Acta Pharmaceutica Turcica XXXVIII (4) 117-121 (1996)

COATING OF MICROPELLETS CONTAINING SODIUM SALICYLATE USING FLUID-BED METHOD

FLUİD-BED YÖNTEMİ KULLANILARAK SODYUM SALİSİLAT İÇEREN MİKROPELLETLERİN KAPLANMASI

KANDEMİR CANEFE, CANAN OĞAN

University of Ankara, Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey

The aim of this study was to develop suitable micropellet formulations which contain sodium salicylate as a model drug by using Fluid-bed method. With in-process and quality controls that were conducted during these procedures, the investigation of the productivity and efficiency of the products was also aimed.

Micropellet formulations which contain sodium salicylate could have irritating effect to the stomach, so micropellets were enteric coated in order to have a smooth surface and also to release drug in the intestinal tract.

The release of drug from micropellets was examined by dissolution rate studies and kinetic equations were analysed.

Bu çalışmada Fluid-bed yöntemi kullanılarak model etken madde olarak seçilen sodyum salisilat ile uygun mikropellet formulasyonlarının saptanmasına çalışılmıştır. Bu işlemler sırasında yapılan in-process ve kalite kontrolleri ile ürünlerin verimliliği ve amaca uygunluğunun incelenmesi hedeflenmiştir.

Mikropelletler, midede tahriş edici olan sodyum salisilatın barsakta açılmasını ve daha düzgün bir yüzeyin oluşmasını sağlanmak amacı ile enterik kaplanmıştır.

Mikropelletlerden etken madde çıkışı çözünme hızı deneyleri ile incelenmiş ve sonuçlar kinetik olarak değerlendirilmiştir.

Keywords : *Micropellet; Fluid-bed; Pelletization; Coating*

Anahtar kelimeler :*Mikropellet; Fluid-bed; Pelletizasyon; Kaplama*

Introduction

Micropellets have been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions (10). Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-eflowing, narrow particle size distribution, spherical or semi-spherical units, referred to as micropellets. Micropellets range in size, typically, between 0.5-1.5 mm, though other sizes could be prepared, depending on the processing technologies employed. Micropellet mixtures are easily made homogeneous and packed uniformly, thereby alleviating handling and packaging problems.

Pelletization enables incorporation of incompatible active substances into the same product, or even into the same micropellet, by situating the active substances in different layers and/or by separating the layers from each other with coating. Furthermore, whole micropellets are easy to coat with polymers, which offers a practicable method to control the site and rate of drug dissolution in the gastrointestinal tract (9,11). Specially significant, however, is the role which micropelleted products play when ingested into the body, when they are formulated as multiple unit formulations in controlled-release preparations, micropellets maximize drug absorption (6), reduce variations in gastric emptying rate and over-all transit times(3), eliminate local irritance or anesthetizing effect of a drug and avoid dosedumping. Consequently, pelletization, the manufacturing of micropellets, has been the subject of intensive research both in terms of innovative formulation and process equipment(10).

Materials

Sodium salicylate 149 µm (Merck), which is a useful analgesic and has anti-inflammatory and antipyretic properties, was selected as a model drug. The additives used were: lactose (Sigma), Aerosil 200 (Degussa), Avicel (microcrystalline cellulose pH 101, FMC Co.

Ltd). Polyvinylpyrrolidone (PVP-25, Basf), hydroxypropyl methylcellulose (HPMC, Sigma), gelatin (DGF), Eudragit NE 30 (polymethacrylate, Röhm Pharma) were used as binder solutions. Polymers used for coating were acrilic resins (Eudragit L 100 and Eudragit S 100, Röhm Pharma). Triacetine (Röhm Pharma) was used as plasticizer. All solvents were of analytical grade.

Methods

Preparation of micropellets

In our study, fluid-bed equipment (1) which was modified to work with small amounts, has been used. The device had a capacity to hold nearly 100 g of product. As shown in Table 1 micropellet formulations have been prepared using various excipients and binders. The purpose is to select the formulation providing the best sphericity.

