ORIGINAL ARTICLE

Hydrotropic Technique: A Promising Method to Enhance Aqueous solubility of Nimesulide and to Reduce Difficulties in Bioavailability

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Abstract

Aim: Nimesulide is poorly water soluble (0.1 mg/ml). The low aqueous solubility gives difficulties in bioavailability. To improve the aqueous solubility and to enhance bioavailability the hydrotropic technique were used. **Materials and Methods:** In this research, hydrotropes such as ascorbic acid, sodium p-hydroxy benzoate, and sodium gentisate, and sodium ascorbate were used. Solid complexes of nimesulide and hydrotropes were prepared using coprecipitation method. The precipitates were amorphous in nature. In general, solid complexes can be characterized by techniques such as melting point, infrared-spectroscopy, differential scanning calorimetry, Fourier transformed infrared spectral studies were carried out for nimesulide and hydrotropes for their pure form and their complexes. **Results and Discussion:** A hydrotrope solubilizes hydrophobic part of nimesulide in aqueous solutions. In general, hydrotropes consists of both hydrophilic part and a hydrophobic part in which the hydrophobic part is very small to form immediate self-aggregation. Hydrotropy is one of the solubility enhancement techniques which improve solubility to many folds with use of hydrotropes. It is one of the recognized techniques available for resolving the solubility issue in nimesulide. **Conclusion:** The present work investigates the solubility enhancement and hence the bioavailability of the drug. The solubility of the drug can be increased by a variety of contemporary methods such as hydrotropic solubilization and solid dispersions. Hydrotrophy refers to a solubilization process, whereby the addition of large amounts of a second solute results in an increase in the aqueous solubility of a poorly soluble compound.

Key words: Enhancement, hydrotropic, nimesulide, solubility

INTRODUCTION

Many drugs and drug candidates are poorly water soluble, which limits their clinical applications. Increasing numbers of newly developed drugs are poorly water soluble and poor water solubility causes significant problems in producing formulations of a sufficiently high bioavailability with reproducible effects. A "poorly water-soluble" drug[1] (or simply "poorly soluble" drug) refers to a "practically insoluble" drug in the U. S. Pharmacopoeia and is defined as a drug having a water solubility of >0.1 mg/ml (or 100 µg/ml).[1] Whenever the drug concentration is much >0.1 mg/ml, its oral absorption is usually poor or at least inconsistent.

Solubility phenomenon is an area of particular importance. Increasing the water solubility of insoluble or slightly soluble compounds is of major concern for pharmaceutical researchers. The aqueous solubility of the drug is often a limiting factor in developing most desirable dosage forms. Since the poor solubility of the drug[1] results in low-absorption and low bioavailability, development of a viable

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and suitable method of solubilization is important especially for new chemical entities.

Solubility

A solution is a molecular dispersion of a solute in a solvent. There can be more than one solute, and the solvent can consist of more than one substance.[2] The solutions must be looked in a more quantitative manner so as to understand the theory and applications of the phenomena of solubility.

The solubility defined in quantitative terms, as the concentration of a solute in a saturated solution at a certain temperature. In a qualitative way, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.[3] Of the nine possible types of mixtures, based on the three states of matter, systems of solids in liquids include the most frequently encountered and probably the most important type of pharmaceutical solutions.[4] Solutes are classified as nonelectrolytes and electrolytes. The solubility of nonelectrolytes and weak electrolytes mostly belongs to the classes of weak acids and weak bases, which is of considerable importance to the pharmacist.[5] The related aspects of solubility are discussed in the following sections.

Applications

The solubility of drugs in liquids has wide-ranging applications in pharmacy.[6]

- Solubility of drugs in water and hydroalcoholic solutions is necessary for the manufacture of liquid orals such as syrups and elixirs.
- Intravenous, intramuscular and subcutaneous injections are prepared by dissolving the drugs in solvents, for example, 5% w/v dextrose infusion fluids.
- The solubility of drugs in gastrointestinal fluids (dissolution) is an important step for better absorption of drugs. If the aqueous solubility of the drug is >1% in the pH range of 1–7 at 37°C, there will not be any problem for absorption. Beyond this limit, potential problems can occur. A solubility of >1 mg/ml indicates the need of a soluble salt, particularly if the drug is to be formulated as a tablet or a capsule.
- The release and absorption of a drug from an ointment or an intramuscular injection depend on the degree of saturation of the drug in the solvent.[7]
- The action of a drug can be severely limited by poor aqueous solubility. Similarly, side effects of certain drugs are the result of their poor solubility.
- Solubility of a substance serves as a standard test for purity.
- Solubility provides information regarding the structure and intermolecular forces of interaction. Such information is useful for predicting drug-receptor interactions.[8]
- Saturated solution theory is important for the crystallization of drugs from solvents.

FACTORS AFFECTING SOLUBILITY

- The physicochemical properties of a solute.
- The properties and nature of solvent.
- Temperature.

Physical modification of drugs

The aqueous solubility of hydrophobic drug particles increases as the particle size decreases. Microparticulate preparations of poorly soluble drugs are commonly prepared by spray drying, emulsion-solvent extraction, micro fluidization, high-pressure homogenization, ball milling, media milling, jet milling, and rapid expansion from supercritical fluid.[9]

Use of cosolvents

Cosolvent systems can increase the water solubility of a drug significantly, but the choices of biocompatible solvents are limited, such as to glycerine, propylene glycol, polyethylene glycols, dimethyl sulfoxide, N, N-dimethylformamide, cremophor, and ethanol. Cosolvent systems are not as biocompatible as aqueous solutions.[10]

Emulsions, micelles, and liposomes

Emulsions are dispersions of droplets of one liquid in another immiscible liquid. In general emulsifiers, surfactants, employed to prevent the droplets from coalescing. For delivery of poorly soluble drugs, oil-in-water (o/w) emulsions are usually used. Commonly used oil cores are triolein, triglyceride, propylene glycol dicaprylate, and soybean oil. Liposomes and micelles also have been studied quite extensively for delivery of important poorly soluble drugs. The main limitation of this approach is that the liposomes and micelles tend to have poor stability.[11]

Complexation

The complexation approach has been frequently used to increase the water solubility of poorly soluble drugs.[12]

Solid dispersion technology[13]

Solid dispersion is the dispersion of a poorly soluble drug in an inert polymeric carrier (such as PVP) in the solid state. These are prepared by the melting or solvent method. This method requires the knowledge of the melting of the drug or the use of organic solvents.

Use of hydrotropic agents (hydrotropes)[14]

Hydrotropic agents have also been used to increase drug solubility. The hydrotropic effect involves the use of a large

amount of a solute to increase the solubility of poorly water-soluble compounds. Examples of substances which can be classified as hydrotropes are sodium salicylate, sodium gentisate, sodium glycinate, nicotinamide, ß-cyclodextrin, lysine, gentisic acid, urea, and tryptophan. Of the various approaches discussed above, the hydrotrope approach is a highly promising new method with great potential for poorly soluble drugs in general.

The present work investigates the solubility enhancement and hence bioavailability of the drug. The solubility of the drug can be increased by the variety of contemporary methods such as hydrotropic solubilization, and solid dispersions. Hydrotrophy refers to a solubilization process, whereby the addition of large amounts of a second solute results in an increase in the aqueous solubility of a poorly soluble compound.

OBJECTIVES OF THE PRESENT STUDY

The techniques involved for enhancing the solubility and further dissolution are micellar solubilization, cosolvency, complexation, solid dispersion, monomolecular complexation, and hydrotropy. One of the techniques is employed in the present work.[15]

The objectives of the present work are:

- To select hydrotropes[16] based on "*triangular pattern hypothesis.*"
- To determine suitable analytical methods for estimation of the drug.
- To determine the drug and hydrotrope compatibility for the analysis of drugs.
- To identify the drug and hydrotrope compatibility for analysis of drugs.[17]
- To prepare the solid complexes of the nimesulide and hydrotropes.[17]
- To characterize the complexes using modern instrumental techniques.[17,18]

The triangular area of drug and hydrotropes is calculated with the help of Chemoffice 2004 software. From the above hypothesis, the hydrotropes selected are ascorbic acid, sodium gentisate, and sodium ascorbate, and sodium p-hydroxybenzoate. Drug selected for the present work is nimesulide. It has the log PC value 2.376, which may be considered as semi-polar. These substances do not get solubilized greatly by cosolvents or for that matter by surfactants or complexing agent. Hence, hydrotrope is one of the options left for improved solubilization.[19,20]

The interaction of a drug with a hydrotrope results in increased aqueous solubility. The exact mechanism of interaction is not known. It is assumed some type of drug interaction with the hydrotrope, may be hydrogen bonding or acid-base type. Given the assumption that the drug and hydrotrope are nearly planar (benzene ring), it may be appropriate to consider three sites of interaction.[21] The sites in the chemical structure of the drug and the complementary sites in the chemical structure of the hydrotrope are expected to interact, such an architectural arrangement provides adequate stability for the interaction. This hypothesis is tested in this work.

