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Solubility Enhancement of Nimesulide and Ibuprofen by Solid Dispersion Technique

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An attempt has been made to enhance solubility and dissolution of nimesulide and ibuprofen by solid dispersion techniques and complexation using various hydrophilic excipients. Drug-excipients solid dispersions and complexes of nimesulide were prepared by solvent evaporation method. Solid dispersions of ibuprofen were prepared by fusion, solvent evaporation and fusion-solvent method. Solubility profiles of the drug from the solid dispersions and complexes of nimesulide were studied in buffered pH 6.6, whereas the solubility of drug-excipients dispersions of ibuprofen were evaluated in 0.1 N sodium hydroxide media. Solid dispersions of nimesulide with PEG-6000 enhanced the solubility of nimesulide by more than 1000%. Dispersion of ibuprofen in sorbitol showed maximum enhancement of solubility (up to 75%). Dispersions in combined carriers: PVP k-30-MCC and PVP k-30-PEG-6000 also markedly increased the solubility of ibuprofen. Inclusion complexes of nimesulide in β-cyclodextrin also increased the solubility by 663%. Intrinsic dissolution rate studies of solid dispersions of nimesulide with PEG-6000 and ibuprofen with sorbitol were further studied. The intrinsic dissolution rate constant (K_i) for the dispersions of these drugs were 1.62 (+62%) and 1.80 (+80 %) times that of pure nimesulide and ibuprofen, respectively.

Nimesulide (NIM), a methyl sulfonamide derivative, is a relatively new non-steroidal antiinflammatory and analgesic drug. It is a potent and selective cyclo-oxygenase-2 inhibitor, highly effective in the treatment of various forms of pain and inflammatory conditions with minimum drug related side-effects[1]. Ibuprofen (IBP), a propionic acid derivative, is another commonly used non-steroidal antiinflammatory and analgesic drug used in the treatment of postoperative pain, rheumatoid arthritis and other musculo-skeletal and joint disorders (sprains and strains)[2]. Although they are completely absorbed upon oral administration, their peak plasma concentration is reached in 1.2-3.2 h after oral ingestion[3,4], the reason for delay being slow rate of absorption due to poor aqueous solubility and low dissolution rate[5,6]. Thus, these two factors act as the rate determining step or the barrier to rapid onset of action upon oral ingestion of NIM and IBP. In this study, an attempt was made to enhance the solubility of these drugs and thus the dissolution rate by making solid dispersions and complexes using various pharmaceutical excipients and to compare their effectiveness. Different techniques were used for preparing solid dispersions using different proportions of the excipients.

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Solid dispersion technique, which reduces the drug particle size and changes the micro-environment of the drug particle, increases the rate of dissolution and absorption and thus changes the biopharmaceutical properties of poorly water-soluble drugs, was developed and reported by Sekiguchi and Obi[7]. This technique has since been used to increase the solubility and improve the dissolution of many poorly water-soluble drugs such as, nimesulide[8,9], griseofulvin[10], and paracetamol[11]. IBP-β-cyclodextrin complexes have been studied[12] in an attempt to increase the solubility and dissolution rate and thus the oral bioavailability of the drug.

MATERIALS AND METHODS

NIM and IBP were obtained as gift samples from Dr. Reddy's Laboratories, Hyderabad and E. Merck, Raigad,

respectively, β-Cyclodextrin (β-CD) was obtained from Sigma, USA. Microcrystalline cellulose (MCC), polyvinylpyrrolidone k-30 (PVP), polyethylene glycols (PEG-4000 and PEG-6000), sucrose, mannitol, dextrose, lactose, sorbitol, DL-alanine (DL-ala) and L-alanine (L-ala) used were of pharmaceutical grade. All other chemicals used were of analytical grade.

Preparation of solid dispersion by solvent evaporation method:

The drug and the excipients in different proportions were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40-45° with continuous stirring to obtain dry granules. This technique was employed to prepare dispersions of NIM with PVP (1:1.5), PEG-4000 (1:1.5), PEG-6000 (1:1, 1:1.5, 1:2 and 1:3) using 60% methanol, DL-ala (1:1 and 1:2) and L-ala (1:1 and 1:2) both using 80% methanol. Solid dispersions of NIM with combination of PEG-4000 and PEG-6000 were prepared in the ratios 1:1:1, 1:1.5:1.5, 1:1:2,1:2:1 and 1:2:2. Compositions of solid dispersions of NIM prepared are presented in Table 1. This process was also employed to pre-

TABLE 1: PERCENTAGE INCREASE IN THE SOLUBILITY OF NIMESULIDE IN VARIOUS SOLID DISPERSIONS.

