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Comparison of The Effect of Tromethamine and Polyvinylpyrrolidone on Dissolution Properties and Analgesic Effect of Nimesulide

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ABSTRACT

The solubilizing and absorption enhancer properties towards nimesulide (ND) of tromethamine (Tris) and polyvinylpyrrolidone (PVP) have been investigated. Solid binary systems were prepared at various drug-polymer ratios by mixing or coprecipitation, characterized by differential scanning calorimetry, X-ray diffractometry, and Fourier transform infrared spectroscopy, and tested for dissolution behavior. Both carriers improved drug dissolution and their performance depended on concentration of the hydrophilic carrier in coprecipitates. Tris was more effective than PVP, despite the amorphizing power of PVP as revealed by solid state analyses. Complete drug amorphiztion was attained at 1:3 (wt/wt) drug:PVP, 25% (wt/wt) ND in PVP. According to thermal behavior of ND and Tris, ND-Tris systems present a eutectic behavior. The eutectic composition was 30% ND-70% Tris at ~129°C. Amorphous ND-PVP and eutectic ND-Tris mixtures showed an improvement of 5.55 and 6.6 times of drug dissolution efficiency, respectively. In vivo experiments in mice demonstrated that administration of 50 mg/kg of drug coprecipitated with PVP or Tris resulted, respectively, in a 50% and 94% reduction of acetic acid–induced writhings in comparison with pure drug, which, instead, was statistically ineffective as compared with the control group. Moreover, the eutectic mixture of ND-Tris demonstrated antiwrithing potency 1.88 times higher than amorphous ND-PVP coprecipitate. Thus, the solubilizing power, dissolution-enhancing effect, and analgesic effect enhancer ability toward the drug make Tris particularly suitable for developing a reduced-dose, fast-release solid oral dosage form of nimesulide.

KEYWORDS: Nimesulide, Polyvinylpyrrolidone, Tromethamine, Analgesic effect, Coprecipitation.

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INTRODUCTION

Tromethamine (Tris)(Figure 1) is an organic amine proton acceptor that used as an alkalinizing agent in the treatment of metabolic acidosis. It acts as a weak osmotic diuretic. It is mainly used during cardiac bypass surgery and during cardiac arrest. It may also be used to reduce the acidity of citrated blood for use in bypass surgery.[1]

In recent years, there has been growing interest in Tris as a promising pharmaceutical excipient because it is possible to increase the dissolution rate of drugs, to alter membrane permeability, to increase the bioavailability of sparingly soluble drugs, and to increase drug stability.[2-12]

Tris salt of prostaglandin-F2 was selected as a raw material for its better crystallinity and purity.[2] Tris salt of some nonsteroidal anti-inflammatory agents showed decreased hygroscopicity and improved solubility and dissolution rates when compared with free acids and sodium salts.[3] Tris salt of fosfomycin was reported to be more bioavailable than the calcium salt.[4] Further, Tris was found to enhance percuteneous absorption of tenoxicam through hairless mouse skin by increasing drug solubility.[5] Tris also showed a stabilizing effect on N-nitrosoureas[6] and thimerosal[7] in aqueous solutions. In addition, dissolution rates of benzoic acid,[8] glibenclamide,[9] hydrochlorothiazide,[10] and furosemide[11] were markedly increased by the use of Tris as a carrier.

Nimesulide (ND) (Figure 2) is an acidic nonsteroidal anti-inflammatory drug (NSAID) that differs from many similar compounds in that it is acidic by virtue of a sulfonanilide rather than a carboxyl group.[12] It is an inhibitor of cyclooxygenase 2, hence inhibits the synthesis of destructive prostaglandins and spares cytoprotective prostaglandins. ND belongs to the class II biopharmaceutical classification scheme,[13,14] a low solubility-high permeability drug. ND is very sparingly soluble in water (0.01 mg/mL).[14] The poor aqueous solubility and wettability of ND give rise to difficulties in pharmaceutical formulations for oral and parenteral delivery, which may lead to variable bioavailability. Therefore, the favorable effect of polyvinylpyrrolidone (PVP) on ND solubility and dissolution rate has been demonstrated.[15] Recently, the effectiveness of Tris in enhancing the dissolution properties of ND was also demonstrated.[16] Therefore, it seemed worthy of interest to extend our investigation and

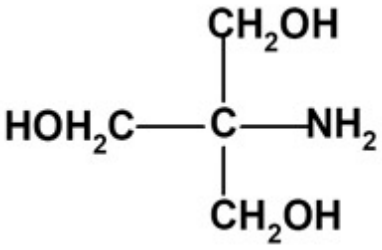

Figure 1. Schematic of tromethamine.

compare in detail the performance of such excipients in improving ND dissolution behavior.