MATERIALS AND METHODS

Nimesulide was presented from AARTI Drug LTD., Gujarat, India. Ascorbic acid, sodium gentisate, sodium p-hydroxyl benzoate, sodium ascorbate, sodium hydroxide, sodium chloride, and acetone were purchased from Rays Organics Vijayawada Andhra Pradesh.

Analytical methods used for the estimation of drug

Analysis of nimesulide

Stock solution of nimesulide (100 µg/ml)

Dissolve 10 mg of nimesulide in few ml of 0.01 N sodium hydroxide solution, and the volume was made up to 100 ml with 0.01 N sodium hydroxide solution.

Scanning of nimesulide in 0.01 N sodium hydroxide solution

From the nimesulide stock solution, 1 ml is taken and diluted to 10 ml using 0.01 N sodium hydroxide solution.[22] A ultraviolet (UV) scan of the above solution was taken between 200 and 400 nm. From the spectrum, λ_{max} of 393 nm was selected and utilized for further analysis.

Nimesulide λ_{max} was reported to be 398 nm in 0.1 N sodium hydroxide solution.[22] The λ_{max} of this work agrees with the λ_{max} of literature. About 11% value at 393 nm is 583. Molecular weight of nimesulide is 308.3 g/mol.

Analysis of hydrotropes

Stock solution of ascorbic acid (100 µg/ml)

Dissolve 10 mg of ascorbic acid in few ml of double distilled water, and the volume was made up to 100 ml double distilled water.

Stock solution of sodium p-hydroxyl benzoate (100 µg/ml)

Dissolve 10 mg of sodium p-hydroxy benzoate in few ml of double distilled water, and the volume was made up to 100 ml double distilled water.

Stock solution of sodium gentisate (100 µg/ml)

Dissolve 10 mg of sodium gentisate in few ml of double distilled water, and the volume was made up to 100 ml double distilled water.

Stock solution of sodium ascorbate (100 µg/ml)

Dissolve 10 mg of sodium ascorbate in few ml of double distilled water, and the volume was made up to 100 ml with double distilled water.

SPECTROPHOTOMETRIC ANALYSIS OF COMPLEXATION

Nimesulide-ascorbic acid-interaction

Preparation of standard solutions for the spectral analysis of nimesulide-ascorbic acid-interaction (I.P)

Stock solution of nimesulide (100 µg/ml)

Dissolve 10 mg of nimesulide in few ml of 0.01 N sodium hydroxide solution, and the volume was made up to 100 ml with 0.01 N sodium hydroxide solution.[23]

Nimesulide solution (10 µg/ml)

From the nimesulide stock solution, 1 ml is taken and diluted to 10 ml using 0.01 N sodium hydroxide solution.

Stock solution of ascorbic acid (1.0 M solution)

Dissolve 17.613 g of ascorbic acid in few ml of double distilled water, and the volume was made up to 100 ml with double distilled water.

Second stock solution of ascorbic acid (0.1 M solution)

From the ascorbic acid stock solution, 5 ml is taken and diluted to 50 ml using double distilled water.

Procedure for verification of complexation

Nimesulide concentration is kept constant in all samples (10 µg/ml). Ascorbic acid solutions are taken at different concentrations and mixed with the nimesulide solutions. The volume is made up to 10 ml with double distilled water. The quantities of additions at lower concentrations are reported in Tables 1-10 and at higher concentrations are reported. These samples are scanned between 200 and 400 nm, and the spectrum was obtained as an overlay method.

Table 1: The triangular areas of nimesulide and hydrotropes

S.No.	Nimesulide area (s)	Hydrotrope areas		
		Ascorbic acid	P-hydroxy benzoic acid	Gentisic acid
1	7.1543	4.4386	9.7677	7.6134
2	7.3904	8.2233	-	8.6687
3	9.0939	13.1459	-	13.4249
4	8.0528	-	-	-
Average area	8 A^{o2}	10 A^{o2}	10 A^{o2}	10 A^{o2}

Table 2 : Various concentrations of ascorbic acid and nimesulide (10 µg/ml) solution for spectral analysis

Ascorbic acid concentration (M)	Volume of ascorbic acid solution (ml)	Nimesulide solution (100 µg/ml) volume (ml)	Water (ml)
0	0	1	9
0.001	1	1	8
0.002	2	1	7
0.003	3	1	6
0.004	4	1	5
0.005	5	1	4

*Ascorbic acid (0.001–0.005M)[27]

Table 3: Various concentrations of ascorbic acid and nimesulide (10 µg/ml) solution for spectral analysis

Ascorbic acid concentration (M)	Volume of ascorbic acid solution (ml)	Nimesulide solution (100 µg/ml) volume (ml)	Water (ml)
0	0	1	9
0.01	1	1	8
0.02	2	1	7
0.03	3	1	6
0.04	4	1	5
0.05	5	1	4
0.06	6	1	3
0.07	7	1	2
0.08	8	1	1
0.09	9	1	0

*Ascorbic acid (0.005–0.09M)

Table 4: Various concentrations of sodium p-hydroxy benzoate and nimesulide (10 μg/ml) solution for spectral analysis

Sodium p-hydroxy benzoate concentration (M)	Volume of sodium p-hydroxy benzoate solution (ml)	Nimesulide solution (100 μg/ml) volume (ml)	Water (ml)
0	0	1	9
0.01	1	1	8
0.02	2	1	7
0.03	3	1	6
0.04	4	1	5
0.05	5	1	4

*Sodium p-hydroxy benzoate (0.01–0.05 M)

Table 5: Various concentrations of sodium p-hydroxy benzoate and nimesulide (10μg/ml) solution for spectral analysis

Sodium p-hydroxy benzoate concentration (M)	Volume of sodium p-hydroxy benzoate solution (ml)	Nimesulide solution (100 μg/ml) volume (ml)	Water (ml)
0	0	1	9
0.1	1	1	8
0.2	2	1	7
0.3	3	1	6
0.4	4	1	5
0.5	5	1	4
0.6	6	1	3
0.7	7	1	2
0.8	8	1	1
0.9	9	1	0

*Sodium p-hydroxy benzoate (0.05–0.9M)

Nimesulide-sodium p-hydroxybenzoate interaction

Preparation of standard solutions for the spectral analysis of nimesulide-ascorbic acid-interaction (I.P)

Stock solution of nimesulide (100 μg/ml)

Dissolve 10 mg of nimesulide in few ml of 0.01 N sodium hydroxide solution, and the volume was made up to 100 ml with 0.01 N sodium hydroxide solution.

Nimesulide solution (10 μg/ml)

From the nimesulide stock solution, 1 ml is taken and diluted to 10 ml using 0.01 N sodium hydroxide solution.

Stock solution of sodium p-hydroxybenzoate (1.0 M solution)

Dissolve 16.010 g of sodium p-hydroxy benzoate in few ml of double distilled water, and the volume was made up to 100 ml with double distilled water.

Second stock solution of sodium p-hydroxybenzoate (0.1 M solution)

From the sodium p-hydroxy benzoate stock solution, 5 ml is taken and diluted to 50 ml using double distilled water.

Nimesulide-sodium gentisate-interaction

Preparation of standard solutions for the spectral analysis of nimesulide-ascorbic acid-interaction (I.P)

Stock solution of nimesulide (100 μg/ml)

Dissolve 10 mg of nimesulide in few ml of 0.01 N sodium hydroxide solution, and the volume was made up to 100 ml with 0.01 N sodium hydroxide solution.

