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IN VITRO RELEASE KINETICS OF POORLY WATER-SOLUBLE CARDIOVASCULAR DRUGS FROM PEG - NANOPARTICLES

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In this paper, poorly-water soluble drugs: valsartan (VAL) and amlodipine besylate (AML) were loaded with two different amount of polyethylene glycol (PEG) 4000 and 6000 polymers in order to obtain nanocomposites to improve the bioavailability and efficacy of active pharmaceutical ingredients (APIs). All the prepared polymeric nanoparticles have shown good entrapment efficiency (EE%). The in vitro drug release behavior of APIs was determined by using a dialysis membrane method under sink conditions and various kinetic models were exploited to predict drug release profile.

Keywords: drug release, release kinetics, nanoparticles, cardiovascular drugs

1. Introduction

Nowadays, the most frequently encountered and crucial obstacle for the development of innovative therapies is represented by a wide range of drugs with low water solubility which leads to low quantities of APIs (active pharmaceutical ingredients) become available for diffusion, insufficient drug concentrations at the site of action and failure of the treatment *in vivo* [1], meaning poor bioavailability and hence therapeutic failure.

According to the biopharmaceutical classification system (BCS), which categorizes APIs for oral administration into four groups: class I (high solubility and high permeability), class II (low solubility and high permeability), class III (high solubility and low permeability), and class IV (low solubility and low

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permeability), currently more than 40% of the top 200 oral drugs marketed in the USA and Europe fall in the BCS Class II and Class IV categories [2-4]. In addition, they represent 90% of new chemical entities, 75% of compounds under development, and more than 33% of drugs listed in the US Pharmacopeia, used for the treatment of cancer and cardiovascular diseases [5].

Over the past decades, many efforts have been made in the development of novel formulations, as well as the application of new technologies to achieve enhanced bioavailability of drugs with poor aqueous solubility. Although conjugating drug to dendrimers, complexing drugs with cyclodextrins, salt formation of ionizable drugs, prodrugs, solid dispersions, use of co-solvents, hot melt extrusion and spray-drying technology, all have been capable to circumvent solubility, dissolution rate, and bioavailability problems of poorly water-soluble drugs, a universal solubilization technique suitable for most hydrophobic drugs is still highly desirable [6,7].

The interest in nanoscience, nanotechnology in medicine and nanopharmacy is in continuous growing mainly due to their several advantages for the delivery of low water-soluble drugs. Thereby, drug nanoparticle dispersion systems (micelles, nanocrystals, polymeric nanoparticles, nano-/micro-emulsions, liposomes, mesoporous silica nanoparticles) (1) improve the dissolution rate and solubility of poorly water-soluble drugs, (2) enhance specific interactions with cells and tissues, (3) promote absorption and enhance bioavailability for BCS class II and IV drugs, (4) enhance the chemical stability of some drugs and control their release profile in gastrointestinal tract, (5) could be tailored via surface functionality to achieve long circulation and targeted delivery [8,9].

One of the most studied carriers for drug dispersion formulation is polyethylene glycol (PEG), also known as Macrogol. The molecular weight of this semi-crystalline, synthetic polymer usually lies between the range of 200 and 300,000, although molecular weights between 1500 and 20,000 only are used, due to their less hygroscopicity and solid nature at room temperature and probably due to the fact that lower molecular weights have slight toxicity issues [10-12]. Their low melting points (65°C), as well as good solubility in both aqueous and organic solvents, make them good candidates for both solvent and fusion based methods [13]. Withal, the PEG chain length, molecular weight, and drug loading influence the dissolution rate of the drug.

In view of the aforementioned, the current research aims to develop PEG - NPs loaded with a fixed-dose combination (amlodipine besylate:valsartan) and to investigate the effect of PEG molecular weight and concentration on entrapment efficiency and release behavior. Amlodipine besylate - AML (a calcium channel blocker) and valsartan - VAL (an angiotensin II receptor antagonist drug) are both very poorly-water soluble (BCS class II). Also, in this paper we have shown the mathematical models used to determine the kinetics of drug release from drug delivery systems. The quantitative analysis of the values obtained in release rates is easier when mathematical formulae are used to describe the process. Consequently, the mathematical modeling can ultimately help to optimize the design of a therapeutic system to yield information on the efficacy of various release models.