Materials and Methods

Materials

Nimesulide was a generous gift from Pharo Pharm (Alexandria, Egypt). Polyvinylpyrrolidone (PVP K-30) was purchased from Sigma (St Louis, MO). Tromethamine (Tris) was purchased from Acros Organics (Morris Plains, NJ). Sodium carboxymethylcellulose (CMC) was purchased from Shin-Etsu Chemicals (Tokyo, Japan). Glacial acetic acid was purchased from BDH Poole Co. (Dorset, UK).

Preparation of ND-PVP-K30 Solid Dispersions and Physical Mixtures

Physical Mixtures

Physical mixtures (PM) of ND and PVP K-30 in drug:carrier weight ratios of 1:1, 1:2, and 1:3 were prepared by mixing accurately weighed amounts of ND and specified amounts of PVP in geometric proportions for 3 minutes using a spatula. The blends were passed through a 250-µm sieve.

Coprecipitated Mixtures

Coprecipitates (Coppt) of ND and PVP K-30 in drug:carrier weight ratio of 1:0, 2:1, 1:1, 1:2, 1:3, and 1:5 were prepared. Being that ND is sparingly soluble in ethanol 95%,[17] 1 g of ND was dissolved in 60 mL acetone. The suitable amount of PVP was dissolved in minimum amount of ethanol 95% and was added with mixing to drug solution. The solvent was removed under reduced pressure at ~50°C using a rotary evaporator (Heidolph, Germany). The resulting mass was treated as described above.

Preparation of ND-Tris Coprecipitates and Physical Mixtures

Physical Mixtures

PMs of ND and Tris, containing 10%, 30%, 50%, 70%, and 90% wt/wt of drug, were prepared by mixing accurately weighed suitable quantities of ND and specified amounts of Tris in geometric proportions for 3 minutes using a spatula. The blends were passed through a 250-µm sieve.

Coprecipitated Mixtures

Coppt of ND and Tris were prepared by dissolving 1 to 2 g of the corresponding physical mixtures in ethanol 95% and evaporating the solvent under vacuum at ~50°C using a rotary evaporator. The resulting mass was ground using a mortar and pestle and passed through a 250-µm sieve. It is worthy to note that there was no need to add a minimum amount of acetone to dissolve the specified amount of ND where the calculated amounts of the drug completely dissolved in the suitable Tris ethanolic solutions. In other words, the solubility of ND in ethanol 95% was markedly increased in presence of Tris. This observation may be thought to indicate a certain interaction occurred between Tris an ND.

Thermal analysis

Thaw-melt method: This was accomplished using a digital melting point apparatus (Stuart Scientific SMP10, London, UK), which enabled accurate heating rates, better visualization, and improved temperature hold capabilities. A sample was placed in a glass capillary tube and heated at a rate of 2°C/min. The sample was heated at a constant rate by means of a heating stage interfaced with a digital temperature display. Visualization was possible using a high-powered magnifying glass fixed on a mount over the sample and heating stage. The apparatus thus resembled a hot-stage microscope but lacked the polarizing lenses of the latter. All determinations were made in triplicate. For the purpose of constructing phase diagrams for ND-Tris system, observation were made during heating as previously elaborated. These included noting the temperature at which melting started

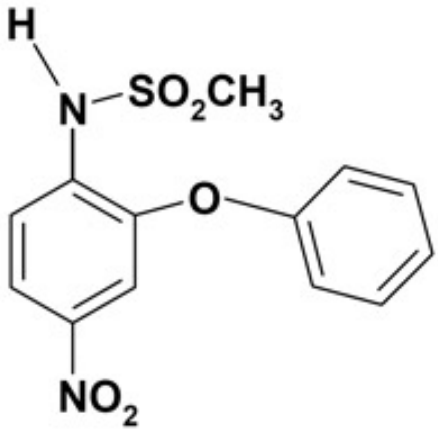

Figure 2. Schematic of nimesulide.

(thaw point) and the temperature at which complete melting was affected (melting point). These 2 temperatures were used to define the melting point range.

Differential Scanning Calorimetry (DSC): DSC thermograms were performed using a DSC (Perkin-Elmer, 2-C, New York, NY) with a thermal analysis data station TADS system, computer, and plotter interface. The instrument was calibrated with an indium standard. Analysis was made by heating 3- to 5-mg samples from 30°C to 300°C at a constant scanning speed of 5°C/min in sealed aluminum pans and using nitrogen flow at 40 mL/min as a purging gas.

X-ray Powder Diffraction

X-ray powder diffraction (XRD) patterns of some selected samples were obtained using a Jeol XR diffractometer system (Tokyo, Japan). The radiation source was a copper (λ= 1.54184 Å) high-intensity x-ray tube operated at 35 KV and 15 mA.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FT-IR) spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Jasco FTIR-5300 spectrophotometer (Tokyo, Japan). Samples were prepared in KBr disks by means of a hydrostatic press.

