COMPLEXATION OF NAPROXEN WITH BETA-CYCLODEXTRIN WITH AND WITHOUT POLOXAMER 407 TO ENHANCE DRUG DISSOLUTION

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ABSTRACT

Non steroidal anti-inflammatory drugs (NSAID) have adverse effects on stomach. The histological appearance of affected mucosal cells ranging from mild to sever inflammation. Accordingly, the purpose of this study was to investigate the effects of: (i) ß-cyclodextrin (ß-CD), Poloxamer-407 (PLX) and sorbitol (Sorb) as carriers and (ii) freeze drying and physical mixing as techniques on solubility and dissolution of a model poorly water soluble NSAID drug, Naproxen (Nap) for the ultimate aim to avoid gastric discomfort via enhancement drug release. Therefore, two binary drug/carrier (1:1 and 1:4 w/w Nap/carrier ratios) combinations were prepared. The effect of multicomponent carrier systems, using ternary physical mixtures of Nap with ß-CD and PLX on the drug solubility and dissolution were also studied. All formulations were characterized using solubility, content uniformity, dissolution studies, Fourier transform infra-red (FT-IR) spectroscopy, and differential scanning calorimetry (DSC). All tested Nap/ combinations showed enhancement in drug release compared to pure drug, except Sorb that show a slight improvement only at high sugar concentration. Ternary Nap combinations showed the highest improvement of drug dissolution, compared to binary ones. Freeze dried formulations showed a marked enhancement in drug release especially in the first few minutes, compared to physical mixtures. Thermal studies indicated a reduction in drug crystallinity with freeze dried samples giving a higher amorphous yield obtained compared to binary physical mixtures.

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Running Title: Naproxen in freeze dried and physically mixed forms

INTRODUCTION

The oral route of administration is the most popular due to the advantages afforded to patients for self-administration. However, aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic drugs show poor or fluctuated aqueous solubility and hence

cause serious delivery problems due to erratic drug absorption. Many techniques have been used to improve the drug aqueous solubility. Among these techniques: conversion of poorly water-soluble drugs into amorphous state in order to improve the biopharmaceutical properties of solid dosage forms [1], application of liquisolid technique [2], using solid dispersion preparations [3]; [4] or formulation of nanoparticles [5]; microcrystals [6] and spray dried particles [7]. In this study, naproxen (Nap) was selected as a model poorly water soluble drug. Nap is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties whose efficiency is offset by its low solubility and slow dissolution while orally administered.

Cyclodextrins (CDs) are cyclic oligosaccharides that widely used in the pharmaceutical industry for their capabilities to modify physical, chemical and biological properties of a number of hydrophobic drug molecules through the formation of inclusion complexes [8]; [9]. These inclusion complexes in addition to improving the drug solubility, they can enhance drug stability; prevent drug/excipient interactions or mask the drug unpleasant taste. Literatures describing the complexation of NAP with cyclodextrins and enhancing its dissolution properties are available (See for example: [10]. However, using combinations of cyclodextrins and poloxamers and/or sorbitol have not been studied before. Accordingly, the aim of the present study was to investigate and compare the effect of using ß-CD with and without adjuvant additives (Pluronic F-127 and sorbitol) on dissolution of NAP in physically mixed and freeze dried forms. Pluronics are polyethylene oxide (PEO)-polypropylene oxide (PPO)- polyethylene oxide (PEO) copolymers, also known as Poloxamers. Poloxamer consists of a hydrophilic corona (ethylene oxide, EO) and hydrophobic core (polypropylene oxide, PO) blocks arranged in a triblock structure resulting in an amphiphilic structure. They are non-ionic surfactants that have been extensively used as wetting and solubilizing agents. Poloxamers were first introduced by late 50th and since then they have been proposed to diverse pharmaceutical applications such as emulsifiers, solubilizing agents, suspension stabilizers and wetting agents [11]. Their ability to self-aggregate, thereby forming micelles and liquid crystalline phases, and greater hydrophilicity is another advantage for the solubilization of poorly water-soluble drugs [12]; [13]; [14]; [15]. These amphiphilic co-polymers are available in different grades as poloxamer 188 and poloxamer 407. Sorbitol is a type of sugar which has been reported to improve the solubility of some poorly water-soluble drugs [16]; [17]. The influences of different drug to carrier ratio and the adopted technique on the physicochemical characterization of NAP formulations were performed.

MATERIALS AND METHODS

Materials

Naproxin (Nap) was obtained from F. Hoffman-La Roche Ltd. (Mexico), ß-cyclodextrin (ß-CD), sorbitol (Sorb), and Poloxamer 407 (Pluronic[TM] F-127; PLX) were purchased from Sigma-Aldrich (USA). Other reagents were of analytical grade and used as received.

