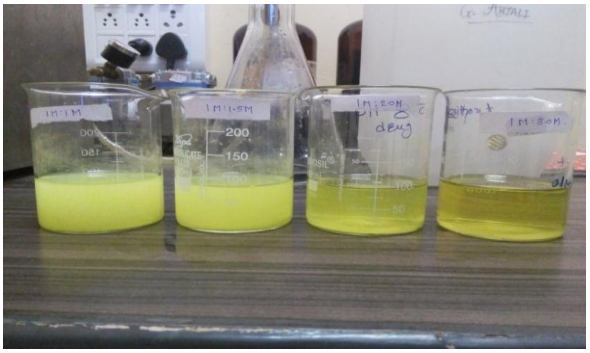
D. Phase solubility study of Nepafenac in SBE-β-CD

Nepafenac and SBE-β-CD were mixed in the following ratios: 1:1, 1:1.5, 1:2, and 1:3. For the 1:1 ratio, Nepafenac (50 mg) was added to a solution of SBE-β-CD (865.24 mg in 50 ml water) and the suspension was kept under agitation (125 rpm) at R.T. for three days. After the agitation period, the supernatants were filtered through a Whatmann filter paper, diluted with water, and analyzed by UV spectroscopy.

RESULTS AND DISCUSSION

1. Physical Observation

By physical observation amongst all above solutions, 1M: 3.0M solution of Nepafenac with SBE-β-CD was found to be clear after sonication for 1 hr.



2. UV Spectroscopy studies

A. Determination of maximum wavelength of Nepafenac: The absorbance of 6 µg/ml solution of Nepafenac was measured at 200 nm to 400 nm. The maximum wavelength of Nepafenac was found to be 238 nm and depicted in Fig. 1.

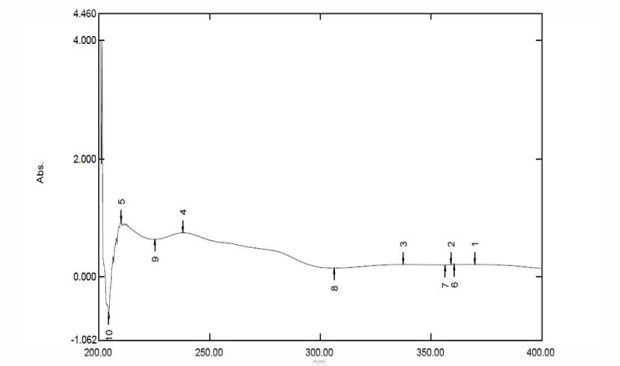


Fig 1. UV Spectrum of Nepafenac depicting maximum wavelength

B. Standard graph of Nepafenac in ATF: The absorbance of Nepafenac at different concentrations was measured using UV-VIS spectrophotometer at 238 nm (Fig. 2)

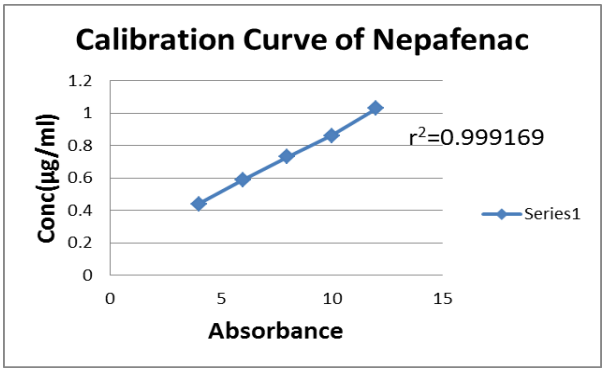


Fig 2. Calibration curve of Nepafenac in water

C. Effect of SBE-β-CD on aqueous solubility of Nepafenac

Fig 3 shows the Calibration curve of Nepafenac with SBE-β-CD in water.

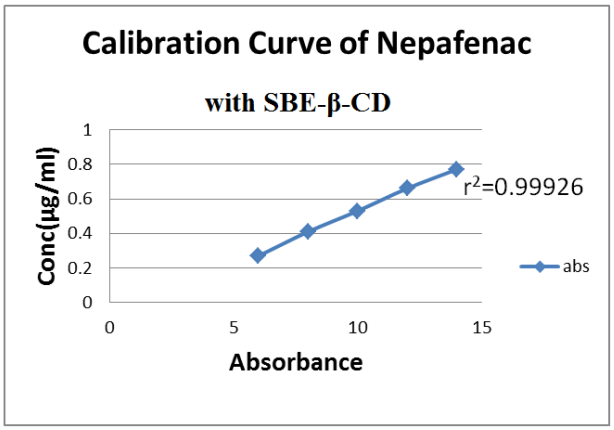


Fig 3. Calibration curve of Nepafenac with SBE-β-CD in water

D. Phase solubility study of Nepafenac in SBE-β-CD

The phase solubility diagram of Nepafenac in SBE-β-CD obtained by plotting the changes in the drug solubility as a function of SBE-β-CD but with increase in concentration of SBE-β-CD to 2M and 3M, increased solubility was observed. The increase in solubility with 1 M, 1.5 M, 2 M and 3 M of SBE-β-CD was found to be 2.38 times, 2.725 times, 4.401 times and 5.857 times respectively (compared to standard solubility in water 0.0197mg/ml). The drug solubility was increased linearly up to 3M of SBE-β-CD. The solubility curve was classified as the Ap type, which revealed a formation of soluble Nepafenac/ β-CD inclusion complex with 1:3 molar ratio stoichiometry according to Higuchi and Connors (Higuchi, Connors, 1965). The complex exhibited higher solubility than the drug molecule, but its limit was reached within the tested SBE-β-CD concentration range. The highest drug solubility of about 0.1154 mg/ml in SBE-β-CD solution was observed with 3M SBE-β-CD and selected for further studies.

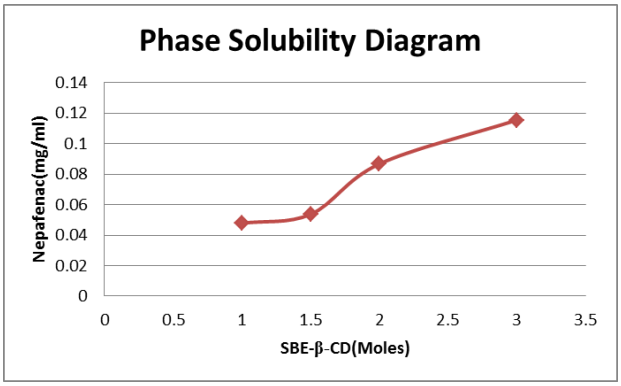


Fig 4: Phase solubility diagram

CONCLUSION

Solubility of Nepafenac was not significantly increased with the solubilizing agents- PEG 400, Cremophor RH and Polysorbate 80 whereas, SBE-β-cyclodextrin (3M) increased the solubility of Nepafenac by 5.857 times. Among all the selected solubilizers SBE-β-CD was found to be the best solubilizer. Hence can be used with Nepafenac in different formulations as solubilizer.

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