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Controlled release multiple layer coatings

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Abstract

Purpose: In a fluid-bed coating machine, the coating solutions are normally sprayed using a manually controlled peristaltic pump. This study provides a process where two or more coating solutions can be sprayed consecutively using two or more syringe pumps controlled by a computer, to form multiple layers. In this process, the spraying parameters can be controlled easily from a computer. *Methods*: Propranolol HCl was used as a model drug. Nine different drug-loaded controlled release coated beads were prepared by using a combination of ethylcellulose and/or chitosan solutions. The pulse-coated beads were prepared by changing the spray rate and/or volume of the polymer solutions. *Results*: There was a fourfold increase (18 versus 75 minutes) in lag time when the same amount of ethylcellulose (4 g) was dissolved in 100 mL of ethanol instead of 160 mL. When the same amount of drug and ethylcellulose solution was applied on the acrylic coated beads as multiple layers coating, the lag time decreased to only 6 minutes. Similarly, the 50% drug release time also decreased significantly. *Conclusion*: An overall comparison of the dissolution profiles showed that drug release from these coated beads was changed significantly when the sequence of the drug and polymer layers was changed.

Key words: *Coating; controlled release; fluid bed; multiple layers; Wurster coater*

Introduction

Controlled release formulations are designed to deliver the active ingredients slowly at a preset rate over a prolonged period[1,2]. Research in controlled drug release during the last three decades has resulted in numerous novel pharmaceutical formulations for human use[3]. One of the most popular methods in achieving controlled drug release is the application of a polymer coating surrounding a solid dosage form, including tablet and bead[4]. Two of the most common coating techniques in the pharmaceutical industry are pan coating[5] and fluid-bed coating[6]. The pan-coating technique is older than the fluid-bed coating technique and requires artistic skill to apply preset coating on the surface of a solid dosage form. In contrast, the fluid-bed coating technique is more flexible and offers numerous advantages compared to the pan-coating techniques: (i) less time consuming and (ii) more uniform coating.

A fluid-bed coating machine may utilize a top spray system or a bottom spray system, also known as Wurster coater, or a combination of both. A coating solution or dispersion is atomized and sprayed onto the air-suspended formulations and the formulations are then dried when supported by air. The formulations are repeatedly recirculated within the column, whereas successive layers of a coating solution are applied through aerosol spray until the desired thickness of that coating is formed. Each cycle of each coating consists of two phases: (i) spraying the formulations with a coating solution and (ii) drying. The coating solution can be (i) only a drug dissolved in a suitable media, (ii) one or more polymer(s) dissolved in a suitable media, or (iii) a mixture of a drug and polymer(s) dissolved in a suitable media. Based on the compositions of the coating solutions, the drug release from these coated formulations can follow several models[7–9]. In one model, the drug release may show zero-order release kinetics[10,11], whereas in another model the drug release may show first-order release kinetics[7]. Although these two are the most common release models, a third model follows pulsatile release kinetics with or without initial lag time[5,12–15]. With these

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goals in mind, a formulation scientist needs to try numerous compositions to achieve the desired release profiles.

A typical fluid-bed coating machine requires an external device to supply the liquid coating solution to the fluidized bed machine. Typically, a semiautomatic, single peristaltic pump performs this function. However, the use of a peristaltic pump limits the application in a number of ways. First, a peristaltic pump only facilitates the application of a single liquid-coating solution at a time. To apply a plurality of coating solutions through the same spray nozzle, the parameters of the pump must be manually adjusted. Recently, El-Malah and Nazzal[16] have described a dual programmable peristaltic pump's setup for spraying the coating solutions. The purpose of this modification was to evaluate the effect of gradient drug deposition on the beads. However, if the various coating solutions cannot be intermixed because of their respective chemical properties, the tubing that carries the coating solutions must be physically replaced. Having to manually adjust a peristaltic pump can be especially problematic during a product's research and development phase because it is necessary to repeatedly manipulate parameters such as the spray rate of the spraying solution, the polymer types, the volume and concentration of the polymer solutions, and the number and composition of the layers to achieve the ideal release properties for a given pharmaceutical formulation. Hence, it is desirable to provide a method that facilitates the manipulation of such parameters.

The objective of this study was to develop an automated novel spraying technique that coupled with a fluid-bed coating machine can be used for various controlled release coated formulations. The novel coating process of this study allows precise manipulation of the controlled release characteristics[17].

