FORMULATION AND EVALUATION OF ACECLOFENAC SYRUP USING THE MIXEDSOLVENCY CONCEPT TECHNIQUE

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ABSTRACT

Based on the numerous experiments on the solubilization of poorly water-soluble drugs, the author believes that hydrotropy is another type of cosolvency and all water-soluble substances, whether solid, liquid or gas, have solubilizing properties. Therefore, aqueous solutions containing small amounts of several water-soluble excipients, resulting in a concentrated solution, can serve as a solvent system for some poorly water-soluble drugs. This is one of the mixed solvency concepts. The same concept was studied to formulate the syrups (solutions) of the poorly water-soluble drug aceclofenac(as a model drug). Mixtures with solubilizers from the category of hydrotropes, co-solvents and water-soluble solids were used for this purpose. The mixtures of randomly selected solubilizers were used for solubility studies. Based on the solubility studies, a few blends that showed the greatest solubilities were used to make the syrup. This can reduce the individual concentration of solubilizers and thus their toxicity potential. The formulated syrups have been subjected to accelerated stability studies and found to be fairly stable.

KEYWORDS:Hydrotropy, Mixed Hydrotropy, Mixed Solvency, Syrups.

INTRODUCTION

The formulation development of oral liquid solutions presents industrial pharmacists with many technical problems. Special techniques are required to solubilize poorly water-soluble drugs. The solubilization of poorly water-soluble drugs has been a very important topic in screening studies of new chemical entities as well as in formulation research. Solubility prediction in the pharmaceutical field is still a challenging topic and requires further investigations from both experimental and computational perspectives.

Maheshwari and various co-workers have applied the hydrotropesolubilization technique to quantitatively estimate a large number of poorly water-soluble drugs.He thinks that the hydrotropesolubilization is just like the co-solubilization[1-26].

Maheshwari has proposed the concept of mixed solvency [27-29]. The author is of the opinion that all substances have dissolving power and all soluble substances, whether liquid, solid or gas, can improve the water solubility of poorly water-soluble drugs. He has performed solubility studies on the poorly water-soluble drug aceclofenac(as a model drug). Solubility studies were performed in the solutions containing hydrotropes (urea and sodium citrate), co-solvents (glycerol, propylene glycol, PEG 200 and PEG 1000) and water-soluble solids (PEG 4000 and PEG 6000) individually and in 10 randomly prepared mixtures, use the solubilizers from these categories, keeping the total concentration constant, i.e.40% w/v. The results showed that seven out of ten mixtures produced a synergistic effect on improving solubility.

Application of the same principle was used in the present research work to prepare the syrup formulations of the poorly water-soluble model drug Aceclofenacusing the solubilizers from the hydrotrope category (Urea, niacinamide,sodium benzoate, sodium citrate and sodium acetate), co-solvents (PEG 200, PEG 300, PEG 400, PEG 600, propylene glycol and ethanol) and water-soluble solids (PEG 4000 and PEG 6000). It excludes the use of organic solvents, thus avoiding the problem of toxicity, pollution, cost, etc. It can reduce the individual concentration of solubilizers, thus reducing their associated toxicity. It can reduce the total concentration of solubilizers needed to produce a modest increase in solubility by using a combination of agents at lower concentrations.

MATERIALS AND METHODS

A Shimadzu UV/Vis recording spectrophotometer (Model UV 1800) with 1 cm matched silica cells was used. Aceclofenac was obtained from IPCA Laboratories Limited, Ratlam (M.P.). All other chemicals used were analytical grade.

PREPARATION OF STANDARD SOLUTIONS AND CALIBRATION CURVES

The standard solutions (100 µg/ml) of the drug were prepared in distilled water. The standard solutions (100 µg/ml) were diluted with distilled water to obtain different dilutions (5, 10, 15, 20 and 25 µg/ml). Solutions containing 10 µg/mldrug were scanned between 200 and 400 nm. The

maximum for Aceclofenac was found at 274.5 nm in each case. A linear relationship was observed for aceclofenacover the range of 5-25 µg/ml.

PRELIMINARY SOLUBILITY STUDIES OF ACECLOFENAC

The determination of the solubilities of the drug in mixed mixtures and distilled water were carried out at 28 ± 1ºC. A sufficient amount of the drug was placed in 30 ml screw-cap glass vials containing various solutions of solubilizers and distilled water [30, 31]. The vials were mechanically shaken for 12 h at 28 ± 1ºC in a round bottom flask shaker (Khera Instrument Pvt. Ltd., India). The solutions were allowed to equilibrate for the next 24 h and then centrifuged for 10 min at 1000 rpm (Remi Instruments Private Limited, Mumbai). The supernatant of each vial was filtered through Whatmann #41 filter paper. The filtrates were diluted with distilled water as appropriate and analyzed spectrophotometrically to determine solubilities.

