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NAPROXEN: A CHALLENGING APPROACH FOR SOLIDLIPID NANOPARTICLES, DOSAGE FORM, DESIGN, DEVELOPMENT AND EVALUATION OF BCS-II DRUGS

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ABSTRACT

Nanoparticle is the simplest form of structures with sizes in the nm range. In principle any collection of atoms bonded together with a structural radius of ~< 100 nm can be considered a nanoparticle. In the present time nanoparticle are widely used in many dosage forms due to their good solubility, less size and better penetrability. Nanoparticle can be prepared by using the various methods such as Emulsion-Solvent Evaporation Method, Double Emulsion and Evaporation Method, Salting out Method, Emulsion Diffusion Method, Solvent Displacement Precipitation method, Polymerization method and Conservation or ionic gelation method. Applications of nanoparticle in micro wiring are cell specific, microalization, vaccine delivery and gene delivery. Nanoparticles are used in the field of medicines also for the treatment of cancer or for the orthopaedic implants. Nanoparticles show high solubility and fast penetration that's why they are used in almost formulation now a day.

KEYWORDS: Gold Nanoparticle (AuNPs), Magnetic Resonance Imaging (MRI), Polyvinylpyrrolidone (PVP), Blood brain barrier (BBB).

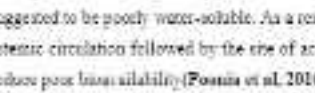
INTRODUCTION

In today's drug development world, combinatorial chemistry, high-throughput screening, and genomics have provided a technologic platform that produces a large number of new chemical entities (NCE) with therapeutic potential each year. The pharmaceutical drug delivery market is also expected to grow from $1048.1 billion in 2015 to $1554.7 billion by 2020, with a compound annual growth rate of 7.5%. Despite a vast number of novel drug

molecules developed, only a few of them are successfully launched in the market(**Poonia et al. 2016**).[2] Because discovering and developing a drug is a time consuming and costly process with a recent estimation of about 13 years and US$800 million, respectively. As well, the lack of efficacy (accounting for ~30% of failures), safety (toxicology and safety accounting for ~30%), low bioavailability and adverse pharmacokinetic profile (accounting for ~40%) were the prime reason for attrition in the clinic. Hence, more drug candidate molecules are withdrawn before reaching clinical evaluation. Also, the newly discovered drugs from the discovery and development processes are not suitable for oral delivery(**Lipinski et al.2001**).[3] Because the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity. Consequently, the poor aqueous solubility of the lipophilic compounds has become an enduring problem in drug discovery as well as the early and late-stage pharmaceutical development process. Also, it was reported that ~40% of currently marketed drugs and up to 70% of compounds currently under development had been suggested to be poorly water-soluble. As a result, an insufficient amount of drug reaches the systemic circulation followed by the rise of action with a lack of pharmacological action and produce poor bioavailability.(**Poonia et al. 2016**).[2]

MATERIAL AND METHODS

Naproxen(M=230.2 g/mol) were purchased from Dhamnec Pharma and Consultants, Mumbai India.Naproxen were used without any further purification.

Drug	Naproxen
Structure	 2-(6-methoxynaphthalen-2-yl)propanoic acid
Groups	Approved, Investigational
Molecular Weight	Average: 230.26
Chemical Formula	$C_{14}H_{14}O_3$
Pharmacology	Naproxen is an established non-selective NSAID and is useful as an analgesic, anti-inflammatory and antipyretic
Solubility	It is lipid-soluble, practically insoluble in water with a low pH (below pH 4), while freely soluble in water at 6 pH and above
XLogP3	3.3
Toxicity	Although the over-the-counter (OTC) availability of naproxen provides convenience to patients, it also increases the

	likelihood of overdose. Thankfully, the extent of overdose is typically mild with adverse effects normally limited to drowsiness, lethargy, epigastric pain, nausea and vomiting.
As with other non-selective NSAIDs, naproxen exerts it's clinical effects by blocking COX-1 and COX-2 enzymes leading to decreased prostaglandin synthesis. Although both enzymes contribute to prostaglandin production, they have unique functional differences.The COX-1 enzymes is constitutively active and can be found in normal tissues such as the stomach lining, while the COX-2 enzyme is inducible and produces prostaglandins that mediate pain, fever and inflammation.The COX-2 enzyme mediates the desired antipyretic, analgesic and anti-inflammatory properties offered by Naproxen, while undesired adverse effects such as gastrointestinal upset and renal toxicities are linked to the COX-1 enzyme	

