Synthesis of the Core/Shell Structure of Polycaprolactone@Curcumin-Gluten for Drug Delivery Applications

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Abstract: In this study, polycaprolactone (PCL) nanoparticles were effectively synthesized as novel drug delivery systems by the electrospray method. Curcumin (Cur) was selected as the model drug with further enhanced stability of its composition with gluten (GLU). The physical-chemical characterization, including FTIR, UV-vis, and thermal analysis of PCL@Cur-GLU nanocapsules, are explored. The in vitro release profiles described by Ritger–Peppas models were also investigated, showing sustained release for 15 h after a burst release within the first five hours.

Keywords: polycaprolactone; curcumin; gluten; drug delivery.

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1. Introduction

Studying on the carriers of drug delivery systems (DDSs) has been recently growing on some of the related materials such as mesoporous inorganic substances [1-3], membranes [4,5], microspheres [6,7], natural polymers [8,9], and other polymer-based structures [10-12] for drug loadings and releases to offer enduring robustness and targeted therapy, other than enlightening constancy of loaded drugs and their bioaccessibility [13,14]. Therefore, the efficacy of treatment methods is influenced by drugs and carriers of DDSs and construction methods. Considering the biocompatibility and biodegradation of natural polymers, they are under huge research as improved drug carriers [15,16]. Besides, using natural materials can reduce toxicity and other undesired side effects in the body [17].

Among the most studies, biomaterials such as chitosan (CS) [18], polyethylene glycol (PEG) [19], and polyvinyl alcohol (PVA) [20], polycaprolactone (PCL) [21], modified nano-complexes as delivery systems [22], anticancer nanofibers [23] and engineering of epidermis skin grafts [24,25] have been extensively engaged in various biomedical applications including pH-sensitive release system [26], thanks to its admirable biodegradation properties.

Curcumin (diferuloylmethane) is a herbal polyphenol extracted from the turmeric rhizome (Curcuma longa) [27], and it is widely used as an Asian food additive, however its various healing features and valuable biological activities such as being used as an antioxidant,
antitumor, antiphlogosis, and antibacterial applications [28-30]. Curcumin molecules are unstable in some chemical (high pH) and physical mediums (high heat and light). Also, its poor solubility in aqua solutions leads to less bioavailability and somehow confining its applied clinical trials. Consequently, a series of enhanced drug delivery systems have been improved using Cur molecules [19,29] to overcome these weaknesses.

We initially produced PCL using the electrospray method based on operating factors such as flow rate, solvent, polymer, and drug concentrations. Then, we used PCL to entrap the as-prepared Curcumin-gluten nanoparticles (Cur-GLU) by mixing drugs with the polymer mixture to form the core/shell structure during the electrospray process (Figure 1). The characteristics of the resulted products were analyzed by FTIR, FESEM, and TEM. The in vitro sustained release of Cur was also tested in 5 wt% sodium dodecyl sulfate (SDS) solution.

**Figure 1.** Schematic illustration of core/shell structure of polycaprolactone @ curcumin-gluten.

### 2. Materials and Methods

#### 2.1. Material.

PCL ($M_w = 80000$), and Curcumin (Cur) were supplied by Sigma-Aldrich. (Guangdong, China). Chloroform and dimethylformamide (DMF) were purchased from Merck. 5 wt% sodium dodecyl sulfate (SDS) was utilized in vitro drug release experiments. All other materials and reagents used in this work were analytically graded unless otherwise noted.

#### 2.2. Experiment setup.

Spinning solutions were prepared in advance by dissolving different amounts of PCL in DMF/chloroform (1:2) to achieve a polymer concentration fraction of 0.5%, 1%, and 2% M/V under stirring at 25 °C for 1 hour followed by stirring at room temperature overnight. Cur-GLU (1:5) was added to the polymeric solution. All solutions were degassed and fed into the syringe, combined with a stainless steel capillary. Coaxial electrospray, a special concentric nozzle was used to develop core/shell structure. Solutions were pumped using two separate precision syringe pumps and syringes. The distance between the needle and receptor (10 cm), flow rates (2, 3, and 4 μL/min), voltages (10, 12, and 13 kV) and PCL concentrations (0.5, 1, and 2 % w/v) were investigated. The obtained powders on grounded aluminum foil, glass, and
liquid surface (foil covered by ethanol (96%)) were collected and then treated under 50 °C to remove the residual solvent.

