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Formulation and Evaluation of Tinidazole Syrup Made by Mixed Solvency Concept Technique

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ABSTRACT

Based on the large number experiments on solubilization of poorly water- soluble drugs, the author is of the opinion that hydrotropy is another type of cosolvency and all water soluble substances whether solids, liquids or gases have solubilizing properties. Therefore, 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 tinidazole (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.

Keywords: Mixed solvency, hydrotrophy, co-solvency, syrup, tinidazole.

INTRODUCTION

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.

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

Maheshwari [27-29] has proposed the concept of mixed solvency. The aurther 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.

The application of the same principle has been employed in the present research work to develop the syrup formulations (solutions) of the model poorly water-soluble drug, tinidazole employing the solubilizers from the category of hydrotropes (sodium benzoate, sodium citrate, sodium acetate, urea and niacinamide), co-solvents (PEG 200, PEG 300, PEG 400, PEG 600, propylene glycol and ethanol) and water soluble solids (PEG 4000 and PEG 6000). It precludes the use of organic solvents and thus avoids the problem of toxicity, pollution, cost etc. It may reduce the individual concentration of solubilizers and so reduce their toxicity associated with them. It may reduce the total concentration of solubilizers, necessary to produce modest increase in solubility by employing combination of agents in lower concentrations.

MATERIALS AND METHODS

A shimadzu UV/ Visible recording spectrophotometer (Model- UV 1700) with 1 cm matched silica cells was employed. Tinidazole were obtained from IPCA laboratories limited, Ratlam (M.P). All other chemicals used were of 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 various dilutions (5, 10, 15, 20, and 25 µg/ml). Solutions containing 10 µg/ml of drug were scanned between 200 and 400 nm. The λ_{\max} for tinidazole were found at 318.2 nm respectively. A linear relationship was observed over the range of 5-25 µg/ml for tinidazole.

Preliminary solubility studies of tinidazole

Determination of solubilities of the drug in mixed blends and distilled water were carried out at $28 \pm 1^\circ\text{C}$. Sufficient amount of drug was added to screw capped 30 ml glass vials containing different solutions (of solubilizers) and distilled water. The vials were shaken mechanically for 12 h at $28 \pm 1^\circ\text{C}$ in orbital flask shaker (Khera Instrument Pvt. Ltd., India). The solutions were allowed to equilibrate for next 24 h and then centrifuged (Remi Instruments Private Limited, Mumbai) for 5 min at 2000 rpm. The supernatant of each vial was filtered through Whatmann filter paper no.41. The filtrates were diluted with distilled water suitably and analyzed spectrophotometrically to determine the solubilities.

Formulation development of syrups

Based on solubility determination studies, tinidazole syrups (containing 2% w/v tinidazole) were prepared using the blends of solubilizers. The required quantities of all solubilizers were transferred to a volumetric flask (100 ml capacity) containing 50 ml of distilled water and the flask was shaken to dissolve the solubilizers, completely. Then, the required amount of tinidazole 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. First few ml of syrup was discarded and filtered syrup was preserved in airtight container.

Table 1: composition of tinidazole syrup formulations

Composition (%w/v)	Formulation code		
	FT1	FT2	FT3
Tinidazole	2.00	2.00	2.00
Sodium benzoate	8.00	8.00	7.00
Urea	8.00	8.00	7.00
Niacinamide	8.00	8.00	7.00
PEG 200	8.00	-	7.00
PEG 400	-	-	7.00
PEG 4000	-	8.00	-
PEG 6000	-	8.00	-
Ethanol	8.00	-	5.00
Sucrose	10.00	10.00	10.00
Distilled water q.s.	100.00	100.00	100.00

Determination of pH:

The pH of the developed tinidazole syrup formulations were determined using digital pH meter (Cyber Scan 510, Eutech Instruments Singapore) and were found almost neutral. The pH of FT1, FT2 and FT3 were 7.01, 7.01 and 7.02 respectively.

