Manufacture and Release Characteristics of Indomethacin Sustained Release Capsules

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เรื่องย่อ

การผลิตและลักษณะการปลดปล่อยตัวยาของยาแค็ปซูลออกฤทธิ์เนิ่นอินโดเม็ทธาซิน

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แกรนูลที่ใช้เตรียมยาออกฤทธิ์เนิ่นอินโดเม็ทธาซินประกอบด้วยแลกโตสเป็นสารเพิ่มปริมาณ และสารละลายโพวีโดนเป็นสารยึดเกาะ เตรียมโดยวิธีแกรนูลเปียก จากนั้นนำเอาส่วนที่คัดแล้วขนาด 12/20-mesh มาทำให้ผิวเรียบ แล้วเคลือบด้วยฟิล์มที่มีส่วนผสมของเอ็ทธิลเซลลูโลส กับ กลีเซอริล โมโนสเตียเรท โดยวิธี air-suspension ให้มีน้ำหนักของเคลือบที่เปอร์เซ็นต์ต่างๆ จากการตรวจสอบแกรนูลเคลือบนี้ด้วยกล้องจุลทรรศน์อีเล็กตรอน พบว่าฟิล์มที่เคลือบบนผิวมีลักษณะเรียบสม่ำเสมอ ยาแค็ปซูลออกฤทธิ์เนิ่นอินโดเม็ทธาซินถูกเตรียมขึ้นโดยอาศัยความสัมพันธ์ระหว่างน้ำหนักของเคลือบกับอัตราเร็วในการปลดปล่อยตัวยาซึ่งได้พัฒนาขึ้น การประเมินผลยาออกฤทธิ์เนิ่นดังกล่าวนี้ใน *in vitro* พบว่ามีรูปแบบการปลดปล่อยตามที่ต้องการทั้งในเครื่องหาการละลายและใน absorption simulator

Abstract

Granules containing indomethacin as a model drug, with lactose excipient, were prepared by means of wet granulation using povidone solution as a binder. The smoothed 12/20-mesh fractions of granulation were coated in an air-suspension coater with film of ethylcellulose – glyceryl monostearate mixture at various percents by weight of coat. Visual inspection of coated granules using scanning electron microscopy showed the coating film with uniform appearance. The indomethacin sustained release capsules were prepared based on the coating weight – release rate constant relationship previously developed. *In vitro* evaluation of these sustained release capsules revealed considerably good performance both in dissolution test apparatus and in absorption simulator.

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INTRODUCTION

The main objective in fabrication of sustained release product is to generate a tissue or blood concentration versus time profile whereby the level of drug is maintained constant throughout therapy. In order to accomplish a constant level of drug in some desired target tissue, it is necessary to know the release rate constant of drug from the delivery system.[1] In the previous study on the release of indomethacin from granules coated with ethylcellulose-glyceryl monostearate mixture by means of the air-suspension coating process, it has been reported that the relationship between the weight of coat and the release rate constant provided a valuable tool in preparation of sustained release products.[2] The present work is an examination of the *in vitro* release of indomethacin from sustained release capsules which were prepared being based on the relationship of percent coat to drug release rate.

MATERIALS AND METHODS

Materials

Indomethacin used in this study was obtained from China National Chemicals Import and Export Corporation. Lactose and providone used in preparation of granules were from DMV, Veghel, Holland, and BASF, Germany, respectively. Ethylcellulose, Dow Chemicals, U.S.A. Glyceryl monostearate, Oleofina, Belgium. All of the materials were B.P., U.S.P., or reagent grades.

Methods

Preparation of Indomethacin Sustained Release Capsules: Lactose granules containing 19.8% w/w indomethacin were prepared by means of wet granulation. The fractions of drug and lactose diluent that passed through a 60-mesh sieve were mixed in Rotomixer (Forster Equipment Co. Ltd., England) for 10 minutes and wet-granulated using 5%w/v povidone aqueous solution as a binder in planetary mixer (Kenwood, U.S.A.). The granulation composition is presented in Table 1. The wet mass was passed through a 14-mesh sieve after which the surfaces of granules were smoothed for 10 minutes in a coating pan, and oven-dried at 50°C for 8 hours.

Table 1 Composition of Indomethacin Granules

Indomethacin	100 g
Lactose	400 g
Polyvinylpyrrolidone (as 5%w/v aqueous solution)	5 g

Table 2 Composition of Coating Solution

Ethylcellulose	15.0 g
Glyceryl monostearate	5.0 g
Chloroform	400.0 g

The 12/20-mesh fractions of granulation were classified and coated by using air-suspension coater (Aeromatic AG, Switzerland). Some modifications were made on this machine in order to get an improved systematic fluidization effect by placing a stainless steel cylinder with diameter of 8 cm and 11 cm long at the center of the settling chamber.

