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ANALYSIS AND SIMULATION OF CAPSULE DISSOLUTION PROBLEM ENCOUNTERED DURING PRODUCT SCALE-UP

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ABSTRACT

An *in vitro* capsule dissolution rate problem was encountered during scale-up of cefadroxil monohydrate, a water-soluble drug product. Initial formulation development had been carried out on a Zanasi LZ-64 with a blend containing 1.0% magnesium stearate lubricant. Scale-up capsules manufactured using a Hoflinger-Karg model GFK-1500 (H&K) showed a significantly slower dissolution rate when compared to those produced on a Zanasi LZ-64. Analysis of the problem indicated that during encapsulation on the H&K capsule machine, powder was being sheared resulting in slower *in vitro* capsule dissolution rate.

Shear simulation studies were conducted to select the level of magnesium stearate for encapsulation on the H&K which would maintain a satisfactory *in vitro* capsule dissolution rate. A 0.3% level of magnesium stearate was selected on the basis of the simulation studies. At this lubricant level, capsules have been routinely produced on the H&K with satisfactory dissolution and encapsulation characteristics.

INTRODUCTION

Lubricants are often included in tablet and capsule formulations to assist in the manufacturability of such products. Occasionally, the presence of lubricants leads to problems. During blending of lubricant-containing powder mixtures, the lubricants form a thin film around the substrate particles.[1] Magnesium stearate is well known to be a hydrophobic material, and the film of magnesium stearate formed around the substrate particles may decrease the wettability of the resulting powders and retard dissolution.[1,2]

Several automatic capsule filling machines (e.g., Zanasi, Martelli, Hoflinger & Karg, etc.) have found wide use in pharmaceutical production. These machines utilize different filling mechanisms[3] which can have a profound effect on the resulting capsule characteristics. This situation may have additional significance for multi-national pharmaceutical companies, since different type of encapsulation equipment may be utilized at different production sites.

A capsule dissolution problem was encountered with a product which was developed using a Zanasi LZ-64 and scaled-up on a Hoflinger & Karg (H&K) model GFK-1500 capsule filler. Cefadroxil monohydrate, a freely water soluble drug with good powder flow characteristics was formulated into a 500 mg capsule with the addition of only a lubricant, magnesium stearate. During the process development stage, blending experiments were carried out using 1.0% magnesium stearate. A 10 Kg lot of this formula was blended for up to 40 minutes in a V-blender. Samples from this blend were withdrawn at different blending time intervals and encapsulated on the Zanasi LZ-64. The resulting capsules showed satisfactory dissolution. Based on the experimental results, a

15 minute blending process was recommended with a dissolution specification of Q75% in 45 minutes for this product.

A scale-up batch of 570 Kg was manufactured using production equipment. The formulation was blended in a V-blender for 15 minutes and encapsulated on the H&K capsule filler. The capsules resulting from this trial did not meet the proposed dissolution specification. Since it is well known that overblending with magnesium stearate can lead to a slower dissolution rate[1,4], a second scale-up lot was prepared in which blending time was reduced from 15 minutes to 5 minutes. The capsules produced from this trial did not show any significant improvement in the capsule dissolution rate. Thus, overblending was not a major factor in reducing the dissolution rate. Therefore, further investigation of the relationship between slower capsule dissolution and the scale-up process was needed. This report summarizes the investigations that led to the resolution of this dissolution problem.

EXPERIMENTAL SECTION

Dissolution testing was performed using USP Apparatus I (Basket Method) at 100 RPM in Purified water, USP (900 mL at 37°C). An automated Hanson Dissograph was used in-line with a Beckman UV spectrophotometer set at wavelength of 229nm, a Hewlett Packard 9815A computer, and a Hewlett Packard HP-987A printer/plotter to calculate and plot the data.

