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Ibuprofen syrup made by mixed solubilization technique: Formulation and evaluation

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***Abstract*---**The aim of the present study was to prepare a liquid dosage form (syrup) of a NSAID (ibuprofen) by mixed solvency technique. The syrup formulation was prepared by using mixed hydrotropic method in which potassium citrate, sodium citrate, potassium acetate and disodium hydrogen phospahte were used as hydrotropes. Glycerine and tween 80 were also used in the formulation. The syrup was prepared by agitation method. At first solubility of the model drug Ibuprofen was identified by dissolving it with different hydrotropes. It was observed that the solubility of ibuprofen increased with increase in concentration of the hydrotropes. However, it is difficult to develop a formulation with very concentration of hydrotropes. Therefore, co-solvent and surfactants were also added to enhance the solubility of the ibuprofen. Glycerine and tween 80 were used along with blends of hydrotropes to increase the solubility of Ibuprofen. The results, showed 3000 times increase in solubility of the ibuprofen drug. Also, the drug content of the prepared formulation was found to be 99.67% which proved the mixed

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solubilizing technique as a efficient and stable method for development of pharmaceutical dosage forms.

***Keywords*---**NSAID, hydrotropes, mixed hydrotrophy techniques, solubility enhancement.

Introduction

Nearly 70% of newly discovered drug candidates have poor aqueous solubility, hence attempts to improve aqueous solubility are currently the most pressing topic in the pharmaceutical business(Khadka et al. 2014). One of the most important properties of a drug is its solubility, which is essential for achieving the intended pharmacological action. The therapeutic efficacy of a medicine is determined by its bioavailability, which is ultimately determined by the solubility of the drug moiety. The most important parameter for the suitable pharmacological action is solubility. The therapeutic efficacy of a medicine is determined by its bioavailability, which is ultimately determined by the solubility of the drug moiety(Brahmankar Jaiswal, Sunil B., 2005). Many formulation approaches are currently available to improve solubility and dissolution profile in order to improve oral bioavailability(Jagtap et al. 2018). As we know that, according to BCS classification the drugs are classified into four categories. Drugs that come under Class II and Class IV are the drugs which are poorly water soluble. Hydrotrophy is one of the techniques that can be used to enhance the solubility of these poorly water-soluble drugs.

Sir Neuberg used the term "hydrotropic agent" (HDA) in 1916 to describe the tendency of anionic organic salts to improve the solubility of poorly soluble solutes at high concentrations. Hydrotropy is defined as a solubilizing technique in which addition of an excess amount of one solute will enhance the solubility of another solute(Sampath Kumar, Raja, and Jayakumar 2014). A hydrotrope is a substance that dissolves hydrophobic substances in water. Hydrotropes usually have a hydrophilic and a hydrophobic component (similar to surfactants), but the hydrophobic component is usually too tiny to cause spontaneous self-aggregation. Maheshwari has already reported hydrotropic solubilization technique for quantitative estimation of various poorly water-soluble drug. The concept of dual solvency was proposed by Maheshwari(Maheshwari and Rajagopalan 2012). The author proposes that, all components whether solid, liquid or gases have solubilizing property and they all can be used to enhance the solubility of poorly water-soluble drugs. Moreover, the author has used salicylic acid as model drug for demonstrating enhancement of solubility by using such method. He conducted solubility studies in separate solutions containing hydrotropic agents (urea and sodium citrate), co-solvents (glycerine, propylene glycol, PEG 300 and PEG 400. He prepared 10 random blends containing different solubilizers but maintaining the total concentration to 40%w/v. The results demonstrated that out of 10 blends, seven blends confirmed synergistic effect on the solubility.

In present study, similar opinion was used to develop the syrup formulation of ibuprofen. The formulation was developed using solubilizers like potassium citrate, sodium citrate and potassium acetate as hydrotropes. Co-solvents and

surfactants like glycerine and tween 80 were used respectively for development of the formulation. The procedure eliminates the use of organic solvents, avoiding issues such as toxicity, pollution, and cost. The formulation developed by this method has potential to lower the individual concentration of individual solubilizers. Thus, this would eliminate the toxicity associated with high concentration of individual solubilizers as well as it would improvise the solubility of poorly water-soluble drug.

Material & Method

Model drug ibuprofen was procured from Mendley pharmaceuticals Mumbai, as free gift sample. The hydrotopes (potassium citrate, sodium citrate and potassium acetate) were bought from S.D.Fine Limited Chemicals, Mumbai. The co-solvent glycerine and surfactant tween 80 were also procured from S.D. Fine Limited Chemicals, Mumbai. Triple distilled water was used for preparation of hydrotropic solutions.

Preparation of calibration curve

The standard solutions (100 µg/ml) of the drug were prepared in distilled water. The standard solutions (100 µg/ml) were diluted further to get different dilutions (5, 10, 15, 20, and 25 µg/ml) of drug. The diluted solutions were then scanned between 200 and 400 nm. The maximum absorbance of Ibuprofen was noted at 261 nm. A linear connection was then drawn for ibuprofen in the concentration range of 5-25 µg/ml.

Initial determination of equilibrium solubility:

The equilibrium solubility of ibuprofen, excess was introduced to 30 ml glass vials containing various mixes and distilled water. Previously, the solubility of ibuprofen in separate hydrotropes, co-solvents, and surfactants was determined, from which mixed blends were selected. After that, the vials were mechanically shaken for 24 hours at 2810C in an orbital shaker (Remi Instruments Private Limited, Mumbai). After that, the solutions were centrifuged for 5 minutes at 2000 rpm. The supernatant was then filtered with Whatmann filter paper no.41 from each vial. The filtrates were diluted with distilled water and spectrophotometrically (Shimadzu 1700) examined at 261nm to determine their solubilities.

