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Modulation of solubility and development of a formulation of Plumbagin using hydrotropic solubilization technique

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***Abstract*---**The present work aimed to increase the solubility of poorly water-soluble drug plumbagin using the hydrotropic solubilization technique. Plumbagin is a potent natural product extracted from the plant *Plumbago zeylanica* L. belonging to the family *Plumbaginacea.* It can be used to treat rheumatoid arthritis, dysmenorrhea, injury, and cancer. An oral liquid syrup was prepared using caffeine as a hydrotropic agent. The results showed 97 folds increase in the solubility of the plumbagin when caffeine was used as a hydrotropic agent. Moreover, various evaluation tests like pH, refractive index determination, and drug content of the developed syrup were performed. All the results showed satisfactory outcomes and proved that it is possible to create a stable dosage form using the hydrotropic solubilization technique.

***Keywords*---**Hydrotropic agent, solubilization technique, refractive index, solubility.

Introduction

In the solubilization process known as hydrotropy, a considerable amount of a second solute is added to the mixture of a third component and water to raise the third component's water solubility. The solute comprises a wide variety of metal alkali salts of organic acids. It has been hypothesized that hydrotropic agents are ionic organic salts. On the other hand, salts that reduce a solute's ability to dissolve are said to "salt out" the solute. However, hydrotropism is the process by which many salts that contain large anions or cations and are themselves highly soluble in water cause the "salting in" of non-electrolytes that are referred to as "hydrotropic salts." This phenomenon is also known as "salting in."(Badwan et al. 1982; Chen and Micheau 2002). Hydrotropic solutions lack colloidal properties and demonstrate a weak contact between the hydrotropic agent and solute. Hydrotropy is a process in which the water solubility of poorly water-soluble drugs gets increased by inducing a substantial amount of salts. The improvement in solubility of poorly water-soluble drugs occurs by adding hydrotropic substances such as sodium benzoate, sodium acetate, sodium alginate, urea, and many other similar compounds. In other words, hydrotropy is a revolutionary and unparalleled method of solubilization that uses specific chemical components that are referred to as hydrotropes. This method increases the solubility of sparingly soluble or poorly water-soluble solutes by several orders of magnitude under normal conditions. Likely, the creation of organized assemblies of hydrotrope molecules at the threshold concentration is responsible for this increase in water solubility (Dharmendira Kumar and Nagendra Gandhi 2000; Varade and Bahadur 2004). The solubility of organic solutes, such as acids, esters, alcohols, aldehydes, ketones, hydrocarbons, and lipids, can be considerably improved by adding hydrotropes, which are frequently surface-active molecules that are also water-soluble. The extraction of scents, the solubilization of pharmaceuticals, the formulation of detergents, health care, and household uses are all typical applications for hydrotropes (Friberg 1997; Khan et al. 2011).

Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is a secondary metabolite found in plants belonging to the Plumbaginaceae, Ebenaceae, Dioncophyllaceae, Ancestrocladaceae, and Droseraceae families (Padhye et al. 2012). Plumbagin exhibits many pharmacological properties, including anticancer, antiatherosclerosis, anti-inflammatory, antibacterial, hypolipidemic, and neuroprotective properties(Ahmad et al. 2016; Liu et al. 2017). Unfortunately, the limited water solubility of plumbagin makes its therapeutic use challenging. The solubility of a drug has a fundamental effect on its pharmacokinetics, rate, degree of absorption, and bioavailability following oral administration, and hence its therapeutic effectiveness(Amidon et al. n.d.). As the medicine moves into clinical trials, it becomes crucial to produce a formulation that significantly improves its solubility while potentially decreasing its systemic toxicity. A superior formulation would enhance the patient's quality of life and improve its therapeutic potential. A liquid oral formulation of plumbagin is prepared and evaluated in this paper. Potential benefits of the developed syrup for oral administration of active pharmaceutical components include enhanced solubility for weakly water-soluble medicines and stable formulation of the medication (Salvia-Trujillo et al. 2017; Wang et al. n.d.). We have developed and evaluated a liquid oral syrup of plumbagin by employing caffeine as the hydrotropic agent.

Material & Method

Model drug plumbagin was purchased from PC chem, Mumbai. The hydrotropes caffeine, sodium benzoate, PABA, and succinic acid were bought from S D Fine Limited chemicals, Mumbai. Triple distilled water was used for the preparation of hydrotropic solutions.

Selection of hydrotropes (Gurumurthaih et al. 2013)

The selection of hydrotropes was performed by determining the solubility of plumbagin in different hydrotropic solutions. The hydrotropes with constant concentration, i.e., 2% w/v caffeine, 2%w/v sodium benzoate, 2% w/v PABA, and 2% w/v succinic acid, were used to determine the solubility of plumbagin. Caffeine showed the highest solubility enhancement of plumbagin, and thus, it was selected for further formulation development. Solubility of Plumbagin in Caffeine (Maheshwari et al. 2013; Maheshwari and Rajagopalan 2012)

The drug's solubilities in caffeine and distilled water were determined at 28 1°C. A sufficient amount of drug was added to screw-capped 30 mL glass vials containing solubilizer solution and distilled water. The vials were mechanically shaken for 12 hours at 28 ±1°C in an orbital flask shaker (Khera Instrument Pvt. Ltd., India). The solutions were allowed to equilibrate for the following 24 hours before centrifuging for 5 minutes at 2000 rpm (Remi Instruments Private Limited, Mumbai). Each vial's supernatant was filtered with Whatman filter paper no.41. The solubility was then determined by UV/Visible spectrophotometer at 461 nm.
Formulation of syrup (Maheshwari et al. 2013; Maheshwari and Rajagopalan 2012)

The necessary amounts of caffeine were transferred to a volumetric flask (100 ml capacity) containing 50 ml of distilled water, and the flask was shaken until the solubilizer (caffeine) was completely dissolved. The appropriate amount of drug was then added, and the flask was shaken to dissolve the drug thoroughly. The required amount of sucrose was then added, and the flask was shaken again to dissolve it. The syrup was then filtered using filter paper after the volume was made up with distilled water. The filtered syrup was kept in an airtight container. Based on the findings of the solubilization experiments of plumbagin, two formulations were prepared.