Methods

1. *Preparation of drug-carrier Physical mixture (PM):*

Nap/carrier systems were prepared from the previously sieved (38-63µm) individual components. Binary physical mixtures (PM) at 1:1and 1:4 (w/w) drug-to-carrier (PLX, ß-CD or Sorb) ratios were prepared. A ternary system Nap/ß–CD /PLX and Nap/ß–CD /Sorb were

prepared at 1:2:2 (w/w ratio). Drug and carrier(s) PMs were prepared by simple blending of the powders by turbula mixer (Type T2C, Glen Creston Ltd, UK) for 10 min at 31 rpm.

2. Preparation of drug-carrier freeze-dried (FD) systems:

The calculated amounts of drug and carrier were dissolved in ethanol/water (40%v/v) mixture, aided by sonication for 15 minutes. For CD formulations, heating up to 70°C was necessary to aid the solubility and the formation of drug-CD inclusion complexes, then the solutions were frozen at -85°C for 5 hours before the freeze drying process using the VirTis freeze dryer (Biopharma, USA).

3. Drug content uniformity:

Drug content for the prepared PM and FD formulations were determined by dissolving an exact amount of the prepared powders in 20 ml of ethanol and analyzing the samples, after suitable dilution, spectrophotometrically at 271nm using UV/VIS spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK).

4. Dissolution studies:

The dissolution studies of Nap and its formulations (PM and FD) were performed under sink conditions using United State Pharmacopoeia type II dissolution test apparatus (Erweka DT 6, Heusenstamm, Germany). Test samples of each formulation containing drug equivalent to 12 mg were placed in 900 ml of distilled water at 37 °C (paddle method at 100 rpm). At appropriate time interval, aliquots of 10 ml were withdrawn with a filter-syringe and drug content was assayed spectrophotometrically. The withdrawn aliquots were replaced by a fresh dissolution medium to keep the volume constant.

5. Differential Scanning Calorimetry (DSC):

The changes, if any, in the thermal characteristics of Nap, carriers and Nap formulations were studied using DSC (DSC Q1000, TA instrument, England). Samples equivalent to about 3-6 mg of the powder, in hermetically sealed aluminium pans, were scanned from 20-300°C/min at 10°C/min. The instrument was calibrated with sapphire and indium before running the samples. The percentage crystallinity for the preparations was calculated using the following equation [18]:

Percentage crystallinity = (Δ H$_{mTP}$ / Δ H$_{mNap}$ × W) × 100

Where,

Δ H$_{mTP}$ = the melting enthalpy of tested preparation (Jg^{-1})

Δ H$_{mNap}$ = the melting enthalpy of naproxen (Jg^{-1})

W = the weight fraction of naproxen in the preparation.

6. Fourier-Transform Infrared (FT-IR) Spectroscopic Analysis

Infrared spectra for individual components as well as different formulations were obtained using Perkin-Elmer FT-IR system Spectrum BX (Beaconsfield, Buckinghamshire, UK). The samples were scanned over the wave number range from 4000 to 550 cm^{-1} at 4 cm^{-1}. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions.

7. Statistical analysis

The student *t-test* was applied, results are quoted as statistically significant when P < 0.05.

RESULTS AND DISCUSSION

1. Content uniformity:

Monitoring drug content uniformity in the early stages of the formulation is an important issue in the pharmaceutical field as it required for the control of drug quality and sturdiness of the process. Also the information obtained from drug content uniformity can be quite helpful in relation to possible segregation as well as other process issues [19]. All of the Nap/PLX and Nap/ ß–CD binary systems (PM and FD) showed reasonable drug content uniformity (97-101%), indicating a homogeneous distribution of the drug in the prepared formulations. On the other hand, formulations with Sorb showed lower drug content uniformity ranging from 92 to 95%.

2. Dissolution study:

The dissolutions of Nap from various binary and ternary physical mixtures as well as freeze dried systems are presented as percentage of drug released versus time curves (Figures 1 and 2). The time necessary for dissolution of 50% of the drug (t_{50}) was calculated for each system and is presented in Table 1. To elucidate the effect of carrier type and the method of preparation on drug dissolution, the relative dissolution efficiencies (RDE) after 5 min were calculated as the ratio of drug released from each formulation to that of the pure drug at that time (Table 1).

Table (1): Time required for dissolution of 50% of drug (t_{50}) and relative dissolution efficiency (RDE) from Nap/carrier physical mixture (PM) and freeze dried (FD) systems.

