DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(8), 1137-1159 (1989)

PREPARATION OF A CONTROLLED RELEASE DRUG DELIVERY SYSTEM OF INDOMETHACIN: EFFECT OF PROCESS EQUIPMENT, PARTICLE SIZE OF INDOMETHACIN, AND SIZE OF THE NONPAREIL SEEDS

Shun Por Li[1,2], Kenneth M. Feld[1] and Chana R. Kowarski[2]

[1]Pharmaceutical Research and Development Division, Rorer Central Research, Rorer Pharmaceutical Corp., Fort Washington, PA 19034
[2]Department of Pharmacy, School of Pharmacy, Temple University Philadelphia, PA 19140

ABSTRACT

Indomethacin pellets (IS) were prepared by spraying a slurry of indomethacin, Eudragit® S-100, dibutyl sebacate and alcohol onto an appropriate mesh fraction of nonpareil seeds using appropriate processing equipment. Factors affecting this layering process were studied and identified. The average particle diameter and the overall particle size distribution of the indomethacin powder were found to be critical factors influencing the physical properties of the IS pellets. Micronized indomethacin powder, having an average particle diameter of four microns and a particle size distribution ranging from one to thirteen microns, was found to be the optimum for this layering process. Altering the mesh fraction of the starting nonpareil seeds for the layering process was found to greatly affect the release characteristics of the drug from the beadlets. The Wurster column process was found to be better than a fluid-bed granulator process for the manufacture of IS beadlets.

INTRODUCTION

In a previous study, indomethacin sustained release pellets were successfully prepared via a Wurster column process. However, the yield of indomethacin Eudragit® S-100 pellets from this layering process was far from ideal[1]. The average yield of five batches of IS pellets were equal to 89% of the theoretical yield. In reviewing the pharmaceutical literature, several fluid-bed processes were used to prepare granules or microspheres utilized micronized drug.[2-4] Furthermore, the quality and quantity of the finished pellets or microspheres was affected by the types of processing equipment used for manufacturing.[5-7] In this study, the effect of indomethacin particle size on yield and the effect of manufacturing process on the quality of the finished product were examined.

EXPERIMENTAL

Materials

Indomethacin[a] was NF grade. Talc[b], nonpareil seeds[c] (18/20 and 25/30 mesh) and alcohol were USP grade. Dibutyl sebacate[d] was used as received. Eudragit® S-100[e] was a gift from Rohm Pharma. All reagents were analytical grade or better.

Preparation Methods for Indomethacin Sustained Release Pellets

Micronization of Indomethacin Powder

Indomethacin powder was micronized via an air impact pulverizer[f]. Two throughputs were evaluated, 100 and

300 g/hour. The air pressures for the grinding jet and the feeding nozzle were set at 60 and 80 psi, respectively.

Preparation of Indomethacin/Eudragit® S-100/Alcohol Slurry

To a two-liter stainless steel container holding 500 g of alcohol equipped with a lightning mixer, 6.8 g of dibutyl sebacate was added and mixed. Sixty eight grams of Eudragit® S-100 were added gradually into the container and mixed until all the Eudragit® S-100 powders were dispersed. Three hundred grams of indomethacin was then introduced and mixed until all powders were dispersed. The resultant slurry was then passed through a Colloid mill[g]. The slurry was then filled to 1080 g total weight with additional alcohol. The solids content of the slurry was 34.6% w/w.

Preparation of Indomethacin Eudragit® S-100 Pellets (IS Pellets)

Pellets containing indomethacin were prepared by spraying the indomethacin/Eudragit® S-100/alcohol slurry onto an appropriate mesh fraction of nonpareil seeds via either a fluid-bed granulator process or a Wurster column process[h]. The formulations used to prepare various batches of IS pellets are given in Table 1. The resultant pellets were dried at 50°C for 32 hours to remove the residual volume of solvent from the pellets.

Testing

Particle Size Distribution of Indomethacin Powders

The particle size measurements for the two types of micronized powders and the "as is" indomethacin powder were determined using a Microtrac® particle size analyzer[i]. An appropriate amount of indomethacin powder was added into the

TABLE 1

THE AMOUNT OF INGREDIENTS USED TO PREPARE INDOMETHACIN EUDRAGIT® S-100 PELLETS

Ingredients	Formulation I	II	III	IV
Indomethacin "As is"	300 g	___	___	___
Micronized (High throughput)	___	300 g	___	___
Micronized (Low throughput)	___	___	300 g	300 g
Non-Pareil Seeds - 18/20 Mesh	500 g	500 g	500 g	___
25/30 mesh	___	___	___	500 g
Eudragit® S-100	68 g	68 g	68 g	68 g
Dibutyl Sebacate	6.8 g	6.8 g	6.8 g	6.8 g
Alcohol USP	705.2 g	705.2 g	705.2 g	705.2 g

analyzing chamber containing deionized water as the medium. A few drops of Triton solution [j] (1% w/w) were added to disperse the powders. Test results of the three types of powders were recorded. In addition, these powders were examined under a microscope[k] with a magnification of 400X. Photomicrographs were taken with a Polaroid SX-70 camera[l].

