African Journal of Pharmacy and Pharmacology Vol. 5(15), pp. 1757-1764, 22 October, 2011
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP10.224
ISSN 1996-0816 ©2011 Academic Journals

Full Length Research Paper

Formulation, optimization and biopharmaceutical evaluation of the fast release tablets of nifedipine-cyclodextrin

Saleh A. Al-Suwayeh[1]*, Jia-You Fang[1,2], Ibrahim M. El-Bagory[1,3], Ehab I. Taha[1] and Mohsen A. Bayomi[1,3]

[1]College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.
[2]Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Kweishan, Taoyuan, Taiwan.
[3]Center of Excellence in Biotechnology Research, King Saud University, Box 2460 Riyadh 11451, Saudi Arabia.

Accepted 11 August, 2011

In this study, nifedipine tablets were formulated with different types of cyclodextrins (CDs) by direct compression method. Spray dried lactose and microcrystalline cellulose (MCC) were used as tablet fillers. The prepared tablets showed good appearance with acceptable crushing strength and disintegration time. The tablets showed fast dissolution within 11 to 68 min for 80% of the drugs depending on the type of CD and tablet filler. Some of the formulated tablets presented good fast release properties similar to soft gelatin capsules (USP XXIV) and based on the calculated dissolution efficiency (DE%), tablets containing hydroxypropyl-β-CD and lactose as a filler were chosen for *in vivo* study by oral administration to beagle dogs when compared with the commercially available 10 mg soft gelatin capsule (Adalat®) and 10 mg film coated tablets (Corinfar ®). The formulated tablets showed significantly higher area under the curve ($AUC_{0-\infty}$) than the commercial soft gelatin capsule and film coated tablets as result of increased drug absorption. It was concluded that the formulated fast release tablets could replace the nifedipine soft gelatin capsules with the advantages of ease of preparation and less restricted storage and handling conditions.

Key words: Nifedipine tablets, cyclodextrins, bioavailability, beagle dogs.

INTRODUCTION

Cyclodextrins (CDs) and their derivatives play an important role in the development of drug formulation due to their multifunctional characteristics and bioadaptability, that is, they are capable of alleviating the undesirable properties of drug molecules through the formation of inclusion complexes (Baboota and Agarwal, 2003; Rasheed et al., 2008). These inclusion complexes have also been shown to improve the stability, solubility, dissolution rate and bioavailability of drugs (Duchene and Wouessidjewe, 1990; Bekers, 1991). In most cases, this association increases the solubility of poorly soluble drugs (Bekers, 1991). The drug-CD binary systems are also useful in dosage form development for poorly soluble drugs in tablet or capsule form (Nalluri et al., 2007; Melia and Davis, 2007).

Nifedipine, a calcium-channel blocking agent, is widely used for the treatment of hypertension. The bioavailability of nifedipine is relatively low after oral administration of crystalline form due to its limited solubility in water. Various oral formulations of Nifedipine, such as solid dispersions, nanocrystal and micronization of drug were developed to improve the solubility and bioavailability of nifedipine. In our previously published report, we succeeded to protect nifedipine against the effect of light along with improving its dissolution profile by inclusion complexation with different types of CDs (Bayomi et al., 2002), namely: β-CD, HP-β-CD or DM-β-CD.

Also, compressing the drug with polymeric carrier was successfully utilized for protecting it against the effect of light (Varshosaz and Dehghan, 2002). Improving drug dissolution was reported by using super disintegrants (Yen et al., 1997) and solid dispersions with different

*Corresponding author. E-mail: ssuwayeh@ksu.edu.sa.

types of polymers (Suzuki and Sunada, 1998; Chowdary and Ramesh, 1994).

Preparation of tablets containing inclusion complex of nifedipine with CD may solve the problem of low bioavailability after oral administration by increasing drug solubility and dissolution rate (Chutimaworapan et al., 2000; Hecq et al., 2005). In addition, tablets would need less restricted light protection during manufacturing, storage and handling.

In this study, different nifedipine cyclodextrin inclusion complex powders were physically evaluated and directly compressed into tablets. Microcrystalline cellulose (MCC, Avicel PH 101) and spray dried lactose were compared as direct compression tablet fillers. The physical properties of the differently formulated nifedipine tablets as well as drug content and dissolution profiles of nifedipine were evaluated. The most promising formulation was compared with commercial available 10 mg soft gelatin capsules (Adalat®) and 10 mg film coated tablets (Corinfar ®) *in vitro* and after oral administration to beagle dogs in an *in vivo* study.