Formulation	*Drug/carrier ratio (w/w)*	*t_{50} (min)*	*RDE^a*
Pure Nap		>90	1.0
Nap/PLX PM	1:1	6.0	7.2
	1:4	9.0	4.5
Nap/CD PM	1:1	5.0 (±0.6, 3)	8.3
	1:4	5.0 (±0.5, 3)	8.3
Nap/Sorbitol	1:1	>90	1.33
	1:4	30.0 (±2.1, 3)	3.07
Nap/ CD /PLX PM	1:2:2	2.7 (±0.3, 3)	14.0
Nap/ CD /Sorb PM	1:2:2	5.0 (±0.8, 3)	8.04
Nap/POL FD	1:1	3.0 (±0.6, 3)	11.0
	1:4	2.0 (±0.3, 3)	12.0
Nap/ CD FD	1:1	3.5 (±0.4, 3)	10.4
	1:4	3.5 (±0.5, 3)	11.1

- [a] Ratio between the percentage drug released from Nap/carrier system and that of drug alone at 5 min.

- Numbers between brackets are standard deviation and number of replicates, respectively.

2.1. Dissolution of Nap from binary and ternary physical mixture (PM):

For binary Nap/PLX PMs, the percentage drug released was significantly ($P<0.05$) higher than that of the pure drug at the two drug/carrier ratios (Figure 1A). This could be due to the solubilizing effect of the carrier as a result of improving in the wetting of the hydrophobic Nap. At low concentration, PLXs like other surfactants form monomolecular micelles by change in configuration in solution. PLX at the lower concentration of 1:1 drug:carrier ratio showed a better ($P<0.05$) dissolution data regarding t_{50} and RDE, compared to that with higher carrier concentration (Table 1). However, after about 40 min both formulations showed a similar dissolution pattern.

In a trial to explain such results, the thermoreversible gelation behavior of the copolymer could be considered, which is well known properties of PLX. The gel formation capability of the copolymer based on both critical micelle temperature (CMT) and micellar packing. CMT is the temperature where micelles are formed, and is reported to be about 24°C (Lin and Alexandridis, 2002). Above the critical micelle concentration, self assembled micellar structure is obtained. The liquid-phase micelles formed by PLXs undergo transition into liquid crystal gel phases in response to increased temperature (Wanka, 1994). It was reported that PLX 407 forms gel above a certain concentration of about 15% w/v [20]; [21]. In this study, though the temperature of the dissolution medium was above CMT, but the concentration of the copolymer was too small to form the gel structure. But deep at the microenvironment level around the copolymer specifically in the diffusion layer, the concentration may be at the saturation level. This may resulted in the formation of a gel microenvironment that would slow down drug movement through it, and consequently drug dissolution. This may explain why higher PLX concentration showed less drug release compared to the lower concentration. This would signify the use of a small amount of PLX during the preparation of PM of the drug instead of the larger amount of 1:4 ratio to obtain a reasonable weight of the drug dose that is easily administered.

For binary Nap/ß-CD PMs, there was a significant difference ($P<0.05$) in terms of percentage of Nap released compared to the drug alone (Figure 1B). This indicates that ß-CD was effective in enhancing Nap dissolution by simple mixing. Drug release was better than that obtained using PLX as carrier. The improvement of the initial dissolution rate obtained with PMs can be attributed to both improved drug particle wettability, due to the surfactant-like properties of the carrier, and "in situ" formation of readily soluble complexes in the dissolution medium [22]; [23]. There was no significant difference ($P>0.05$) in terms of t_{50} and RDE in the two drug:carrier ratios; 1:1,and 1:4 (Table 1). This would indicate that the concentration of ß-CD in 1:1 (w/w) system was enough to entrap and accommodate Nap molecules in the same efficiency as the higher carrier concentration (1:4 w/w ratio). This result is useful as it eliminates the use of large amount of ß-CD, as it can cause toxicity at such high concentrations [24].   For   Sorb combinations, Nap/Sorb 1:1 PM did not significantly ($P>0.05$) improved drug dissolution compared to control (Figure 1C). Moreover, t_{50} was not reached till the end of the experiment time (Table 1). Increasing Sorb concentration in the PM to 1:4 Nap/Sorb resulted in slight improvement in drug dissolution with a t_{50} of 30 minutes. Using Sorb, with the known dose of Nap of about 250 mg at low doses, such high ratio will increase the bulkiness of the dose that would be non-convenient for patients. Accordingly, sorbitol is not a good choice of carriers to enhance naproxen dissolution. On the other hand, PLX and ß-CD gave about 7- and 8-fold, respectively, enhancement in RDE with the lower ratio of 1:1 Nap/carrier that would reduce their