Preformulation Study

Preparation of naproxen standard solutions: An amount of 1.15 mg of naproxen was accurately weighed and placed in a 10 mL brown-colored volumetric flask. Methanol was added to volume to make the concentration of the stock solution exactly 500 µM. Samples of 100, 200, 500, 1000 and 2000 µL of the stock solution were respectively transferred to 10 mL brown-colored volumetric flasks. To each flask, 500 µL of indomethacin in methanol of 25 µM concentration was added as the internal standard and diluted with methanol to volume. The concentrations of the five standard solutions were 5.0, 10, 25, 50 and 100 µM, respectively. The samples were filtered by 0.45 µm Millipore membranes, and the filtrates were then subjected to HPLC analysis(Re et al,2008).[20]

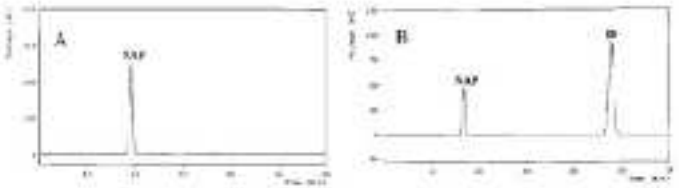


Figure 1.1: HPLC chromatograms of Naproxen (NAP) in methanol: (A) standard solution; (B) NAP with Indomethacin (IN) asthe internal standard.

Evaluation Parameter

Bulk Density

Apparent bulk density (B.D) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the initial volume (V_o) weight of powder (W). The bulk density was calculated using the formula

Bulk Density (B.D) = W / V_o

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed number of taps. The minimum volume (V_f) occupied in the cylinder and the weight of powder (W) was measured. The tapped density was calculated using the formula.

Tapped Density (T.D) = W / V_f

Angle of repose

Angle of repose (a) was determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$a = \tan^{-1}$ (h/r)

Flowability	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-45
Poor	45-55
Very poor	56-65
Very very poor	>66

Methods of Preparation

(1) High energy input methods.

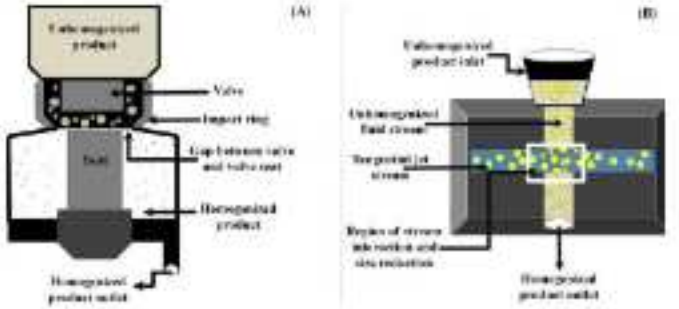
(2) Low energy input methods, and

(3) Miscellaneous methods.

Hot HPH Technique: This is the most widely used method for industrial production of various lipid-based formulations such as microemulsions, liposomes, SLNs, and NLCs. In the case of nanoparticles production, the liquid lipid (used in the case of preparation of parenteral emulsion) is replacedhigh speed stirring to form the preemulsion. The preemulsion thus formed is subjected to ultrasonication, followed by nano-sizing using a piston-gap homogenization principle or a jet-stream homogenization principle to form a hot colloidal emulsion, which is then cooled to room temperature, sub-zero temperatures or refrigerated to cause recrystallization of the lipid phase, thus forming the. The piston-gap homogenizers cause particle size reduction by forcing the macrosuspension/preemulsion through a small gap (of a few microns). The cavitational shear forces and impaction forces act on the particles to cause their size reduction. Whereas in the case of the jet-stream homogenizers, the size

reduction occurs due to impact forces generated by the collision of two high velocity streams. The formed nanoparticles exhibit an average particle size of 50-400 nm(**Humberstone et al, 1997**).[24]

Cold HPH technique: This modified homogenization method is called "high pressure milling of liquid suspension". Mechanism of formation of nanoparticles through cold HPH technique: A lipid melt is obtained by heating solid lipids (in the case of SLNs) or a mixture of solid lipid and liquid lipid (in the case of NLCs) at 5C above the melting point of the solid lipids. A drug lipid premix is obtained on dissolving/dispersing the drug in the previously made lipid melt. This drug lipid premix is rapidly solidified using dry ice or liquid nitrogen to favor drug.



Schematic diagram of (A) piston-gap homogenization principle and (B) a jet-stream

Homogenization principle

Entrapment and stabilization in the lipid matrix. The solidified lipid melt is then subjected to milling/grinding to form microparticles. The obtained microparticles are then allowed to disperse in cold aqueous surfactant solution using high speed stirrer. The dispersion thus obtained is passed through the HPH to reduce the size of microparticles to nanorange for the formation of nanoparticles. The cold HPH method requires harsher homogenization conditions compared to the hot homogenization method as heating is not involved. The hot HPH technique has shown better results, compared to the cold HPH, as far as the monodispersity and particle size uniformity is concerned(**Humberstone et al, 1997**).[24]