MATERIALS AND METHODS

Nifedipine was a gift from Dar Al Dawa (Na"ur, Jordan). The complexing agents, β-cyclodextrin (β-CD), Hydroxypropyl-β-cyclodextrin (HP-β-CD) with 0.8 average degrees of substitution and dimethyl-β-cyclodextrin (DM-β-CD) were purchased from Sigma Chemical Company (St. Louis, MO, USA). Potassium bromide and magnesium stearate were obtained from Merck Co. (Darmstadt, Germany). Starch was supplied by Mainland (Frankfurt-M, Germany) while, microcrystalline cellulose (MCC, Avicel PH 101) was obtained from Serva (Heidelberg, Germany) and spray dried lactose from Winlab limited (Maidenhead-Berkshire, U.K). Solvents used for chromatographic determinations were high performance liquid chromatography (HPLC) grade while, all other solvents and reagents were of analytical grade.

Generally, preparation and evaluation of powders, as well as preparation of tablets containing complexed and uncomplexed nifedipine, were carried out under light protection condition and sodium lamp was used when necessary as a light source to prevent undesirable photodecomposition of nifedipine.

Preparation of nifedipine-CDs physical mixture

Physical mixtures of different types of CDs with nifedipine at stoichiometric ratio of 1:1 were prepared by simple dry mixing appropriate amounts of the drug with the polymers in a Turbula mixer (Erweka-Appartebau, Type S2Y 220, Heusentamm, Germany) until a homogeneous mixture was obtained (15 min). Before mixing, all used powders were passed through a British standard laboratory sieve of 63 µm opening size (Endecotts Ltd., London, England).

Preparation of nifedipine solid inclusion complexes

The inclusion complexes of nifedipine with different types of CDs were prepared at a stoichiometric ratio of 1:1 using the coprecipitation method (Bayomi et al., 2002). Briefly, nifedipine was dissolved in the least volume of ethanol at 40°C and then, the required amount of each type of CDs in distilled water was added gradually to the ethanolic solution with continuous sonication. The obtained solution in each case was then maintained under stirring for 24 h at room temperature. The solvent was then evaporated under vacuum at 40°C using a rotary evaporator (Rotavapor RE120, Model B-465, Buchi, Switzerland) until a constant weight was obtained. All samples were protected from light and kept in a vacuum desiccator till further use.

Determination of angle of repose and compressibility index of powder samples

The flowability of nifedipine-CD of each powder sample was evaluated by the determination of angle of repose and compressibility index after passing the powders through a sieve of 63 µm opening size. The fixed funnel technique (Banker and Anderson, 1986) was employed for the determination of the static angle of repose (θ). Angle of repose was determined in triplicate and the mean angle ± standard deviation was recorded for each sample. Compressibility index values (I) of the powder samples was determined by carefully measuring the initial volume (v_0) and final volume (v) of the samples after subjecting to tapping in a vortex mixer (Vortex-2 Genie, Scientific Industries Inc., Bohemia, N.Y., U.S.A.) until no further reduction in volume was noticed using the equation:

$$I = [1- (v/v_0)] \times (100)$$

The tapping process was carried out in triplicate to assure reproducibility for each sample and the mean compressibility index ± standard deviation was recorded.

Preparation of tablets

The equivalent of 10 mg of nifedipine in solid inclusion complex or in physical mixture with CD at 1:1 molar ratio was tableted using either Avicel PH 101 or spray-dried lactose as tablet filler. The compositions of the prepared tablets are shown in Table 1. The powders of all ingredients were passed through a sieve of 63 µm opening size and then, thoroughly mixed using Turbula mixer (Erweka-Appartebau, Type S2Y 220, Heusentamm, Germany) for 15 min before tableting. The powder blends were then directly compressed into tablets using a single punch tablet machine (Type EKO, Nr. 10026, Erweka-Appartebau, Heusentamm, Germany) fitted with a 9 mm flat faced punch. The compression force was adjusted for each formulation to end up with tablets of acceptable crushing strength (4 to 7 kp).

Evaluation of tablets

Crushing strength

The crushing strength of the prepared tablets was determined by diametrical compression using an electric tablet hardness tester (TBH 28, Erweka-Appartebau, Heusentamm, Germany). The mean crushing strength ± standard deviation was calculated on six replicates readings for each sample. Weight variations of tablets were carried out for each sample, where twenty tablets were weighed individually prior to preparation and the mean weight ± standard deviation was recorded.

Disintegration

The disintegration time of the prepared tablets was tested in 750 ml of distilled water and was maintained at 37°C using a standard

apparatus (Erweka G.m.b.H., Type ZT4, West Germany) according to United States Pharmacopeia (USP) method for uncoated tablets. Disintegration time was calculated from the results of six tablets for each sample and the reported disintegration time was the time when all of the six tablets disintegrated and all particles had passed through the lower plate.