Samples of the formulation were compared for dissolution characteristics before and after encapsulation on the H&K and Zanasi. Samples prior to encapsulation were obtained from experimental and scale-up blends. Powder samples after encapsulation were obtained by emptying 100 filled capsules. The contents of these capsules were hand screened through a 40 mesh screen (to

remove any lumps) and blended for 2 minutes at 30 RPM in a rotary bottle blender.

A laboratory model high speed grinder/blender (model BK106 supplied by Laboratory Supply Co. Inc. of Hicksville, N.Y. 11801) was used to simulate the powder shear experienced during encapsulation on H&K. A rheostat was used at setting of 70 to slow the blender speed to impart shear while avoiding grinding of the drug particles. A 40 g sample was used for each shearing experiment. Before shearing, drug was blended with magnesium stearate for 15 minutes in a rotary bottle blender at 30 RPM. A single lot of magnesium stearate was used in preparing these blends. The resulting blends were sheared in the high speed grinder/blender for a specified time. This set-up was used to investigate the effect of shear and magnesium stearate level on capsule dissolution. The blends for the capsule dissolution study were encapsulated by manually tamping the capsule body into the desired blend to obtain a fill weight within ± 3% of the target fill weight.

RESULTS AND DISCUSSION

Figure 1 shows the dissolution characteristics of the scale-up lot which was blended for 5 minutes and encapsulated on the H&K (C) along with the dissolution of two experimental lots which were blended for 5 (A) and 40 minutes (B) respectively, and encapsulated on the Zanasi. The dissolution rate for the scale-up lot was significantly slower than the experimental lot blended for 5 minutes and encapsulated on the Zanasi. Furthermore, the dissolution of the 5 minute blended, H&K encapsulated scale-up lot was slower than the 40 minute blended experimental lot which was encapsulated on the Zanasi. This indicated that the dissolution problem encountered during the scale-up was not due to blending time but may be related to the difference between the two machine encapsulation processes.