Sieve Analysis

The size distribution of IS pellets and nonpareil seeds were evaluated by a sieve-analysis technique using a set of US standard sieves; namely, #12, #14, #16, #18, #20, #25, #35 and base pans. The sieve load was 10 g. The sieve nest was shaken using an ATM Sonic Sifter[m] for five minutes. The net weights that were retained on each sieve were then determined and recorded. Duplicate samples were run for each batch of IS pellets and nonpareil seeds. The average values were used for the calculation of particle size distribution. The arithmetic mean diameter of IS pellets was then determined by the method as discussed by Parrott[8].

True Density

The true density of each sample of IS pellets was determined by using a solvent displacement method[9].

Assay Procedure

Total drug content of the IS pellets was determined by dissolving accurately weighed portions of each batch in 100 ml methanol and observing the spectrophotometric absorbance[n] at 318 nm. Duplicate samples were assayed and the mean values reported.

In-Vitro Dissolution Studies

Dissolution tests were conducted using apparatus II, USP XXI/NF XVI with paddles. An agitation speed of 100 rpm was used in

this study. An appropriate amount of indomethacin sustained release pellets containing 75 mg of indomethacin was used with 900 ml of dissolution medium at 37°C. The dissolution medium consisted of either a pH 6.5 or 7.2 phosphate buffer. Samples were removed at suitable time intervals. The collected samples were assayed spectrophotometrically using a Beckman DU®-6 spectrophotometer[n] at 318 nm for indomethacin content. Each determination was carried out in triplicate. Absorbance followed Beer's Law over the range of concentrations encountered.

RESULTS AND DISCUSSIONS

Effect of Manufacturing Process on the Physical Properties of Indomethacin Eudragit® S-100 Pellets (IS)

Table 2 shows a comparison between the Wurster column and the fluid-bed methods for the preparation of IS pellets. The Wurster column process resulted in a higher yield and a higher drug load than the fluid-bed process. The differences in the nature of the spraying techniques between the two processes can account for the observed differences. In a top-spray, fluid-bed granulator process, spray-drying of the coating slurry was more pronounced than in the Wurster column process. In the former, nonpareil seed flow was more random and the liquid slurry was sprayed against the inlet air (countercurrent spray).[5] This arrangement promotes solvent evaporation before contact with the substrate. This causes a change in the ratio of solid to liquid in the coating droplets. Spray-drying of the droplet occurred. However, in the Wurster column process, the application of the coating solution was done

TABLE 2
COMPARISON OF THE PHYSICAL PROPERTIES OF INDOMETHACIN EUDRAGIT® S-100 PELLETS MANUFACTURED VIA TWO DIFFERENT FLUID-BED COATING PROCESSES*

Process	Actual Yield of the Pellets (%)	Assay Drug Content (SD)	Efficiency of the Process $\frac{\text{Actual Assay}}{\text{Theoretical Assay}} \times 100\%$
Fluid-Bed Granulator	83%	22.2% (± 0.23)	64.7%
Wurster Column	91%	27.3% (± 0.25)	79.6%

*Indomethacin powder "as is" and 18/20 mesh nonpareil seeds were used for these two experiments.

concurrently with the flow of the inlet air and product. Furthermore, the nozzle in the Wurster column was immersed in the fluidized particles. The solution droplets travelled only a short distance before contacting the substrate. The drug slurry could be applied more evenly.[6,7] Consequently, spray drying of the coating slurry in the Wurster column process was reduced to a minimum, and in turn, provided a much higher yield of IS pellets.

Effect of Indomethacin Particle Size on the Physical Characteristics of Indomethacin Eudragit® S-100 Pellets

Table 3 shows the effect of indomethacin particle size on the yield of IS pellets. The finer the powder, the higher the yield of IS pellets. For example, the average yield for batches 1 and 2 (Formulation I) which were prepared using the as is indomethacin powder (particle diameter of 40.6 μ), was approximately 89%. Batches 3 and 4, prepared using two types of micronized indomethacin powders, produced a higher yield of product.

