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A HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF THE AMOUNT OF HYDROXYPROPYL METHYLCELLULOSE APPLIED TO TABLETS DURING AN AQUEOUS FILM COATING OPERATION

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ABSTRACT

A method for determination of the amount of polymer film coat actually applied to tablets as a result of aqueous film coating was developed using gel permeation chromatography (GPC). A styrene-based GPC column (Ultrastyragel^{R} 100A) was found to provide good separation of a commercially available polymer film coat (Opadry^{R}) from other tablet constituents. The assay method is simple, rapid and reproducible with coefficients of variation less than 2.6% in all cases. The assay is sensitive enough to discriminate between tablets containing different levels of microcrystalline cellulose (MCC) when coated simultaneously. The assay was conducted on polymer extracted from the tablets with a solution of 50/50 methanol/methylene chloride. The addition of MCC to tablet formulations was found to increase the amount of film applied, in a competitive coating operation, when all other factors were held constant.

INTRODUCTION

Aqueous film coating of tablets is gaining wide acceptance in the pharmaceutical industry due to the numerous advantages it has over organic film coating. The use of water in place of organic solvents eliminates concern about recovery costs, residual solvent in the film, and personnel safety in the work environment.[1] The literature has widely covered methods of assessing adhesion of films to tablet surfaces and the effects different tablet excipients can have on adhesion.[2,3,4,5] However, there has been little interest given to determining what tablet formulation factors affect coating efficiency as reflected by the fraction of polymer actually deposited on tablets during an aqueous film coating operation.

The most common method of estimating the amount of film coat applied to tablets is by percentage weight gain. The average percentage weight gain is determined by weighing a sample of tablets after coating to determine the net increase in weight. When the goal is to apply a film coat that is 1 to 2% of the tablet weight, the average percentage weight gain may be adequate for in-process monitoring to determine when the coating operation is complete. However, because of inherent weight variation in the cores, attrition during coating, and loss of moisture, the average percentage weight gain method is inadequate in any instance when comparisons are to be drawn between different tablet formulations coated in the same operation or even between two separate batches of coated tablets. Variation in film coat applied as a result of tablet formulation changes has been found in this study to be as small as 0.125% of total tablet weight. This difference would be impossible to detect using a gross assessment tool like average weight gain.

A small difference in the amount of film coat applied can affect the quality and performance of the dosage form. Since the amount of polymer applied is relatively small, differences of this magnitude can represent a significant change in efficiency of the coating operation that is directly related to the expense of this unit operation.

Gel permeation chromatography (GPC) has been used to characterize the molecular weight distribution of hydroxypropyl methylcellulose polymers used in tablet film coating.[6] GPC separates molecules by size exclusion and thus is uniquely suited to assay polymers of varying sizes. The particular gel permeation column selected for an assay will depend on the objective of the experiment. If characterization of the molecular weight distribution is desired, then a column which has a molecular weight range covering the expected range is the appropriate choice.

If determination of the total amount of polymer on a given tablet is the objective, then a column which separates the polymer in general from the tablet components is desirable. Commercially available coating products are mixtures of one or more grades of film forming polymer and plasticizer. In this case the choice of the column would be based on the objective of excluding from the pore volume of the column the smallest molecular weight polymer.

The objective of this study was to develop an HPLC assay for the amount of film coat applied to tablets as a result of an aqueous film coating operation. The HPLC assay method should not be affected by variation in tablet core weight and is expected to be sensitive enough to detect small differences in the amount of film coat applied. An examination of the effect of varying selected tablet constituents on the amount of

film applied during a competitive film coating operation is used to test the feasibility of the method.