FORMULATION DEVELOPMENT OF SYRUPS

Based on solubility determination studies, Aceclofenac syrups (containing 3 % w/v aceclofenac) were prepared using the mixtures of solubilizers. The required amounts of all solubilizers were transferred to a volumetric flask (100 mL capacity) containing 50 mL of distilled water and the flask was shaken to completely dissolve the solubilizers[30, 31] (Table.1). Then the required amount of aceclofenac drug was added and the flask was shaken to completely dissolve the drug. The required amount of sucrose was added and the flask shaken again to dissolve it. Then the volume was made up to the mark with distilled water and the syrup filtered through the filter paper. The first few ml of syrup were discarded and the filtered syrup was stored in an airtight container.

Table 1: Composition of aceclofenac syrup formulations

Composition (%w/v)	**Formulation code**		
Aceclofenac	**FA1**	**FA2**	**FA3**
	3	3	3
Urea	9	9	8
Niacinamide	9	9	8
Sodium Benzoate	9	9	8
PEG300	-	-	8
PEG 1000	-	9	-
PEG 6000	-	9	-

Ethanol	9	-	5
Sucrose	10	10	10
Distilled water q.s.	100	100	100

DETERMINATION OF pH

The pH of the developed aceclofenac syrup formulations was determined using a digital pH meter (Cyber Scan 510, Eutech Instruments Singapore) and was found to be close to neutral. The pH values of FA1, FA2 and FA3 were 7.03, 7.02 and 7.02, respectively.

FREEZE THAW CYCLING STUDIES

The formulated aceclofenac syrups were subjected to freeze-thaw cycling studies by alternating exposure to 4°C and 40°C for 24 h at each temperature during 14 days [30, 31]. There was no precipitation and no turbidity in syrup formulations.

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 55°C for a period of 10 weeks[30, 31]. The syrups were evaluated for physical parameters such as color, clarity and precipitation (if any) during such studies.

CHEMICAL STABILITY TESTS OF FORMULATED SYRUPS

The selected aceclofenacsyrup formulations were subjected to chemical stability studies at various temperature conditions such as room temperature 25°C, 40°C/75% relative humidity and 55°C over a period of 10 weeks [30, 31]. For this study, the syrups were analyzed for drug content at different time intervals (Table. 2; Figure. 1).

Table 2: Test data on chemical stability of aceclofenac syrup formulations

Time (days)	Percent residual drug								
	Room temperature			40±2°C/75%RH			55°C		
	FA1	FA2	FA3	FA1	FA2	FA3	FA1	FA2	FA3
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
7	99.89	99.86	99.89	98.99	99.59	99.43	98.92	98.89	98.15

14	99.59	99.67	99.78	97.99	99.00	98.79	95.89	97.80	96.98
21	99.50	99.56	99.67	96.98	98.78	97.98	94.98	95.90	94.91
28	98.85	99.40	98.98	95.78	97.87	95.89	93.91	94.76	93.89
35	98.59	98.89	98.78	94.98	95.89	93.89	90.89	94.82	91.95
42	97.99	98.67	98.67	93.78	93.23	92.76	88.98	91.90	89.98
49	97.89	98.34	98.54	92.89	91.48	91.89	87.90	90.34	88.56
56	97.78	97.98	97.99	91.98	90.78	90.78	86.34	88.99	86.89
63	96.98	97.87	97.67	90.78	88.10	90.65	84.23	87.90	85.98
70	95.89	96.98	96.99	89.10	87.90	88.98	*	86.11	*

*Further studies were stopped due to development of pale yellow color in the syrups.