High shear homogenization technique

This method is similar in principle to that described by Speiser (1986) for the preparation of lipid nanopellets for oral administration. This method involves the formation of emulsions by high shear mixing of hot lipid phase and hot aqueous surfactant phase at about 500025,000 rpm. at a temperature above the melting point of lipids. The high shear forces generated between rotor and the stator causes breakdown of the emulsion globules(Humberstone et al, 1997).[44]

Electro-spray technique

This is a comparatively newer method for producing nanoparticles. A solution of the lipidding matrix is prepared by dissolving them in aliphatic alcohols. This lipid matrix solution is sprayed through a metallic syringe with a cone-jet nozzle attached to a high voltage power supply. High interfacial tension and electrical forces results in generation of small hemispherical droplets. The droplets loose the solvent while passing through the electrical field due to evaporation, thus forming powder of nanoparticles. These highly charged powdered nanoparticles are collected by a metal foil that acts as a counter electrode. The technique requires optimization of liquid flow rate and the applied voltage according to the properties of the liquid in order to generate the nanoparticles of desired particle size and shape(Benet et al, 2011).[45]

Development of tablets

Naproxen solid lipid nanoparticle (NAP-SLN) tablets were prepared by the wet granulation method. All thecomposition, with the exception of magnesium stearateand talc were thoroughly mixed in a tumbling mixer for 5 min and wetted in a granulating fluid PVP isopropyl alcohol. Accurate quantity of drug and polymers were weighed according to formula shown in Table4.8

The wet mass obtained was passed through sieve #16 and granules were dried at 60°C for 2 hours. The dried granules were passed through sieve #22 and these granules were lubricated with a mixture of magnesium stearate and talc (2:1) and the biopolymer chitosan was added in the mixture. The tablets were prepared using an electrically operated punching machine. Compression was performed after granulationprocess with a single punch press applying a compression force of a 9 KN (preliminary work) or 12 KN (experimental design), equipped with a 8 mm concave punch. For the preliminary work, batches of 10 tablets were prepared. Each batch of experimental design consisted of 10 tablets (drug content in the tablet was 15

mg). Six batches were prepared for each formulation and the compositions of different batches of Naproxen tablets are given in Table below. The compressed tablets were evaluated for average weight & weight variation, thickness, diameter and content uniformity, hardness, friability (Xu et al, 2011).[45]

Composition of tablets

Ingredients	Formulation code (Quantity in mg)								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
NAP-SLN	100	100	100	100	100	100	100	100	100
Chitosan	150	150	150	140	120	120	130	140	140
Pvp	60	56	56	56	60	60	56	56	60
Sodium Bicarbonate	80	80	80	75	72	72	80	80	80
Magnesium Stearate	8	12	8	10	12	12	8	10	12
Talc	6	6	46	6	4	6	6	6	6
SLS Powder	4	6	5	7	6	6	7	6	7

Evaluation of tablets

Hardness

The hardness of a tablet is indication of its strength. It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg and the hardness of about 4 kg is considered to be satisfactory for uncoated tablets. Monsanto hardness tester is used for this purpose. The hardness of 6 tablets was measured and the average hardness was calculated**(Mehnert et al, 2007)**[46]

4.1.1. Friability test

Friability is the loss of weight of tablets in the container, due to removal of fine particles from their surfaces. Friability test is carried out to assess the ability of the tablet to withstand abrasion in packing, handling and transport. Electrolab friability tester was used for finding out the friability of the tablet. A number of tablets (6) were weighed accurately and placed in the chamber of the apparatus. After 100 rotations, the tablets were taken out from the apparatus, re dusted and weighed. The loss in weight indicates the friability of the tablets. A maximum friability of 1% is acceptable for tablets as per Indian Pharmacopoeia (IP). Percentage friability was determined by using the formula given below.

% friability = (W1 - W2 / W1) × 100

Where,

W1 = weight of tablets before test

W2 = weight of tablets after test

Dissolution Testing

The prepared tablets were evaluated for in-vitro drug release studies using with Auto sampler. The dissolution of core tablets is carried out under following conditions. The results obtained are tabulated and used for selection of best formulation. The results were given in Table below for Nateglinide(Lachman et al. 1986).[42]

