International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 5, 2023

Original Article

PREPARATION AND EVALUATION OF PROPRANOLOL HCL AND CARBAMAZEPINE RELEASE PROFILES FROM POLY(Є-CAPROLACTONE) MICROPARTICLE BLENDS SYSTEM

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Received: 09 Jun 2023, Revised and Accepted: 29 Jul 2023

ABSTRACT

Objective: The goal of this research was to look into the physicochemical properties of poly(-caprolactone) microparticle blends that contained medicines of various solubilities (Propranolol HCl [Pro] and carbamazepine [CBZ]).

Methods: W/O/W emulsion for Pro and O/W emulsion for CBZ were used to create microparticle blends. With dispersion time intervals (DTI) of 0 and 60 min, the Pro emulsion (W/O) and CBZ oil phase (O) were dispersed in an external aqueous phase (W). Scanning electron microscopy was used to examine the morphology of microparticle blends (SEM). Focused beam reflectance measurements were utilized to monitor the particle size mean of emulsion droplets/hardened microparticles (FBRM). In phosphate buffer (pH 7.4), encapsulation efficiency (EE) and *in vitro* drug release were also examined.

Results: The final microparticle blends generated by solvent evaporation method were spherical and had two populations, according to the findings. The size of microparticle blends prepared with DTI 60 min and stirring duration 4 h was bigger than those prepared with DTI 0 min, according to FBRM data. In microparticle blends, encapsulation efficiency ranged from 62.05±3.74 percent to 66.38±4.16 percent for Pro and 70.56±4.62 percent to 73.85±4.11 percent for CBZ. After 28 d, drug release in phosphate buffer revealed that Pro release (33%) was shorter than CBZ release (60%) from microparticle blends with DTI 60 min. This was related to the interaction of the oil phase (CBZ) with hard particles from the primary emulsion (Pro), in which the oil phase occluded and covered surface structure of the harsh particles from the primary emulsion.

Conclusion: Novel microparticle blends comprising drugs/medicines with varying solubilities (e. g. propranolol HCl and carbamazepine) have a lot of promise as controlled-release drug delivery systems. The physical properties of microparticle blends were impacted by the type of dispersion time interval used.

Keywords: Microparticle blends, Propranolol HCl, Carbamazepine, Poly(ϵ-caprolactone), FBRM, Solvent evaporation method

DOI: https://dx.doi.org/10.22159/ijap.2023v15i5.48574. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Microparticles are widely employed in a variety of applications, including medicine delivery, cosmetics, and chemical reagents. In the realm of controlled drug delivery, several approaches for generating microparticles may be useful. The solvent evaporation method is one of the most frequent ways for preparing microparticles [1-3]. Controlling the microparticle preparation processes is critical for achieving the required mean size, size distribution, and shape of microparticles. When choosing emulsion phases for a microparticles preparation process, the solubility qualities of the pharmaceuticals of the microparticles are key parameters to consider. To reach the optimum yield, the medicines must have different solubilities in the continuous phase. Many types of medications, including tiny molecules, proteins, and nucleic acids, can be encapsulated in microparticles. Simple or multiple emulsion procedures such as oil-in-water (O/W) or water-in-oil-in-water (W/O/W) are utilized based on the drug's solubility [3-6]. In the encapsulation and release of pharmaceuticals, the process of microparticle production is a determinant. Furthermore, a complex array of factors such as the type of polymer, the polymer molecular weight, the copolymer composition, the nature of any excipients added to the microparticle formulation (e. g., for drug stabilization), porosity, and microparticle size can all have a major effect on distribution rates [6-11].

Polymers have been utilized extensively to modulate the rate of medication extraction from formulations. Polymers have the potential to adhere solid dosage form particles. Taste masking, controlled release (e. g., prolonged, pulsatile, and targeted), better stability, and higher bioavailability are all common uses for pharmaceutical polymers. Drug carriers include biodegradable and nonbiodegradable polymers with strong biocompatibility, like polycaprolactone, PLGA, and ethyl cellulose (degradable but non-biodegradable).

