

## INTERFACIAL EMULSIFIER FREE EMULSION COPOLYMERIZATION OF DRUG LOADED NANOSYSTEMS AND THEIR DRUG RELEASE PROPERTIES

<sup>1</sup>B. Kostova, <sup>1</sup>D. Georgieva, <sup>2</sup>E. Kamenska, <sup>1</sup>D. Rachev, <sup>2</sup>G. Georgiev

<sup>1</sup>Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmacy, Medical University

<sup>2</sup>Faculty of Chemistry, Department of Applied Organic Chemistry, Sofia University

**Summary:** p(VA-co-DMAPS) latex nanosystems with two different compositions have been synthesized by interfacial emulsifier-free emulsion copolymerization and loaded with Metoprolol tartrate. The mole fractions ratio between VA and DMAPS in the initial monomer feed was 0.98/0.02 (copolymer 1); 0.95/0.05 (copolymer 2). It has been shown that the copolymerization method applied (no emulsifier added) renders copolymer nanoparticles with narrow size distribution. SEM micrographs of the synthesized latexes are presented. It is seen that the latex particles have a regular spherical shape. It is shown that the average diameter of latex nanoparticles decrease with increasing  $m_{DMAPS}$ . The nanoparticles, based on the copolymer 1 provide sustained of the release of the drug up to the 8<sup>th</sup> hour. This is very positive result and can be concluded that copolymer 1 is very suitable as drug delivery nanosystem for a great number of hydrophilic drugs, e.g. Metoprolol tartrate. The change in 0.03  $m_{DMAPS}$  in copolymer 2 leads to a significant difference in release kinetics. The 90% of the drug is released for 3.5 hours, which makes impossible to control the process. Copolymer 2, as well as compositions with a higher concentrations of DMAPS can be used with drugs with very low solubility and good absorption, where its solubilizing effect can be used, which can improve the bioavailability of these drugs.

**Key words:** nanosystems, sustained and controlled release systems, polymer careers

## НАНОСИСТЕМИ ПОЛУЧЕНИ ПО МЕТОДА НА МЕЖДУФАЗОВА ЕМУЛСИОННА СЪПОЛИМЕРИЗАЦИЯ И ЛЕКАРСТВЕНО ОСВОБОЖДАВАЩИТЕ ИМ ХАРАКТЕРИСТИКИ

<sup>1</sup>Б. Костова, <sup>1</sup>Д. Георгиева, <sup>2</sup>Е. Каменска, <sup>1</sup>Д. Рачев, <sup>2</sup>Георги Георгиев

<sup>1</sup>Катедра „Технология на лекарствата с биофармация“, Фармацевтичен факултет, Медицински Университет

<sup>2</sup>Катедра „Приложна органична химия“, Химически факултет, Софийски университет

**Резюме:** p(VA-co-DMAPS) латексни наносистеми с две различни мономерни съотношения са синтезирани по метода на междуфазова емулсионна съполимеризация и за заредени с Метопролол тартарат. Отношението между молните фракции между VA и DMAPS в инициалната мономерна смес бе 0.98/0.02 (съполимер 1); 0.95/0.05 (съполимер 2). Показано е, че използваният съполимеризационен метод (без емулгатор), дава възможност за получаване на съполимерни наночастици с близки размери. Представени са SEM микрографиите на синтезираните латекси. Латексните частици са с сферична форма и диаметърът им намалява с нарастване на  $m_{DMAPS}$ . Наночастиците на база на съполимер 1 осъществяват контрол на освобождаването на Метопролол тартарат в продължение на 8 часа. Промяната в 0.03  $m_{DMAPS}$  при съполимер 2 води до значителна разлика в кинетиката на освобождаване на лекарственото вещество. 90% от Метопролол тартарат се освобождават за 3.5 часа, което затруднява контрола върху освобождаването. Съполимер 2, както и вероятно състави с по-високи  $m_{DMAPS}$  вероятно биха могли да бъдат използвани като системи, контролиращи освобождаването на лекарствени вещества с ниска разтворимост и добра резорбция, където солубилизиращия им ефект може да бъде използван, което да подобри биологичната им наличност.