Nimesulide solution (10 μg/ml)

From the nimesulide stock solution, 1 ml is taken and diluted to 10 ml using 0.01 N sodium hydroxide solution.

Stock solution of sodium gentisate (1.0 M solution)

Dissolve 16.010 g of sodium gentisate in few ml of double distilled water, and the volume was made up to 100 ml with double distilled water.

Second stock solution of sodium gentisate (0.1M solution)

From the sodium gentisate stock solution, 5 ml is taken and diluted to 50 ml using double distilled water.

Table 6: Various concentrations of sodium gentisate and nimesulide (10 μg/ml) solution for spectral analysis

Sodium gentisate concentration (M)	Volume of Sodium gentisate solution (ml)	Nimesulide solution (100 μg/ml) volume (ml)	Water (ml)
0	0	1	9
0.001	1	1	8
0.002	2	1	7
0.003	3	1	6
0.004	4	1	5
0.005	5	1	4
0.006	6	1	3
0.007	7	1	2
0.008	8	1	1
0.009	9	1	0

*Sodium gentisate (0.0001–0.0009 M)

Table 7: Various concentrations of sodium ascorbate and nimesulide (10 μg/ml) solution for spectral analysis

Sodium ascorbate concentration (M)	Volume of sodium ascorbate solution (ml)	Nimesulide solution (100 μg/ml) volume (ml)	Water (ml)
0	0	1	9
0.001	1	1	8
0.002	2	1	7
0.003	3	1	6
0.004	4	1	5
0.005	5	1	4

*Sodium ascorbate (0.001–0.005 M)

Nimesulide-sodium ascorbate-interaction

Preparation of standard solutions for the spectral analysis of nimesulide-ascorbic acid-interaction (I.P)

Stock solution of nimesulide (100 μg/ml)

Dissolve 10 mg of nimesulide in few ml of 0.01 N sodium hydroxide solution, and the volume was made up to 100 ml with 0.01 N sodium hydroxide solution.

Nimesulide solution (10 μg/ml)

From the nimesulide stock solution, 1 ml is taken and diluted to 10 ml using 0.01 N sodium hydroxide solution.

Stock solution of sodium ascorbate (1.0 M solution)

Dissolve 16.010 g of sodium ascorbate in few ml of double distilled water, and the volume was made up to 100 ml with double distilled water.

Second stock solution of sodium ascorbate (0.1 M solution)

From the sodium ascorbate stock solution, 5 ml is taken and diluted to 50 ml using double distilled water.

TRIANGULAR PATTERN HYPOTHESIS

The entire literature available on the solubilization of poorly water-soluble drugs was collected. A list of drugs that has potential applications and a list of hydrotropes that have potential applications are documented. For the 1st time, we are proposing triangular pattern hypothesis. The chemical structures of drugs and hydrotropes were drawn. The functional groups (-OH, -COOH, -NH_2, etc.) available in the structure and their contribution toward the formation of hydrogen bonding were identified.[24]

- The drugs structure, functional groups, and the distance between these functional groups were measured in Armstrongs.
- The hydrotrope structure, functional groups, and the distance between these functional groups were measured in Armstrongs.

Assumption

The interaction of a drug with a hydrotrope results in increased aqueous solubility. The exact mechanism of interaction is not known. It is assumed some type of drug interaction with the

Table 8: Solubility data for nimesulide in different concentrations of ascorbic acid, sodium p-hydroxy benzoate, sodium gentisate and sodium ascorbate solutions at 25°C

Molar concentrations of hydrotrope solutions (M)	Solubility of nimesulide *Concentration (mg/ml)			
	Hydrotrope solutions			
	Ascorbic acid	Sodium p-hydroxy benzoate	Sodium gentisate	Sodium ascorbate
0	0.011	0.011	0.011	0.011
0.05	0.001	-	-	-
0.1	0.0005	0.012	1.132	0.059
0.2	0.0011	0.014	2.778	0.119
0.4	0.0032	0.018	5.231	0.251
0.6	0.0048	0.024	-	0.401
0.8	0.0072	0.03	11.595	0.613
1	0.0098	0.037	12.933	0.768
1.2	0.0148	-	-	-
1.4	0.017	-	-	-

*Average of three determinations

Table 9: Solubility data for nimesulide in different concentrations of ascorbic acid, sodium p- hydroxy benzoate, sodium gentisate and sodium ascorbate solutions at 37°C

Molar concentrations of hydrotrope solutions (M)	Solubility of nimesulide *Concentration (mg/ml)			
	Hydrotrope solutions			
	Ascorbic acid	Sodium p-hydroxy benzoate	Sodium gentisate	Sodium ascorbate
0	0.0182	0.0182	0.0182	0.0182
0.05	0.0027			
0.1	0.0019	0.0256	1.046	0.157
0.2	0.004	0.0271	1.99	0.314
0.4	0.0068	0.0326	4.511	0.651
0.6	0.0116	0.0418		0.871
0.8	0.0145	0.0502	8.302	1.217
1	0.0193	0.0625	15.763	1.452
1.2	0.0199	-	-	-
1.4	0.0239	-	-	-

Table 10: IR spectral analysis of nimesulide and hydrotrope complexes

Nimesulide 3282 cm-1 (N-H, str)	Ascorbic acid	Nimesulide-ascorbic acid complex	Inference
	3526 cm^{-1} (OH str, broad), 1666 cm^{-1} (C=Carbonyl, exocyclic)	3285 cm^{-1} (N-H, str), 3527 cm^{-1} (OH str, broad), 1666 cm^{-1} (C=O, carbonyl, exocyclic)	Presence of nimesulide, presence of ascorbic acid in the complex indicates the formation of complexation
	Sodium gentisate	Nimesulide-sodium gentisate complex	Inference
	3462 cm^{-1} (OH str, broad)	3287 cm^{-1} (N-H, str), 3466 cm^{-1} (OH str, broad)	Presence of nimesulide, presence of sodium gentisate in the complex indicates the formation of complexation

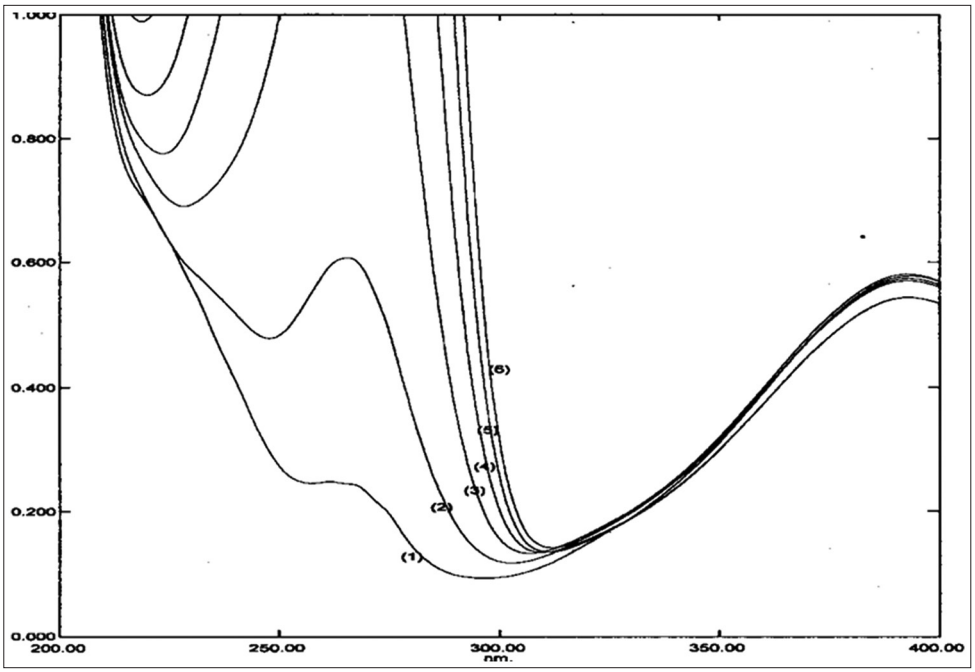

Figure 1: Ultraviolet absorption spectrum of nimesulide (10 µg/ml) solution and various concentrations of ascorbic acid (0.001–0.005 M) for spectral analysis