EXPERIMENTAL

Materials and Equipment

Dicalcium Phosphate Dihydrate, Unmilled (Di-Tab^{R}), Stauffer Chemical Co., CT. 06881.
Magnesium Stearate N.F., Mallinckrodt Inc., MO. 63147.
Microcrystalline Cellulose N.F. (Avicel^{R}ph102), FMC Corp. PA. 19103.
Opadry^{R} YS-1-7006 concentrate, Colorcon Inc., PA. 19486.
Acetonitrile, HPLC grade, J.T. Baker Chemical Co., N.J. 08865.
Methanol, HPLC grade, J.T. Baker Chemical Co., N.J. 08865.
Methylene Chloride, HPLC grade, J.T. Baker Chemical Co., N.J. 08865.
Tetrahydrofuran (THF), HPLC grade, J.T. Baker Chemical Co., N.J. 08865.
Stokes RB-2 Rotary Tablet Press, F.J. Stoke Machine Co. PA.
P-K Twin Shell Blender, Patterson-Kelly Co. PA.
Hi-Coater Model HCT-30, Freund Industrial Co.,LTD. Japan.
Erweka TBH 28 Tablet Hardness Tester, Heusenstam Kr., West Germany.
Waters Associates Model 6000A Solvent Delivery System and Model U6K injector, Mass., 01757.
Ultrastyragel^{R} 100A GPC Column, Waters Chromatography Division, Mass. 01757.
Ultrahydrogel^{R} 500 GPC Column, Waters Chromatography Division, Mass. 01757.

Waters Associates Differential Refractometer R401 Detector, Mass. 01757.
Linear Stripchart Recorder, Linear Instruments Corp., Calif.

Tablet Manufacturing Procedure

The composition of each tablet formulation is listed in Table 1. All formulations consisted of Dicalcium phosphate as the major excipient. Microcrystalline cellulose (MCC) and magnesium stearate were added to provide formulations with varying degrees of surface hydrophilicity. The magnesium stearate is a common tablet lubricant that is known to decrease tablet wetting, while microcrystalline cellulose is a common compression aid that is known to increase the hydrophilicity of a tablet formulation.

The dicalcium phosphate and MCC were blended for 5 minutes in a V-Blender. Magnesium stearate was added and the formulation was blended for an additional 5 minutes.

The powder blend was directly compressed on a Stokes RB-2 rotary tablet press. Tablets were 0.794 cm (5/16 inch) in diameter with an average weight of 330 mg. The compression force was held constant at 1050 kg. Tablet weight variation was determined by individually weighing ten tablets. Tablet thickness was determined to within 0.00254 cm (.001 inch) and the average of 10 tablets was reported. Tablet hardness was also reported as an average of 10 tablets. Average tablet weights, thicknesses and hardnesses are reported in Table 2.

Tablet Film Coating Process

The coating operation described here is a competitive film coating operation due to the fact that all

Table 1

Percentage Composition of Tablet Formulations

Excipient	Formulation # 1	2	3	4	5	6
Dicalcium Phosphate	99	89	79	98	88	78
Microcrystalline Cellulose	0	10	20	0	10	20
Magnesium Stearate	1	1	1	2	2	2

TABLE 2

Tablet Properties

Formulation #	Tablet Weight (mg) Avg. (%RSD)	Tablet Thickness (mm) Avg. (%RSD)	Tablet Hardness (kg) Avg. (%RSD)
1	340.7 (0.562)	0.4379 (0.405)	5.70 (12.3)
2	329.7 (0.738)	0.4498 (0.320)	6.84 (7.5)
3	325.7 (0.764)	0.4577 (0.351)	9.18 (7.8)
4	340.6 (0.772)	0.4392 (0.427)	6.63 (13.8)
5	341.7 (0.844)	0.4542 (0.441)	6.97 (6.4)
6	330.5 (0.764)	0.4597 (0.368)	7.96 (6.4)

six formulations were simultaneously coated. The competitive operation is useful since it allows one to determine the relative coatability of different tablet formulations. In addition, tablets can be compared with the assurance that the coating conditions were identical for each of the formulations. Individual formulations were identified by applying a small distinguish-

ing mark to the tablet prior to coating. Tablets were coated in a laboratory size Hi-Coater^R with a total charge of 800 g, using equal weights of each formulation. The coating solution was a 5% W/W aqueous solution of Opadry^R YS-1-7006 Clear using an air pressure spray nozzle for atomization of the solution. An 8 g quantity of Opadry^R was applied by spraying 160 mL of a 5% W/W aqueous solution. This approach would yield a weight gain of 1% if the operation were 100% efficient. The following coating conditions were used for the coating operation in the Hi-Coater:

Inlet Air Temperature: 54 - 56^{o}C
Outlet Air Temperature: 31 - 33^{o}C
Coating Solution Flow Rate: 7 mL/min
Atomization Air Pressure: 1.5 kg/cm^2
Pan Speed: 15 RPM

Chromatographic Conditions

A methacrylate-based polymer GPC column (Ultrahydrogel^R 500) was used to illustrate the difference between a column which separates the hydroxypropyl methylcellulose (HPMC) according to its molecular weight distribution and a column which separates the total amount of polymer from all other tablet constituents.

An styrene-based GPC Column (Ultrastyragel^R 100A) was used to assay for the total amount of polymer present on a tablet. The mobile phase was HPLC grade Tetrahydrofuran (THF) which was delivered to the column by a reciprocating pump solvent delivery system (Waters Assoc., Milford, Mass.). The mobile phase was degassed and filtered by vacuum through a 0.45 micron membrane filter (Millipore Corp., Bedford, Ma.). The flow rate

was 1 mL/min and the injection volume was 30 uL for all standard and test samples. A differential refractometer was used as the detector, which was operated at 1/2X attenuation. A stripchart recorder (Linear^R) was used to record the detector output; Peak heights were determined to the nearest 1/2 mm. The mobile phase for the Ultrahydrogel^R column was a 10% solution of acetonitrile in water. The flow rate was 0.7 ml/min, while all other conditions were as state above.

Preparation of Standard Solutions

The standard solutions were prepared by weighing individual amounts of Opadry^R concentrate to the nearest 0.1 mg and dissolving the quantity in a solution of 50/50 methanol/ methylene chloride. The resulting standard solutions were the following concentrations: 1, 2, 3, 4, 5, 6 and 8 mg/mL, respectively.

Preparation of Sample Solutions From Tablets

Coated tablets were separated on the basis of the distinguishing mark associated with each formulation. Thirty coated tablets were randomly selected from each of the six formulations for assay. Ten coated tablets were placed in a 15 mL test tube to which 5 mL of 50/50 methanol/methylene chloride solution was added to extract the coat from the tablets. The tablets were shaken in the solvent for 5 minutes and then centrifuged for 3 minutes to permit withdrawal of a particulate free sample from the solution over the tablets. After sample injections were made, the tablets were removed from the solution and placed in fresh solvent, shaken, centrifuged and assayed again to determine if

the coat was fully removed by the first washing. Uncoated tablets were washed using the same procedure as above to determine if any tablet components would interfere with the assay for the film coat.

RESULTS AND DISCUSSION

Tablet Properties

The average tablet weights, thicknesses, and hardnesses are listed in Table 2. The geometric surface area of the tablets (surface area calculated from tablet dimensions) is the most important parameter to consider when comparing the amount of coat applied to different formulations. The tablets were all the same diameter, so that a change in tablet thickness would be the only factor that would change geometric surface area. Therefore, the tablet thickness was considered the most important parameter to hold constant throughout the manufacturing of the tablets. Tablet thickness varied by no more than 5% between formulations, such that the maximum difference in geometric surface area was 2.6%.

Assay Method

The use of Gel Permeation chromatography allows one to accurately assay for compounds that have a range of molecular weights and sizes, such as hydroxypropyl methylcellulose (HPMC). The use of standard chromatographic techniques such as normal phase and reverse phase are not useful in this case due to the size and distribution of the molecules of HPMC.[7] GPC separates compounds by size exclusion based on the size of the pores in the column. The Ultrahydrogel^{R} 500 column has

a pore size range which is suitable for characterization of the molecular weight distribution of HPMC. Figure 1A shows a chromatogram from a sample of Opadry^R (5 mg/mL) using the Ultrahydrogel^R 500 column, which illustrates the varying range of sizes of HPMC in Opadry^R. This broad chromatogram could be used to qualitatively compare different lots of OpadryR, but it is not accurately and reproducibly integrated when the total amount of polymer present in the sample is small.

