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Preparation and Evaluation of Ibuprofen Syrup

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ABSTRACT

The aim of the study was to formulate and evaluate ibuprofen syrup using the cosolvency technique. The cosolvency technique involves combining various water miscible solvents at low concentrations to enhance drug solubility while minimizing solvent toxicity and ensuring formulation safety. Different formulations (F1, F2, F3) were prepared using combinations of cosolvents like propylene glycol, polyethylene glycol 400, glycerol, and ethanol. The prepared formulations were evaluated for their organoleptic properties, pH, viscosity, and drug content. Formulation F1 showed the highest drug content, making it the most effective and stable formulation. The study confirms cosolvency as a practical and scalable method for producing liquid dosage forms of poorly soluble drugs.

Keywords: Cosolvency, Solubility,Syrup.

INTRODUCTION

A drug's solubility is one of its most important physico chemical characteristics since it is necessary to achieve the desired pharmacological effect. The solubility of the drug moiety ultimately determines a drug’s bioavailability, which in turn determines its therapeutic efficacy. [1]. Drugs having aqueous solubility <1% have potential bioavailability problems. The solubility of drug molecules plays a key role in their bioavailability. Poorly aqueous soluble drugs often require high doses to reach therapeutic plasma concentrations. After oral administration, any drug to be absorbed must be present as aqueous solution at the site of absorption. However, nearly 40% of newly discovered drug candidates have poor aqueous solubility; hence efforts to improve aqueous solubility are currently the most pressing topic in the pharmaceutical business. According to the BCS classification the drugs are classified into four categories. Drugs that come under Class II and Class IV are the drugs that are poorly water soluble. Various techniques have been used to improve bioavailability, such as particle size reduction, salt formation, hydrotropy, solid dispersions and cosolvency.

Reducing the particle size increases the surface area, thereby enhancing dissolution properties. Hence, particle size reduction is also a method to increase solubility. Nowadays, Particle size reduction can be achieved by micronization and nanosuspension. But particle size reduction can cause degradation of the drug particle leading to the drug losing its pharmacological activity and this technique may not be suitable for all the drugs [2].

Nanoparticles are being explored for enhancing the solubility of drugs but nanoparticles may lead to genotoxicity due to insufficient toxicological assessment studies. Also, elimination and metabolism vary

with different types of materials used in nanoparticle synthesis. The technology involves high development and production costs [3].

Hydrotropy denotes a specific solubilization technique used to describe the increase in a solute's solubility due to the addition of a large amount of a second solute, which enhances the aqueous solubility of a different solute. There may be toxicity issues if hydrotropic drugs are used excessively. The need for relatively high concentrations to reach the Maximum Hydrotropic Concentration (MHC) limits the practical use of hydrotropes in commercial applications [4].

Cosolvents are the mixtures of solvents miscible with water, which will increase the solubility of poorly soluble drugs. By using a mixture of solvents, we can increase the solubility of poorly soluble drugs. This process is known as cosolvency, and the solvents used to increase solubility are known as cosolvents. A cosolvent system works by reducing the interfacial tension between the aqueous solution and the hydrophobic solute. It is also commonly referred to as solvent blending. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with water's hydrogen-bonding network, reducing the overall intermolecular attraction of water. By disrupting water self-association, cosolvents reduce water's ability to squeeze out nonpolar, hydrophobic compounds, thus increasing solubility [5].

The cosolvency technique uses small amounts of solvents, which reduces the toxicity and assures safety and biocompatibility.

The cosolvency also enables us to formulate a diverse pharmaceutical liquid dosage form using different solvents in different combinations/ratios. It is very convenient, affordable and easy to do on a laboratory scale. It also has potential for use commercially in large scale manufacturing. Some commonly used cosolvents are polyethylene glycol (PEG), propylene glycol and glycerol.

This study focuses on aqueous phase cosolvency (where water is the primary component of the solvent mixture), and the cosolvents will include solvents that are either completely miscible with water (in any proportion) or partially miscible (in certain proportions). The extent of cosolvency will be quantitatively defined by the difference in solute solubilities in pure water compared to a water-cosolvent(s) mixture.

MATERIALS

Ibuprofen, sucrose, methyl paraben, propyl paraben, glycerol were purchased from Molychem, Mumbai. Propylene glycol, PEG 400, Glycerol were procured from Finar, Gujarat.