Materials and methods

Materials

Sugar spheres NF (60/80 mesh size) were a gift from Paulaur Corporation (Cranbury, NJ, USA). Eudragit L100 was a gift from Evonik Degussa GmbH (Essen, Germany). Ethylcellulose (Ethocel, viscosity 10 cp) was a gift from Dow Chemical Company (Midland, MI, USA). Propranolol HCl, chitosan (low-molecular weight; viscosity 20,000 cps), talc, dibutyl sebacate, coumarin-6, Nile red, ethanol (200 proof), acetic acid, and potassium phosphate were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Methods

Figure 1 shows a schematic diagram of the automated multiple layers coating process. A computer (1) controls two programmable syringe pumps (2). Two fluoridated ethylene propylene tubes (internal diameter: 1/16 inch) (3) are connected via a three-way connector (4) to another section of tubing (5) that is connected to the fluid bed apparatus (6). Propranolol hydrochloride was used as a model drug and ethylcellulose and chitosan were used as coating materials.

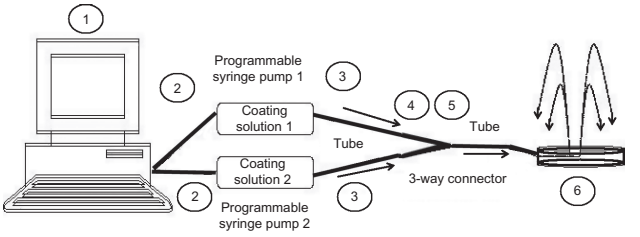

Figure 1. Schematic of the automatic multiple layer coating setup. A computer (1) controls two programmable syringe pumps (2). Two fluoridated ethylene propylene tubes (internal diameter: 1/16 inch) (3) are connected through a three-way connector (4) to another section of tubing (5) that is connected to the fluid-bed dryer (6).

A bench top fluid-bed coater (MP-Micro, Niro Inc., Columbia, MD, USA), fitted with a bottom spray coater, was charged with 50 g sugar beads. Before coating the sugar beads with drug and polymer, the beads were coated with an acrylate solution using a peristaltic pump. The purpose of the acrylate subcoating was to prevent premature disintegration of the sugar beads because of permeation of coating solvent during the process. The acrylate subcoating solution was prepared by mixing 1.5 g Eudragit L100, 0.5 g ethylcellulose (dissolved in 30 mL of 200 proof ethanol), 0.5 g talc, and 50 mL of a pH 7.4 50-mM potassium phosphate buffer. The pH of the final precoating solution was adjusted to 7.2 using 0.1N sodium hydroxide. The subcoating conditions included inlet air temperature (70°C), product temperature (40°C), exhaust air temperature (38°C), atomizing air pressure (2 bar), air velocity (2.35–2.5 m/s), and a fluid delivery rate (2 mL/min). After subcoating, the beads were desiccated under vacuum for a minimum of 48 hours. Nine different formulations were prepared using either regular coating (RC) or pulse coating (PC) process as outlined below.

Formulation 1: RC1

The bottom spray coater was charged with 20 g of the acrylate-coated beads. A propranolol HCl solution was prepared by dissolving 2 g propranolol HCl and 1 mg coumarin-6 dye in 100 mL of 200 proof ethanol. The purpose of the coumarin-6 was to visualize the coating on the surface of the beads. The above-mentioned drug solution was used to coat the specified amount of the

sugar beads using the following conditions: The coating conditions included inlet air temperature (60 ± 5°C), product temperature (30 ± 5°C), exhaust air temperature (28 ± 5°C), atomizing air pressure (2 bar), air velocity (2.35 m/s), and a fluid delivery rate (2 mL/min). After coating with the drug, the beads were dried for an additional 5 minutes in the coater at 60 ± 5°C.

The drug-coated beads were then coated with the ethylcellulose solution under the following conditions: inlet air temperature (65 ± 5°C), product temperature (36 ± 5°C), exhaust air temperature (34 ± 5°C), atomizing air pressure (2 bar), air velocity (2.35 m/s), and a fluid delivery rate (1 mL/min). After coating, the beads were dried for an additional 10 minutes in the coater at 65 ± 5°C. The ethylcellulose solution was prepared by dissolving 4 g of ethylcellulose, 0.11 g of dibutyl sebacate, and 1 mg of Nile red dye in 160 mL of 200 proof ethanol. The purpose of the Nile red dye was to visualize coating on the surface of the beads.