Table 1. The formulations of micropellets prepared with sodium salicylate (The amounts are given as per cent)

Formulation	Na salicylate	Lactose	Aerosil 200	Avicel pH 101	Binder solution
F1	80	20	1	-	3%PVP
F2	80	20	1	-	5%PVP
F3	80	20	1	-	10%PVP
F4	80	10	1	10	10%PVP
F5	80	10	1	10	3%HPMC
F6	80	10	1	10	5% Eudragit NE 30
F7	80	10	1	10	5% Gelatin

The particle size distribution and mean particle diameter

The size distribution of the micropellets was evaluated by a sieve analysis technique using a series of 1500-125 μm sieves (Retsch Analysensieb ASTM). The sieves were shaken with an automatic sieve shaker for 10 min.

The mean micropellet diameter d_m (μm) was calculated by the following method of Meshali et al. (8).

$$d_m = \frac{1}{\sum x_i/d_i}$$

Where x_i = weight of a given fraction (g)

d_i = mean geometrical diameter of granules of a given fraction which is equal to $\sqrt{d_1 x d_2}$, where d_1 and d_2 are the opening sizes of the two sieves retaining in between a given size fraction.

Bulk density of micropellets

Bulk densities were determined by averaging the weight of three separate samples from each batch required to fill a 100-ml graduated cylinder without being tapped.

Friability of micropellets

10 grams of micropellets were placed in a friabilitor (2) at 25 rpm for 4 min. The weight of the micropellets then was compared to the initial weight. Friability, expressed as a percentage, was determined as the fraction that passed through the sieve.

Repose angle of micropellets

The angle of repose of the micropellets was determined by the fixed height and free standing cone method. The height of the funnel was maintained at 10 cm and the average internal diameter of the funnel stem was 0.9 cm. 20 grams of the micropellets were poured gently through the vertical funnel until the apex of the cone pile just touched the tip of the funnel.

The repose angle (Ø) was determined using the following equation : tan Ø = pile height/pile radius.

Coating of micropellets

The coating process was performed in a fluid-bed column (7). The coating dispersion was supplied and atomized from the top of the column at a rate 8 ml/min. The inlet air temperature was set at 50°C. The coated micropellets were dried in the column for 10 min after completion of the coating process. The percentage of the coating applied to the 354-707 μm micropellets, based on the weight increase of the uncoated micropellets, was calculated in terms of the total weight of the coated micropellets. Micropellets obtained from formulation F4 with fluid-bed method have been coated with acrylic resin in ratios of 20% and 30%. In order to achieve the release of sodium salicylate from the coated micropellets in the intestinal tract, we used Eudragit L 100 and Eudragit S 100 in etanol: isopropanol (60:40) mixtures as coating solutions and also triacetine was used as the plasticizer.

Dissolution testing

In vitro drug release from coated micropellets was measured using USP XXI dissolution apparatus 1 at a basket rotational speed of 50 rpm. Hydrochloric acid solution at pH 1.2 and phosphate buffer at pH 7.2 were used as the dissolution media. The drug released in the medium was determined by means of UV spectrometry.

Results and Discussion

In this study, conventional fluid-bed method has been chosen to develop and then to coat micropellet formulation.

In micropellet production, the design of the formulation is as importanat as the method

chosen. In order to provide spheronization which is an important parameter in micropellet production and to obtain efficient micropellets, we tried to determine a main formulation(10). As shown in Table 1, micropellet formulations have been prepared using various excipients and binders. The physical properties of fluid-bed micropellets are strongly influenced by the binder and the binder concentration. An increase in the binder concentration increases the binder adhesiveness.