METHODOLOGY:

Percentage of cosolvents can be calculated using the following formula:

Log C_s= Log C_0+Σ(%cosolvent used) (LogC_s-LogC_0) [7] …… (1)

Where, C_s = required solubility of solvent

C_0 =solubility of solute in water

Σ = sum of % of solubility of solute in different cosolvents used

It can be expressed as,

Log C_s= Log C_0+ % of co-solvent A (log C_A-logC_0) +
%of co-solvent B (log C_B-logC_0) +----------+of co-solvent n (log C_n-logC_0) …… (2)

The solubility of ibuprofen in few solvents is given in the following table:

Table 1: Solubility of Ibuprofen in Various Solvents

Solvents	**Ibuprofen Solubility in Excipient (mg/ml)**
Water	0.11
Propylene Glycol	312.5
Polyethylene glycol 400	210
Glycerol	5
Ethanol	1003

F1 was formulated using a blend of propylene glycol, polyethylene glycol 400 and glycerol.

F1: Polypropylene Glycol, Polyethylene glycol 400, Glycerol

Propylene glycol:

Log20=log 0.11+ **x** (log 310.78-log 0.11) …… (3)

⇒2.25 =**x** (2.49+ 0.95)

⇒x=65%

But 65% of propylene glycol will render the syrup very viscous and not pourable. Hence it was proposed to use a blend of solvents to tackle this problem.

Polyethylene glycol:

Log20=log 0.11+ 0.30(log 310.78-log 0.11) + **x** (log 210-log 0.11) …… (4)

⇒2.25 = 0.30(2.49+ 0.95) + **x** (2.32 + 0.95)

⇒2.25=1.032 + **x** (3.27)

⇒1.218= **x** (3.27)

⇒x=37%

A combination of 30% propylene glycol and 37% polyethylene glycol can be used to formulate a syrup, but we wanted to include glycerol in the formulation. So, we had to decrease the percentage of propylene glycol and polyethylene glycol.

Glycerol:

Log20=log 0.11+0.30(log 310.78-log 0.11) + 0.3 (log 210-log 0.11) +**x** (log5-log 0.11) …… (5)

⇒2.25 = 0.30(2.49+ 0.95) + 0.30(2.32 + 0.95) + **x** (0.69 + 0.95)

⇒2.25=1.032 + 0.981 + **x** (1.64) = 2.013 + **x** (1.64)

⇒x =14%

So, formulation F1 has 35% of propylene glycol, 30% of polyethylene glycol and 14% glycerol.
F2 was formulated using propylene glycol and polyethylene glycol 400

F2: Polypropylene Glycol, Polyethylene glycol 400

Propylene glycol:

Log20=log 0.11+ **x** (log 310.78-log 0.11) …… (6)

⇒2.25 =**x** (2.49+ 0.95)

⇒x=65%

Propylene glycol concentration was reduced and Polyethylene glycol 400 was included:

Polyethylene glycol 400

Log 20=log 0.11+0.35(log 310.78- log0.11) + **x** (log 210- log0.11) …… (7)

⇒2.25=0.35(2.49+0.95) + **x** (2.32 + 0.95)

⇒2.25= 1.204 + **x** (3.27)

x = 31%

A combination of 35% propylene glycol and 31% polyethylene glycol was used to make formulation F2.

F3: Polypropylene Glycol, Polyethylene glycol 400, Ethanol

F3 was formulated with the combination of propylene glycol, ethanol and PEG 400.

Propylene glycol:

Log20=log 0.11+ **x** (log 310.78-log 0.11) …… (8)

⇒2.25 =**x** (2.49+ 0.95)

⇒x=65%

But 65% of propylene glycol will render the syrup very viscous and not pourable. Using a blend of solvents can tackle this problem.

Ethanol:

Log 20=log 0.11+0.35(Log 310.78- log 0.11) + **x** (log 1003- log 0.11) …… (9)

⇒2.25= 1.03+0.35(2.32+0.95) +**x** (3.00+0.95)

⇒2.25=1.03+1.14+ **x** (3.95)

⇒x= 2%

A combination of 35% propylene glycol and 2% ethanol can be used to prepare a syrup formulation, but we wanted to include polyethylene glycol 400 in this formulation.

Polyethylene glycol 400:

Log 20=log 0.11+0.35(Log 310.78-log 0.11) +0.02(log1003- log 0.11) +**x** (log 210- log0.11) …... (10)

⇒2.25= 1.03+0.30(2.32+0.95) +0.02(3.00+0.95) +**x** (2.32+0.95)

⇒2.25=1.03+0.98+0.079+**x** (3.27)

⇒2.25= 2.03 +**x** (3.27)

⇒x= 4%

A combination of 35% propylene glycol, 1% ethanol and 4% polyethylene glycol 400 was used to prepare the formulation F3.