Due to the importance of the parameters on the process output, available facilities, and cost and time savings, the three factors of concentration, flow rate, and voltage applied as the main parameters with specifically selected levels, which are listed in Table 1, is entered in Design EXPERT 11 software (StatEase). By the surface response method and Box-Behnken design model and three repetition steps, 20 test steps were designed and shown in Table 2.

### Table 1. Variation of operating parameters setup of experiment designs for ES fabrication process.

| Parameters     | Symbol | Levels          |
|----------------|--------|-----------------|
|                |        | Low level (-1)  |
|                |        | Middle level (0) |
|                |        | High level (+1) |
| Concentration  | A      | 0.5             |
| Voltage        | B      | 10              |
| Flow rate      | C      | 2               |

### Table 2. The Box-Behnken designed parameters.

| Experiment Run | Concentration (%w/v) | Voltage(kV) | Flow rate (μL/min) |
|----------------|----------------------|-------------|--------------------|
| 1              | 0.5                  | 13          | 4                  |
| 2              | 0.5                  | 13          | 2                  |
| 3              | 1                    | 12          | 3                  |
| 4              | 1                    | 12          | 4                  |
| 5              | 1                    | 13          | 3                  |
| 6              | 0.5                  | 10          | 4                  |
| 7              | 1                    | 13          | 2                  |
| 8              | 0.5                  | 10          | 2                  |
| 9              | 1                    | 12          | 3                  |
| 10             | 1                    | 12          | 3                  |
| 11             | 2                    | 10          | 4                  |
| 12             | 2                    | 13          | 4                  |
| 13             | 1                    | 12          | 3                  |
| 14             | 2                    | 10          | 2                  |
| 15             | 2                    | 13          | 2                  |
| 16             | 2                    | 12          | 3                  |
| 17             | 0.5                  | 12          | 3                  |
| 18             | 1                    | 12          | 3                  |
| 19             | 1                    | 10          | 3                  |
| 20             | 1                    | 12          | 3                  |

2.3. Characterization.

The microcapsules’ morphology and profile were observed via scanning electron microscope (FESEM) from different operating conditions. The mean particle sizes and distributions were analyzed by FESEM micrographs using the software nano-measurer (ImageJ2, www.imagej.net). Transmission Electron microscope (TEM) was used to determine the drug particles’ distribution on the carrier (PHilips, S208). FT-IR (BRUKER, EQUINOX 55) was used to evaluate drugs entrapped in carriers' structural composition and stability. The drug release behavior was studied by using a UV-vis spectrophotometer (UV-370).

3. Results and Discussion

3.1. Synthesis of PCL-based nanocapsules.

Electrospray parameters of flow rate, polymeric concentrations, and voltage as the most important were examined [4]. Experiments were designed to synthesize the nanoparticles and find the optimal electrospray parameters. Then, three samples of the drug particles were compared according to the optimal, efficient drug delivery system under the drug release conditions. As reported previously [31], micro-sized rod-shaped PCL formation under
chloroform solvent was more capable of drug loading than spherical forms. As a result, to increase the electrical conductivity, the combination of DMF/chloroform (2:1) was used for PCL-based microcapsules. The distance between the needle and the collection plate was fixed at 10 cm, and the needle with a size of 22 mL and a length of 2.8 cm was considered for particle synthesis and 45 minutes for the electrospray process for all particles.

3.2. The effects of PCL concentration, flow rate and voltage.

As an accepted important feature in morphology controlling, PCL concentrations in the range of 0.5-2 %w/v were examined. As shown in Figures 2 a, b, and c, polymer structures had different shapes of discrete spheres to beaded fibers which were supposed to be relevant to the polymer concentration used in ES process. In the low concentration of PCL (0.5 %w/v), microspheres are not completely formed. The agglomerated particles are shaped when polymer concentration reaches 1 %w/v. Besides, as the concentration of polymer became higher (2 %w/v), the tendency to form beaded nanofibers emerged. It can be attributed to the spinning solutions' electrical conductivity and surface tension with different polymer concentrations [17]. Figures 2d, e, and f reveal the influence of flow rate on the morphology of PCL capsules during ES process. As is obvious in optical micrographs, 2 μL min⁻¹ can be the optimal flow rate to fabricate uniform and monodisperse PCL spheres. Figure 2 g, h, and i reveal the influence of implied voltage on the morphology of PCL capsules during ES process. As seen in FESEM images, there is a reverse relationship between the voltage and size of produced particles. 12 kV can be the optimal voltage to fabricate uniform and monodisperse PCL spheres.