Solid dispersions (drug:carrier)	Nature of the product	Solubility[a] (μg/ml)	% increase in solubility[a]
NIM (Pure drug)	Yellowish white crystalline powder	11.3±0.4	-
PHYSICAL MIXTURE OF NIM WITH EXCIPIENTS (1:1)			
NIM+PVP	Yellowish white powder	11.4±0.3	ϕ
NIM+PEG 4000	Yellowish white powder	12.0±0.2	ϕ
NIM+PEG 6000	Yellowish white powder	12.2±0.4	ϕ
NIM: β-CD	Yellowish white powder	12.5±0.5	ϕ
NIM: DL-ala	Yellowish white powder	12.8±0.9	ϕ
DISPERSIONS BY SOLVENT EVAPORATION METHOD			
NIM:PVP (1:1.5)	Free flowing powder	59.8±4.8	430±42
NIM:PEG 4000 (1:1.5)	Free flowing powder	76.8±2.3	581±21
NIM:PEG 6000 (1:1)	Yellowish white powder	37.0±2.1	229±18
NIM:PEG 6000 (1:1.5)	Yellowish white powder	124.7±0.5	1007±04
NIM:PEG 6000(1:2)	Yellowish white powder	50.0±6.8	344±60
NIM:PEG 6000 (1:3)	Yellowish white powder	48.0±0.2	326±02
NIM:PEG 4000:PEG 6000 (1:1:1)	Yellowish white powder	39.8±3.5	254±31
NIM:PEG 4000:PEG 6000 (1:1.5:1	Yellowish white powder	31.3±2.7	178±24
NIM:PEG 4000:PEG 6000 (1:1:2)	Yellowish white powder	45.0±5.7	299±51
NIM:PEG 4000:PEG 6000 (1:2:1)	Yellowish white powder	26.6±1.3	136±12
NIM:PEG 4000:PEG 6000 (1:2:2)	Yellowish white powder	33.8±2.7	200±24
NIM:DL-ala (1:1)	Yellowish white crystalline powder	34.2±1.2	204±11
NIM:DL-ala (1:2)	Yellowish white crystalline powder	67.6±1.7	500±15
NIM:L-ala (1:1)	Yellowish white crystalline powder	51.8±1.3	359±11
NIM:L-ala (1:2)	Yellowish white crystalline powder	108.5±1.6	863±13
COMPLEXES WITH β-CD			
NIM:β-CD (1:1)	Yellowish granules	65.9±1.9	485±17
NIM:β-CD (2:1)	Yellowish granules	86.0±1.6	663±14
NIM:β-CD (3:1)	Yellowish granules	63.2±0.7	461±15

[a] All values are average of triplicate samples±standard deviation in sodium phosphate buffer, pH 6.6, ϕ No increase in solubility.

pare solid dispersions of IBP:PVP:MCC in the ratios 1:1:2 and 1:1:3. Dispersions of IBP with sucrose, mannitol, dextrose, lactose and sorbitol were prepared by similar method using methanol. Compositions of different dispersions of IBP prepared by this method are listed in Table 2.

Preparation of solid dispersion by fusion method:

Dispersions of IBP with PEG-6000 were only prepared by this method. Accurately weighed amount of PEG-6000 was melted in a porcelain dish at 80-85° and to this, calculated amount of IBP was added with thorough mixing for 1-2 min followed by quick cooling. Dispersions of IBP and PEG-6000 in the ratios 1:2,1:3,1:4 were prepared by this method (Table 2).

Preparation of solid dispersion by fusion-solvent method:

This method was employed only for making dispersions of IBP with PVP and PEG-6000 combined carrier systems. Calculated amount of drug and PVP were dissolved in minimum amount of methanol. This solvent mixture was added to melted PEG-6000 and stirred for 1-2 min. The solvent was then completely evaporated at 80-85° followed by cooling to obtain dry granules, the compositions of which are listed in Table 2.

Preparation of complexes of nimesulide with β-cyclodextrin:

Inclusion complexes of NIM with β-CD (Table 1) in the ratios 1:1, 2:1, 3:1 and 3.68:1 were prepared using 60% methanol by solvent evaporation technique. NIM and β-CD taken in different proportions were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40-45° with continuous stirring to obtain dry granules.

