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Drug Release from Ethylcellulose-Glycerylmonostearate Coated Granules(การปลดปล่อยตัวยาออกจากแกรนูลที่เคลือบด้วยส่วน ผสมของ Ethylcellulose และ Glyc...

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ORIGINAL ARTICLE

การปลดปล่อยตัวยาออกจากแกรนูลที่เคลือบด้วยส่วนผสมของ Ethylcellulose และ Glycerylmonostearate

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บทคัดย่อ

ในการเคลือบแกรนูล chlorpheniramine maleate ด้วยส่วนผสมของ ethylcellulose และ glycerylmonostearate โดยวิธี Wurster airsuspension พบว่า จากการเคลือบแกรนูลที่ความหนาต่าง ๆ โดยควบคุมน้ำหนักของแกรนูลที่เพิ่มขึ้น จะสามารถหาความสัมพันธ์ระหว่างอัตราการปลดปล่อยของ chlorpheniramine maleate กับน้ำหนักของเคลือบได้ ซึ่งความสัมพันธ์เป็นแบบ exponential function นอกจากนี้ยังพบว่าอัตราการปลดปล่อยของ chlorpheniramine maleate ออกจากแกรนูลเป็นแบบ first-order จากความสัมพันธ์ขั้นต้นสามารถนำไปเตรียมยาออกฤทธิ์เนิ่นที่มีแบบการปลดปล่อยของตัวยาตามต้องการได้

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Drug Release from Ethylcellulose–Glycerylmonostearate Coated Granules

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Abstract

Chlorpheniramine maleate granules were coated with the ethylcellulose–glycerylmonostearate mixture employing Wurster airsuspension coating technique. The coat thicknesses were manipulated by controlling the increased weight of coated granules. The relationship between the coating weight and the release rate of chlorpheniramine maleate from granules was evaluated and appears to conform to exponential function. The kinetics of release was also found to be first-order. The sustained-release dosage form with the desired release pattern then can be formulated based on this relationship.

One of the successful developments in pharmaceutical technology is the production of sustained-release dosage forms. This increased awareness of the potentials of oral sustained-release products has not only led to the development of additional techniques for providing the desired effects, but also has attracted the attention of investigators who have developed new materials for drug sustainment. It is possible to obtain the time release of a drug by embedding in, or coating the drug granules with dissolution retarding materials.

Prior to 1956, coating was performed by means of the classical rotating pan method, but in that year Spaulding (1) introduced a controlled spray technique for application of the coating solution to the pan contents known as the rotating

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pan-spray technique. The original work that developed the air suspension technique has been reported by Wurster (2,3). The process later has been utilized to control drug release from coated particles (4-6).

The coating material may be soluble or insoluble in the fluids of the digestive system. In the case of soluble coating materials, the dosage form may include a variety of granules or cores having different coat thicknesses. The release rate in such a system may be governed by the dissolution or diffusion mechanism or both. However, with insoluble coating materials, the ralease process will be controlled solely by the diffusion through the coat. These considerations are applicable on condition that the process is not controlled by drug dissolution rate and the rate-limiting process is penetration of the coating layer. The hydrophobic polymer, ethylcellulose, is accepted as a non-toxic pharmaceutical agent, having proved to be useful as a binder in tableting. It is insoluble in water and digestive fluids (7). Glyceryl monostearate, which is a water insoluble wax, is also widely used as a thickening and emulsifying agent for ointments.

The aim of the present work is to study on the preparation of sustained-release chlorpheniramine maleate granules, coated with ethylcellulose-glyceryl-monostearate mixture by means of the air-suspension coating technique. The kinetics of release from such granules is to be investigated as well as the relationship between the coating weight and the release rate.

Experimental

Materials : Chlorpheniramine maleate used in this study was obtained from May and Baker, Dagenham, England. Lactose and starch used in preparation of granules were from DMV, Veghel, Holland. Hydrochloric acid used in the preparation of dissolution medium was from Mallinckrodt, Missouri, U.S.A. Ethylcellulose, BDH Chemicals, Poole, England. Glycerylmonostearate, Nippon and Fats, Japan. Chloroform used as the solvent for coating solution was from Fisher Scientific, New Jersey, U.S.A. All of the materials were B.P., U.S.P., or reagent grade.