In the majority of trials so far, only one medication was captured at a time within sustained-release microparticles. Merely a few efforts at co-encapsulating two medications have been undertaken, especially if the latter has a markedly altered solubility behavior. Pérez *et al.* (2003) successfully inserted the hydrophilic drug propranolol HCl and/or the lipophilic drug nifedipine into non-degradable, ammonio methacrylate copolymers (Eudragit RS: RL 4:1 blends) based microparticles independently as well as concurrently [12]. They were made using the solvent evaporation methods of oil-in-water (O/W) and water-in-oil-in-water (W/O/W). Nippe and General (2012) developed lipophilic steroidal drugs ethinyl estradiol and drospirenone poly(lactic-co-glycolic acid) (PLGA) microparticles, whereas Nippe and General (2012) evolved a mixture of lipophilic steroidal drug related ethinyl estradiol and drospirenone poly(lactic-co-glycolic acid) (PLGA) microparticles [13, 14].

There haven't been any reports of microparticle mixes comprising two medicines with varying solubilities. In this study, a lipophilic and a hydrophilic medication were combined in polycaprolactone-based microparticle blends using the solvent evaporation method. Model medicines included the hydrophilic propranolol HCl and the lipophilic carbamazepine. The production of microparticle blends from oil-in-water (O/W) and water-in-oil-in-water (W/O/W) technologies needs proper particle size analysis throughout the solvent evaporation [14-19]. The benefit of this style is that data is collected in real-time and on-line to provide particle diameter data and demographic patterns of suspended particles, colloid, and other media [9, 17-21].

The focus of this research was to see how the dispersion time interval (DTI) and the preparation of the new primary oil droplets affected poly(-caprolactone) predicated microspheres blends that enclosed drugs with distinct solubilities (Propranolol HCl and carbamazepine) and were made using the evaporation method.

MATERIALS AND METHODS

Materials

All materials were of at least reagent grade and used as received: poly (ε-caprolactone) (Mw. 10000) (Sigma-Aldrich Chemie GmbH, Steinheim, Germany); polyvinyl alcohol (PVA, Mowiol® 40–88, Kuraray Europe GmbH, Frankfurt, Germany); propranolol HCl, carbamazepine, sodium chloride, sodium hydroxide, potassium dihydrogen phosphate and dichloromethane (Carl Roth GmbH and Co. KG, Karlsruhe, Germany).

Methods

Microparticle preparation

Microparticle containing propranolol HCl or carbamazepine

Drug-loaded microparticles based on poly (ε-caprolactone) were prepared using an oil-in-water (O/W) and a water-in-oil-in-water (W/O/W) solvent evaporation method. The drug-loaded systems contained either one drug only (propranolol HCl or carbamazepine). For the O/W method, 300 mg of poly (ε-caprolactone) were dissolved in 4 ml dichloromethane. 60 mg carbamazepine were dissolved within this organic phase. The organic phase was then emulsified into 800 ml aqueous PVA solution (0.25% w/v) containing 0.5 M NaCl and NaOH at pH 12. The emulsion was stirred for 4 h at 500 rpm with a propeller stirrer (Heidolph Elektro GmbH and Co. KG, Kelheim, Germany) to allow microparticle hardening.

For the W/O/W method, 60 mg propranolol HCl were dissolved in 0.25 g purified deionized water. Propranolol HCl aqueous solution was first emulsified by probe sonication (Sonoplus® HD 250, Bandelin Electronic GmbH and Co. KG, Berlin, Germany) for 30 s under ice-cooling into 4 ml dichloromethane containing 300 mg of poly (ε-caprolactone). This first emulsion (W/O) was then dispersed into 800 ml aqueous PVA solution (0.25% w/v) containing 0.5 M NaCl and NaOH at pH 12. A W/O/W emulsion was formed by extensive stirring with a propeller stirrer for 4 h at 500 rpm to allow microparticle hardening. In all cases, after 4 h, the microparticles were separated from the external aqueous phase by wet sieving (stainless steel test sieves ISO 3310-40, 70, 100 and 160 µm) followed by washing with 200 ml deionized water, desiccator-drying for 24 h and storage in a desiccator.