Drug content

Drug content of tablets was also measured in order to determine drug content uniformity of nifedipine in the tablets upon preparation. Drug content was determined by analyzing the drug using an HPLC system as previously described (Bayomi et al., 2002). Briefly, each tablet was crushed individually in a mortar into fine powder, and then an 80 mg sample was subjected to extraction with 2 ml of methanol/chloroform (50:50) in a clean dry screw-capped glass centrifuge tube (10 ml). The mixture was shaken using a vortex mixer (Vortex-2 Genie, Scientific Industries Inc., Bohemia, N.Y., U.S.A.) for 1 min and then centrifuged for 5 min using MSE Mistral 1000 centrifuge (Loughborough, Manchester, U.K.). An aliquot of 50 µl of supernatant solution was diluted to a final volume of 2 ml with 50% methanol/chloroform solution and vortexed for 30 s. An 80 µl volume of the diluted solution was then transferred to another glass centrifuge tube containing 50 µl aliquot of 1.2 µg/ml diazepam as internal standard. The sample was then evaporated to dryness in a rotary evaporator and reconstituted with 250 µl of methanol and the solution was then shaken with a vortex mixer for 15 s and centrifuged for 2 min in a microcentrifuge (Model 1 to 13, Sigma Co., Osterode am Harz, Germany). An aliquot of 50 µl of each sample was then injected directly into the loop of the injector of the HPLC system and was subjected to analysis to determine the concentration of nifedipine. The HPLC system (Waters Associates, Milford, MA, U.S.A.) was equipped with model 6000 A reciprocating pump and a model U6K universal injector. A model 486 variable wavelength detector was used to monitor the drug at 236 nm and the output was recorded using model 730 data module (Waters Associates). Chromatographic separation was performed using a Nova-Pak C-18 Cartridge column (100 mm length × 5 mm i.d., 4 µm particles). The mobile phase consisted of a solvent system of acetonitrile, methanol and water (3:2:5, v/v), and was pumped at a flow rate of 2.8 ml/min. Sample preparation and analysis were conducted at room temperature under sodium lamp.

Dissolution studies

Formulated tablet as well as commercial 10 mg soft gelatin capsules and 10 mg film coated tablets were subjected to dissolution studies. The dissolution studies were carried out at 37 ± 0.5°C with 50 rpm paddle rotation speed in a USP XXIV dissolution test apparatus II, using an automated monitoring system (Caleva Ltd., Model 85 T). The monitoring system consisted of an IBM computer PK 8620 series and PU 9605/60 dissolution system software, Philips UV/Vis/NIR single beam spectrophotometer PU 8605/50 eight cells program, Epson LX 850 printer and Watson-Marlow peristaltic pump. Samples were allowed to dissolute in 900 ml dissolution medium of simulated gastric fluid without pepsin. Drug dissolution was monitored spectrophotometrically at 236 nm for up to 90 min. Sink condition was maintained throughout the dissolution time since the amount of dissolved nifedipine in the medium was much lower than its solubility. Each experiment was carried out in triplicate and the mean of the three dissolution tests was recorded.

In vivo studies

Five healthy male beagle dogs weighting between 10 and 14 kg (mean weight: 10.8 kg) were used. The dogs were fasted for 24 h before drug administration and continued fasting until 4 h post dose, but allowed free access to water. Each dog was administered two (10 mg) commercial soft gelatin capsules, two (10 mg) film coated commercial tablets or two (10 mg) formulated fast release CD tablets. A washout period of 2 weeks was ensured between different phases. No other medication was taken during the study period. Venous blood samples (5 ml) were taken from the femoral vein into heparinized tubes before drug administration and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00 and 10 h after drug administration. Blood samples were centrifuged at 3000 rpm for 10 min and plasma samples were collected and kept at -70°C pending analysis.

Assay of nifedipine in dog plasma

Sample preparation and analysis were conducted at room temperature under sodium lamp. Nifedipine was assayed using a modified HPLC method that was previously reported (Abou-Auda et al., 2002). Briefly, a 50 µl aliquot of 1.2 µg/ml diazepam (internal standard) was added to plasma sample, and then vortex-mixed for 30 s in 10 ml glass stopered tube. An aliquot of 5 ml diethylether was then added. This mixture was vortex-mixed for 1 min and centrifuged at 3000 rpm for 10 min. The supernatant organic layer was quantitively transferred to another 10 ml glass centrifuge tube and the contents were evaporated to dryness at room temperature under a stream of pure nitrogen. The residue was reconstituted in 250 µl of mobile phase; vortex-mixed for 30 s. Aliquots of 50 µl were then injected into the column. The mobile phase was consisted of acetonitrile-methanol-water (3:2:5, v/v). The pH of the mixed solvents was adjusted to 3.0 with acetic acid. The mobile phase was pumped isocratically at a flow rate of 1.8 ml/min during analysis at ambient temperature. The HPLC system was similar to that used in the assay of tablets and detector was used to monitor the drug at 236 nm. Chromatographic separation was performed using a Nova-Pak C-18 Cartridge column (100 mm length × 5 mm i.d., 4 µm particles).

Statistical analysis

Data of physical properties, drug content for different tablet samples as well as blood samples of *in vivo* study were compared statistically using one-way analysis of variance (ANOVA) at a significant level $P \leq 0.05$.

