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IMPROVMENT OF SOLUBILITY OF AMPELOPSIN BY USING DIFFERENT SOLUBILIZATION TECHNIQUES

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Abstract:

Ampelopsin one of the most common flavonoids reported to possess numerous pharmacological activities and shows poor aqueous solubility. In order to improve solubility and dissolution rate of Ampelopsin different solubilization techniques like; hydrotropic solubilization, mixed hydrotropy and hydrotropic solid dispersions were used. The objective was also aimed to explore the application of different hydrotropic agents at their optimum concentration; thus decreases the chances of their own toxicity. Result concluded that the toxic level of hydrotropic agents was decreased because their minimum concentrations were found to be sufficient to produced desired results. Solubility enhancement ratio was found to be 72.69 times and 232.52 times more as compared to pure drug in different blends A and B respectively. It was also concluded that the solubility of ampelopsin increased synergistically by mixed hydrotropy. Solid dispersions of ampelopsin were prepared by using carriers like, lactose and urea. Dissolution rate was found to be more with Lactose as compared to urea.

Keywords: Ampelopsin, hydrotropy, solid dispersions, mixed hydrotropy.

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 [1]. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the rate of dissolution is highly desirable for such compounds. Recent techniques provide many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area and solubility; therefore focused on particle size reduction or generation of amorphous states [2, 3].

Ampelopsin isolated from the tender stem and leaves of the plant species *Ampelopsis Grossedentata (Hand- Mazz) W.T. Wang*, was one of the most common flavonoids. Ampelopsin was reported to possess numerous pharmacological activities, such as anti-inflammatory and antimicrobial activity, relieving cough, antioxidation, antihypertension, hepatoprotective effect, and anticarcinogenic effect [4–9]. Uses of hydrotropic agents for the enhancement of aqueous solubility have already been reported for various poorly soluble drugs [10, 11]. Thus in present research work different physiologically compatible hydrotropic agents were used for the synergistic enhancement effect on solubility of Ampelopsin in water, various blends of hydrotropic agents were tried to decrease the amounts of hydrotropic agents for desired solubility enhancement ratio.

Material and Methods:

Hydrotropic Solubilization [12]

Aqueous solutions of hydrotropic agents (urea and sodium citrate) of known concentrations (10% and 15 %) were prepared in distilled water. Sufficient excess amount of Ampelopsin 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 shaker. The solutions were allowed to establish equilibrium for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge. The supernatants of each vial were filtered throughWhatman filter paper. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed spectrophotometerically at 292 nm against respective reagents as blank. The solubility was determined using the corresponding regression equations. The solubility of drug in 10% and 15% of urea and sodium citrate solution were determined.

Mixed Hydrotropy:

Selection of hydrotropic blends

Optimum concentrations of hydrotropic agents were used in the present investigation. It was found that there was significant enhancement in aqueous solubility of Ampelopsin due to the synergistic effect by use of different blends of urea and sodium citrate (blend A comprise 10 % urea with 10% sodium citrate and blend B comprise 10% urea and 5% sodium citrate solutions). Blends were prepared by adding sodium citrate, urea and sugar in distilled water (DW) followed by gentle heat to get a clear solution. Ampelopsin 2 gm then dissolved in it. When the solution attained room temperature, volume was made with distilled water and filtered. Solution was also prepared excluding Ampelopsin.

Solid Dispersion

Hydrotropic solid dispersions

Hydrotropic solid dispersion containing drug and hydrotropic blend (10% urea and 5% sodium citrate) were prepared. Minimum (possible) quantity of distilled water at 80-85^{0}C contained in a 250 ml beaker was used to dissolve the urea and sodium citrate. Then, drug was added to this solution and stirred using magnetic stirrer, maintaining the temperature. Stirring was continued until a semisolid mass was obtained. Then semisolid mass was dried on watch glasses as thin layers after almost complete drying, the powder of solid dispersion passed through sieve and stored in air-tight glass bottles.

Determination of Drug Content in Different Formulations:

Powdered formulation containing Ampelopsin was accurately weighed and transferred to a 500 ml volumetric flask. About 450 ml of distilled water was added and flask was shaken to completely dissolve formulation. Then, volume was made up to the mark with distilled water and the absorbance of this solution was measured at 292 nm against blank. In each case, analysis was carried out in triplicate.

Determination of Dissolution Rate:

Dissolution rates of different formulation were studied Distilled water was used as dissolution medium. Different formulations equivalent to 100 mg drug were used to perform dissolution studies. The stirrer was adjusted at 50 rpm. Temperature (37±0.5^{0}C) was maintained throughout the experiments. Samples (10ml) were withdrawn from dissolution medium after particular time intervals and replaced with same volume of distilled water after each withdrawal. The samples were analyzed for drug contents by measuring the absorbance at 292 nm after appropriate

dilution with distilled water. Calculations for amounts of drug released were done using regression equation.