Granulation : Granules were prepared containing 4.07% w/w of Chlorpheniramine maleate. The fractions of the drug and lactose (diluent) passing through a 60-mesh sieve were used, and were wet-granulated using 10% w/w starch paste as a binder in planetary mixer (Kenwood). The granule composition is presented in Table I. The dough mass was passed through 14-mesh sieve and the granules were

Table I Composition of Chlorpheniramine Maleate Granules

Chlorpheniramine maleate	20.3	g
Lactose	467.8	g
Starch (10% w/w paste)	11.9	g

oven-dried at 50°C for 8 hours. The dried granules were then classified using 16/20 mesh sieves (Ro-Tap Testing Sieve Shaker) to remove aggregates and fine particles, and used in the coating experiments.

Coating Experiments : The 16/20 mesh size granules were coated by using air-suspension coating machine (Aeromatic AG Model STREA-1). Some modifications were made on this machine in order to get a systematic fluidization effect by adding a stainless steel cylinder with a diameter of 8 cm and 11 cm in length at the center of the settling chamber, and a central-holed 18-mesh sieve with the hole diameter of 3 cm at the bottom of the chamber. The general construction of the apparatus is shown in Fig. 1.

Batches of 200 g of the granules were coated in each experiment with the coating solution containing ethylcellulose and glycerylmonostearate in the ratio of 6 : 2 by weight in chloroform. The granules were fluidized in the chamber until the temperature in the coating region of the apparatus reached 50°C after which spraying was operated. The pressure at which satisfactory fluidization occurred was 6 units (Aeromatic AG). Coating solution was pumped through a squeezing pump (Aeromatic AG) at a flow rate of 8 ml./min. to the spray nozzle, which was operated at a spray pressure of 5 psi. 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, the granules were fluidized for a further 10 min. to ensure complete removal of chloroform and drying. The amount of coat was evaluated by the increased weight of coated granules. It should be borne in mind that the optimal conditions defined for the apparatus described will differ in air-suspension coaters of other dimensions and designs.

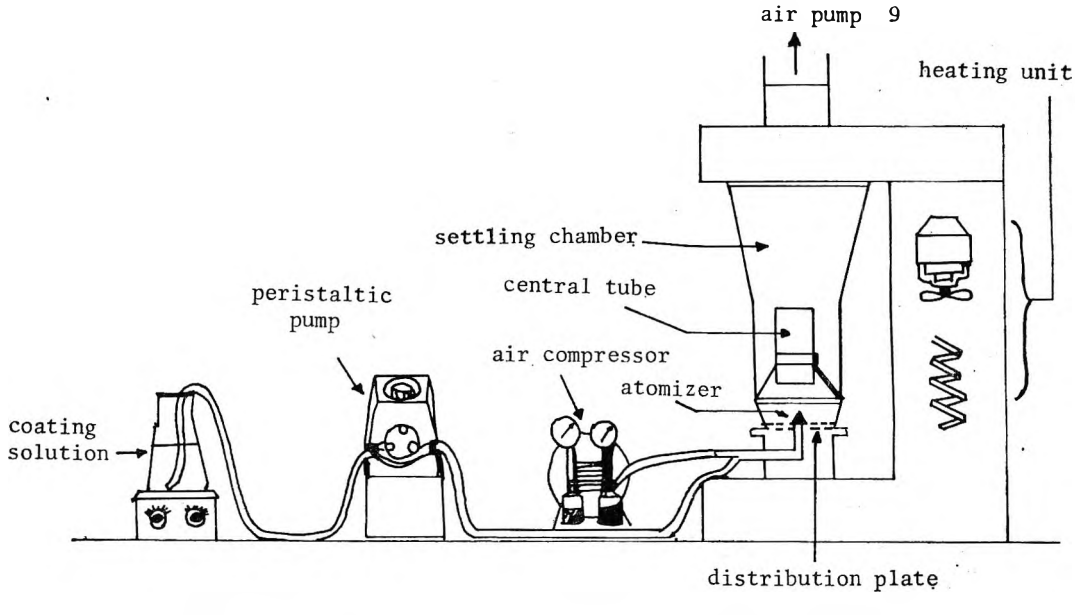


Figure 1. General construction of the coating apparatus.