TABLE 3

PHYSICAL PROPERTIES OF FOUR BATCHES OF IS PELLETS MANUFACTURED VIA THE WURSTER COLUMN PROCESS

Formulation No.	Batch No.	Type of Indomethacin Powders	Average Particle Diameter of Indomethacin (Microns) (S.D.)	Yield of the Mfg. Process (%)	Assay Drug Content (%)	Efficiency of the Process (%) $\frac{\text{Actual Assay}}{\text{Theoretical Assay}} \times 100\%$
I	1	As is	40.6 (± 32.5)	89.9	27.3	79.5
I	2	As is	40.6 (± 32.5)	89.3	27.1	79.0
II	3	Micronized (High throughput)	6.4 (± 15.4)	93.8	30.3	88.4
III	4	Micronized (Low throughput)	3.3 (± 2.4)	98.2	33.1	96.6

Microscopic examination of these three different types of indomethacin powders indicated that there were tremendous differences in particle size distributions (Figure 1). Figure 1b showed that the majority of the particles prepared via a high throughput micronization process were below 10 μ. However, a few larger particles (20 - 80 μ) were also found in the sample. Indomethacin powder micronized via a low throughput process exhibited a very uniform particle size distribution (Figure 1c). Particles were below ten microns on average. Further examination of data presented in Table 3 revealed the fact that batch 4 (Formulation III), which utilized low throughput micronized powder, gave a higher yield of pellets (98.2%) and a higher assay of indomethacin content of the finished pellets (33.1%) than batch 3 (Formulation II) (high throughput micronization process). These results seem to indicate that the distribution of particle sizes within a sample of indomethacin powder may affect the yield from this layering process.

To substantiate this hypothesis, the particle size distributions of the three different types of indomethacin powders tested were examined using a laser scanning analyzer.[i] Data are presented in Table 4. As expected, indomethacin powder micronized via a high throughput process (used to prepare batch 3) showed a particle size distribution ranging from 2 to 75 microns. However, 31% of the total amount of the particles were larger than ten microns. On the other hand, indomethacin powders, micronized via a low throughput process (used to prepare batch 4; Formulation III) exhibited a very narrow particle size distribution of indomethacin ranging from one to thirteen microns. Since the two batches of IS pellets prepared from the micronized drug samples were manufactured using similar processing

