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DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM SOLID DISPERSION BY MIXED HYDROTROPIC TECHNIQUE

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ABSTRACT

The present study aimed to explore the mixed hydrotropic solubilization technique in the various fields of pharmacy. The objective of present research work is the novel application of mixed hydrotropic solubilization technique in the formulation development of poorly water soluble non steroidal anti-inflammatory drugs Diclofenac sodium. In the present investigation hydrotropic blend of two hydrotropic agents like urea and sodium citrate was selected for the preparation of solid dispersions of Diclofenac sodium. By using same hydrotropic blend as water-soluble carrier, hydrotropic solid dispersions of Diclofenac sodium were prepared in 1:6, 1:8 and 1:10 ratio (Drug: hydrotropic blend) on dried basis. The sample of Diclofenac sodium procured for the present studies were characterized by UV analysis. Hydrotropic solid dispersions (1:6, 1:8 and 1:10) and physical mixture (1:10) of the drug were prepared and drug contents were determined by spectrophotometric analysis at 254 nm. Equilibrium solubilization of Diclofenac sodium in different media by excess solute method and solubility enhancement ratios were calculated. The result of solubility data the aqueous solubility of Diclofenac sodium was increased more than 250 times in hydrotropic blends. The results were similar to the one reported in the official compendia, hence the procured drug samples were considered as pure and used for further studies. This formulation was evaluated for loss on drying, Dissolution rate study, Chemical stability testing.

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Key Words

Diclofenac sodium; Urea; Sodium citrate; Hydrotropy; Solubilization.

INTRODUCTION

Solid dispersion technology is one of the methods of increasing the dissolution rate and hence the rate of absorption and/or total bio-availability of poorly water-soluble drugs. The common methods of making solid dispersions are solvent evaporation, fusion and fusion-solvent methods. Newly developed hydrotropic solid dispersion technology 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. Then, water is removed by suitable evaporation technique to get solid mass (a solid dispersion). Since in absence of hydrotropic agent, water is not a solvent for poorly water-soluble drug, therefore,

The proposed method is different from common solvent method and is a novel application of hydrotropic solubilization phenomenon. The so formed solid dispersions shall be denoted as hydrotropic solid dispersions.

SELECTION OF HYDROTROPIC BLENDS

1. Equilibrium solubility of Drug: To determine solubility of Diclofenac sodium in distilled water; Solubility enhancement of drug in respect to distilled water in solutions of individual solubilizers like 30% w/v urea solution, 30% w/v sodium citrate solution, Phosphate buffer(7.8pH), Phosphate buffer(8pH), Alkaline borate buffer(9pH) and two different blends (compositions are shown in Table 1), were determined at room temperature ($25 \pm 2^\circ\text{C}$). The drug contents of all the saturated solutions were determined by help of U.V. spectroscopy.

Table:1 Equilibrium solubility of Diclofenac sodium in different Solvent

S. No.	Solvent			Solubility (mg/ml)	Solubility* (%)	Solubility Enhancement ratio
1.	Distilled water			0.23	0.023	1
Solubility in hydrotropic agent in water solution						
2.	30% urea solution			5.62	0.562	24.43
3.	30% sodium citrate dihydrate solution			0.92	0.092	4.00
Solubility in different blends of mixed Hydrotropic agent						
	Blends	% of urea	% of sod. Citrate			
4.	Blend A	15	15	16.89	1.689	73.44
5.	Blend B	20	10	64.4	6.440	280.38
Solubility in different pH buffer solutions						
6.	Phosphate buffer(7.8pH)			0.83	0.0830	3.611
7.	Phosphate buffer(8pH)			0.94	0.094	3.938
8.	Alkaline borate buffer(9pH)			0.982	0.098	4.266

* Average of 3 determinations

2. Thin layer chromatographic studies: R_f values: Drug in methanol = 1.493

Drug in blend B = 1.494

3. Maximum Absorbency λ_{max} : Diclofenac sodium sodium/Methanol = 254nm

Diclofenac sodium Blend B = 253.5nm

MATERIALS AND METHODS

Diclofenac sodium, Urea, Sodium citrate, Distilled water

Table: 2: Ingredients and their Hydrotropic ratio

S. No.	Ingredients	Quantity for 10g HSD		
		DUSC 1:6 HSD	DUSC 1:8 HSD	DUSC 1:10 HSD
1.	Aceclofenac	1.428	1.111	0.909
2.	Urea	5.714	5.926	6.061
3.	Sodium citrate	2.857	2.963	3.030

DUSC: Diclofenac sodium Urea Sodium citrate, HSD-Hydrotropic solid dispersion

PREPARATION:

For preparation of 10 g hydrotropic solid dispersion containing Diclofenac sodium and hydrotropic blend (20% urea and 10% sodium citrate) in 1:6 ratio. Diclofenac sodium (1.423g), urea (5.714), sodium citrate (2.857) were accurately weighed. Minimum (possible) quantity of distilled water at 80-85°C contained in a 250 ml beaker was used to dissolve the urea and sodium citrate for quick dissolution. Then, Diclofenac sodium 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 30-40°C. Diclofenac sodium got completely solubilized. Stirring was continued till a semisolid mass was obtained in the beaker (after evaporation of a large quantity of water). Semisolid mass so obtained 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 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 # 100 and was kept for 6 days in a desiccator containing blue silica gel. After this the hydrotropic solid dispersion powder was stored in air-tight glass bottles.