Batches of 200 g of granules were coated with the coating solution containing ethylcellulose and glyceryl monostearate whose composition is shown in Table 2. The granules were fluidized in chamber until the temperature in the coating region of the apparatus reached 40°C after which spraying was operated. The pressure at which satisfactory fluidization occurred was 7 units on the Aeromatic scale. Coating solution was pumped through a peristaltic pump (Aeromatic AG, Switzerland) at a flow rate of 4 ml/min to the spray nozzle, which was operated at a spray pressure of 5 psig. These conditions above were found to be optimal since there was no blockage of the spray nozzle as well as aggregation of the granules.

On completion of coating, granules were fluidized for a further 10 minutes to ensure complete removal of chloroform and drying. The amount of coat was evaluated by the increased weight of coated granules in percent by weight based on the non-coated granules. Since fluidization of granules in the chamber during warming period prior to coating operation may cause violent attrition between granules, friability of granules must be taken into account. This was carried out by fluidizing non-coated granules in the coating chamber for a time after which the coating temperature was reached, and friability of granules could be calculated from the difference between initial and final weight of granules without fine particles. Loss of granule weight determined by this way was found to be 0.75% and used in actual

weight correction.

The relationship between weight of film coat and release rate constant (k_r^1) obtained from previous study[2] along with some necessary pharmacokinetic parameters of indomethacin were used in calculating and formulating the sustained release capsules. The release of indomethacin from this capsule should prolong for at least up to 8 hours with the desired release rate. For this reason, appropriate amount of both non-coated and 0.75 %w/w coated granules were filled in a capsule # 0. The sustained release capsule is therefore composed of 126.2 mg of non-coated granules (equivalent to 25 mg indomethacin) as the loading dose, and 381.6 mg of 0.75%w/w coated granules (equivalent to 75 mg indomethacin) as the maintenance dose.

Microscopic Examination of Coated Granules: The uniformity of coated granules may be visualized by scanning electron microscopy (Jeol Model JSM-35 CF, Japan) of granule surfaces. The granules were coated with gold plate by ion sputter (Jeol Model JFC-1100, Japan) before scanning.

***In vitro* Evaluation of Indomethacin Sustained Release Capsules:**

I. Method Using Dissolution Apparatus: The USP XIX dissolution test apparatus 1 (Hanson Research, U.S.A.) was used in this investigation. One capsule was placed in each basket and total of six capsules were evaluated in this study. The basket was immersed in 900 ml of USP phosphate buffer pH 7.2 at 37°C and rotated at a speed of 100 rpm. The withdrawn samples were analyzed spectrophotometrically for indomethacin.

II. Method Using Absorption Simulator: The release characteristics of indomethacin sustained release capsules were examined in absorption simulator (Sartorius, West Germany) in addition to the dissolution apparatus. This apparatus mainly consisted of an artificial lipid membrane mounted between the front and back plate of the plexiglass diffusion cell. Each diffusion chamber on each side of the membrane was connected to a 120-ml container by tube connections, which was opened and closed by a tap. The magnetic stirrer was used in the container to provide sufficient agitation. Solution in each container was kept at constant temperature by temperature controlling jacket and circulated simultaneously through the diffusion chamber at the same flow rate by a peristaltic pump. Samplings of the solution at given time intervals were made by controlling taps on the distribution caps.

The Sartorius® artificial intestinal barrier was used as the diffusion membrane in this study. This artificial barrier consisted of an inert frame (Sartorius® membrane filter) the pores of which were filled with a liquid lipid-phase commercially available (Sartorius, West Germany). The barrier was used once only and was prepared shortly before the start of the experiment. The diffusion chamber used was type AZ having 2 barrier with total effective area of 80 $cm.^2$ One hundred milliliters of USP phosphate buffer pH 7.2 were placed in one container as artificial gastrointestinal juice (phase I), and the other as artificial plasma (phase II).

When the temperature of solutions in both containers reached 39 ± 1°C, an indomethacin sustained release capsule as well as non-coated granules equivalent to 25 mg indomethacin and 0.75 %w/w coated granules equivalent to 75 mg indomethacin were placed in phase I-container one at a time. The pump was immediately switched on at an output of 10-15 ml/min. Samples were taken at one-hour intervals up to 8 hours and were analyzed spectrophotometrically for indomethacin.