Dissolution Studies

Dissolution rate studies were performed in 0.1 M hydrochloric acid solution containing 0.1% wt/vol sodium lauryl sulfate (SLS) without enzymes (pH 1.2) at 37 ± 0.5°C, using USP apparatus 2 (Hanson Research SR8 plus, Chatsworth, CA) rotating at 50 rpm. The pure drug, physical mixtures, and dispersed mixtures, each containing 10 mg of the drug, were added to 900 mL of the dissolution medium (near sink conditions). At fixed time intervals, samples were withdrawn, and filtered (pore size 0.22 μm). The samples were rendered alkaline to ~pH 10 by adding 1 to 2 drops of 10 M sodium hydroxide solution and analyzed spectrophotometrically at 392 nm. Each test was performed in triplicate (correlation of variance (CV) < 1.5%). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.[18] Also, The relative dissolution rate (RDR_{20}) data of the different samples were calculated by determining the amount of ND dissolved from a particular sample and normalizing for the amount of drug dissolved from pure drug sample over the same time interval (20 minutes).

Protocol for In Vivo Experiments

Adult mice weighing 19 to 25 g at the time of experiments were used. The analgesic effect of ND alone and some selected formulations were tested by evaluating the drug's ability to inhibit the acetic acid-induced writhing response,[19-22] a technique widely used for the study of peripheral analgesic drugs (NSAIDs). The mice were randomly divided into 6 groups of 6 animals. From literature survey, a dose equivalent to 50 mg nimesulide/Kg was administered orally as aqueous suspensions with 0.25% CMC.[19,21] The equivalent volume (~0.5mL) of the dose was withdrawn from a stock aqueous suspension (2 mg ND equivalent/mL) of each tested formulation, then ingested by the aid of an insulin syringe 100 IU associated with a canula. An aqueous solution of 0.25% CMC (0.5 mL) was administered orally to the control group. Afterwards, the mice were put in individual cages and, 20 minutes after drug administration, 10 μL/g of a 0.6% acetic acid solution was injected intraperitoneally into each one. The induced writhes were then counted for 15 minutes after acetic acid injection. For scoring purposes, a writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb. The formula for computing percent inhibition is: average writhes in the control group minus writhes in the drug group divided by writhes in the control group times 100%. An unpaired *t*-test, GraphPad Software, Inc., 3.05 (San Diego, CA), was used to evaluate the significance of the observed differences.

RESULTS AND DISCUSSION

Characterization of ND-PVP K-30 Systems

The thermal behavior of pure components and of some selected drug-PVP physical and dispersed mixtures are depicted in Figure 3. DSC curve of the pure drug showed a sharp endothermic peak (T_{peak} 150°C) that indicated the crystalline anhydrous state of ND. In contrast, the large endotherm over the temperature range 50 to 100°C associated with water loss, shown by PVP K-30 was typical of amorphous hydrated substance.[22] The thermal behavior of ND-PVP system demonstrated the presence of intense solid-state interactions between ND and PVP. In fact, the fusion endotherm of ND strongly broadened, shifted to lower values, and reduced in intensity in drug:PVP K-30 1:1, and 1:2, including simple PM and Coppt mixtures, as well, until fully disappearing in ratios of 1:3 pm, 1:3, and 1:5 Coppt, revealing total drug amorphization. The amorphizing power of PVP toward the drug was also confirmed from the results of XRD analysis, Figure 4. In fact, the drug crystallinity peaks were still evident in drug alone, whereas the simple blending with PVP K-30 caused a strong decrease of ND crystallinity, probably as a consequence of a loosening of crystal forces of ND finely dispersed within the amorphous

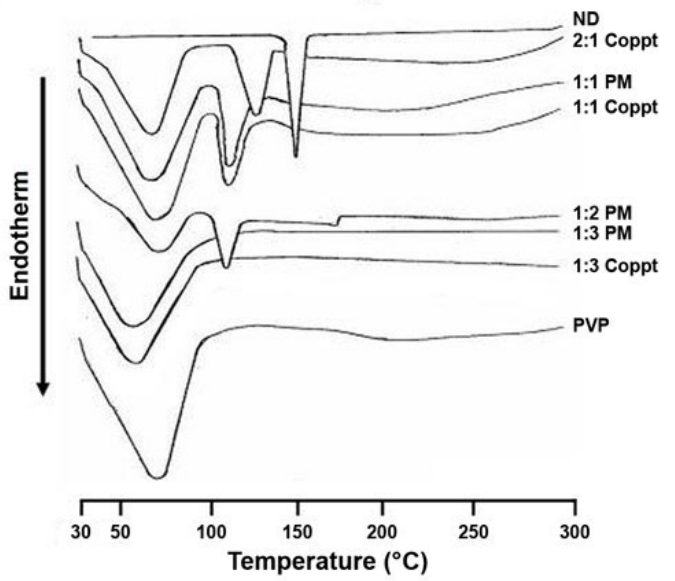

Figure 3. DSC curves of nimesulide and various binary systems with PVP.