Table 1. Solubility enhancement of Ampelopsin by different formulations

Hydrotropic solution	Equilibrium solubility of Fenofibrate (% w/v)	Solubility enhancement ratio
Urea 10% (F1)	0.051%	4.48
Sodium Citrate 10% (F2)	0.019 %	1.44
Urea 15% (F3)	0.062%	5.81
Sodium Citrate 15% (F4)	0.038%	3.18

Table 2. Solubility enhancement of Ampelopsin by different blends (mixture) of hydrotropic agents.

Mixture of Hydrotropic reagents	% of Urea	% of Urea	% Solubility of Fenofibrate	Solubility enhancement ratio
Blend A (F5)	10	10	1.445	72.69
Blend B (F6)	10	5	5.039	232.52

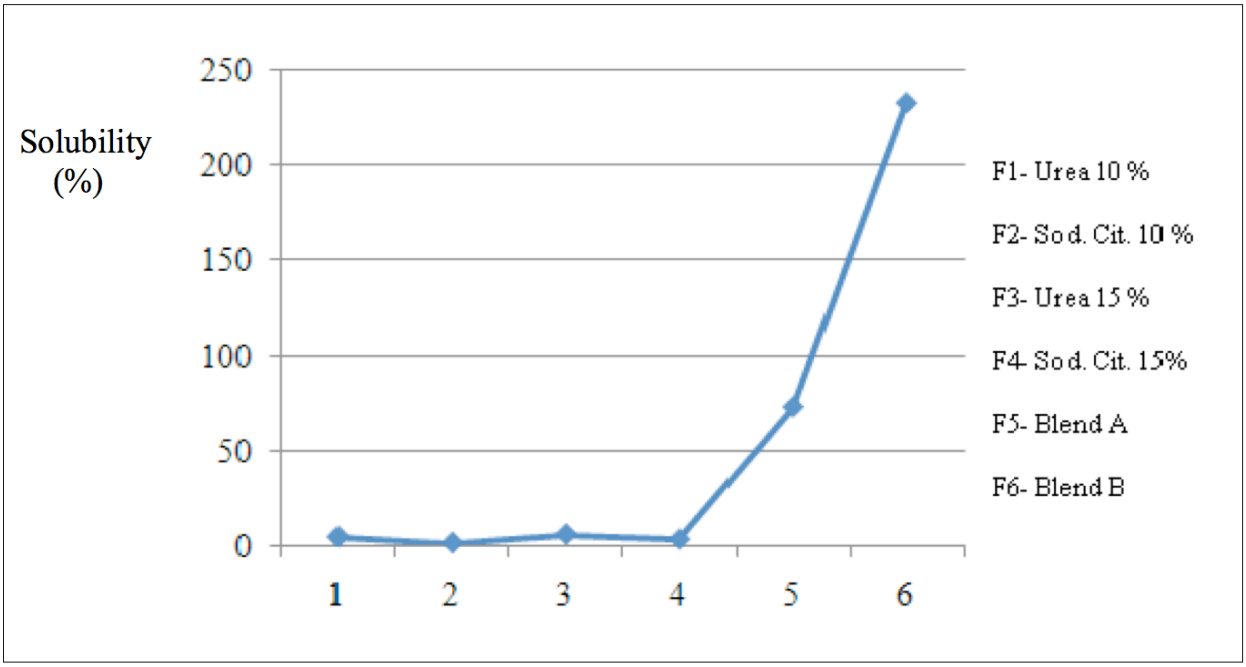

Figure 1. Synergistic effect of hydrotropic reagents on solubility of Ampelopsin

Results and Discussion

Solubility in hydrotropic solubilization:

Equilibrium solubility of Ampelopsin in different concentration of urea solution i.e; 10% and 15% were found to be 0.051% and 0.062% respectively and equilibrium solubility of drug in different concentration of sodium citrate i.e; 10% and 15% were found to be 0.019 % and 0.038% respectively **(Table 1)**.

Solubility in mixed hydrotropy:

Equilibrium solubility of Ampelopsin in mixed hydrotropy was carried out in distilled water, mixed hydrotropy were performed by making two different blends of hydrotropic mixture containing various concentrations of hydrotropic reagents i.e; Blend A comprise 10 % urea with 10% sodium citrate and Blend B comprise 10% urea and 5% sodium citrate solutions, Solubility enhancement ratio was found to be 72.69 times and 232.52 times in blend A and in blend B respectively **(Table 2)**. It was concluded that the solubility of drug increases synergistically by mixed hydrotropy **(Fig. 1)**. Solid dispersions of Ampelopsin were prepared by using carriers like, lactose and urea. Solid dispersions were found to be fine and free flowing. *In vitro* release studies revealed that there was marked enhancement in the dissolution rate of drug in solid dispersions when compared to pure drug itself. This may be attributed to the increase in drug wettability, conversion in amorphous form and solubilization of drug due to hydrophilic carrier. Dissolution rate increased more with lactose as carrier compared to urea.

Conclusion

Different solubilisation techniques were used for the poorly soluble drug Ampelopsin, using various hydrotropic agents, results from studies were found satisfactory. It was concluded that aqueous solubility of Ampelopsin greatly enhance by the synergistic effect of different hydrotropic agents together. Thus the research work overcome the problem of poorly water soluble drugs and present methodology can be adopted to prepare economical formulation of poorly water soluble drug.

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