RESULT AND DISCUSSION

5.1. Drug Identification Test

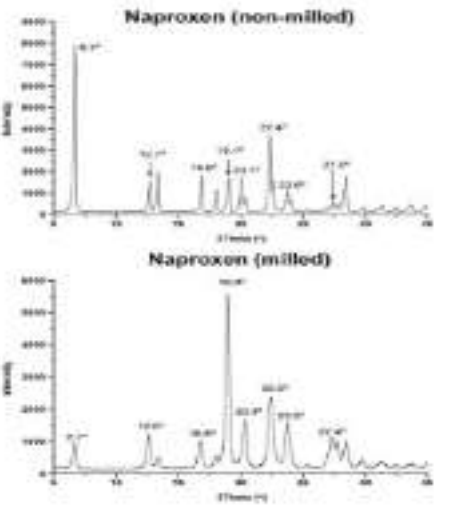
5.1.1. Solid State Characterization

In addition to the co-milled binary mixtures of naproxen and cimetidine, the two single components were milled separately forcomparison. The X-ray diffractogram of cimetidine (Form A) shows shafts after milling, suggesting the formation of amorphous cimetidine. This finding is supported by DSC, revealing a glass transitionfor this phase at 36.1±2.0 °C (Fig. 1and Table 1) Although not directly comparable, a previous study investigatedthe effects of milling metastable cimetidine (Form B) for 10 h using amortar mill. In that study, milling induced a solid-state transition into the stable Form A with a concomitant formation of amorphous material. It is, however, not known whether the amorphization in that study proceeded through the stable (Form A) or metastable (Form B) polymorph. Naproxen presents a different case, as an amorphous phase is not easily formed upon milling. From (Fig. 5.1) it can be seen that naproxen is retained in a crystalline state even aftermilling for 60 minat 4 °C, and the unaltered position of diffractions in the X-raydiffractograms suggests that the same crystal form of naproxen ispresent in the non-milled and milled material. The discrepancybetween diffraction intensities of non-milled and milled material isattributed to preferred orientation effects, while the minor peak shiftsand peak broadening could be due to a slight disordering of thecrystals upon milling. The inability to form an amorphous form ofnaproxen by cold milling was not unexpected(**Zecchi et al, 1984**).[43] Gupta et al foundthat milling naproxen for 48 h at 25 °C did not induce any change inthe crystal lattice. In contrast, amorphous naproxen prepared byquench cooling showed a glass transition at 6.2±0.6 °C (Table 5). Hence, after 60 min of milling, the powder temperature of naproxen(25 °C) was above the Tg, which led to an amorphization. This is incontrast to cimetidine where the powder temperature (25 °C) wasbelow the Tg (36.1±2.0 °C), thus allowing amorphous formation. (Fig. 5.3) shows the XRPD data for co-milled mixtures of naproxen andcimetidine

at 1:2, 1:1, and 2:1 molar ratios. The lack of crystallinepeaks and the detection of a single Tg for each sample (Figs. 12 and 11, respectively), confirm the formation of amorphous material at allthree ratios. The Tgs for the three mixtures vary from 31.5 °C to 40.2 °C.i.e. they are close to the Tg of amorphous cimetidine and, surprisingly, much higher than the Tg of quench-cooled naproxen (Table 5.1).Furthermore, the mixture with an excess of cimetidine (the 1:2 ratio) has the highest Tg (40.2 °C), while the 2:1 mixture, having naproxen asthe excess component, has the lowest Tg (31.5 °C) (Table 5). A similarpatternwas also observed in the binary mixtures of indomethacin andranitidine–HCl prepared by co-milling at various ratios. It wasfound that the newly observed Tg, relative to other binary mixtures,tends to be closer to the Tg of the component presence in excesswithin the mix. The Tgs also showed good correlation between theexperimental and calculated (using Gordon–Taylor equation) values(**Hsu et al, 2006**).[53]

Table: 5.1 Glass transition temperatures of mixtures and single components determined by DSC and calculated values using the Gordon–Taylor equation.

Sample	Tg (°C) – Experimental	Tg (°C) – Calculated
Naproxen (NAP)	6.2±0.6	N/A
Cimetidine (CIM) (milled)	36.1±2.0	N/A
(1:2) NAP-CIM	40.2±1.1	14.0
(1:1) NAP-CIM	34.5±0.3	10.7
(2:1) NAP-CIM	31.5±0.7	8.6