PVP.[23] However, some characteristic peaks, indicative of the presence of residual ND crystals, were detectable in the 1:3 pm, in contrast with the results of DSC analysis, which indicated total loss of drug crystallinity in this system, Figure 3. Evidently, the thermal energy supplied during the DSC scan was responsible for complete amorphization of ND, which was brought to a high dispersed (but not totally amorphous) state by simple physical mixing.[22] According to the DSC and XRD findings, the loss of ND crystallinity

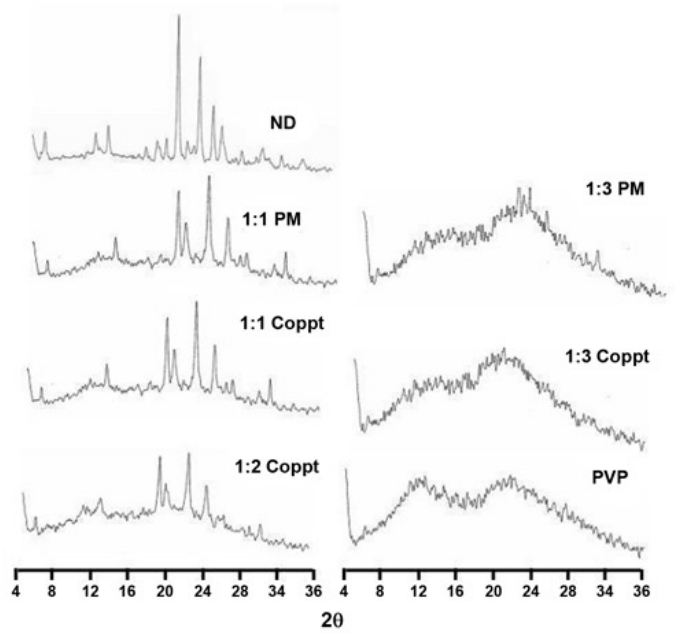

Figure 4. XRD spectra of nimesulide and various binary systems with PVP.

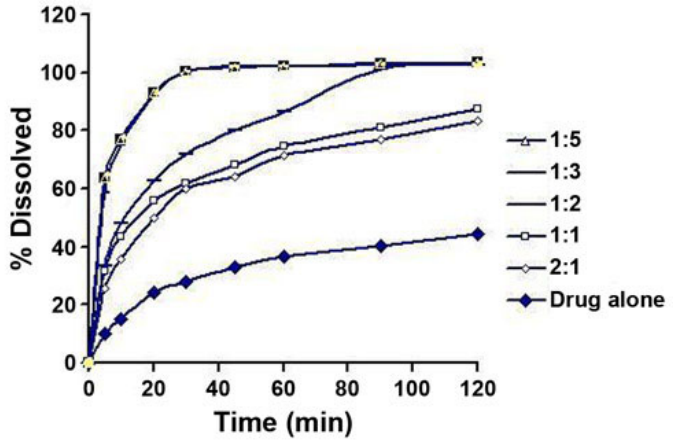

Figure 5. Dissolution profile of nimesulide and its coprecipitates with PVP.

became more evident at increasing the carrier content in the mixture and as a consequence of coevaporation of the sample, owing to the more intimate contact between the components, as well as the finer dispersion of the drug into the amorphous matrix of the polymer.

The results of dissolution studies are presented in Figures 5 and 6, and summarized in Table 1, in terms of dissolution efficiency after 10 minutes (DE_{10}), and relative dissolution rate at 20 minutes (RDR_{20}). As can be seen, PVP was effective in enhancing the drug dissolution performance, and its efficacy depended on its content in the mixture and the system preparation method, coprecipitation being better than physical mixing. The drug dissolution rate, in terms of DE_{10} and RDR_{20} from dispersed mixtures, was markedly higher than that from the drug alone, or corresponding physical mixtures. The enhanced drug dissolution performance from ND-PVP dispersed mixtures might be attributed to many factors. Particle size reduction of the drug, improved wettability, and loss of crystallinity occurring during the

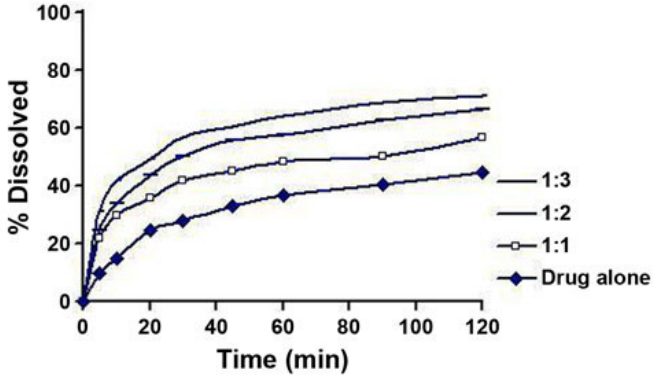

Figure 6. Dissolution profile of nimesulide and its physical mixtures with PVP.