Release Rate Studies : A USP XIX dissolution test apparatus method I (Hanson Research) was used to examine the release patterns of each core and coated granule preparation. A quantity of granules containing 30 mg of chlorpheniramine maleate was placed in the basket and immersed in 900 ml. of 0.1N HCl at 37°C, with the basket rotating at 100 rpm. Sample of 10 ml. was withdrawn every 15 min. for the first half an hour, and every 30 min. thereafter. Sample replacement was made with 10 ml. of 0.1N HCl to maintain a constant volume.

After appropriate dilutions had been made, samples were read at 265 nm. using a UV-grating spectrophotometer (Pye-Unicam). Data obtained from wavelength scanning of each ingredient in 0.1N HCl showed no interference of excipients at the wavelength used.

Results and Discussion

The cumulative percents released of chlorpheniramine maleate at each time interval from uncoated and coated granules with various percentages of coat are tabulated in Table II and shown in Fig. 2. It clearly shows that granules coated with higher amount of coat exhibited more prolonged release property than those coated with lower amount. The uncoated granules required only about 5 min. to release 90% of the dose in vitro. Coated granules comprising 9.5% of the coat to the total weight of the granule resulted in a $t_{50\%}$ of 30 min. Increasing the coat to 20.9% total granule weight further increased the $t_{50\%}$ to about 4 hr. For 29.2% and 33.6% coat, the $t_{50\%}$ absolutely exceeded 10 hr.

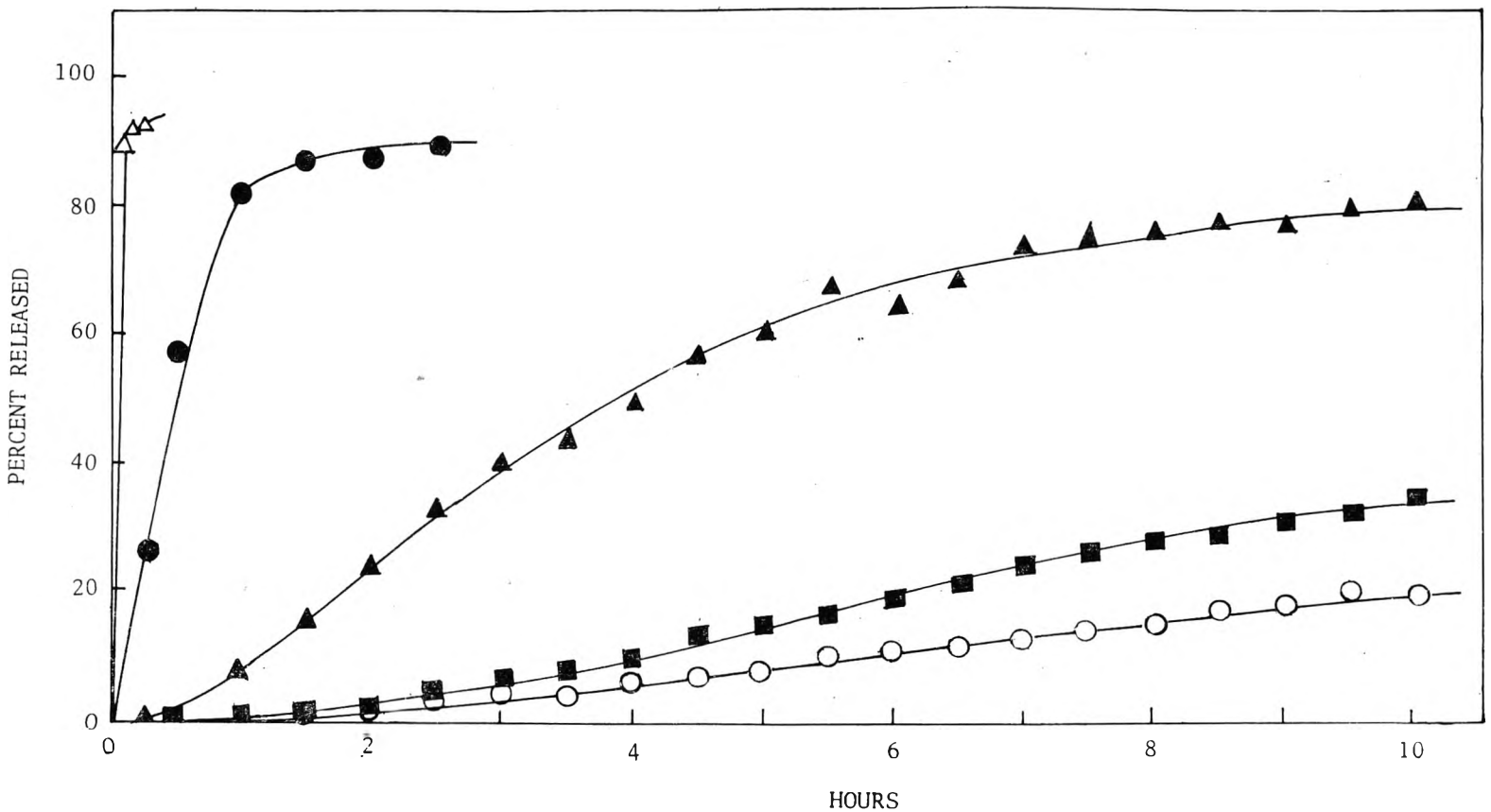
During dissolution, the coated granules remained essentially intact after several hours of exposure to the dissolution medium in the rotating basket and did not disintegrate. Drug was presumably released by passive diffusion from a relatively unchanging surface. The dissolution of granules coated with ethylcellulose film and releasing their soluble components by diffusive mechanisms has been treated by first-order kinetics (8,9). The coated granules prepared for this study could also be characterized by a typical first-order release model as seen in Fig. 3. The release rate constants and the corresponding half-lives at various percentages of coat presented in Table III were calculated from slopes of the lines in Fig. 3. The effect of increasing the amount of the coat was to reduce the apparent first-order release rate constant. Linearity was found up to 10 hr. under these conditions.

