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In Vitro Evaluation of Ibuprofen Using Mixed Hydrotrophic Solid Dispersion Approach

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ABSTRACT

The aim of this study is to enhance the solubility of poorly water soluble drugs via the mixed hydrotrophic solid dispersion strategy using ibuprofen as a model drug because Ibuprofen is absorbed after oral administration, it is critical to improve the dissolution rate to enhance the bioavailability, due to its low water solubility. Solid dispersions were prepared by mixed hydrotrphic method. *In vitro* dissolution studies showed remarkable improvement in solubility and drug dissolution profile of these new ibuprofen solid dispersions over pure ibuprofen. It was observed that dissolution rate of ibuprofen enhanced to a great extent by solid dispersion technique using citric acid and urea as a hydrotrophic agents.The results indicates that mixed hydrotrophic solid dispersion may serve as a successful strategy for enhancing solubility of poorly water soluble drugs.

Keywords: Mixed Hydrotrophic solid dispersions, Solubility, Drug release study, Dissolution

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INTRODUCTION

It is estimated that 40% or more of new chemical entities (NCEs) being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability and solubility of many newly developed high-potential drugs is an obstacle in formulation development, in addition Biopharmaceutical Classification System (BCS) highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs. Conventional dosage forms of these drugs, therefore, often have erratic and variable performance in preclinical and clinical evaluation leading to sub-optimal therapeutic concentration. [1, 2]

Newly developed hydrotropic solid dispersion (HSD) technology precludes the use of organic solvent. Salient feature of the new method is that the hydrotropic agent (carrier) is water-soluble, whereas the drug is insoluble in water. However, in presence of large amount of hydrotropic agent in water, the drug gets solubilized due to hydrotropic solubilization phenomenon. Then, water is removed by suitable evaporation technique to a get solid mass (a solid dispersion). [3, 4, 8]The formulation of poorly water soluble drugs for oral delivery is an ongoing challenge for scientists. [5] Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. [6, 7]

Ibuprofen belongs to Biopharmaceutics classification system [BCS Class II] - High permeability, low solubility and it has low 49-73% bioavailability. The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found. [9, 10] Ibuprofen selected as a model drug to increase bioavailability by mixed hydrotrophic solubilization technique.

'Mixed-hydrotropic Solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the aqueous solution containing blends of hydrotropic agents, which may give synergistic enhancement effect on solubility of poorly water-soluble drugs and to reduce concentrations of each individual hydrotropic agent to minimize their toxic effects due to high concentration of hydrotropic agents. [11]

Solid dispersion can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties. The development of solid dispersion as a practically viable method to enhance bioavaibility of poorly water soluble drugs overcame the limitations of previous approaches such as salt formation solubilization by co-solvent, and particle size reduction. [12]

MATERIALS AND METHODS

Ibuprofen was purchased from Rajesh chemical company Mumbai, Citric acid purchased from Loba chemical Pvt, Ltd. Mumbai, Urea purchased from Loba chemical Pvt, Ltd. Mumbai, Distilled water.

Preparation of standard curve for ibuprofen

Preparation of stock solution

For preparation of Standard curve 100mg of ibuprofen dissolved in 100ml of freely soluble solvent (Ethanol). 10ml of this solution was further diluted to 100ml with ethanol to give a concentration of 100µg/ml.

Preparation of aliquots

For preparing aliquots, 0.1 ml of sample was withdrawn from stock solution and it was diluted with 10 ml of ethanol, it give a concentration of 1 µg/ml. similarly solution of different strength 1 to 15 µg/ml. were prepared and absorbance of each solution was noted at 221nm using distilled water as blank by UV-Visible Spectrophotometer.

Preparation of Solid Dispersion by Mixed hydrotropic method

The required amount of Ibuprofen and carrier (Citric acid, urea) in 1:1, 1:3, 1:5, 1:7, 1:9 ratio were dissolved in sufficient volume (10 ml) of distilled water with continuous stirring. Solvent from solution was removed at 45^0C with continuous stirring to obtain a dry mass. The mass was passed through 44- mesh sieve and stored in desiccators until for further use.

Physical mixture

The physical mixture of Ibuprofen prepared using Citric acid, and Urea. In 1:1, 1:3, 1:5, 1:7, 1:9 ratios were obtained of powder drug and various carriers with the help of spatula. [13]

Table 1: Solid dispersion prepared by mixed Hydrotropy and physical mixture

Formulation code	Drug carrier ratio	Name of carrier
DC1	1:1	Citric acid + Urea
DC2	1:3	Citric acid + Urea
DC3	1:5	Citric acid + Urea
DC4	1:7	Citric acid + Urea
DC5	1:9	Citric acid + Urea

Evaluation parameters

Particle size analysis (optical microscopy)

Particle size analysis was determined by optical microscopy a number of particles was observed. In this method ocular and stage micrometer were calibrated by fixing the stage micrometer on stage and ocular micrometer on upper portion. Least count was calculated as follow.

