

Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of hydrotropic solid dispersion of aceclofenac

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In the present investigation, newly developed mixed hydrotropic solid dispersion (HSD) technology precludes the use of organic solvent and also decreases the individual concentration of hydrotropic agents, simultaneously decreasing their toxic potential. 'Mixed-hydrotropic solubilization' technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the aqueous solution containing blends of hydrotropic agents, which may give synergistic enhancement effect on solubility of poorly water-soluble drugs and to reduce concentrations of each individual hydrotropic agent to minimize their toxic effects due to high concentration of hydrotropic agents. Maheshwari has made HSD of paracetamol using urea. In the present study, the aqueous solution of hydrotropic blend (20% urea and 10% sodium citrate) has been found to increase aqueous solubility of poorly water-soluble drug, aceclofenac. This mixed hydrotropic blend was used to prepare solid dispersion of aceclofenac. The prepared solid dispersions have been characterized by IR and XRD studies. They have been studied for dissolution rate enhancement effect. The prepared solid dispersions were found very stable (chemically).

Key words: Aceclofenac, mixed-hydrotropic solubilization, sodium citrate, urea

INTRODUCTION

Solid dispersion technology^[1-9] is one of the methods of increasing the dissolution rate, and hence the rate of absorption and/or total bioavailability of poorly water-soluble drugs. The common methods of making solid dispersions are solvent evaporation, fusion, and fusion-solvent methods. In the solvent method, an organic solvent (volatile) is used to dissolve the drug as well as the water-soluble carrier. Then, solvent is removed by suitable evaporation technique to obtain solid dispersion. Toxicity of residual solvent, high cost of solvent, and pollution are major drawbacks of this method.

Newly developed hydrotropic solid dispersion (HSD) technology^[9] precludes the use of organic solvent. Salient feature of the new method is that the hydrotropic agent (carrier) is water-soluble, whereas the drug is insoluble in water. However, in presence of large amount of hydrotropic agent in water, the drug gets solubilized due

to hydrotropic solubilization phenomenon. Then, water is removed by suitable evaporation technique to get solid mass (a solid dispersion). In absence of hydrotropic agent, water is not a solvent for poorly water-soluble drugs; therefore, the proposed method is different from common solvent method and is a novel application of hydrotropic solubilization phenomenon. Then, so formed solid dispersions shall be denoted as HSDs.

MATERIALS AND METHODS

Material

Aceclofenac was received as a gift sample from IPCA Laboratories Limited (Ratlam, India). Urea (Merck Ltd., Mumbai), tri-sodium citrate dihydrate (Loba Chemie, Mumbai) were used. All other chemicals and solvents were of analytical/HPLC grade.

Selection of hydrotropic blends

As evident from the research work,^[10] it was found that there was significant enhancement in aqueous solubility (a synergistic effect) of aceclofenac by use of a combined hydrotropic blend of urea (22.5% w/v) and sodium citrate (22.5% w/v). Keeping this point in mind and using total dissolved hydrotropes concentration at least 30% w/v (at random), different blends of hydrotropes [Table 1] were made and the solubility of aceclofenac was determined in them.

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Determination of equilibrium solubility

Equilibrium solubilities of aceclofenac in different aqueous mediums were determined at room temperature. Sufficient or excess amount of drug was added to screw capped 10 ml glass vials containing distilled water, aqueous solutions of hydrotropic agents, aqueous solutions of hydrotropic blends, and buffers of pH 7.4, 8.0, and 9.0 (pH range of hydrotropic blend solutions) separately. The vials were shaken mechanically for 12 hours at room temperature in Orbital flask shaker (Khera Instruments Private Limited, Delhi, India). The solutions were allowed to equilibrate for next 24 hours and the solutions were transferred into Eppendorf tubes, and then centrifuged for 30 min at 2000 rpm using a centrifuge (Remi, Mumbai, India). The supernatants of each vial were filtered through Whatmann filter paper number 41. Filtrates of saturated solutions after appropriate dilution of aceclofenac were analyzed spectrophotometrically at 275 nm (wavelength). Enhancement ratios in solubility [Table 2] were determined by following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

Table 1: Composition of hydrotropic blends selected for aceclofenac

Blends	Urea (% w/v)	Sodium citrate (% w/v)
A	15	15
B	20	10
C	20	20
D	25	25
E	30	10
F	30	15
G	30	20