RESULTS AND DISCUSSION

Powder samples of nifedipine-CD complexes showed angles of repose ≥ 45 (°) and compressibility index values >35% which suggest poor flowability of the powders. Nifedipine-DM-β-CD complex powder showed the highest value for angle of repose 52.0 ± 2.0 (°) and a value of compressibility index equal to 44.4 ± 1.2%. On the other hand, the least values were 45.0 ± 1.8 and 35.7 ± 1.0%, respectively for nifedipine-β-CD complex powder. The aforementioned results indicated that the amount of nifedipine-CD powders should not exceed 25% of tablet weight (Rubenstien, 1996) and it was necessary to choose direct compressible vehicles having good flow properties. Microcrystalline cellulose (MCC; Avicel PH101) and spray dried lactose were chosen as tablet

Table 1. Tablet formulations using lactose (A) or MCC (B) as fillers.

Ingredient	Formulation A (%w/w)	Formulation B (%w/w)
The equivalent of nifedipine*	5	5
Starch	5	5
Magnesium stearate	0.5	0.5
Spray dried lactose	to 100	-
Microcrystalline cellulose	-	to 100

*Equivalent of nifedipine in CD inclusion complex or in physical mixture with CD at 1:1 molar ratio.

Table 2. Evaluation of different formulated nifedipine tablets.

Evaluation parameter	Filler	Nifedipine	Nifedipine β-CD tablets	Nifedipine HP-β-CD tablets	Nifedipine DM-β-CD tablets
Weight (mg) ± SD	A	194.9 ± 4.70	191.6 ± 6.7	197.8 ± 7.08	196.6 ± 6.70
Drug content (mg) ± SD		10.04 ± 0.12	10.08 ± 0.20	10.05 ± 0.19	9.99 ± 0.23
Crushing strength (kp) ± SD		4.61 ± 0.33	5.25 ± 0.45	6.04 ± 1.08	5.81 ± 0.63
Disintegration time (s)		300	308	291	208
Weight (mg) ± SD	B	202.8 ± 3.51	2.04.6 ± 3.47	201.0 ± 4.44	201.7 ± 5.22
Drug content (mg) ± SD		10.1 ± 0.18	9.93 ± 0.15	10.0 ± 0.1	9.96 ± 0.26
Crushing strength (kp) ± SD		6.02 ± 0.62	6.03 ± 0.36	6.62 ± 1.43	5.05 ± 0.89
Disintegration time (s)		52	39	21	13

A: Tablet filler is spray dried lactose; B: Tablet filler is microcrystalline cellulose.

fillers (base) while, the other tablet components were chosen to be compatible and commonly used for tablet preparation, and their amounts were kept the same for all studied tablet formulations (Table 1). All the prepared tablets have good appearance and tablet weights in the range of 200 ± 15 mg. The mean drug content for the prepared tablets was 10.04 ± 0.12 mg. Table 2 shows the physical properties of the prepared tablets. All tablet batches had acceptable crushing strength (as designed) and were fast disintegrating.

Although, a constant compression force was used in preparing the tablets, tablets crushing strength is depended on filler and CD used in the formulation (Table 2). Generally, nifedipine-HP-β-CD tablets showed the highest crushing strength values for both tablet fillers with higher value with microcrystalline cellulose (6.62 ± 1.43 kp) when compared with spray dried lactose (6.04 ± 1.08 kp). In addition, for the spray dried lactose tablets, the crushing strength was decreasing in the following order: nifedipine-HP-β-CD> nifedipine-DM-β-CD> nifedipine-β-CD> uncomplexed nifedipine tablets. Furthermore, for the microcrystalline cellulose tablets, the crushing strength was decreasing in the following order: nifedipine-HP-β-CD> nifedipine-β-CD> uncomplexed nifedipine tablets> nifedipine-DM-β-CD. Disintegration times for tablets containing complex of nifedipine were also different depending on the type of complexing agent as well as tablet filler. Disintegration time was decreasing in the following order: uncomplexed nifedipine tablets> nifedipine-β-CD> nifedipine-HP-β-CD> nifedipine-DM-β-CD tablets. Tablets prepared with MCC gave fast disintegration time (13 to 52 s) when compared with spray dried lactose (208 to 308 s).

Figures 1 and 2 show the dissolution profiles of nifedipine in the tablets with nifedipine-CD inclusion complexes or nifedipine in physical mixtures with CDs that were prepared with spray dried lactose and MCC, respectively. The dissolution of nifedipine from different tablet formulations was found to be mainly dependent on the type of CD. It was also clear that the dissolution of nifedipine in physical mixtures with CD was generally much slow due to the low water solubility of the uncomplexed drug, while tablets containing complex of nifedipine showed fast drug dissolution. The dissolution of the complexes of nifedipine was ranked in an ascending order as follows: nifedipine-HP-β-CD> nifedipine-β-CD> nifedipine-DM-β-CD tablets. According to the USP XXIV, nifedipine soft gelatin capsules (as immediate release oral dosage forms) should release 80% of its drug content within 20 min. Based on that, the dissolution properties of nifedipine from the proposed fast release CD tablet formulations were evaluated using dissolution efficiency (DE) in 20 min, percent of drug dissolved in 20 min (DP) and time to dissolve 80% of the