Table 1. Dissolution Efficiency at 10 Minutes (DE_{10}) and Relative Dissolution Rate (RDR) at 20 Minutes of Nimesulide (ND) from ND-PVP Coprecipitates

ND%	ND/PVP wt/wt Ratio	Preparation Technique	$DE_{10\%}$	RDR_{20}
100.0	1:0	—	8.66	—
66.6	2:1	Coppt	21.72	2.03
50.0	1:1	PM	18.33	1.46
50.0	1:1	Coppt	26.74	2.28
33.3	1:2	PM	20.83	1.79
33.3	1:2	Coppt	28.88	2.65
25.0	1:3	PM	26.65	2.02
25.0	1:3	Coppt	48.19	3.67
16.6	1:5	Coppt	50.41	3.78

PVP, polyvinylpyrrolidone; Coppt, coprecipitate; PM, physical mixture.

coprecipitation are considered the principal factors responsible for the enhanced dissolution behavior of the drug.[24] Interestingly, amorphous dispersions prepared with drug: PVP K-30 weight ratio of 1:3, and 1:5 allowed a 5.55- and 5.82-fold increase in dissolution efficiency compared with the pure drug, respectively. Amorphous drug would be expected to dissolve faster than crystalline material because of its high energy state. The effectiveness of the carrier was directly related to its amorphizing power toward the drug. This is shown from the values of DE_{10} and RDR_{20} of the drug from dispersed mixtures, which proportionally increased until the drug:PVP weight ratio reached 1:3. Then, the increase in the proportion of PVP did not affect drug release significantly. For instance, the decrease in the proportion of ND from 1:2 to 1:3 allowed 1.67- and 1.47- fold increases in the values of DE_{10} and RDR_{20}, respectively. On the other hand, when ratio of ND decreased from 1:3 to 1:5, the dissolution parameters did not significantly change (1.04- and 1.01 fold, respectively); whereas, the drug:PVP weight ratio of 1:5 was expected to give a higher dissolution rate than that of the 1:3 dispersed mixture because of higher dispersability and higher solubilizing efficiency. These enhancing effects could be suppressed by pronounced increase in the viscosity of the diffusion layer due to higher PVP concentration.

Characterization of ND-Tris Systems

A phase diagram of ND-Tris coprecipitated mixtures is presented in Figure 7. The melting points determined from the capillary tube method were used to construct the phase diagram. It revealed that the ND-Tris system is a simple eutectic mixture and the eutectic composition is 30% ND to 70% Tris at ~129°C. Melting point analysis showed a constant melting point (solidus point) of eutectic peak at 129 to 130°C at all compositions. The liquidus point, defined as the temperature above which no more crystals were visible,[25] increased as the proportion of drug increased. The liquidus cusp met the solidus line at ~30% ND to 70% Tris composition. Furthermore, the 2 components formed a completely miscible melt. This point is known as the eutectic point and represents the lowest temperature (~129°C) at which equilibrium between the liquid and solid binary mixes may exist. On further cooling, the system solidifies to form a eutectic mixture. It is worthy to note that both pure Tris and treated Tris (coprecipitated alone from ethanol 95%) showed a start of melting at 142°C, suggesting a solid-solid transition and an end of melting at 171°C, the melting point of Tris.[11] From Figure 7, the end of melting of 10% ND to 90% Tris is 137°C. These findings might suggest that ND had a stabilizing effect on Tris-solid transition peak at 142°C. DSC thermogram of the drug alone showed an endothermic peak at 150°C, corresponding to the melting point of ND, Figure 8. Also, DSC curve of pure Tris demonstrated two endothermic peaks. The former is showed at 142°C, corresponding to solid-solid transition (metastable polymorph),[11] and the other at 173°C, very close to reported melting point of Tris 168 to 172°C.[26] DSC curves of 70% ND to 30% Tris PM and Coppt mixtures, ~1:1 molar ratio, revealed 2 endothermic peaks; a new peak of higher intensity at 132°C corresponding to eutectic peak, suggesting solid state complexation, while the second peak at 142°C represents the end of melting, indicating presence of residual ND crystallites. These results support the idea that the heat supplies during DSC scan might be responsible for breaking the weakly formed ND-Tris 1:1 molar complex, as previously mentioned in another report.[16] Similarly, thermograms of 50% ND in Tris PM and Coppt revealed 2 endothermic peaks; a new peak at 130°C corresponding to eutectic peak while the second peak of relatively higher intensity at 145°C represents the end of melting, suggesting presence of much separated crystallites of ND. A thermogram of 30% ND to 70% Tris Coppt showed a single eutectic peak at 131°C.