Table 2: Equilibrium solubility of aceclofenac in different media

Solvent	pH of solvent system	Solubility* (g/100 ml)	Solubility enhancement ratio
DM water	6.5 – 7.2	0.018	-
30%w/v urea solution	7 – 7.5	0.529	29.39
30%w/v sodium citrate solution	7.8 – 8.0	0.076	4.22
Blend A	8 – 8.5	1.322	73.44
Blend B	8 – 8.5	5.047	280.39
Blend C	8 – 8.5	5.082	282.33
Blend D	8.5 – 9	5.214	289.67
Blend E	8.7 – 8.9	5.733	318.50
Blend F	8.5 – 9.0	6.562	364.55
Blend G	8.5 – 9.0	7.354	408.55
Phosphate buffer	7.4	0.065	3.61
Phosphate buffer	8.0	0.069	3.83
Alkaline borate buffer	9.0	0.075	4.17

*Average of three determinations

Selection of ratios of drug and carrier in HSD and PM

There was significant enhancement in solubility of drug using blend B (which was having comparatively less amounts of hydrotropic agents). Therefore, ratios of drug : carrier (a blend of urea and sodium citrate in 2 : 1 ratio) used for solid dispersions were 1 : 6, 1 : 8, and 1 : 10.

Preparation of hydrotropic solid dispersions of aceclofenac

For preparation of 10 g HSD containing aceclofenac and hydrotropic blend (20% w/w urea and 10% w/w sodium citrate) in 1 : 6 ratio, aceclofenac (1.423 g), urea (5.714), and sodium citrate (2.857) were accurately weighed. Minimum (possible) quantity of distilled water at 80 to 85°C contained in a 250 ml beaker was used to dissolve the urea and sodium citrate for quick dissolution. Then, aceclofenac was added to this beaker (at 30 – 40°C) and a Teflon-coated magnetic bead was dropped in it. Stirring of magnetic bead in beaker was started using a magnetic stirrer, maintaining the temperature at 30 to 40°C. Aceclofenac got completely solubilized. Stirring was continued till a semisolid mass was formed in the beaker (after evaporation of a large quantity of water). Semisolid mass so formed was spread on several watch glasses in thin layers for quick drying. The watch glasses were kept in oven, maintained at 40°C for drying. When the mass became pulverizable, it was triturated with the help of pestle mortar and again kept in oven for drying.

After almost complete drying, the powder of solid dispersion was passed through sieve number 100 and was kept for six days in a desiccator containing blue silica gel. After this, the HSD powder was stored in air-tight glass bottles.

Same procedure was repeated to prepare HSDs containing aceclofenac and hydrotropic blend (urea : sodium citrate - 2 : 1) in ratios of 1 : 8 (using 1.111 g aceclofenac) and 1 : 10 (using 0.090 g aceclofenac).

Physical mixture of aceclofenac

Drug : carrier ratio 1 : 10 was used for preparation of physical mixture (PM). Aceclofenac (0.090 g), urea (5.926 g), and sodium citrate (2.963 g) were accurately weighed and mixed intensely for 10 min using glass pestle and mortar with intensive trituration. Then, powder mass was shifted through sieve number 100. After this, the physical powder was stored in air-tight glass bottles.

Determination of drug content in aceclofenac formulations (HSD and PM)

Powdered solid dispersion/PM containing about 10 mg of aceclofenac was accurately weighed and transferred to a 500 ml volumetric flask. About 450 ml of distilled water was added and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark with distilled water and the absorbance of this solution was measured at 275 nm against reagent blank. In each case, analysis was carried out

in triplicate. The drug content [Table 3] was determined using regression equation $Y = 0.0243 X + 0.0043$.

Powder X-ray diffraction studies of formulated HSD and PM

The powder X-ray diffraction spectra of the prepared HSDs and the PMs were obtained using RU-H₃R, horizontal rotaxflex rotating anode X-ray generator instrument, Rigaku, Tokyo.

Dissolution rate studies of drug and their formulations

Dissolution rates of bulk drug sample of aceclofenac, PM (1 : 10), and HSD containing drug : hydrotropic blend B of 1 : 6 and 1 : 8 ratios were studied using USP XXIV (type II) dissolution rate test apparatus. Distilled water was used as dissolution medium. Bulk drug sample, PM, and HSDs equivalent to 100 mg drug were used to perform dissolution rate studies. The stirrer was adjusted to rotate at 50 rpm. A temperature of $37 \pm 0.5^\circ\text{C}$ was maintained throughout the experiments. Samples (10 ml) of dissolution medium were withdrawn at known time intervals and replaced with same volume of distilled water after each withdrawal. The samples were analyzed for drug contents by measuring the absorbance of appropriately diluted sample solutions with distilled water at 275 nm wavelength. Calculations for amounts of drug released were done using regression equation $Y = 0.0244X + 0.0041$.

