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Quantitative Assessment of Factors Contributing to Mottling of Colored Tablets II: Formulation Variables

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Abstract □ The effects of several formulation variables were quantified with respect to factors affecting tablet mottling. Tablet mottling occurred with several commonly used binders and could not be prevented by using highly viscous binding solutions. However, mottling was reduced initially by increasing granule strength. Tablet diluents and dye–adsorbent materials had a profound effect on mottling, not by preventing dye migration but by affecting granule fragmentation on compression and the extent to which the dye-deficient material at the center of the granule was revealed. The lake form of FD&C Blue No. 1 was found to bleed in the presence of diluents that raised the pH of the granulating fluid above 6.4. Anionic impurities in the diluents also caused leaching of free dye and, consequently, increased tablet mottling. The conclusions from this study and previous papers were drawn together to give general principles for the production of uniformly colored tablets by aqueous granulation techniques.

Keyphrases □ Mottling—surface of colored tablets, effects of several formulation variables □ Tablets, colored—effects of several formulation variables on mottling

Recently, a method for measuring the amount of color variation on the surface of a tablet (mottling) was described (1), and this method enabled a study to be made of those factors that contribute to mottling in tablets. The manner in which some manufacturing variables can be controlled to minimize mottling was discussed earlier (2), but the underlying cause of mottling, the migration of dye to the periphery of the granule during drying, cannot be avoided simply by manipulation of manufacturing techniques.

King (3) reviewed some methods by which dye migration can be reduced, but the success of the techniques has been judged subjectively. By using the quantitative method for determining tablet mottling, the relative importance of formulation factors in the control of tablet color uniformity was assessed.

EXPERIMENTAL

General Method of Tablet Preparation—The solids to be tableted were colored with 0.0333% of FD&C Blue No. 1 dye or 0.2357% of FD&C Blue No. 1 lake (equivalent to the same dye concentration) dissolved in water. Each colored powder was massed with the appropriate quantity of granulating agent and sieved through a 2.8-mm mesh screen using an oscillating granulator[1]. The wet granulate was dried for 20 min in a fluid bed drier[2] (air inlet temperature 60°) and sieved on a vibratory sieve shaker[3]. Without further comminution, the 1000–1400-μm fraction was lubricated with magnesium stearate (1%) colored with the same concentration of dye. This size fraction was selected because previous work (1) had shown that such granules gave highly mottled tablets so any changes in mottling could be more readily detected. The lubricated granules were compressed by a single-stroke tablet machine fitted with flat-faced, 12.5-mm, stainless steel punches[4]. The tablet thickness was constant (4.00 mm), and the tablet weight for each diluent is shown in Table I.

Measurements of Tablet Mottling—Full details of this technique, using a microdensitometer[5], were published previously (1).

Measurement of Granule Crushing Strength (Fig. 1)—The apparatus consisted of two concentric cylinders, and their bases were separated by a washer of 1.0 mm thickness. A single granule was mounted centrally in the washer, and the inner cylinder was placed in position. Lead shot was poured into the inner cylinder until the granule fractured or deformed and the inner cylinder made contact with the washer. This contact completed an electric bell circuit, so granule fracture was signaled audibly.

Twenty-five granules of specified dimensions were assessed from each batch to give a mean value for granule crushing strength. A control on granule size was necessary since Capes (4) showed that granule strength is dependent on granule diameter. For this reason, a relatively narrow sieve fraction was selected (2.0–2.8 mm). An additional control on granule weight was also necessary to obtain reproducible results; the granule weight fraction for granules composed of different diluents varied according to the density of the granules (Table I).

The viscosity of starch mucilages used as binding agents was determined at 25° using a rotational viscometer[6].