Preparation Of Ibuprofen Syrup

The solvent blend was prepared by taking the measured quantities of co-solvents. The blend of solvents was then sonicated for five minutes. Weighed quantity of ibuprofen drug was added with simultaneous stirring until it dissolved completely. The simple syrup USP prepared was filtered and then added to the solvent blend to make up the volume. The prepared syrup was then preserved in an airtight container.

Table 2: Formulation of Syrups

Ingredients	**F1**	**F2**	**F3**
Ibuprofen	0.4 g	0.4 g	0.4 g
Propylene glycol	6 ml	7 ml	7 ml
Polyethylene glycol 400	6 ml	6.2 ml	6 ml
Ethanol	-	-	0.2 ml
Glycerol	2.7 ml	-	-
Methyl paraben	0.004 g	0.004 g	0.004 g
Propylparaben	0.04 g	0.04 g	0.04 g
Simple syrup USP (q. s)	20 ml	20 ml	20 l

Figure 1: Formulated Syrups

EVALUATION OF IBUPROFEN SYRUP

The prepared syrup formulations were then evaluated for their organoleptic, rheological properties and drug content.

Organoleptic properties:
The prepared formulations were stored and checked for their appearance, color, and odour and all the formulations were found to be clear and stable with a pleasant odour.

Measurement of pH:
pH was measured using a pH meter (ELICO ®). pH meter was calibrated using buffer tablets 4 and 7. The pH of the formulations was then measured using a pH meter.

Viscosity
Viscosity of the formulations was determined using the Ostwald viscometer. The densities of both water and syrup formulations were calculated and the viscosity of the formulations was calculated using the below formula:

$$\eta_Y = \eta_W \frac{d_Y t_Y}{d_W t_W}$$

η_W: viscosity of water

η_Y: viscosity of syrup

d_W: density of water

d_Y: density of syrup

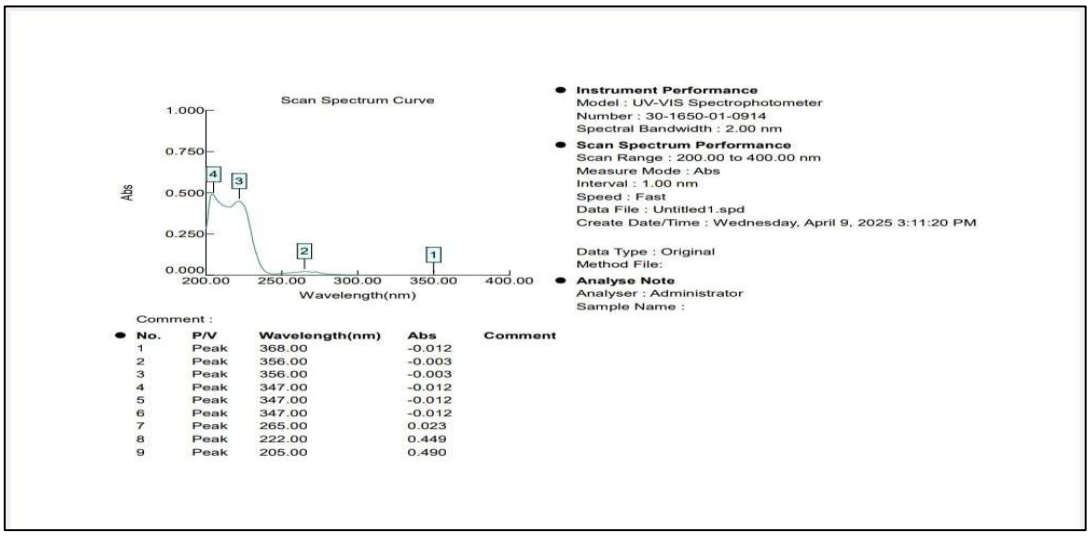
t_W: timing of runoff of water

t_Y: timing of runoff of syrup

STANDARD GRAPH OF IBUPROFEN
Determination of λmax:

- 10µg/ml solution of ibuprofen in pH 7.2 phosphate buffer was scanned in a UV-visible spectrophotometer in the range 200-400 nm.
- λmax was found to be 222 nm as per figure 2.
- Dilutions of 4,8,12,16 and 20 µg/ml were prepared from 100µg/ml solution and the absorbance of these solutions were measured at 222nm.