workable amount in pharmaceutical formulations, that would be more suitable from the economic and administration point of view.
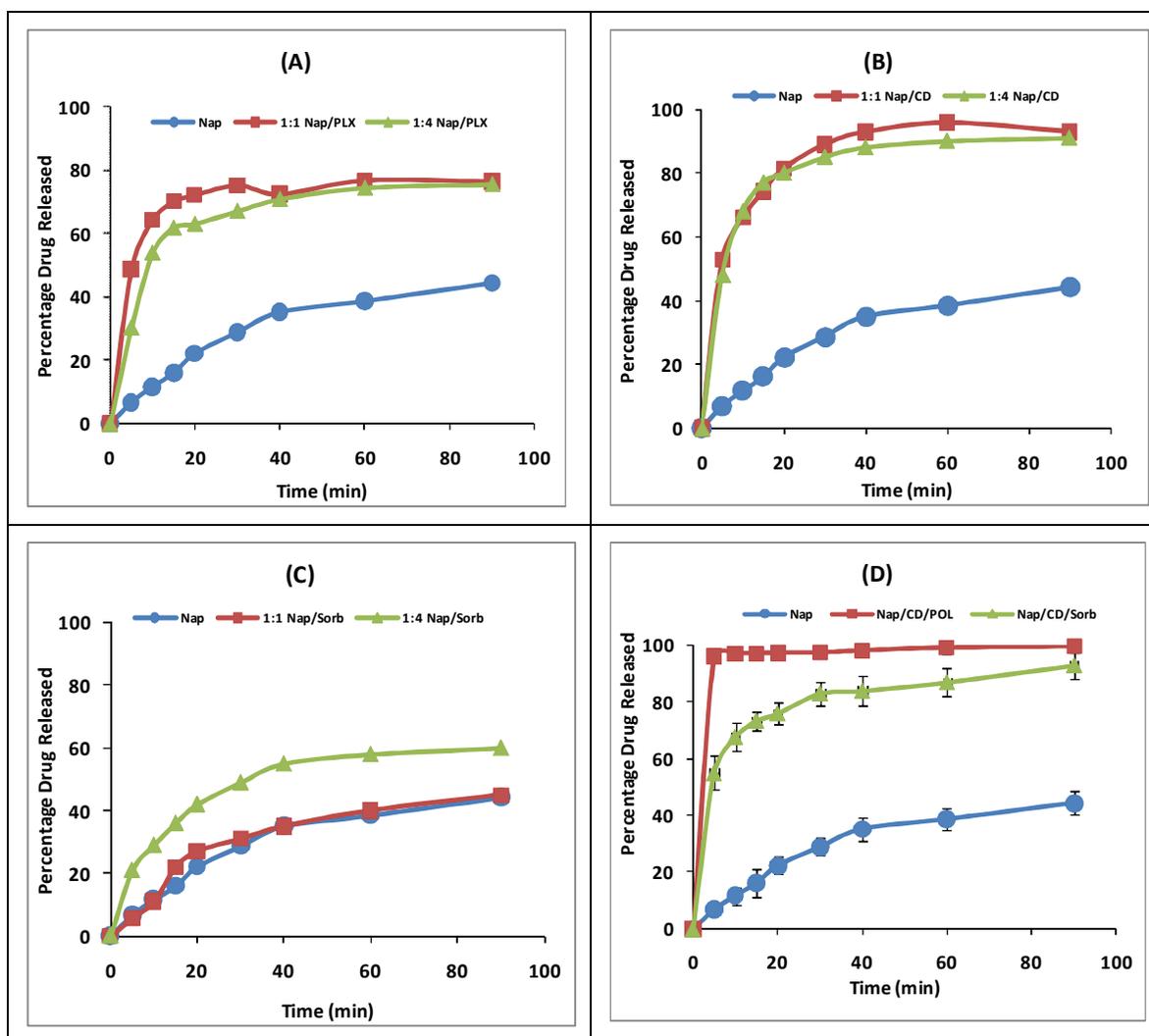

Figure 1: Percentage drug released from pure drug and its binary physical mixture with poloxamer 407 (A), ß-cyclodextrin (B), sorbitol (C) and ternary drug/ ß-cyclodextrin/poloxamer and drug/ ß-cyclodextrin sorbitol mixture (D).

The overall results for the binary drug/carrier PMs indicated the superiority of ß-CD in improving Nap dissolution over the other two carriers. However, the use of CDs in the pharmaceutical area is hindered by problems such as high cost, relatively low water solubility, and potential toxicity [25]. Increasing the complexation and solubilization efficacy of CDs is a possible means to reduce their workable amount. Among the strategies suggested towards this aim is the addition of a suitable auxiliary substance so as to increase and strengthen the CD solubilizing capacity [25], [26]. It was reported that the addition of an auxiliary substance can