Same procedure was repeated to prepare hydrotropic solid dispersions containing Diclofenac sodium and hydrotropic blend (20% urea and 10% sodium citrate) in ratios of 1:8 and 1:10 using accurately weighed 1.111 g, 0.090 g Diclofenac sodium, 5.714g, 5.926 g urea and 2.857g, 2.963g sodium citrate respectively.

PHYSICAL MIXTURE (PM) OF DICLOFENAC SODIUM

Drug carrier ratio 1:10 was used for preparation of physical mixture. Diclofenac sodium (0.909g), urea (5.926g), sodium citrate (2.963) were accurately weighed and mixed intensely for 10 min using glass pestle and mortar with intensive trituration. Then, powder mass was shifted through sieve # 100. After this the physical powder was stored in air-tight glass bottles.

CHARACTERIZATION**DETERMINATION OF DRUG CONTENT:**

Powdered solid dispersion/physical mixture 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 254 nm against reagent blank. In each case, analysis was carried out in triplicate. The drug content was determined using regression equation $Y = 0.0317 X + 0.0034$ $R^2 = .9998$. The results of analysis are presented in table.

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

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

PM-Physical mixture

DISSOLUTION RATE STUDIES OF DRUG AND THEIR FORMULATIONS:

Experimental conditions

Apparatus : USP (type I) dissolution rate test apparatus

Model : Model-TDT 6P, Electrolab, Mumbai

Dissolution media : Distilled water

Stirring speed : 50 rpm

Temperature : 37±0.5°C

Sampling intervals : 1, 3, 5, 10, 15 and 30 min

Sampling volume : 5 ml

Weight of sample : Equivalent to 100mg

 λ_{\max} : 254 nm**Table: 5** Dissolution Profile of Diclofenac Sodium Pure Drug in Distilled Water

S. No.	Time (min)	Cumulative percent drug dissolved			
		Set1	Set2	Set3	(Mean ± S.D.)
1	1	9.39	9.80	8.89	9.54±0.403
2	3	15.20	15.31	16.39	15.63±0.007
3	5	21.09	20.12	22.13	21.10±0.028
4	10	30.32	37.32	31.42	33.35±0.700
5	15	42.31	45.68	41.21	43.15±0.176
6	30	52.26	57.10	53.11	54.15±0.014

Table: 6 Dissolution Profile of DUSC 1:10 Pm, 1:6, 1:8 And 1:10 HSD In Distilled Water

S. No.	Time (min)	Cumulative percent drug dissolved (Mean±SD)			
		DUSC 1:10 PM	DUSC 1:6 HSD	DUSC 1:8 HSD	DUSC 1:10 HSD
1.	1	25.05±0.431	60.34±0.915	65.78±0.183	71.33±0.870
2.	3	31.34±0.336	85.36±0.210	91.01±0.609	88.12±0.736
3.	5	39.02±0.183	98.87±0.319	98.75±0.174	98.4±0.671
4.	10	49.47±0.538	98.15±0.432	99.99±0.265	98.83±0.653
5.	15	56.82±0.220	99.23±0.530	99.03±0.461	98.93±0.698
6.	30	71.09±0.254	99.11±0.685	99.08±0.328	98.95±0.490

