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# Propranolol Hydrochloride Sustained-Release Pellets Prepared with Laboratory Scale Top Spray Fluid Bed System

# Laboratuvar Ölçekli Üstten Püskürtmeli (Top Spray) Akışkan Yatak Sistemi ile Hazırlanan Propranolol Hidroklorür Sürekli-Salım Pelletleri

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## Abstract

The aim of the present study was to prepare propranolol hydrochloride sustained release pellets using a laboratory scale top spray fluid bed system and to evaluate the suitability of the system. Drug-binding agent formulation was sprayed onto nonpareils, then drug loaded pellets obtained were coated with aqueous ethylcellulose dispersion. Coated pellets were evaluated for their particle size and size distribution, bulk and tapped densities, and flowability. Hence the process of laboratory scale top spray fluid bed system was evaluated in respect of suitability to prepare sustained release pellets.

**Key words:** sustained release pellet, coating, top spray fluid bed, similarity factor.

## Introduction

Pellets are spheroidal particles that contain the drug either layered on the surface or distributed throughout the mass of the pellet. This term can be expanded to include all forms of multiparticulates including drug-containing granules, drug/ion-exchange resin complexes, drug crystals and minitablets (Porter and Ghebre-Sellassie, 1994). During the last 25 years, the interest on pellet production has increased considerably. High therapeutic advantages of pellets such as increased bioavailability, higher patient compatibility, less sensitive to dose damping, etc. and the innovations in the production and modification technologies of these systems have also affected the increase of this interest. Especially the use of the fluid bed technology, capable of controlling the process parameters and increasing the reproducibility, have become widespread in the pharmaceutical industry. Despite its advantages, high cost still stands an important disadvantage of this technology. Among these the most economical one with the simplest set-up process is the top spray technique where granulation, pelletization and coating performed, the control of the process parameters is easier and the mechanical stress on the product is low (Rubino, 1999).

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Coating of pellets with a polymer is often used as a means of controlling the drug release rate. The coating should be reproducible, uniform, and free from physical imperfections. Consequently, the evaluations of the coating are critical (Mehta and Jones, 1985).

In this study, sustained-release propranolol hydrochloride pellets were prepared with the use of a top spray fluid bed system, of which the design and flowability tests were performed by Arici and Güneri (2003). It was built with a processing capacity of 25-50 g. The pellets thus obtained were characterized for their size, density, flowability, etc. In this way was examined the performance of laboratory scale top spray fluid bed system as well.

## Materials and Methods

*Materials:* Propranolol hydrochloride (Amphar b.v., Netherlands), nonpareils: 20/25 mesh (710-850 μm), (Hanns W. Werner GmbH, Germany), hydroxypropyl methylcellulose (HPMC-E5) and Surelease® (aqueous ethylcellulose dispersion) (Colorcon Inc., England). All other chemicals were of analytical grade.

*Preparation of drug loaded pellets:* Drug loaded pellets containing propranolol hydrochloride were prepared by spraying an aqueous solution of drug-binding agent onto batches of 35 g of nonpareils using laboratory scale top spray fluid bed system. Process conditions used were: inlet air temperature= 63-67°C, atomizing air pressure= 16 psi, spray rate= 0.57 ml/min and fluidizing air rate= 3.45-3.68 m/s. Formulations are shown in Table 1.

*Coating of drug loaded pellets:* Drug loaded pellets were coated by spraying Surelease® (diluted, 15%) with the aid of top spray fluid bed system. Process conditions used were: inlet air temperature= 58-62°C, atomizing air pressure= 16 psi, spray rate= 0.86 ml/min and fluidizing air rate= 3.45-3.68 m/s. Formulations are shown in Table 1.