Formulation 2: RC2

Ethylcellulose-coated, drug-layered sugar beads were produced in a similar manner as RC1 with the following differences. The ethylcellulose solution was prepared in 100 mL of ethanol instead of 160 mL, and the fluid delivery rate of the ethylcellulose solution was 5 mL/min as opposed to 1 mL/min. The purpose of this formulation was to study the effect of polymer concentration (i.e., the volume of the coating solvent) on the drug release.

Formulations 3–9

The purpose of the following seven formulations was to study the effect of PC on the drug release. Figure 2 shows an example of pulse-coated bead. In this example, a sugar bead is coated with a layer of acrylate polymer followed by successive layers of drug and polymer. To enable PC, a few modifications were made to the fluid delivery device of the fluid-bed coating machine. First, the single peristaltic fluid delivery line was replaced by a single line branching into two lines, and the peristaltic pump was replaced by two controllable and programmable syringe pumps, 2 as shown in Figure 1

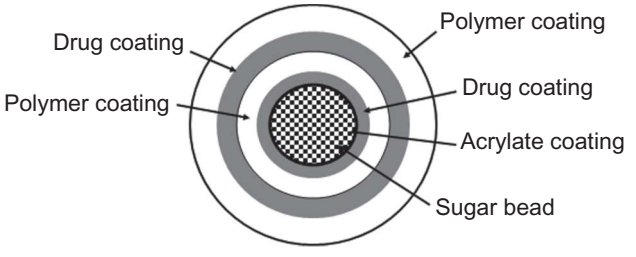

Figure 2. Schematic two-dimensional view of a multiple layer-coated bead (formulation PC1).

(NE1000, New Era Pump System, Farmingdale, NY, USA). The syringe pumps were fitted with 60-mL syringes and the pumps were connected to a computer (1 in the Figure 1) for automated control. Control of the pumps was accomplished by sending a series of programming commands to the pumps. These commands controlled the spray rate of each pump, the total volume, and the total number of pump cycles. In addition, the computer was used to control the withdrawing of fluid from the delivery tube to eliminate mixing of the two components.

Formulation 3: PC1

Drug and ethylcellulose overcoat solutions were prepared as in formulation RC1. The syringes were filled with their respective drug and polymer solutions. The fluid-bed coater was charged with 20 g of acrylate-coated sugar beads and set to the operating parameters as outlined in RC1 with the exception that the propranolol and ethylcellulose solution was delivered by the computer-controlled syringe pump setup of Figure 1 using the parameters outlined in Table 1.

Formulation 4: PC2

This formulation was produced in the same manner as the formulation PC1 with the exception that the total volume of ethylcellulose solution was 100 mL and the solution delivery program was changed to the values in Table 1.

Formulation 5: PC3

This formulation was produced in the same manner as formulation PC1 with the exception that the solution delivery program was changed to the values in Table 1.

Formulation 6: PC4

This formulation was produced in the same manner as formulation PC2, except, in the place of having five uniform delivery cycles, the drug and coating was delivered in three different cycles as outlined in Table 1.

Formulation 7: PC5

This formulation was prepared by spraying successive layers of a solution of drug/ethylcellulose in ethanol and a chitosan solution in 1% acetic acid. The drug/ethylcellulose solution was prepared by dissolving 2 g propranolol, 4 g ethylcellulose, 0.11 g dibutyl sebacate, and 1 mg Nile red in 100 mL of 200 proof ethanol. The chitosan solution was prepared by dissolving 0.5 g low-molecular-weight chitosan in 100 mL of a 1% acetic acid solution. Then 0.5 g of talc was dispersed in the solution.

The coating process involved charging the fluid-bed coater with 20 g of acrylate-coated sugar beads. Next the beads were coated with the drug/ethylcellulose and

Table 1. Description of processing conditions of various formulations.

