Formulation and Evaluation of Hydrotropic Solublization Based Suspensions of Griseofulvin

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Abstract:

Purpose: Hydrotropes increases the solubility of organics in water. Objective of present investigation was to enhance the solubility of griseofulvin using the technique of hydrotropic solubilization technique and convert them into suitable oral liquid dosage form (suspension) useful for enhancement of bioavailability.

Methods: 0.5M, 1M, 2M of the hydrotropes (tri sodium citrate, urea, sodium acetate, sodium benzoate and sodium salicylates) were used to study the saturation solubility. Solubility was found to be greater with sodium benzoate. Suspensions were prepared by using sodium benzoate solution, greseofulvin, xanthan gum, acacia, sodium alginate as a aqueous phase, dispersed phase and suspending agents respectively. Prepared suspensions were characterized for appearance of phases, density, particle size of dispersed Phase, pourability, sedimentation volume and invitro drug release.

Results: All formulations of sodium benzoate suspension were uniformly distributed, density in the range of 1.020 to 1.050gm/ml, particle size of the dispersed phase was 10µm to 20µm, suspensions were easily pourable from the bottle and sedimentation volume in the rage of 0.5-1. More than 70% drug release was obtained at the end of the 45 minutes.

Conclusions: Hydrotropic solublization technique for preparation of suspensions of poor water soluble drugs will gave stability to the formulation and helps in enhancement of bioavailability of greseofulvin.

Key words: hydrotropic, solublization, greseofulvin, suspensions, bioavailability

Introduction:

Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. Because of their low aqueous solubility and high permeability, dissolution from delivery systems forms the rate limiting step in their absorption and systemic bioavailability. A more than 60% drug product suffers from poor water solubility. Currently number of techniques addressed the poor solubility and dissolution rate of poorly soluble drugs

Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. Hydrotropes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Often strong synergistic effects are observed when hydrotropes are added to aqueous surfactant or polymer solutions.

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self-aggregation 'suddenly' starts to occur (as found for micelle- and vesicle-forming surfactants, which have a critical micelle concentration or cmc and a critical vesicle concentration or cvc, respectively).

Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self-aggregate at all, unless a solubilisate has been added. Hydrotropes are in use industrially. Hydrotropes are used in detergent formulations to allow more concentrated formulations of surfactants. [1,2]

The ability of hydrotropes to increase the solubility of organics in water is often strongest when the hydrotropes concentration is sufficient to induce the formation of associated structures. The concentration at which self association begins is denoted as the minimum hydrotrope concentration (MHC) and is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility.

Quantitative analysis of poorly water-soluble drugs involves use of various organic solvents. Major drawbacks of organic solvents include high cost, volatility and toxicity. Safety of analyzer is affected by toxicity of the solvent used. Sodium benzoate is one of the widely used hydrotropic agents and has demonstrated the enhancement in aqueous Solubilities of a large number of poorly water-soluble drugs. Various organic solvents used to solubilise the poorly water-soluble drugs to facilitate the acid-base titrations include methanol, ethanol, chloroform, dimethyl formamide and acetone. Most of the organic solvents are costly and toxic.

Hydrotropic solublization is new, simple, economic, safe method, can be used in analysis of drug. The use of sodium benzoate solution (2 M) in place of organic solvents for the purpose of solubilization to facilitate the titrimetric analysis of the poorly water- soluble NSAIDs, ibuprofen [(RS)2-(4-isobutylphenyl) propionic acid], flurbiprofen and naproxen . Hence objective of present investigation was to enhance the solubility of griseofulvin using the technique of hydrotropic solubilization and formulation, evaluation of hydrotropic solubilization based suspension of griseofulvin which will helpful to provide stability to formulation and enhancement of bioavailability.

Materials and Methods:

Griseofulvin was grerously donated by Ajanta Pharma, Pvt. Ltd. Mumbai. All other chemicals were analytical grade obtained from Loba Chemie, Mumbai.

Experimental:

Preparation of hydrotropic solutions:

Different molar concentrations 0.5M, 1M, 2M of the hydrotropes (tri sodium citrate, urea, sodium acetate, sodium benzoate and sodium salicylates) were prepared, by dissolving hydrotropes in triple distilled water.