**Ключови думи:** наносистеми, системи със удължено и контролирано освобождаване, полимерни носители.

## Introduction

Polymeric nanotechnologies are of great importance for contemporary medical science in order to assure controlled release of the drug precisely and safely to its target site to achieve maximum therapeutic effect [9]. Nanoparticles are defined as solid, submicron-sized drug carriers that may or may not be biodegradable [3, 4]. The methods of preparation are of great importance which is due to the fact that they give an opportunity of preparing of particles with suitable characteristics to assure drug delivery and targeting [2, 10]. Depending on the physicochemical characteristics of a drug, it is now possible to choose the best method of preparation and the best polymer to achieve an efficient entrapment of the drug. Many methods have been developed for preparing nanoparticles and they can be divided into two main groups according to whether the formulation requires a polymerization reaction, or is achieved directly from a macromolecule or preformed polymers. Emulsion polymerization is one of the fastest methods for preparation of nanoparticles and is readily scalable [8]. The method is classified into two categories, depending on the continuous phase - organic or aqueous [11]. The other method is interfacial polymerization. The main advantage of this method is that the polymer is formed in situ, allowing the polymer membrane to follow the contours of the inner phase of an oil/water or water/oil emulsion, as well as the high-efficiency drug encapsulation [5,11]. The main disadvantage of the method is the use of organic solvents required for the external phase. Washing of solvents and replacement by water represents a time-consuming and difficult procedure [1, 11].

In our previous paper we reported the preparation of new zwitterionic copolymer latexes, based on vinyl acetate (VA) and 3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate (DMAPS) (p(VA-co-DMAPS)). Using emulsifier-free emulsion copolymerization, latexes with different compositions were obtained. These latexes were used as matrix carriers for Metoprolol tartrate (MT) and Verapamil hydrochloride (VH) sustained delivery [6, 7]. The purpose of the present study was: (i) synthesis and characterization of nanoparticles, based on p(VA-co-DMAPS), with different concentration of zwitterionic monomer

DMAPS ( $m_{\text{DMAPS}}$ ), containing hydrophilic drug - MT, which was loaded at the time of performing EFC; (ii) use of the obtained p(VA-co-DMAPS) nanoparticles for sustained release of MT.

## Materials and methods

### Materials

Vinyl acetate (VA) (Merck, Darmstadt, Germany) was further purified by vacuum distillation. 3-Dimethyl(methacryloyloxyethyl)ammonium propane sulfonate (DMAPS) (Merck, Darmstadt, Germany) was used as obtained. The initiator potassium peroxide disulfate (KPS, Fluka, Switzerland) was purified by recrystallization from water. Distilled water was used in all emulsion polymerizations. Metoprolol tartrate EP was supplied by Indukern Chemie AG (CH-89-52 Schlieren, Switzerland).

### Methods

#### *Interfacial emulsifier-free emulsion copolymerization of VA and DMAPS*

Interfacial emulsifier-free emulsion copolymerization (IEFC) of VA and DMAPS was performed in distilled water with previously dissolved MT in a glass flask with a ground-glass stopper. The total amount of MT was 2wt% vs. the total monomer feed. The total monomer concentration was 4.75 M. The mole fractions ratio between VA and DMAPS in the initial monomer feed was 0.98/0.02 (copolymer 1); 0.95/0.05 (copolymer 2). The initiator potassium peroxide disulfate concentration was 1 wt.%. The reaction mixture was purged with nitrogen to remove oxygen from the system. The IEFC was carried out without stirring and was heterogeneous. It takes place at the interface between the two phases - lower water phase and upper phase, consisting of VA. The glass flask was thermostated at  $52 \pm 1$  oC for 29 h (for copolymer 1) and 30 h (for copolymer 2) to reach 99.8% conversion (q). Reaction mixture samples were removed from the reaction mixture periodically to determine the conversion. The latter was monitored gravimetrically. The obtained p(VA-co-DMAPS) latex nanoparticles with MT were stable in period of 1 month.

#### *Scanning electron microscopy investigations*

The particle size ( $D_n$ ) of the copolymer microspheres was determined by means of scanning electron microscopy (SEM, JEOL JSM - 5500, Tokyo, Japan). A very dilute dispersion of copolymer microspheres was placed on a glass plate and air-dried. These samples were sputter-coated with gold (Sputter Coater Jeol Fine Coater 1200, Tokyo, Japan). The size distribution was measured by dynamic light scattering (DLS, Malvern System 1700 C, UK).

#### *In vitro drug dissolution studies*

Drug release profiles were evaluated using a dissolution test apparatus (Erweka DT 600, Hensenstmm, Germany). The USP paddle method was applied. The suspension of drug nanoparticles was placed in dialyze artificial gut. The test was carried out at a paddle rotation speed of 50 rpm, maintained at  $37 \pm 0.5$  °C, in 900 mL an aqueous medium pH value pH 6.8 phosphate buffer solution. Five mL aliquots of the dissolution media were withdrawn at selected intervals up to 8 h. Each sample was filtered through a  $0.45 \mu\text{m}$  membrane filter (Sartorius cellulose acetate filter, Germany). The quantity of MT in the sample solutions was determined from the UV absorbance at  $278 \pm 2$  nm. The quantity of the Metoprolol tartrate in the sample solution was determined by UV spectroscopy

(absorbance at  $278 \pm 2$  nm)) using a Hewlett-Packard 8452 A Diode Array spectrophotometer (USA). The cumulative percentage of drug release was calculated and the average of six determinations was used in the data analysis.