Formulation: RC1					Ethylcellulose solution: 4 g in 160 mL ethanol					
Drug solution: 2 g propranolol in 100 mL ethanol										
Formulation: RC2					Ethylcellulose solution: 4 g in 100 mL ethanol					
Drug solution: 2 g propranolol in 100 mL ethanol										
Formulations: pulse coated										
Pump 1					*Pump 2*					
Formulation: PC1					Ethylcellulose solution					Total cycles
Drug solution										
Spray rate		Total amount per cycle	Total volume per cycle	Pause	Spray rate		Total amount per cycle	Total volume per cycle	Pause	
mL/min	g/min	g	mL	seconds	mL/min	g/min	g	mL	seconds	
2	0.04	0.4	20	120	1	0.025	0.8	32	120	5
Formulation: PC2					Ethylcellulose solution					
Drug solution										
2	0.04	0.4	20	120	5	0.2	0.8	20	120	5
Formulation: PC3					Ethylcellulose solution					
Drug solution										
2	0.04	0.4	20	120	1	0.04	0.8	20	120	5
Formulation: PC4					Ethylcellulose solution					
Drug solution										
2	0.04	1	50	120	5	0.2	1.0	25	120	1
2	0.04	0.5	25	120	5	0.2	1.0	25	120	1
2	0.04	0.5	25	120	5	0.2	2.0	50	120	1
Formulation: PC5					Chitosan solution					
Drug/ethylcellulose solution										
2	0.12	0.4/0.8	20	120	2	0.01	0.1	20	120	5
Formulation: PC6					Ethylcellulose					
Drug/chitosan										
2	0.05	0.4/0.1	20	120	2	0.08	0.8	20	120	5
Formulation: PC7										
20 g drug coated beads										
Ethylcellulose solution					Chitosan solution					
2	0.08	0.8	20	120	2	0.01	0.1	20	120	5

chitosan solutions using the dual syringe pump setup of Figure 1 and the following coating conditions. These included inlet air temperature (70 ± 5°C), product temperature (36–44°C), exhaust air temperature (34–40°C), atomizing air pressure (3 bar), and air velocity (3.9 m/s). The fluid delivery parameters are listed in Table 1.

Formulation 8: PC6

Acrylate-coated beads were prepared in a similar manner as formulation 1 (RC1) with the exception that the beads were dried in a desiccator for a minimum of 3 days. The beads were then treated with 40 mL of ethanol in fluid-bed drier using the operating parameters as in formulation 1 (RC1). Again the beads were dried for 4 days. The purpose of the ethanol treatment was to improve the film adhesion properties of the aqueous solution of the mixture of drug and chitosan. During our preliminary studies, we have observed that the aqueous solution of the mixture of drug and chitosan failed to form satisfactory film on the acrylate-coated beads because of poor adhesion between the acrylate layer and the drug/chitosan layer (data not included). However, pretreatment with ethanol eliminated the problem and allowed uniform drug/chitosan coating on the surface of the acrylate-coated beads. An ethylcellulose solution was prepared by dissolving 4 g ethylcellulose, 0.11 g dibutyl sebacate, and 1 mg Nile red in 100 mL of ethanol. A drug/chitosan solution was prepared by dissolving 2 g propranolol and 0.5 g chitosan in 100 mL of a 1% acetic acid solution. Then 0.5 g talc was dispersed in the solution. The fluid-bed coater was then charged with 20 g of the acrylate sugar beads and the coater was operated with the same parameters as in formulation 6. The syringes were loaded with the ethylcellulose and drug/chitosan solutions and the solutions were sprayed using the parameters outlined in Table 1.

Formulation 9: PC7
In this formulation, the acrylate-coated beads were first coated with the drug solution as in RC1. Next the beads were coated with successive layers of ethylcellulose solution (as in PC2) and chitosan solution (as in PC5). The process involved coating 20 g of drug-coated beads using the same operating parameters as those in formulation PC5 and using the fluid delivery program outlined in Table 1.

In vitro dissolution study

The dissolution rates of propranolol from various coated formulations (200 mg each sample) were studied using a rotating paddle-automated dissolution apparatus, USP Apparatus II (VK 7000;, Varian Inc., Palo Alto, CA, USA), connected to a UV spectrophotometer (Carry 50 Tablet; Varian Inc.). Phosphate buffer (900 mL) at pH 7.4 was used as dissolution media and the temperature was maintained at 37 ± 1°C. The paddle rotation speed was maintained at 50 rpm. A fixed volume of samples was automatically withdrawn through a filter at various preset time intervals and analyzed for the concentration of propranolol using an automated spectrophotometer connected to the apparatus. The amount of propranolol dissolved at any time was determined by measuring the absorbance at a wavelength of 296 nm. The concentration of propranolol in each sample was determined by plotting the measured absorbance value to the propranolol standard curve. Each experiment was performed in triplicate.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism, version 5.0 software package (GraphPad Software, Inc., San Diego, CA, USA). The dissolution data were reported as cumulative percent drug released at a given time. The dissolution data were compared using one-way analysis of variance. Cochran's test was used to determine the homogeneity of variance of the data. A P-value of <0.05 was considered as evidence of a significant difference. In the event of a significant difference, the mean values were further compared using Student–Newman–Keuls multiple range test to determine which formulation was significantly different from the others.