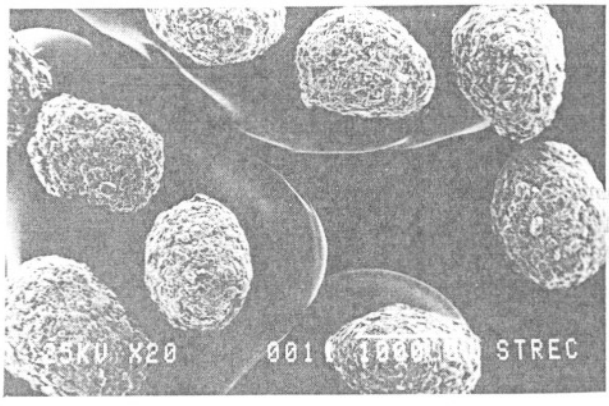

Fig. 1 Scanning electron photomicrograph of non-coated granules. Manification 20 X

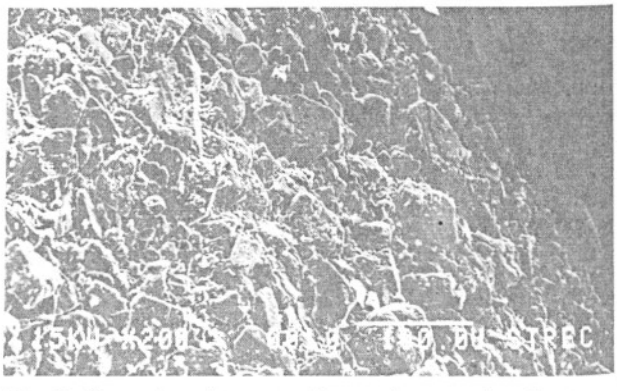

Fig. 2 Scanning electron photomicrograph of a non-coated granule. Magnification 200 X

RESULTS AND DISCUSSION

Microscopic Appearance of the Coated granules: By means of smoothing the pellet granules using the rotating pan and coating using air-suspension coater, one may anticipate uniform and even surface of the coated granule. The uniformity of granules coated at various percents by weight may be visualized microscopically by scanning electron microscopy of granule surfaces as shown in Figures 1 to 4. Typical granules produced by the wet granulation process with smoothing of the surfaces are shown in Figure 1, and a view of the surface is shown in Figure 2. The non-coated cores appear to be regular crystalline agglomerates, generally spherical with an occasional rod- or dumbbell-shaped particle. The horizontal bars seen in pictures indicate the dimension in microns. The diameters of non-coated granules according to Figure 1 are in the order of 1,000 μ which are in accordance with the 12/20-mesh fractions of dry granulation used. Although the granules are not quite spherical in shape, their sizes as well as surfaces are acceptably uniform considering the characteristics of wet massing and screening process. As the amount of coat is increased, the degree of smoothness is appreciably increased as depicted in Figures 3 and 4 which represent the photomicrographs of 0.75 %w/w and 2.79 %w/w coated granules, respectively. Glossy appearance of the surface that was produced by ethylcellulose – glyceryl monostearate film can be seen in the pictures. The coat can be characterized by many layers of thin film depositing one after the other on the granule surface. This characteristics may be explained on the basis of the working principle of air-suspension coater; that is, minute amount of coating solution is sprayed and deposited on the surfaces of granules as they travel pass the spray nozzle, and then are dried by fluidizing air in the coating chamber after which they come to receive another lot of coating solution beginning the next cycle. Such behavior will certainly cause a multiple-layer build up of film coat on the granule surfaces.

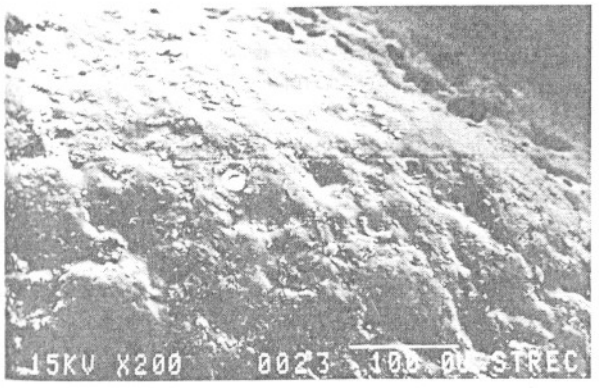

Fig. 3 Scanning electron photomicrograph of 0.75% w/w coated granule. Magnification 200 x

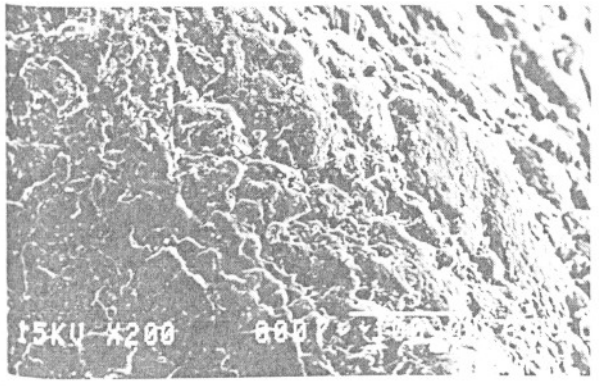

Fig. 4 Scanning electron photomicrograph of a 2.79 %w/w coated granule. Magnification 200 X