Microparticle blends containing propranolol HCl and carbamazepine

The first primary emulsion containing propranolol HCl (W/O/W) and second primary oil phase containing carbamazepine (O/W). For the W/O/W method, 60 mg propranolol HCl were dissolved in 0.25 g purified deionized water. Propranolol HCl aqueous solution was first emulsified by probe sonication for 30 s under ice-cooling into 4 ml dichloromethane containing 300 mg of poly (ε-caprolactone). This gave the first primary emulsion containing propranolol HCl. For the O/W method, 300 mg of poly (ε-caprolactone) were dissolved in 4 ml dichloromethane. 60 mg carbamazepine were then dissolved in this organic phase. This process produced the second primary oil phase containing carbamazepine. Following, the first primary emulsion containing propranolol HCl and the second primary oil phase containing carbamazepine were dispersed in an external aqueous phase (800 ml aqueous PVA solution [0.25% w/v] containing 0.5 M NaCl and NaOH at pH 12), with dispersion time intervals (DTI) of 0 and 60 min, and stirred for 4 h at 500 rpm with a propeller stirrer to allow microparticle hardening. The subsequent process steps were similar to the preparation of microparticles containing single drug process.

Determination of the actual drug loading and encapsulation efficiency

Microparticles (10 mg) were extracted in 1 ml methanol, followed by agitation in a horizontal shaker (IKA HS 501 digital horizontal Shaker, Janke and Kunkel GmbH and Co. KG IKA Labortechnik, Staufen, Germany) for 2 h (n = 3). 0.1 ml of methanol extract was diluted in 10 ml of pH 7.4 phosphate buffer. The polymer was separated from aqueous solution by filtration using filter paper (Whatman®, GE Healthcare UK Limited, Buckinghamshire, UK). Propranolol HCl and/or carbamazepine concentration in the obtained aqueous solution was determined by UV-spectrophotometry at wavelengths of 289 nm and 285 nm, respectively (HP 8453 UV-Vis spectrophotometer, Agilent Technologies Deutschland GmbH, Waldbronn, Germany). The actual drug loading and encapsulation efficiency were calculated as follows:

Actual drug loading (%) = (drug mass in microparticles/mass of microparticles) x 100 %

Encapsulation efficiency (%) = (actual drug loading/theoretical drug loading) x 100 %

For microparticle blends, the amounts of incorporated propranolol HCl and carbamazepine were determined UV-spectrophotometrically by simultaneously measuring at wavelengths of 227 and 285 nm. The subsequent process steps were similar to the above process.

Particle size analysis

Particle size mean and size distribution of the microparticles were measured by focused beam reflectance measurement. FBRM probe (Lasentec® FBRM D600T, Mettler Toledo AutoChem, Inc., Redmond, WA, USA) was immersed and positioned in the emulsification vessel (WO/W and O/W emulsions mentioned above) to ensure good flow against the probe window and hence allowing a representative sample of the particle system to be measured. The measurement range of the FBRM D600T probe is 0.25-4000 µm. In these experiments, FBRM measurements were performed every 10 seconds during a period of 4 h. All batches were measured in triplicate. The size information was extracted through the iC FBRM® 4.0 software (Mettler Toledo AutoChem, Inc., Redmond, WA, USA).

Microparticle characterization

Optical microscopy

Microparticles were spread on microscope slides and observed with an optical light microscope (Axiotrop 50, Carl Zeiss AG, Jena, Germany) equipped with an image analysis system (INTEQ Informationstechnik GmbH, Berlin, Germany) consisting of a digital camera (type MC1) and the EasyMeasure® software (version 1.4.1).

Scanning electron microscopy

Scanning electron microscopy was used to examine the exterior and internal morphology of microparticles (SEM). The microparticles were double-sided taped to a specimen holder for surface imaging. The particles were distributed on transparent tape and then chopped with a razor blade to explore the inner structure. In a high-vacuum chamber, all samples were placed with gold to a thickness of 8 nm in an argon atmosphere (SCD 040, Bal-Tec GmbH, Witten, Germany). After that, the samples were examined using a scanning electron microscope (S-4000, Hitachi High-Technologies Europe GmbH, Krefeld, Germany).