![Figure 2](https://biointerfaceresearch.com/)

**Figure 2.** FESEM of synthetized nanocapsules under different concentrations (a) 0.5 %w/v, (b) 1 %w/v, (c) 2 %w/v, under different flow rate (d) 3 μL min⁻¹, (e) 4 μL min⁻¹, (f) 5 μL min⁻¹ and different voltage ((a) 11 kV, (b) 12 kV, (c) 13 kV.
3.3. Optimal Experiment Design (OED).

Based on the ES parameters, 20 runs were performed in Design-Expert software. According to FESEM images, each run's particle size and distribution were determined (Table 3).

### Table 3. Experiment runs, parameters, and responses.

| Run | Factor A (PCL % w/v) | Factor B Voltage(kV) | Factor C flow rate (µL.min⁻¹) | R1 Particle Size(nm) | R2 Particle Distribution |
|-----|----------------------|----------------------|-------------------------------|----------------------|--------------------------|
| 1   | 0.5                  | 13                   | 4                             | 18                   | 139                      |
| 2   | 0.5                  | 13                   | 2                             | 23                   | 44                       |
| 3   | 1                    | 12                   | 4                             | 77                   | 167                      |
| 4   | 1                    | 12                   | 3                             | 46                   | 197                      |
| 5   | 1                    | 13                   | 3                             | 90                   | 136                      |
| 6   | 0.5                  | 10                   | 4                             | 52                   | 87                       |
| 7   | 1                    | 12                   | 2                             | 80                   | 181                      |
| 8   | 0.5                  | 10                   | 2                             | 37                   | 98                       |
| 9   | 1                    | 12                   | 3                             | 95                   | 291                      |
| 10  | 1                    | 12                   | 3                             | 102                  | 247                      |
| 11  | 2                    | 10                   | 4                             | 23                   | 122                      |
| 12  | 2                    | 13                   | 4                             | 25                   | 452                      |
| 13  | 1                    | 12                   | 3                             | 55                   | 254                      |
| 14  | 2                    | 10                   | 2                             | 44                   | 274                      |
| 15  | 2                    | 13                   | 2                             | 66                   | 185                      |
| 16  | 2                    | 12                   | 3                             | 54                   | 199                      |
| 17  | 0.5                  | 12                   | 3                             | 58                   | 44                       |
| 18  | 1                    | 12                   | 3                             | 85                   | 165                      |
| 19  | 1                    | 10                   | 3                             | 65                   | 255                      |
| 20  | 1                    | 12                   | 3                             | 89                   | 165                      |

The results of determination coefficients ($R^2$), model accuracy, and variance analysis for particle size and distribution are obtained for the particle size (R1) and distribution (R2) (Table 4).

### Table 4. Values of determination coefficients.

| Response | Adeq precision $R^2$ | Adjusted $R^2$ | $R^2$ |
|----------|----------------------|----------------|-------|
| Size     | 12.3421              | 0.9033         | 0.9593|
| particle distribution | 6.5545              | 0.8254         | 0.9339|

Figure 3. FESEM of synthetized nanocapsules under optimum operational conditions.
The predicted model was further assessed by RSM analysis. The 3D plot provides a means to visualize interactions between the variables and rapidly estimate each variable's optimum level for maximum response. The statistical significance of the model equation was checked by an F test (ANOVA). The F test of particle size and particle distribution suggested that the model had the F value of 21.81, and 23.11, indicating that this model is acceptable. The analysis of variance (ANOVA) of particle size and distribution gained indicated that experimental data had a determination coefficient ($R^2 = 0.95$ and 0.93, respectively). The software predicted that the optimum PCL concentration, voltage, and flow rate were 1 % w/v, 12 kV, and 3 μL/min, respectively. The particle size and distribution were 77 nm and 167, respectively (Figure 3) based on the software prediction.

3.4. Characterization.

TEM images for the sprayed particles of Cur-GLU (1:5) added to PCL under optimum operating conditions are shown in Figure 4. The core/shell structure (spheres of about 180 nm) can be observed.