Chemical stability studies

Powders of various formulations were kept in 10 ml amber

colored glass vials which were plugged and sealed. Vials were kept at room temperature, at 40°C with 75% RH, and at 55°C . The samples were withdrawn at different time intervals and drug contents were determined by HPLC method.^[11] The initial drug content for each formulation was considered as 100%.

RESULT AND DISCUSSION

The results of the solubility data [Table 2] showed that the aqueous solubility of aceclofenac was increased more than 250 times in the hydrotropic blends except blend A (73.44 times) and 5 and 25 times in 30% sodium citrate and 30% urea, respectively. It is concluded that the solubility of aceclofenac increases synergistically by mixed hydrotropy.

The % loss on drying in 1 : 6, 1 : 8, and 1 : 10 HSDs were found to be less than 1%. XRD diffraction patterns [Figure 1] were recorded for the HSDs AUCS 1 : 10 and PM AUCS 1 : 10, which exhibited a series of intense peaks. The peaks found in case of HSDs and the respective PMs are quite comparable. This study confirmed that HSDs were not present in amorphous form; rather they were of crystalline nature.

From the results [Table 4 and Figure 2] of dissolution rate study, it is evident that the bulk drug sample exhibited poor drug release profiles. Initial rates of dissolution of drug from HSDs were very quick as compared with initial rates of dissolution from bulk drug sample. PM also showed slightly better drug release profiles compared with drug release profiles from bulk drug sample. Drug release profiles from HSDs were still better than the drug release profiles from PM. Also, it is indicated that as the proportions of water-soluble carrier (blend B; urea : sodium citrate - 2 : 1) was increased in solid dispersions, there was negligible difference in dissolution behavior. As the initial rates of dissolution of drug from HSDs were significantly high as compared with initial dissolution rates from bulk drug sample, the quick

Table 3: Drug contents of physical mixtures and hydrotropic solid dispersions (n = 3)

Drug: Hydrotropic blend B	Percent drug content (mean \pm S.D.)	
	PM	HSD
AUCS 1 : 6	-	14.237 \pm 0.044
AUCS 1 : 8	-	11.294 \pm 0.086
AUCS 1 : 10	9.671 \pm 0.056	9.052 \pm 0.109

PM - physical mixture; HSD - hydrotropic solid dispersion; SD - standard deviation; AUCS -

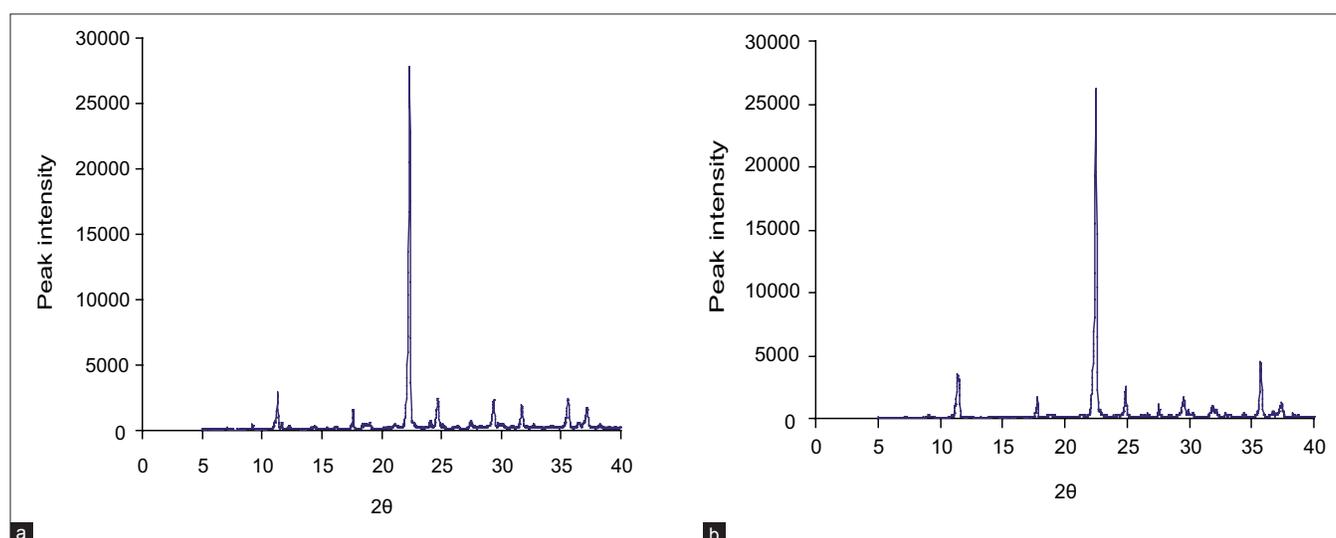
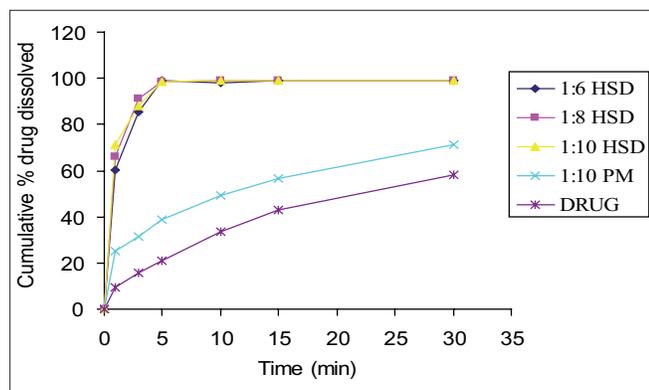