In vitro drug release studies

10 mg microparticles/microparticle blends (particle size: <70 µm) were placed in 10 ml pH 7.4 phosphate buffer (USP XXIV) and shaken at 37 °C in a horizontal shaker (GFL 3033, Gesellschaft für Labortechnik GmbH, Burgwedel, Germany) at 75 rpm. At predetermined time points, 1 ml samples were withdrawn and replaced with 1 ml fresh medium each 7 d, filtered and analyzed. Propranolol HCl and/or carbamazepine concentration was detected UV spectrophotometrically at wavelengths of 289 nm and 285 nm, respectively (n = 3) (HP 8453 UV-Vis spectrophotometer, Agilent Technologies Deutschland GmbH, Waldbronn, Germany).

The concentrations of propranolol HCl and carbamazepine in microparticle blends were measured using UV spectrophotometry at wavelengths of 227 and 285 nm (n = 3).

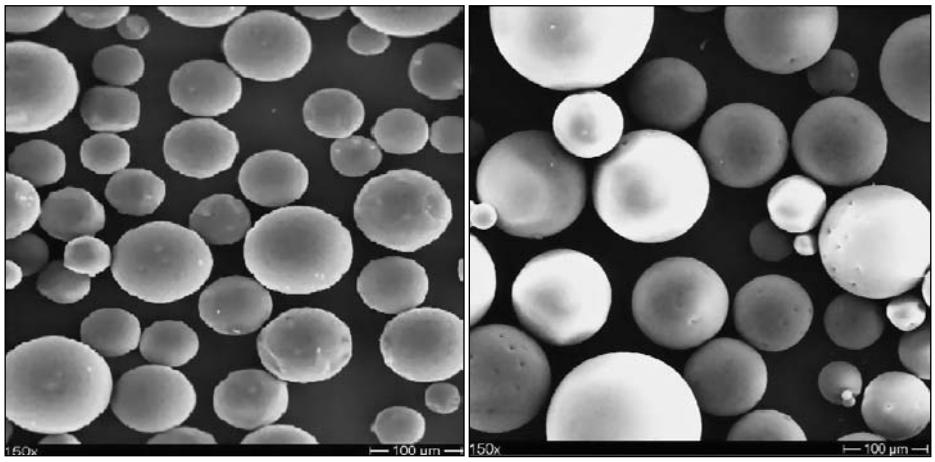
RESULTS AND DISCUSSION

Morphology and particle size/distribution of microparticle blends

Scanning electron microscopy was used to examine the microparticles' surface morphology (SEM). Surface analysis of drug-loaded microparticle blends generated by the WO/W (Pro) and O/W (CBZ) revealed that the microparticles were spherical and not aggregated (fig. 1), with diameters ranging from 73 to 81 µm. Microparticle blends, including both propranolol HCl and carbamazepine, generated by the WO/W (Pro) and O/W (CBZ) procedures with DTI 60 min appeared in two populations, smooth and rough surface (fig. 1a). Microparticles created using DTI 0 min, on the other hand, produced microparticles with pores and a smooth surface (fig. 1b). Micropores on the surface of the propranolol HCl loaded poly (ε-caprolactone) microparticles were observed, indicating that they were propranolol HCl microparticles. There were no pores on the surface of the microparticles, indicating that they were carbamazepine-loaded poly (ε-caprolactone) microparticles.

The morphology and porosity of the microparticles were significantly impacted by the preparation procedures. The microparticles displayed a porous interior structure due to the inner aqueous phase in the W/O/W procedure. The aqueous droplets are predecessors of pores and are the product of phase inversion in the organic phase during microparticle hardening [21-26].