The products obtained by each of the above four methods were dried in vacuum desiccator for 24 h. The dry granules obtained were passed through sieve no. 80 and dried further at room temperature (25°) for 24 h. The dispersions/complexes were then stored in airtight containers.

Analysis of nimesulide and ibuprofen:

Analyses were carried out by UV spectrophotometric method [UV/Vis spectrophotometer: Jasco, model-7800]. For the estimation of NIM, method previously reported[13] by our group using 50% v/v acetonitrile, was employed. By this method NIM was estimated at 300 nm in the concentration range of 10-50 μg/ml. IBP was analysed at 264 nm in the concentration range of 100-400 μg/ml in 0.1 N NaOH.

Solubility determination:

The solubility of NIM as bulk drug, its physical mixture with the excipients used in the present study and its solid dispersions and β-CD complexes was determined in pH 6.6 sodium phosphate buffer (0.1 M $NaH_2PO_4.H_2O$-68.5 parts and 0.1 M $Na_2HPO_4.H_2O$-31.5 parts). Ten milliliters of the buffer was taken in a 25 ml stoppered conical flask. The samples, equivalent to 1.0 g NIM, were dispersed in the media and shaken for 24 h at room temperature (25°) on a platform shaker. After 24 h, samples were filtered and aliquots were suitably diluted for estimation. The solubility values for NIM in pure form, its physical mixture with excipients and dispersions are presented in Table 1. In case of IBP, the solubility from bulk drug, its physical mixture with the excipients and from its solid dispersions, the same procedure was followed but 0.1 N NaOH was used instead of phosphate buffer of pH 6.6. Table 2 shows the solubility values of IBP in pure form, its physical mixture with excipients and its dispersions.

IR analysis:

IR spectra of pure drug, their solid dispersions, β-CD complexes and physical mixtures with selected excipients were obtained using KBr pellet or mull method. The excipients selected were those that gave very high solubility enhancement. The IR spectra obtained were studied for possible drug-excipient interactions in solid dispersions and in complexes.

Intrinsic dissolution rate determination:

Intrinsic dissolution study was carried out for solid dispersions having good solubility enhancement. Pellets of (1.25 cm diameter) of pure drug and drug-excipient dispersion of NIM:PEG-6000 (1:1.5) and IBP:sorbitol (1:2) were prepared (containing 2 g of drug per pellet) on IR pelletiser separately by applying 10 ton/sq.cm of pressure for 5 min. Pellets were then mounted on lower side of basket shaft of the dissolution test apparatus (USP type I) with molten mixture of white bees wax and hard paraffin wax in such a way that the dissolution of the drug (IBP and NIM) took place from the open flat surface only. 500 ml of 0.1 N NaOH and phosphate buffer of pH 6.6, maintained at 37±0.5° was used as the dissolution media for IBP and NIM respectively. The speed of the shaft was fixed at 50 rpm. Samples were withdrawn at predetermined time intervals and analyzed by UV spectrophotometric method mentioned earlier after suitable dilution, if required. The plot between amount dissoluted per unit sur-

face area vs. time and the respective intrinsic dissolution rate constants (g/sq.cm/h) for NIM and IBP, in pure form and their solid dispersions, are given in fig. 1.

RESULTS AND DISCUSSIONS

In this study solid dispersions prepared using various hydrophilic carriers enhanced the solubility of the nimesulide and ibuprofen to varying degree. Physical mixture of these drugs with the same carriers, in the same proportions did not show any solubility enhancement (Table 1 and 2). The water solubility of NIM was enhanced by solid dispersion technique using PEG 4000, PEG 6000 and PVP. The solu-

TABLE 2: PERCENTAGE INCREASE IN THE SOLUBILITY OF IBUPROFEN IN VARIOUS SOLID DISPERSIONS.