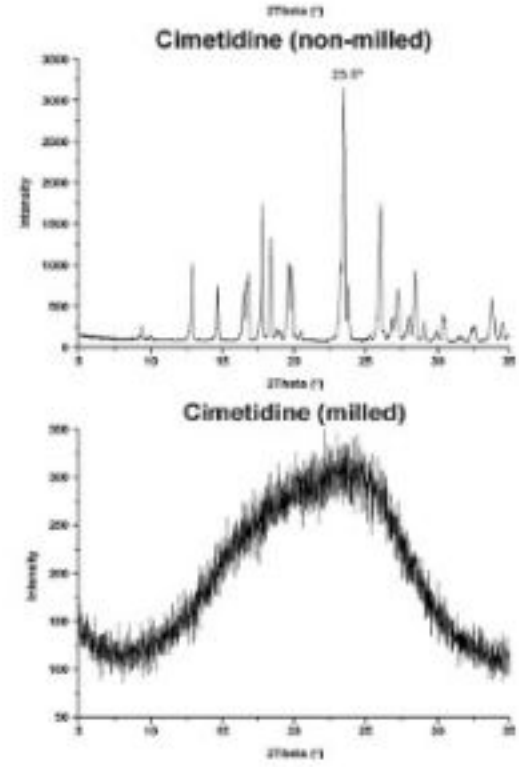
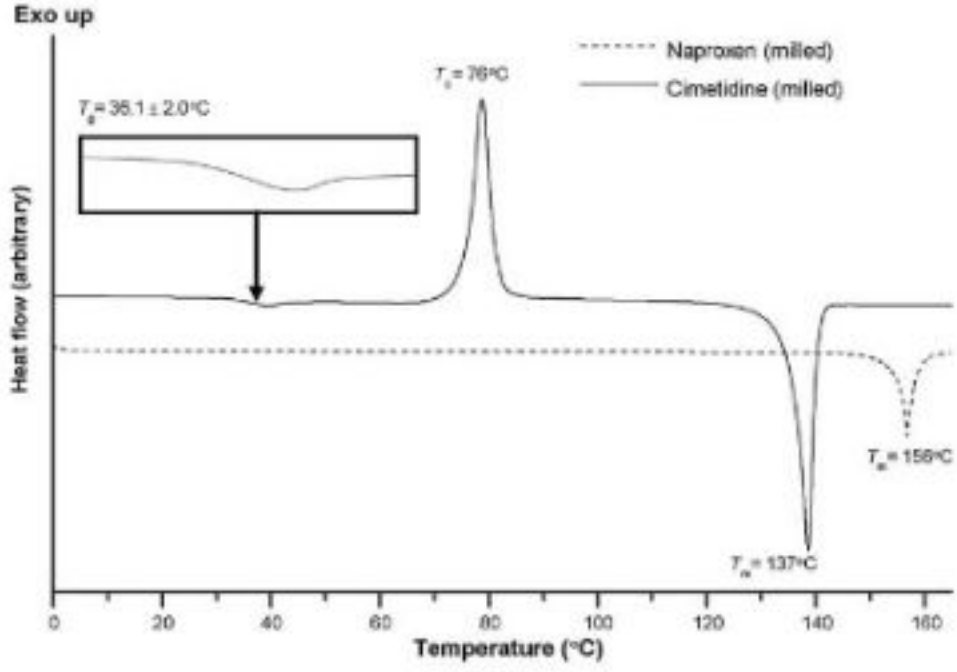


Fig-5.1: X-ray powder diffractograms of naproxen before and after milling for 60 min at 4 °C.



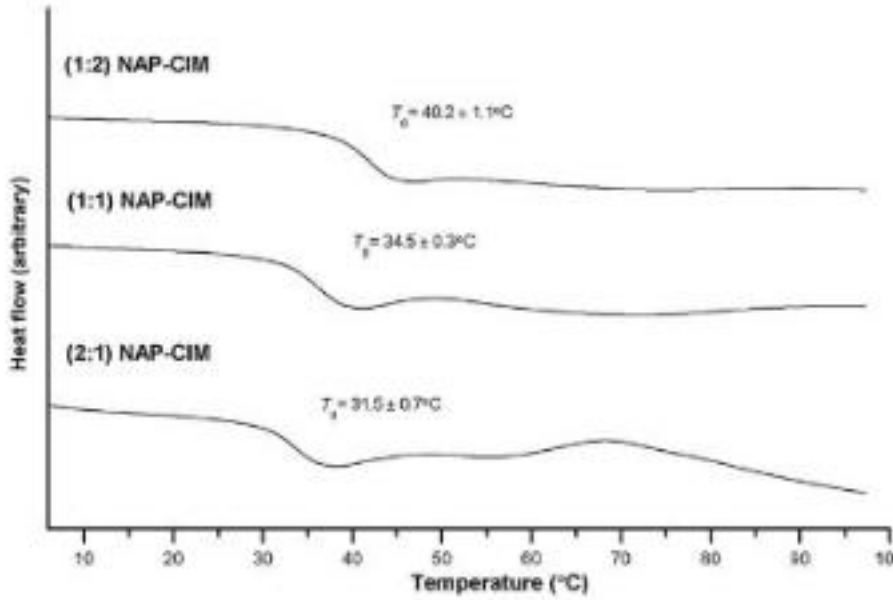
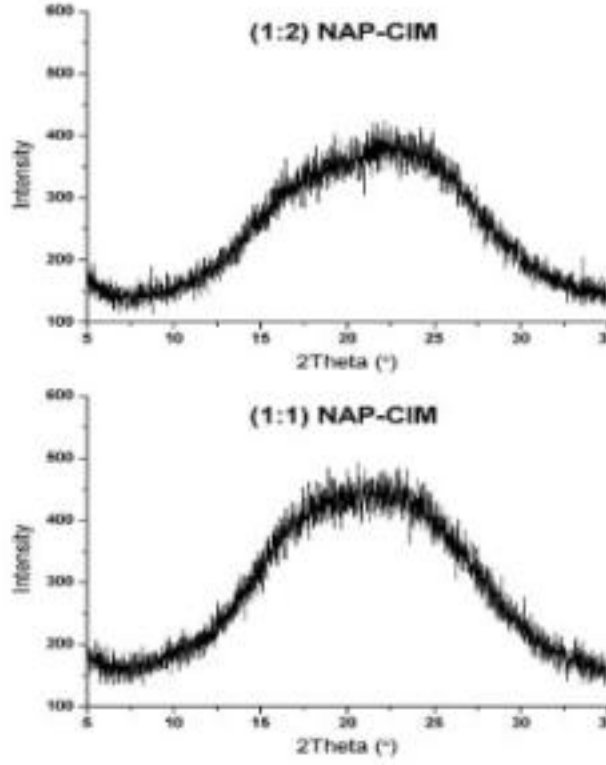