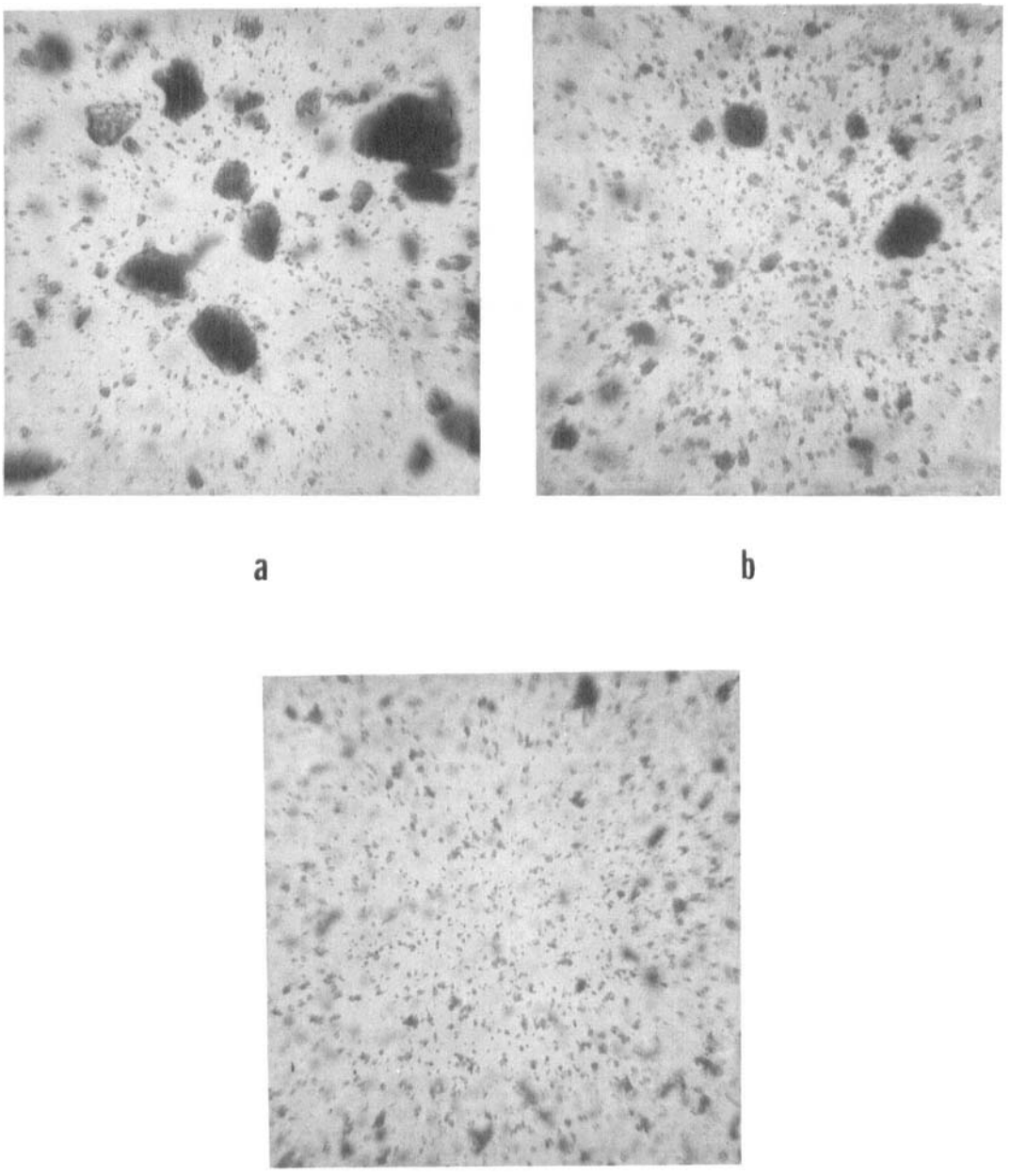


FIGURE 1

Photomicrographs of three different types of indomethacin in powders. a- unmicronized (as is); b- micronized (high throughput); c- micronized (low throughput). 400X magnification

TABLE 4

PARTICLE SIZE DISTRIBUTION OF THREE TYPES OF INDOMETHACIN POWDERS DETERMINED BY THE PARTICLE SIZE ANALYZER

Formulation Number	Batch Number	Type of Indomethacin Powder	Particle Size (Microns) 106	75	53	38	27	19	13	9.4	6.6	4.7	3.3	2.4	1.6	1.2	0.8
I	1 & 2	Unmicronized (As is)	11	15	17	17	12	9	8	7	4	-	-	-	-	-	-
II	3	Micronized (High throughput)	1	3	6	6	4	3	8	10	9	11	16	11	4	2	6
III	4	Micronized (Low throughput)	-	-	-	-	-	-	3	5	14	17	20	17	11	9	5

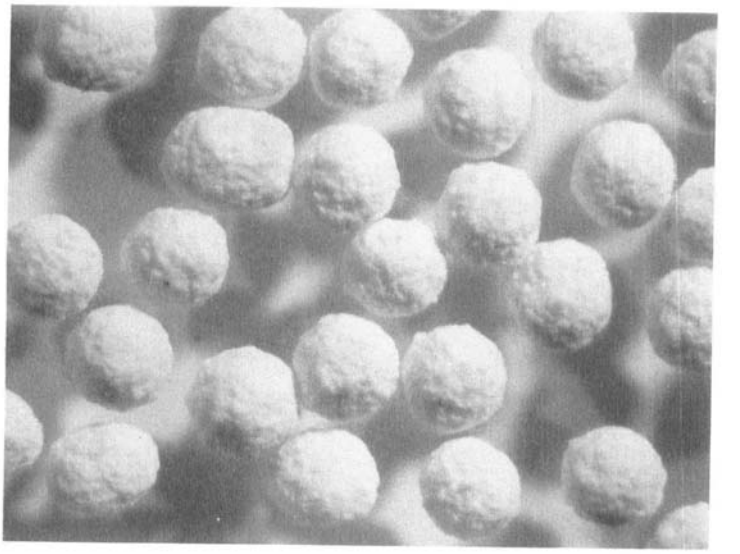
parameters and the same batches of raw materials, it can be concluded that the distribution of particle size within a sample of indomethacin powder can account for the differences seen in yield and end product drug load.

Particle size of drug may affect the ability of the "wet" polymer to hold the larger drug particles on the surface of the nonpareil seeds as the seeds move through the coating chamber (6 to 10 cycles per minute) during the layering process.[10]. This is in agreement with the results observed above. IS pellets prepared with drug which was not micronized produced a resultant product of lower yield and lower drug load than for the batches of IS pellets prepared from micronized powders. The differences in final pellets from batches 3 and 4 also support this explanation.