Least count: - Reading of stage micrometer/ reading of ocular micrometer

0.4mm/0.4mm = 1

A small quantity of Pure Drug (Ibuprofen) and Solid Dispersion (Ibuprofen: Citric acid+Urea in ratio of 1:7) were spread on stage micrometer carefully and particles were analyzed in terms of mm, these observed reading were multiplied by least count. About 100 particles were analyzed and mean was calculated.

Particle size of pure drug (Ibuprofen) - Observed reading × least count

0.8×1 =0.8mm

Particle size of solid dispersion (Ibuprofen: Citric acid+Urea)- Observed reading × least count

0.4×1= 0.4mm

Drug content

Drug content was determined by U.V. spectrophotometer. Solid dispersion equivalent to 50mg of ibuprofen were weighed accurately and dissolved in a suitable quantity (100ml) of ethanol. The solution was filtered through membrane filter (0.45µg). The drug content was determined at 221nm by U.V. spectrophotometer after suitable dilution.

FTIR. (Fourier Transform Infrared Spectroscopy)

FTIR spectrophotometer (Shimadzu – 4100,) was used for infrared analysis. Best ratio (1:7) of solid dispersion was mixed dry potassium bromide and the sample was examined in transmission mode over wave number range of 4000-400cm^{-1} [12].

Drug release study

The dissolution was studied with accurately weighed of the formulation (containing approx 10 mg pure drug and drug carrier 1:7) using USP paddle type apparatus at $37^0C \pm 2^0C$. Aliquots (5ml each) were withdrawn at predetermined time intervals (10min.) for hrs, sink condition was maintained. The sample was analyzed for drug content using U.V. spectrophotometer at 221nm.

RESULTS AND DISCUSSION

Standard Curve of Ibuprofen in Ethanol

The standard curve of Ibuprofen in ethanol showed linearity in concentration range of 1-15µg/ml. Thus it followed the beer- lamberts law.

Particle size analysis

The significant reduction of particle size in the prepared Solid Dispersion **(**Ibuprofen: Citric acid+Urea) was obtained by Mixed Hydrotropy method. It is approximately half of pure drug. So

possible mechanism of dissolution enhancement may be due to increased surface area, than wet ability is increased and local solubilization effect of the carrier at diffusion layer.

- Pure drug (Ibuprofen) 0.8mm
- Solid dispersion (Ibuprofen::citric acid: urea) 0.4mm

Drug content

Mixed Hydrotropy solid dispersion showed a high drug content in ratio of 1:7 that is 78%. Drug content was constantly increased when ratio of carrier is also increased.

Table 2 Estimation of drug content of Ibuprofen: Urea+ Citric acid Solid dispersion

S. No.	Ratio (Ibuprofen: Urea+ Citric acid)	% Drug content
1	1:1	42
2	1:3	44
3	1:5	58
4	1:7	78
5	1:9	69

FTIR. (Fourier Transform Infrared Spectroscopy)

1:7 Ratio of solid dispersion (Ibuprofen: Urea+ Citric acid) was selected for FTIR drug interaction study. In case of pure drug (Ibuprofen) characteristic peak of COOH. C-N, O-H, C-H (Aromatic), C=O were observed, but in Solid Dispersion N-H in place of O-H. It indicates drug-carrier interaction. [14] FTIR analysis indicated that Ibuprofen mixed hydrotrophic solid dispersions undergo some polymorphic changes during the preparation of the solid dispersions. In this study it was found that drug is converted from highly crystalline state to amorphous form which is mainly responsible for solubility enhancement. Table 3&4, Graph No. 1&2

Table 3 Interpretation of FTIR spectrum of Pure Drug

Functional groups	Reported	Observed
C=O	1720-1706	1799-1725
C-O	1090-1049	1068
C-Cl	850-550	779-640
C-H(CH_3)	2962-2872	2832-2632
OH (COOH) Stretching	3300-2500	3456-2632
C-C=O (Deformation bend)	689-620	669-634
C-O-C	1275-1200	1267-1225
C-N (Viberational)	1400-1100	1375-1122
C-O-H (In plane bend)	1413	1456
O-H (Bending)	1320-1210	1267-1225
C-H (Aromatic)	3080-3010	2980
C-C (Skeletal band)	1500-1430	1510-1456
C-N (Skeletal band)	1500-1430	1510-1456

Table 4 Interpretation of FTIR spectrum of Solid Dispersion after interaction .