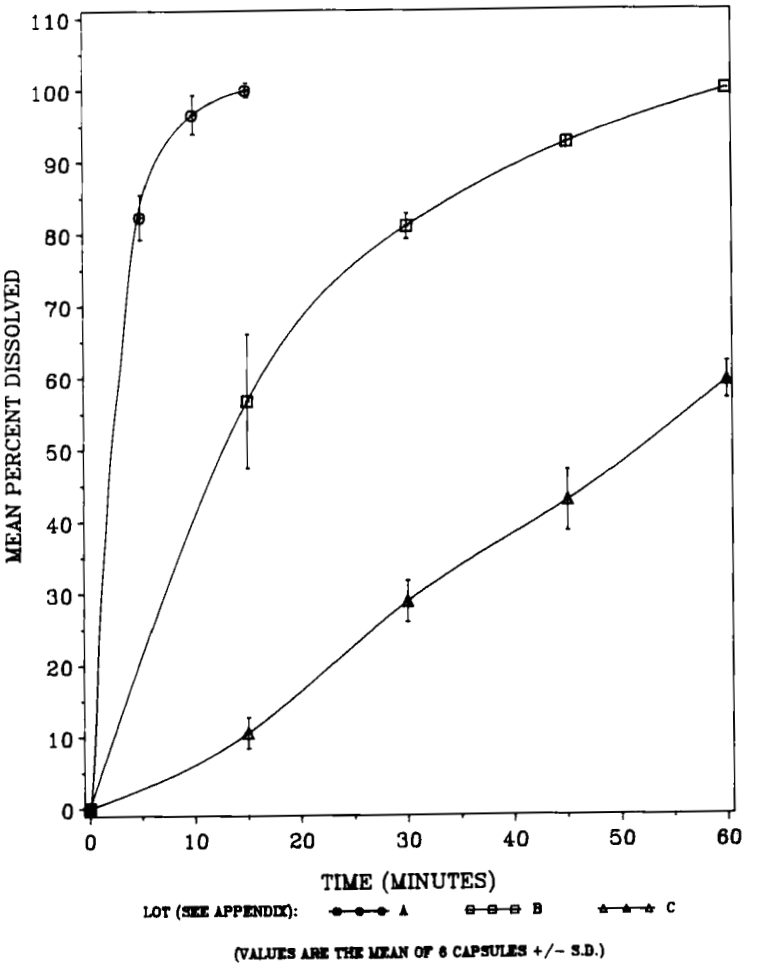

FIGURE 1

EFFECT OF BLENDING TIME AND ENCAPSULATION MECHANISM ON CAPSULE DISSOLUTION

In order to analyze this observation, a processing technique had to be developed which would be independent of the capsule machines (H&K and Zanasi), but could reflect the inherent dissolution characteristics of the powders. A manual encapsulation technique as described

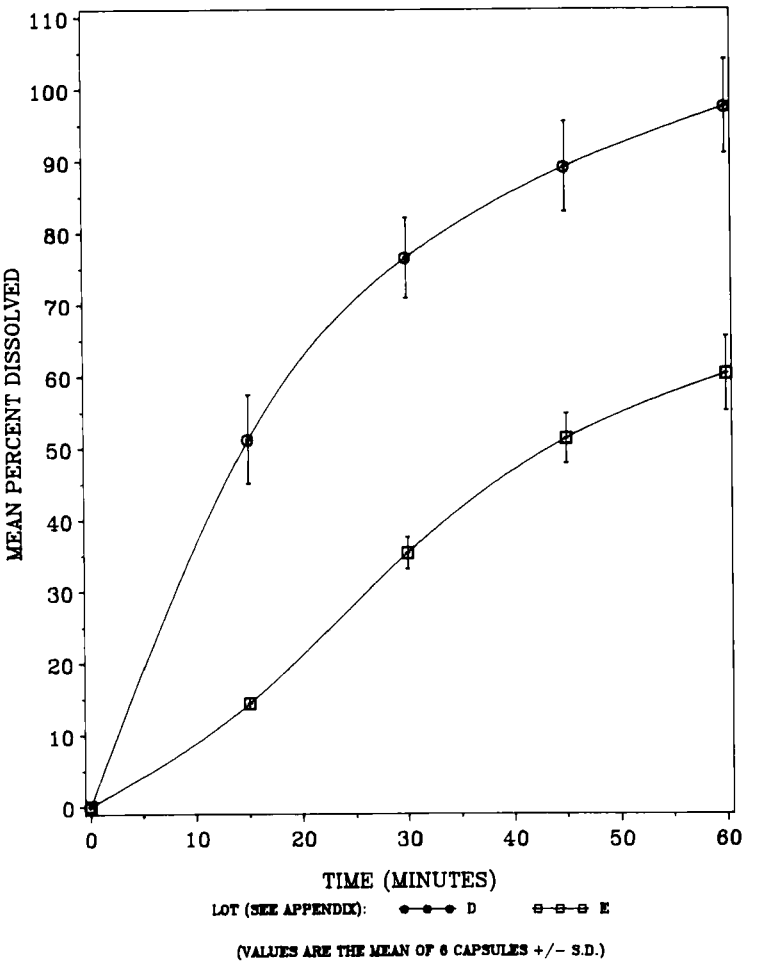

FIGURE 2

EFFECT OF HAND RE-ENCAPSULATION ON CAPSULE DISSOLUTION

under the experimental section was evaluated for this purpose. Figure 2 shows the dissolution of the hand-filled capsules prepared from the powder recovered from the H&K and Zanasi-filled capsules used in Figure 1. The dissolution profiles for the hand re-encapsulated