significantly increase CD solubilizing and complexing effect by synergistic multi-component complex formulation. The addition of a suitable water-soluble polymer to drug/ß-CD system has been proven to enhance solubilizing efficiencies of ß-CD [26], [27]. Therefore, in this study PLX and Sorb were added separately to Nap/ß–CD PM at the ratio of 1:2:2 w/w Nap:ß–CD:((PLX or Sorb). The percentage drug released versus time plots are illustrated in Figure 1D. For Nap/ß-CD/Sorb PM, the data revealed that addition of Sorb did not significantly ($P>0.05$) improve drug dissolution compared to that for Nap/ß-CD PM regarding dissolution parameters (Table 1). It could be assumed that Sorb in this amount was not enough to elucidate a noticeable enhancing power. On the other hand, ternary Nap/ß-CD/PLX mixture showed a marked improvement in drug dissolution with a burst drug release showing a t_{50} of about 2.5 ±0.3 min compared to about 5.0 min for Nap/ß–CD system. Regarding the dissolution efficiency, ternary PLX mixture showed 14- and 2-fold enhancement in dissolution compared to pure drug and binary Nap/ß-CD, respectively, indicating the augmenting effect of PLX to CD in enhancing the drug dissolution. Consequently, it is possible to suggest that this behavior may be due to having Nap/ß-CD complex in a more close dispersed state within the triblock polymer (PLX) matrix via interactions between the exterior of the complex and PLX, this suggestion is supported by Moore et al [26]. In addition, being amphiphilic, PLX would increase the solubility of the free, un-complexed drug. The better performance of this ternary complex will allow further reduction in the amount of ß-CD needed to solubilize a given amount of drug. Besides, it could be suitably utilized to formulate a fast-dissolving Nap solid dosage form as evidenced from the dissolution profile.

2.2 Dissolution of Nap from freeze dried (FD) formulations:

For the FD formulations, Figure (2) shows the dissolution profiles of FD formulations. Freeze dried (FD) preparations are shown in Figure 2A. FD drug showed a significant (P< 0.05) increase in drug dissolution compared to control untreated drug. After 5 min the amount of drug dissolved was around 11% for freeze-dried naproxen compared to only 6% for the control untreated drug, in a good agreement with previous findings [29]. The FD Nap:PLX binary systems markedly improved drug dissolution with a burst drug release of about 75 and 83% after 5 min with RDE of 11 and 12 for 1:1 and 1:4 Nap/PLX, respectively. A complete drug dissolution was obtained in about 15 min from 1:4 Nap:PLX formulation. Comparing those results with drug dissolution from Nap/ß-CD FD formulations; there was a marked increase in the drug dissolution. Figure (2B) shows that, similar to some extent to PLX combinations, there is a burst release of Nap with a percentage drug release after 5 minutes of about 58 ±1.7 and 76± 0.9% for 1:1and 1:4 ratios, respectively, compared to only 7.0 ±1.1% of the pure drug. The lower Nap/ß-CD ratio showed less enhancement compared to the CD higher concentration (see Table 1). The better performance of FD formulations in the early time of dissolution process compared to PM ($P < 0.05$) can be attributed to: (i) the effect of processing, freeze drying, and (ii) a higher solubility of Nap as a consequence of its in-depth interaction and more effective complexation with ß–CD, as well as to the high energetic amorphous state reduction of drug crystallinity following complexation as will be explained by the DSC data. The results are in agreement with a study by Lin and Kao [22].
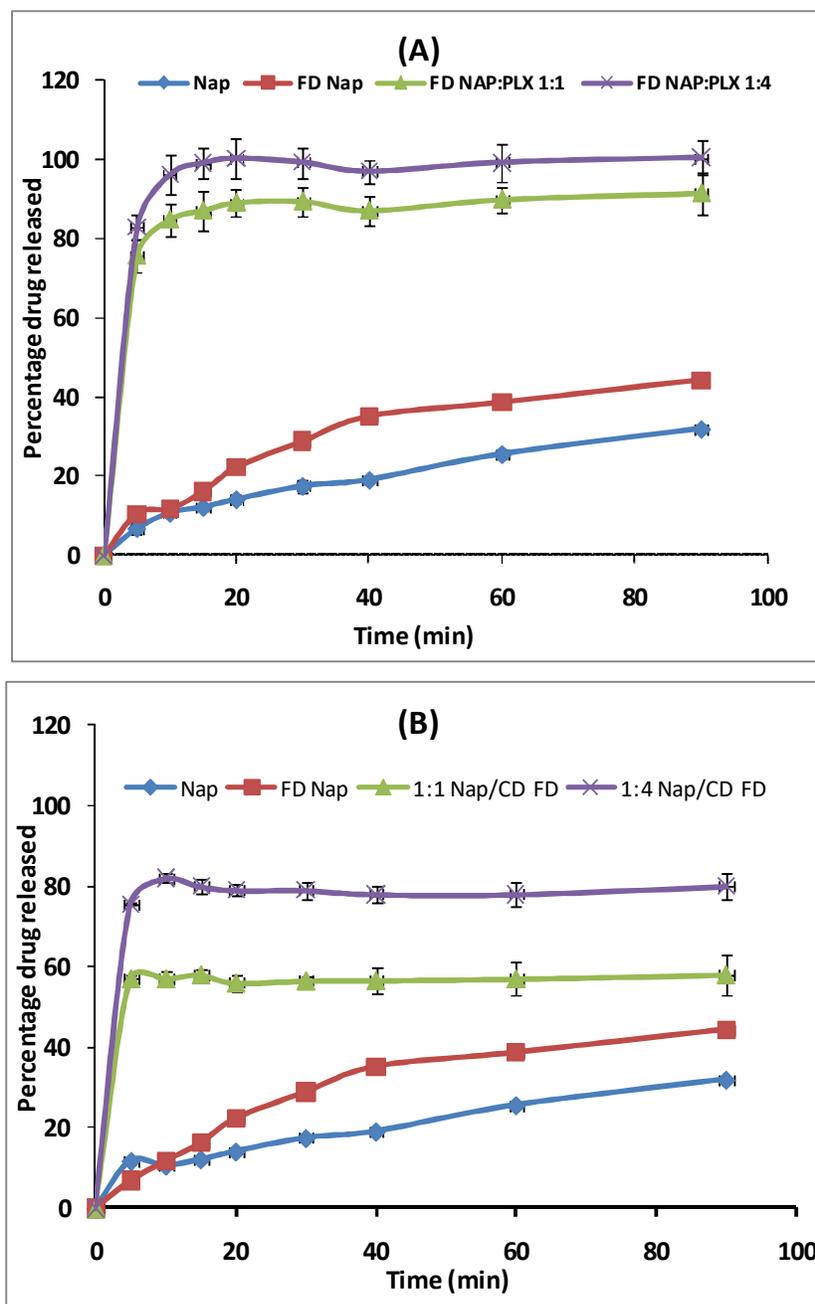
Figure 2: Percentage drug released from pure untreated drug (Nap) and freeze dried drug (FD Nap) and binary formulations with poloxamer 407 (A) and ß-cyclodextrin (B).

