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SOLUBILITY ENHANCEMENT TECHNIQUES AS A STRATEGY TO IMPROVE THE SOLUBILITY OF LORNOXICAM

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ABSTRACT

Lornoxicam is a BCS class- II non-steroidal anti-inflammatory drug (NSAID) of oxicam class that exhibits analgesic, anti-pyretic and anti-inflammatory activities. The aim of study was to enhance the solubility of lornoxicam using different solubility enhancement techniques. Three approaches viz; hydrotropy, cosolvency and mixed solvency techniques were carried out to enhance the solubility of lornoxicam. Many hydrotropes like sodium acetate, sodium salicylate, sodium ascorbate, sodium citrate, sodium benzoate, urea and nicotinamide in different molar concentration and cosolvents like polyethylene glycol (PEG), propylene glycol and glycerin in different percentage were used to enhance the solubility of poorly soluble drug. In addition to that, a mixed solvency technique was also adopted to study maximum solubility of drug. A 7.25 fold and 26 fold increase in solubility of drug was observed compared to water by using 2M nicotinamide and 40% PEG 600, respectively. Similarly, A 358 fold solubility enhancement was obtained with mixed solvency technique using mixture of 10% sodium citrate, 10% sodium benzoate, 10% nicotinamide, 5% PEG 600, 5% PEG 400 and 5% propylene glycol. The study concluded that suitable solvent system can be developed using hydrotropy, cosolvency or mixed solvency techniques for BCS class- II category drug like lornoxicam to design suitable liquid dosage form.

KEYWORDS: Lornoxicam, poorly soluble, mixed solvency, hydrotrope, cosolvents.

INTRODUCTION

Poor solubility has been recognized to almost half of the new molecular entities, synthesized annually by pharmaceutical companies, and is also claimed to reduce the performance of more than 10% of successfully marketed drugs. Poorly soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability. Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and/or solubility *in vivo* by achieving their fine dispersion at absorption level [1-3].

Many techniques are employed to enhance the solubility of poorly soluble drugs like; pH modification, cosolvency, hydrotropy, solubilization, use of surfactants with pH modification, and mixed solvency. The amount of hydrotropes and cosolvents used should be minimum in order to avoid toxicity. The term hydrotropy has been designated the increase in aqueous

solubility of various poorly water soluble compounds due to presence of large amount of additives. Concentrated aqueous hydrotropic solution of urea, nicotinamide, sodium benzoate, sodium citrate, sodium acetate, sodium ascorbate, and sodium salicylate have been studied to enhance the aqueous solubility of many poorly soluble drugs. The addition of an organic polar cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and non polar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Many cosolvents like polyethylene glycol (PEG), propylene glycol (PG) and glycerin have shown high improvement in aqueous solubility of poorly soluble drugs [4-6].

Mixed solvency technique of enhancing the solubility of poorly soluble drug has been proved by precluding organic solvents with titrimetric estimation [7]. The mechanism of mixed solvency is not known but it is hypothesized that it is another type of cosolvency in which instead of one solubilizer many solubilizers are used in large concentration for obtaining a desired level of solubility for poorly soluble drug [7-10].

Lornoxicam is a Non-steroidal anti-inflammatory drug (NSAID) of oxicam class that exhibits analgesic, anti-pyretic and anti-inflammatory activities. It is practically insoluble in water as it belongs to BCS class- II category. Therefore, the less solubility of drug in aqueous media may create a hurdle in formulating a suitable liquid dosage form which may reduced its absorption followed by less bioavailability [11].

The objective of the present study was to adopt an appropriate solvent system exploring various solubility enhancement techniques for poorly soluble lornoxicam.

MATERIALS AND METHODS

Lornoxicam was obtained as gift sample from Sun Pharmaceutical Industries Ltd, Vadodara. Sodium benzoate, sodium citrate, urea, sodium salicylate, sodium Ascorbate, sodium acetate, sodium lauryl sulphate, PEG 400, PEG 600, PEG 6000, PG were purchased from Sulab laboratories, Vadodara. Nicotinamide was purchased from loba chemie, Mumbai.