The size of microparticle mixes made by W/O/W (propranolol HCl) and O/W (carbamazepine) procedures (with DTI 60 min and stirring duration 4 h) were greater than microparticle blends (with DTI 0 min) and microparticles normal (fig. 2). According to FBRM data, adding a second main oil phase containing poly (-caprolactone), carbamazepine, and dichloromethane (with DTI 60 min) increased particle size.



a **b**

Fig. 1: SEM pictures of poly (ε-caprolactone) microparticles blend with dispersion time interval of (a) 60 min and (b) 0 min between Pro (W/O/W) and CBZ (O/W)

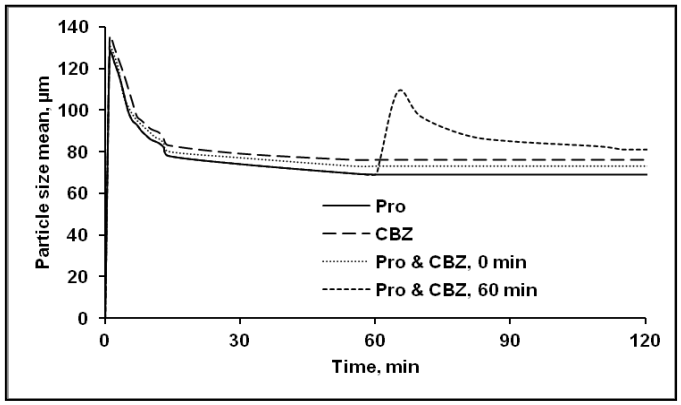


Fig. 2: Particle size mean of poly (ε-caprolactone) based microparticle blends obtained by the FBRM method (before and after primary oil phase addition) during the solvent evaporation process (primary oil phase is added at time = 60 min)

Entrapment efficiency within microparticle blends

In microparticle blends, encapsulation efficiency (EE) ranged from 62.05±3.74 percent to 66.38±4.16 percent for propranolol HCl and 70.56±4.62 percent to 73.85±4.11 percent for carbamazepine.

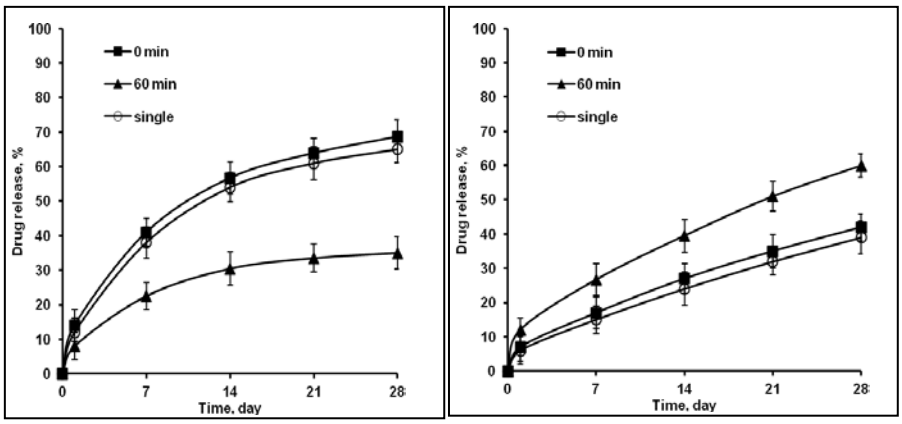
The varying solubilities of the medications in the aqueous continuous phase employed for the two encapsulating procedures can explain the variation in the EE of the two pharmaceuticals in the microparticle mixes. The drug leaked into the continuous phase due to the high solubility of propranolol HCl in the external aqueous phase and its large volume as opposed to the internal aqueous phase (W/O/W method). However, due to its hydrophilic character, propranolol HCl prefers to permeate through the polymeric matrix into the external aqueous phase once the polymer has precipitated. Furthermore, for the entrapment of ionizable pharmaceuticals such as propranolol HCl, the degree of ionization of the drug and the pH of the external aqueous phase are crucial [6, 12, 27, 28]. When the pH of the external phase is raised above the pKa of propranolol HCl, its

solubility decreases and, as a result, its confinement in microparticles increases.