Solid dispersions (drug:carrier)	Nature of the product	Solubility[a] (mg/ml)	% increase in solubility[a]
IBP(Pure drug)	White crystalline powder	20.5±0.5	-
PHYSICAL MIXTURE OF IBP WITH EXCIPIENTS (1:1)			
IBP+PEG 6000	White powder	20.7±0.3	ϕ
IBP+MCC	White crystalline powder	20.6±0.2	ϕ
IBP+PVP	White powder	21.0±0.7	ϕ
IBP+Sucrose	White crystalline powder	20.9±0.9	ϕ
IBP+Mannitol	White crystalline powder	20.6±0.5	ϕ
IBP+ Dextrose	White crystalline powder	20.8±0.9	ϕ
IBP+Lactose	White crystalline powder	20.6±0.4	ϕ
IBP+Sorbitol	White crystalline powder	21.6±0.8	ϕ
DISPERSIONS BY FUSION METHOD			
IBP:PEG-6000 (1:2)	White sticky granules	20.9±0.3	2.0±1.5
IBP:PEG-6000 (1:3)	White sticky granules	22.9±0.2	12.0±0.9
DISPERSIONS BY SOLVENT EVAPORATION METHOD			
IBP:Sucrose (1:2)	Free flowing powder	20.2±0.3	12.0±0.9
IBP:Sucrose (1:3)	Free flowing powder	19.9±0.3	ϕ
IBP:Sucrose (1:4)	Free flowing powder	19.8±0.5	ϕ
IBP:Mannitol (1:2)	White powder	22.6±0.2	10.0±0.7
IBP:Mannitol (1:3)	White powder	21.6±0.2	5.0±1.0
IBP:Mannitol (1:4)	White powder	21.8±0.2	6.0±1.0
IBP:Dextrose (1:2)	White powder	23.0±0.3	12.0±1.4
IBP:Dextrose (1:3)	White powder	22.6±0.2	10.0±0.8
IBP:Lactose (1:2)	White powder	25.2±0.1	23.0±0.4
IBP:Lactose (1:3)	White powder	24.3±0.1	18.0±0.5
IBP:Sorbitol (1:2)	Free flowing powder	35.9±0.2	75.0±0.7
IBP:Sorbitol (1:3)	Free flowing powder	34.1±0.2	66.0±0.7
IBP:PVP:MCC(1:1:2)	Free flowing granules	24.3±0.1	19.0±0.6
IBP:PVP:MCC(1:1:3)	Free flowing granules	23.5±0.2	15.0±0.9
DISPERSIONS BY FUSION-SOLVENT METHOD			
IBP:PVP:PEG-6000 (1:0.5:2)	Free flowing granules	24.0±0.4	17.0±2.0
IBP:PVP:PEG-6000 (1:1: 2)	Free flowing granules	24.3±0.3	18.0±1.5

[a] All values are average of triplicate samples ± standard deviation in 0.1 N NaOH, ϕ No increase in solubility.

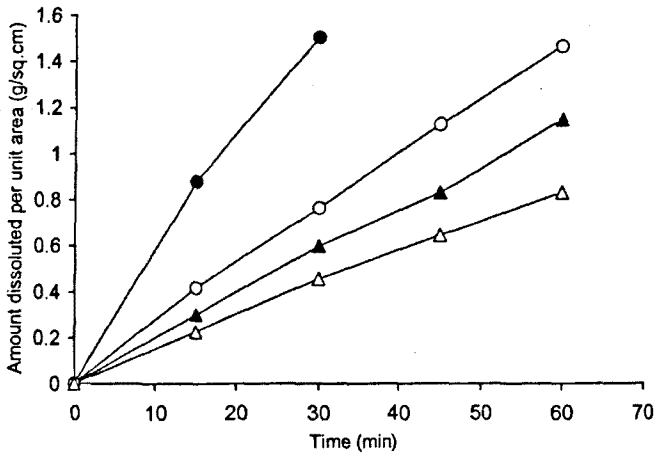

Fig. 1: Instrinsic dissolution profiles of nimesulide, ibuprofen and their solid despersions.

Intrinsic dissolution profile of pure nimesulide (△), pure ibuprofen (o) and their solid dispersions NIM:PEG 6000 (1:1.5) (▲) and IBP:sorbitol (1:2) (●).

bility of drug in solid dispersion using PVP (1:1.5), PEG 4000 (1:1.5) and PEG 6000 (1:1.5) are enhanced by 430, 581 and 1007% respectively. PEG 6000 gave maximum enhancement of solubility. When these polymers were used in combination, solubility was enhanced but to a lesser degree as can be seen from Table 1. NIM dispersions with alanine increased the solubility by 500% and 863% for NIM:DL-ala (1:2) and NIM-L-ala (1:2) respectively when 80% methanol was used as evaporating solvent. Dispersions in the same ratios prepared in 100% methanol had lesser effect on solubility enhancement (data not presented). Among the dispersions with different ratios of NIM and PEG 6000, the dispersion in the ratio 1:1.5 enhanced the solubility of NIM by 11 times. There was an increase in the solubility as the proportion of PEG 6000 increased from 1:1 to 1:1.5, but solubility decreased as the proportion increased from 1.5 to 2 and 3. This may be due to the presence of excess amount of PEG 6000 as free polymer and as this has higher water solubility, the drug solubility was lowered.