Functional groups	Reported	Observed
C=O	1720-1706	1799-1725
C-O	1090-1049	1068
C-Cl	850-550	779-640
C-H(CH_3)	2962-2872	2832-2632
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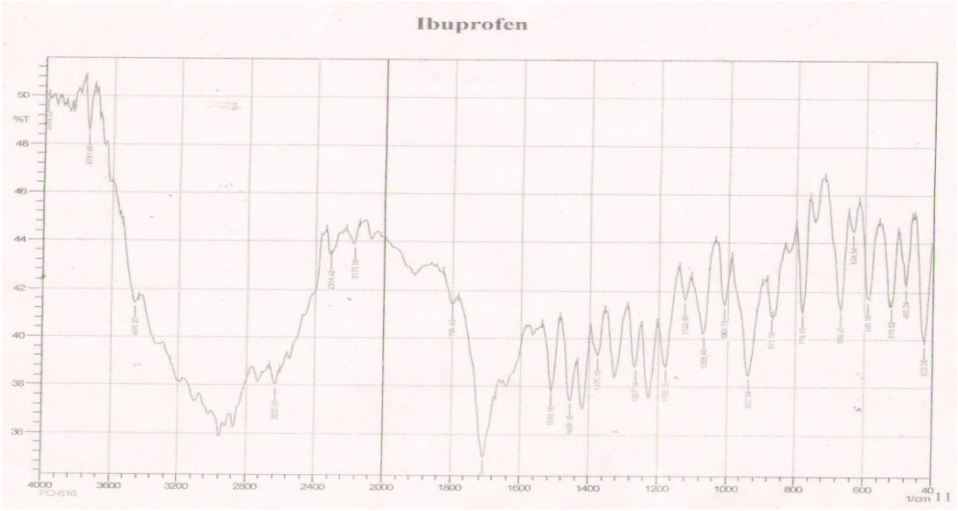
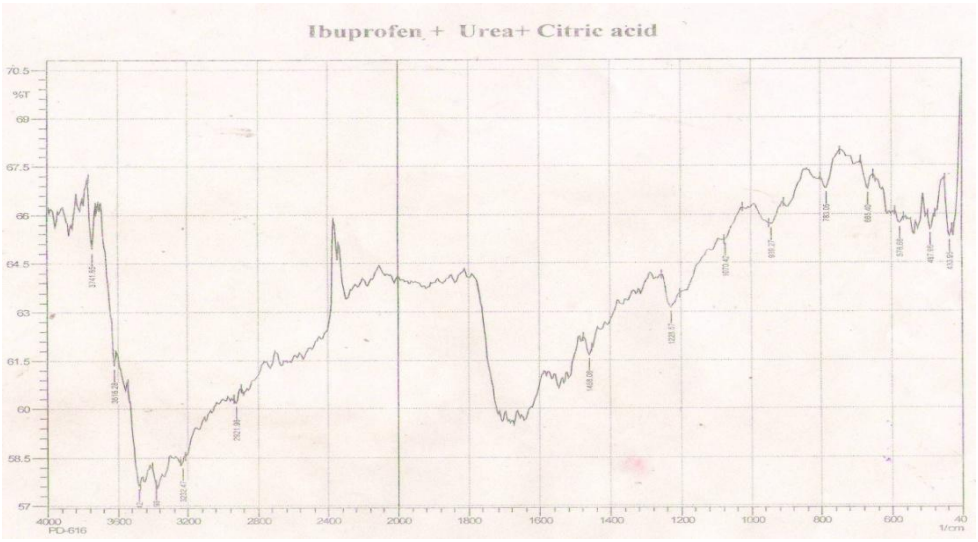
C-C=O (Deformation bend)	689-620	669-634
C-O-C	1275-1200	1267-1225
C-N (Viberational)	1400-1100	1375-1122
C-O-H (In plane bend)	1413	1456
N-H	3456-2210	3456-2800
C-H (Aromatic)	3080-3010	2980
C-C (Skeletal band)	1500-1430	1510-1456
C-N (Skeletal band)	1500-1430	1510-1456



Graph 1- FTIR of Ibuprofen



Graph 2- FTIR of Solid dispersion (Ibuprofen: Urea+ Citric acid)

Drug release study

2.880% of pure drug was released in first 10 min. while 9% of pure drug from solid dispersion was released in first 10 min. indicating rapid release of drug from solid dispersion. Total drug release from solid dispersion after 1.10 hrs., 89.1% while only 27.9% of drug was released when pure drug was used. The Dissolution study revealed that, dissolution was greatly increased approximately doubles of pure drug. Table 5

Table 5 Dissolution data for pure drug and Ibuprofen: Urea+ Citric acid Solid Dispersion

S. No.	Time (min.)	% Drug Release (Pure drug)	% Drug Release (Solid Dispersion)
1	10	2.880	9.0
2	20	6.300	18.90
3	30	10.260	30.60
4	40	14.400	42.750
5	50	18.720	56.250
6	60	23.220	72.00
7	70	27.900	89.100

CONCLUSION:

Although Ibuprofen is absorbed after oral administration, it is critical to improve the dissolution rate to enhance the bioavailability, due to its low water solubility. Solid Dispersion of Ibuprofen with Urea and Citric acid was prepared by using Mixed Hydrotropy method. The prepared solid dispersion was free flowing and showed good percentage of drug content (78%w/w). The FTIR study reveals chemical interaction between Ibuprofen and carrier used. The in-vitro dissolution studies of formulated solid dispersion showed that the solid dispersion of Ibuprofen with the ratio 1:7 enhances the solubility of Ibuprofen. Prepration of solid dispersions by Hydrotrophy method is most fruitful in terms of higher release rate, simplicity, economy, less hazardous (due to use of aqueous solvents).

Hence, we can say that Mixed Hydrotrophic Solid Dispersions are more suitable for formulation development.

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