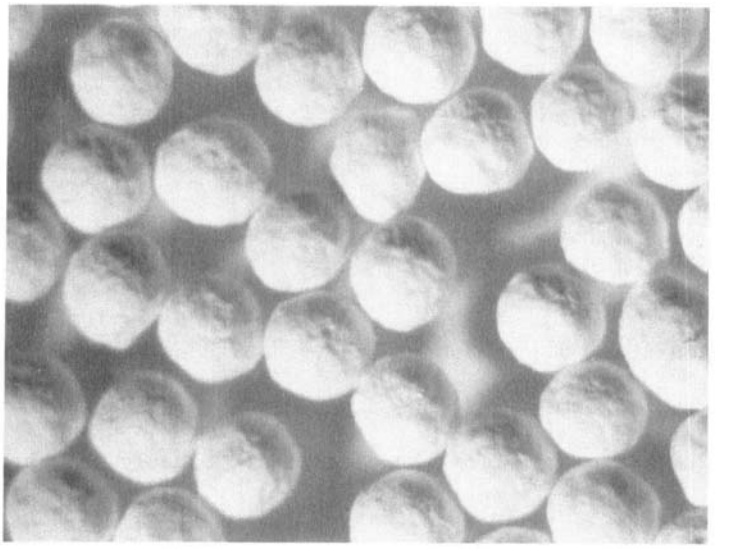
Figure 2 shows photomicrographs of two batches of IS pellets. Pellets shown in Figure 2a (batch 1, Formulation I) exhibited very rough surfaces. These imperfections can be attributed to the particle size and to the irregular particle size distribution of the indomethacin powder (Figure 1a) used to prepare this batch of pellets. Surface characteristics of pellets (shown in Figure 2B) (batch 4, Formulation III) were very smooth with few imperfections noted. The fine particle size and the uniform size distribution of the micronized indomethacin powder can account for these observations.

In-Vitro Release Rate of Indomethacin Eudragit® S-100 Pellets

Figure 3 is a cumulative plot of percent of indomethacin released versus time for four batches of IS pellets. The release rate of the drug from the pellets can be seen to be proportional to the yield of the particular batch. Batch 4, Formulation III, having the highest yield of IS pellets, showed the fastest release rate of



a



b

FIGURE 2

Photomicrographs of indomethacin Eudragit® S-100 pellets. a-pellets prepared with unmicronized indomethacin powder; b-pellets prepared with low throughput micronized indomethacin powder. 15X magnification

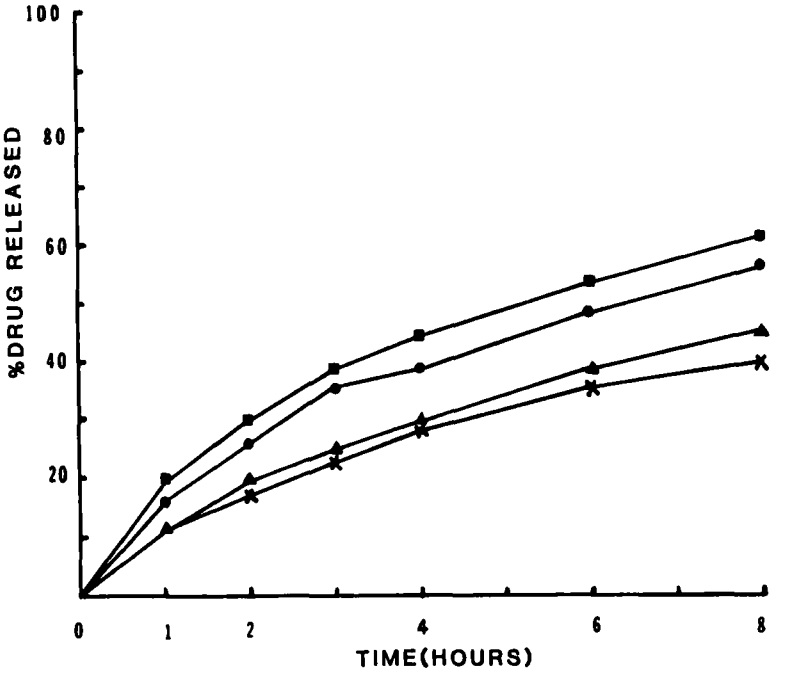


FIGURE 3

Cumulative amount (%) of indomethacin released from four batches of IS pellets in pH 6.5 phosphate buffer.

