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Note

Fluid bed coating: The utility of dual programmable pumps for controlled gradient drug deposition on pellets

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Abstract

The objective of this study was to demonstrate the potential use of dual programmable pumps in a fluid bed coating process to manufacture pellets coated with gradient layers of a drug. To achieve this goal, two matrix forming dispersions with an equivalent amount of solids, one containing verapamil HCl as a model drug, and the other without the drug, were forced in a gradient pattern into a fluid bed coater using two pumps joined at Y junction. The two pumps were operated at opposing flow rates via a computer guided program to maximize drug concentration in the inner layers around the core. The difference between gradient and non-gradient drug coating was demonstrated by dissolution studied. Depending on the drug to polymer ratio, verapamil HCl release from gradient layered pellets was delayed over an extended period of time and was significantly different from the non-gradient coated pellets.

Keywords: Fluid bed coating; Gradient system; Dual pumps; Diffusional matrix; Controlled release; Gradient layering

Recently there was a growing interest in solid dosage forms that could release a drug in a constant, zero-order, pattern in-order to improve its pharmacologic performance (Chidambaram et al., 1998; El-Malah et al., 2006). According to Fick's first law of diffusion; however, the release of a drug from a dosage form, whereby the drug is uniformly distributed within a matrix, is inherently non-linear due to the increase in diffusional-pathway with time (Chidambaram et al., 1998). Several innovative approaches were therefore proposed to overcome Fick's law, such as those reported by Lee (1984), Hildgen and McMullen (1995) and Chidambaram et al. (1998).

Among the solid dosage forms intended for oral drug delivery are the multi-particulate units, or pellets. Pellets coated with uniform, non-gradient, matrix were shown to release the drug in a curved square-root of time profile (Lee, 1986; Li and Tu, 1991). In order to release the drug from pellets in a linear, zero-order, pattern, the drug should be concentrated in deeper layers of the matrix around the core to compensate for the traveling distance of the drug during the dissolution process. Such a system where the drug is deposited in a gradient matrix around a core has been the subject of several studies (Chang, 1986; Chang, 1987; Li and Tu, 1991; Wan and Lai, 1994). Graphical depiction of pellets coated with gradient and non-gradient drug matrix is given in Fig. 1. Of practical significance; however, is a patent granted to Bogentoft and Appelgren (1981), which documented one of the earliest processes that could be used to manufacture pellets coated by the gradient drug deposition process. Briefly, as the drug solution is sprayed on the pellets a second dispersion containing a matrix forming material is gradually added to the drug solution, thereby changing the concentration of the drug in the mixture with time. Although this invention was not based on highly theoretical principles, it is a highly intuitive demonstration of the non-uniform drug deposition (coating) concept. Later, mathematical models and scalable coating processes were developed whereby the matrix forming dispersion is forced into the drug solution using electronic pumps (Li and Tu, 1991; Scott and Hollenbeck, 1991). In recent years; however, only few studies proposed alternative technologies or discussed the broader concept and application of the non-uniform drug coating process (Huang et al., 2002).

The study outlined in this paper is based on the seminal work by Scott and Hollenbeck (1991), who predicted that the release of drugs from pellets could be manipulated by drug-gradient layering around the core. Scott and Hollenbeck (1991) suggested

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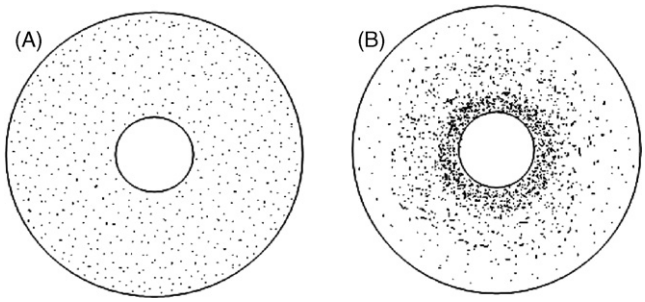

Fig. 1. (A) Uniform and (B) non-uniform drug distribution around the core in a matrix coated pellets.

the use of multiple automated and computer-guided pumps to achieve this goal. Such a system; however, was never materialized nor further investigated. One of the impediments was the unavailability of instrumentation and advanced software that could simultaneously control multiple peristaltic pumps, and thereby the gradient coating process.