Release of propranolol HCl and carbamazepine from microparticle blends

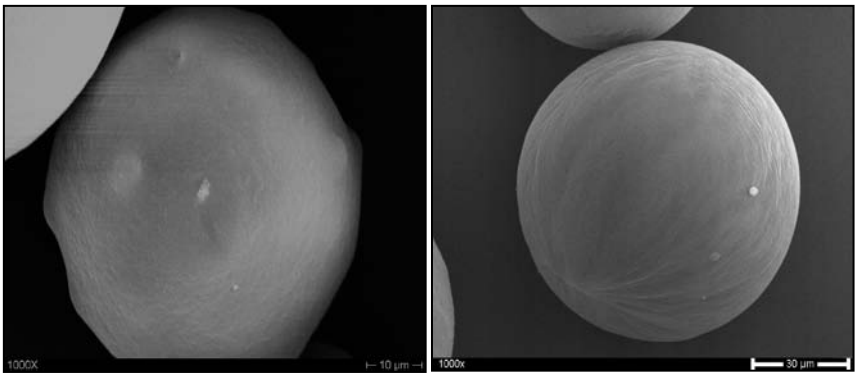
In a pH 7.4 phosphate buffer, different development rates of propranolol HCl and carbamazepine from poly(ε-caprolactone) microparticle blends were detected (fig. 3). The release of propranolol HCl from microparticle normal and microparticle blends (with DTI 0 min) was faster than the release of carbamazepine (fig. 3). Propranolol HCl release was slower (33%) than carbamazepine release (60%) from poly(-caprolactone) microparticle mixes (with DTI 60 min) (fig. 3). After 28 d, the cumulative percent of propranolol HCl and carbamazepine released from each microparticle blend (the range of ADL Pro 9.32±0.25 percent to 9.86±0.47 percent and ADL CBZ 10.69±0.38 percent to 10.97±0.45 percent) at pH 7.4 is 33±4.25 percent to 69±3.88 percent (propranolol HCl) and 41±3.17 percent to 60±3.55 percent (carbamazepine).

The resulting release rate(s) of the integrated drug(s) was/were determined to be regulated over at least 28 d in all situations. Furthermore, carbamazepine release was often slower than propranolol HCl release, which can most likely be due to carbamazepine's significantly lower solubility in the release medium (0.2 mg/ml vs. 250 mg/ml), resulting in lesser concentration gradients, which are the major factors for diffusion [24, 29-35].



a **b**

Fig. 3: Effects of dispersion time interval on propranolol HCl and carbamazepine release from polycaprolactone microparticle blends (phosphate buffer, pH 7.4, 37 °C, 75 rpm). [(a) Propranolol HCl and (b) Carbamazepine], data are expressed as mean±SD, n=3



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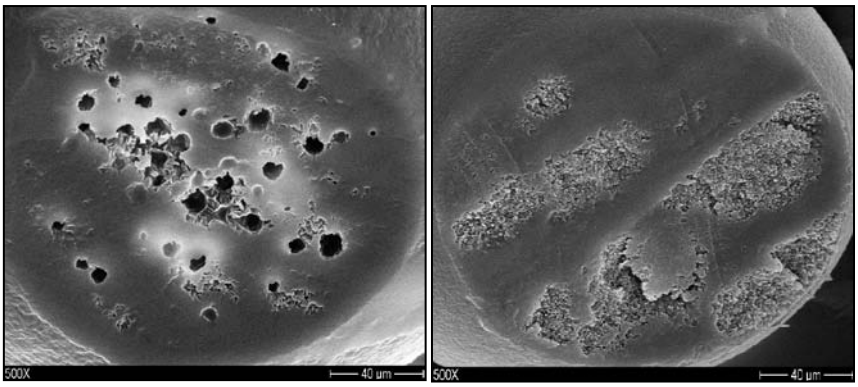

b

Fig. 4: SEM pictures of polycaprolactone microparticle blends with dispersion time interval of 60 min between primary emulsion and primary oil phase (a. higher magnification and b. cross-section)

The integration of carbamazepine on the surface of propranolol HCl loaded microparticles may explain the increased carbamazepine release from microparticle blends with the W/O/W (Pro) and O/W (CBZ) (DTI 60 min). When compared to microparticles generated using the W/O/W method, where propranolol HCl is either molecularly distributed or amorphous in the matrix, this may have reduced propranolol HCl migration to the surface of the microparticles and their leakage into the dissolution medium. Furthermore, the porous membrane found in microparticles generated using the W/O/W technique favored rapid release of the hydrophilic propranolol HCl. The hydrophobic character of carbamazepine and its extremely low water solubility may contribute to its inadequate release from microparticles [24, 31].