Key: X Batch 1 (Formulation I)
▲ Batch 2 (Formulation I)
● Batch 3 (Formulation II)
■ Batch 4 (Formulation III)

indomethacin at pH 6.5 phosphate buffer. Batches 1 and 2, Formulation I, having the lowest yield, showed the slowest release rate. Two explanations are offered for these results. Firstly, as the yield of indomethacin increased in the finished pellets, the ratio between indomethacin and Eudragit® S-100 polymer in each of the matrix pellets would shift in favor of indomethacin. Consequently, these pellets released indomethacin more rapidly because there was more indomethacin available. Secondly, the particle size of the indomethacin powder may also influence the release characteristic of the drug from the matrix

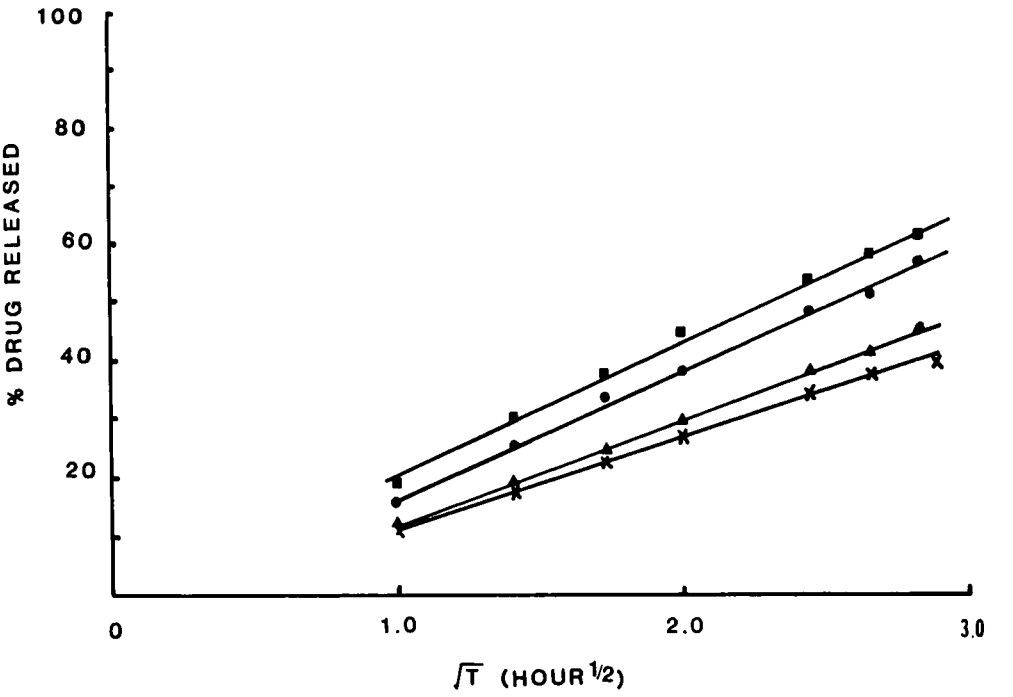


FIGURE 4

Release profiles of indomethacin from four batches of IS pellets plotted assuming Higuchi matrix equation.

Key X Batch 1 (Formulation I)
▲ Batch 2 (Formulation I)
● Batch 3 (Formulation II)
■ Batch 4 (Formulation III)

pellets. As shown above, finer particle sizes of indomethacin gave greater yield of IS pellets. According to the Noyes-Whitney equation[11], the release rate of drug is directly proportional to the surface area of the drug. Therefore, batch 4, Formulation III, having the highest yield, would also be expected to exhibit the fastest in-vitro release rate profile.

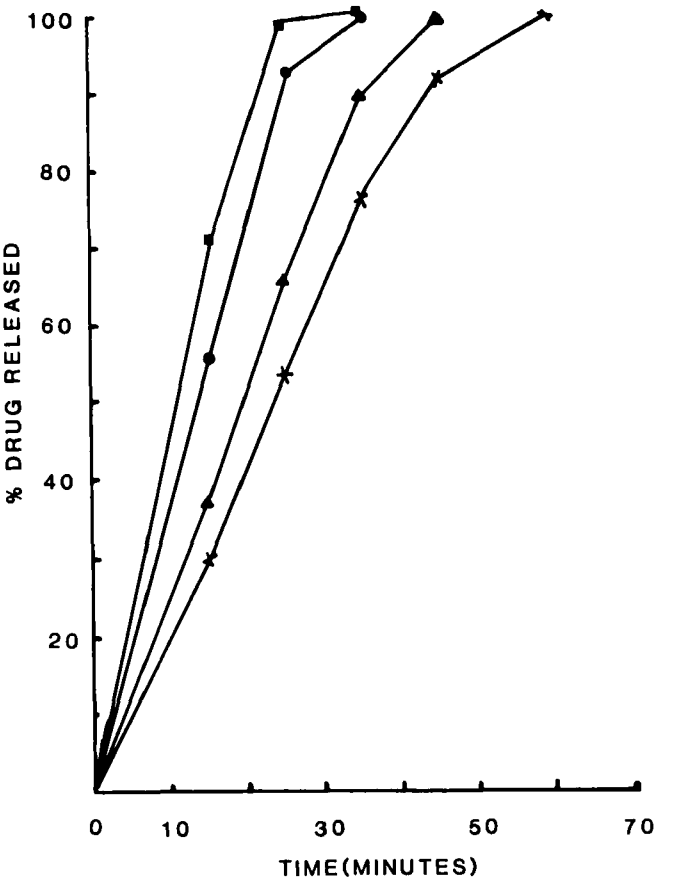


FIGURE 5

Cumulative amount (%) of indomethacin released from four batches of IS pellets in pH 7.2 phosphate buffer.