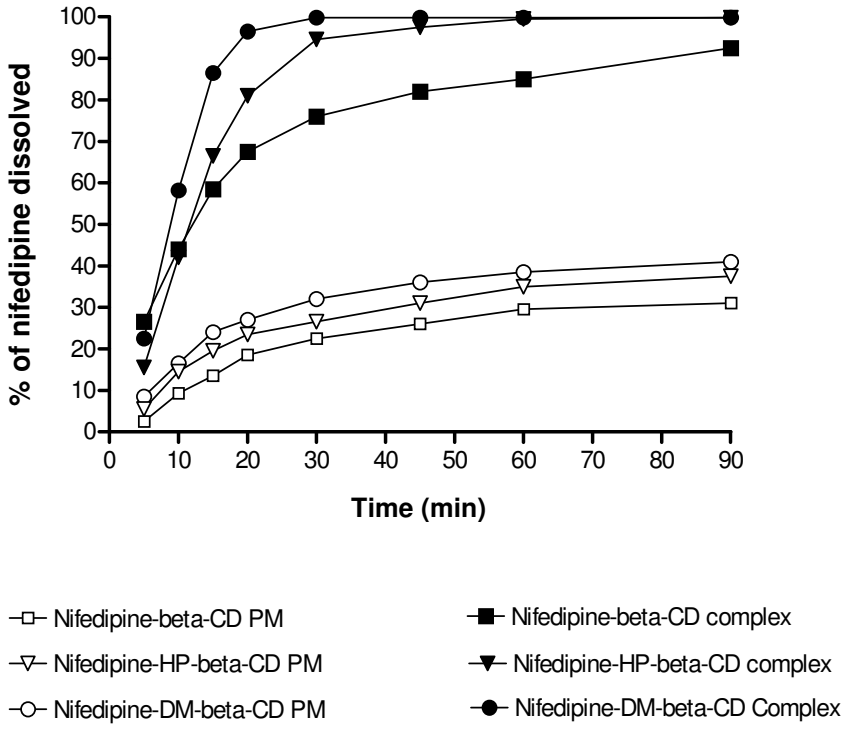

Figure 1. Dissolution profiles of nifedipine from spray dried lactose based tablets containing nifedipine-cyclodextrin inclusion complexes or corresponding physical mixtures (PM) at 37 ± 0.5°C (n = 3).

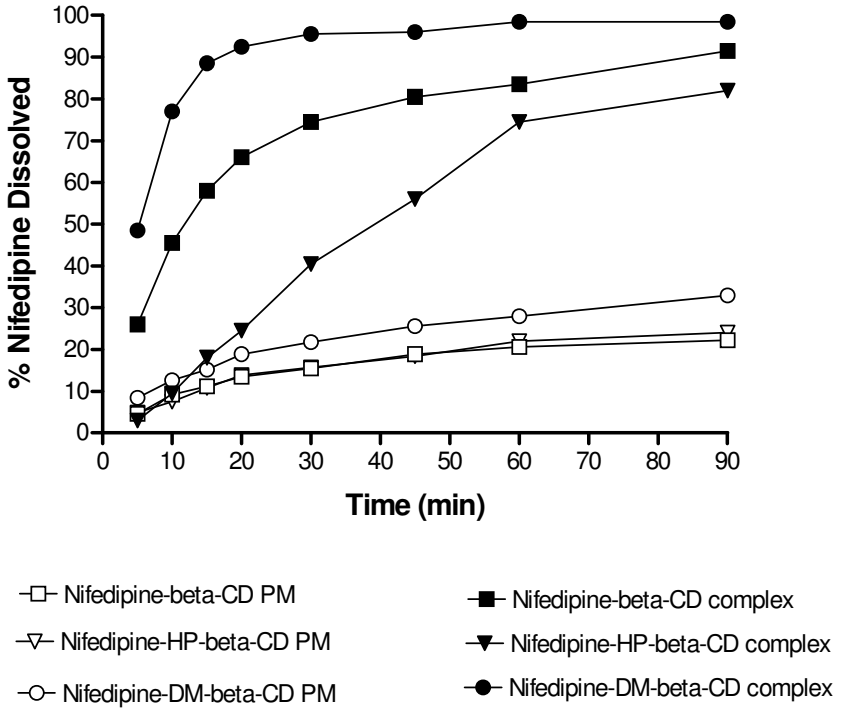

Figure 2. Dissolution profiles of nifedipine from microcrystalline cellulose based tablets containing nifedipine-cyclodextrin inclusion complexes or corresponding physical mixtures (PM) at 37 ± 0.5°C (n = 3).