Fig. 5.2: DSC thermograms of milled naproxen and cimetidine and co-milled binary mixtures. The T_g of amorphous cimetidine has been enlarged to improve clarity.



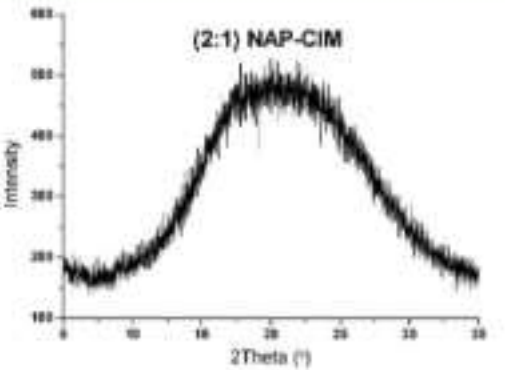


Fig. 5.3: X-ray powder diffractograms of co-milled naproxen–cimetidine (NAP-CIM) binary mixtures at three different ratios.

5.2. Physical stability testing

Results from the physical stability study are shown in (Fig. 5.4). It was found that the 1:1 amorphous mixture is the most physically stablesample after 33 days storage at all three temperatures, as a halopattern could still be observed (Fig5.4; 1:1 naproxen–cimetidine). The2:1 sample, in contrast, is stable at 4 °C, while traces of crystallinenaproxen, the excess component, are found at 25 °C. At 40 °Ccrystallization of naproxen is more pronounced. Surprisingly, although the 1:2 sample has the highest Tg (40.2 °C), traces ofcrystalline cimetidine are detected at all three temperatures(**Helena Amaral et al, 2001**).[48] This kindof discrepancy between experimental Tgs of the amorphous mixturesand their physical stability has also been observed previously by ourgroup in an indomethacin–ranitidine–HCl study. Here, in spite ofnot having the highest Tg, the 1:1 mixture of indomethacin andranitidine–HCl was still found to be the most stable amorphous phase.Combined with the results from this study, these findings indicate thatthe stability of amorphous systems is governed not only by bulk-levelphenomena but also by interactions at the molecular level. In addition,the 1:1 co-milled sample remained amorphous after 186 days ofstorage (approximately 6 months) at all three storage temperatures.X-ray diffractograms for this long-term stability study are provided inSupporting Information(**Hsu et al, 2006**).[31]

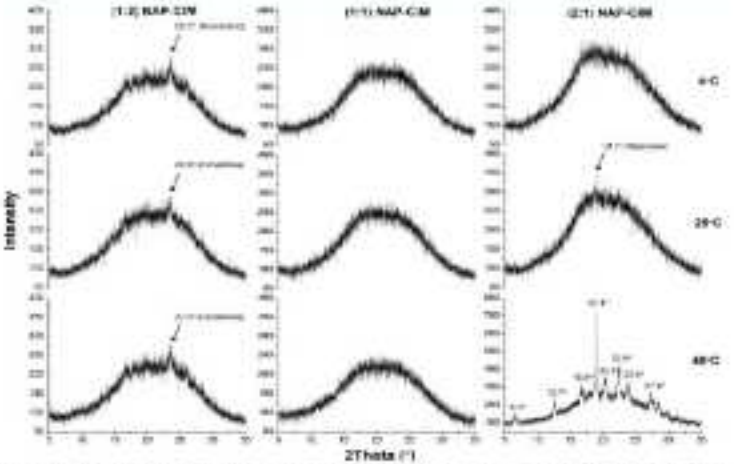


Fig. 5.4: X-ray powder diffractograms of co-milled naproxen–cimetidine (NAP-CIM) samplesstored for 33 days at 4 °C, 25 °C and 40 °C under dry conditions (silica gel). The observed peaks associated with the 2:1 sample at 40 °C are all related to the crystallization ofnaproxen (see Fig. 11).

