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# OBTAINING AND CHARACTERIZATION OF POLYETHER-URETHANE NANOSTRUCTURES – A POSSIBLE DRUG CARRIER SYSTEM

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## SUMMARY

Transdermal drug carrier systems are used to ensure a constant level of drug during the administration. Polyurethane derivatives were recently considered as possible material in the field. The study intends to obtain a possible drug carrier at nano level. Polyether-urethane (PEU) nanostructures were synthesized by using the technique of interfacial polycondensation combined to spontaneous emulsification. For synthesis, it were used an organic phase which contain lysine diisocyante ester (LDI) and a lipophilic surfactant (Span®85) in water-miscible solvent (acetone) and an homogeneous aqueous phase formed by water, diol or polyether and a hydrophilic surfactant (Tween®20 or Tween®60). The obtained nanostructures were finally characterized.

Keywords: drug carrier; polyether-urethane; nanostructure; lysine diisocyanate; polycondensation.

## INTRODUCTION

Polyurethanes still remain on a leading position in biomaterials applications after almost half a century of use in medicine due to its unique physical and mechanical

properties and its favorable biocompatibility [1]. The popularity enjoyed by this class of macromolecular compounds is supported by the blocks segmented copolymers character which gives the possibility of final materials properties to vary greatly with only a small adjustment of mixing ratio of raw materials [2]. These polymers can be considered the most suitable material to be in contact with blood in long-term medical applications: heart valves, aortic grafts, intra-aortic balloons, pacemakers, stents, breast implants, prosthetic bone, biocompatible polymer membranes with the role of artificial pancreas, membranes for dialysis, gastric ring with controlled bioresorbtia used to cure morbid obesity surgery etc. [3-5].

Medicine, biology and biomaterials domains have benefited enormously from the implementation and development of the nanostructures in the last decade. The micro and nanoparticles based on polymer present a few advantages over other systems, including the site-specific distribution of drugs within the body via cell-specific targeting of the nanoparticle delivery system and the possibility to control the drug release kinetics [6, 7].

Most biological active substances are given as pills or injections, but these two ways are not always effective [8]. Oral medication is not totally absorbed in the gastrointestinal tract because of the hostile environment, rich in enzyme and in addition suffer various trials when passing through the liver. Substances which are not prescribed oral, are used in injectable form and in this case it put the issue of occurrence of possible risks (shocks), the infections and the need for specialized personnel. These routes are limited due the attention to the risk of overdosage. As an alternative to the two methods, the transdermal drug carrier systems has developed as a method of slow administration which avoid the limitations described above [9, 10]. Taking into account all the advantages of this method has been approved worldwide use of transdermal patches for quitting smoking, painkillers, weight loss or with role in contraception. Despite all the advantages, transdermal drug release is currently only useful for a small number of substances because most compounds can not cross the skin with therapeutic speeds. [11].

It has been proved that the polyurethane biomaterials based on aromatic diisocyanates have an *in vivo* degradation to carcinogenic aromatic amines and the allowed level of its concentration is still debate [12]. As an alternative to this problem, we have developed two series of polyether-urethane (PEU) nanostructures based on lysine diisocyanate ester and used for the transdermal drug delivery.

## MATERIALS AND METHODS

Lysine diisocyanate ester (LDI) was furnished by Hangzhou Imaginechem Co., Ltd

(China). Mono-ethylene glycol (MEG) is from Lach-Ner s.r.o. (Czech Rep.) and 1,4-butanediol (1,4-BD) from Carl Roth GmbH (Germany); all the other raw materials, the solvent (acetone), polyethylene glycol (PEG 200) and surfactants (Span®85, Tween®20 and Tween®60) were obtained from Merck (Germany).

The procedure for obtaining PEU nanostructures by interfacial polycondensation combined with spontaneous emulsification present three steps (Fig. 1.):

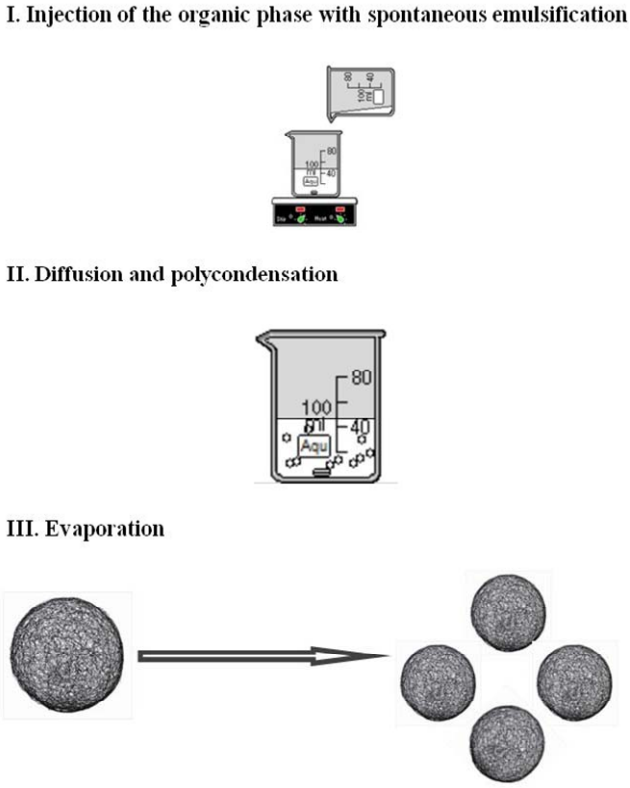



Fig. 1. Mechanism of nanostructures synthesis using the interfacial polycondensation

Step I.

a. Preparation of the organic solution composed of 1.5 mL LDI, 1 mL lipophilic surfactant (Span®85) in 20 mL water-miscible solvent (acetone);

b. Preparation of the homogeneous aqueous phase: 40 mL water, MEG, 1,4-BD, PEG 200 and 1 mL hydrophilic surfactant (Tween®20 or Tween®60);

c. Injection of the organic phase in the aqueous phase under magnetic stirring (4000 rpm) and mild heating (40 $^{o}$C). The nanostructures precipitate instantaneously.