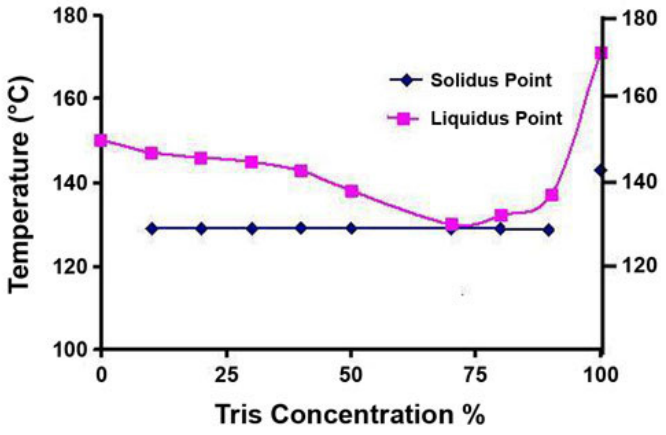

Figure 7. Phase diagram of coprecipitated mixtures of nimesulide and Tris; liquidus point, solidus point.

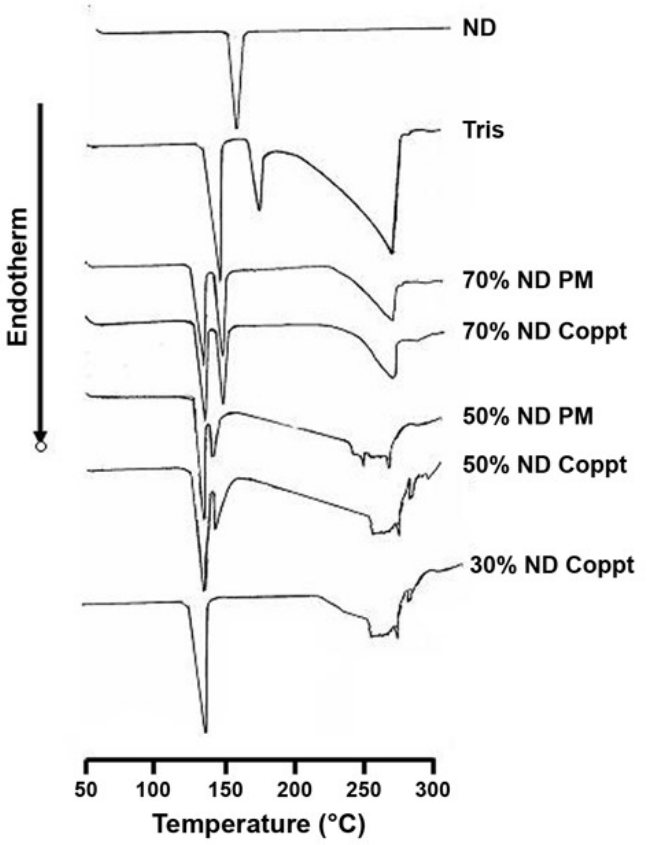

Figure 8. DSC curves of nimesulide and various binary systems with Tris.

Figure 9 represents the FT-IR spectra of ND, Tris, ND-Tris PM containing 50% wt/wt ND, its Coppt, ND-Tris PM containing 30% wt/wt ND, and its Coppt. FT-IR spectroscopy was employed to study the interaction between the acidic hydrogen (N-H) of sulfonanilide group of ND[12] and the basic amino group of Tris.[1] And this region of interest might show the possibility of true salt formation between an acidic drug and Tris, as mentioned in many reports.[3,4,8,11] The IR spectrum of the drug shows the characteristic bands of ND which occur at 1593 cm^{-1} (aromatic rings), 1153 cm^{-1} (SO_2 antisymmetric stretch), 1342 cm^{-1} and 1520 cm^{-1} (aryl nitro group stretching), and 3288 cm^{-1} (NH-stretch).[17] The IR spectrum of Tris shows the characteristic band of Tris that occurs at 1580 cm^{-1} due to the NH_2 (N-H bending vibration of NH_2).[11] All the above characteristic peaks appear in the spectra of all binary systems at same wave number indicating no modification or interaction between the drug and the carrier. In other words, these results suggested exclusion of true salt formation between ND and Tris.