2. Experimental

2.1. Materials

Polyethylene glycols (PEG, average M.W. = 4000 and average M.W. = 6000) were purchased from Acros Organics (Germany). Both APIs: amlodipine besylate ($C_{26}H_{31}ClN_2O_8S$, 2-[(2-aminoethoxy)-methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester benzene sulfonate) and valsartan ($C_{24}H_{29}N_5O_3$, N-(1-Oxopentyl)-N-[[2′-(2H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine) were obtained from Sigma Aldrich (USA). As stabilizer was used Poloxamer 407, known as Pluronic F127 (poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)) obtained from Sigma-Aldrich (USA). Acetone (AdraChim SRL, Bucharest, Romania), analytical grade, was used in the precipitation process. The water used for all experiments was distilled. The *in vitro* drug release studies were performed in 0.1 M phosphate buffer at pH 6.8. All other chemicals were of analytical grade obtained from standard sources and used without further purification.

2.2. Preparation of PEG 4000/ PEG 6000 NPs with AML, VAL and AML-VAL encapsulated

NPs were prepared according to nanoprecipitation method [14]. The experimental procedure was as follows. PEG 4000 and 6000 at two different concentrations (5, 7.5 mg) were dissolved in acetone (5.0 mL). AML:VAL in a fixed-dose combination (1:16 mg) was each solved in PEG 4000/acetone, PEG 6000/ acetone mixture respectively. Pluronic-F127 (5 mg) was dissolved in distilled water (10 mL). The organic phase was added dropwise into the aqueous phase solution and stirred magnetically at 1200 rpm at room temperature (25ºC) until complete evaporation of the organic solvent (Table 1).

Table 1

Preparation of PEG 4000 and PEG 6000 NPs with AML-VAL encapsulated

Sample cod	m_{AML} (mg)	m_{VAL} (mg)	$m_{PEG4000}$ (mg)	$m_{PEG6000}$ (mg)	m_{F127} (mg)	Drop rate (mL/min)	Stirring speed (rpm)	Stirring time (min)
F1	1	16	-	5	5	0.5	1200	60
F2	1	16	-	7.5				
F3	1	16	5	-				
F4	1	16	7.5	-				

All samples were prepared in triplicate. The final nanosuspensions were centrifuged at 10 000 rpm (Universal 320R Hettich, Germany) for 30 minutes at 4°C to separate free drug from loaded polymeric nanoparticles.

2.3. Evaluation of APIs encapsulation efficiency

The PEG-NPs were centrifuged, and the supernatant was separated. The amount of drug encapsulated in the polymeric NPs was determined as the difference between the initial number of APIs used for NPs preparation and the number of APIs present in the supernatant. The percentage of encapsulated drugs was determined by using UV-VIS spectrophotometer at 365 nm for AML and 250 nm for VAL (JASCO V-630 Spectrophotometer, Jasco International Co., Ltd., Japan). APIs encapsulation efficiency was expressed as Encapsulation Efficiency (EE, %) and was calculated using the following equation (1):

$$EE\,(\%) = \frac{\text{Initial amount of APIs} - \text{Amount of APIs in supernatan t}}{\text{Initial amount of APIs}} \times 100 \tag{1}$$

2.4. Measurement of particle size and polydispersity index

Particle size and polydispersity index (PDI) were determined by Dynamic Light Scattering (DLS) technique using a particle size analyzer - Beckman Coulter N4 PCS Submicron, Coulter Company, with measurement range between 3 nm and 3 µm. Particle size and PDI were measured on samples appropriately diluted with distilled water (1:20). All the measurements were performed at a scattering angle of $90^{0,}$ temperature of 25^{0}C, solvent refractive index of 1.458 and solvent viscosity of 0.8872 cP. For each sample the mean value ± standard deviation of ten determinations were established. Values reported are the mean value ± standard deviation for three replicate samples.

2.5. *In vitro* drug release study of AML-VAL from the nanoparticulate formulation

The APIs release from the PEG-NPs was determined by a dialysis membrane method under sink conditions [15]. 1.0 mL of the nanoparticle suspension was placed in a dialysis tubing cellulose membrane (dialysis bag) with 14,000 molecular weight cut-off (Sigma Aldrich, USA), the ends of the dialysis bag were tightened and then immersed into a 100 mL previously prepared of 0.1 M sodium phosphate buffer pH 6.8 at 37 °C. The whole system was under stirring at 150 rpm. Samples were taken at predetermined intervals (15', 30', 45', 60', 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 24 h, 2 days, 3 days, 4 days, 5 days) from the receiver solution. The released drugs in each time point were determined by spectrophotometry using a UV-VIS spectrophotometer. During the release process, a dialysis medium of 3.0 mL was removed at a predetermined time point while adding the same volume of fresh medium (0.1 M sodium phosphate buffer, pH 6.8). The release studies were performed in triplicate.