Table 1. Formulations for drug loaded and coated pellets.

| | Drug loading | | Coating |
|---|---|---|---|
| Formulation | Drug (g) | Binding agent[a] (g) (HPMC-E5) | Coating material[b, c] (g) |
| F1 | 4 | 4 | 2.25 |
| F2 | 4 | 4 | 4.50 |
| F3 | 4 | 4 | 6.25 |
| F4 | 4 | 2 | 6.25 |
| F5 | 4 | 8 | 6.25 |

[a] Dry substance from 2% aqueous solution.
[b] Dry substance from 15% aqueous dispersion.
[c] Corresponds to different coating levels (4, 8, and 12% w/w).

The drug content of pellets was determined spectrophotometrically (Shimadzu UV-1208 spectrophotometer) at 289 nm.

In vitro drug release studies: Drug release studies were carried out using the USP XXII rotating basket method (900 ml deionized water, 37°C and 100 rpm) (1990). An appropriate amount of coated pellets (equivalent to 60 mg of propranolol hydrochloride) was used. Collected samples at suitable time intervals were filtered and assayed for propranolol hydrochloride content

spectrophotometrically at 289 nm.

Processing efficiency: Processing efficiencies examined by determining the drug content uniformity and loading and coating efficiencies. Loading and coating efficiencies calculated from the percent weight gain after the application of the drug-binding agent formulations and coating solutions, respectively. In addition, to check the reproducibility of the manufacturing procedure, three batches of F5 formulation were prepared. Drug release studies were conducted in 900 ml of deionised water. Release profiles of three repeat batches of F5 formulation were compared using model independent pair-wise approach, where "difference factor" $f1$ and "similarity factor" $f2$ were calculated. The two release profiles were considered to be similar; if $f1$ value is below 15 and $f2$ value is over 50 (Shah *et al.*, 1998).

Coating homogeneity: The coated pellets were dispersed in O.C.T. compound and frozen at -25°C, the cross sections of 8 µm were obtained by using Microtome (Cryo-Cut, American Optical Corporation, USA). These cross sections were investigated under the polarization microscope to check the success of coating process (Reichert Zetopan, Vienna, Austria).

Particle size and size distributions: Particle size and size distributions of coated pellets were measured by laser diffractometry (Malvern Mastersizer 2000) using a dry powder feeder.

Bulk and tapped density: Bulk and tapped densities of coated pellets were run with 10 g sample of each formulation.

Hausner ratio and flowability: Hausner ratio (HR) is the ratio between tapped ($\rho_t$) and bulk densities ($\rho_b$) (Hausner, 1967).

$$HR = \frac{\rho_t}{\rho_b} \qquad (1)$$

The closer the ratio to 1 results better flow characteristics. Particles with poor flow generally have a Hausner ratio greater than 1.25. The flow rate and angle of repose were also investigated on the coated pellets.

## Results and Discussion

The top spray fluid bed system is simply constructed where controlling the process parameters (e.g. the location of the nozzle, efficient heat transfer) is easy. The mechanical stress ratio on the product is low (Rubino, 1999). But countercurrent stream of particles and spray solution affects the loading efficiency because of spray drying. In our system, the drug loading yield is 60% while coating is yielded 70%.

Optimization of drug release from the coated pellets depends on the uniformity of the drug loading and coating. In general the success of coating process is based on the uniformity and reproducibility of the process from batch to batch. To reduce the variations, similar size pellets are taken for coating.