RESULTS AND DISCUSSION

Role of Granulating Agent in Tablet Mottling—The granulating agent has been reported to inhibit solute migration in granules by means of imbibition (5) and complexation (6) and by its effect on the viscosity of the granulating fluid (4). Furthermore, since one fundamental cause of mottling is disruption of the granular structure on compression, thereby exposing the dye-deficient

[1] Type 143A, Apex Construction Co., London, United Kingdom.
[2] Type SSE65, Apex Construction Co., London, United Kingdom.
[3] Pascall Engineering Co. Ltd., Crawley, United Kingdom.
[4] Model E2, Manesty Machines Ltd., Liverpool, United Kingdom.
[5] Joyce-Loebl microdensitometer Mark IIIS, Joyce Loebl and Co. Ltd., Gateshead, United Kingdom.
[6] Epprecht Rheomat-30, Contraves A. G., Zurich, Switzerland.

Table I—Experimental Data for Tablets of 4.0 mm Thickness and Granules Prepared from Various Tablet Diluents and Used for Crushing Strength Tests

Tablet Diluent	Density of Diluent, g/ml	Tablet Weight, mg	Tablet Porosity	Density of Granule, g/ml	Weight of One Granule, mg
Dibasic calcium phosphate	2.18	660	0.39	2.26	11–13
Lactose	1.53	485	0.35	1.50	6.5–8.5
Mannitol	1.49	480	0.34	1.42	7.0–8.0
Mannitol (65%) and dibasic calcium phosphate (35%)	1.73	540	0.37	1.60	8.0–9.0
Mannitol (35%) and dibasic calcium phosphate (65%)	1.94	590	0.38	1.81	9.0–10.5
Wheat starch (20%) and dibasic calcium phosphate (80%)	2.08	620	0.39	1.92	9.5–11.0
Potato starch (20%) and dibasic calcium phosphate (80%)	2.09	624	0.39	1.90	9.5–11.0
Wheat starch (20%) and lactose (80%)	1.55	490	0.35	1.49	7.0–8.5
Potato starch (20%) and lactose (80%)	1.56	495	0.36	1.49	7.0–8.5

granule interior, the granulating agent probably plays an important role in mottling by virtue of its effect on granule strength.

Dibasic calcium phosphate was granulated with several commonly used binding agents at a range of concentrations. Calcium phosphate was selected as the basis for the tablets because of its low solubility in water. Interparticulate bridges, therefore, made no contribution to granule strength, and dissolution of the solid could not significantly alter the viscosity of the granulating fluid.

The relationship between binder type and concentration and the crushing strength of the granules so formed is shown in Fig. 2. As expected, granule strength increased almost linearly with binder concentration. However, the relationship between granule strength and mottling was more complex (Fig. 3). In general, at low concentrations of the binding agent, mottling decreased as the constituent granules became more resistant to fragmentation, although migration of the dye to the granule periphery occurred in all cases. However, in the case of gelatin and povidone, as binder concentration and granule strength increased still further, mottling also increased. This finding resulted because, at high granule strengths, a few of the hardest granules remained intact after compression and appeared as dark blue patches on the tablet surface.

Dibasic calcium phosphate tablets prepared with acacia showed considerably reduced mottling compared with tablets prepared with other binding agents. This result is thought to be related to the observation that these tablets were pale blue-gray in color; consequently, the contrast between white and colored regions on the tablet surface was diminished. In the presence of acacia, an aqueous solution of FD&C Blue No. 1 showed a hypsochromic shift in its visible spectrum. Bornstein *et al.* (7) showed that acacia and FD&C Blue No. 1 form a complex, and it is concluded that the reduction in mottling is primarily due to a reduction in the overall degree of color saturation of the tablet surface rather than any effect of the acacia on the granule properties.