To compare between all Nap formulations prepared by PM to that by FD, ternary Nap/ß–CD/PLX PM showed the highest dissolution parameters of all tested formulations. This would indicate that simple blending of the drug with the two carriers is enough to give dissolution performance that is better than freeze drying technology of the binary Nap/ß–CD. This is more economically favored and easier for possible scale-up and industrial applications compared to FD technique.

From this study, the overall results would strongly recommend the use of PLX as in combination with ß–CD. This would boost the safety issues of the administered formulation as we can reduce CD amount, as in the ternary PM. Furthermore, it has been reported that PLX 407 is the least toxic of commercially available copolymers (32).

3. Solid state characterization of the binary and ternary Nap systems

To understand the possible mechanism of improved dissolution, differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy

(FTIR) were used for solid state characterization of binary (PM and FD) and ternary systems. The DSC thermograms for Nap, PLX, ß–CD alone or in combinations are presented in Figure (3). The calculated parameters for the melting transitions (T_{peak} and % crystallinity) were determined and are presented in Table 2. The sharper the peak obtained in the DSC thermogram, the higher the melting point, and the higher the degree of crystallinity of the structure [30].

For pure Nap, the DSC curve was typical of a crystalline anhydrous substance showed a sharp endothermic peak at 158.9°C and fusion enthalpy of 139 ±3.8 Jg^{-1}, this is in agreement with previous findings [31]. For pure PLX, a single endothermic peak was obtained at about 55°C, with regard to the drug PM, thermograms indicated a marked change in the drug endothermic behavior. For 1:1 ratio, there was a shift in T_{peak} to a lower value with reduction in peak sharpness, fusion enthalpy and percent crystallinity (Table 2). For the higher carrier concentration, the drug endothermic peak was completely eliminated, with only PLX peak shifted to a lower temperature. Such results can be explained on the basis that if a polymer having a low meting point compared to that of the drug and if the drug is soluble in the molten polymer, then the drug and polymer might form eutectic system [32]; [33]; [34]; as PLX has a low melting point than Nap, then during the heating stage of the DSC measurement Nap may have dissolved in the melt and formed the eutectic mixture.
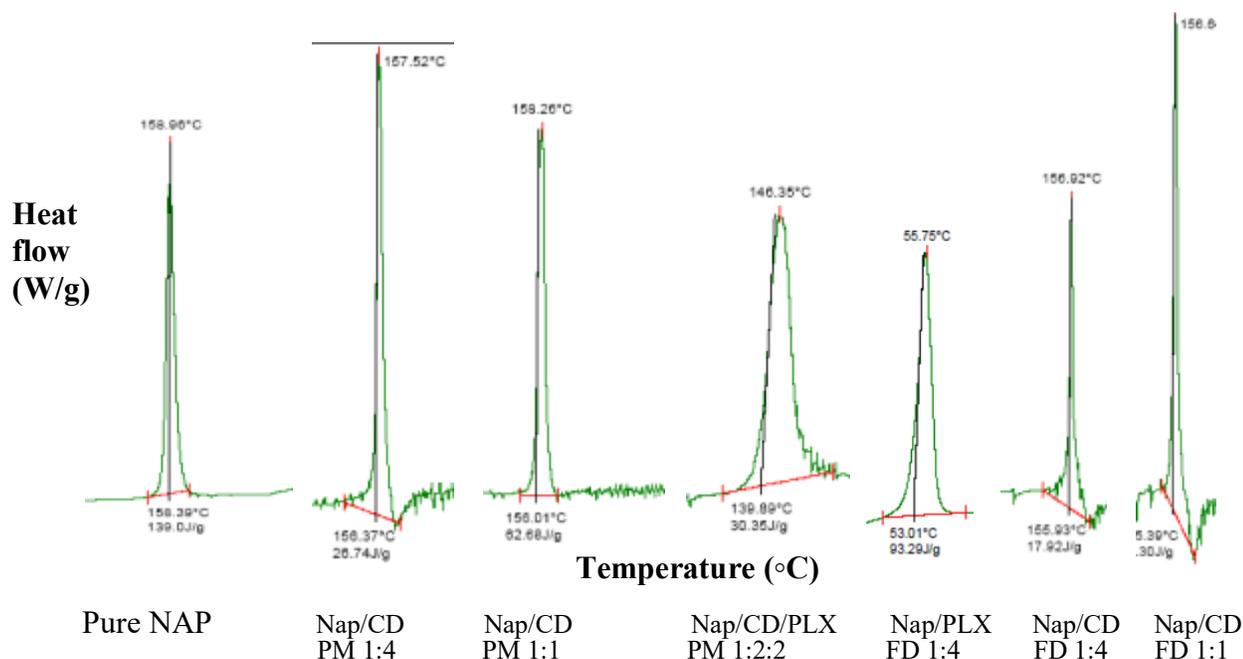

