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Research Article

MIXED CO-SOLVENCY CONCEPT: A PROMISING TOOL TO ENHANCE SOLUBILITY OF POOR SOLUBLE DRUG ACECLOFENAC

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ABSTRACT

The present work proposes hydrotropy as a type of co-solvency method to increase the solubility of Aceclofenac as the drug candidate due to its poor solubility. Aqueous solutions containing small quantities of several water-soluble excipients giving a concentrated solution, may act as a solvent system for some poorly water-soluble drugs. This is one of the concepts of mixed-solvency. This same concept has been explored to formulate the syrups (solutions) of poorly water-soluble drug Aceclofenac (as a model drug). For this, the blends containing solubilizers from the category of hydrotropes, co solvents and water soluble solids were employed. The blends of randomly selected solubilizers were used for solubility studies. Based on the solubility studies, few blends showing largest solubilities were employed to make the syrup. This may reduce the individual concentration of solubilizers and so reduce their potential of toxicities. The formulated syrups were subjected to accelerated stability studies and they were found quite stable.

Key words: Mixed solvency, syrup, Aceclofenac.

INTRODUCTION

Up to 40 per cent of new chemical entities (NCEs) discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. So solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Relative to highly soluble compounds, low drug solubility often manifests itself in a host of *in vivo* consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher inter-patient variability. Poorly soluble compounds also present many *in vitro* formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the *in vivo* absorption. These *in vivo* and *in vitro* characteristics and the difficulties in achieving predictable and reproducible *in vivo*/*in vitro* correlations are often sufficiently formidable to halt development

on many newly synthesised compounds due to solubility issues. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class III and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250mL water over a range of pH from 1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 per cent absorption of the administered dose. In contrast, compounds with solubilities below 0.1mg/mL face significant solubilisation obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilisation during formulation[1]. Development of drugs with highly solubility in one of the major concerns in pharmaceutical Industry. This is due to the solubility phenomenon, which is an area of particular importance and therefore by producing viable and proper procedures of solubilisation is such an importance matter[2]. As to increase the solubility of poorly water soluble drugs, there are a few methods that have been established including a use of co-solvents[3].

The formulation development of oral liquid solutions presents many technical problems to the industrial pharmacist. Special techniques are required to solubilize poorly water- soluble drugs. Solubilization of poorly water-soluble drugs has been a very important issue in screening studies of new chemical entities as well as in formulation research. Solubility prediction in pharmaceutical area is still a challenging subject and requires further investigations from both experimental and computational points of view. The author has applied hydrotropic solubilization technique to quantitatively estimate a large number of poorly water-soluble drugs[3-29]. **Maheshwari etal**[30-32] has the opinion that hydrotropic solubilization is just like co-solvency and 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 poorly water-soluble drugs. He has carried out solubility studies on poorly water-soluble drug, salicylic acid (as model drug). Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium citrate), co solvents (glycerin, propylene glycol, PEG 300 and PEG 400) and water soluble solids (PEG 4000 and PEG 6000) individually as well as in 10 randomly prepared blends employing solubilizers from these categories keeping total concentration constant i.e. 40% w/v. Results showed that seven out of ten blends produced synergistic effect on solubility enhancement.

Materials

Aceclofenac (anhydrous form) was a gift sample from Rantus Pharma Pvt. Ltd. Hyderabad, Sodium Citrate, PEG 300, PEG 400, Propylene Glycol, PEG 4000 and Sucrose are procured from S.D fine Chemicals and Ethanol is of analytical grade.

Preparation of Standard Solution and Calibration Curve:

Weighed quantity of Aceclofenac (20mg) was dissolved in 2ml methanol in a 100ml volumetric falsk. Volume was made up to 100ml with distilled water, to obtain various dilutions (2, 4, 6, 8 and 10mcg/ml) solutions respectively. The absorbance's of these solutions were determined in U.V spectrophotometer at 274nm and calibration curve was plotted. A linear relationship was observed over the range 2 – 10mcg/ml of Aceclofenac (Table – 3).

Preliminary Solubility Studies of Aceclofenac

Determination of solubilities of the drug in mixed blends and distilled water were carried out at 25 ± 1^{0}C. Sufficient amount of drug was added to screw capped 30ml glass vials containing different solutions (solubilizers) and distilled water. The vials were shaken mechanically for 12h at 25 ± 1^{0}C in Rotary water bath shaker (Remi Equipments, Bangalore). The solutions were allowed to equilibrate for next 24h and then centrifuged (Remi Equipments, Mumbai) for 10min at 1000rpm. The supernatant of each vial was filtered through Whatmann filter

paper no.41.The filtrates were diluted with distilled water suitably and analyzed spectrophotometrically 274nm to determine the solubilities.

Formulation Method

Based on the solubility determination studies, Aceclofenac syrups (4%w/v and 6%w/v Aceclofenac) were prepared using blends of solubilizers. The required quantities of all solubilizers were transferred to a volumetric flask (100ml capacity) containing 50ml of distilled water and flask to dissolve the solubilizers completely. Then, the required amount of Aceclofenac drug was added and the flask was shaken to dissolve the drug completely. The required amount of sucrose was added and again the flask was shaken to dissolve it. Then, the volume was made up to the mark with distilled water and the syrup was filtered through the filter paper (Table -1).