Table no. 1. Composition of Plumbagin Syrup

Composition (%w/v)	Formulation Code	
	F1	F2
Caffeine	1	2
Plumbagin	2	2
Simple syrup	q.s.	q.s.

Selection of optimized formulation of plumbagin syrup

Both the two advanced formulations of plumbagin syrup underwent physical stability at room temperature for two weeks to observe color change or for the

development of any precipitation. The formulation F2 showed no precipitation and color change while the F1 formulation showed color change and precipitation formation when kept for 14 days. Therefore, formulation F2 was selected for further evaluation.

Determination of pH

The pH of the developed plumbagin syrup was determined using a digital pH meter. The pH of the syrup was approximately neutral. The pH of the formulation was found to be 7.02.

Determination of physical and chemical stability (Domb and Khan 2013)

The physical stability of the developed plumbagin syrup was determined. For ten weeks, the prepared syrup was placed at three different temperatures, i.e., room temperature, at 55^{O}C and 70^{O}C at 75% RH value.

Chemical Stability determination

The chemical stability of the syrup was determined for ten weeks. The syrup was placed at different temperature conditions, 25^{O}C,40 ^{O}C, 75% RH, and 55 ^{O}C. The drug content of the syrup was determined from time to time to identify the chemical stability of the developed plumbagin syrup.

S.No.	Time (days)	Formulation Code	Drug content (%)			
			Temperatures			
			25^{O}C	40 ^{O}C	75% RH	55 ^{O}C
1.	0	F2	100.00	100.00	100.00	100.00
2.	7	F2	99.93	99.56	98.50	98.21
3.	14	F2	99.89	99.47	97.79	97.14
4.	21	F2	99.65	99.23	94.52	93.45
5.	28	F2	99.57	98.67	92.69	91.34
6.	35	F2	99.43	98.31	90.23	89.67
7.	42	F2	99.39	98.24	89.02	87.45
8.	49	F2	99.30	98.16	87.56	86.67
9.	56	F2	99.25	97.86	85.23	84.57
10.	63	F2	99.17	97.23	83.42	80.49
11.	70	F2	99.06	96.79	81.76	*

- More studies were withdrawn due to development of turbidity in the syrup. *

Freeze-thaw cycling Studies

The freeze-thaw cycling studies of the developed plumbagin syrup were performed by placing the syrup at alternate temperatures of 4^{O}C and 40^{O}C for 24 hours. The syrup was placed for 14 days at the above temperature.

Refractive index determination(Anon n.d.)

The refractive index of the prepared formulation was determined using Abbes's refractometer. The refractive index was determined to examine whether impurity was present in the syrup solution. The refractive index of the syrup preparation was found to be 1.4607.

Determination of drug content(Pande 2016)

Drug content was determined using a UV/visible spectrophotometer at 461nm. The process involves the preparation of reference stock solution, 100ml, by

dissolving hydrotrope in water and excluding the drug. The solution thus, prepared was called a blank reference solution. The test sample was also prepared the same way but with the addition of a drug. Afterward, the absorbance of the test solution was observed by UV/Visible spectrophotometer at 461nm.

Result and Discussion

The pH determination study of the developed formulation showed the pH of syrup as neutral, making it suitable to be consumed orally. The visual examination revealed that the syrup was clear and transparent with slight orange color. The refractive index of the syrup was found to be 1.4607, which was again inside the limit for the refractive index for liquids, which proved the absence of any impurity in the syrup. The freeze-thaw cycling studies for 14 days showed no precipitation formation in the syrup preparation. The physical and chemical stability testing was also performed. The physical stability testing showed no precipitations or color change of the syrup even when placed at three different temperatures, i.e., room temperature, 55^{O}C, and 70^{O}C at 75% RH value for ten weeks. Thus, the syrup proved to be physically stable even when kept at several different temperature conditions. The chemical stability studies showed no significant change in the syrup's drug content when kept at room temperature. The drug content of the syrup was 99.06%, even during the 10 weeks when kept at room temperature. However, the change in temperature showed development of turbidity in the 10th week. Hence, the syrup preparation was found to be stable at room temperature.

Conclusion

Plumbagin has received a lot of interest in the scientific field because of its various medicinal properties. It is reported as a secondary metabolite found in plants belonging to the Plumbaginaceae, Droseraceae, and Ebenceae families. Research on plumbagin shows that it is a natural gift for humankind to treat chronic diseases such as cancer, diabetes, malaria, bacterial infection, and cardiovascular disease regulation. However, developing plumbagin as a medicinal drug has various obstacles. The first is its low solubility and bioavailability in the mouth. This paper overcame this obstacle by using the hydrotropic solubilization technique. The hydrotropic solubilization approach helped to develop a stable plumbagin liquid dosage form. Moreover, the results indicated a 97-fold increase in solubility of plumbagin solubility. A stable syrup liquid dosage form was developed using the hydrotropic solubilization technique. Thus, this technique opens a different and novel approach to establishing stable dosage forms for various poorly water-soluble drugs.

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