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Enhancement of solubility of aceclofenac by using different solubilization technique

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Abstract

The objective of present research is to explore the application of different solubilization technique in the water-insoluble drugs and to reduce concentration of hydrotropic agent produce its own toxicity. In case of synergistic effect in solubility due mixing of hydrotropic agent , say, the toxic level of individual can further be lowered because still less concentration of the hydrotropic agents shall be sufficient for a desired enhancement in solubility.

Key-Words: Aceclofenac, Solubilization, Hydrotropic agents

Introduction

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Currently, only 8% of new drug candidates have high solubility and permeability. The aqueous solubility of drugs is often a limiting factor in developing the most desirable dosage forms. Many drugs and drug candidates are poorly water-soluble which limit their clinical applications. Increasing number of newly developed drugs are poorly water-soluble and such poor water solubility causes significant problems in producing formulations of a sufficiently high bioavailability with reproducible effects[1].

Aceclofenac, a non steroidal anti-inflammatory agent is selected as a model drug which is BCS class II drug (highly permeable and low soluble) and solid dispersion by the use of various physiologically compatible hydrotropic agents For the synergistic enhancement effect on solubility of this poorly water-soluble drug in water, various blends of hydrotropic agents were tried to decrease the amounts of hydrotropic agents employed for a desired solubility enhancement ratio[2-3].

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Thus, the successful completion of the research work will enable the preparation of stable soluble form of aceclofenac. The study further opens the chances of preparing other poorly water soluble drugs which are not stable in aqueous solution, ready to use formulation if not any stability associated problem with drug and solubilizing process can be prepared economically, to open a new era of more stable products of poorly water soluble drugs in cheaper cost in the market[1].

Material and Methods

Techniques of solubility enhancement[4-6]

Hydrotropic solubilization

Aqueous solutions of hydrotropic agents (urea, sodium citrate) of known concentrations (10%, 20 %,) were prepared in distilled water. Sufficient excess amount of aceclofenac was added to screw capped amber coloured glass vials containing fixed volumes (10 ml) of the hydrotropic solutions separately. The vials were shaken mechanically for 12 hours at room temperature in orbital flask shaker. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge. The supernatants of each vial were filtered through Whatman filter paper # 41. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed on UV/Visible spectrophotometer (Shimadzu 1700) at 333 nm against respective reagent blank solutions. The solubilities were determined using the corresponding regression equations given in table 15. The solubility of drug in 10%, 20% urea solution, 10%, 20%, sodium citrate solution was determined using regression equation of

corresponding 40% solution. The solubility enhancement ratios were also calculated.

Solubility enhancement ratio = Solubility in particular hydrotropic solution/solubility in water

Calculate the amount of aceclofenac present in 10 ml of saturated solution using this value. (Each ml of 0.1 M NaOH is equivalent to 0.0138 g of aceclofenac). From this relationship, determine % w/v solubility.

Solubility Enhancement Ratio = Solubility of aceclofenac in 20% w/v sodium benzoate solution (a hydrotropic solution) / Solubility of aceclofenac in dw

Mixed hydrotropy

Selection of hydrotropic blends

It is evident from the literature survey that more is the concentration of hydrotrope, more is the aqueous solubility of poorly water-soluble drugs. Therefore, highly concentrated solutions of hydrotropic agents were used in the present investigation. De-mineralized water was used in making hydrotropic solutions.

As evident from the research work[34], it was found that there was significant enhancement in aqueous solubility (a synergistic effect) of aceclofenac by use of a blend of urea (22.5%) and sodium citrate (22.5%). Keeping this point in mind and using total dissolved hydrotrope concentration at least 30% level (at random), different blends (table 6.1) were made and the solubility of aceclofenac was determined in them.