In comparison to the regular microparticles, the release of propranolol HCl was greatly slowed in the case of the microparticle blends (DTI 60 min). With DTI 60 min, only 33% of propranolol HCl was released from microparticle mixes made using the W/O/W (Pro) and O/W (CBZ) techniques. It is important to note that the propranolol HCl was inside the microparticle and the carbamazepine was on the microparticle's exterior surface. As a result, only the medicine near to the outer surface could be discharged at first. The discharge of a ground drug creates water-filled channels that allow the medications inside the microparticles to diffuse. Diffusion via water-filled pores is a significant route for propranolol HCl and carbamazepine discharge.

It may be expected that there is contact between the first primary emulsion (propranolol HCl) and the second primary oil phase (carbamazepine) during the preparation of microparticle blends based on release data for each microparticle blend. The surface morphology of the microparticles blend (fig. 4a) and FBRM data on particle size mean before and after the addition of second primary oil phase into a single external aqueous phase (fig. 2) have suggested it. In addition, the microparticles' cross sections revealed a porous inner structure and the absence of pores (fig. 4b). The internal structure of microparticle blends created with DTI 60 min looked to be shrinking in terms of the number of pores and their size (fig. 4b). This behavior might be explained by the interaction of the second primary oil phase (CBZ) with hard particles from the first primary emulsion (Pro), in which the second primary oil phase (CBZ) occluded and coated pores on the hard particle's surface. Optical microscopy images back up this hypothesis. It means that the first W/O/W (Pro) emulsification stage and the second (CBZ/dye) emulsification phase produced two types of microparticle mixes (fig. 5). A microparticle with a black plaque on the surface and black microparticles was shown in this image [24, 31, 32, 36, 37].

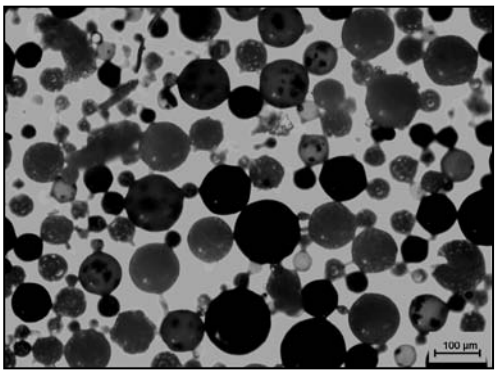

Fig. 5: Optical microscopy pictures of polycaprolactone microparticle blends with the dispersion time interval of 60 min. [Microparticles containing dye (black)]

CONCLUSION

Novel microparticle blends comprising drugs/medicines with varying solubilities (e. g. propranolol HCl and carbamazepine) have a lot of promise as controlled-release drug delivery systems. Propranolol HCl release was slower than carbamazepine release in microparticle blends (with DTI 60 min) comprising drugs of varying solubility. The particle size of microparticles from the first primary emulsion (Pro) was smaller than the particle size of microparticles after the addition of the second primary oil phase (CBZ) according to FBRM experiments (with DTI 60 min). It was induced by the interaction of the second primary oil phase (CBZ) with microparticles from the first primary emulsion (Pro). Microparticle blends (DTI 60 min) were spherical and had two populations, according to optical and SEM. These microparticle blends included smooth and rough-surfaced microparticles. This phenomenon might be explained by the interaction of the second primary oil phase with the hard particles from the first primary emulsion, in which the second primary oil phase closed and coated pores on the surface of the hard particles. The physical properties of microparticle blends were impacted by the type of dispersion time interval used.

ACKNOWLEDGEMENT

The authors gratitude the Directorate General of Higher Education; the Ministry of Education, Culture, Research, and Technology, Republic of Indonesia for their support on this project under the National Competitive Basic Research Grant year 2023 and Academic Leadership Grant Universitas Padjadjaran 2023.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

No conflicts of interest is associated with this work.

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