The results of dissolution studies are presented in Figures 10 and 11, and summarized in Table 2, in terms of dissolution efficiency after 10 minutes (DE_{10}), and relative dissolution rate at 20 minutes (RDR_{20}). As can be seen, Tris was effective in enhancing the drug dissolution performance, and its efficacy depended on its content in the mixture and he system preparation method, coprecipitation being better than physical mixing. The results in terms of DE_{10}, and RDR_{20} for solid dispersions were markedly greater than those for the drug alone, or corresponding physical mixtures (Table 2). The enhanced drug dissolution performance of ND-Tris Coppt might be attributed to many factors: reduction in the drug particle size by coprecipitation, increased wettability of the drug particles, and in situ increase in pH in the diffusion layer of dissolution media when Tris, in intimate contact with ND particles, dissolved. It is interesting to note that the dissolution rate of ND from physical mixtures was quite higher than that of the drug alone. Such increase in the dissolution rate was thought to be basically due to wetting of particles and instantaneous increase in pH in the diffusion layer of the dissolution medium especially at the initial part

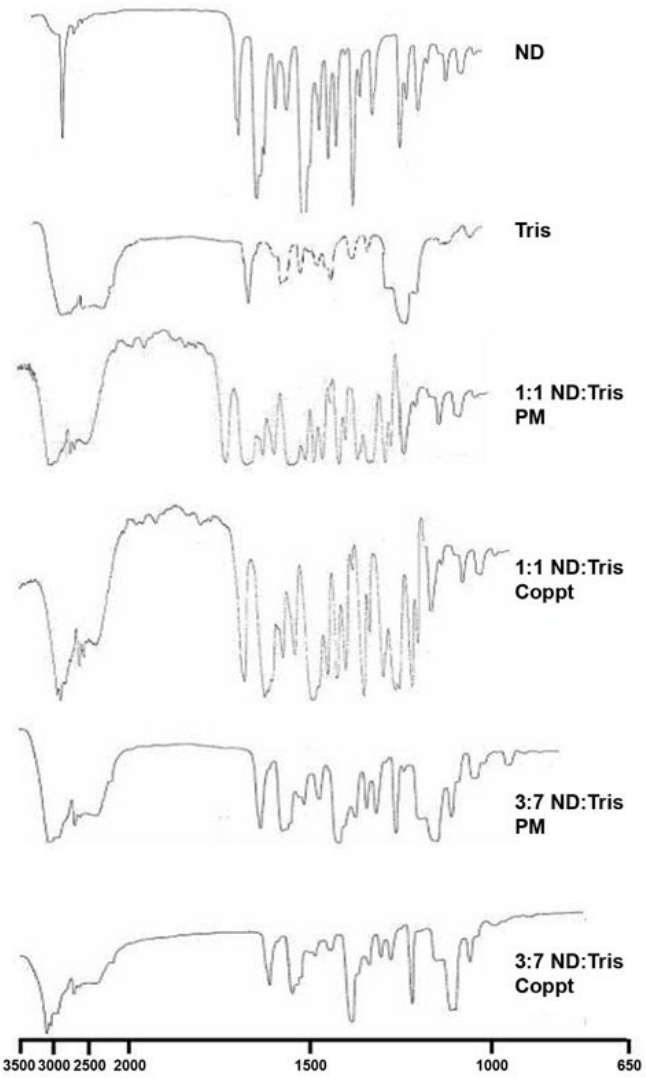

Figure 9. FT-IR spectra of nimesulide and various binary systems with Tris.

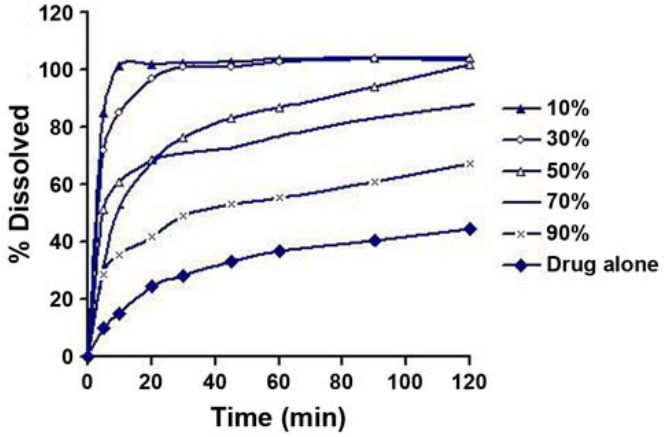

Figure 10. Dissolution profile of nimesulide and its coprecipitates with Tris.

of dissolution but the latter enhancing effect disappeared quickly, Figure 10. Furthermore, ND-Tris coprecipitates showed a higher dissolution rate than that of ND-PVP dispersed mixtures. For instance, the 30% ND wt/wt coprecipitate product in Tris allowed a 6.6-fold increase in dissolution efficiency, compared with a 5.55-fold increase in dissolution efficiency from 25% ND wt/wt coprecipitate in PVP. However, even though amorphous drug would be expected to dissolve faster than in crystalline material, due to its "high energy state," the effectiveness of the carrier was not directly related to its amorphizing power toward the drug. In fact, PVP was always less effective than Tris in promoting ND dissolution properties in spite of its better amorphizing properties, as revealed by solid state analyses. Moreover, the higher dissolution efficacy of Tris can be attributed to initial better wettability of ND-Tris systems, in situ increase in pH of the diffusion layer, and a higher specific solubilizing effect of Tris, due to formation of soluble drug-carrier complex. The presence of relatively stronger electrostatic attractions favoring and stabilizing complexation can be supposed, due to the anionic nature of the drug and the strong positive charge of this carrier in the diffusion layer.