The hypothesis tested here is that a column should be selected such that the pore size is smaller than the polymer, if determination of the total amount of polymer present is the objective. In this case all of the polymer is excluded from the pore volume of the column and the total amount elutes at the exclusion volume. Such is the case when the Ultrastyragel^R 100A column is used for Opadry^R samples, as illustrated in Figure 1B where a well defined peak appears after 4 minutes. There is evidence of separation of the lower molecular weight constituents known to be present in Opadry^R, such as polyethylene glycol 400, as illustrated by the slight inflection on the ascending portion of the peak in Figure 1B.

A chromatogram representing polyethylene glycol 400 is presented in Figure 2A. The HPMC in Opadry^R is totally excluded from the pore volume of the column and elutes at the exclusion volume of the column (5 mL), as illustrated in Figure 2B, where a chromatogram for a low viscosity grade HPMC (3cps) is shown. Higher viscosity grades of HPMC would have larger molecules and hence would also elute in a similar manner. Figure 1B is actually a composite of all the polymer present in the commercial product Opadry^R. It is recognized that the shape of the peak may vary from lot to lot of Opadry^R or any other commercially available coating

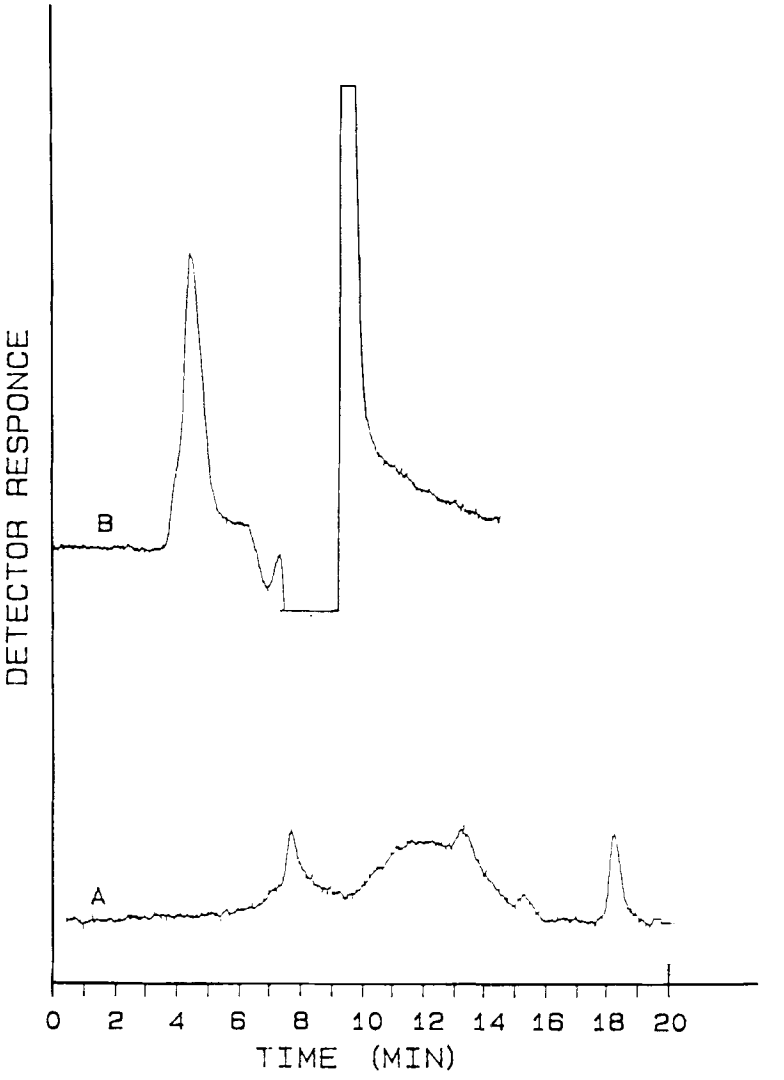

FIGURE 1

Gel Permeation Chromatography of Solutions of a Commercially Available Aqueous Film Coating Product (Opadry^{R} YS-1-7006).