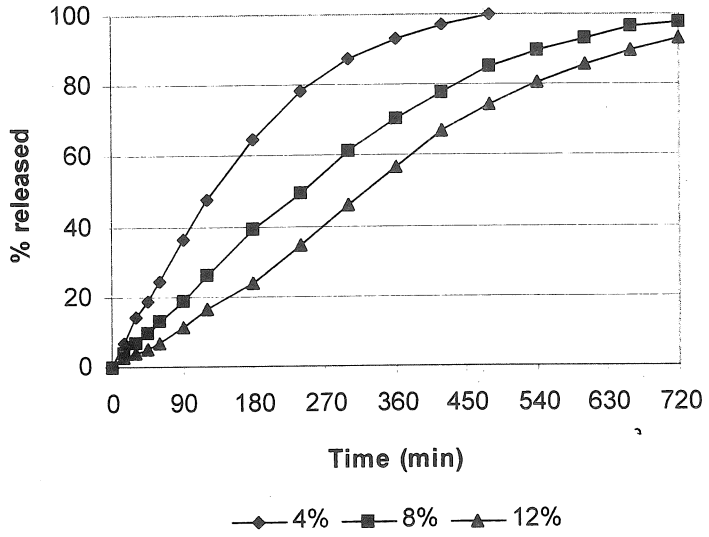


Fig. 1. Drug release profiles of pellet formulations prepared using different coating levels (F1-F3 formulations)

Fig. 1 shows the amount of drug released from coated pellets. As expected, the release rate decreased with the increase in coating thickness. Drug released from coated pellets decreased with higher ethylcellulose content resulting in reduction of the permeability.

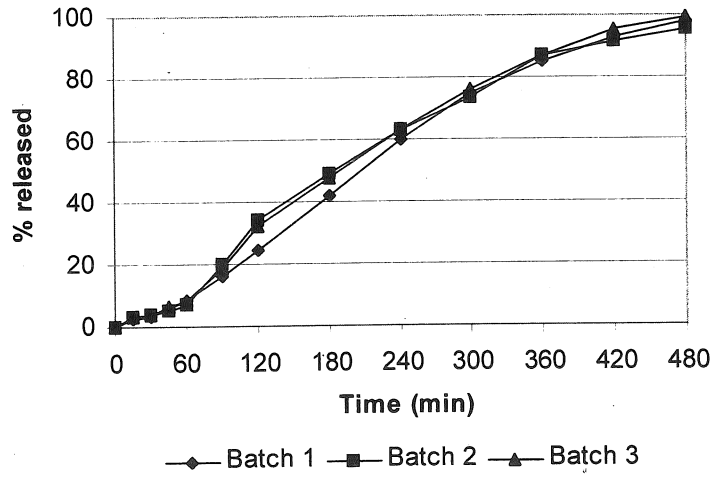


Fig. 2. Reproducibility of the manufacturing procedure – drug release from three repeat batches of F5 formulation (n=3).

It is clearly evident from Fig. 2 that the release profile is similar in all batches indicating reproducibility of the manufacturing procedure. The difference factor $f1$ and similarity factor $f2$ were found to be 6.52 and 71.76 (between batch 1 and 2), 5.30 and 76.36 (between batch 1 and 3), and 3.72 and 83.52 (between batch 2 and 3), respectively.

The most commonly used technique in the determination of the film thickness and uniformity is the scanning electron microscopy (SEM) (Mehta and Jones, 1985; Mehta, 1986). Another technique used is the image analysis with fluorescence microscopy (Andersson *et al.*, 2000). The analysis of the film coating uniformity with the use of polarization microscopy can be described as a practical approach. By this technique, is possible performing series of sample analysis in shorter period of time while the images of very thin slides (2-20 μm) are investigated and photographed as well. The black region in the interior section in Fig 3a and 3b is nonpareil section. The bright white section is the starch in the composition of the nonpareil. Above this section is the drug-binding agent layer followed by the coating layer. The drug-binding agent and the coating layers are observed having very unique uniform distribution.