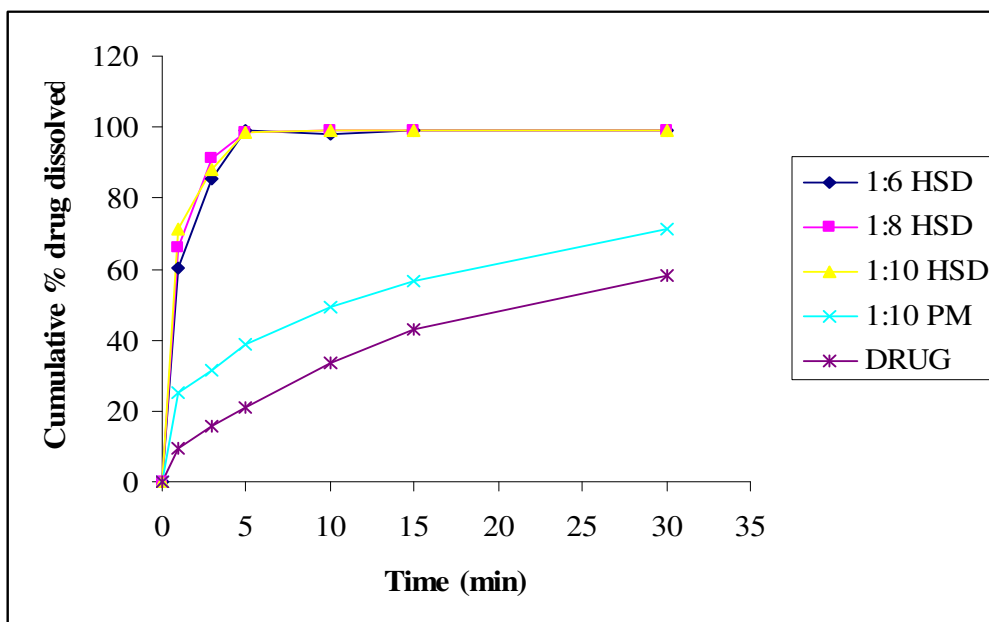


Fig.1: Dissolution profile of Diclofenac sodium, DUSC 1:10 PM, 1:6, 1:8 and 1:10 HSD in distilled water

DETERMINATION OF LOSS ON DRYING:

1 g of hydrotropic solid dispersions was transferred into glass vials and vials were covered with rubber closure. Then, the vials with their contents were accurately weighed. After that the contents in vials were distributed by gentle shaking to a depth not exceeding 10 mm. The loaded vials were placed in oven and closures were removed and vials were left in oven for 2 hr at temperature 105°C. After complete drying, the

oven was opened and closed the vials promptly and allowed it to cool up to room temperature. Then, finally the vials with their content were weighed and % loss on drying were calculated for different ratios (1:6, 1:8 and 1:10) of hydrotropic solid dispersion by following formula –

$$\% \text{ Loss on drying} = \frac{\text{Initial Wt (I)} - \text{Final Wt(F)}}{\text{Initial Wt (I)}} \times 100$$

Table: 4 Loss on drying of DUSC 1:6, 1:8 and 1:10 HSD

S. No.	HSD	Initial weight (I) (g)	Final weight (I) (g)	% Loss on drying
1.	DUSC1:6	13.096	13.074	0.167
2.	DUSC1:8	14.931	14.899	0.214
3.	DUSC1:10	14.054	14.052	0.0142

CHEMICAL STABILITY TESTING:

Different hydrotropic solid dispersions and physical mixtures of drug were subjected to chemical stability testing. Powders of various formulations were kept in 10 ml amber coloured glass vials and vials 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. The initial drug content for each formulation was considered as 100.00%. The percent residual drugs for each formulation at different time intervals are recorded.

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

Condition	Time (days)	Percent residual drug in formulations			
		DUSC 1:6 HSD	DUSC 1:8 HSD	DUSC 1:10 HSD	DUSC 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	0	100.00	100.00	100.00	100.00
40°C	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

The results showed that the residual drug content The residual drug content after storage for 1 month at room temperature in all formulations was above 98% showing and above 95% (40°C and 55°C), Showing very good chemical stabilities. The physical mixture DUSC 1:10 was also subjected to chemical stability and the chemical stabilities observed were very comparable to the chemical stabilities of corresponding hydrotropic solid dispersion indicating that the chemical stability was not influenced by making respective solid dispersions (with hydrotropic blend of urea and sodium citrate).

SUMMARY & CONCLUSION:

So we concluded that the present research work is the novel application of mixed hydrotropic solubilization technique in the formulation development of poorly water-soluble drug Diclofenac sodium. The procured sample of Diclofenac sodium was characterized by UV(λ_{max} = 254nm), and melting point(284°C) studies, , it can be concluded that the drug sample is pure Diclofenac sodium and used for hydrotropic solid

dispersion studies. The Equilibrium solubility study concluded that the enhancement of solubility of Diclofenac sodium in blend B is higher than others solvents. There are also toxic level is lower because still less concentration of the hydrotropic agents shall be sufficient for a desired enhancement in solubility. Solubility was increased more than 250 times in hydrotropic blends B, then the excess solute method. The % loss on drying is (not more than 0.5%) and % drug content not less than 98.5 per cent and (not more than 101.0 per cent of C₁₆H₁₃Cl₂NO₄) is matched with reported data². From the results of TLC study, Refractive index is between 1.490 to 1.495, it can be concluded that there is no salt or complexation of drug and hydrotrope molecule. On the bases of drug release study we concluded that increase dissolution rate, absorption and bioavailability of poorly water soluble drug.

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