Key X Batch 1 (Formulation I)
▲ Batch 2 (Formulation I)
● Batch 3 (Formulation II)
■ Batch 4 (Formulation III)

It was very interesting to observe that in pH 6.5 phosphate buffer all four batches of IS pellets, regardless of the type of indomethacin used to prepare these pellets, showed a release pattern with $\sqrt{T}$ dependance (Figure 4). This indicated release from a typical matrix formulation as described by Higuchi[12]. The differences in

TABLE 5
CALCULATION OF SPECIFIC SURFACE AREA OF TWO BATCHES OF INDOMETHACIN EUDRAGIT® S-100 PELLETS

Formulation No. of IS Pellets	True Density of IS Pellets (ρ)	Average Arithmetic Diameter (D)	Specific Surface Area (SA)*	Ratio of Specific Surface Area of IS Pellets = Batch 4 (Formulation III) / Batch 5 (Formulation IV)
III	1.191 g/cm^3	1284 μ	39.24 $\frac{cm^2}{g}$	0.70
IV	1.170 g/cm^3	911 μ	56.29 $\frac{cm^2}{g}$	

NOTE: *$SA = \frac{6}{\rho D}$ (See appendix 1)

TABLE 6
THE PARTICLE SIZE DISTRIBUTION OF INDOMETHACIN EUDRAGIT® S-100 PELLETS

Formulation Number	Sieve Analysis (% Retained On Mesh#) 16	18	20	25	30	Average Pellet Diameter (microns)
III	97.3%	2.6%	0.1%	-	-	1284
IV	-	0.1%	93.3%	6.5%	0.1%	911

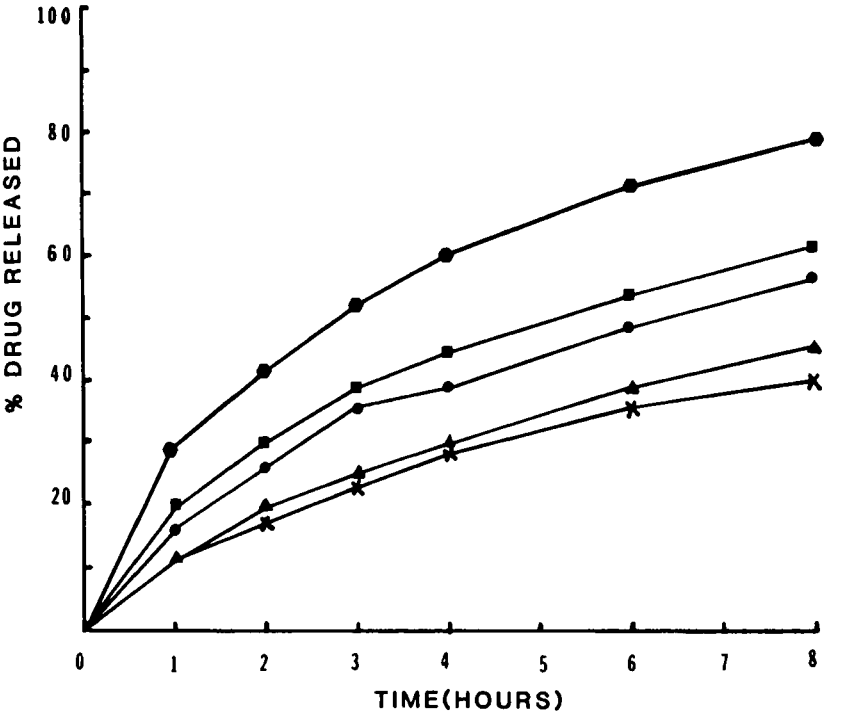


FIGURE 6

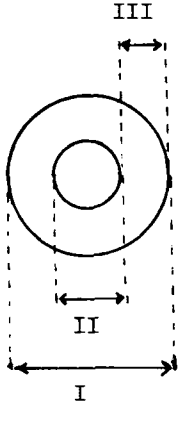
Cumulative amount (%) of indomethacin released from five batches of IS pellets in pH 6.5 phosphate buffer,

Key X Batch 1 (Formulation I)
▲ Batch 2 (Formulation I)
● Batch 3 (Formulation II)
■ Batch 4 (Formulation III)
⬤ Batch 5 (Formulation IV)