Figure 1: X-ray diffractogram of PM and HSD; (a) 1 : 10 PM (b) 1 : 10 HSD

Table 4: Dissolution profile of pure drug, AUSC 1 : 10 PM, 1 : 6, 1 : 8, and 1 : 10 HSD in distilled water

Time (min)	Cumulative percent drug dissolved (Mean \pm SD)				
	Pure drug	AUSC 1 : 10 PM	AUSC 1 : 6 HSD	AUSC 1 : 8 HSD	AUSC 1 : 10 HSD
1	9.54 \pm 0.403	25.05 \pm 0.431	60.34 \pm 0.915	65.78 \pm 0.183	71.33 \pm 0.870
3	15.63 \pm 0.007	31.34 \pm 0.336	85.36 \pm 0.210	91.01 \pm 0.609	88.12 \pm 0.736
5	21.10 \pm 0.028	39.02 \pm 0.183	98.87 \pm 0.319	98.75 \pm 0.174	98.4 \pm 0.671
10	33.35 \pm 0.700	49.47 \pm 0.538	98.15 \pm 0.432	99.99 \pm 0.265	98.83 \pm 0.653
15	43.15 \pm 0.176	56.82 \pm 0.220	99.23 \pm 0.530	99.03 \pm 0.461	98.93 \pm 0.698
30	58.15 \pm 0.014	71.09 \pm 0.275	99.11 \pm 0.685	99.08 \pm 0.328	98.95 \pm 0.490

HSD - Hydrotropic Solid Dispersion; SD – standard deviation; AUSC - Aceclofenac urea sodium citrate

**Figure 2:** Dissolution profiles of pure drug, AUSC 1 : 10 PM, 1 : 6, 1 : 8, and 1 : 10 HSD in DW

onset of action and better extent of absorption is expected after oral administration of these HSDs.

The results of chemical stability study [Table 5] showed that the residual drug content after storage for one month at room temperature in all formulations was above 98%, showing very good chemical stabilities at room temperature. The residual drug contents after storage for one month at 40°C/75% RH and 55°C in all formulations was above 95%, showing good chemical stabilities at moderate and high temperature.

CONCLUSION

The solid dispersions of aceclofenac were developed using the concept of mixed hydrotropic solubilization technique. Solid dispersions containing blend of urea and sodium citrate as water-soluble carriers show fast release of drug as compared with the pure bulk drug sample and PM; the quick onset of action and better extent of absorption is expected after oral administration of these HSDs. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing solid dispersion of poorly water-soluble drugs. If chemical stability of the drug remains unaffected, to open a new era of more stable economic and safe products in the market.

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Table 5: Chemical stability data of aceclofenac hydrotropic solid dispersions and physical mixture

Condition	Time (days)	Percent residual drug in formulations			
		AUSC 1 : 6 HSD	AUSC 1 : 8 HSD	AUSC 1 : 10 HSD	AUSC 1 : 10 PM
Room temperature	0	100.00	100.00	100.00	100.00
Room temperature	30	99.92	99.91	98.87	100.00
40°C/75% RH	0	100.00	100.00	100.00	100.00
40°C/75% RH	30	99.64	98.53	97.11	99.94
55°C	0	100.00	100.00	100.00	100.00
55°C	30	98.34	97.45	96.76	98.78

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