Correlation for the semilog plots of undissolved drug against time over the first 10 hr. was relatively high ($r = 0.905 - 0.996$). The regression lines were not constrained to pass through the point 100% remaining at t_0. The extrapolated t value found for the initial concentration within the granule was considered to be a

Table II Release of Chlorpheniramine Maleate in 0.1N HCl from Granules Coated at Various Percents Weight by-Weight of Coat

Time	Cumulative Percent Released				
(min.)	Uncoat	9.5% Coat	20.9% Coat	29.2% Coat	33.6% Coat
5	89.3	–	–	–	–
10	92.3	–	–	–	–
15	92.7	27.0	0.7	0.3	0.3
30	–	57.3	1.7	0.7	0.7
60	–	82.0	8.3	1.3	0.7
90	–	87.3	16.7	2.0	1.3
120	–	87.3	24.7	2.0	2.0
150	–	89.0	33.7	4.0	3.7
180	–	–	40.0	6.7	4.7
210	–	–	43.3	8.0	4.7
240	–	–	49.7	10.0	6.3
270	–	–	56.3	13.3	7.3
300	–	–	60.0	15.0	8.0
330	–	–	66.7	16.7	10.0
360	–	–	64.3	19.3	11.7
390	–	–	68.0	21.0	11.7
420	–	–	73.3	24.3	12.3
450	–	–	74.0	25.7	14.3
480	–	–	75.3	28.0	15.3
510	–	–	77.0	28.3	17.0
540	–	–	76.7	30.7	18.0
570	–	–	79.3	32.7	20.7
600	–	–	80.7	34.7	20.3

Figure 2. Release of chlorpheniramine maleate in 0.1N HCl from a series of coated granules. Key: △, uncoated; ● ,9.5% coated; ▲, 20.9% coated; ■ 29.2% coated; and ○ , 33.6% coated granules.