Freeze-thaw cycling studies:

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

Physical stability testing of formulated syrups:

The selected tinidazole 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. 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 tinidazole syrup formulations were subjected to chemical 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. For this study, the syrups were analyzed for drug contents at different time intervals.

Table 2: chemical stability testing data for tinidazole syrup formulations

Time (days)	Percent residual drug								
	Room temperature			40±2°C/75%RH			55°C		
	FT1	FT2	FT3	FT1	FT2	FT3	FT1	FT2	FT3
0	100.00	100.0	100.0	100.00	100.00	100.00	100.00	100.00	100.00
7	99.81	99.85	99.84	98.51	99.00	98.50	98.21	98.70	98.08
14	99.52	99.51	99.51	97.83	98.08	97.70	95.63	97.71	96.02
21	99.02	99.32	99.02	96.12	97.71	96.71	94.22	95.81	94.60
28	98.80	99.10	98.80	94.71	95.50	95.32	93.01	94.20	93.81
35	98.12	98.87	98.52	93.01	94.90	93.80	90.52	91.62	91.21
42	97.91	98.31	98.13	91.52	93.81	92.91	88.44	90.50	89.52
49	97.53	98.01	98.00	90.24	93.01	91.40	86.42	88.91	88.83
56	97.00	97.90	97.80	88.83	91.32	90.23	84.31	87.83	86.51
63	96.42	97.22	97.14	87.32	90.11	88.81	82.05	86.11	84.30
70	95.71	96.32	96.51	85.21	88.80	87.21	*	83.60	*

**Further studies were discontinued due to development of deep yellow colour in the Syrups.*

RESULTS AND DISCUSSION

The physical stability studies revealed that all three syrups remained clear (no precipitation) during 10 weeks at all temperature conditions. All three syrups were colourless at room temperature upto 10 weeks at least. All three syrups kept at 40°C/75% RH developed slight yellow colour after 6th or 7th week. All three syrups developed slight yellow colour after 4 weeks at 55°C. There was moderate yellow colour development in all three syrups at 55°C after 8 weeks. Syrups FT1, FT3, developed deep yellow colour after 9 weeks and 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 10th week was more than 90.00% at room temperature in all the syrup formulations of tinidazole. The residual drug content at 10th week time period in the tinidazole syrup formulation FT1 was found to be 95.71% at room temperature, 85.21% at 40°C/75% RH and 82.05% at 55°C, whereas in formulation FT2, the residual drug content was found to be 96.32% at room temperature, 88.80% at 40°C/75% RH and 83.60% at 55°C, whereas in formulation FT3 the residual drug content was found to be 96.51% at room temperature, 87.21% at 40°C/75% RH and 84.30% at 55°C. This study indicates that the selected tinidazole formulations are quite stable.

Like tinidazole syrup formulations made by use of combination of physiologically compatible mixed solubilizers, there is a good scope for development of syrup formulations of other poorly water-soluble drugs by the use of combination of mixed solubilizers using their reduced concentrations. The proposed mixed solubilizers are known to be safe; hence, toxicities/safety related issues may not raise concern, suggesting the adoptability for large scale manufacturing i.e. industrial feasibility. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing such syrup (oral liquid solution) formulations of poorly water-soluble drugs. This may reduce the individual concentration of solubilizers and so reduce their potential of toxicity associated with them. If by combining the solubilizers, synergistic solubility enhancement is achieved, there is further reduction in the concentrations of solubilizers for desired solubility and hence further reduction in toxicities.

CONCLUSION

Thus, it can be concluded that with the carefully designed experimental technique, solubility of poorly water-soluble drugs can be improved by using “mixed-solvency approach.” The author further suggests that instead of taking a single solubilizer in large concentration (which may prove toxic) for development of a dosage form, a number of solubilizers may be taken in small concentrations curtailing their toxic levels. This mixed-solvency shall prove definitely a boon for pharmaceutical industries for the development of dosage forms of poorly-water soluble drugs.

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