TABLE 7

CALCULATION OF AVERAGE MATRIX THICKNESS OF INDIVIDUAL INDOMETHACIN EUDRAGIT® S-100 PELLETS

Formulation No. of IS Pellets	Average Particle Diameter of IS Pellets (I)	Average Particle Diameter of Non-Pareil Seeds (II)	Matrix Layer Thickness $\frac{(I) - (II)}{2} = III$	Ratio of Average Thickness of IS Pellets: Batch 4 (Formulation III) / Batch 5 (Formulation IV)
III	1284 μ	920 μ	182 μ	1.30
IV	911 μ	654 μ	129 μ	



particle size distribution of these three types of indomethacin powders only affected the rate of drug release from the pellets but not the extent of drug release (Figure 5).

Effect of Variation in Size of the Starting Nonpareil Seeds on In-Vitro Release Rate of Indomethacin Eudragit® S-100 Pellets

Tables 5 and 6 and Figure 6 compare IS pellets prepared from an 18/20 fraction of nonpareil seeds (Formulation III) to pellets prepared from a 25/30 fraction of nonpareil seeds (Formulation IV). All raw materials and processing conditions were kept constant. Low throughput micronized drug was used to prepare these two formulations. As can be seen, IS pellets prepared from the 25/30 fraction of nonpareil seeds (Formulation IV) exhibited a smaller diameter and a larger surface area. Release of indomethacin from these smaller pellets was significantly faster than from the larger IS pellets (Figure 6). In addition to the surface area consideration (major contribution to the release rate profile of IS pellets), the thickness of the matrix layer may also contribute to alter the release rate profile of IS pellets (minor contribution).

Table 7 shows the determination of the matrix layer thickness for each preparation. The matrix layer for the pellets of Formulation IV was found to be 30% thinner than the pellets of Formulation III. A thinner matrix layer would allow for a more rapid diffusion of indomethacin.

CONCLUSIONS

The data presented in this article clearly demonstrate that the Wurster column process is a superior method for preparing indomethacin

Eudragit® S-100 pellets compared to a fluid-bed granulator process. The particle size of indomethacin powder was found to be a critical factor influencing the physical characteristics of the IS pellets. Both the average particle diameter and the overall particle size distribution of indomethacin powders should be closely monitored to ensure the maximum yield for a layering process. It was found that the particle size of the starting nonpareil seeds could be utilized as another means to alter the physical properties of indomethacin sustained release pellets.

ACKNOWLEDGMENTS

The authors wish to thank Mr. Robert N. Galante, Mr. Walter Hause and Dr. Michael J. Rutledge for their analytical support and Dr. Robert Felt for his helpful suggestions in the preparation of this manuscript and Ms. Mary Pellak for typing this manuscript.

FOOTNOTES

a. Industrie Chimiche Parmaceutiche Italiane.

b. Charles B. Chrystal Company, Inc., New York, NY.

c. Ingredient Technology Corporation, Pennsauken, NJ.

d. Union Camp, Chemical Division, OH.

e. Rohm Tech., Inc., Malden, MA.

f. Gem-T Research Model Jet Mill, Garlock Inc., Plastomer Product/Friends Lane, Newtown, PA.

g. Gifford-Wood, Model W200V, Greerco Corp., Hudson, NH.

h. Aeromatic Strea-1 Coater, Aeromatic Ltd., Towaco, NJ.

i. Model #7995-30, Leeds & Northrup Instruments, North Wales, PA.

j. Sigma Chemical Company, St. Louis, MO.

k. Olympic Model POM Microscope, Olympus, Tokyo, Japan.

l. Polaroid Corp., Cambridge, MA.

m. ATM Corporation, Milwaukee, WI.

n. Smith Kline Beckman, Inc., Philadelphia, PA.

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APPENDIX 1

THE CALCULATION OF SPECIFIC SURFACE AREA OF INDOMETHACIN EUDRAGIT® S-100 PELLETS

The specific surface area (SA) was expressed by Martin, et al [13] as:

$$SA = \frac{6}{\rho dvs}$$

where ρ = true density

dvs = mean-volume-surface diameter

As can be seen from Table 6, the particle size distributions of IS pellets from the two batches of pellets were very narrow. Ninety-seven percent of the pellets were retained on a 16 mesh screen for Formulation III. Whereas 93% of the pellets were retained on a 20 mesh screen for Formulation IV. To simplify the calculation, the average arithmetic pellet diameter (D) was used to calculate the specific surface area of the two batches of IS pellets. The equation used was as follows: $SA = \frac{6}{\rho D}$