Table 3. Dissolution efficiency (DE, %)(a), percent of drug dissoluted in 20 min (DP,%) and time to dissolve 80% of drug (t80%, min) of nifedipine from tablets containing complex of nifedipine using spray dried lactose as a filler when compared with commercial soft gelatin capsules and film coated tablets.

Formulation	DE[a] (%)	DP (%)	$T_{80\%}$ (min)
Nifedipine- β-CD tablets	40.29	66.48	36.5
Nifedipine–HP-β-CD tablets	41.06	81.74	19.5
Nifedipine-DM- β-CD tablets	52.95	96.17	14
Soft gelatin capsules (Adalat®)	38.4	93.3	14.6
Film coated tablets (Corinfar®)	8.8	12.3	-

(a)Dissolution efficiency calculated from the area under dissolution curve at t =20 min and expressed as % of the area of the rectangle described by 100% dissolution in the same time.

Table 4. Dissolution efficiency (DE, %)[(a)], percent of drug dissoluted in 20 min (DP,%) and time to dissolve 80% of drug ($t_{80\%}$, min) of nifedipine from tablets contain complex of nifedipine using MCC as a filler when compared with commercial soft gelatin capsules and film coated tablets.

Formulation	DE[a] (%)	DP (%)	$T^*_{80\%}$ (min)
Nifedipine- β-CD tablets	40.47	65.56	44.5
Nifedipine–HP-β-CD tablets	10.69	24.97	68
Nifedipine-DM- β-CD tablets	64.75	92.81	11
Soft gelatin capsules (Adalat®)	38.4	93.3	14.6
Film coated tablets (Corinfar®)®)	8.8	12.3	-

[(a)]Dissolution efficiency calculated from the area under dissolution curve at t = 20 min and expressed as % of the area of the rectangle described by 100% dissolution at the same time.

drug ($t_{80\%}$), where dissolution efficiency can be calculated from the area under dissolution curve at t = 20 min and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975). According to the obtained values of DE% and $t_{80\%}$ (Table 3), it was concluded that the prepared tablets that can give fast nifedipine release comparable to that of soft gelatin capsules are tablets containing nifedipine-HP-βCD and nifedipine-DM-β-CD prepared with spray dried lactose as tablet filler. Similarly, it can be observed from Table 4 that tablets containing nifedipine-DM-β-CD prepared using MCC can give fast nifedipine release comparable to that of soft gelatin capsules. On the other hand, nifedipine-HP-βCD tablets prepared with lactose filler showed much comparable DE% value to the soft gelatin capsules as compared to the nifedipine-DM-β-CD tablets prepared using lactose (Table 3) or prepared using MCC (Table 4). Thus, tablets of nifedipine-HP-βCD equivalent to 10 mg nifedipine in lactose were selected for *in vivo* studies and compared with commercial 10 mg nifedipine soft gelatin capsules (Adalat®) and 10 mg film coated tablets (Corinfar®).

Figure 3 shows the dissolution profiles of the prepared nifedipine-HP-βCD tablets in comparison to nifedipine soft gelatin capsules (Adalat®) and nifedipine film coated tablets (Corinfar®). As expected and since the prepared nifedipine-HP-βCD tablets are fast release tablets, their dissolution profile is similar to the nifedipine soft gelatin capsules (Adalat®) and very dissimilar to the film coated nifedipine tablets (Corinfar®).

Figure 4 shows dog plasma concentration versus time curve of nifedipine after oral administration of two doses of the commercial soft gelatin capsule Adalat® and film coated tablet Corinfar® when compared with the prepared fast release tablets of 10 mg nifedipine. Table 5 shows the pharmacokinetic parameters of nifedipine after oral administration of the three dosage forms to dogs. It was obtained that there were no significant differences ($P > 0.05$) for maximum drug concentration (C_{max}) between Adalat and the prepared fast release tablets while there were significant differences ($P < 0.05$) between Adalat (soft gelatin capsule) and Corinfar (film coated tablets) as well as Cornifar and formulated tablets. The high C_{max} values for soft gelatin capsule and the formulated fast release tablets indicates faster drug absorption for both formulation when compared with the film coated tablets. It was also interesting to figure out that the formulated tablets gave no significant difference in the amount of drug absorbed (as indicated from C_{max}) with that of soft gelatin capsules that is used for fast nifedipine therapeutic effect. On the other hand there were no significant differences ($P > 0.05$) in T_{max} between all the tested formulations which support the findings and reveals that soft gelatin capsule and formulated tablets