In our lab we acquired a set of newly released computerized drives (MasterFlex® L/S® Model 7550-50, Cole-Parmer Instrument Co., Vernon Hills, IL), which are controlled by an advanced WinLIN® V2.0 software (Cole-Parmer Instrument Co., Vernon Hills, IL). This software has the ability to simultaneously and independently control the flow rate of multiple pumps as well as the run-time for each pump. The objective of the present study was therefore to investigate the potential use of these computerized drives to achieve non-uniformity in drug depositions within the matrix around the surface of inert cores. To achieve this goal, two automated peristaltic pumps controlled by the WinLIN® software, were employed in this study. Each pump (pump 1 and 2) was connected to a separate coating dispersion (dispersion 1 and 2) via silicone tubing. Tubes exiting the pumps were connected and the dispersions were mixed at a Y junction that fed the mixture into a fluid bed coater (MFL.01, Vector Corp. Marion, IA). A schematic representation of the pump assembly is given in Fig. 2. Both coating dispersions (1 and 2) had equivalent total solid content, excluding the amount of plasticizer. The first coating dispersion (dispersion 1) contained a matrix forming material and verapamil HCl, as the model drug. The second coating dispersion (dispersion 2) contained the matrix forming material without the drug. In both dispersions, Eudragit® RS 30D (RÖhm America Inc. Piscataway, NJ), a water insoluble polymer, was used as the matrix forming material. Talc powder was added as the anti tacking agent at 50% (w/w) loading based on dry polymer weight. Two experiments were performed at two different drug concentrations to study the impact of drug to polymer ratio on drug release. The exact composition of the coating dispersions used in each experiment is given in Table 1.

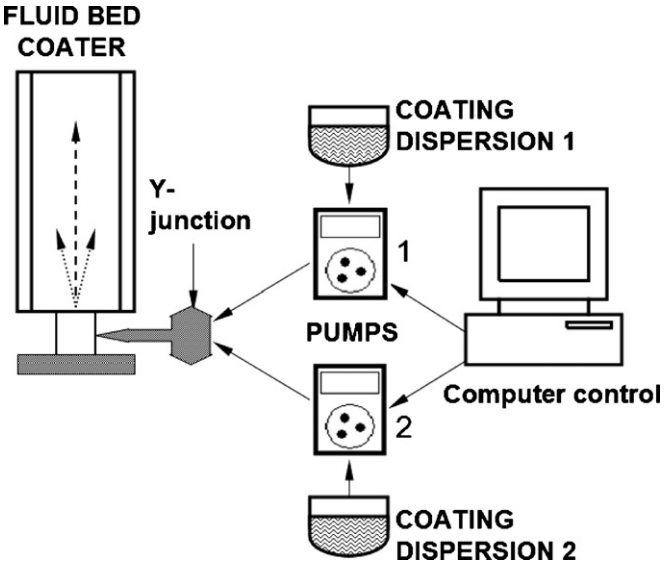

Fig. 2. A schematic diagram of the coating and gradient pump assembly.

Coating experiments were performed using 20 g of Nu-pariel sugar spheres (mesh-size 14/18, CHR Hansen, Vineland, NJ) as a charged load. The maximum flow rate that could be employed using the current coating assembly was found to be 0.75 mL/min. To create a drug gradient at this flow rate and maximize drug concentration in the inner layers around the core, the flow rate of pump 1 was pre-set to decrease from 0.64 to 0.11 mL/min while simultaneously the flow rate of pump 2 was set to increase from 0.11 to 0.64 mL/min over the entire duration of the experiment. The duration of each experiment was determined from the following equation, which was modified from the work by Scott and Hollenbeck (1991):

$$W = \delta K \frac{R_1 + R_2}{2} t$$

where W and δ are the total weight and density of each coating dispersion, respectively; K is the slope obtained from plotting the displayed versus the actual pump flow rates. This value was equal to 1 for the coating dispersions used in this study; R_1 and R_2 are the starting and ending flow rates for pumps 1 and 2, respectively, and t is the time in min. By substituting in the above equation the operating time was found to be 196.95 min.

For comparison purposes, pellets uniformly coated with verapamil HCl were manufactured using one pump that delivered a coating dispersion containing a matrix forming material, talc, and the drug at the concentrations given in Table 1. Processing parameters for matrix coating with gradient and non-gradient drug layering were similar and are given in Table 2. At the end of the coating process, pellets were cured in an oven (VWR, Model 1350 GM, Bristol, CT) at 40 °C for 24 h. Drug release from the pellets was tested in 900 mL of distilled water using a standard USP type II (paddle) dissolution apparatus (VK 7000, Varian Inc., Cary, NC) at a paddle speed of 50 rpm. Temperature of the dissolution bath was maintained at 37 ± 0.5 °C. Amount of verapamil HCl released from the pellets was measured by UV analysis at the wavelengths of maximum absorbance at 275 nm using filtered portions of the solution under test.