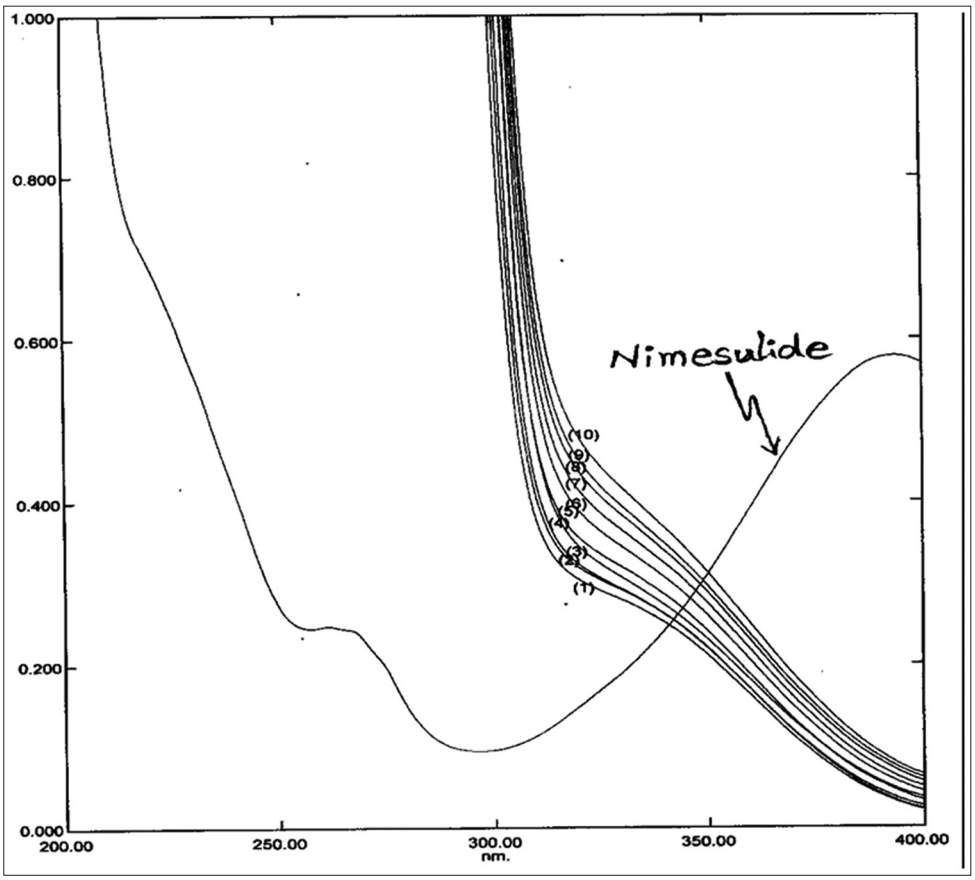

Figure 2: Ultraviolet absorption spectrum of nimesulide (10 µg/ml) solution and various concentrations of ascorbic acid (0.005–0.09 M) for spectral analysis

hydrotrope, may be hydrogen bonding or acid-base type. Given the assumption that the drug and hydrotrope[25] are nearly planar (benzene ring), it may be appropriate to consider three sites of interaction. The sites in the chemical structure

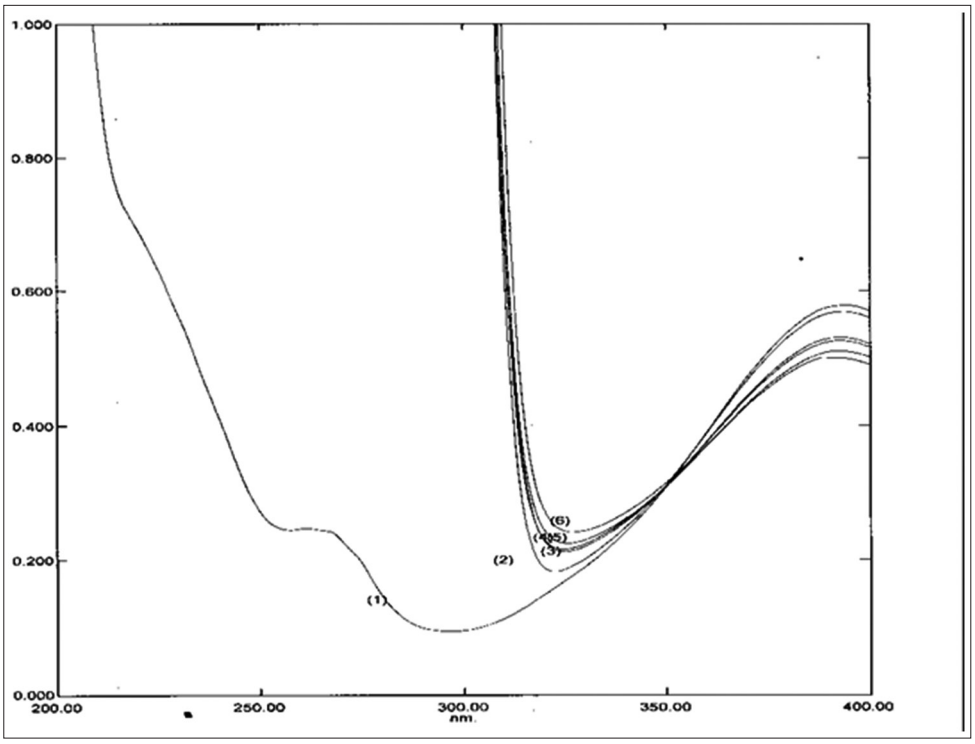

Figure 3: Ultraviolet absorption spectrum[32] of nimesulide (10 µg/ml) solution and various concentrations of sodium p-hydroxy benzoate (0.01–0.05 M) for spectral analysis

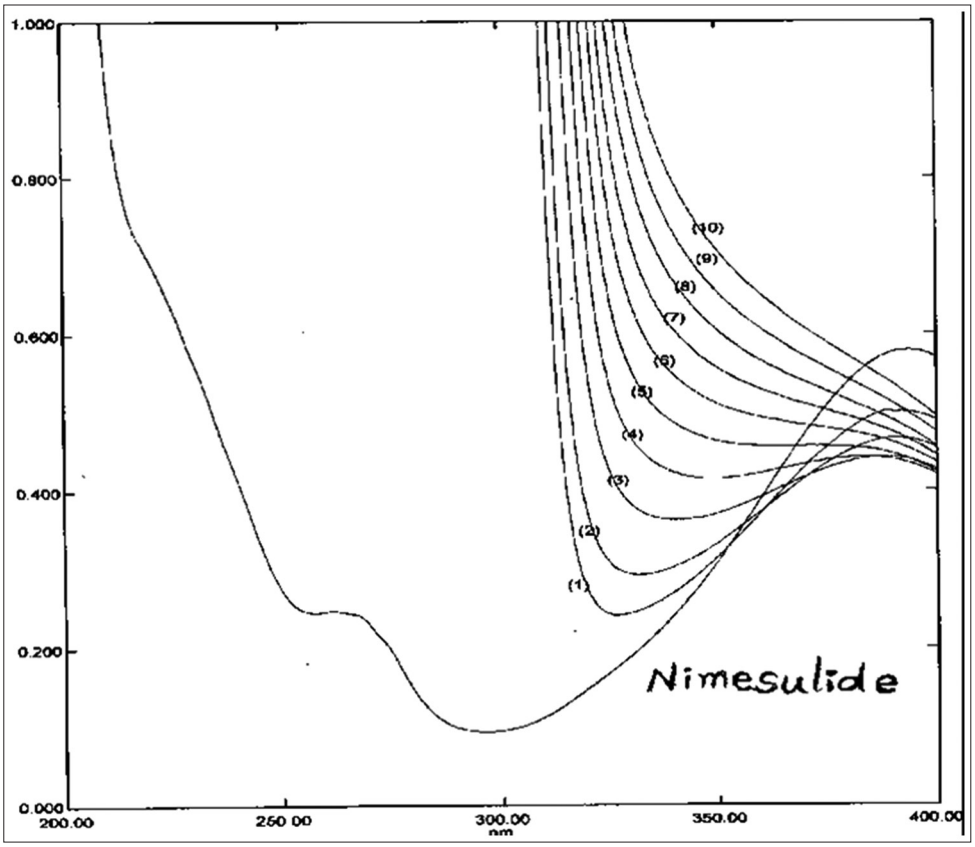

Figure 4: Ultraviolet absorption spectrum of nimesulide (10 µg/ml) solution and various concentrations of sodium p-hydroxy benzoate (0.05–0.9M) for spectral analysis

of the drug and the complementary sites in the chemical structure of the hydrotrope are expected to interact[26] such as architectural arrangement provides adequate facility for the interaction. This hypothesis tested in the work.