Determination of drug content:



- The syrup formulations were diluted using methanol in a ratio of 1:1. The absorbance of these solutions were measured at 222 nm using UV-Visible spectrophotometer

RESULTS AND DISCUSSION:

The prepared formulations were found to be clear and stable with a pleasant odour and they were stored in an airtight container.
The prepared formulations were then evaluated. The results are shown in Table 3.

Table 3: Evaluation of pH, Viscosity and Density of syrups

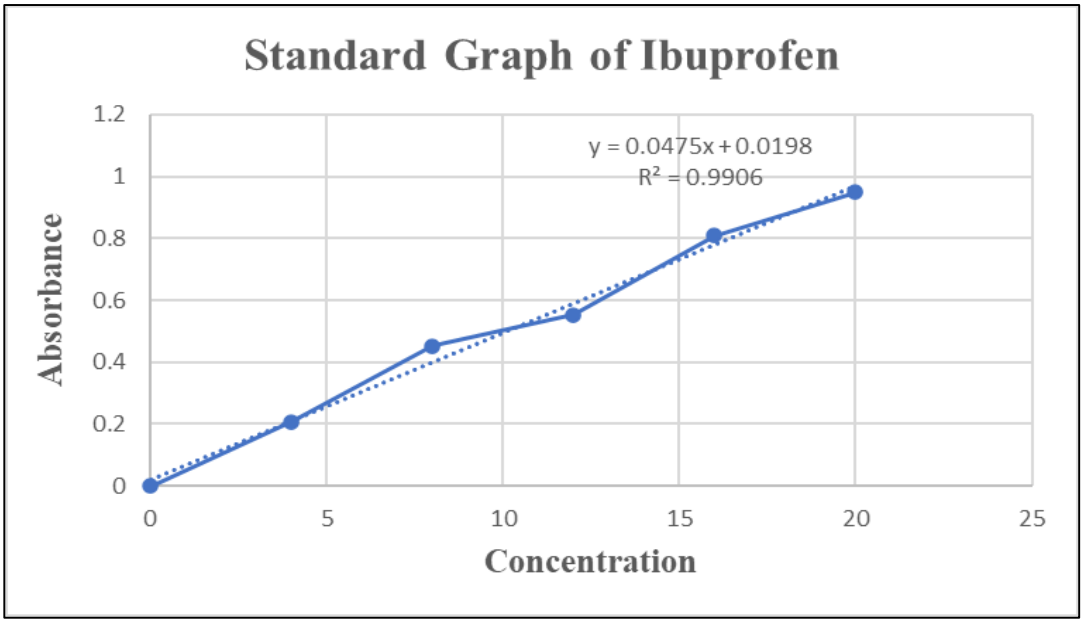
Formulations	**pH**			**Viscosity**	**Density**
	Trial-1	**Trial-2**	**Average**		
F1	4.76	4.80	4.78	30.6cP	0.87g/ml
F2	4.68	4.70	4.69	17.1cP	1.09 g/ml
F3	4.85	4.90	4.87	13.6cP	1.14 g/ml

Determination of Absorption maxima Figure 2: Determination of λmax

Standard Graph of Ibuprofen in pH 7.2 Phosphate buffer

The use of a calibration curve is essential for qualitative and quantitative analysis.. A standard graph was used to calculate the concentration of the unknown samples. A graph was plotted by taking the concentration of ibuprofen on X-axis and the absorbance was taken on Y-axis. The regression coefficient was found to be close to unity and the graph was found to be linear in the range 4-20 µg/ml.

Figure 3: Standard graph of Ibuprofen



The equation of the graph was found to be y = 0.046x + 0.0456.

Drug Content

The drug content of the formulations was calculated and the results are shown in table4.

Table 4: Evaluation of Drug content of Syrups

Formulations	% Drug Content		
	Trial-1	Trial-2	Average
F1	94.7	92.3	93.5
F2	81.5	78.9	80.2
F3	90.5	89.1	89.2

From the above table, we can observe that formulation F1 has the highest drug content followed by F3. Formulation F1 can be potentially more effective and stable than the formulations F2 and F3. Based on the observations we can say that F1 is a better formulation.

CONCLUSION

Ibuprofen syrup was successfully formulated using the cosolvency technique. This technique can easily be scaled and replicated on a laboratory scale. Using lower concentrations of different solvents ensures that the formulation is nontoxic and safe to consume. Cosolvency is a viable technique for preparing formulations of poorly soluble drugs and to increase patient compliance.

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