Prescott (6) claimed, although without apparent experimental

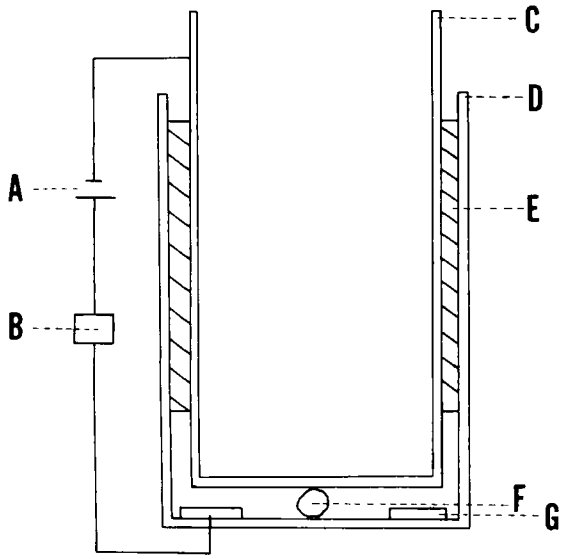

Figure 1—*Apparatus for the determination of granule crushing strength. Key: A, 4.5-v battery; B, buzzer; C, inner cylinder; D, outer cylinder; E, guide coated with Teflon; F, granule; and G, washer.*

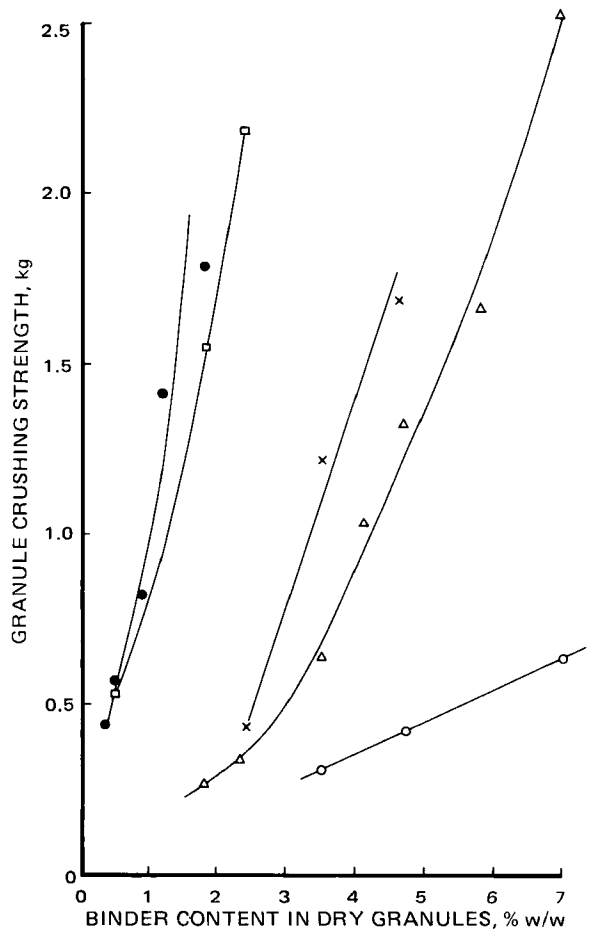

Figure 2—*Crushing strength of dibasic calcium phosphate granules prepared with various binding agents. Key: ●, gelatin; □, potato starch mucilage; ×, acacia; △, povidone; and ○, polyethylene glycol 4000.*

Table II—Influence of Binding Solution Viscosity on the Degree of Mottling of Dibasic Calcium Phosphate Tablets Prepared with Potato Starch Mucilage

Starch Mucilage		Starch Concentration in Dried Granules, % w/w	Degree of Mottling	
Concentration, % w/w	Viscosity at 25°, poises		Mean of 10 Tablets, units	Limits of Error (p = 0.95)
2.0	217	0.47	22.5	2.2
7.5	38,200	1.75	20.7	1.3
10.0	97,600	2.33	21.3	3.4

justification, that povidone solves the problem of tablet mottling because it "actually anchors the color evenly throughout the granulation," implying the formation of a povidone–dye complex which does not migrate to the granule surface on drying. Povidone does form complexes in aqueous solution of some dyes (8, 9), although the existence of such complexes in tableted systems has not been established. In the present study, tablets prepared with povidone were severely mottled, there was no evidence that dye migration was reduced, and the spectral absorbance of FD&C Blue No. 1 was not changed significantly by the presence of povidone. Furthermore, Ridgway and Rubinstein (10) found that on drying, povidone migrated to the granule periphery. Therefore, even if a povidone–dye complex does form, the complex also probably migrates to the surface of the granule, so mottling would not be visibly affected.