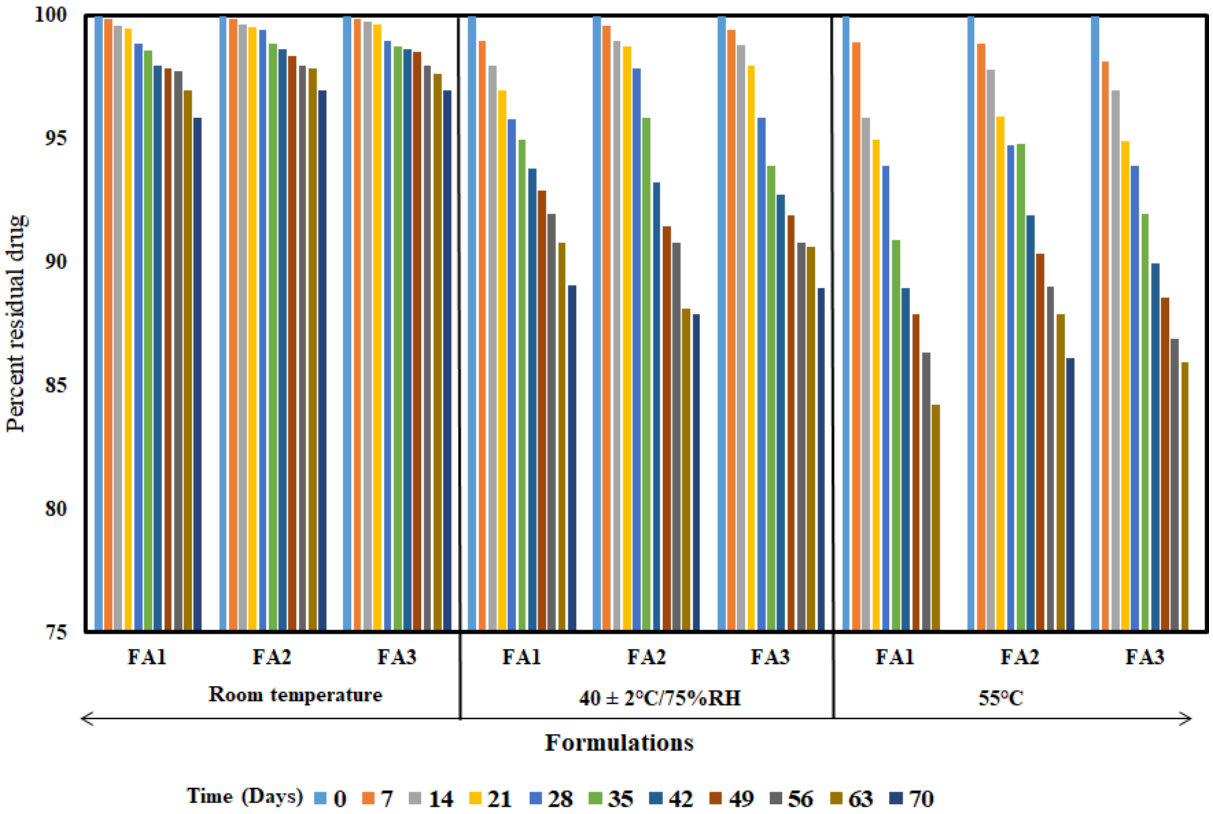

Figure 1: Diagrammatic representation of chemical stability test of formulated syrups

RESULTS AND DISCUSSION

The physical stability studies showed that all three syrups remained clear (no precipitation) for 10 weeks at all temperature conditions. All three syrups were colorless at room temperature for at least 10 weeks. All three syrups kept at 40°C/75% RH developed a light yellow color after the 6th or 7th week. All three syrups developed a light yellow color after 4 weeks at 55°C. All three syrups showed moderate yellow color development after 8 weeks at 55°C. The syrups FA1, FA3

developed a deep yellow color after 9 weeks and were discarded. There was no precipitation after 14-day freeze-thaw studies.

The results of the chemical stability studies showed that the residual drug content in all syrup formulations of aceclofenacwas greater than 90.00% at the end of week 10 at room temperature. The residual drug content at week 10 in the aceclofenacsyrup formulation FA1 was 95.89 % at room temperature, 89.10% at 40°C/75% RH and 84.23% at 55°C, whereas in formulation FA2 the residual drug content was found 96.98% at room temperature, 87.90% at 40°C/75% RH and 86.11 % at 55°C, while in formulation FT3 the residual drug content at room temperature is 96.99 %, 88.98 % at 40°C /75% RH and 85.98 % at 55°C. This study shows that the selected aceclofenacformulations are quite stable.

Like aceclofenac syrup formulations made by using a combination of physiologically compatible mixed solubilizers, there is good latitude for the development of syrup formulations of other poorly water-soluble drugs through the use of a combination of mixed solubilizers using their reduced concentrations. The proposed mixed solubilizers are known to be safe; therefore, toxicity/safety related issues cannot be a concern, indicating applicability for large-scale manufacturing, i. e. on industrial feasibility. The proposed techniques would be economical, convenient and safe. Thus, the study opens up the possibility of producing such syrup formulations (oral liquid solution) of poorly water-soluble drugs. This can reduce the individual concentration of solubilizers and thus reduce their associated toxicity potential. When a synergistic increase in solubility is achieved by combining the solubilizers, there is a further reduction in solubilizer concentrations for the desired solubility and thus a further reduction in toxicities.

CONCLUSION

Thus, it can be concluded that with the carefully designed experimental technique, the solubility of poorly water-soluble drugs can be improved by using a mixed solution approach. The author further suggests that instead of taking a single solubilizer in high concentration (which may prove toxic) to develop a dosage form, a series of solubilizers can be taken in small concentrations, thereby reducing their toxic concentrations. This mixed solvency will definitely prove to be a boon for the pharmaceutical industry to develop dosage forms of poorly water soluble drugs.

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