Saturation solubility study:

Saturation solubility studies were performed in triplicate according to the method reported by Higuchi and Connors. [3] Excess of pure drug were added to 20 mL of different molar solutions of hydrotropes in a screw-cap tube and shaken in a rotary flask shaker at room temperature for 24 hrs. Once equilibrium had been achieved, appropriate aliquots were withdrawn and filtered through 0.2µ filters (Ultipor®N_{66}, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with different molar solutions of hydrotropes and analyzed at 296.2 nm by UV-visible spectrophotometer (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan).

Formulation of suspensions:

From the results of saturation solubility it was observed that sodium benzoate enhances the solubility to the greater extent than other hydrotropes so that formulations were prepared in sodium benzoate hydrotope as a structured vehicle in different molar concentrations, xanthan gum, acacia and sodium alginate as a suspending agent, sodium saccharin as a sweetener and menthol as a flavoring agent and negative coolant. All formulations are shown in table 1.

Table 1. Formulation of suspension

Ingredients	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Griseofulvin (mg)	500	500	500	500	500	500	500	500	500
Xanthan gum (mg)	40	40	40	-	-	-	-	-	-
Acacia(gm)	-	-	-	1	1	1	-	-	-
Sod. Alginate (gm)	-	-	-	-	-	-	0.2	0.2	0.2
Sod. Benzoate (gm)	0.72	1.44	2.88	0.72	1.44	2.88	0.72	1.44	2.88
Sod. Saccharin (mg)	30	30	30	30	30	30	30	30	30
Menthol (mg)	2	2	2	2	2	2	2	2	2
Water (upto ml))	20	20	20	20	20	20	20	20	20

Evaluation of suspension:

Appearance of Phases:

The visual inspection was done for the appearance dispersed phase and dispersion medium.

Determination of Density:

Selected a thoroughly clean & dry psychomotor calibrate the psychomotor by filling it with recently boiled & cooled water at 25^0c weighing the contents. Assuming that the wt. of 1ml of water at 25^0 when weighed in air of density 0.0012 g/ml is 0.99602 g- calculate the capacity of psychomotor. Adjusted the temperature of the substance being examined to about 20^0 & Filled the psychomotor to 25 ml, removed any excess of substance weigh. Subtract the tare wt. of psychomotor from the filled wt. of psychomotor Determined the wt. per liter by dividing the wt. in air in g. of the quantity of liquid which fills the psychomotor at the specified temp, by the capacity expressed in ml of psychomotor at the same temperature.

Particle Size of Dispersed Phase:

Optimum size of drug particle in the dispersed phase plays a vital role in stability of final suspension. So this test is carried out to microscopically analyze and find out particle size range of drug then it is compared with optimum particle size required. If any difference is found, stricter monitoring of micronisation step is ensured.

Determination of pH:

pH of the phases of suspension also contributes to stability and characteristics of formulations. So pH of the different vehicles, phases of suspension ,before mixing and after mixing are monitored and recorded time to time to ensure optimum pH environment being maintained.

Pourability:

This test is carried out on the phases of suspension after mixing to ensure that the final preparation is pourable and will not cause any problem during filling and during handling by patient.

Sedimentation volume (F): [4-7]

Sedimentation volume is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (V_O) before settling. Some time 'F' is represented as 'Vs' and as expressed as percentage. Similarly when a measuring cylinder is used to measure the volume.

$$F = H_u / H_O$$

Where, Hu = final or ultimate height of sediment

H_O = original height of suspension before settling.

***In Vitro* Dissolution Study of Suspensions:** [8]

The in vitro drug release of prepared suspensions were measured in triplicate by using dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using apparatus USP Type II. Dissolution studies were carried out by using 900mL 0.1 N HCL (0.54 % SLS) (2 hrs) at 50 rpm. Samples were withdrawn after 1 hr. for first two hours and after every two hours for remaining time and replaced each time with 5 mL dissolution medium. The solutions were immediately filtered through 0.45 mm membrane filter, diluted and the concentration of greseofulvin determined spectrophotometrically at 296.2 nm.