Results and discussion

The cumulative dissolution profiles of the formulations are shown in Figure 3. A comparison of the overall cumulative percent drug release showed that, although, six out of nine formulations contained the same amount of propranolol and ethylcellulose, the formulation RC2 showed the slowest drug release compared with the other formulations. Each of the formulations was also compared using the lag time before the drug release. Lag time is defined as the time when the initial drug release is observed. The dissolution lag time was determined from the dissolution profiles. A comparison of the lag times of the drug release also revealed that both RC1 and RC2 showed significantly longer lag time (18 and 75 minutes, respectively, Table 2) compared with

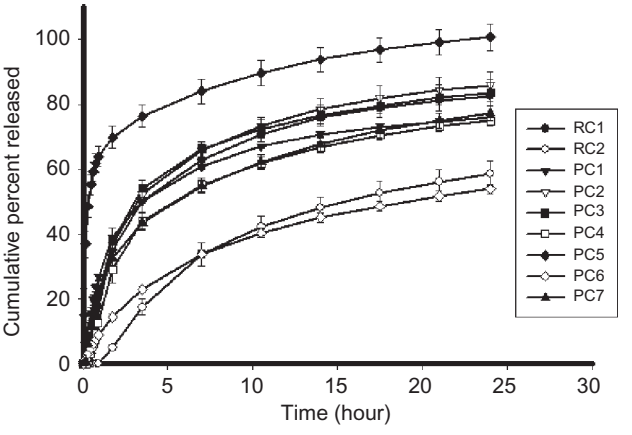

Figure 3. In vitro dissolution profiles, at 37°C in a pH 7.4 phosphate buffer, of the coated beads.

Table 2. The dissolution of propranolol from various formulations.

		Cumulative percent drug released mean (SD); $n = 6$			
Formulation	Lag time (minutes)	3 hours	6 hours	12 hours	23 hours
RC1	18	47.04 (3.8)	59.9 (3.5)	73.14 (2.4)	82.34 (1.8)
RC2	75	14.2 (2.1)	29.96 (3.2)	44.93 (3.2)	57.85 (3.7)
PC1	6	47.48 (0.7)	58.36 (0.8)	68.85 (0.8)	75.56 (0.8)
PC2	6	49.33 (0.9)	62.61 (1.5)	75.66 (3.1)	85.38 (4.1)
PC3	12	50.8 (2.9)	63.83 (2.1)	74.35 (2.9)	83.15 (4.2)
PC4	21	41.06 (2.8)	52.61 (2.4)	64.16 (1.7)	74.36 (1.5)
PC5	0	74.75 (3.4)	82.06 (3.7)	91.56 (3.9)	100.28 (4.1)
PC6	6	20.78 (1.06)	31.2 (1.2)	42.5 (1.4)	53.18 (1.7)
PC7	9	41.06 (1.8)	52.16 (1.9)	64.73 (2.0)	76.51 (2.2)

Table 3. The results of statistical analysis of the dissolution data.

Dissolution time (hours)	Results of Student–Newman–Keuls multiple range test
3	RC2 < PC6 < PC4 = PC7 < RC1 = PC1 = PC2 = PC3 < PC5
6	RC2 = PC6 < PC7 = PC4 < PC1 = RC1 = PC2 = PC3 < PC5
12	PC6 = RC2 < PC4 = PC7 < PC1 < RC1 = PC2 = PC3 < PC5
23	PC6 < RC2 < PC4 = PC7 = PC1 < RC1 = PC3 = PC2 < PC5

the three comparable formulations prepared by PC1, PC2, and PC3 (6, 6, and 12 minutes, respectively). A comparison of the drug release between these two formulations (RC1 versus RC2) also revealed that the overall drug release from RC2 formulation was significantly slower than the RC1 formulation (Table 3). This difference in dissolution was because of the effect of high concentration of ethylcellulose-coating solution in RC2 formulation, which may have provided a thicker polymer coat on the surface of the drug-layered beads. Hence, it is appropriate to infer that during the RC technique the volume of the coating solution is critical because RC1 formulation was coated with 4 g of ethylcellulose in 160 mL of ethanol, whereas RC2 formulation was coated with the same amount of ethylcellulose in a much smaller volume (100 mL) ethanol.