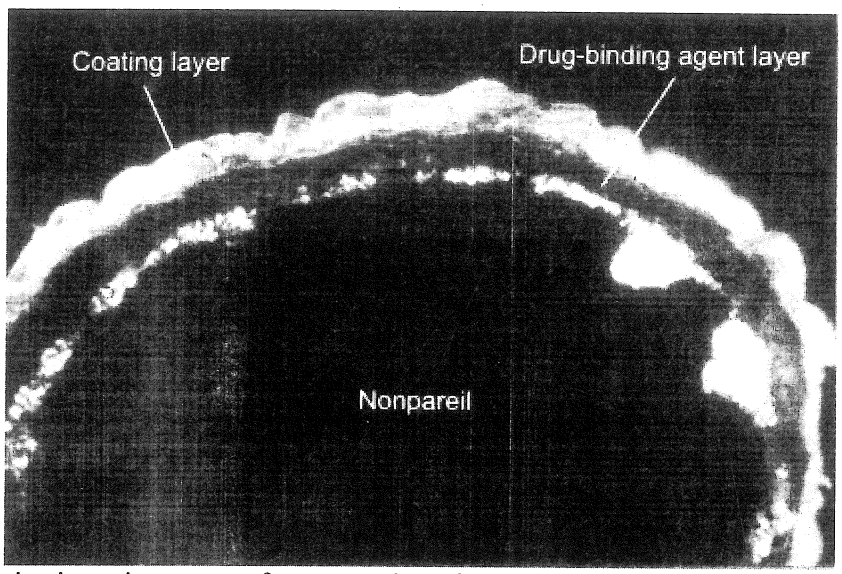


Fig. 3a. Polarization microscope of cross-section of propranolol hydrochloride sustained release pellet (10x6.3 magnification).

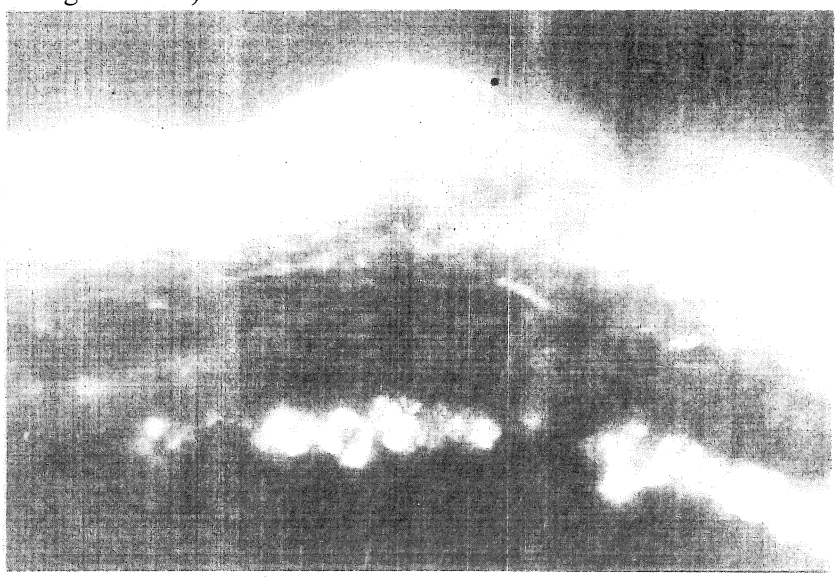

Fig. 3b. Polarization microscope of cross-section of propranolol hydrochloride sustained release pellet (40x6.3 magnification).

In addition, smooth surface of core material (nonpareil) enables uniform coating thickness for each pellet and also reduces intra-batch variability.

All pellets showed good spherical geometry. As shown in Table 2, average diameter of 928-991 μm was obtained depending on amount of binding agent and coating level. Especially, amount of binding agent affected the mean particle size. As the amount of binding agent increased, dramatic increases in particle sizes of F3-F5 formulations were observed (Table 2). In addition, very narrow particle size distributions were obtained in all formulations as seen in Fig. 4.

Table 2. Physical properties of coated pellets.

| Formulation | Mean diameter (μm) | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Hausner ratio | Angle of repose (θ) | Flow rate (g/s) |
|---|---|---|---|---|---|---|
| F1 | 928 | 0.769 | 0.800 | 1.040 | 22.45 | 4.285 |
| F2 | 958 | 0.800 | 0.816 | 1.020 | 23.27 | 2.727 |
| F3 | 969 | 0.800 | 0.833 | 1.041 | 23.27 | 3.333 |
| F4 | 960 | 0.800 | 0.833 | 1.041 | 22.45 | 3.333 |
| F5 | 991 | 0.784 | 0.833 | 1.062 | 24.08 | 3.333 |

As shown in Table 2, all angle of repose values were below 30° and the angle of repose was not significantly affected by the particle size of the pellets. According to flow rate, angle of repose and Hausner ratio values, all of the pellet formulations have good free flowing nature.