It is known that when the viscosity of the binder solutions is increased, solvents evaporate more slowly and thus the particles obtained are tight with suitable friability. The friability of the micropellets is decreased with increasing binder solution concentration(4). As shown in Table 2 less friable micropellets have been obtained in formulation F3 when compared to formulations F1 and F2. Among the formulations, where various binder solutions were used and which contain Avicel pH 101, formulation F6 where Eudragit NE 30 was used as a binder has been more friable. Although formulation F7 showed less friability, it has not been found successful because of having rough surface and small particle sizes.

As a result of bulk density controls, no big differences have been obtained among micropellets (Table 2). However the bulk density is highly dependent on the surface characteristics of the micropellets.

In flow property controls performed with the formulations available in Table 2, the best flowability has been shown by F3 and F4 formulations from which smooth surfaced and

Table 2. The pharmaceutical controls of micropellets (n=3)

Controls	F1	F2	F3	F4	F5	F6	F7
Friability (%)	2.93±0.17	1.67±0.89	0.95±0.13	0.98±0.26	1.01±0.84	1.52±0.15	0.86±0.18
Bulk density (g/ml)	0.44±0.03	0.48±0.03	0.49±0.08	0.51±0.06	0.36±0.09	0.41±0.05	0.34±0.11
Repose angle (Ø)	32.86±0.10	32.44±0.21	30.12±0.19	29.87±0.33	34.53±0.37	33.74±0.46	34.90±0.57
Average micropellet size (µm)	485	494	524	514	524	522	465

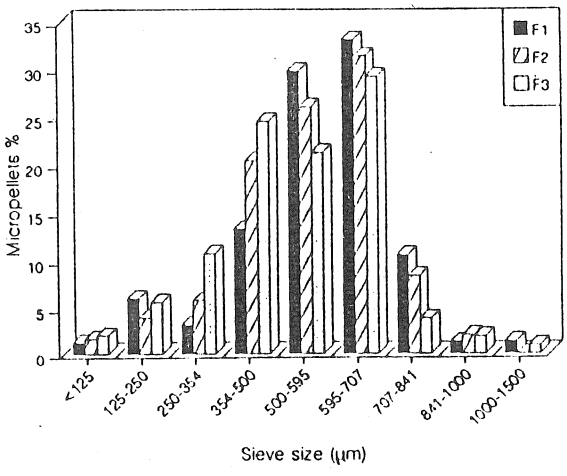

Fig. 1. The particle size distribution prepared with F1, F2 and F3 formulations of micropellets

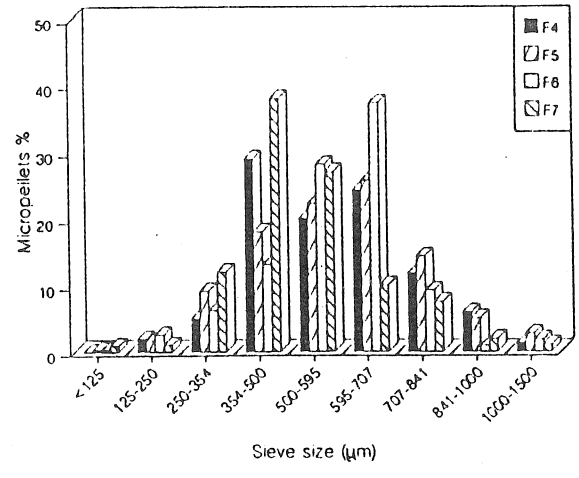

Fig. 2. The particle size distribution prepared with F4, F5, F6 and F7 formulations of micropellets

more spherical micropellets were obtained.

As a result of the physical controls, the most suitable properties have been shown by formulation F4 which contains Avicel pH 101 to increase sphericity and where 10% water solution of PVP was used as the binder solution.

Micropellets are dosage forms with certain sizes. In Table 2, the particle size distributions of micropellets obtained from the formulations are established. The results are show in Figs 1and 2. At the formulations F1, F2 and F3 which were prepared with different ratios of PVP, larger particles have been obtained as a result of the increase in the concentration of the binder. Then Avicel pH 101 was added to the formulations in order to increase spheronization and also various binder solutions (gelatin 5%, HPMC 3%, Eudragit NE 30 5%, PVP 10%) with different ratios were studied for acceptable particle size distribution of micropellets. The optimum particle size distribution has been obtained in formulation F4.