***In Vitro* Evaluation by Means of Dissolution Apparatus:** The result of indomethacin release *in vitro* in dissolution test apparatus are shown graphically in Figure 5. Almost all of the initial dose of 25 mg is release within the first half-an-hour interval, the sustaining dose thereafter plays a major role in the release pattern. Although the release pattern from half

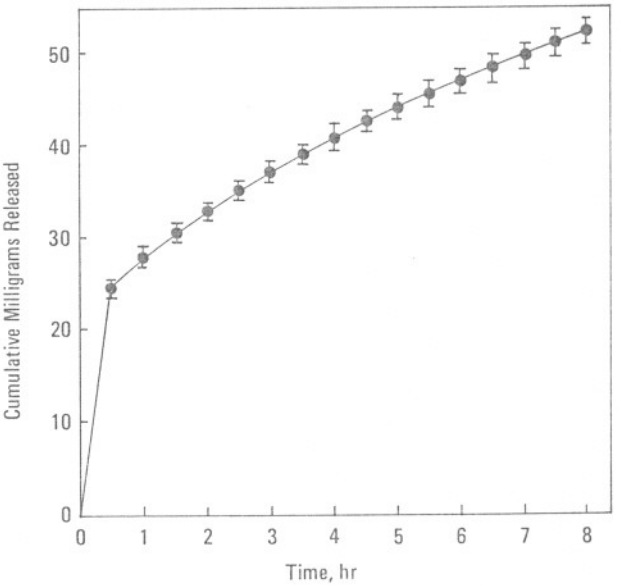

Fig. 5 Drug release pattern of indomethacin sustained release capsules in USP phosphate buffer pH 7.2 by means of USP XIX dissolution test apparatus 1, with points showing mean values of six determinations and bars indicating 95% confidence intervals.

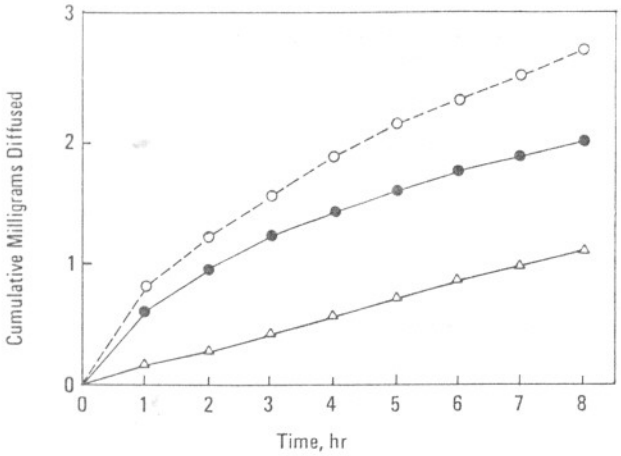

Fig. 6 *In vitro* availability of indomethacin sustained release capsule in absorption simulator.
Key: ●, non-coated granules equivalent to 25 mg indomethacin; △, 0.75 %w/w coated granules equivalent to 75 mg indomethacin; ○, indomethacin sustained release capsules.

an hour up to 8-hour period exhibits non-zero-order kinetics, the release rate gradually decreases within only a small degree as a function of time. The initial rate of release found at the first half an hour is 7.26 mg/hr. This is certainly attributed to the first-order release behavior of the sustaining portion as previously reported.[2]

***In Vitro* Evaluation by Means of Absorption Simulator:** The absorption simulator allows the evaluation of sustained release product to be carried out on the diffusion of the drug under conditions similar to those in the gastro-intestinal tract. The most important feature of the unit is the lipid barrier whose permeability to "passively" transported drugs is similar to that of the gastric and intestinal walls.[3] The drug availability of indomethacin sustained release capsule is shown in Figure 6. The very small amount of drug, not more than 3 mg, diffuses through the lipid barrier within 8 hours. The coated granules alone seem to follow apparent zero-order kinetics owing to dosage form-controlled release while the non-coated cores exhibit a non-linear membrane-controlled release kinetics. The uppermost profile represents the availability of indomethacin from prepared sustained release capsule which is the sum of the other two curves below. The results of this study evidently verify that the diffusion rate of drug through the barrier will be appreciably constant if the release rate of drug from the dosage form is controlled to be readily constant at quasi-steady-state, provided the latter be the rate-limiting step. The situation is highly expected to take place in the *in vitro* absorption system.

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