In contrast, the effect of the volume of the coating solution during the pulse-coating process was relatively less significant (PC1 and PC2). Irrespective of the volume of the coating solution, these two formulations showed exactly the same lag time (6 minutes; Table 2). However, PC2 formulation showed slightly higher drug release ($P < 0.05$) after 12 hours. The amount of drug released from PC2 formulation was 86% in 24 hours compared with the amount of drug released from PC1 formulation (76%) during the same period. Although the amount of propranolol and ethylcellulose were same in PC1 and PC2 formulations, the volume and spray rate of ethylcellulose solutions during the PC2 formulation were different. The total volume of ethylcellulose solution in PC2 formulation was less (100 mL) compared with the volume of the same in PC1 formulation (160 mL). Also, the spray rate of ethylcellulose solution in PC2 was five times higher than the same in PC1 formulation. So, the difference in dissolution was either because of the difference in the volume and/or the difference in the spray rate of the ethylcellulose solution. However, a comparison between the two regular coated formulations (RC1 and RC2) revealed that a reduction in the volume of the ethylcellulose solution significantly reduced the dissolution rates ($P < 0.05$; RC2 < RC1). So, it was possible that because of the faster spray rate in formulation PC2, the coating solution was unable to coat the drug-coated surface uniformly and resulted in faster drug release due to the imperfection in coating; however, no visual discontinuation of color coating was observed to support this hypothesis. The next formulation (PC3) was coated with the ethylcellulose solution at a rate, 1 mL/min, similar to the formulation PC1. This particular formulation showed slightly higher lag time (12 versus 6 minutes), but the overall cumulative amount of drug released was similar to the formulation PC2. Hence, we reject our previous hypothesis that faster spray rate failed to apply uniform coating. Hence, the difference in dissolution was mainly because of the difference in the volume of the ethylcellulose solution. It can be concluded from this result that the effect of the coating solution volume during PC was opposite to the RC process.

The next formulation (PC4) was prepared to study the effect of gradual decrease in propranolol amount and increase in ethylcellulose amount in successive coatings. So, unlike the previous formulations, this formulation was coated in three cycles with different amount of drug and ethylcellulose, respectively. Although the amount of the total drug and polymer was similar to the other formulations, 50% of the ethylcellulose was used as an outside coat. The purpose for this increase in the amount of ethylcellulose was to study the effect of outside coating thickness. As expected, the drug release from this formulation was delayed up to 21 minutes (lag time, Table 2) and the overall drug released from this formulation was significantly slower than the previous three pulse-coated formulations (PC1, PC2, and PC3).

The next three formulations (PC5, PC6, and PC7) were prepared to study the effect of chitosan on the drug release profiles. Chitosan is a commonly used polymer and it is gaining popularity in pharmaceuticals because of its nontoxic nature[18,19]. Chitosan was also selected in this study to evaluate how two physically incompatible coating solutions perform during the processing. A chitosan solution in acetic acid is physically incompatible with an ethylcellulose solution in ethanol. As a result, it is necessary during the process that these solutions do not come in contact. To achieve this goal, the syringe pumps were programmed to withdraw the previous coating solution (ethylcellulose or chitosan) following its cycle. This setup allowed us to spray two incompatible coating solutions to achieve the desired release profile, without changing the tubing in between two cycles of spray.

Formulation PC5 was prepared by mixing the drug with the ethylcellulose solution and sprayed through the pump 1 and chitosan solution was sprayed through the pump 2. In comparison to any other formulation, the drug release from this formulation was immediate (i.e., no lag time) and significantly higher. This high drug release was due to the presence of chitosan in the outermost coating. Chitosan is known in the literature as a highly swellable polymer[18,20], as the outermost

coating. This coating swelled immediately in the presence of the dissolution medium and allowed easy penetration of the dissolution medium, which resulted in fast drug release compared with the other formulations. In contrast, the formulation PC6 was prepared by mixing the drug and chitosan and sprayed through the pump 1 and ethylcellulose solution was sprayed through the pump 2. This particular formulation (PC6) showed the drug release somewhat similar to the formulation RC2. The presence of ethylcellulose coating on the outermost surface slowed the release profiles. Similar slow release profiles were also observed when an ethylcellulose coating was applied on the surface of drug-coated beads (PC7), along with the presence of an outer chitosan coating. In contrast, the formulation PC5 showed relatively faster drug release, where the drug was mixed with the ethylcellulose solution and sprayed through the pump 1.