Step II.

The stirring is still maintained for three hours at 40 $^{o}$C in order to ensure the maturation of the nanostructures walls.

Step III.

The solvent (acetone) as well as a part of water is removed by evaporation by keeping the suspension as thin layers (1-2 mm) in Petri dishes at 40 $^{o}$C for 2 hours.

Four experiments were done by using the same procedure already described. We varied the raw materials as are presented in Table I in order to obtain different nanostructures.

Table I. The aqueous phase for PEU synthesis

| Experiment no. | MEG, mL | 1,4-BD, mL | PEG, mL | Hydrophilic surfactant |
|---|---|---|---|---|
| 1 | 0.8 | 0.6 | 0.1 | Tween®20 |
| 2 | 0.8 | 0.6 | 0.1 | Tween®60 |
| 3 | 0.2 | 0.3 | 1.0 | Tween®20 |
| 4 | 0.2 | 0.3 | 1.0 | Tween®60 |

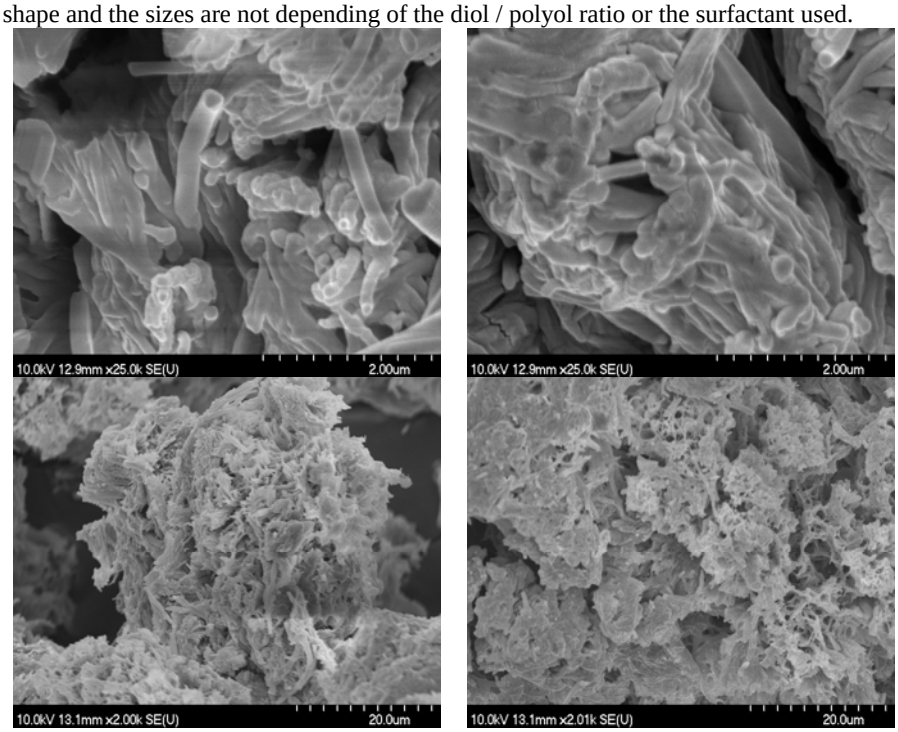
## RESULTS AND DISCUSSION

In order to establish the nanostructures solubility in water and acetone we dried the suspensions by keeping as thin layers (1-2 mm) in Petri dishes at 40 $^{o}$C for other 6 hours (Table II). The solubility was measured at 25 $^{o}$C and expressed in grams of sample per 100 grams water. The pH values were measured with a Schott TitroLine by simply plunging the electrode into the aqueous solutions (0.08% w/w).

Table II. The solubility and pH of the nanostructures samples

| Experiment no. | Solubility (g/100 g), 25 $^{o}$C | | pH |
|---|---|---|---|
| | water | acetone | |
| 1 | $8 \cdot 10^{-2}$ | $4 \cdot 10^{-2}$ | 7.2 |
| 2 | $9 \cdot 10^{-2}$ | $3 \cdot 10^{-2}$ | 7.4 |
| 3 | $10^{-1}$ | $3 \cdot 10^{-2}$ | 6.9 |
| 4 | $9 \cdot 10^{-2}$ | $3 \cdot 10^{-2}$ | 6.8 |

The shape and the morphology of the produced nanostructures were investigated by a scanning electron microscope Hitachi S4700 (Hitachi Scientific Ltd, Japan). It was detected the existence of nanostructures with tube shape and with different lengths (Fig. 2); the shape and the sizes are not depending of the diol / polyol ratio or the surfactant used.




a b

Fig. 2. Scanning electron microscopy of (a) diol and (b) polyol nanostructres samples at different magnification

## CONCLUSION

We have obtained PEU nanostructures using the interfacial polycondensation technique combined with spontaneous emulsification. The PEU nanostructures have a good solubility in water and with a suitable pH for a transdermal drug carrier system. We demonstrated that the usage of a very reactive diisocyanate (lysine diisocyanate ester, LDI)

with the advantage of non-carcinogenic products after its degradation is a way to obtain nanostructural polymers which can be candidate as transdermal drug carrier.

## ACKNOWLEDGEMENTS

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