Solubility determination:

Solubility of lornoxicam in various solvents was determined by equilibrium solubility method. Excess amount of lornoxicam was added separately to 100 ml volumetric flasks containing solvents as shown in table 1 and shaken mechanically for 24 h continuously at 37 ± 2 C to obtain saturated solutions. Each saturated solution was centrifuged for 5 min at 2000 rpm. The supernatant of each centrifuge was filtered through 0.45μm membrane filter in a Petri dish. Filtrate was evaporated to precipitate the dissolved drug. Precipitated drug was completely dried and weigh to determine the solubility [12].

Solubility enhancement techniques

Various methods like hydrotropy, cosolvency and mixed solvency were used to enhance the solubility of lornoxicam.

Hydrotropy method: A hydrotrope is a compound that improves the solubility of poorly soluble drugs in aqueous solutions. An association of hydrotrope molecules takes place preliminary in a pair wise manner followed by consecutive steps to form trimers, tetramers and so on that leads to significant improvement in aqueous solubility of hydrophilic compounds.

Various hydrotopes like 0.1M sodium acetate, 1M sodium salicylate, 0.2M urea, 0.5M sodium ascorbate, 1M sodium ascorbate,0.1M urea, 1M sodium citrate, 1M sodium benzoate and 2M nicotinamide were utilized to enhance the solubility of lornoxicam by equilibrium solubility method discussed earlier [13-15].

Cosolvency method: Cosolvent system is working by reducing interfacial tension between the aqueous solution and hydrophobic molecule. Cosolvent disrupts the waters self association that may reduce the ability of water to squeeze out hydrophilic compounds which results in enhancement in solubility.

Various cosolvents like 40% PEG 400, 40% PEG 600, 40% PEG 6000 and 40% PG were utilized to enhance the solubility of lornoxicam by equilibrium solubility method discussed earlier [16].

Mixed solvency method:

Three mixed solvent systems containing combination of hydrotopes and cosolvents were developed as shown below to determine the solubility of lornoxicam. 5 mg of drug was added repeatedly in 50 ml of each mixed solvent system at a time with constant stirring till the solution turns hazy. The clear solution before getting the hazy solution, was selected for further addition of drug in parts of 1 mg each to obtain the maximum solubility in the mixed solvent systems [16].

Mixed solvent system A: This system contains 10% sodium citrate, 10% sodium benzoate, 5% PEG 600, 5% PEG 400 and 5% PG.

Mixed solvent system B: This system contains 5% sodium citrate, 5% sodium benzoate, 5% nicotinamide, 5% PEG 600, 5% PEG 400 and 5% PG.

Mixed solvent system C: This system contains 10% sodium citrate, 10% sodium benzoate, 10% nicotinamide, 5% PEG 600, 5% PEG 400 and 5% PG.

Accurately weighed 5 mg of Lornoxicam was added in 50 ml solvent system A in volumetric flask followed by subsequently addition of 5mg in parts with constant stirring till the solution turned hazy. Same method was followed for remaining systems B and C.

Result and discussion

Solubility study

Lornoxicam was categorized under class II as per BCS classification system i.e. low solubility and high permeability. It had a low solubility in biological fluid which subsequently results into poor bioavailability after oral administration. The rationale of study was to enhance the solubility of lornoxicam by utilizing the concepts of various solubility enhancement techniques to design its liquid dosage form.

Table 1 Solubility of lornoxicam in different solvents at room temperature

Solvent system	Solubility (g/100ml) ± SD
Water	0.0012 ± 0.0001
Methanol	0.0018 ± 0.0001
Hydrochloric acid buffer pH 1.2	0.0023 ± 0.0001
Acid phthalate buffer pH 4	0.0030 ± 0.0013
Hydrochloric acid buffer pH 2.2	0.0030 ± 0.0002
Phosphate buffer pH 5.8	0.0034 ± 0.0001
Phosphate buffer pH 8	0.0058 ± 0.0001
Alkaline borate buffer pH 9	0.0062 ± 0.0001
Alkaline borate buffer pH 10	0.0070 ± 0.0013

As shown in table 1, solubility of lornoxicam was carried out in different solvents by equilibrium solubility method to check the solubility of drug. From the study, it was found that drug has solubility in the range from 0.0012 ± 0.0001 to 0.0070 ± 0.0013 g/100 ml with lowest solubility in distilled water and highest in alkaline borate buffer pH 10, but still this solubility is not adequate to prepare a stable and suitable liquid dosage form.

