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Research Article

Improvement of Solubility of Flavonoids by Using Different Solubilization Techniques

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Abstract

Quercetin 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 quercetin 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 61.71 times and 122.42 times more as compared to pure drug (quercetin) in different blends A and B respectively. It was also concluded that the solubility of quercetin increased synergistically by mixed hydrotropy.

Key Words: Quercetin, hydrotropy, flavonoids, mixed hydrotropy. Solid Dispersion

Introduction

Flavonoids are an abundant group of compounds found in many plants and have beneficial pharmacological effects including anti-oxidant, anti-cancer, anti-inflammatory, antiulcer activity, antiproliferative and antimutagenic effects [1, 2]. Two such flavonoids are quercetin and curcumin. Quercetin is a flavonoid responsible for the coloring in many fruits and vegetables, such as apples and onions. Curcumin is a polyphenolic compound derived from turmeric and gives the spice its yellow colour [2]. The main problem in the study and application of flavonoids is their low bioavailability due to poor water solubility. These polyphenols have an oral bioavailability in the range of 2-20%. Researchers have developed some methods for increasing water solubility of flavonoids and often bioavailability [3, 4]. Recent techniques also 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 [5, 6]. Uses of hydrotropic agents for the enhancement of aqueous solubility have already been reported for various poorly soluble drugs Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydrotropic solubilization is one of them. The term hydrotropy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives. Sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents [7, 8, 9, 10, 11, 12, 13, 14, 15, 16,] Thus in present research work different physiologically compatible hydrotropic agents were used for the synergistic enhancement effect on solubility of flavonoids (quercetin) in water, various blends of hydrotropic agents were tried to decrease the amounts of hydrotropic agents for desired solubility enhancement ratio.

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Material and Methods

Extraction [17]

Quercetin was extracted from 20-g ground onion powder in 80 mL of 80% EtOH by filtering twice through number 8 and grade 42 Whatman; filter paper. Filtrate was collected in Eppendorf tubes and stored under suitable condition.

Hydrotropic Solubilization [18]

Aqueous solutions of hydrotropic agents (urea and sodium citrate) of known concentrations (5% and 10 %) were prepared in distilled water. Sufficient excess amount of flavonoid 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 through Whatman filter paper. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed spectrophotometerically at 362 nm against respective reagents as blank. The solubility was determined using the corresponding regression equations. The solubility of drug in 5% and 10% 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 quercetin due to the synergistic effect by use of different blends of urea and sodium citrate (blend A comprise 5 % urea with 5% sodium citrate and blend B comprise 5% urea and 10% 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. quercetin was then dissolved in it. When the solution attained room temperature, volume was made with distilled water and filtered. Solution was also prepared excluding quercetin.

Solid Dispersion prepared by using hydrotropic agents [19, 20]

Hydrotropic solid dispersion containing drug and hydrotropic blend (5% urea and 10% 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 quercetin was accurately weighed and transferred to a volumetric flask, 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 362 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 quercetin 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 (quercetin) contents by measuring the absorbance at 362 nm after appropriate dilution with distilled water. Calculations for amounts of drug (quercetin) released were done using regression equation.

Results and Discussion

Solubility in hydrotropic solubilization:

Equilibrium solubility of quercetin in different concentration of urea solution were found to be 0.069% and 0.071% respectively and equilibrium solubility of drug in different concentration of sodium citrate were found to be 0.027 % and 0.046% respectively (Table no1)

Solubility in mixed hydrotropy:

Equilibrium solubility of quercetin 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 and Blend B which comprise urea with sodium citrate, Solubility enhancement ratio was found to be 61.71 times and 122.42 times in blend A and in blend B respectively. **(Table 2)**

It was concluded that the solubility of drug increases synergistically by mixed hydrotropic technique.**(Fig. 1)**.

Solid dispersions of quercetin 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 quercetin 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.

Conclusion:

Different solubilisation techniques were used for the poorly soluble flavonoids; quercetins, using various hydrotropic agents, results from studies were found satisfactory. It was concluded that aqueous solubility of quercetin 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 is a viable and cost-effective means to increase the solubility of poorly water-soluble drugs. Solubility enhancements of such magnitude are a clear indication of its potential to be used in future for other poorly water-soluble drugs.

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Table 1: Solubility enhancement of quercetin by different formulations

Hydrotropic solution	Equilibrium solubility of Fenofibrate (% w/v)	Solubility enhancement ratio
Urea 5% (F1)	0.069%	4.6
Sodium Citrate 5% (F2)	0.027 %	1.8
Urea 10% (F3)	0.071%	4.73
Sodium Citrate 10% (F4)	0.046%	3.06

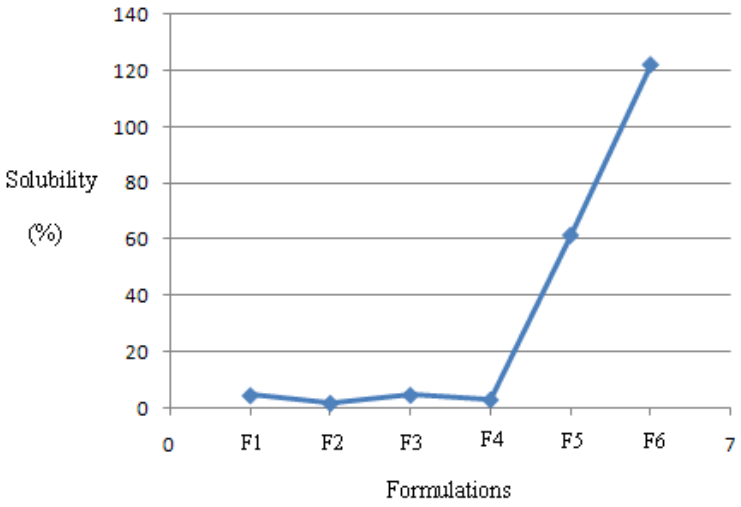

Fig 1. Synergistic effect of hydrotropic reagents on solubility of quercetin

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

Mixture of Hydrotropic reagents	**% of Urea**	**% of** Sodium Citrate	**% Solubility**	**Solubility enhancement ratio**
Blend A (F5)	5	5	0.925	61.71
Blend B (F6)	5	10	1.83	122.42