Physical stability testing of formulated syrups

The selected Aceclofenac syrup formulations were subjected to physical stability studies at different temperature conditions such as room temperature (25°C), 40°C/75% RH and 65°C for a period of 7 weeks. The syrups were studied for physical parameters like colour, clarity, and precipitation (if any) during such studies.

Chemical stability testing of formulated syrups

The selected Aceclofenac syrup formulations were subjected to chemical stability studies at different temperature conditions such as room temperature(25°C), 40°C/75% RH and 65°C for a period of 7 weeks. For this study, the syrups were analyzed for drug contents at different time**.**

Freeze – Thaw cycling Studies

The formulated Aceclofenac syrups were subjected to freeze-thaw cycling studies by exposing them alternately at 4^{o}C and 40^{o}C (for 24h at each temperature) during 14 days. There was no precipitation and no turbidity in syrup formulations.

Chemical stability testing of formulated syrups

The selected Aceclofenac syrup formulations were subjected to chemical stability studies at different temperature conditions such as room temperature (25°C), 40°C/75% RH and 65°C for a period of 07 weeks. For this study, the syrups were analyzed for drug contents at different time intervals.

RESULTS AND DISCUSSION

The physical stability studies revealed that two formulated syrups remained clear (no precipitation) during 7 weeks at all temperature conditions. Two formulated syrups were colour less at room temperature up to 7 weeks at least. Two formulated syrups kept at 40±5 ^{o}C/75% RH developed slight yellow colour after 7th or 8th week. Two formulated syrups developed slight yellow colour after 5 weeks at 55^{o}C. Syrup FA_2 developed deep yellow colour after 7 week and they were discarded. There was no precipitation after freeze-thaw cycling studies for 14 days. The results of chemical stability studies showed that, the residual drug content at the end of 7th week was more than 95.0% at room temperature in the syrup formulations of Aceclofenac. The residual drug content at 7th week time period in the Aceclofenac formulation FA_1 was found to be 97.1% at room temperature, 93.20% at 40^{o}C/75% RH and 90.28% at 65^{o}C where in formulation FA_2 the residual drug content was found to be 95.0% at room temperature, 92.15% at 40^{o}C/75% RH and 81.25% at 65^{o}C. This study indicates that the selected Aceclofenac formulations are quite stable.

CONCLUSION

Thus, it can be concluded that the proposed techniques would be economical, convenient, and safe when carefully designed to improve solubility of poorly water-soluble drugs by using “mixed-solvency approach”. Thus, the study opens the chances of preparing such syrup (oral liquid solutions) formulations of poorly water-soluble drugs.

Table 1: Formulation of Aceclofenac Syrup

Composition (%w/v)	Formulation Code	
	FA_1	FA_2
Aceclofenac	4	6
Sodium Citrate	4	--
PEG 300	4	8
PEG 600	4	8
Propylene Glycol	4	--
PEG 4000	4	8
Ethanol	4	6
Sucrose	15	15
Distilled Water	100	100

Table 2: Chemical Stability Testing data for Aceclofenac Syrup Formulations

Time (days)	Percent Residual Drug					
	Room Temperature (°C)		40±5°C/75% RH		65°C	
	FA_1	FA_2	FA_1	FA_2	FA_1	FA_2
0	100.0	100.0	100.0	100.0	100.0	100.0
7	99.90	99.79	99.1	99.68	99.4	99.3
14	99.62	99.73	98.86	99.55	99.05	98.90
21	99.0	97.64	95.2	94.25	96.08	91.02
28	98.4	96.89	94.87	94.00	95.75	85.76
35	98.2	95.90	94.2	93.27	94.68	81.25
42	97.9	95.25	93.90	92.56	92.15	*
49	97.1	95.0	93.20	92.15	90.28	*

* Further Studies were discontinued due to development of deep yellow colour in the syrups

Table 3: Calibration curve of Aceclofenac in Distilled Water at 274nm

Concentration (mcg/ml)	Absorbance (±SD), n=4
0	0(0.000)
2	0.056(0.005)
4	0.101(0.010)
6	0.155(0.015)
8	0.202(0.017)
10	0.255(0.021)
12	0.314(0.014)

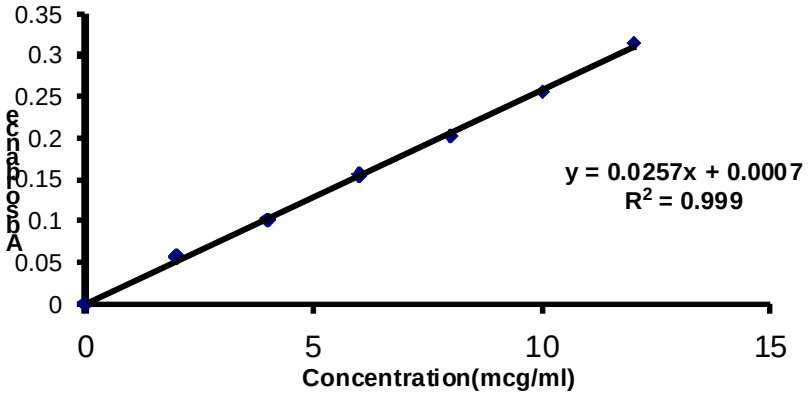

Fig. 1: Calibration Curve of Aceclofenac in Distilled Water

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