Results & Discussion:

Phase Solubility:

From the phase solubility study it was found that the solubility of the drug increases in the hydrotropic solutions, among different hydrotropes solubility was found maximum in the hydrotrope –Sodium Benzoate. Thus it was used to further formulations.

Table 2: Phase Solubility analysis

Batch code	Solubility (mg/ml) ± S.D
Griseofulvin	0.01666 ± 0.002
U (0.5 M)	0.07363 ± 0.003
U (1 M)	0.20636 ± 0.001
U (2 M)	0.07696 ± 0.005
SS (0.5 M)	0.08613 ± 0.004
SS (1 M)	0.11557 ± 0.002
SS (2 M)	0.13472 ± 0.003
SA (0.5 M)	0.04681 ± 0.004
SA (1 M)	0.14666 ± 0.003
SA (2 M)	0.08151 ± 0.004
TSC (0.5 M)	0.01834±0.003
TSC (1 M)	0.23712 ± 0.004
TSC (2 M)	0.22121 ± 0.004
SB (0.5 M)	0.32378 ± 0.005
SB (1 M)	0.62969 ± 0.004
SB (2 M)	1.19333 ± 0.001

U: Urea, SS: Sodium salicylate, SA: Salicylic acid, TSC: Tri sodium citrate, SB: sodium benzoate.

Appearance of Phases:

The different suspensions were observed optically & it was found that all formulations of sodium benzoate were uniformly distributed. The color of suspensions was fond pleasant.

Determination of Density:

The density of all suspensions was measured and it was found in between 1.020 to 1.050gm/ml.

Particle Size of Dispersed Phase:

The particle size of the suspensions was found to be 10µm to 20µm

Pourability:

The suspensions, formulated were checked for their pourability from the bottle, it was found that suspensions were easily pourable from the bottle.

Sedimentation volume (F):

The sedimentation volume was measured for the suspensions formulated by using three different conc. of hydrotrope Sodium Benzoate & three different suspending agents; it was found that the suspending agent sodium alginate at the concentration of 1M and 2M showed the F values 0.91 and 0.97 respectively; with xanthan gum it showed F values 0.2, 0.39, and 0.52 respectively at the concentration of 0.5, 1 and 2 M. Suspensions prepared by using acacia showed F values 0.83,0.87 and 0.92 respectively at the concentration of 0.5, 1 and 2 M of sodium benzoate.

The value of F ranges between 0 and 1 and increases as the volume of suspension that occupied by the sediment increases. It is normally found that the greater the value of F, the more stable the product. When F=1, no sediment is apparent and caking is absent, and suspension is esthetically pleasing. Tingstad indicated that a flocculated suspension that settles to a level that is 90% of the initial suspension height (F=0.9) and no further is probably satisfactory. We can conclude that suspensions prepared by using sodium alginate as a suspending agent are more stable than other agents (Figure 1, 2and 3).