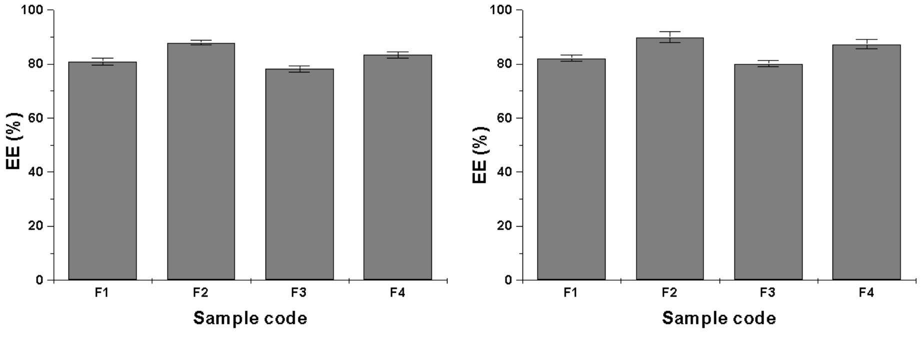
2.6. Statistical analysis

Statistical analysis of the data was performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Values are represented as mean ± standard deviation (SD). Differences were considered significant at $p < 0.05$.

3. Results and discussions

3.1. Entrapment efficiency

In order to develop a formulation with high entrapment efficiency of a fixed-dose combination AML-VAL, PEG-NPs were synthesized and the effects of PEG molecular weight (4000 and 6000) and polymer amount (5 and 7.5) on entrapment efficiency were studied. The entrapment efficiency of PEG-NPs was reported in Fig. 1.



a) AML

b) VAL

Fig. 1. Entrapment efficiency of PEG-NPs loaded with AML-VAL

All formulations showed high EE (%) for both APIs, ranged from 80.01 ± 0.11% to 89.88 ± 2.01% for VAL and from 78.21 ± 0.12% to 87.88 ± 0.10% for AML. An increase in the molecular weight of PEG led to a slight increase in the entrapment efficiency of the formulations. Also, an increase in PEG amount enhanced the entrapment efficiency of the nanoparticles. It was observed that the polymer amount influenced in a greater extent the drug entrapment efficiency than PEG molecular weight. A possible explanation for these results is that using PEG with higher molecular weight or a larger amount of a polymer resulted in an increase in the viscosity of the polymer solution; thus a much less likelihood of particle breakage in a more viscous environment under the same stirring energy. Therefore, the formulation with a higher amount of polymer and molecular weight (F2) had the best results with a EE% of 89.88 ± 2.01% for VAL and 87.88 ± 0.10% for AML. Similar results were also reported in literature [16, 17].

3.2. Particle size and polydispersity index

PEG-NPs with cardiovascular APIs encapsulated were characterized in terms of mean particle size and PDI. As shown in Table 2, PEG-NPs had mean particle size in the range of 205.5 ± 1.24 - 240.4 ± 1.55 nm. As the content and Mw of PEG were increased, the particle size of PEG-NPs was also increased. As the concentration and Mw of PEG increase, the viscosity of the nanosuspension increases proportionally; thereby these phenomena lead to an increase in the size of the nanoparticles [17]. Also, particle size analysis showed a narrow range of variability in dispersion (PDI, 0.079 ± 0.03 – 0.108 ± 0.03). All samples showed a narrow size distribution (PDI < 0.11), which means significantly higher homogeneity of the systems and a low tendency of aggregation.

Table 2

Characteristics of PEG 4000 and PEG 6000 NPs with AML-VAL encapsulated

Formulation code	$m_{PEG4000}$ (mg)	$m_{PEG6000}$ (mg)	Mean particle size (nm)	PDI
F1	-	5	218.5 ± 1.14	0.095 ± 0.05
F2	-	7.5	240.4 ± 1.55	0.089 ± 0.02
F3	5	-	205.5 ± 1.24	0.108 ± 0.03
F4	7.5	-	211.4 ± 1.30	0.079 ± 0.03

3.3. *In vitro* drug release studies

A release study of AML and VAL from PEG-NPs was performed in PBS 0.1M at pH 6.8 by using the dialysis method. Also, a combination of AML-VAL (free drugs) was subjected to the same release conditions as control. The release data, expressed as cumulative drug release (CDR) vs. time, were presented in Fig. 2 and Fig. 3.