Dissolution profiles of coated pellets with 5 and 13.6% verapamil HCl gradient and non-gradient within the matrix are given in Fig. 3. Analysis of variance (ANOVA) followed by least square (LS) mean contrast analysis were performed on the dissolution data. No significant difference (P-value >0.05) in dissolution was observed between the pellets loaded with 13.6%

Table 1
The composition of the dispersions used for the uniform and non-uniform drug coating process

Ingredient	Non-uniform drug coating				Uniform drug coating	
	5% Drug loading dispersion		13.6% Drug loading dispersion		5% Drug loading	13.6% Drug loading
	1	2	1	2		
Verapamil HCL (g)	1.00	0.00	3.00	0.00	1.00	3.00
Eudragit® RS (g)[a]	6.00	6.67	5.34	7.34	12.67	12.68
Talc powder (g)	3.00	3.33	2.67	3.67	6.33	6.34
Triethyl citrate (g)[b]	1.20	1.33	1.07	1.47	2.53	2.53
Water ad. to (g)	76	76	76	76	152	152
Total solid	10.00	10.00	11.01	11.01	20.00	22.00
Drug/polymer ratio	1/12.7		3/12.7		1/12.7	3/12.7

[a] Calculated based on dry polymer weight.
[b] Excluded from the calculations.

Table 2
Coating process parameters

Parameter	Setting
Nozzle diameter	0.029 mm
Wurster insert	Bottom spray
Atomization air pressure	25 psi
Preheating temperature	38 °C
Preheating time	5 min
Batch size[a]	20 g
Spray rate	0.75 ml/min
Inlet temperature	38 °C
Bed temperature	29–30 °C

[a] Mesh size 14/18 (1400–1000 μm in diameter).

of the drug. A significant difference; however, was observed between the gradient and non-gradient coated pellets loaded with 5% verapamil HCl (P-value <0.05 and f_2, similarity factor = 29.3), which suggests that the drug to polymer ratio plays a critical role in drug release. Pellets coated with 5% verapamil HCL using the non-gradient process released 97% of the drug in 10 h, while those coated by the gradient process released 95% of the drug in 18 h. This effect is due to the fact that drug release from matrix pellets is controlled by its diffusion through the polymeric matrix and/or the pores formed by the leached drug. At higher drug loading more pores are formed through which the drug particles could diffuse into the dissolution medium. Therefore, at high drug to polymer ratio the drug will diffuse rapidly from the matrix irrespective of the coating process. The effect of non-uniformity in drug coating; however, was evident at lower drug to polymer ratio, in which the drug diffuses primarily through the polymeric matrix (Li and Tu, 1991; Scott and Hollenbeck, 1991; Wan and Lai, 1994; Huang et al., 2002). These results demonstrate the utility of dual, and potentially multiple, automated pumps in coating pellets with gradient drug layers to attain variable drug release profiles. The apparent effect of drug to polymer ratio, which was evaluated in this study, is only one of many factors that might have an effect on drug release and deposition during the coating process. Another parameter that is expected to have a profound effect is the flow rate of the individual pumps and the ratio of flow rate between the pumps. Unfortunately due to the limited capacity of the MFL.01 fluid bed coater used in this study, it was impractical to evaluate alternative flow rates. This; however, should not be a hindrance when larger coating instruments are used.

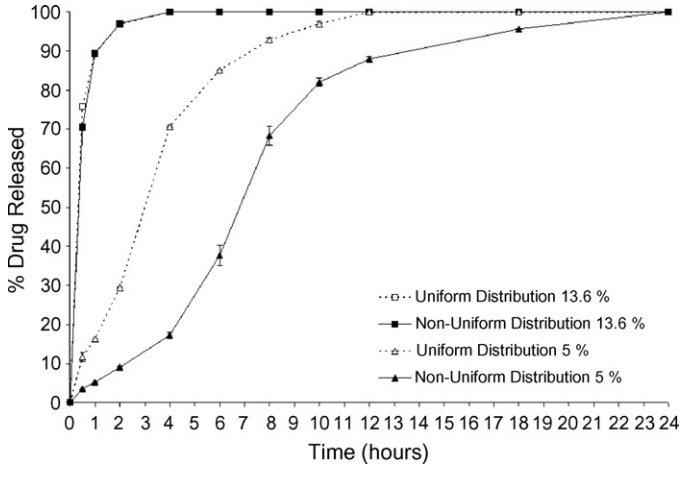

Fig. 3. Dissolution profile of uniform and non-uniform pellets loaded with 5 and 13.6% verapamil HCl.

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