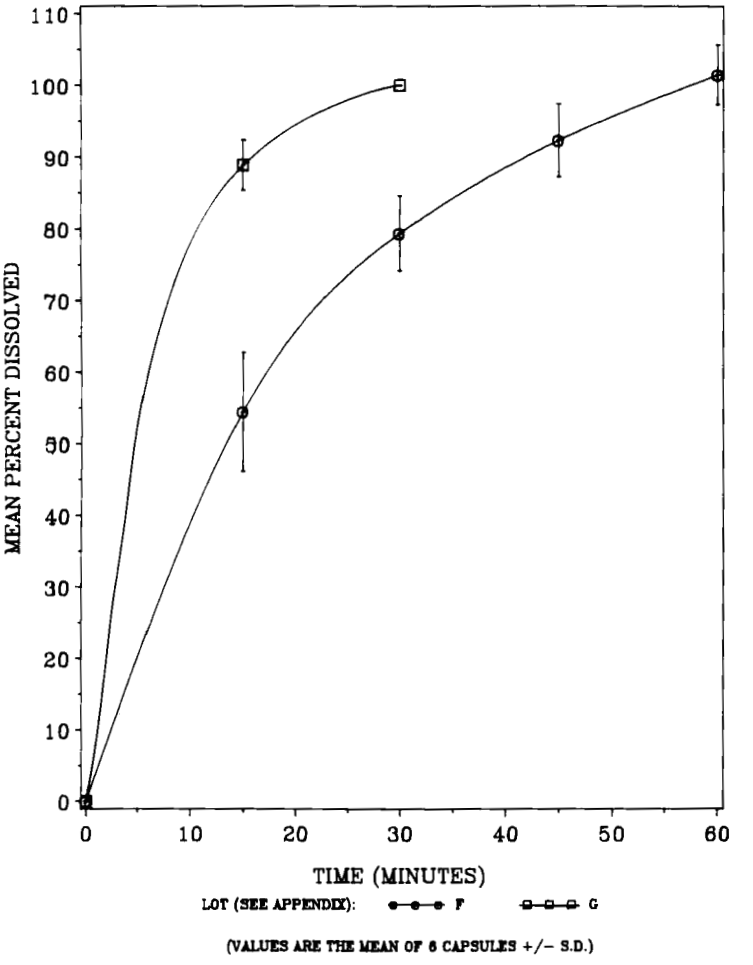

FIGURE 3

DISSOLUTION OF HAND FILLED CAPSULES PREPARED FROM POWDER PRIOR TO MACHINE ENCAPSULATION

capsules were similar to those of the original capsules from each respective machine. These data indicated that the manual encapsulation technique satisfactorily reflected the inherent dissolution characteristics of the powder blends.

Figure 3 shows the dissolution characteristics of the capsules which were hand-filled using virgin powder blends (i.e., blends which had not been machine encapsulated). A comparison of the data presented in Figures 3 and 1 (i.e., G *vs* C) indicates that a drastic change occurred in the H&K encapsulated blend dissolution characteristics. The Zanasi encapsulated blend, on the other hand, remained unchanged. This implicated the H&K encapsulation mechanism as contributory cause of the slower *in vitro* dissolution observed with the scale-up lots.

The H&K model GFK-1500 capsule machine delivers the powder from the feed hopper onto the dosing disk by means of a vertical auger (approx. 45 cm long). The powder falls into cavities in the dosing disk and is successively forced by five sets of tamping pins to form cylindrical plugs. These plugs are then inserted into the capsule bodies and the bodies rejoined with the caps. With this filling mechanism, it is reasonable to suspect that powder shearing on the H&K could occur during auger feeding and/or powder tamping.

Figure 4 shows similar dissolution profiles for the capsules produced from the before (H) and after (I) auger-feeding powders, but significantly slower dissolution for the capsules produced by the tamping mechanism (J). These data suggest that the dissolution change occurred during the tamping step of the encapsulation process and not during auger feeding.