(A - 10% Acetonitrile Solution, Ultrahydrogel^{R} 500 Column; B - 50/50 Methylene Chloride/Methanol Solution, Ultrastyragel^{R} 100 Column)

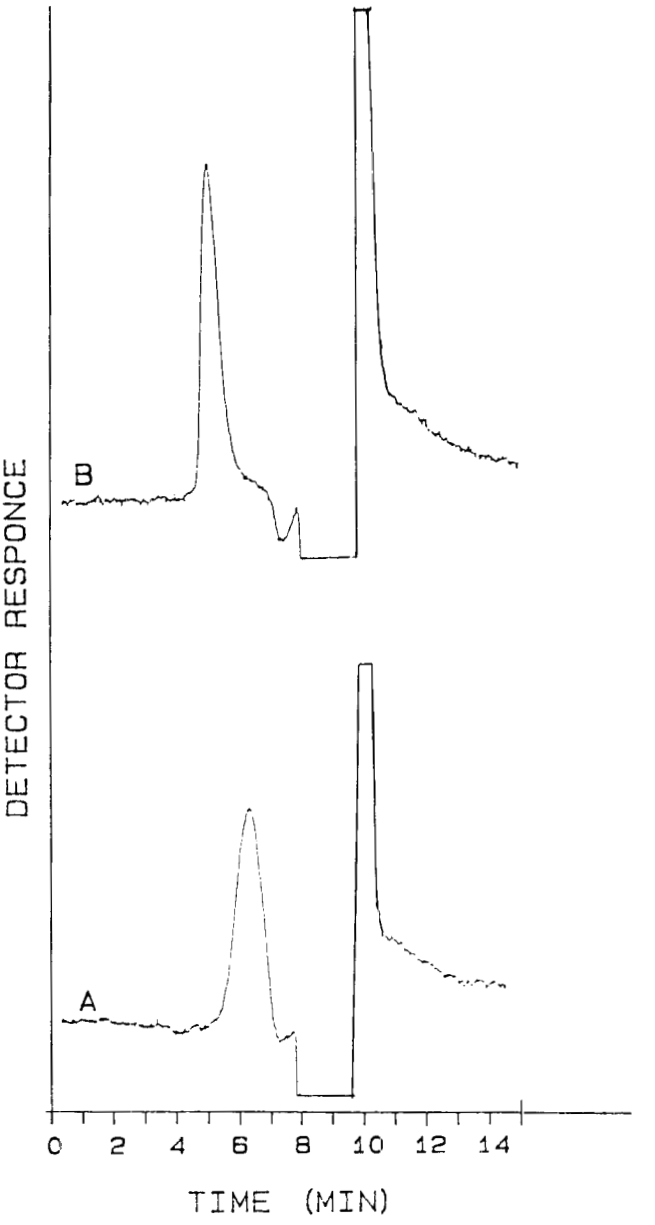

FIGURE 2

Gel Permeation Chromatography of Polyethylene Glycol 400 (A) and Hydroxypropyl Methylcellulose (B).

(50/50 Methylene Chloride/Methanol Solution, Ultrastyragel^{R}100 Column)

system whose actual composition may vary. Using this approach such variation is of little concern as long as a sample of the actual coating system is used to construct the standard curve.

The Ultrastyragel^{R} 100A column was used to assay for the total amount of polymer present and standard curves for the Opadry^{R} were prepared each day to account for possible changes in refractive index. Separate injections of seven different concentrations (1, 2, 3, 4, 5, 6 and 8 mg/mL) were made each day. High linear correlation was found for all standard curves over the range examined. The least squares regression analysis of the peak height vs. concentration gave correlation coefficients greater than 0.99 for all standard curves on all days.

The reproducibility of the assay was examined by determining the coefficient of variability (CV) of the predicted concentrations for the standard solutions run each day. The %CV was calculated as:

$$CV = \frac{100\ sd}{X}$$

where sd is the standard deviation of ten determinations of the concentration, based on the standard curve for each day, and X is the mean of the ten determinations. The results are shown in Table 3 which includes the mean, range and percent coefficient of variability.