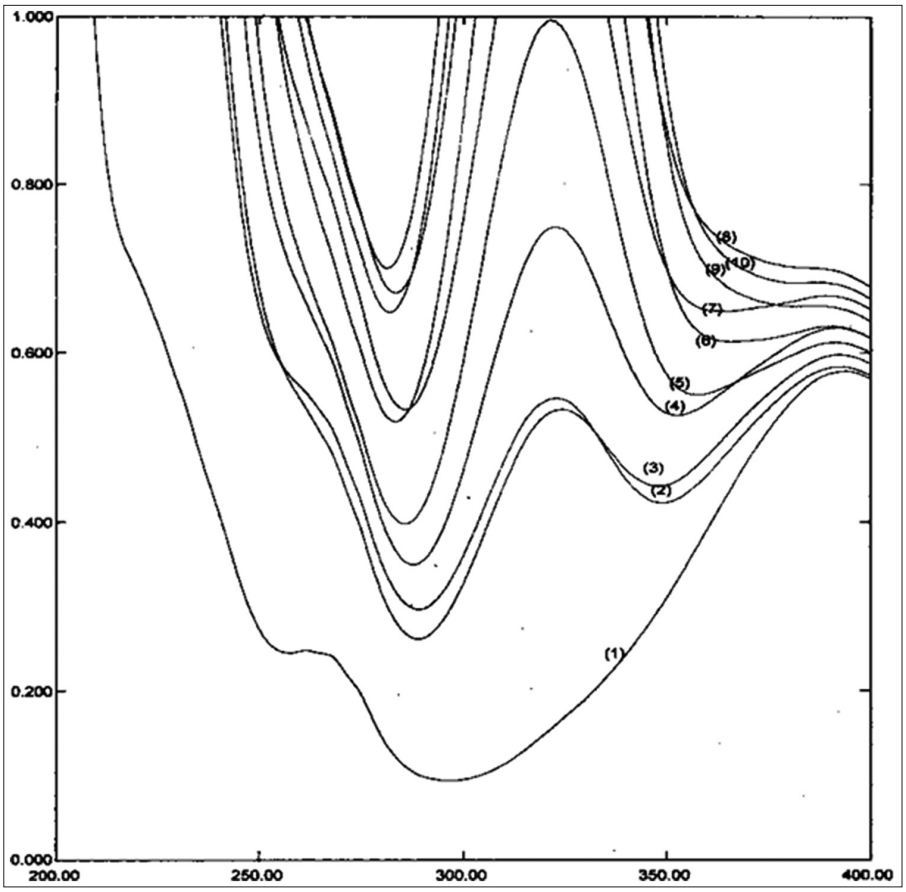

Figure 5: Ultraviolet absorption spectrum of nimesulide (10 µg/ml) solution and various concentrations of sodium gentisate (0.0001–0.0009 M) for spectral analysis[33]

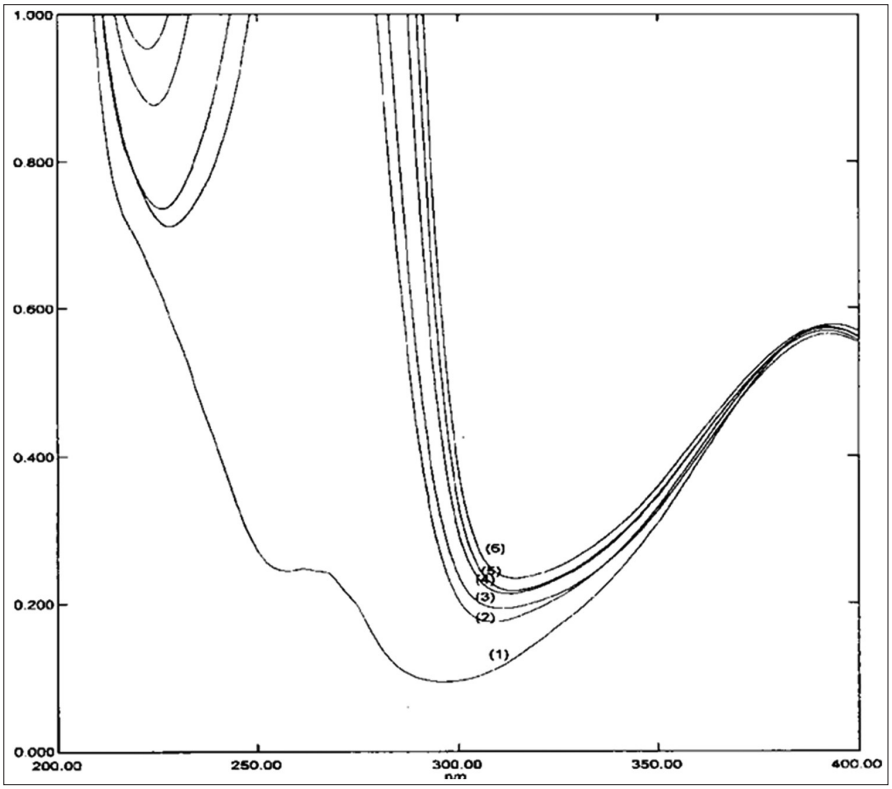

Figure 6: Ultraviolet absorption spectrum of nimesulide (10 µg/ml) solution and various concentrations of sodium ascorbate (0.001–0.005M) for spectral analysis