Figure 4 shows the amount of drug released, from each of these formulations, throughout the dissolution study. The amount of drug released was calculated as the difference between the cumulative amounts of drug released at two consecutive sampling times and plotted at the midpoint between these two sampling times. The purpose of this analysis was to evaluate the drug release behavior throughout the dissolution study, whereas Figure 3 showed the overall cumulative drug release. A

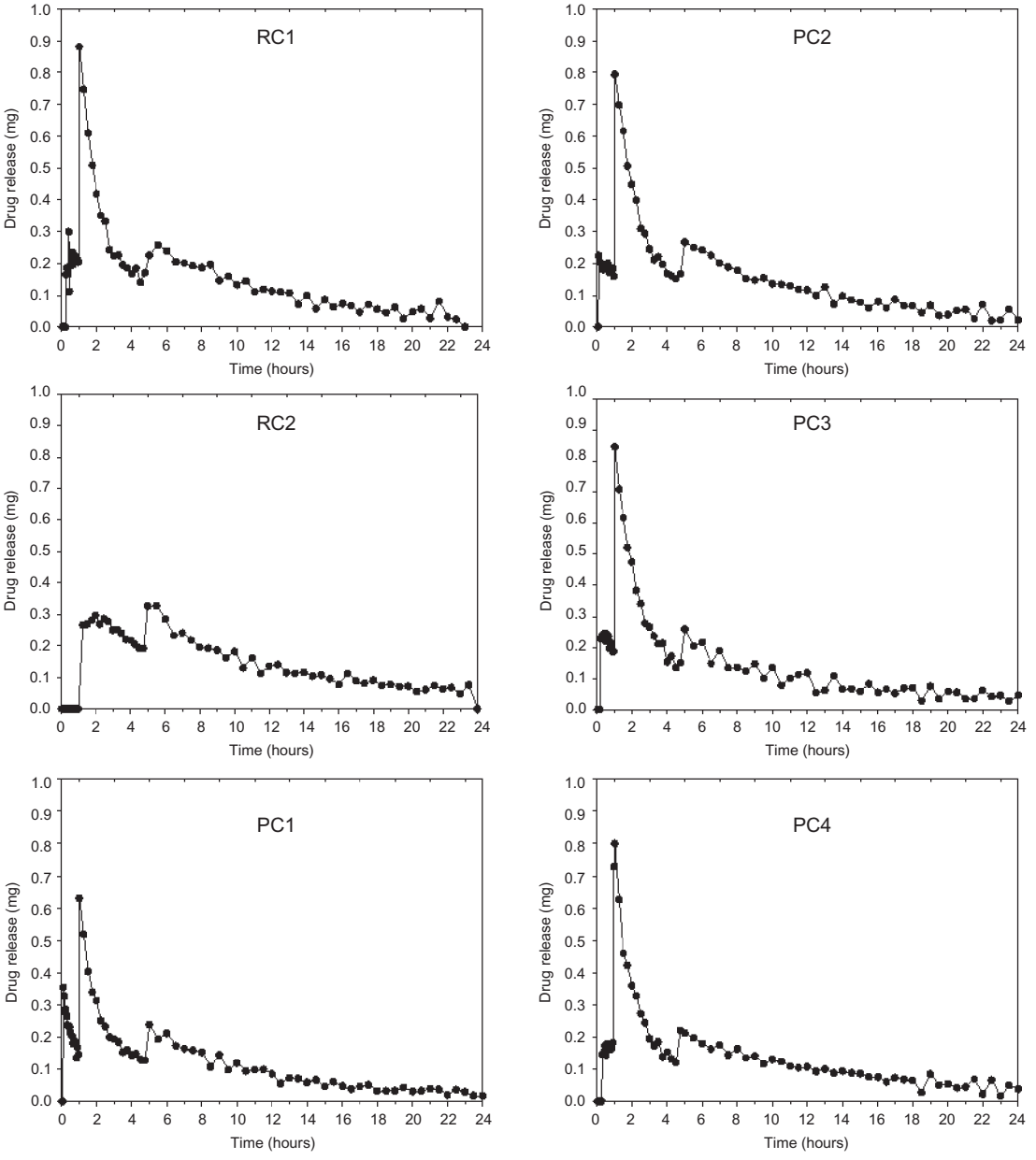

Figure 4. Amount of propranolol released at a given time throughout the dissolution process.