The higher CV's for the 1 and 2 mg/mL concentrations indicate that the lower limit of the assay under the stated conditions is around 1 mg/mL. Due to the broad nature of the peaks in GPC it is difficult to accurately measure the peak height of small peaks such

TABLE 3

Assay Reproducibility

Standard Solution Concentration (mg/mL)	Mean Concentration (mg/mL)	Concentration Range (mg/mL)	% CV
1.00	0.9924	0.96 - 1.04	2.20
2.00	2.0295	1.92 - 2.09	2.62
3.00	3.0049	2.94 - 3.09	1.51
4.00	3.9850	3.95 - 4.06	0.60
5.00	5.058	4.90 - 5.21	1.27
6.00	6.016	5.98 - 6.06	0.47
8.00	8.0044	7.98 - 8.03	0.22

as those seen at 1 and 2 mg/mL. The %CV for concentrations above 2 mg/mL are within acceptable limits.

Determination of the Amount of Coat Applied to Tablets

Figure 3A shows a chromatogram of a typical coated tablet extraction, in which the peak shape and retention time are the same as the standard solutions. Figure 3B is a chromatogram of the solution obtained with an uncoated tablet using the same extraction procedure showing that there is no interference from tablet components in the assay. After extraction of the tablets a second time no Opadry^{R} was detected; these chromatograms were identical to those obtained for the uncoated tablets.

The quantity of coat on each tablet was determined by measuring the peak height for the given injection and calculating the concentration of the solution from

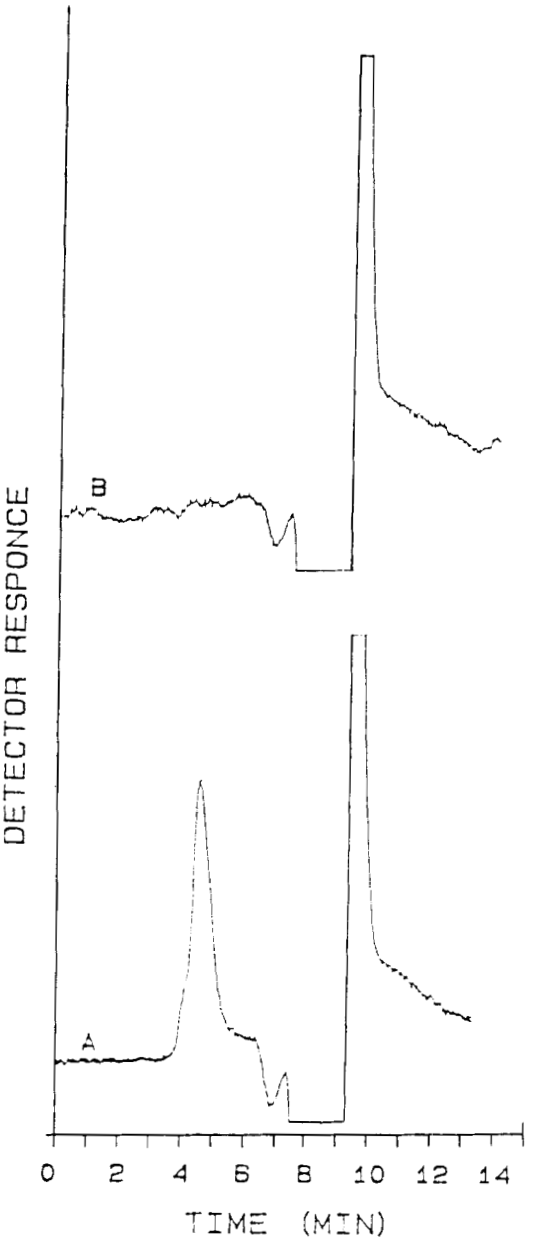

FIGURE 3

Gel Permeation Chromatography of Extractions from Coated (A) and Uncoated (B) Tablets.