During encapsulation of this formulation on the H&K, it was observed that plugs would not easily form. During each tamping, part of the powder would squeeze through the narrow clearance between the wall of the tamping pin and the wall of the dosing disk cavity and thus be sheared in the process. This repeated shearing, redepositing, and mixing with the virgin powder eventually results in a powder which is significantly different in

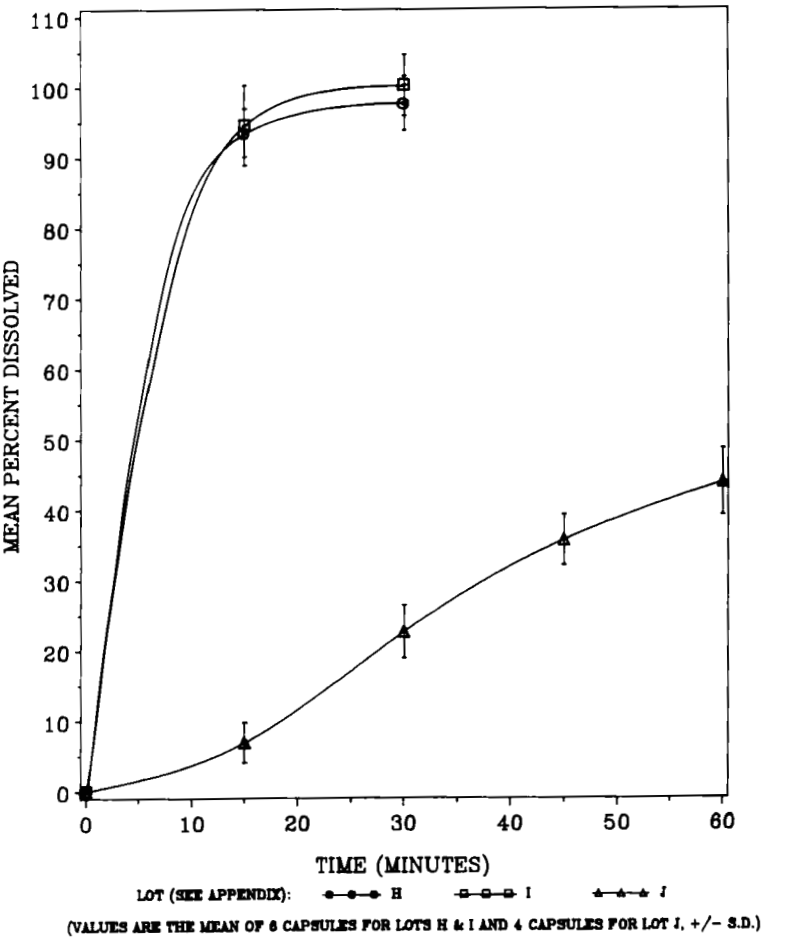

FIGURE 4

EFFECT OF AUGER FEEDING AND POWDER TAMPING ON THE DISSOLUTION OF CAPSULES PREPARED BY ENCAPSULATION ON AN H&K MACHINE

wetting properties from the original blend. This shearing results in increased coating of drug particles with magnesium stearate, thereby making the drug particles more hydrophobic and retarding the dissolution rate.

The Zanasi LZ-64, on the other hand, fills capsules by dipping the dosator into a powder bed and compacting

the powder bed into a cylindrical plug. In this case, the clearance between the dosator tube and compaction pin does not allow the powder to be squeezed out and sheared in the encapsulation process. As a result the blend encapsulated on the Zanasi dissolved readily before and after encapsulation (see Figures 1 and 3, B vs F).

While it is not possible to eliminate powder shearing on the H&K, it can be reduced by proper adjustment of the pin settings. Because sufficient pin pressure must be applied to obtain the target fill weight, however, a formulation not overly sensitive to the effect of shearing is desirable. In the present case, it was decided that the magnesium stearate level should be reduced such that the capsules could be produced with satisfactory dissolution (Q75% in 45 minutes) under normal shear conditions that may occur on the H&K. Titration of the magnesium stearate level on the H&K was considered uneconomical and time consuming. Small scale laboratory experiments using a high speed grinder/blender were therefore designed to simulate the shearing that occurs with this formulation when encapsulated on the H&K machine.