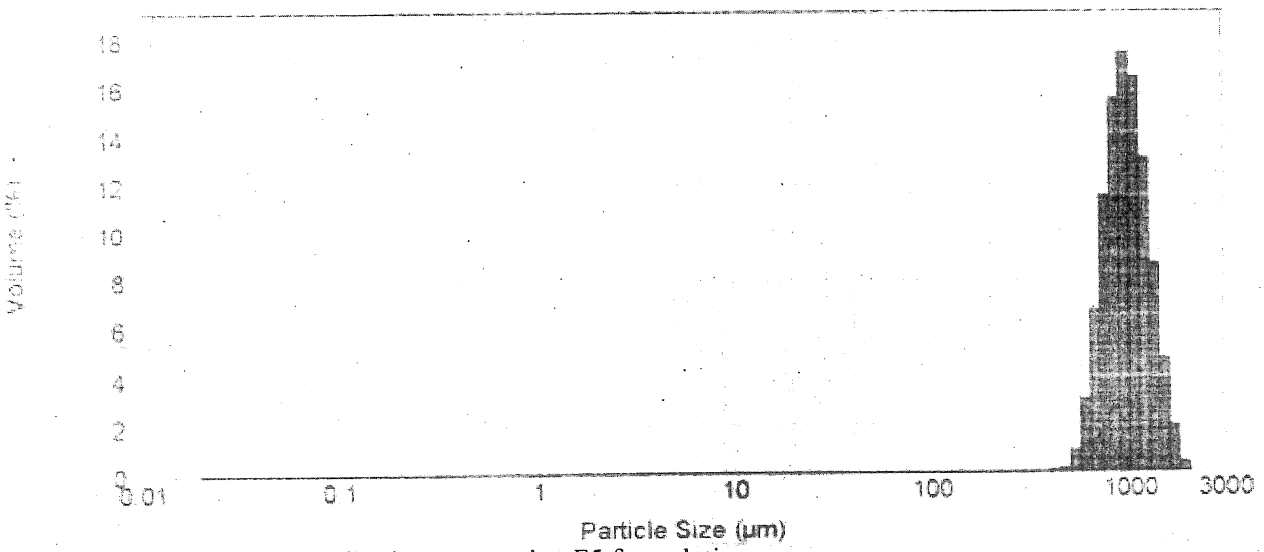


Fig. 4. Particle size distribution concerning F5 formulation.

## Conclusion

In conclusion, drug-loading of nonpareils and followed by coating processes can be made with laboratory scale top spray fluid bed system. Sustained release pellets thus obtained show good flowability properties. With laboratory scale top spray fluid bed system is possible to shorten the process and additonally, the technique of polarization microscope is very suitable and a simple method for analysis of coating layer homogeneity.

## Özet

Mevcut çalışmanın amacı, laboratuvar ölçekli üstten püskürtmeli (top spray) akışkan yatak sistemi kullanılarak propranolol hidroklorürün sürekli salım pelletlerini hazırlamak ve prosesi değerlendirmektir. Nötral pelletler (nonpareils) üzerine ilaç-bağlayıcı ajan formülasyonu püskürtülmüş ve daha sonra elde edilen ilaç yüklü pelletler etilselülozun sulu dispersiyonu ile kaplanmıştır. Kaplı pelletler, partikül boyutu ve dağılımı, serbest ve sıkıştırılmış yoğunluk ve akışkanlık özellikleri için incelenmiştir. Böylece laboratuvar ölçekli üstten püskürtmeli (top spray) akışkan yatak sistemi prosesi sürekli salım pelletlerin hazırlanmasına uygunluğu açısından değerlendirilmiştir.

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