(50/50 Methylene Chloride/Methanol Solution, Ultrastyragel^{R}100 Column)

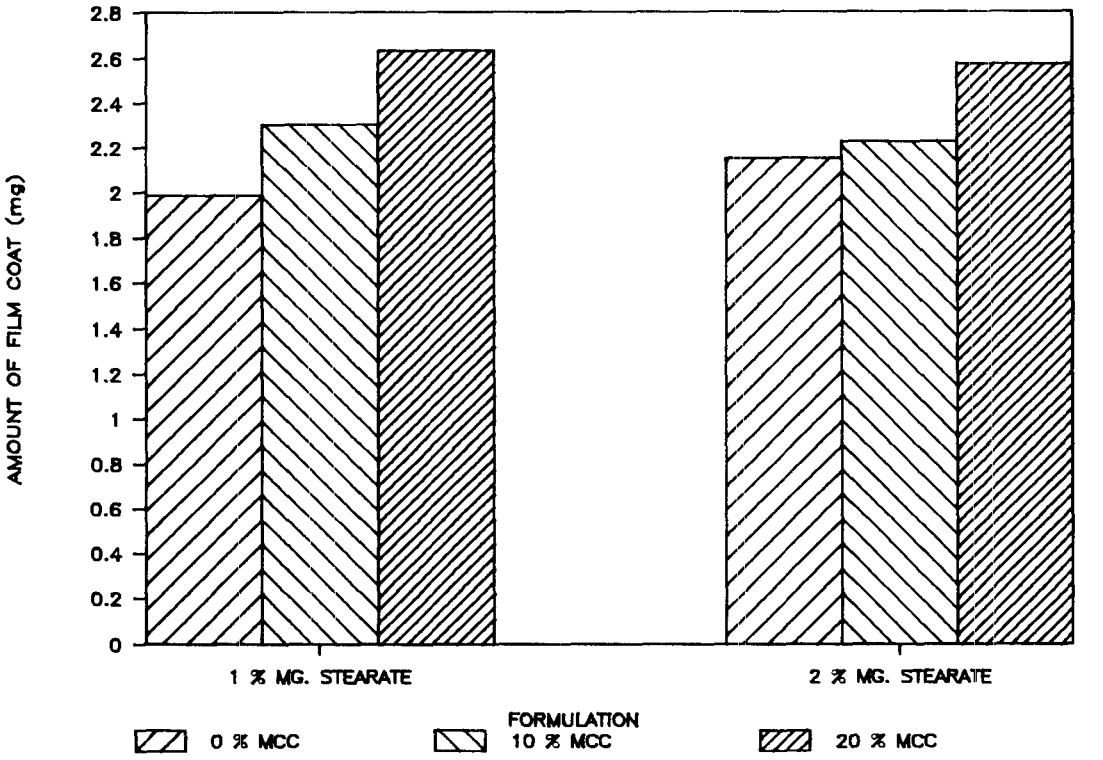

FIGURE 4

The Effect of Microcrystalline Cellulose (MCC) and Magnesium Stearate Content on the Amount of Film Coat Applied to Dicalcium Phosphate Based Tablets in a Competitive Aqueous Film Coating Operation.

the regression equation for the standard curve of the day. The total quantity of coat extracted was then divided by ten to determine the average amount of film coat on each of the tablets. Figure 4 shows that irrespective of magnesium stearate level, the average amount of film coat applied for each tablet formulation increases as the amount of MCC in the formulation increases.