Table 1 shows the effect of simulated shearing on the dissolution of the formulation containing 1.0% magnesium stearate. These data show that the dissolution of this formulation in the presence of 1.0% magnesium stearate is very sensitive to the shear applied by the simulation system. The dissolution data from the H&K scale-up lot C (Figure 1), indicated similar dissolution behavior for the blend subjected to 30 seconds of shearing.

Laboratory blends of the formulation were prepared containing 0.1%, 0.3%, 0.6%, and 1.0% magnesium stearate. These blends were sheared for 30 seconds in the simulated shear system. The powders before and after shearing were

TABLE 1

Effect of Simulated Powder Shearing on Capsule Dissolution* For Formulation Containing 1% Magnesium Stearate

Dissolution Time Interval (min.)	Percent Drug Dissolved for Applied Shear (sec.)		
	15	30	60
15	54.2	12.9	6.3
30	83.6	30.3	18.3
45	96.1	43.7	28.6
60	101.5	54.7	38.0

*Each value average of two capsules.

hand encapsulated and dissolution tests performed. Figure 5 shows the dissolution of the capsules before blend shearing, while Figure 6 shows the dissolution after blend shearing. In the absence of shear, the amount of magnesium stearate present in the formulation was not critical in controlling the dissolution rate of this formulation (see Figure 5). Conversely, in the presence of shear, the amount of magnesium stearate had a major impact on the dissolution rate (Figure 6). These data indicated that a formulation containing 0.6% magnesium stearate should meet the proposed dissolution specifications of Q75% in 45 minutes when encapsulated on the H&K capsule machine.

In order to provide a workable formulation for production use on the H&K machine with sufficient margin of safety for dissolution, 0.3% magnesium stearate was selected. Two new scale-up lots were prepared using this level of magnesium stearate. These lots were blended in

