Chapter 1
Print ISBN: 978-93-5547-100-0, eBook ISBN: 978-93-5547-106-2

Investigating the Enhancement of Solubility of Poorly Water-Soluble Drugs Diclofenac Sodium by Mixed Solvency Approach

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DOI: 10.9734/bpi/cacs/v6/1926C

ABSTRACT

One of the difficult tasks that becomes a challenge in the formulation development of an orally administered drug with poor aqueous solubility is increasing solubility. Drugs with low water solubility have a hard time producing formulations with enough bioavailability, preventing them from being used effectively. The 'mixed-solvency' notion refers to the phenomena of increasing the solubility of poorly water-soluble pharmaceuticals in an aqueous solution containing blends of hydrotropic agents, co-solvents, and water-soluble solutes that may have a synergistic influence on drug solubility. In this study, a mixed solvency approach was used to improve the aqueous solubility of the poorly water-soluble drug diclofenec sodium (selected as a model drug) by blending a variety of water-soluble substances from the hydrotropic (urea, sodium acetate); water soluble solutes (PEG4000, PEG6000); and co-solvents (PEG200, PEG400). At room temperature, the aqueous solubility of diclofenac sodium was observed in randomly selected blends of solubilizers containing different combinations while maintaining a total concentration of 50% w/v constant. In the concentration range of 10-60 µg/ml., diclofenec sodium has a λ_{max} of 276 nm and follows Beers Law. The findings suggest that using a mixed solvency approach, the solubility of diclofenac sodium containing blends of various combinations was significantly improved.

Keywords: Solubility; enhancement; mixed-solvency.

1. INTRODUCTION

One of the most important parameters to consider when developing a formulation for an orally administered medication with poor aqueous solubility is solubility enhancement. In quantitative terms, solubility is described as the concentration of a solute in a saturated solution at a certain temperature, while in qualitative terms, it is defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. The saturated solution is the one in which the solute is in equilibrium with the solvent. Parts, percentages, molarity, molality, volume fraction, and mole fraction are all ways to express a drug's solubility. Some writers provided a comprehensive overview of various drug solubilization strategies. They are pH adjustment, micronization, micellar solubilization, co solvency and salting in, hydrotropy etc. The concept of mixed solvency was proposed by Maheshwari. 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 [1-11]. Mixed solvency is the phenomenon basically to increase the solubility of poorly soluble drugs, using blends of solubilizers. This technique can provide additive or synergistic enhancement effect on solubility of poorly soluble drugs. Mixed solvency technique can be employed in injection formulation of poorly soluble drugs in

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order to reduce concentration of individual solubilizer (used for solubility enhancement) to minimize the toxic effects of solubilizers [12-15].

2. MATERIALS AND 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.

2.1 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.

Blends (50%w/v constant) of solubilizers were prepared by using varying concentrations of the solvents. Blend-1 containing urea, PEG4004, PEG400 and Sodium acetate, Blend- 2 contains urea, PEG6000, 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 1. Solubility of diclofenac sodium in purified water

S. No.	Concentration	Absorbance
1	10 µg/ml	0.21
2	20 µg/ml	0.42
3	30 µg/ml	0.64
4	40 µg/ml	0.76
5	60 µg/ml	0.92

Table 2. Contents of blends

BLEND-1		BLEND-2		BLEND-3		BLEND-4	
Hydro-trope	**Percentage**	**Hydro-trope**	**Percentage**	**Hydro-trope**	**Percentage**	**Hydro-trope**	**Percentage**
Urea	10%	Urea	10%	Urea	15%	Urea	15%
PEG-4000	10%	PEG-6000	10%	PEG-200	10%	PEG-400	15%
PEG-400	15%	PEG-200	15%	PEG-400	15%	PEG-6000	10%
Sodium acetate	10%	Sodium acetate	15%	Sodium acetate	10%	Sodium acetate	10%

3. 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 2.31, 3.58, 3.80 and 3.90 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	1.152	139µg/ml
2	Blend-2	1.780	215 µg/ml
3	Blend-3	1.890	228 µg/ml
4	Blend-4	1.932	234 µg/ml

4. 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.

ACKNOWLEDGEMENT

The author is thankful to M/s Aerrow Pharmaceuticals, Indore, M.P., for providing gift sample of drug for the studies.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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He is an Assistant Professor at Devi Ahilya University, Indore, MP, India with an extensive teaching experience of more than 18 years. Formerly into the field of Pharma Marketing, he always had a passion for research and teaching. Industrial Pharmacy is the specialization of author and the thrust area of research is formulation and optimization of various dosage forms. With a sound research background, he has published around 40 research articles in various reputed national and international journals. He has worked as a Principal Investigator on Major research projects, obtained from University Grants Commission (UGC), New Delhi, and Madhya Pradesh Council of Science and Technology (MPCOST), Bhopal, MP. He is a Supervisor and guide to students pursuing Ph.D. He has attended many pharmaceutical conferences, seminars and workshops, refresher courses and orientation programs. He is a Life member of various Professional bodies, like IPA, APTI etc. He has an active participation in corporate life with different capacities.

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This chapter is an extended version of the article published by the same author(s) in the following journal.
International Journal of Research and Development in Pharmacy and Life Sciences, 4(6): 1835-1837, 2015.