5.3. Intrinsic dissolution testing

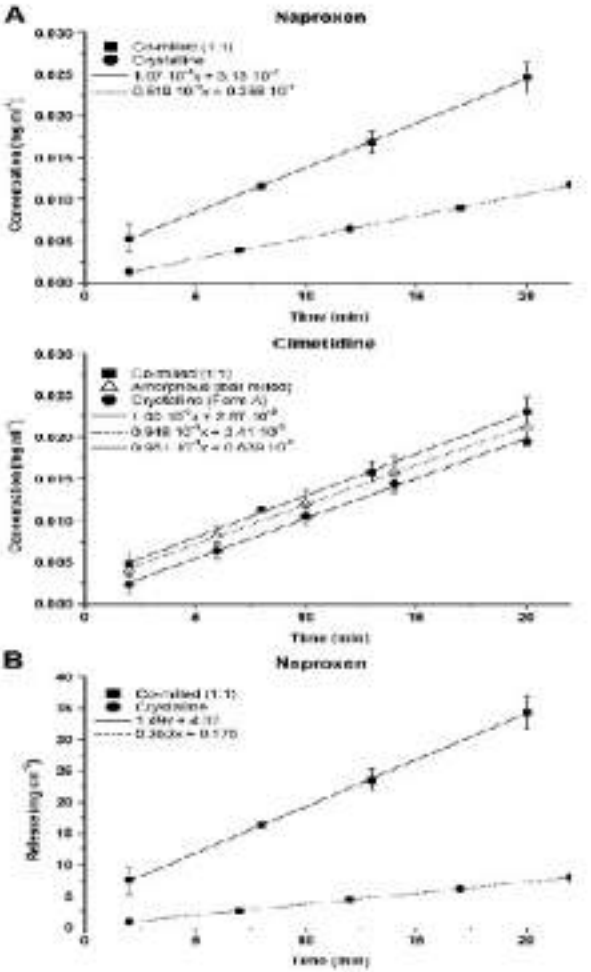
With reference to the stability study, it is obvious that the 1:1 comilledsample carries thehighest formulation potential of all threeratios investigated. This forms the rationale to further explore theamorphous 1:1 binary system by means of intrinsic dissolutiontesting. Shows the concentration-time profiles (mg ml−1) forthe two drugs in the co-milled sample as well as for the pure drugs. Itwas not possible to obtain meaningful dissolution profiles of a 1:1physical mixture of crystalline naproxen and crystalline cimetidine, asthe compact disintegrated within less than 5 min into the dissolutiontesting. This was not the case for the co-milled sample, whichremained intact throughout the entire dissolution experiment.Most notable in fig. is the good linear fit for all five profiles,suggesting that the surface area does not change drastically over thecourse of the dissolution study. The saturation solubilities fornaproxen and cimetidine in phosphate buffer are reported to beapproximately 6mgml−1 (37 °C; pH 7.4)and 19 mg ml−1 (37 °C,pH 7.2), respectively. The dissolution system is thus undersaturatedwith respect to both components, and no precipitation fromsolution would be expected.To calculate release-time profiles (mg cm−2) for the co-milledsamples, an estimate

on the accessible surface area for each drug in the binary compact is needed. The compact contains 400 mg ranitidine corresponding to approximately 191 mg naproxen and 209 mg ranitidine (1:1 molar ratio). Using the theoretical powder densities of 1.265 and 1.398 g cm−3 for naproxen and ranitidine, respectively, the (theoretical) volume of each weighed amount mentioned previously is calculated as 0.151 cm3 for naproxen and 0.149 cm3 for ranitidine. Hence, assuming a monogeneous mixture of the two drugs in the 1:1 co-milled sample, the total surface area of 1.33 cm2 for the binary system is (initially) comprised of 49% naproxen and 51% ranitidine, i.e., 0.644 cm2 and 0.685 cm2, respectively. In contrast, the surface area of the pure sample compacts is 1.33 cm2. Assuming that the surface area remains constant throughout the dissolution study, the release rate profiles (mg cm−2 min−1) may now be calculated as depicted in Fig. 6B. Co-milled naproxen and ranitidine have intrinsic dissolution rates (IDRs) of 0.102 and 0.666 mg cm−2 min−1, respectively (Fig. 6B and Table 4), these numbers are roughly in line with results obtained by Yu et al. For co-milled naproxen there is a significant, approximately four-fold, gain in IDR compared to its pure crystalline counterpart. The enhanced and constant dissolution rate verifies that naproxen in the co-milled sample does not undergo recrystallization. In the case of ranitidine, it was possible to prepare compacts of pure crystalline drug (Form A) as well as pure amorphous material thus to expand the comparison. Surprisingly, there is no significant difference in the IDRs of pure amorphous and crystalline ranitidine (95% confidence level; Table 5.2). XRPD confirmed that the compact of amorphous ranitidine had not crystallized as a result of compression (results not shown). Rather, the explanation can be found in the affinity of the powder for amorphous ranitidine (1.68 mg cm−2) and for crystalline material (0.0072 mg cm−2). The higher affinity for amorphous ranitidine may indicate an initially higher dissolution rate (before 2 min), reflecting the higher solubility of the amorphous material, followed by recrystallization into a less soluble polymorph. Thus, the two profiles would eventually be parallel to each other. A similar phenomenon has been observed for amorphous indomethacin and carbamazepine, where the initial dissolution advantage was lost due to a precipitation in the absence of crystallization during dissolution. Hence, this suggests that pure amorphous ranitidine may not benefit during dissolution in phosphate buffer. Co-milled ranitidine, on the other hand, shows very promising dissolution characteristics. The IDR is improved two-fold over the crystalline material (significant at the 95% confidence level, Table 5.2). This gives further evidence that the solid-state interaction between the two drugs in the amorphous binary system is strong enough to prevent structure/arrangement of naproxen and ranitidine molecules during dissolution. Consequently, enhanced dissolution rate are