The FTIR of PLC@Cur-GLU is shown in Figure 5 compared to curcumin, gluten, and PLC. In the sample of PCL@Cur-GLU, the broad peak at 3500 cm$^{-1}$ is assigned to hydroxyl groups (PLC, Cur, and GLU) [32,33]. The asymmetric vibration of C-H bonds emerged at 2922 cm$^{-1}$, which is obvious in all samples. The symmetric vibrations of C-H at 2876 cm$^{-1}$ and C=O at 1725 cm$^{-1}$ are evidence of the composite's proper formation. The peak of amide moieties at 1655 and 1522 cm$^{-1}$ shows the vibration of amide bonds, which are present in curcumin and gluten samples and the composite. The vibration of aromatic C=C emerged at 1440 cm$^{-1}$ in the sample of PLC@Cur-GLU. Besides, the peaks at 1121 cm$^{-1}$ may be related to the vibrations of C-O-C bonds, which are obvious in all other samples.

![Figure 4. TEM of PCL@Cur-GLU.](image)

![Figure 5. FTIR of (a) Cur, (b) PCL, (c) gluten, (d) PCL@Cur-GLU.](image)
Differential scanning calorimetry (DSC) images are shown in Figure 6. In the PCL sample, the endothermic peak at 57.7 °C is related to the melting of this material, and during this process, about 83.7 J/g is consumed [34]. The obtained melting point is close to the reported melting points reported for PCL [35]. Also, the glass transition temperature of PCL was about 43.1°C, and its specific heat capacity was 0.83 J/gK. No special phenomenon has occurred in the temperature range of 25 to 100 °C for the curcumin sample because the melting point of curcumin is about 170 °C [36] and the temperature required for the evaporation of the structural water of Zein is about 157°C [37]. In the composite sample, the thermal stability is higher than PCL and gluten.

![DSC of Cur, PCL, gluten, and the composite.](https://biointerfaceresearch.com/)

**Figure 6.** DSC of Cur, PCL, gluten, and the composite.

3.5. *In vitro* release.

*In vitro* releases of two samples of PCL-Cur, and PCL@Cur-GLU were studied at pH 5 and 8 to investigate the effect of curcumin encapsulation.

![In vitro release profiles of PCL-Cur, PCL@Cur-GLU (a) pH: 5 and (b) pH: 8.](https://biointerfaceresearch.com/)

**Figure 7.** Drug release profiles of PCL-Cur, PCL@Cur-GLU (a) pH: 5 and (b) pH: 8.
Figure 7a shows in vitro release of two samples at pH 5. The increasing trend of in vitro releases of PCL-Cur (11.60%) and PCL@Cur-GLU (15.70%) indicated the increased drug encapsulation and hydrophilicity of particles by adding gluten. Figure 7b shows in vitro release of three samples at pH 8. The increasing trend of in vitro releases of PCL-Cur (6.19%) and PCL@Cur-GLU (9.11%) indicated the increased stability of curcumin in alkaline conditions based on the design of the drug delivery system. Zhang et al. (2015) found less than 20% release for curcumin in the first 24 hours, compared with 30% release for curcumin particles alone. It can be concluded that the designed system can control the release of drugs for a long time [38]. The release at pH 5 indicates that the designed drug delivery can benefit anticancer applications [39].

Fig. 8 shows the cytotoxicity plot of curcumin concentrations (10-100 ppm). Cell cytotoxicity for the optimized samples with PCL@Cur-GLU after extraction time of 12, 24, and 48 h are illustrated in Fig. 8b. The results showed that cell cytotoxicity of the optimized sample after 48 h was 65%.

4. Conclusions

In summary, we effectively contrived novel PCL@Cur-GLU an electrospray process. Adjusting voltage (11 kV), flow rates (3 µL/min), polymer (1 % w/v), and drug concentration (Cur-GLU, 1:5), the morphology and particle sizes could be optimized. Cur could be encapsulated inside the PCL nanocapsules with good entrapment efficiency (59-88 %)
collected on the aluminum surface area. A sustained release of Cur from the nanocapsules can be reached for up to 24 h. We believe that PCL@Cur-GLU core/shell structures further investigate clinical medicine’s potential drug delivery systems.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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