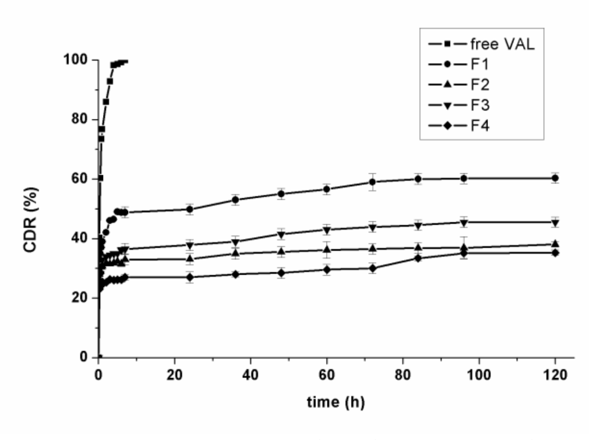


Fig. 2. *In vitro* AML release profile of PEG-NPs vs free drug

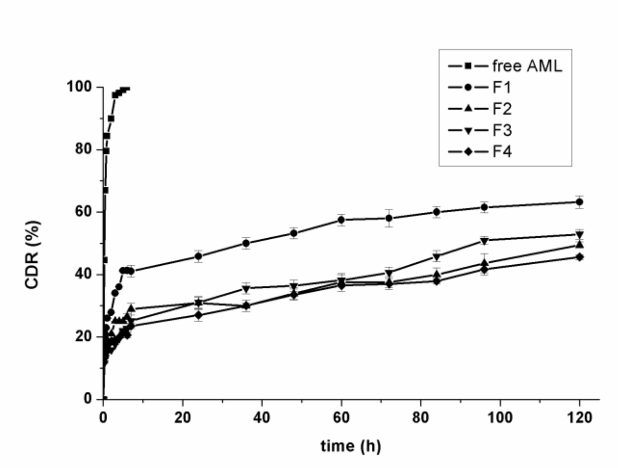


Fig. 3. *In vitro* VAL release profile of PEG-NPs vs free drug

The release profile of free drugs presented an initial “burst effect” with 67 ± 0.28% for AML, and 60.30 ± 0.15% for VAL, respectively, released in 30 minutes. The release of free AML-VAL reached a maximum after 6 h for AML and respectively 7h for VAL. PEG-NPs provided a much slower release than free drugs. The burst effect was drastically decreased in nanoformulations (a CDR below 20 % for AML and 38 % for VAL were released in the initial 30 minutes from all PEG-NPs).

It was observed that both parameters, molecular weight and amount of PEG, influenced AML and VAL release. The formulation with the smaller amount of polymer and 6000 molecular weight (F1) had higher CDR, with release reaching a maximum of 63.20 ± 2.03% for AML and 60.30 ± 1.74% for VAL after five days. As the molecular weight of PEG decreased there was a decrease in CDR of the formulation, for example the release from F3 reaching a maximum of 52.90 ± 1.54% for AML and 44.10 ± 1.67% for VAL in the same time frame. As the proportion of polymer increased, the release of drugs decreased, for example the release from F2 reaching a maximum of 49.50 ± 0.99% for AML and 38.10 ± 0.94% for VAL in the same time frame.

3.4. Analysis of drug release

Over the couple of decennia, mathematical modeling of release process represents a need of time whether the drug remains in the circulation or reaches at the target site. For establishing a better *in vitro – in vivo* correlation, release kinetics models, such as Korsemeyer-Peppas, Higuchi, Weibull, Zero Order and First order including mechanistic models like All-or-None, Toroidal, and Biomembrane models etc. are continuously exploited to predict drug release profile [18-22]. Most of these models rely on the diffusion equations based on the composition of nanoparticles and conditions of release. Here, the *in vitro* release data were subjected to kinetic analysis to establish the drug release mechanism. Therefore, release data were fitted to three empirical models: Zero-order (equation 1), First-order (equation 2), Higuchi (equation 3), and two semiempirical models: Korsemeyer - Peppas (equation 4) and Hixson – Crowell (equation 5):