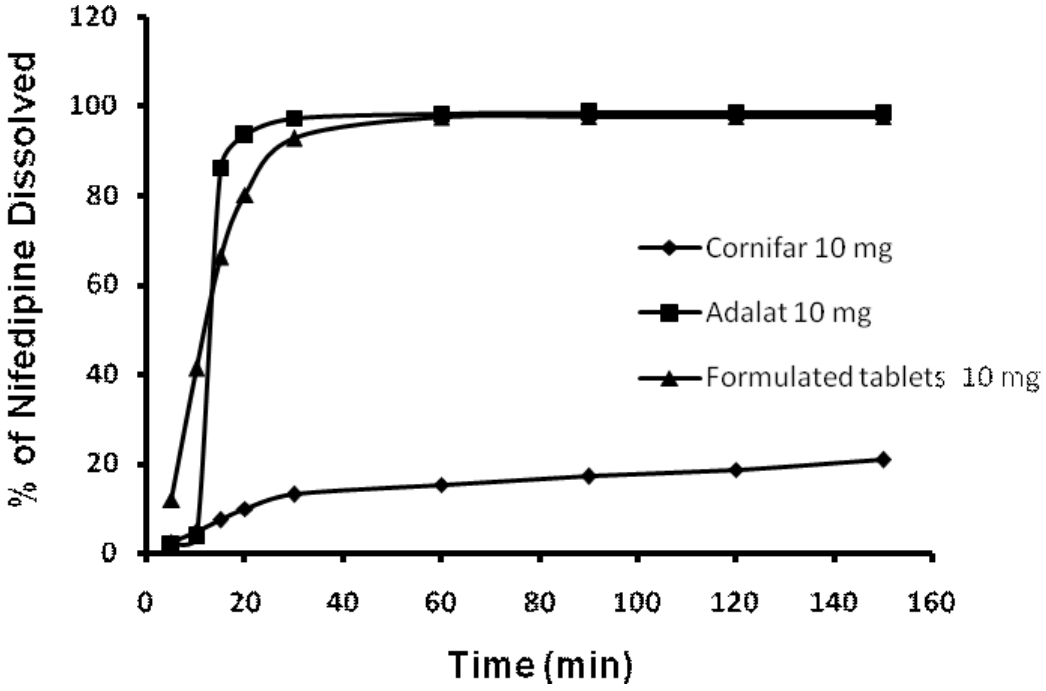

Figure 3. Dissolution profile of formulated tablets of nifedipine-HP-beta-cyclodextrin (10 mg) compared with commercial nifedipine products; Adalat® soft gelatin capsule (10 mg) and Cornifar® film coated tablets (10 mg).

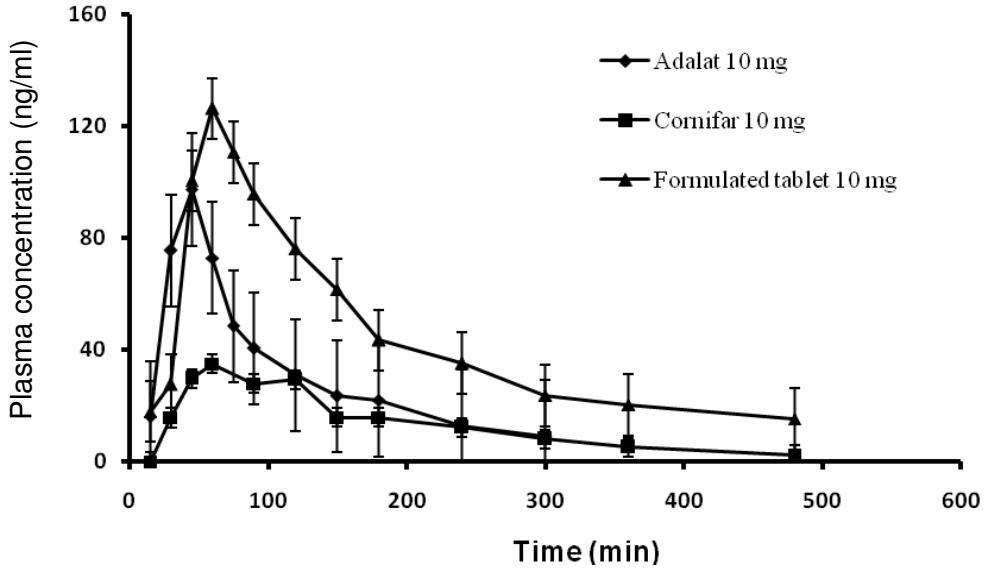

Figure 4. Mean plasma nifedipine concentration versus time curve for formulated tablets when compared with the commercial Adalat® soft gelatin capsule (10 mg) and Cornifar® film coated tablets (10 mg) after oral administration to five beagle dogs.

have the same onset of effect with non-significant difference ($P > 0.05$) in blood level of nifedipine. Film coated tablets showed similar onset of action, however maximum blood level is much smaller than the other two dosage forms. Also, the values of AUC_{0-t} and $AUC_{0-\infty}$ showed no significant difference ($P > 0.05$) between soft gelatin capsules and film coated tablets, indicating similar extent of drug absorption for both dosage form. On the

Table 5. Pharmacokinetics parameters (Mean ± S.E) of nifidipine following oral administration of the commercial tablet Adalat ® (10 mg soft gelatin capsule), Corinfar ® (10 mg film coated tablets) and formulated fast release 10 mg tablets to dogs (n = 5).