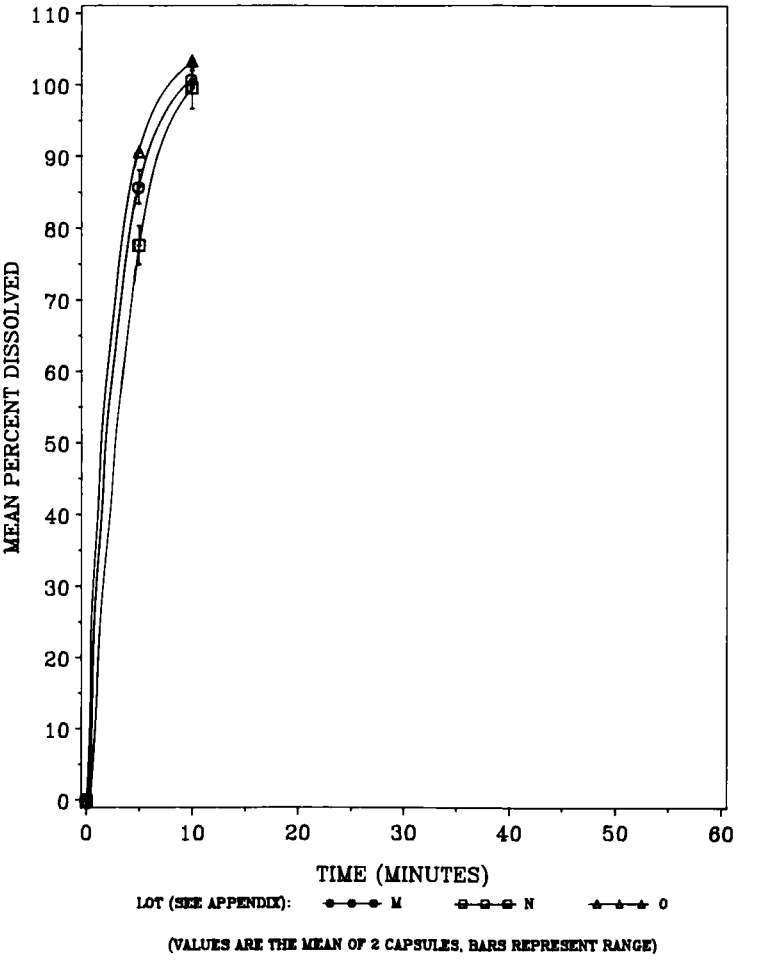

FIGURE 5

EFFECT OF DIFFERENT LEVELS OF MAGNESIUM STEARATE ON CAPSULE DISSOLUTION PRIOR TO EXPERIMENTAL SHEARING

a V-blender for 15 minutes and encapsulated on the H&K without difficulty. The first lot size was 570 Kg, the second a full production size of 1100 Kg. Figure 7 shows the satisfactory dissolution profiles for these lots. As a result, 0.3% magnesium stearate was recommended for

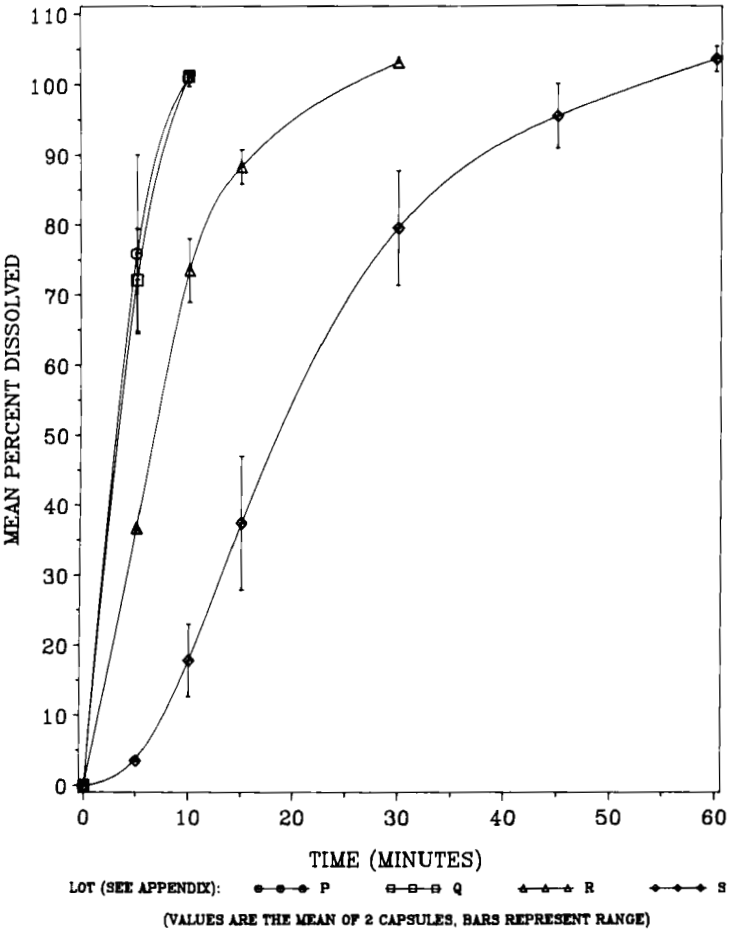

FIGURE 6

EFFECT OF EXPERIMENTAL 30 SECOND SHEARING ON DISSOLUTION OF CAPSULE FORMULATIONS CONTAINING DIFFERENT LEVELS OF MAGNESIUM STEARATE

future production runs. Numerous production lots of this product have since been prepared on the H&K machine without encapsulation or dissolution problems.