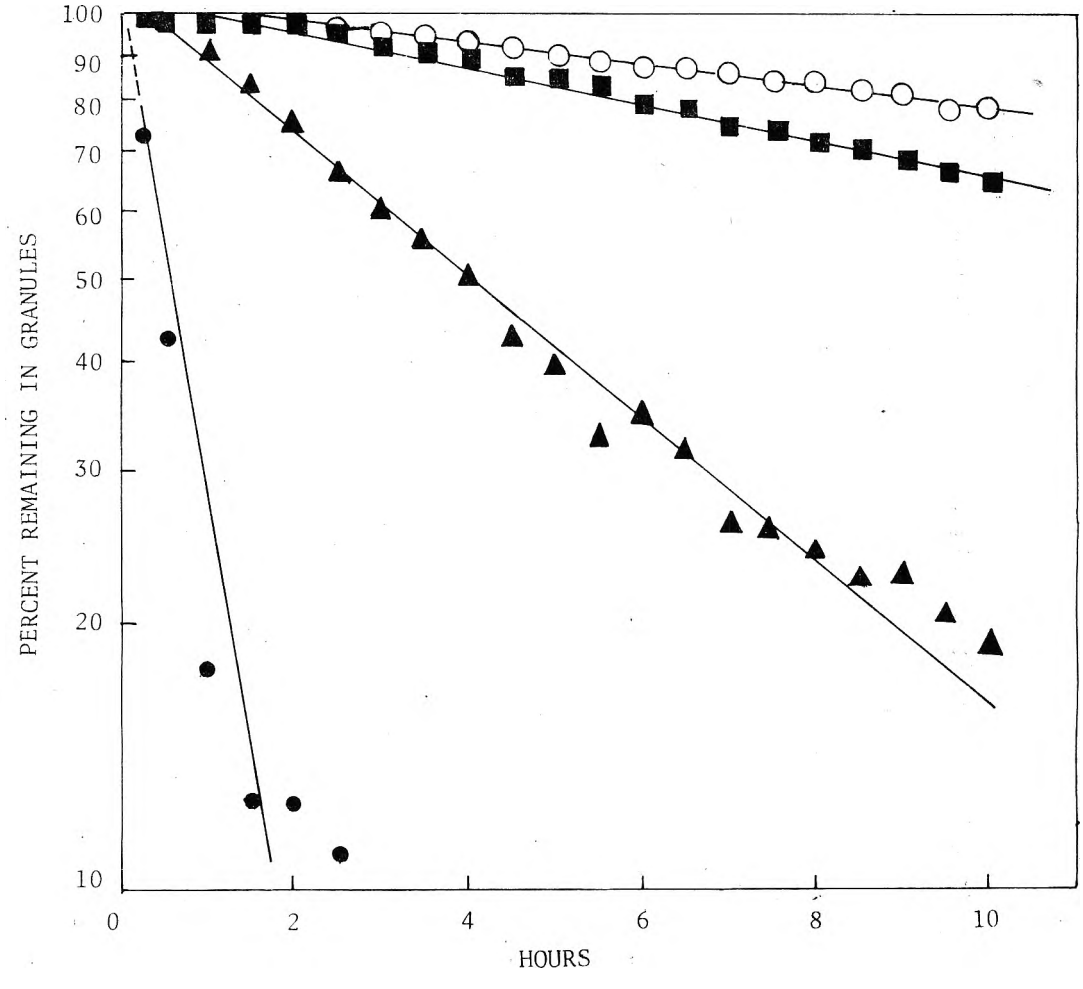


Figure 3. Typical first-order plots of undissolved chlorpheniramine maleate against time. Key: ●, 9.5% coated: ▲, 20.9% coated; ■, 29.2% coated; and ○, 33.6% coated granules.

Table III Release Rate Constants and Corresponding Half-Lives of Chlorpheniramine Maleate from Coated Granules at Various percent Coated

% Coat w/w	k_r^1 (min.$^{-1}$)	$t_{1/2}$ (hr.)	Coeff. of Correlation
9.5	1.34×10^{-2}	0.86	-0.905
20.9	2.95×10^{-3}	3.92	-0.993
29.2	7.60×10^{-4}	15.19	-0.990
33.6	4.00×10^{-4}	28.86	-0.990

measure of the penetration time, i.e., the time required for the dissolution medium (0.1N HCl) to penetrate the coat and to initiate drug release. Thicker films in general led to longer penetration times; therefore, $t_{50\%}$, the time required to release half of the granule content, was equal to the sum of the calculated half-life and the penetration time.