## Results and discussion

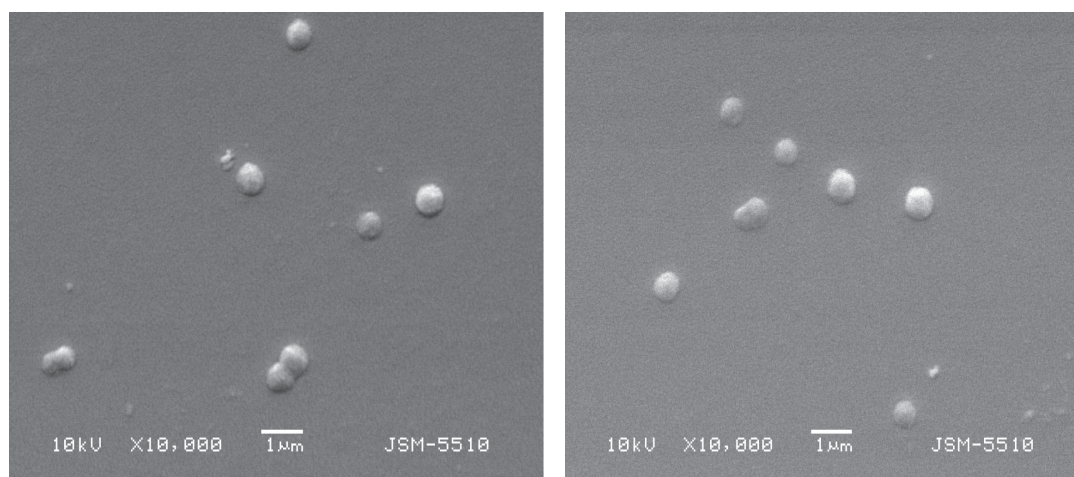
### *Characterization of the p(VA-co-DMAPS) nanoparticles*

Some characteristics of the synthesized p(VA-co-DMAPS)s latexes are given in Table 1. The variation of the DMAPS mol fraction in monomer feed ( $m_{\text{DMAPS}}$ ), in very narrow range does not considerably affect the IEFC duration (29 h for copolymer 1 and 30 h for copolymer 2), reaching conversion over 99%. In Figure 1(a)-1(b) SEM micrographs of the synthesized latex nanoparticles are presented. It is seen that the latex nanoparticles have a regular spherical shape. It is shown that their average diameter decreases with increasing  $m_{\text{DMAPS}}$ .

A particularly important result is that no coagulum formation was observed during IEFC of VA and DMAPS. At the beginning of the copolymerization the reaction mixture was biphasic- upper phase consisted from VA and lower phase - aqueous solution, containing DMAPS, MT and initiator KPS.

**Table 1.** Characteristics of interfacial emulsifier-free emulsion copolymerization of VA and DMAPS and of the copolymer produced; total monomer concentration: 4.75 M; [KPS]: 1 wt.-%; solvent: distilled water;  $T = 52 \pm 1$  °C.

Copolymer No	DMAPS in the monomer feed (mol%)	IEFC duration (h)	q (%)	Z-average diameter of microspheres SEM (nm)
1	0.02	21	99.7	$162 \pm 15.13$
2	0.05	20	99.4	$155 \pm 16.03$



**Fig 1** SEM micrographs of p(VA-co-DMAPS) nanoparticles: (a) copolymer 1; (b) copolymer 2

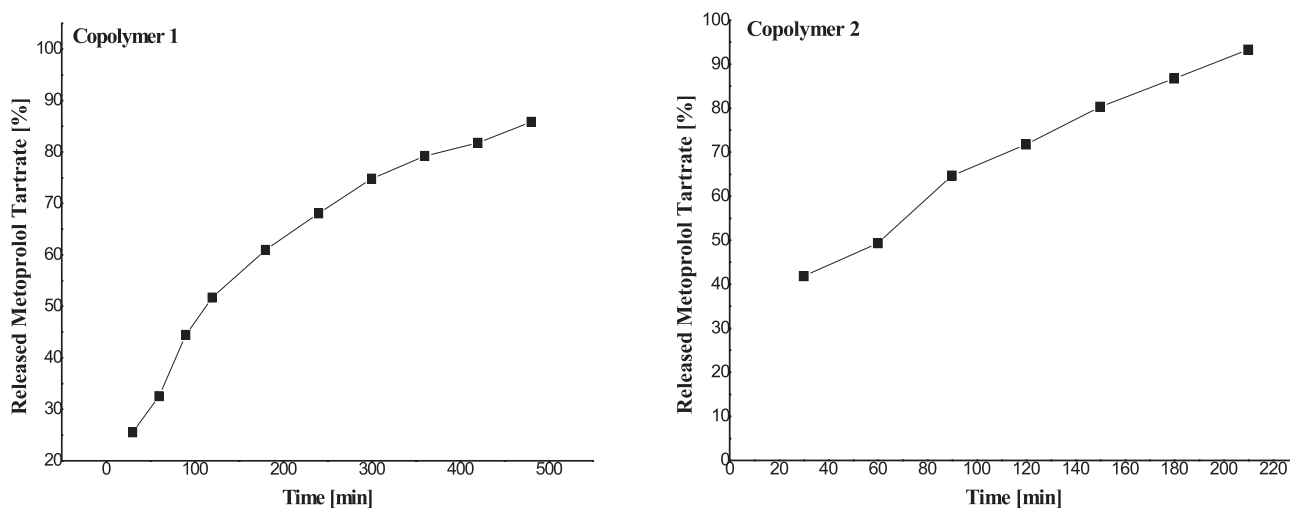
At these conditions copolymerization takes place at the interface between the two phases as interfacial copolymerization. Depending on the monomer feed composition, a non-soluble phase of latex particles started forming as the copolymerization proceeded: after 3 h for copolymer, 3:30 h for copolymer 2. With increasing of mole fraction of DMAPS in monomer feed ( $m_{\text{DMAPS}}$ ), the time prior to the start of phase separation goes up.