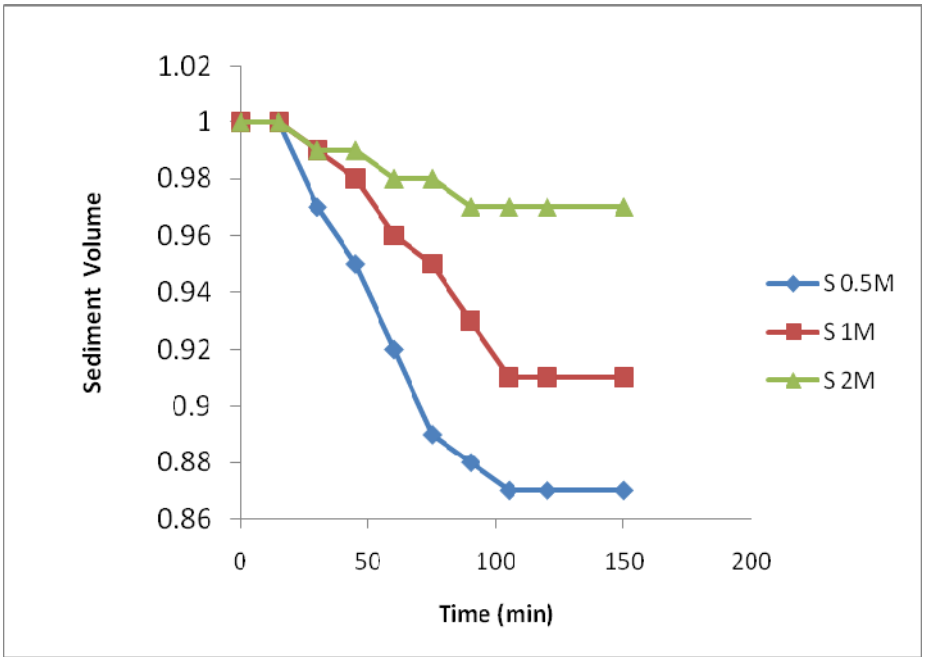

Figure.1: Sedimentation volume of Sodium alginate Vs Time

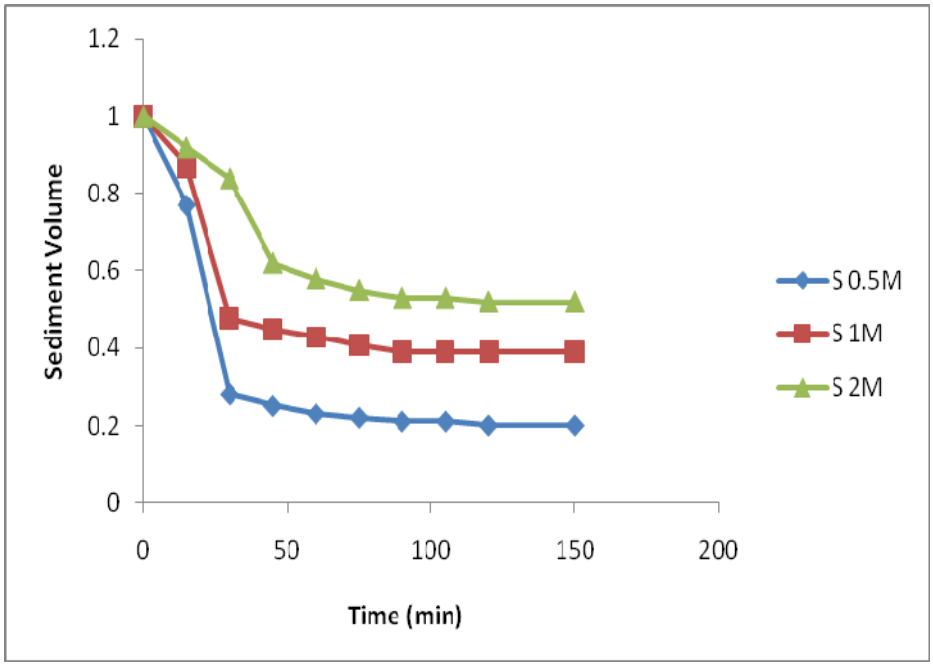

Figure 2: Sedimentation volume of Xanthan Gum Vs Time

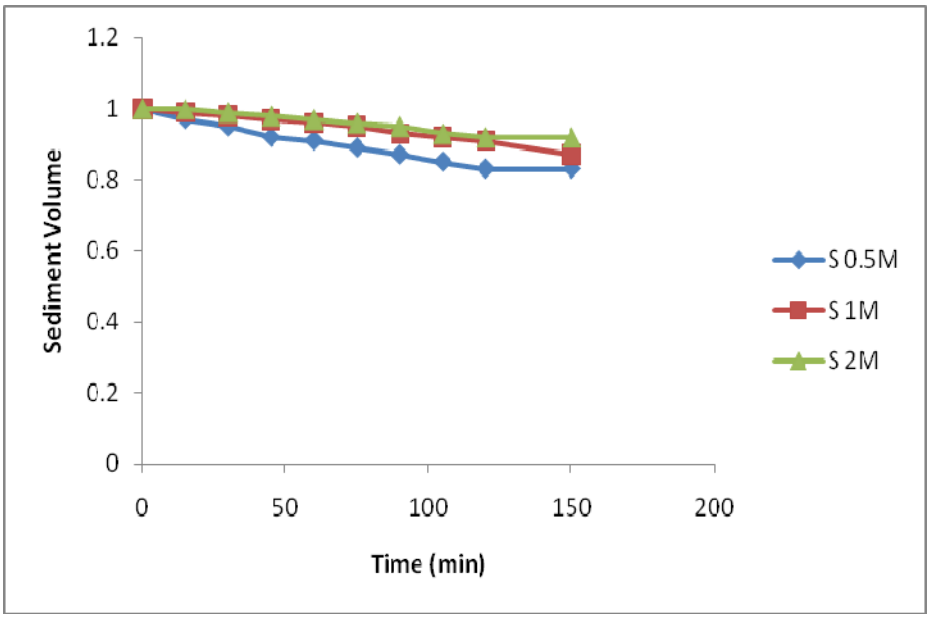

Figure 3: Sedimentation volume of Acacia Vs Time

In Vitro Dissolution Study of Suspensions

Dissolution study was carried with 0.54% SLS, the % drug release was found best for the 2M conc. of sodium benzoate .thus it showed that, hydrotropic solubilization increases the dissolution of the griseofulvin. More than 70% drug release was obtained at the end of the 45 minutes (figure 4).

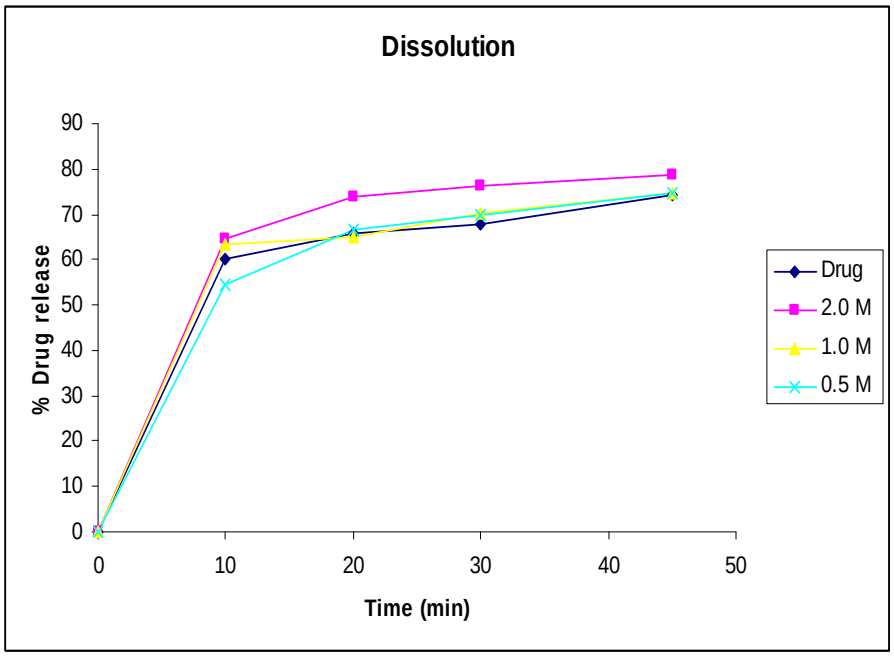

Figure 4: In vitro dissolution profile of suspensions.

Conclusions:

Hydrotropic solubilization was found to be excellent technique in the solubility and dissolution enhancement of poor water soluble drugs. A suspension dosage form is often selected if drug is insoluble in aqueous vehicles at the dosage requires and of when the attempts to solublize the drug through the use of cosolvents, surfactants, and other solubilizing agents would compromise the stability or the safety of the product or in case of the oral administration its organoleptic properties. Hydrotropic solublization technique for preparation of suspension of greseofulvin (low water soluble drug) gives stability to the formulation and will help in enhancement of bioavailability of greseofulvin. This technique will have particular importance in formulation of liquid dosage forms to give new life to old drugs.

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