In conclusion, the mechanism of machine encapsulation can influence the in vitro dissolution character-

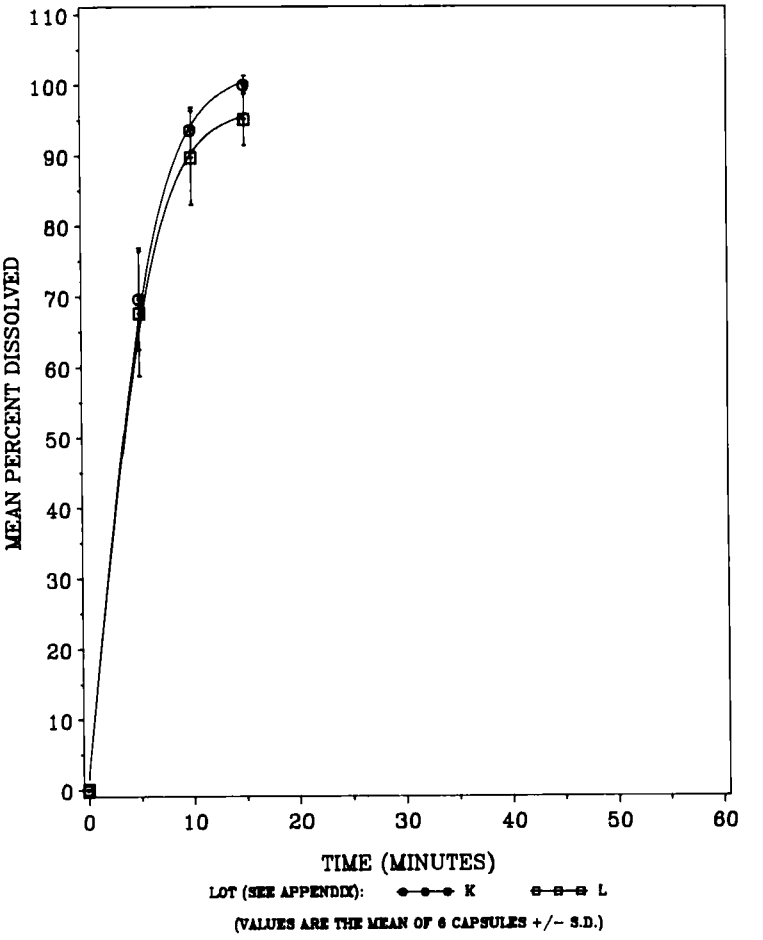

FIGURE 7

DISSOLUTION OF TWO SCALE-UP LOTS CONTAINING 0.3% OF MAGNESIUM STEARATE AND ENCAPULATED ON AN H&K MACHINE

istics of formulations. Such problems can be resolved by systematic analysis of the problem and simulation of the identified critical production equipment mechanism as illustrated in this study.

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APPENDIX

LOT #	DESCRIPTION OF THE LOTS USED IN THIS STUDY
A	Capsules prepared by encapsulating on Zanasi from experimental capsule blend which was blended for 5 minutes.
B	Capsules prepared by encapsulating on Zanasi from experimental capsule blend which was blended for 40 minutes.
C	Capsules prepared by encapsulating on H&K from scale-up capsule blend which was blended for 5 minutes.
D	Capsules prepared by hand encapsulating the powder recovered from lot B capsules.
E	Capsules prepared by hand encapsulating the powder recovered from lot C capsules.
F	Capsules prepared by hand encapsulating the capsule blend used in preparing lot B capsules, prior to any processing.
G	Capsules prepared by hand encapsulating the capsule blend used in preparing lot C capsules, prior to any processing.
H	Capsules prepared by hand encapsulating the capsules from experimental capsule blend which was blended for 15 minutes, prior to any processing.
I	Capsules prepared by hand encapsulating from capsule blend used in preparing lot H capsules, after passing through feed auger for H&K machine.

J	Capsules prepared by encapsulating on H&K from capsule blend used in preparing lot I capsules.
K	First scale-up lot containing 0.3% magnesium stearate encapsulated on the H&K machine.
L	Second scale-up lot containing 0.3% magnesium stearate encapsulated on the H&K machine.
M	Magnesium Stearate Level 0.1%
N	Magnesium Stearate Level 0.3%
O	Magnesium Stearate Level 0.6%
P	Magnesium Stearate Level 0.1%
Q	Magnesium Stearate Level 0.3%
R	Magnesium Stearate Level 0.6%
S	Magnesium Stearate Level 1.0%