Figure 3: DSC thermograms of naproxen formulations.

Table 2: Effect of physical mixing (PM) and freeze drying (FD) of Nap/carrier systems on the peak temperature (T_{peak}) and percent crystallinity.

Sample	Drug/carrier ratio (w/w)	T_{peak} (°C)	%Nap crystallinity
Pure Nap	-	158.9 (±0.2)	100
Nap/PLX PM	1:1	123.9 (±1.0)	6.6
	1:4	ND	ND
Nap/ß–CD PM	1:1	158.3 (±0.6)	45.0
	1:4	157.5 (±0.2)	20.7
Nap/ ß–CD /PLX	1:2:2	146.4 (±0.7)	22.0
Nap/PLX FD	1:1	119.4 (± 1.6)	5.7
	1:4	ND	ND
Nap/ß–CD FD	1:1	156.9 (±0.3)	25.0
	1:4	156.6 (±0.4)	13.0

After complete melting of the eutectic, the remaining solid drug suspended in the liquid melt (which might have exceeded the eutectic concentration) would have resulted in the second endotherm at 123°C. In the case of 1:4 ratio, PLX constituted the major phase with the possibility of complete dissolution of the drug in the copolymer melt, this would explain the complete disappearance of the drug endotherm and highly reduced percent crystallinity of 11% and 7% for 1:1 and 1:4 Nap/carrier ratio, respectively. The presence of a small amount of the drug as impurities might have resulted in the shortening of PLX peak to a lower melting point. The same principle is applicable to the thermograms of freeze dried PLX formulations, with the complete disappearance of the drug peak even at the low copolymer concentration and a similar percent crystallinity to those of physically mixed formulations (see Table 2).

The DSC curve of β-CD shows a broad endotherm in the range of 75°C to 85°C, which can be attributed to desolvation. For Nap/ß-CD physical mixing preparations there was only a trend of reduced T_{peak} of the drug ($P>0.05$), however reduced peak sharpness was observed probably due to greater disorder in the crystal structure. However, when the percentage crystallinity was calculated, the results showed 45% and 20% of crystallinity for 1:1 and 1:4 Nap/carrier ratio, respectively, in comparison to the pure drug (100% crystallinity). This would explain the improvement in dissolution properties of Nap, as the structure had become less crystalline or the drug crystal lattice was disrupted compared to the pure naproxen. Regarding freeze dried combinations (Figure 3), there was a trend ($P>0.05$) of reduced T_{peak} by about 2°C. However, there was a marked decrease in peak sharpness with reduced enthalpy and consequently % crystallinity down to 13% at 1:4 ratio (Table 2). This would indicate a more amorphous preparation with better drug disolution.