According to Table III, there was a rank inverse relationship between weight of film coating and release rate constant. This relationship is shown graphically in Fig. 4 and may be represented by the following empirical function using regression

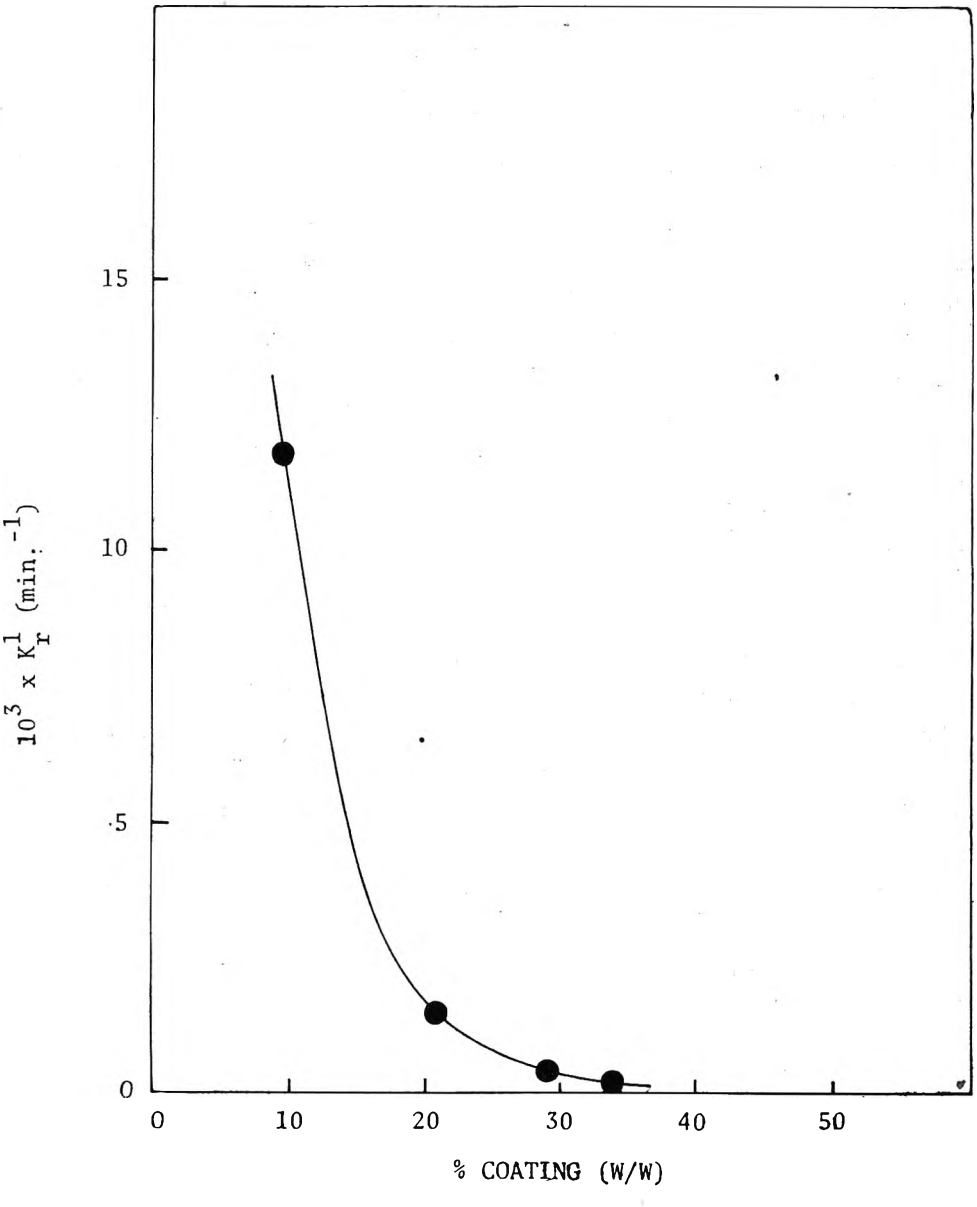


Figure 4. Relationship of % coating weight to the release rate constant, k_r^1, under specified conditions.

$$k_r^1 = 0.0569\ e^{-0.1467\,x}$$

analysis where k_r^1 and x are the release rate constant and weight of coating in percent respectively. The coefficient of determination for this correlation is 0.998. This suggests the highly retarding quality of this mixed coating materials as also evident in Fig. 2.

Conclusion

Generally in formulating the sustained-release dosage forms, it is necessary to know the release pattern of the drug from the delivery systems. In this case k_r^1 appears to be the fundamental parameters governing the release pattern of the drug. In practice the weight of coating may be accurately controlled by monitoring the coating conditions and time. Therefore, this above relationship will provide a valuable tool as a guideline in formulating and developing sustained release product with desired release pattern.

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