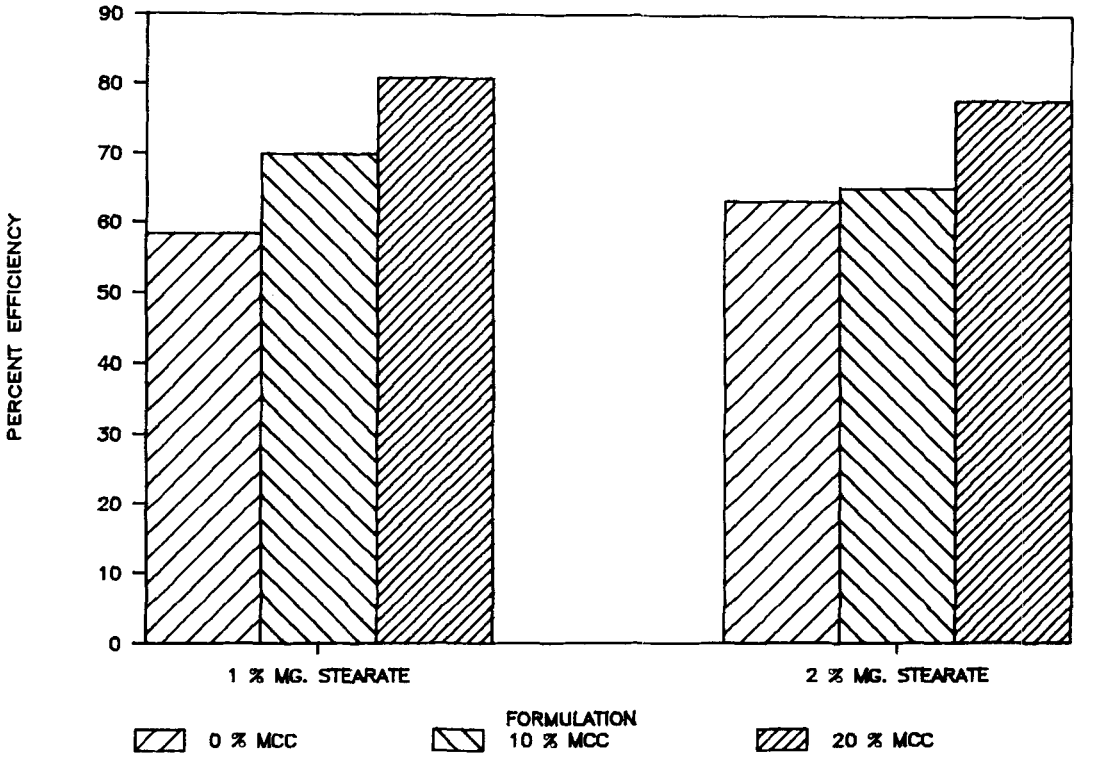

FIGURE 5

An Assessment of Coating Efficiency for Dicalcium Phosphate Based Tablets as a Function of Microcrystalline Cellulose (MCC) and Magnesium Stearate Content.

There is no significant difference in amount of film deposited when comparing the 1% and 2% magnesium stearate levels at any level of MCC. This result suggests a non-linear relationship between substrate wetting and magnesium stearate concentration. The leveling off of the lubricant effect of magnesium stearate between 1% and 2% as commonly seen in tablet lubricant experiments supports this contention.[8]

The increase in the amount of film coat applied as MCC level increases is due to an increase in surface hydrophilicity and/or changes in the effective surface area of the tablet.[9] In the competitive coating process, tablets with more MCC acquire a disproportionate amount of the polymer because of the combination of an increase in effective surface area and substrate hydrophilicity. The aqueous film coating dispersion spreads quickly on the tablet surface and the consequent increase in liquid-air interface facilitates drying.

In this study, coating efficiency was assessed from the amount of coat actually applied, determined from HPLC assay, divided by the total amount of solids in the coating solution. These results are shown in Figure 5. Coating efficiency increases with increasing levels of MCC within the 1% and 2% magnesium stearate levels as seen above. This indicates the important effect that the substrate can have on the processing time required to reach a specified end point in a coating operation. However, it is noted that an increase in efficiency does not necessarily mean there is a commensurate increase in the quality of the coat.

CONCLUSIONS

An HPLC method for the determination of the amount of film coat actually applied during a competitive film coating operation was developed. A GPC column which elutes the total amount of polymer in a short time was found to be the most useful for accurate determination of the total amount of polymer present on a film coated tablet. The HPLC assay is not affected by weight variation in the tablet cores nor by the moisture content of the tablet or the film. The method is

accurate and sensitive enough to detect differences in the amount of film coat actually applied due to differences in the tablet formulation. As such, the assay is uniquely suited for comparing different tablet formulations for film coating efficiency.

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