Solid dispersions of IBP with various pharmaceutical excipients namely, mannitol (1:2), PEG-6000 (1:3), dextrose (1:2), PVP-PEG-6000 (1:1:2), PVP-MCC (1:1:2), lactose (1:2) and sorbitol (1:2) resulted in increased solubility of IBP by 10.0, 11.8, 12.3, 18.4, 18.5, 22.9 and 74.9%, respectively. Whereas sucrose did not show any effect on the solubility of IBP, PEG-6000 produced higher increase in solubility in combined carrier systems than when used alone. Increase in the proportion of PVP in combinations with MCC and PEG-6000 had negligible effect on enhancement of solubility.

PEGs are crystalline water-soluble polymers with two parallel helices in a unit cell. Significant amount of drug can be trapped in the helical interstitial space when PEG-drug melts are solidified. It thus acts to reduce the size of the drug particle by decreasing their aggregation and agglomeration and thereby contributing to the solubility of the drug. On the other hand PVP is a linear chain polymer, which enhances the solubility by retarding the crystallization of poorly water-soluble drugs. It may also contribute to solubility enhancement by improving the wetting of the drug particles due to its surfactant property.

Amongst various sugars studied, sucrose had no influence on IBP solubility, whereas dispersions in mannitol and dextrose showed enhanced solubility (about 10-12% increase). Solid dispersions of lactose and sorbitol markedly increased the solubility of IBP by approximately 23% and 75% respectively. Also it was observed that increase in the proportions of mannitol, dextrose, lactose and sorbitol decreased the solubility of IBP.

Sugars like, lactose and sorbitol possibly increased the solubility of IBP due to their hydrophilicity and greater tendency to form hydrogen bonds in aqueous media. A poorly water-soluble drug when dispersed in the crystal structure of these sugar solubilises at a faster rate due to microenvironment solubilising effect of sugar carriers. These sugars can also increase the viscosity of the medium and thus preventing the agglomeration of the drug particles.

Complexation of NIM with β-CD also enhanced the solubility and the optimum drug to polymer molar ratio was found to be 2:1 with approximately 7 times (663%) increase in solubility.

IR spectra of pure drugs, solid dispersions and physical mixtures of NIM with PEG-6000, IBP with sorbitol indicated no interaction or complexation between the drug and the excipient, as spectra remained unchanged. β-CD-NIM complexes showed an intense broad peak in the region 3364-3365 cm^{-1} indicating possible hydrogen bonding between NIM and β-CD. These observations also indicated that drugs were not degraded in the presence of excipients and solid dispersions or in complexes.

Further studies on comparative intrinsic dissolution rate showed that NIM-PEG 6000 dispersion in the ratio 1:1.5 (K_i=1.33 g/sq.cm/h) the intrinsic dissolution rate constant was 1.62 times (an increase by 62%) when compared with

pure NIM (K_i=0.82 g/sq.cm/h) in phosphate buffer pH 6.6 (fig. 1). Similarly for pure IBP and IBP: sorbitol dispersion (1:2) in 0.1 N NaOH showed that the intrinsic dissolution rate constant in case of IBP: sorbitol dispersion (K_i=2.52 g/sq.cm/h) was 1.80 times than the pure IBP (K_i=1.40 g/sq.cm/h) (fig. 1), an increase by 80%, thus confirming the microenvironment solubilising effect of sorbitol.

The simplicity of method and ease of scale-up for bulk manufacturing renders NIM:PEG 6000 and IBP:sorbitol solid dispersion an economically viable preposition for enhancing the therapeutic efficacy of IBP and NIM from their solid oral dosage forms. As it will increase the dissolution rate and the rate of absorption of IBP and NIM from their formulation (tablet or capsules) using solid dispersion of drugs and thus the problems associated with the delay in onset of action and attaining peak plasma concentration can be overcome. Also the effective therapeutic dose of pure drug in the formulation can be decreased accordingly.

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