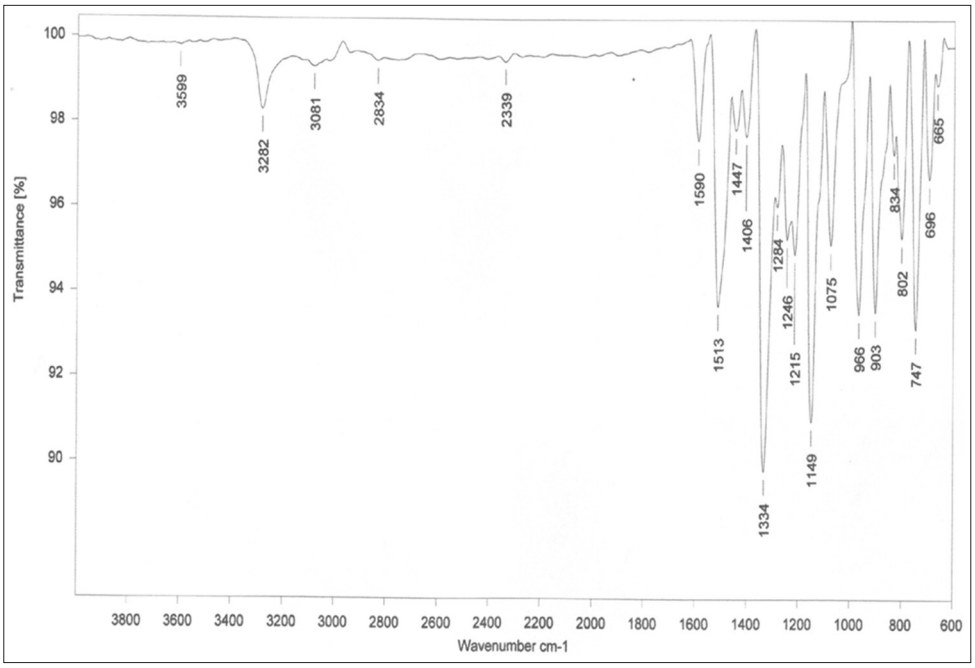

Figure 7: Infrared spectrum of nimesulide

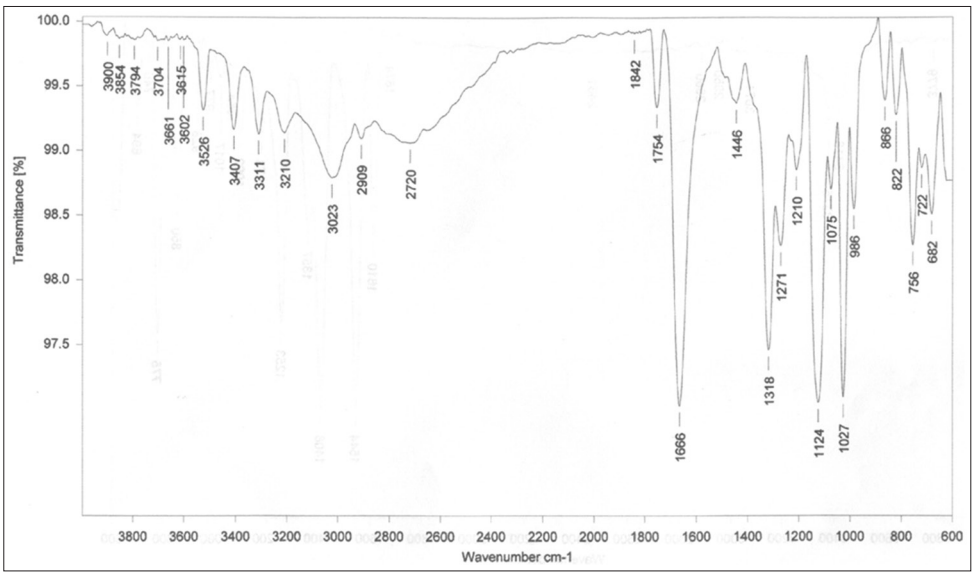

Figure 8: Infrared spectrum of ascorbic acid

Attempts to obtain hydrotropes

Attempts were made to obtain hydrotropes of nimesulide to increase the aqueous solubility of nimesulide. The hydrotropes used in this study are ascorbic acid, sodium p-hydroxy benzoate, and sodium gentisate, and sodium ascorbate. The chemical structures of drugs and hydrotropes were compared for identifying the functional groups that can contribute to hydrogen bonding.

Based on the analysis, nimesulide was chosen as drug and ascorbic acid, sodium p-hydroxy benzoate, sodium gentisate, and sodium ascorbates were selected as hydrotropes. In this study, it was assumed that sodium has no role to play except changing the pH of solutions. However, these effects are treated uniform, as molar solutions of hydrotropes were considered in this study.

The results of nimesulide and hydrotropes distances between the functional groups are measured in Armstrong, and the areas were calculated using the formula:

$$\text{Area}^2 = s(s-a)\,(s-b)\,(s-c).$$

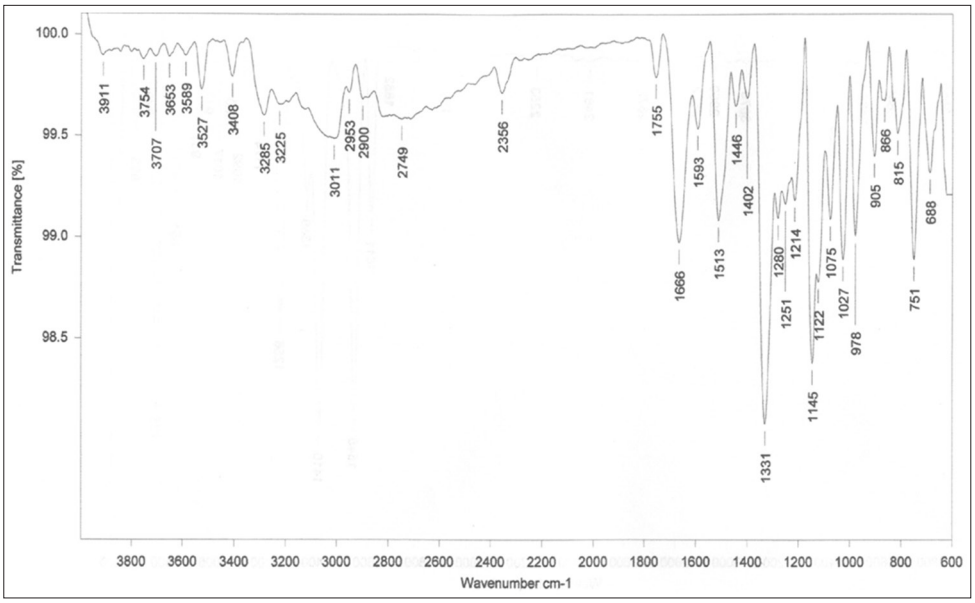

Figure 9: Infrared spectrum of ascorbic acid - nimesulide complex

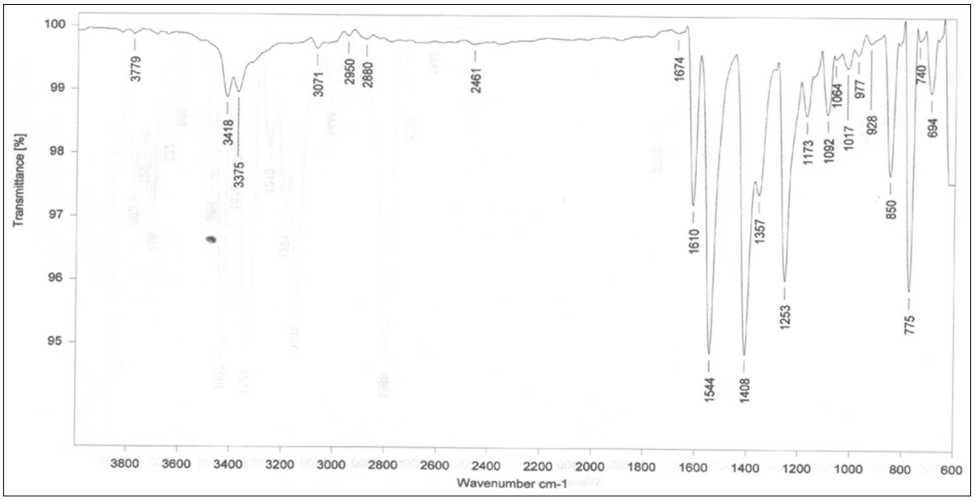

Figure 10: Infrared spectrum of sodium p-hydroxy benzoate

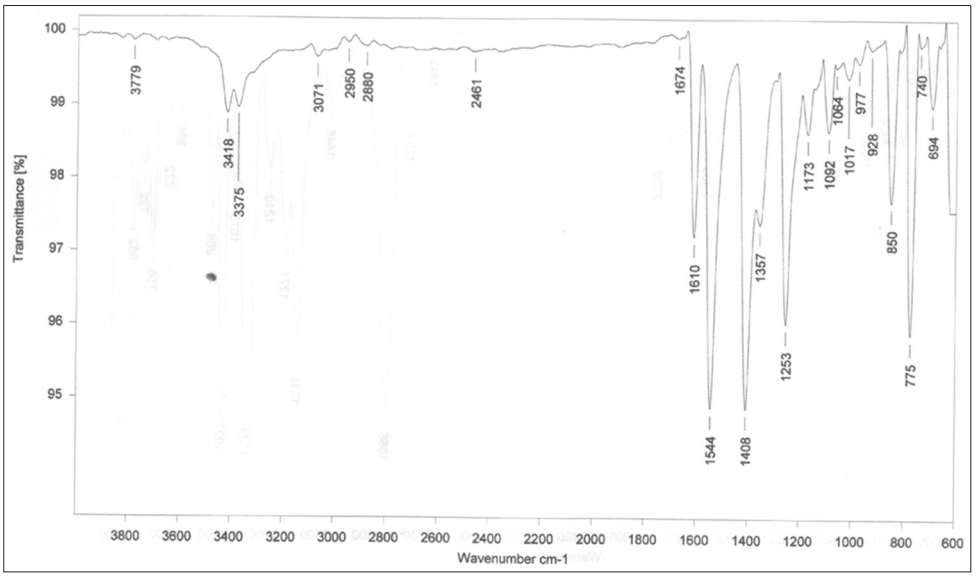

Figure 11: Infrared spectrum of sodium p-hydroxybenzoate - nimesulide complex

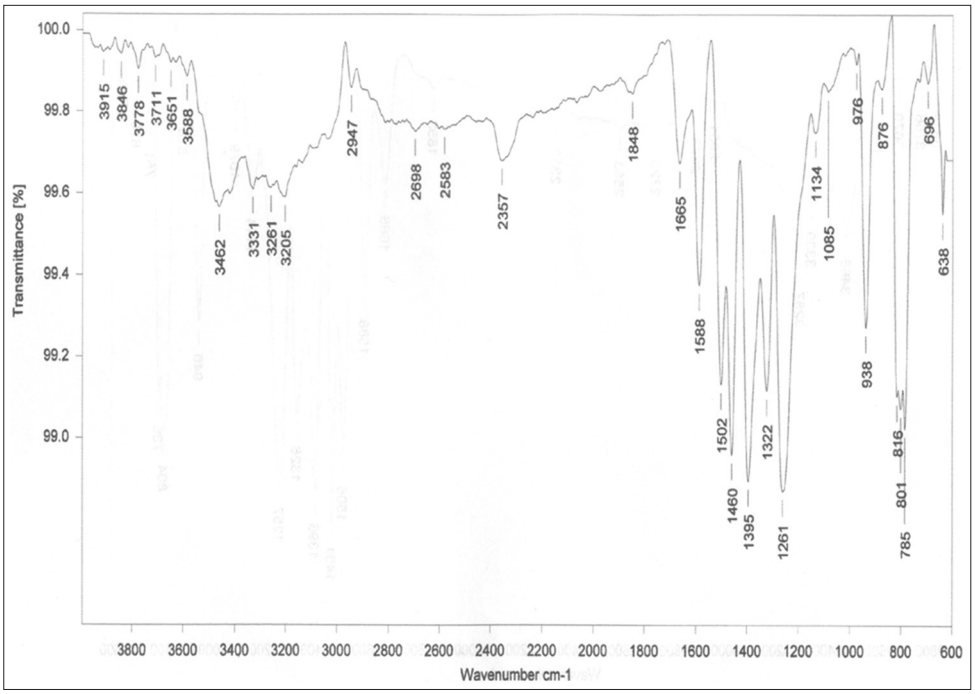

Figure 12: Infrared spectrum of sodium gentisate

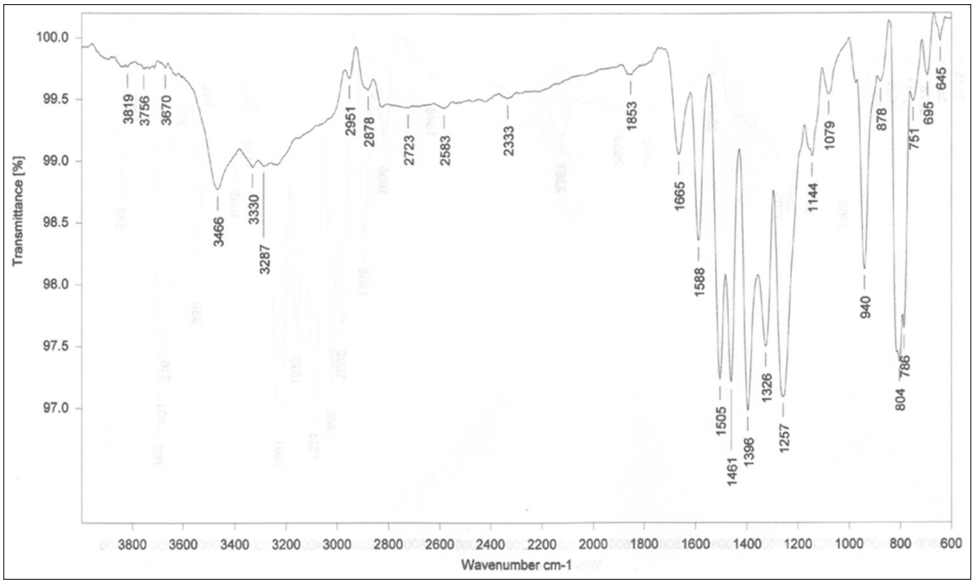

Figure 13: Infrared spectrum of sodium gentisate - nimesulide complex

PREPARATION OF SOLID COMPLEXES OF NIMESULIDE-HYDROTROPES

In general, coprecipitation[13] method was reported to prepare solid complexes. This method was extended for the present studies too. The method used was as follows. About 200 mg of nimesulide was dissolved in acetone (20 ml) in a 200 ml beaker. The beaker was kept on the magnetic stirrer. Ascorbic acid (1 M) solution was taken in a burette and added drop by drop with continuous stirring. After addition of 10 ml, the yellowish precipitate was formed. Then, acetone was evaporated on a constant temperature water bath (60°C) for 20 min. The precipitated solution was kept in the refrigerator (12 h, temperature 10°C). The precipitate was collected by filtration. The residue was dried at room temperature for 36 h in a desiccator. The solid complex was analyzed for its characterization. Nimesulide-ascorbic acid complex was formed as a yellowish-white precipitate. Nimesulide-sodium p-hydroxy benzoate complex was formed as a light yellowish-white precipitate. Nimesulide-sodium gentisate complex was formed as reddish brown colored precipitate. Nimesulide-sodium ascorbate complex was formed as light brown colored precipitate.

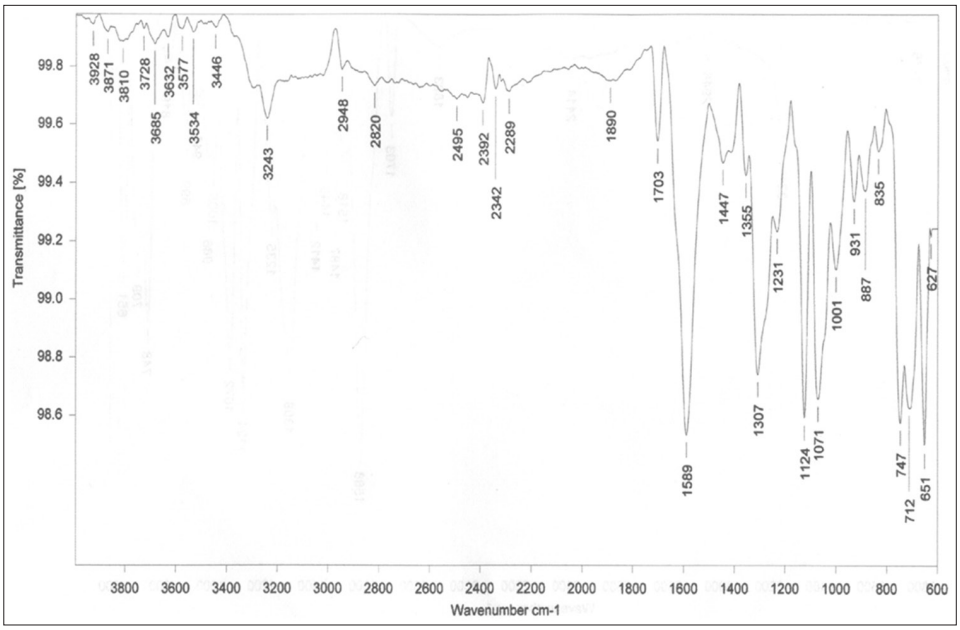

Figure 14: Infrared spectrum of sodium ascorbate

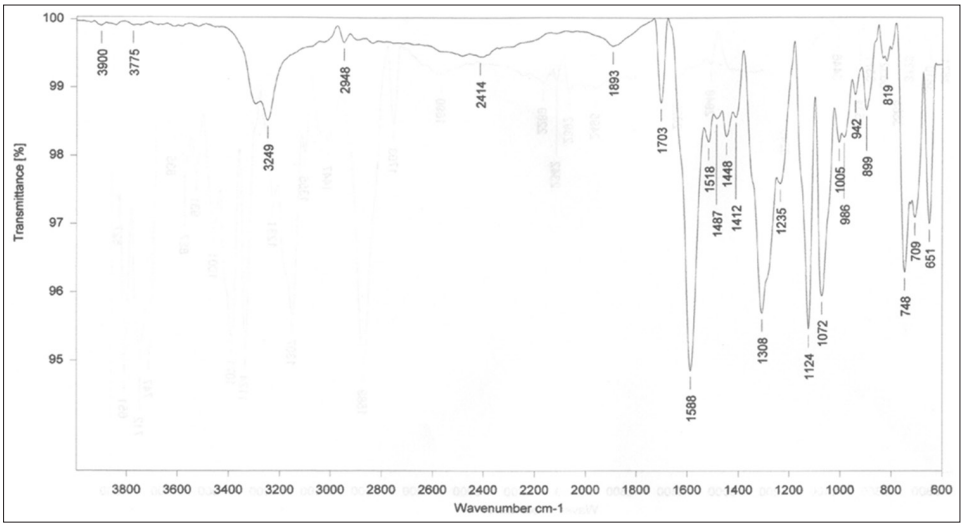

Figure 15: Infrared spectrum of sodium ascorbate - nimesulide complex

Determination of melting point

The melting points of individual components and solid complexes were determined in open capillaries. The dried samples were repeatedly evaluated for melting points for 30 days. The melting point values were measured periodically until constant melting points[27] were obtained. These values were compared with the melting points of individual components for characterization. Melting points of substances having higher than 2500°C were determined in the same method using silicones as the medium of heating.