For the ternary Nap/ ß-CD/PLX PM, only one broad endotherm at 146°C (Figure 3), with the disappearance of the melting endotherm of the two carriers. This suggests the theory of solid dispersion formation due to dissolution of the drug in the molten PLX. The % crystallinity suggests a reduced crystallinity (22% crystallinity) that would explain the obtained high dissolution results (See Figure 1D).
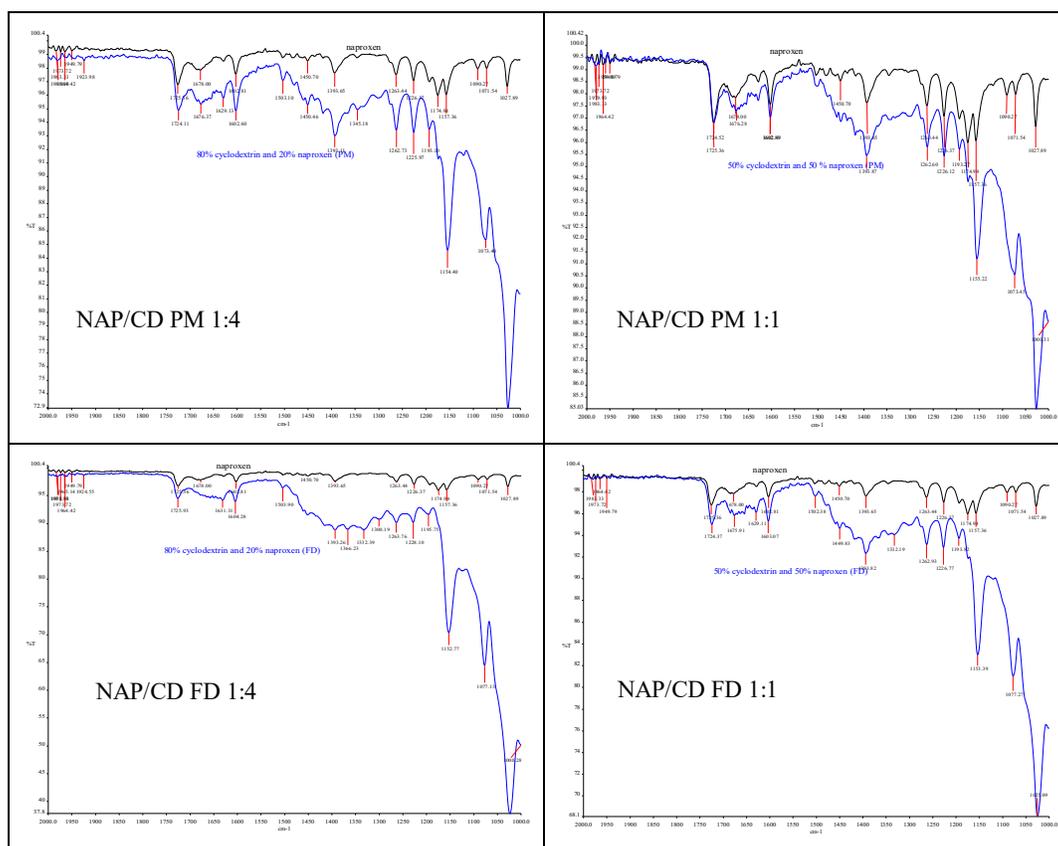

Figure 4: FT-IR spectra of naproxen formulations

In FTIR analysis (Figure 4), Nap showed the characteristic quartet of bands for carbonyl stretching at frequencies of 1724, 1678, 1629 and 1602 cm^{-1} [35]. The spectra of binary and ternary physical mixture did not show a significant difference from that of pure drug in the area of the main Nap absorption bands. The IR spectrum of PLX is characterized by principal absorption bands at 2891 cm^{-1} (C-H stretch aliphatic), 1343 cm^{-1} (in-plane O-H bend) and 1111 cm^{-1} (C-O strech).

In the case of FD preparations, the band at frequency of 1678 cm^{-1}, is broader (1:1 w/w Nap/ ß-CD) or almost disappeared (1:4 w/w Nap/ ß-CD), indicating a possible interaction occurred between the drug and ß-CD due to the change taken place around the bond. This can be explained by the dissociation of the intermolecular hydrogen bonds of Nap through strong interaction between the components through inclusion complex [36]; [10], e.g. formation of hydrogen bonding between carboxylic group of the drug and hydroxyl group of ß-CD. These data are in accordance with solubility and dissolution studies.

CONCLUSION

In the present investigation, poloxamer 407 has improved significantly the dissolution of Nap either by physical mixing or freeze drying techniques. ß-cyclodextrin was more effective than polomaxer in the physically mixed formulation, but less in the freeze drying ones. Among the ratios used both two carriers were effective in the lower drug/carrier ratio of 1:1, alleviating the need for the use of higher excipient concentration. This indicated that an increase in the mass fraction of polymer could not offer any advantage for dissolution enhancement. The incorporation of the two carriers together in a ternary drug physical mixture augmented drug release that was even comparable to those of the freeze dried formulations. Therefore, it could be concluded that solid oral dosage forms of Nap with ß-cyclodextrin and poloxamer 407 physically mixed together could be formulated with a high dissolution, faster onset of action, expected to improve drug bioavailability.

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