Coating of micropellets

When the surface properties of coated micropellets were investigated under microscope, it has been established that their surfaces were more proper and smoother. Flow properties of the micropellets, which have been coated and thus had smoother surfaces, have also increased.

In particle size analyses of coated micropellets it has been observed that the particle size

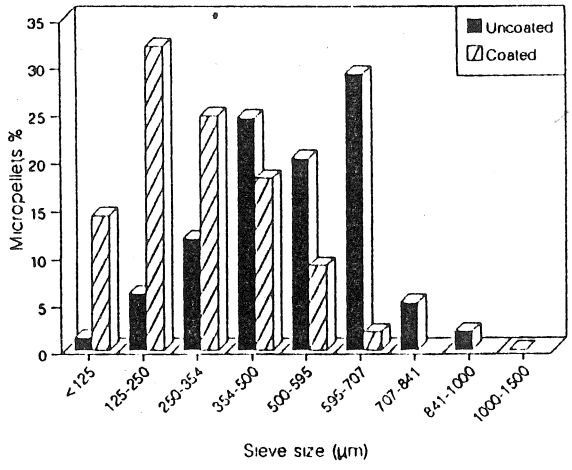

Fig.3. The particle size distribution of coated micropellets and uncoated micropellets

increased in ratio to coating (Fig. 3).

After the coating procedures carried out in ratios of 20% and 30%, it was determined with dissolution rate studies that the release rate of drug from the coated micropellets was controlled by the thickness of the film formed on the surface of micropellets(5).

When the results of dissolution rate studies of micropellets were evaluated, it was observed that in hydrochloric acid solution at pH 1.2 a definite difference between micropellets coated in ratios 20% and 30% appears with regard to dissolution periods depending on the amount of coating (Fig. 4).

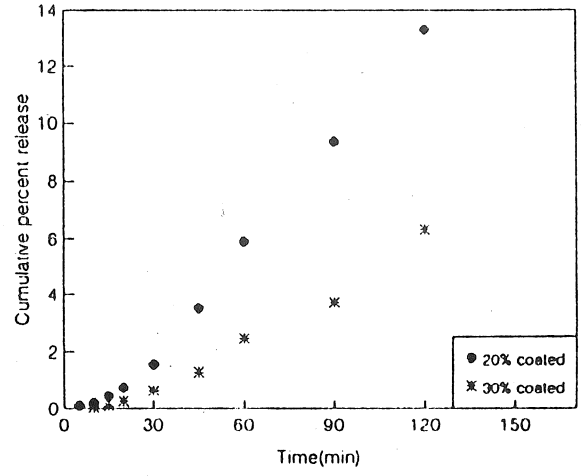

Fig. 4. The dissolution rate profiles obtained from the coated micropellets prepared from F4 formulation in pH 1.2 buffer solution

The difference of thickness of the film has not occured during dissolution rate studies as using the pH-resistant material for a film coating process. The dissolution rate characteristic of coated micropellets fitted the zero order kinetics as in the case of reservuar systems.

As a result of dissolution rate studies performed in phosphate buffer at pH 7.2 the drug was released completely from the micropellets coated in the ratio of 20% after 120 minutes while for the ones coated in the ratio 30% this period was 210 minutes. Thus the coating per cent affected the relase period. Since the coating material dissolution in phosphate buffer at pH 7.2 was retarded the release of drug was prolonged in proportion to the thickness of the coating (Fig. 5)