$$Q_t = k_0 t \tag{1}$$

$$\ln Q_t / Q_0 = -k_1 t \tag{2}$$

$$Q_t = k_H \sqrt{t} \tag{3}$$

$$Q_t = k_{KP} t^n \tag{4}$$

$$Q_t = Q_0 \left[1 - (1 - k_{HC} t)^3\right] \tag{5}$$

where Qt is the amount of drug released at time t, Q_0 is the initial amount of drug from solution, and k_0, k_1, k_H, k_{KP} and k_{HC} are release rate constants for zero-order, first-order, Higuchi model, Korsemeyer-Peppas model and Hixson–Crowell model, respectively. The correlation coefficient (R^2) was chosen for distinguishing among models. For this criteria a closer value to 1 means a better fit. Results are presented in Table 2.

Table 2

Correlation coefficient (R^2) for various mathematical models

Sample	Correlation coefficient (R^2)				
	Zero order	First order	Higuchi	Korsmayer-Peppas	Hixson-Crowell
AML					
free AML	0.8514	0.9680	0.7642	-*	0.9345
F1	0.7481	0.8303	0.8904	0.9724	0.8170
F2	0.8559	0.8874	0.9310	0.9708	0.7391
F3	0.9006	0.9300	0.9631	0.9715	0.9153
F4	0.9152	0.9282	0.9207	0.9725	0.9712
VAL					
free VAL	0.7207	0.9762	0.8301	-*	0.9548
F1	0.7023	0.7675	0.8476	0.9710	0.7463
F2	0.7987	0.8135	0.9146	0.9719	0.8086
F3	0.7654	0.7904	0.8812	0.9713	0.7905
F4	0.9237	0.9266	0.9199	0.9703	0.9258

*for the free drugs the condition for applying Korsemeyer-Peppas model was not fulfilled ($Mt/M < 2/3$)

It was observed that release from free drugs followed an exponential equation (First order), with R^2=0.9680 for AML and R^2=0.9762 for VAL. The Korsemeyer-Peppas model was the model that better described the release from nanoformulations. The term k_{KP} is a constant that depends on the network characteristics and the term n is the diffusional exponent. The value of n shows the nature of the release mechanism; for $n = 0.5$ drug release is dominated by the Fickian diffusion mechanism, for $n = 1$ the drug release is directly proportional to time, for $0.5 < n < 1$ drug release follows anomalous diffusion (non-Fickian diffusion) and $n < 0.5$ indicates a pseudo-Fickian behavior of diffusion.

The terms *n* and *k* can be determined by plotting log Qt against log t, as the slope and the intercept of the straight line fitted to the data. The n and k values are displayed in Table 3. For all the samples the diffusional constant, n, is smaller than 0.5, indicating a pseudo-Fickian release mechanism.

Table 3

Release mechanism: values of n and k for AML and VAL

Sample	**n**	**k**	**Sample**	**n**	**k**
AML			VAL		
F1	0.1980	26.1517	F1	0,0971	39,2374
F2	0.1762	19.0195	F2	0,0451	30,1578
F3	0.2437	15.3851	F3	0,0836	30,8461
F4	0.1940	16.4097	F4	0,0425	24,6718

4. Conclusions

In this paper, we have shown that polymeric nanoparticles are promising carrier for poorly water-soluble APIs, but it is the need of time to monitor drug release for effective drug delivery. All formulations had significant encapsulation efficiency for VAL and AML. According to this characteristic, the best formulation was F2 with a EE% of 89.88 ± 2.01% for VAL and 87.88 ± 0.10% for AML. All samples revealed mean particle size in the range of 205.5 ± 1.24 - 240.4 ± 1.55 nm and a good homogeinity. The *in vitro* release study showed a slow release for both drugs under the physiological condition (pH = 6.8). Various mathematical models were applied to describe the mechanism of release. The representative model describing the kinetics of release for these PEG-NPs was Korsemeyer-Peppas model and its characteristic parameters were calculated and analyzed. Such mathematical model fitting can be a promising approach to deduce release/delivery process to help in designing the safe and efficacious (“Smart”) nanoparticles with application in cardiovascular pathology. However, the phenomenon of drug release still demands crucial investigations at molecular level so as to predict better *in vitro – in vivo* correlation in terms of improved safety and efficacy.

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