Table 1: Hydrotropic blends selected for aceclofenac

Blends	% of urea	% of sodium citrate
Blend A	15	15
Blend B	20	10

Take 40 ml of distilled water (DW) and add 10 g sodium citrate, 10 g urea and 50 g sugar in it. Heat gently to get a clear solution. Dissolve 2 g aceclofenac in it. When the solution attains room temperature, make the volume upto 100 ml with DW. Filter the solution. Prepare solution excluding aceclofenac.

Solid dispersion technology

Preparation of solid dispersions (SDs)

Aceclofenac solid dispersions were prepared by using carriers (i.e., lactose and urea) in .The drug and carrier was dissolved in dichloromethane and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a 250µm sieve before packing in an airtight container.

Formulation Plan of Aceclofenac Solid Dispersions

F-1 Aceclofenac + Lactose 4: 1

F-2 Aceclofenac + Urea 4: 1

Drug release pattern from SDs

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations like zero order (cumulative percent drug released vs. Time), first order (Log cumulative percent drug retained vs. Time), Higuchi (cumulative percent released vs. T), Peppas (log of cumulative percent drug released Vs. log Time) and Hixson- Crowell's cube root model ((Percentage Retained) 1/3 Vs. Time). The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r) values obtained in various models. Peppas model used 'n' value to characterize different release mechanisms. The values of n = 0.5 for Fickian diffusion, between 0.5 to 1.0 for non-Fickian diffusion and n = 1 for zero order.

Hydrotropic solid dispersions

Selection of ratios of drug and carrier in HSD and PM

The ratios of drug:carrier (hydrotropic blend B) for solid dispersions were kept 1:6,1:8 and 1:10 on the basis of solubility in blend B (20%urea+10%sodium citrate) as given in table 1.

Preparationof hydrotropic solid dispersions (HSD) of aceclofenac

For preparation of 10 g hydrotropic solid dispersion containing aceclofenac and hydrotropic blend (20% urea and 10% sodium citrate) in 1:6 ratio. Aceclofenac (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, 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 30-40°C. Aceclofenac 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 solid dispersion powder was stored in air-tight glass bottles.

Determination of drug content in aceclofenac formulations

Powdered solid dispersion containing about 10 mg of acecloenac 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.

Dissolution rate studies of drug

Dissolution rates of bulk drug sample aceclofenac, physical mixture (1:10) hydotropic solid dispersion containing drug:hydrotropic blend B of 1:6, 1:8 ratios were studied using USP XXIV (type II) dissolution rate test apparatus (Model-TDT 6P, Electrolab, Mumbai, India) using a paddle stirrer. Distilled water was used as dissolution medium. Bulk drug sample, physical mixture and hydrotropic solid dispersions 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±0.5ºC 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 absorbances 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. The results of dissolution rate studies are presented in table 5 to 6 and shown.

Results and Conclusion

Solubility study of hydrotropic solubilization

Equilibrium solubility data of aceclofenac and solubility enhancement ratio in urea solution of varying concentrations

Hydrotropic solution	Equilibrium solubility of aceclofenac (% w/v)	Solubility enhancement ratio
U 10%	0.049	4.54
U 20%	0.063	5.83

Equilibrium solubility data of aceclofenac and solubility enhancement ratio in sodium citrate solution of varying concentrations

Hydrotropic solution	Equilibrium solubility of aceclofenac (% w/v)	Solubility enhancement ratio
C 10%	0.015	1.38
C 20%	0.034	3.14

The hydrotropic agents, urea, sodium citrate for solubilization studies on the basis of solubility enhancement ratio. The solubility determination of drug in hydrotropic solutions was carried out at room temperature. The solubility was increased 14.81 fold in 40% urea solution, 11.85 fold in 40% sodium citrate solution.

Solubility study of aceclofenac in mixed hydrotropy

Equilibrium solubility of aceclofenac in mixed hydrotropy.

Mixture	Solubility (%)	Solubility Enhancement ratio
Blend A	1.322	73.44
Blend B	5.047	280.38

The solubility determination of aceclofenac was carried out in distilled water, hydrotropic solutions (30% urea and 30% sodium citrate) and solutions containing different concentrations of hydrotropic agents (urea and sodium citrate). It seems from the results that the aqueous solubility of aceclofenac was increased more than 250 times in hydrotropic blends (except for blend A which was 73.44 times), 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..