The migration of sodium chloride through a granulate of sand and water was reduced by a factor of five by the incorporation of a highly viscous binding agent; the tendency of the liquid to move to the granule surface by capillarity probably was reduced (4). Consequently, evaporation would take place within the granule, and dye migration would be reduced. The effect of the binding agent viscosity on the mottling of dibasic calcium phosphate tablets is shown in Table II. Migration of dye to the granule periphery occurred in each case, and the degree of mottling was not affected by the viscosity of the granulating agent.

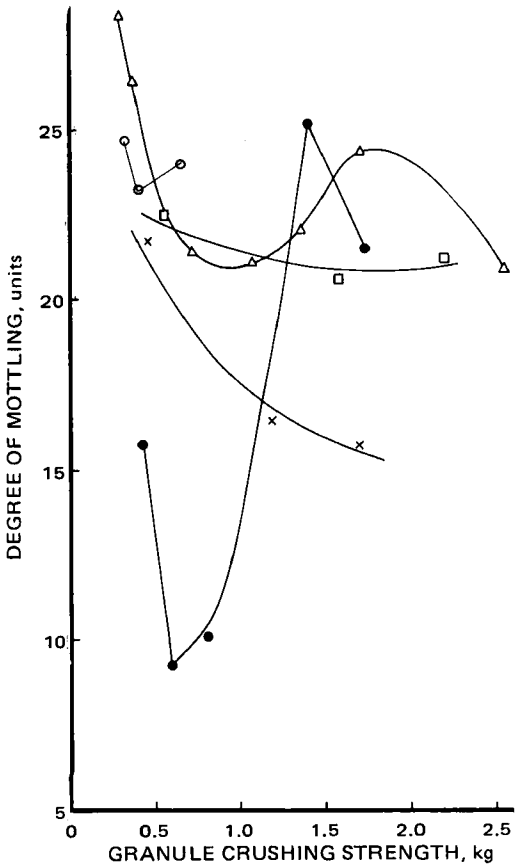

Figure 3—*Effect of granule crushing strength on the degree of mottling of dibasic calcium phosphate tablets colored with FD&C Blue No. 1 dye. Key: ●, gelatin; □, potato starch mucilage; ×, acacia; △, povidone; and ○, polyethylene glycol 4000.*

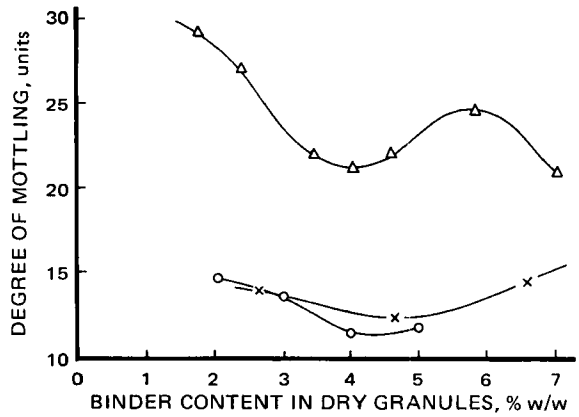

Figure 4—*Degree of mottling of tablets prepared with various diluents colored with FD&C Blue No. 1 dye. Key: △, dibasic calcium phosphate; ×, mannitol; and ○, lactose.*

Some of the binding agent may have been adsorbed by the dibasic calcium phosphate, leaving a less viscous fluid to move by capillarity. In support of this suggestion, it was found that the interior of granules prepared with starch mucilage was stained black by iodine.