Fourier transformed infrared (FT-IR) spectroscopic analysis[28]

FT-IR spectral studies were carried out for nimesulide and the various hydrotropes (ascorbic acid, sodium p-hydroxy benzoate, sodium gentisate, and sodium ascorbate) for their pure form and their complex. The sample was prepared by dispersing the drug/complex in potassium bromide powder and analyzed.[29]

RESULTS AND DISCUSSION

An UV-spectrophotometric analytical method was developed successfully. The λ_{max} was found to be developed successfully. The λ_{max} was found to be 393 nm which may be accounted for the yellow colour of the solution. The results are agreeing the literature reports. The regression equation of the standard plot is used for the estimation of drug in all subsequent methods.

The UV - spectrophotometric method exhibits no interference of hydrotropes with the estimation of nimesulide. This is possible because all the hydrotropic solutions are colour less,

while nimesulide is slightly coloured solution at the working concentrations. Thus the selection of high λmax uniquely suitable as an analytical method.

Analytical report [Figures 1-15]

UV–spectrophotometric analysis-interaction of hydrotropes of nimesulide

Nimesulide-ascorbic acid

At 0.001 to 0.005 M There was a slight difference in absorbances at 393 nm. The λ_{max} of ascorbic acid is 265 nm. At this wavelength, the absorbance of nimesulide must be added to the absorbance value of ascorbic acid. These results did not clearly identify the interaction of UV - spectroscopy. It is further to state that the solutions of nimesulide–ascorbic acid (0.001–0.005 M) have yellow colour.

At 0.005-0.09M when it was mixed with ascorbic acid solution, λ_{max} disappeared. This was reflected by the absence of yellow colour. These spectra clearly demonstrated the presence of some interaction between these two components.

Nimesulide - sodium p-hydroxy benzoate

At 0.01 to 0.05 M the interaction of nimesulide with sodium p- hydroxy benzoate may be weak. The λ_{max} of nimesulide (393 nm) remained same. There was a slight difference in absorbances at 393nm. The λ_{max} of sodium p- hydroxy benzoate was 246nm. Attention was paid, λ value between 300-400 nm for understanding molecular interaction. Between 300-325nm, sodium p- hydroxy benzoate have zero absorbance when it was mixed with nimesulide, the absorbance values increased drastically, which cannot be explained by algebraic addition of two components. Thus directly suggests same type of interaction between the components.[30]

At 0.1 to 0.9 M the interaction of nimesulide with sodium p- hydroxy benzoate indicated that λ_{max} was shifting from 393 nm to 312 nm the drastic increase in the absorbance of sodium p-hydroxy benzoate in the wavelength range of 300-350 nm. Then it proves that there is some type of interaction between the components

Nimesulide - sodium gentisate

At 0.0001 to 0.0009 M concentration when sodium gentisate was mixed with nimesulide, the absorbance values of nimesulide increased drastically, which cannot be explained by algebraic addition of two components. Thus directly suggests same type of interaction between the components.

Nimesulide - sodium ascorbate

At 0.001 to 0.005 M at these concentrations, the interaction of sodium ascorbate and nimesulide may be weak. The λ_{max} of nimesulide (393 nm) remained same. The λ_{max} of sodium ascorbate is 265 nm. At this wavelength, the absorbance of nimesulide must be added to the absorbance value of sodium ascorbate. These results did not clearly identify the interaction of UV-spectroscopy. It is further to state that the solutions of nimesulide–sodium ascorbate (0.001–0.005 M) have yellow colour. This also reflected in the UV spectra (393 nm).

FT-IR spectroscopic analysis

Presence of nimesulide, presence of ascorbic acid in the complex indicates the formation of complexation

Nimesulide: 3282 cm^{-1} (N-H, str).

Ascorbic acid: 3526 cm^{-1} (OH str, broad), 1666 cm^{-1} (C=Carbonyl, exocyclic).

Presence of nimesulide, presence of sodium gentisate in the complex indicates the formation of complexation.

Nimesulide-ascorbic acid complex: 3285 cm^{-1} (N-H, str), 3527 cm^{-1} (OH str, broad), 1666 cm^{-1} (C=O,carbonyl, exocyclic).

Sodium gentisate: 3462 cm^{-1} (OH str, broad)

Nimesulide-sodium gentisate complex: 3287 cm^{-1} (N-H, str), 3466 cm^{-1} (OH str, broad).

CONCLUSION

Nimesulide solubilization was achieved successfully using sodium gentisate and sodium ascorbate using the concept of hydro trophy.

Nimesulide was reported to be poorly water soluble (0.1 mg/ml). The poor aqueous solubility gives rise to difficulties in bioavailability. To improve the aqueous solubility, the hydrotropic technique was used. In the present work, hydrotropes such as ascorbic acid, sodium p-hydroxy benzoate, and sodium gentisate and sodium ascorbate were used.

- The chemical structures of nimesulide and hydrotropes were considered. The functional groups (-OH, -COOH, $-NH_2$, etc.) available in the structure and their contribution toward the formation of hydrogen bonding were identified.
- The average area was found to be 8 A^{o2} for nimesulide and 10 A^{o2} for hydrotropes.
- Suitable UV-spectrophotometric method was developed for the estimation of nimesulide. Beer-Lambert's law obeyed in the range of 4–20 µg/ml at 393 nm. The hydrotropes did not show any interference with estimation of nimesulide at this analytical wavelength, 393 nm.
- The UV-spectrophotometric[31] method is utilized for the identification of drug-hydrotrope interaction. At high concentrations of ascorbic acid, nimesulide λ_{max} was disappeared. The spectral pattern of the mixture nimesulide-sodium p-hydroxy benzoate was not the algebraic sum of the individual components, particularly between 300 and 350 nm. Similar changes are observed in the case of nimesulide and other hydrotropes.
- The solubility profile of nimesulide in the presence of hydrotropes solutions was obtained.

The solubility of nimesulide was enhanced as the concentration of ascorbic acid is increased both at room temperature (25°C) and at (37°C).

The interaction stability constants are 0.839 and 0.677 l/moles, respectively, at 25°C and 37°C.

The type of solubility profile is Type A_L.

The interaction stability constants of nimesulide-sodium p-hydroxy benzoate are 2.516 and 1.693 l/moles, respectively, at 25°C and 37°C.

The type of solubility profile is Type A_L.

The interaction stability constants of nimesulide-sodium gentisate are 1173.408 and 747.65 l/moles, respectively, at 25°C and 37°C.

The type of solubility profile is Type A_L.

The interaction stability constants of nimesulide-sodium ascorbate are 69.716 and 79.206 l/moles, respectively, at 25°C and 37°C.

The type of solubility profile is Type A_L.

All hydrotropes enhanced the solubility[27] of nimesulide. The solubility enhancement of nimesulide by the hydrotropes was observed in decreasing order as sodium gentisate > sodium ascorbate > sodium p-hydroxy benzoate > ascorbic acid.

- Solid complexes are successfully prepared. The melting points of the individual components and the complexes are compared. The obtained complexes are nimesulide-sodium p-hydroxy benzoate, nimesulide-sodium gentisate, nimesulide sodium ascorbate.
- FT-IR spectra indicated two drug-hydrotrope complexes; these are nimesulide ascorbic acid and nimesulide sodium gentisate complexes.

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