*Release kinetics of Metoprolol tartrate from p(VA-co-DMAPS) nanoparticles*

Sustained release nanoparticles, based on copolymer 1-2 compositions, have been developed. The release profiles of Metoprolol tartrate from the model p(VA-co-DMAPS) tablets at pH 6.8 and 37°C are presented in Figure 2 (a, b).

The dependences at Figure 2 show that the  $m_{\text{DMAPS}}$  difference in p(VA-co-DMAPS) nanoparticles affects the MT release kinetics. The nanoparticles, based on the copolymer 1 provide sustained of the release of the drug up to the 8<sup>th</sup> hour. About 33% are released for an hour, after that is reached 85% release at the 8th hour. This is very positive result, because MT belongs to class 1 of Biopharmaceutical Classification System (BCS) and is characterized by very good solubility and absorption. Its usual

dosage in systems for controlled drug delivery is 200 mg. Comprising MT in nanosystems gives an opportunity to reach more precise release profiles, which can lead to achieving of equivalent therapeutic effect in lower dosage. The change in 0.03  $m_{\text{DMAPS}}$  in copolymer 2 leads to a significant difference in release kinetics. The 90% of the drug is released for 3.5 hours, which makes impossible to control the process. This result is logical as we assume our previous studies [6, 7] of swelling of tablet matrices, based on p(VA-co-DMAPS). It was found that increasing of  $m_{\text{DMAPS}}$ , ionic strength of the solution and the temperature lead to increase in the degree of swelling of the matrix systems. In this case, every single nanoparticle is an independent matrix, releasing MT. It is possible then the change of the  $m_{\text{DMAPS}}$  in such a narrow scope to ensure faster swelling of all nanomatrices and the drug can really be released faster. Therefore, we can conclude that the copolymer 1 is very suitable as drug delivery nanosystem for a great number of hydrophilic drugs, e.g. Metoprolol tartrate. Copolymer 2, as well as compositions with higher concentrations of  $m_{\text{DMAPS}}$  can be used with drugs belonging to class 3 of BCS- very low solubility and good absorption, where its solubilizing effect can be used, which can improve the bioavailability of these drugs.



**Fig 2.** Release kinetics of MT from model p(VA-co-DMAPS) nanoparticles at pH 6.8 and  $T = 37^\circ\text{C}$  (a), copolymer 1; (b) copolymer 2.

## Conclusions

p(VA-co-DMAPS) latex nanoparticles with two different compositions have been synthesized by interfacial emulsifier-free emulsion copolymerization and loaded with Metoprolol tartrate. It has been shown that the copolymerization method applied (no emulsifier added) renders copolymer nanoparticles with narrow size distribution. It is seen that the latex nanoparticles have a regular spherical shape and the average diameter of latex nanoparticles decrease with increasing  $m_{\text{DMAPS}}$ . Copolymer 1 is very suitable as drug delivery nanosystem for a great number of hydrophilic drugs, e.g. Metoprolol tartrate. Copolymer 2, as well as compositions with higher concentrations of DMAPS can be used with drugs with very low solubility and good absorption, where its solubilizing effect can be used, which can improve the bioavailability of these drugs.

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### Address for correspondence:

B. Kostova  
Department of Pharmaceutical Technology and Biopharmacy  
Faculty of Pharmacy  
Medical University  
1000 Sofia  
e-mail: bistrakostova@abv.bg

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### Адрес за кореспонденция:

Б. Костова  
Катедра „Технология на лекарствата с биофармация”  
Фармацевтичен факултет,  
Медицински университет  
1000 София  
e-mail: bistrakostova@abv.bg

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