Table 2: *In Vitro* Dissolution Profile of Pure Drug and Different Formulations of Aceclofenac Solid Dispersions

Time (min)	Pure drug	F-1	F-2
0	0	0	0
5	4.72	42.15	31.40
10	10.57	45.73	33.30
15	12.13	50.16	33.93
20	14.12	54.80	35.66
25	17.69	55.64	35.83
30	25.66	57.32	36.67
45	29.71	72.50	40.67
60	33.56	72.50	43.20
90	37.52	72.92	44.89

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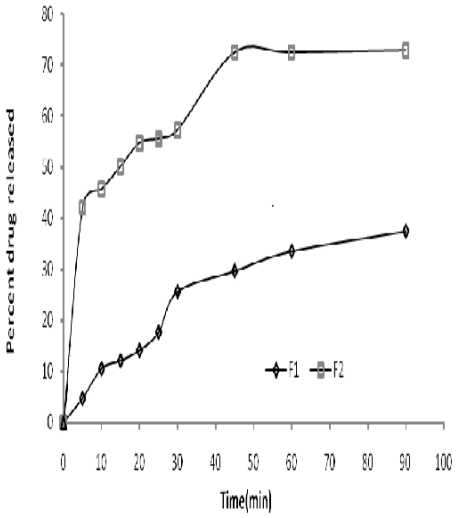

SDs of aceclofenac was prepared by using carriers like, lactose and urea. In the present work, nine formulations were prepared and their complete composition is shown in Table . All the SDs prepared was found to be fine and free flowing powders. *In vitro* release studies reveal that there is marked increase in the dissolution rate of aceclofenac from all the solid dispersions when compared to pure aceclofenac itself. formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The increase in dissolution rate is in the order of Lactose> Urea. in the case of those prepared in the ratio of 4:1 the dissolution rate of drug was decreased. This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. The increase in dissolution rate is in the order of F1> >F2.. The model that gave higher 'r' value was considered as best fit model.

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

Drug : Hydrotropic blend B ratio	HSD
AUSC 1:6	14.237± 0.044
AUSC 1:8	11.294 ± 0.086
AUSC 1:10	9.052 ± 0.109

Table 4: Dissolution profile of aceclofenac pure drug in distilled water

Time (min)	Cumulative percent drug dissolved			
	Set1	Set2	Set3	(Mean ± S.D.)
1	9.39	9.80	8.89	9.54±0.403
3	15.20	15.31	16.39	15.63±0.007
5	21.09	20.12	22.13	21.10±0.028
10	30.32	37.32	31.42	33.35±0.700
15	42.31	45.68	41.21	43.15±0.176
30	53.26	61.10	60.11	58.15±0.014

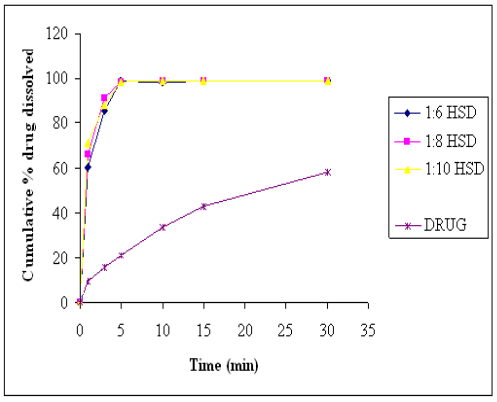

Fig. 1: Dissolution profile of aceclofenac, , 1:6, 1:8 and 1:10 HSD in distilled water

Equilibrium solubility of aceclofenac in different media were determined by excess solute method and the solubility enhancement ratios were calculated. From the results of the solubility data it was concluded that the aqueous solubility of aceclofenac was increased more than 250 times in hydrotropic blends except blend A (73.44), 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.

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