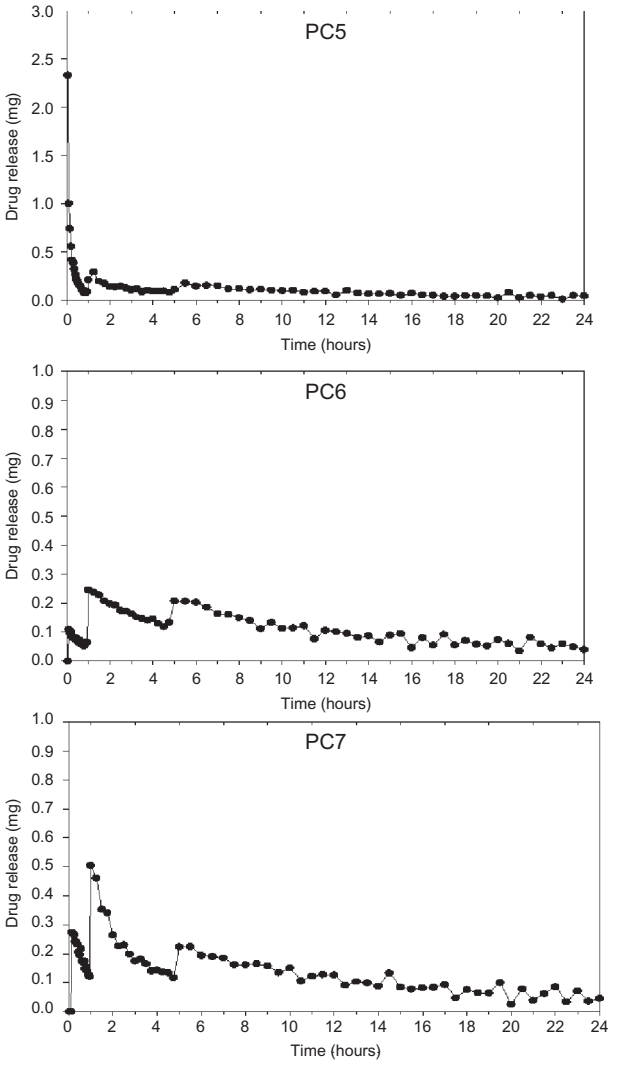

Figure 4. (*Continued*).

comparison among all nine formulations showed that eight of these formulations (RC1, RC2, PC1, PC2, PC3, PC4, PC6, and PC7) showed a peak drug release around 1 hour followed by a second peak around 5–6 hours. In contrast, the formulation PC5 showed maximum drug release (2.3 mg) in 3 minutes. This relatively faster release profile in this formulation was due to the quick swelling of the outer chitosan layer that resulted in easy permeation of drug through the swelled coating.

The coating process described in this article may be used to coat various starting particles, such as seeds, pellets, beads, or other multiparticulate systems, to achieve the desired release properties for a given therapeutically active substance. In this article, a layer of enteric polymer solution was deposited on the surface of the starting beads to delay penetration of water into the substrate matrix. A layer of ethylcellulose solution was applied to reduce the diffusion of the drug through the coating. A layer of chitosan, a water-swellable polymer, was applied to further control the drug diffusion. In some of the formulations (PC5 and PC6), the ethylcellulose or the chitosan layers also contain the drug, in others (RC1, RC2, PC1, PC2, PC3, PC4, PC7) the drug was applied as, either one or multiple, separate layer. However, these layers can be constructed based on the desired release profiles and there is no restriction on how these layers should be applied.

In summary, the setup described in this article can be useful for designing a wide range of coated controlled formulations using two or more compatible or incompatible polymers. Also, the setup allowed very convenient multiple layers coatings. Multiple layer coatings may allow more controlled drug release compared with a RC process.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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