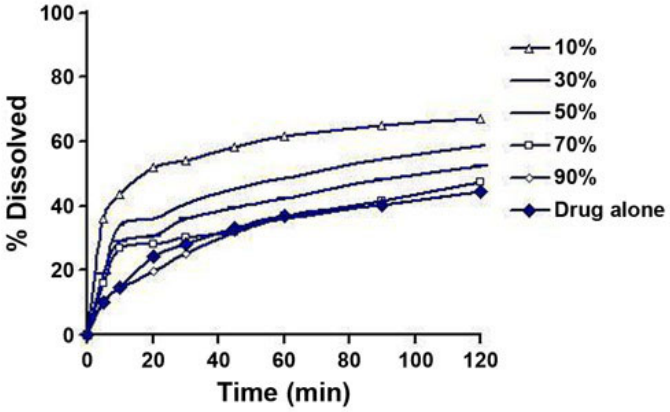

Figure 11. Dissolution profile of nimesulide and its physical mixtures with Tris.

Table 2. Dissolution Efficiency at 10 Minutes (DE_{10}), and Relative Dissolution Rate (RDR) at 20 Minutes of Nimesulide (ND) from ND-Tris Coprecipitates

ND%	ND/Tris wt/wt Ratio	Preparation Technique	$DE_{10\%}$	RDR_{20}
100	1:0	—	8.66	—
90	9:1	Coppt.	23.11	1.71
90	9:1	PM	8.66	0.81
70	7:3	Coppt.	28.77	2.76
70	7:3	PM	14.60	1.14
50	1:1	Coppt.	40.96	2.80
50	1:1	PM	16.64	1.25
30	7:3	Coppt.	57.15	3.84
30	7:3	PM	18.03	1.48
10	1:9	Coppt.	67.67	4.16
10	1:9	PM	18.52	2.11

Tris, tromethamine.

In vivo experiments

The amorphous dispersed mixture of 1:3 wt/wt ND and PVP K-30, and the coprecipitate containing 30% wt/wt Tris were selected for in vivo experiments in mice. The results of writhing test are presented in Table 3. The results demonstrated that all carriers markedly potentiated the analgesic effect of ND. In fact, the dose of ND, when administered alone, was statistically ineffective ($P > .1$, unpaired *t*-test) in reducing the number of writhes, as compared with the control group. These results were in agreement with the findings of Adhage and Vavia[21] when a dose of ND was administered equivalent to 50 mg/kg at a time interval of 20 minutes (time between oral drug administration and injection of the irritant substance intraperitoneally). The respective percent inhibition of the mean number of writhes in comparison to the drug was 50% ($P < .01$, unpaired *t*-test) for 1:3 ND:PVP weight ratio, and 94% ($P < .0001$, unpaired *t*-test) for 3:7 ND:Tris wt/wt ratio. In vivo experiments demonstrated that the analgesic activity of ND was significantly potentiated when the drug was formulated

Table 3. Analgesic Activity Studies of Nimesulide and Its Binary Systems

Carrier	ND:Carrier wt/wt Ratio	Writhes Number	Inhibition, %
—	control	40.8 ± 5.5	—
—	1:0	34.0 ± 4.5	16.6
PVP	1:3	16.8 ± 2.5	58.8
Tris	1:1	2.0 ± 1.5	95.0

in solid dispersions with PVP K-30, and coprecipitated with Tris. Thus, the solubilizing power and amorphizing power were ascribed for faster drug absorption and superior bioavailability of ND. Additionally, the above-mentioned ranking is in accordance with that of the efficiency of carriers in improving the in vitro dissolution rate of the drug indicating that absorption of ND is dissolution dependent. Conclusively, Tris and PVP K-30 appear to be the excipients of choice for the development of a fast-release solid dosage form.

CONCLUSIONS

Tromethamine had higher drug dissolution efficiency than PVP K-30, despite the greater amorphizing power of the latter. Furthermore, the results of in vivo experiments in mice correlated well with the results of in vitro dissolution. Therefore, Tris appears to be an excipient of choice for the development of a fast-release solid dosage form for oral nimesulide administration.

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