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Mixed Solvency Approach- Boon for Solubilization of Poorly Water Soluble Drug Diclofenac Sodium

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ABSTRACT

Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Poor water solubility of drugs often causes significant problems in producing formulations of sufficiently high bioavailability, preventing effective use of the drugs. 'Mixed-solvency' concept is the phenomenon to increase the solubility of poorly water-soluble drugs in the aqueous solution containing blends of hydrotropic agents, co-solvents and water soluble solutes which may give synergistic enhancement effect on solubility of such drugs. Diclofenac sodium has analgesic, antipyretic and anti-inflammatory activities. In the present study diclofenac sodium was selected as a model drug for the enhancement of aqueous solubility by mixed-solvency concept due to its poor water solubility. It was achieved by making blends of randomly selected water-soluble substances from among the hydrotropic (urea, sodium acetate); water soluble solutes (PEG4000, PEG6000); and co-solvents (PEG200, PEG400). The aqueous solubility of diclofenac sodium was observed at room temperature in the randomly selected blends of solubilizers containing different combinations keeping total concentration 50%w/v constant. Diclofenac sodium has λ_{max} 276 nm and obeys Beer's Law in concentration range of 10-60 $\mu\text{g/ml}$. The results suggest that solubility of the diclofenac sodium containing blends of varying combinations was enhanced significantly using mixed solvency approach.

Keywords: diclofenac sodium, poorly-water soluble drugs, solubility, mixed-solvency.

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INTRODUCTION

Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The saturated solution is the one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction. Some authors presented detailed review on different drug solubilization techniques. They are pH adjustment, micronization, micellar solubilization, co solvency and salting in, hydrotropy etc. Maheshwari, has proposed the concept of mixed solvency. The author is of the opinion that all substances have solubilizing power and all soluble substances whether liquids, solids, or gases may enhance the aqueous solubility of poor water-soluble drugs. Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium acetate), co solvents (PEG200 and PEG 400) and water soluble solids (PEG 4000 and PEG 6000) in randomly prepared blends keeping total concentration constant i.e. 50% w/v. Results shows synergistic effect on solubility enhancement of the drug substance [1-9].

MATERIALS AND METHODS

Materials under methods

Gift sample of drug Diclofenac sodium was procured from M/s Aerrow Pharmaceuticals, Indore, M.P. All the chemicals and solvents used were of analytical grade. Purified water was used to prepare the solutions of solubilizers. A spectrophotometer (UV-1700 Shimadzo) was used for quantitative analysis.

Methods

Diclofenac sodium (40 mg) was accurately weighed and transferred to 50 ml volumetric flask. To this 40 ml of distilled water was added. The flask was shaken to dissolve the drug and volume was made up to the mark with distilled water. The stock solution was further diluted with distilled water to obtain various dilutions containing between 10-60 µg/ml. Absorbance was noted at 276nm against reagent blanks to get the calibration curve. The Solubility of diclofenec sodium in distilled water was observed and shown in Table (1).

Table (1): Solubility of diclofenac sodium in purified water

S. No.	Concentration	Absorbance
1	10µg/ml	0.27
2	30µg/ml	0.72
3	60 µg/ml	0.86

Blends (50%w/v constant) of solubilizers were prepared by using varying concentrations of the solvents. Blend-1 containing urea, PEG400, PEG6000 and Sodium acetate, Blend- 2 contains urea, PEG4000, PEG200 and Sodium acetate, Blend -3 contains urea, PEG200, PEG400 and Sodium acetate and Blend- 4 contains urea, PEG400, PEG6000 and Sodium acetate as shown in Table (2). Bulk drug was first dissolved in 10ml of blend 1. The solution was vigorously shaken for a definite time with regular intervals until a supersaturated solution is obtained. The resulting solution was diluted up to 1000ml with the blend. Absorbance of this solution was noted at 276nm against the solvent blend. The same procedure was followed with the other blends i.e. blend2, blend3 and blend4 respectively and absorbance were noted at the same wavelength. The corresponding concentration gives the solubility of the drug and thus the enhanced solubility of the drug was calculated by comparing the solubility of the drug in water.

Table (2): Contents of Blends

BLEND-1		BLEND-2		BLEND-3		BLEND-4	
HYDRO-TROPE	PERCENTAGE	HYDROTROPE	PERCENTAGE	HYDROTROPE	PERCENTAGE	HYDROTR OPE	PERCENTAGE
Urea	10%	Urea	9%	Urea	25%	Urea	28%
PEG-400	15%	PEG-4000	12%	PEG-200	8%	PEG-400	7%
PEG-6000	15%	PEG-200	20%	PEG-400	8%	PEG-6000	7%
Sodium acetate	10%	Sodium acetate	9%	Sodium acetate	9%	Sodium acetate	8%

RESULTS AND DISCUSSION

The results obtained are shown in Table (3) for the solubility of diclofenac sodium in different blends. From the table it is evident that there was improvement in the solubility of diclofenac sodium in blend (50% w/v) containing urea, PEG-200, PEG-400, PEG-4000, PEG-6000 and sodium acetate in varying concentrations. On comparing Table(2) and Table(3) the drug solubility was found to be enhanced by 2.53, 3.68, 3.8 and 4.1 folds with blend-1, blend-2, blend 3 and blend 4 respectively. The greatest enhancement in solubility was observed in the Blend-4 and least in case of Blend-1. These results demonstrate the principle of mixed-solvency concept that water soluble substances whether hydrotropic or solvents or water-soluble solids can be combined randomly in varying concentrations and gives enhanced solubility to poorly water-soluble drugs. Blends of water soluble substances can be prepared in safe level of concentrations of individual solubilizers to give a concentrated solution to act as solubilizing system for development of their different dosage forms.

Table (3): Solubility of diclofenac sodium in different blends

S. No.	Blend No.	Absorbance	Saturated Solubility
1	Blend-1	1.148	152 µg/ml
2	Blend-2	1.892	221 µg/ml
3	Blend-3	1.931	232 µg/ml
4	Blend-4	1.982	246 µg/ml



CONCLUSION

The solubility of the diclofenac sodium containing different combinations of urea, PEG-200, PEG-400, PEG-4000, PEG-6000 and sodium acetate in varying concentrations was enhanced significantly, using this mixed-solvency approach. Therefore the results suggest that mixed –solvency approach can also be used successfully for the enhancement of solubility of other poor water-soluble drugs.

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