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Formulation and Evaluation of Paracetamol Syrup Made by Mixed Solvency Concept

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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 Paracetamol (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, syrup, Paracetamol.

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 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 aurhor 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, paracetmaol employing the solubilizers from the category of hydrotropes (sodium citrate, sodium acetate and urea), 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. Paracetamol 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 λmax for paracetamol were found at 243.2 nm respectively. A linear relationship was observed over the range of 5-25 µg/ml for paracetamol .

Preliminary solubility studies of paracetamol
Determination of solubilities of the drug in mixed blends and distilled water were carried out at 28 ± 1°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 ± 1°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, paracetamol syrups (containing 6% w/v or 5% w/v paracetamol) 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 paracetamol 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 paracetamol syrup formulations

Composition (% w/v)	Formulation code	
	FP1	FP2
Paracetamol	6.00	5.00
Urea	6.00	8.00
Sodium acetate	6.00	8.00
Sodium citrate	6.00	-
PEG 200	6.00	8.00
PEG 400	6.00	8.00
Propylene glycol	6.00	-
Ethanol	4.00	8.00
Sucrose	20.00	20.00
Distilled water q.s.	100.00	100.00

Determination of pH:

The pH of the developed paracetamol syrup formulations were determined using digital pH meter (Cyber Scan 510, Eutech Instruments Singapore) and were found almost neutral. The pH of the developed paracetmol syrup formulation FP1 and FP2 were 7.01, 7.02, respectively.

Freeze-thaw cycling studies:

The formulated paracetamol 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.

TABLE 2: Chemical stability testing data for paracetamol syrup formulations

Time (days)	Percent residual drug					
	Room temperature		40±2°C/75%RH		55°C	
	FP1	FP2	FP1	FP2	FP1	FP2
0	100.0	100.0	100.00	100.00	100.00	100.00
7	99.82	99.58	98.51	98.51	98.50	98.21
14	99.40	99.12	98.08	97.70	97.71	97.03
21	99.22	98.59	96.72	96.22	94.51	93.81
28	98.50	97.90	95.14	94.31	92.73	91.42
35	98.11	97.25	93.61	92.73	90.82	89.23
42	97.42	96.71	92.50	91.51	89.01	87.51
49	97.10	95.36	91.32	89.52	87.52	85.22
56	96.31	93.62	89.21	88.21	85.61	84.31
63	95.45	92.15	88.83	86.73	83.20	82.80
70	93.43	90.91	87.10	83.90	80.12	*

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

Physical stability testing of formulated syrups:

The selected paracetamol 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 paracetamol 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.

RESULTS AND DISCUSSION

The physical stability studies revealed that two formulated syrups remained clear (no precipitation) during 10 weeks at all temperature conditions. Two formulated syrups were colourless at room temperature upto 10 weeks at least. Two formulated syrups kept at 40°C/75% RH developed slight yellow colour after 6^{th} or 7^{th} week. Two formulated syrups developed slight yellow colour after 4 weeks at 55°C. There was moderate yellow colour development in two formulated syrups at 55°C after 8 weeks. Syrup FP2 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 10^{th} week was more than 90.00% at room temperature in the syrup formulations of paracetamol. The residual drug content at 10^{th} week time period in the paracetamol formulation FP1 was found to be 93.43% at room temperature, 87.10% at 40°C/75% RH and 80.12% at 55°C, whereas in formulation FP2 the residual drug content was found to be 90.91% at room temperature, 83.90% at 40°C/75% RH and 82.80% at 55°C. This study indicates that the selected paracetamol formulations are quite stable.

Like paracetamol 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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