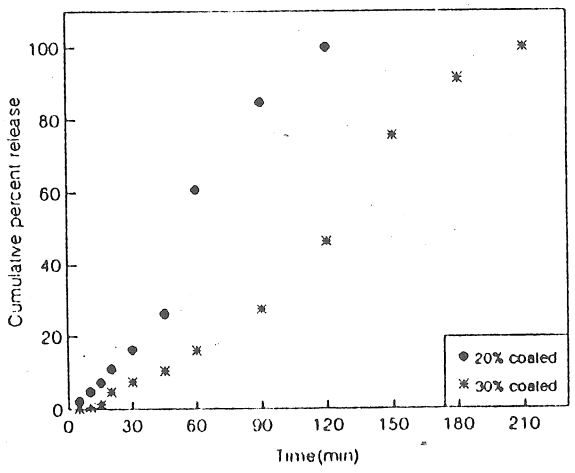

Fig. 5. The dissolution rate profiles obtained from the coated micropellets prepared from F4 formulation in pH 7.2 phosphate buffer solution

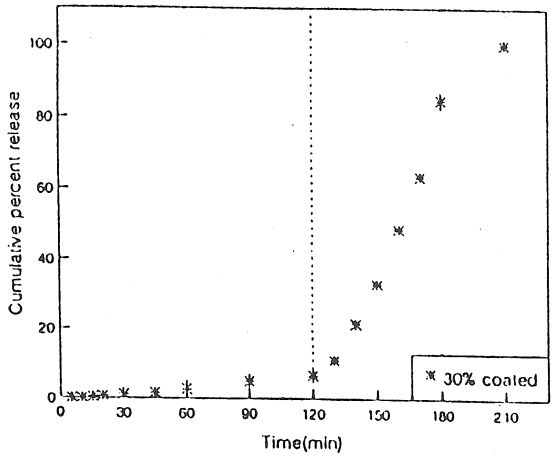

Fig. 6. The consecutive dissolution rate profiles of micropellets coated at 30% ratio first in pH 1.2 and just after in pH 7.2 buffer solution

The release of drug from coated micropellets occured on two levels (Fig. 6). At the first level, the drug was released slowly by diffusion in hydrochloric acid solution at pH 1.2 while the coating layer maintained its integrity. At the second level, when the coating began to disintegrate in phosphate buffer at pH 7.2, the delaying effect of polymer on drug release disappeared and the drug was released rapidly. An adaptation to Q- $\sqrt{t}$ kinetic was observed. When the release profile observed after 120 minutes was compared to that of pure drug, a short delay existed. In our opinion, the use of PVP which has a strong binding property in the ratio of 10% to secure pelletization in the structure of formulation accounts for this (12).

References

1. Aulton, E.M.: Int.J.Pharm. Techn. Prod. Mfr. 2, 24 (1981)
2. Canefe, K., Özyurt, C.: Pharmazie 46, 11 (1991)
3. Das, K.S., Gupta, K.B.: Drug. Dev. Ind. Pharm. 14, 1673 (1988)
4. Davies, L.W., Gloor, T.W.: J. Pharm. Sci. 61, 618 (1972)
5. Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R., Wilson, C.G.: Int. J. Pharm. 21, 167 (1984)
6. Hodges, G., Delargy, A., Aulton, M.: Proceedings of the 9th Pharm. Tech. Conf. Velthoven, Holland, April 4th-6th pp 180-193, 1991
7. Mehta, A.M., Valazza, M.J., Abele, S.E.: Pharm. Tech. 10, 46 (1986)
8. Meshali, M., El-Banna, H.M., El-Sabbagh, H.: Pharmazie 38, 323 (1983)
9. Niskanen, M., Niskanen, T., Yliruusi, K.J., Kristofferson, E.: Pharm. Tech. Int. 10, 22 (1990)
10. Sellassie - Ghebre, I. (Ed.) : Pharmaceutical Pelletization Technology, Marcel Dekker Inc., New York 1989
11. Sellassie-Ghebre, I., Gordon, H.R., Fawzi, B.M., Nesbitt, U.R.: Drug. Dev. Ind. Pharm. 11, 1523 (1985)
12. Scott, C.D., Hollenbeck, G.R.: Pharm. Res. 8, 156 (1991)

Accepted: 09.04.1996