Solubility enhancement techniques

Due to inappropriate solubility of lornoxicam in different solvents and buffer systems, a suitable technique need to be establish for significant improvement in the solubility of poorly soluble drug. For the same reason, three different techniques were utilized to observe the significant changes in the solubility of BCS class –II drug.

Hydrotropy method

Concentrated aqueous hydrotropic solutions of hydrotropes are reported to enhance the solubility of poorly soluble compounds. In this research work, various additives in different molar concentrations were studied to check the improvement in drug solubility.

Form the result shown in table 2, it was found that drug has maximum solubility of 0.0087 ± 0.0001 in 2 M Nicotinamide that improves drug's solubility by 7.25 fold compared to distilled water. This result suggests that hydrotropy method may play an important role in enhancing solubility of poorly soluble drugs.

Table 2 Solubility of lornoxicam in different hydrotropes

Hydrotropes system	**Solubility (g/100ml) ± SD**
0.1M Sodium acetate	0.0007 ± 0.0001
1M Sodium salicylate	0.0008 ± 0.0002
0.1M Urea	0.0030 ± 0.0002
0.2M Urea	0.0010 ± 0.0001
0.5M Sodium ascorbate	0.0023 ± 0.0001
1M Sodium ascorbate	0.0025 ± 0.0002
1M Sodium citrate	0.0058 ± 0.0001
1M Sodium benzoate	0.0075 ± 0.0002
2M Nicotinamide	0.0087 ± 0.0001

Cosolvency method

Moreover, the solubility of lornoxicam was also performed in different cosolvents. In the preliminary study, different concentration viz; 30%, 40% & 50% of each cosolvent was taken to study the solubility of drug. Based on the result obtained in preliminary study, 40% of each cosolvent was optimized owing to its maximum solubility of drug. From the result shown in table 3, it was noted that lornoxicam have higher solubility of 0.0314 ±0.12 g/100ml in 40% PEG 400. The Solubility of lornoxicam in 40% PEG 400 has shown significant improvement in drug solubility which is near by 26 fold more than distilled water.

Table 3 Solubility of lornoxicam in different co solvents

Co solvent systems	Solubility (g/100ml) ± SD
PEG 400 (40%)	0.0198±0.0002
PEG 600 (40%)	0.0314±0.0003
PEG 6000 (40%)	0.0163±0.0002
PG (40%)	0.0260±0.0001

Mixed solvency method

It was reported that the incorporation of hydrotropes with cosolvent solution yields substantially greater drug solubility than that of single cosolvent solution. Accordingly, three different systems were developed for enhancement of lornoxicam solubility. As discussed in methodology part, increment of 5mg of drug was added to each of mixed solvent system to check the improvement in solubility of drug.

Table 4 Solubility of lornoxicam in mixed solvents system A, B and C

Mixed solvent system	Solubility (g/100 ml) ± SD
System A	0.130 ± 0.001
System B	0.200 ± 0.003
System C	0.430 ± 0.005

As the result stated in table 4, it was observed that there is significant enhancement in lornoxicam solubility in all of three systems compared to 2M Nicotinamide and 40% of PEG 600 performed in Hydrotropy and Cosolvency method, respectively. The probable mechanism for solubilization of lornoxicam in blend of cosolvents and hydrotropes may be expected due to involvement of hydrogen bonding and weak Vander Wall forces. Mixed solvent system C showed maximum solubility of 0.430 ± 0.005 gm /100 ml of solvent system compared other mixed systems A and B. So, mixed solvent system C prepared by mixed solvency technique was selected as best solubility enhancement combination for significantly improving the solubility of lornoxicam by 358 fold compared to solubility of drug in distilled water.

CONCLUSION

Poor solubility of any drug in aqueous medium may create a hurdle in gaining an effective absorption and bioavailability of drug in body. The present work demonstrated the utilization of various techniques like; cosolvency, hydrotropy and mixed solvency for enhancement of the

solubility of Lornoxicam. From all of three techniques, mixed solvency technique was considered to be a best technique to significantly enhance the solubility of Lornoxicam by 358 fold compared to distilled water. Thus, from the present work it can be hypothesized that mixed solvency method with the blend of hydrotropes and cosolvents can be utilized with vast solubility improvement effect for the development of suitable lornoxicam liquid formulation

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