Formulation of syrups

The ibuprofen syrup formulation was made with appropriate solubilizer blends that were determined during the solubility testing. Four formulations were made in total, each with a different concentration of solubilizer mixes (also called as mixed hydrotropic blends). All of the needed solubilizers were placed in a volumetric flask containing distilled water and shaken to dissolve the solubilizers fully. The required amount of ibuprofen was then added, and the flask was shaken until the medicine was thoroughly dissolved. After adding the required amount of sucrose, the flask was shaken again to dissolve it. After adding distilled

water to get the volume up to the required level, the syrup was filtered using filter paper. After that, the syrup was kept in a firmly sealed jar.

Table No.1: Composition of Ibuprofen syrup formulations

Composition (%w/v)	Formulation Code			
	F1	F2	F3	F4
Ibuprofen	2	2	2	2
PC	35	-	-	-
SC	10	10	10	-
PA	5	-	-	-
SDP	-	20	20	10
G	10	10	10	-
PG	-	10	-	-
T-80	10	-	10	-

PC-Potassium citrate, SC- Sodium citrate, PA- Potassium acetate, SDP- Sodium dihydrogen Phosphate, G- Glycerine, PG- Propylene Glycol, T-80- Tween 80

Evaluation tests for Ibuprofen Syrups:
The prepared syrups were evaluated from the date of preparation. At first, physical parameters like organoleptic characters which mainly include colour, taste, odour was determined. After that pH and refractive index was determined. Further, the formulations were tested for drug content and pharmacological effect.

a) Physical Properties (Li, Roos, and Miao 2017)
Appearance: Clear and Transparent

b) Determination of pH (Singh, Kumar, and Prasad 2018)
The acidity or alkalinity of an aqueous solution is traditionally represented by the pH value. The glass electrode was used to determine the pH value of a solution potentiometrically. The digital pH meter was made stabilize first. Then it was standardized using buffer tablets. The syrup solution was then placed in pH meter. Readings were noted accordingly.

Table No.2: pH readings of different ibuprofen formulations

S.No.	Formulation	pH			Average
1.	Blend 1	8.23	8.12	8.25	8.2
2.	Blend 2	8.52	8.43	8.55	8.5
3.	Blend 3	7.52	8.01	8.03	7.85
4.	Blend 4	8.12	8.05	8.07	8.08

c) Refractive Index: (Anon n.d.)
The refractive index of the syrup determines the purity of the solution. It is generally identified to identify the impurities if any present in the solution. Abbes's refractometer was used to determine the refractive index of the formulations. A controlled reading was also taken by using simple syrup to identify the variation from the standard, if any.

Table No. 3: Refractive index readings of different ibuprofen formulations

S.No.	Formulation	Refractive index			Average
1.	Blend 1	1.4608	1.4607	1.4608	1.4607
2.	Blend 2	1.4609	1.4608	1.4608	1.4608
3.	Blend 3	1.4608	1.4606	1.4607	1.4607
4.	Blend 4	1.4610	1.4607	1.4608	1.4608
5.	Simple Syrup	1.4606	1.4606	1.4611	1.4607

d) Drug Content:(Pande 2016)
Drug content was identified by measuring the absorbance using Shimadzu UV visible spectrophotometer. The 100 ml reference stock solution was prepared for each formulation by diluting it with water and excluding the drug. The solution thus prepared was used as blank (reference) solution. It was then used to compare the prepared formulation % drug content by measuring the absorbance using Shimadzu UV Visible spectrophotometer at 261nm. The amount of Ibuprofen was determined from standard calibration Curve.

Table No. 4: Drug content readings of different ibuprofen formulations

S.No.	Formulation	Drug Content (%w/w)			Average	Drug Content
1.	Blend 1	1.4608	1.4607	1.4608	1.4607	99.16
2.	Blend 2	1.4609	1.4608	1.4608	1.4608	99.50
3.	Blend 3	1.4608	1.4606	1.4607	1.4607	98.00
4.	Blend 4	1.4610	1.4607	1.4608	1.4608	99.16

e) Freeze thaw cycling Studies: (Maheshwari and Rajagopalan 2012)
The prepared syrup was subjected to freeze thaw cycling studies by keeping them all on consecutively at 4 °C and 40°C (for 24 h at each temperature) during 14 days. The change in the physical form of the syrup was then observed.

Result and Discussion

All the four formulated syrup did not show any change in colour and were clear transparent when visually inspected. The refractive index results showed no presence of impurity in the syrup. Also, the drug content studies showed that all the blends used for preparation of the formulation showed drug content from 99.16 to 99.50 % w/v. Moreover, the freeze thaw cycling studies revealed no precipitation or any physical change in all the four formulations for 14 days. Thus, this study indicates that the prepared formulation of ibuprofen is quite stable.

Moreover, the physically suitable combination of mixed solubilizers and low concentration of these solubilizers make this method a very potential method for development of syrup formulations of poorly water-soluble drugs. The use of all the solubilizers in combination reduces the chances of toxicity if occurred

because of high concentration of a single solubilizer. Hence, it proved to be a safe technique for developing syrup formulations of poorly water- soluble drugs. Furthermore, the combination of two and more hydrotropes give synergistic enhancement in the solubility of poorly water-soluble drug.

Conclusion

All the four-formulation prepared by mixed solvency technique showed stable and positive results. As, a result of this we have reached to a conclusion that, mixed hydrotrophy can be used to develop stable syrup dosage form of poorly water-soluble drugs. Moreover, the suitable combinations of solubilizers along with adequate concentration suggests mixed hydrotrophy method as a safe, economic and efficient process for development of liquid oral dosage form. Furthermore, this study unlocks the chances of preparing more syrup formulations of poorly water-soluble drugs.

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