Pharmacokinetic parameter	Adalat®	Corinfar®	Formulated tablets
C_{max} (ng/ml)	109.24 ± 9.08	37.2 ± 5.34	131.76 ± 6.13
t_{max} (h)	0.70 ± 0.05	1.0 ± 0.14	0.95 ± 0.05
AUC_{0-t} (ng.h/ml)	140.96 ± 14.82	103.21 ± 23.55	297.68 ± 42.89
$AUC_{0-\infty}$ (ng.h/ml)	160.58 ± 17.54	122.05 ± 28.89	377.28 ± 56.47

other hand, the newly formulated fast release tablets showed much higher extend of drug absorption when compared with soft gelatin capsules and film coated tablets as indicated from the significant high values of both AUC_{0-t} and $AUC_{0-\infty}$.

Conclusion

From the earlier discussed *in vitro* results, it was concluded that, fast release nifedipine tablets were successfully prepared using nifedipine-CD complex. The dissolution properties of nifedipine from the formulated nifedipine-CD complex tablets were initially dependent on the type of CD along with the tablet filler. Some of the formulated tablets, using complex of nifedipine with modified β-CDs, were successful to give fast nifedipine release properties resembling that of soft gelatin capsules. *In vivo* studies on the selected formulation of nifedipine-HP-βCD tablets showed bioavailability similar to soft gelatin capsules regarding maximum blood concentration and time to reach that maximum with superiority in extent of nifedipine absorption (AUC) after oral administration to dogs. The formulated fast release tablet is also having the advantages that it would need less restricted light protection during manufacturing, storage and handling which is an important property during nifedipine tablet manufacturing.

ACKNOWLEDGEMENT

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this work through the research group project No. RGP-VPP-143.

REFERENCES

Abou-Auda HS, Najjar TA, Al-Khamis KI, Al-Hadiya BM, Ghilzai NM, Al-Fawzan NF (2000). Liquid chromatographic assay of nifedipine in human plasma and its application to pharmacokinetic studies. J. Pharm. Biomed. Anal., 22: 241-249.

Baboota S, Agarwal SP (2003). Meloxicam complexation with beta-cyclodextrin: influence on the anti-inflammatory and ulcerogenic activity. Pharmazie, 58(1): 73-74.

Banker GS, Anderson NR (1986). Tablets. In The Theory and Practice of Industrial Pharmacy; Lachman L, Lieberman HA, Kanig JL, Eds.; Lea and Febiger: Philadelphia.

Bayomi MA, Abanumay KA, Al-Angary AA (2002). Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state. Int. J. Pharm., 243: 107-117.

Bekers O, Uijtendal EV, Beijnen JH, Bult A, Underberg WJ (1991). Cyclodextrins in pharmaceutical field. Drug. Dev. Ind. Pharm., 17: 1503-1549.

Chowdary KP, Ramesh KV (1994). Improvement of dissolution rate and efficiency of nifedipine by solid dispersion in PVP-MCC and HPC-MCC. Indian J. Pharmaceut. Sci., 56: 95-99.

Chutimaworapan S, Ritthidej GC, Yonemochi E, Oguchi T, Yamamoto K. (2000). Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions. Drug. Dev. Ind. Pharm., 26(11): 1141-1150.

Duchene D, Wouessidjewe D (1990). Pharmaceutical uses of cyclodextrins and derivatives. Drug. Dev. Ind. Pharm., 16: 2487-2499.

Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K (2005).Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int. J. Pharm., 299: 167-177.

Khan KA (1975). The Concept of Dissolution Efficiency. J. Pharm. Pharmacol., 27: 48-49.

Melia CD, Davis SS (2007). Mechanism of drug release from tablets and capsules. 2. Dissolution. APT, 3: 513-525.

Nalluri BN, Chowdary KP, Murthy KV, Becket G, Crooks PA (2007). Tablet formulation studies on Nimesulide and meloxicam-cyclodextrin binary systems. AAPS Pharm. Sci. Tech., 8: 36.

Rasheed A, Kumar A, Sravanthi V (2008). Cyclodextrins as drug carriers molecules: A review. Sci. Pharm., 76: 567-598.

Rubenstien MH (1996). Tablets: In Pharmaceutics: The Science of Dosage Form Design; Aulton ME, Eds.; Churchill Livingstone: New York.

Suzuki H, Sunada H (1988). Influence of water-soluble polymers on the dissolution of nifedipine solid dispersion with combined carriers. Chem. Pharm. Bull., 46: 482-487.

Varshosaz J, Dehghan Z (2002). Development and characterization of buccoadhesive nifedipine tablets. Eur. J. Pharmaceut. Biopharmaceut., 54: 135-141.

Yen SY, Chen CR, Lee MT, Chen LC (1997). Investigation of dissolution enhancement of nifedipine by deposition on superdisintegrants. Drug. Dev. Ind. Pharm., 23: 313-317.