observedfor both drugs. As for pure amorphous cimetidine, there is a positiveshift in offset (i.e., at 0 min) for both analytes in the co-milledsample(Manivannan et al, 2010).[56] The observed increase in dissolution rate confirms that freco-milled sample remained amorphous throughout dissolutiontesting, and recrystallization is therefore not the reason for thehigher offset in the dissolution tests. We speculate that it might beduc to the higher hygroscopicity of the amorphous material(confirmed physically by the stickiness of the amorphous materialduring preparation). This may potentially lead to a rapid adsorptionof water during the first few minutes of the dissolution experimentthereby yielding an initially faster dissolution rate. Extendedintrinsic dissolution testing (120 min) as well as physical inspectionof the compact after dissolution testing corroborated that the 1:1 comilledsample remained amorphous during testing. The IDRs of naproxen and cimetidine in the co-milled sample (1.49 and 1.32mg cm−2, respectively) are not significantly different (95%confidence level; Table 5.2). Put differently, their release is synchronized, suggesting an inter-dependent controlled release of the twodrugs from the compact. Taking into account the 1:1 solid-stateinteraction between the imidazole ring of cimetidine and thecarboxylic acid of naproxen as well as the stability of the co-milledamorphous system upon dissolution, this inter-dependency is notcompletely unexpected; however, remains an interesting finding. Apossible solvation process is believed to be the reason for thesynchronized release, i.e., solvation of one cimetidine molecule leadsto one non-bound naproxen molecule now having an exposedhydrophilic moiety (the carboxylic acid) accessible to solvation, andvice versa. The use of amorphous binary systems prepared bymechanical activation may present an alternative approach tosynchronized release of drug–drug formulations, without relying onthe introduction of a third component, for example a polymer. Taking into account that both drugs are intended for immediaterelease, and that no signs of recrystallization were noticed during anextended intrinsic dissolution study (see Supporting Information), itis reasonable to assume that bioavailability would not be decreaseddue to recrystallization in in vivo conditions either. Further studies on the naproxen–cimetidine binary system aswell as other amorphous model systems are needed to explore thefull potential of this formulation strategy. Such an investigationshould include in-situ solid-state monitoring of the compacts duringdissolution, e.g., by Raman spectroscopy, in order to elucidate theconnection between solid- and solution-state phenomena. Itwould also serve as the basis for addressing the behavior of such coamorphousphases in more complex formulations that include otherexcipients(Manivannan et al, 2010).[56]

Table 5.2: Intrinsic dissolution rates (IDRs) of naproxen and cimetidine along with results from the t-test performed at the 95% confidence level.

API	Description	Intrinsic dissolution rate (mg cm−2 min−1)	t-test				
Naproxen	Co-milled	1.49±0.108	X	X			
	Crystalline	0.352±0.016		X			
Cimetidine	Co-milled	1.32±0.104	X		X	X	
	Amorphous (milled)	0.643±0.068			X		X
	Crystalline (Form A)	0.669±0.038				X	X
Significantly different (95% confidence level)			Yes	Yes	Yes	Yes	No



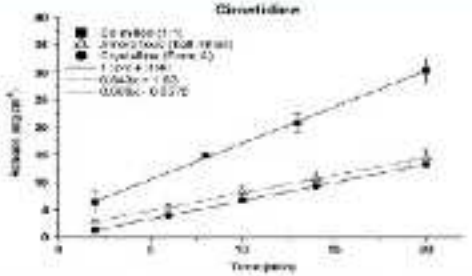


Fig. 5.5: Intrinsic dissolution profiles for naproxen and cimetidine from the co-milled (1:1) sample and for single components at pH 7.2, 37 °C and 50 rpm rotation speed. Conversion of (A) concentration–time profiles to (B) release-time profiles has been performed under the assumption that the co-milled sample is homogeneous and that the surface area of naproxen and cimetidine stays constant throughout the dissolution study.

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