Effect of Diluents on Degree of Mottling—*In a study on the properties of tablets colored with FD&C Red No. 3, Goodhart et al.* (11) noted that tablets prepared from calcium sulfate were

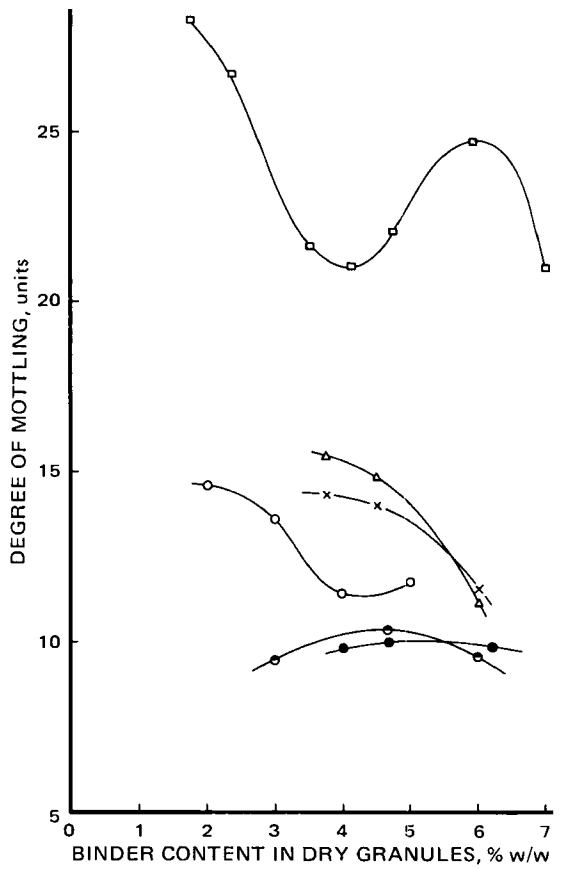

Figure 5—*Effect of potato and wheat starches on the degree of mottling shown by lactose and dibasic calcium phosphate tablets. All tablets were colored with FD&C Blue No. 1 dye and contained povidone as the binding agent. Key: □, dibasic calcium phosphate; △, dibasic calcium phosphate–wheat starch (80:20); ×, dibasic calcium phosphate–potato starch (80:20); ○, lactose; ⊖, lactose–wheat starch (80:20); and ●, lactose–potato starch (80:20).*

Table III—Effect of Tablet Diluents on Elution of Dye from Granules Colored with FD&C Blue No. 1 Lake and on Tablet Mottling

Diluent	Colorant	Degree of Mottling, units: Mean of 10 Tablets	Degree of Mottling, units: Limits of Error (p = 0.95)	pH of Supernatant Dye Solution	Percent Dye Eluted from Granules Containing FD&C Blue No. 1 Lake
Dibasic calcium phosphate	Dye	21.6	2.1	—	—
	Lake	21.8	2.3	7.1	100
Lactose	Dye	13.6	1.2	—	—
	Lake	8.9	1.1	5.9	68.8

more mottled than those produced from calcium phosphate and lactose.

In the present investigation, tablets were prepared from dibasic calcium phosphate, lactose, and mannitol. They were colored with FD&C Blue No. 1 and always granulated with povidone, thereby ensuring that changes in mottling were attributable only to the characteristics of the diluents employed. Figure 4 shows that tablets containing dibasic calcium phosphate were more mottled than those containing mannitol or lactose. However, there was no evidence that any of the substances adsorbed the dye to a significant extent, and examination of cross sections of the granules showed that dye had migrated to the periphery of the granule in all cases. Hence, it must be concluded that the more uniformly colored tablets of lactose and mannitol result from modification of the granule behavior on compression, which reduces granule fracture and the exposure of uncolored material.

Use of Adsorbents to Prevent Mottling—Zografi and Mattocks (12) showed that some anionic dyes are strongly adsorbed by several types of starch but not by potato starch. They concluded that the presence of an adsorbent starch should improve tablet color uniformity by prevention of dye migration. A similar conclusion was reached by Jaffe and Lippmann (5), who found that attapulgite prevented migration of FD&C Blue No. 1 dye in lactose columns. Unfortunately, neither of these studies was supported by the manufacture of uniformly colored tablets.

In the present study, tablets were prepared with a range of concentrations of povidone as the granulating agent. Twenty percent of the calcium phosphate was replaced by either wheat starch, which adsorbs FD&C Blue No. 1, or potato starch, which does not. A similar range of tablets made from lactose with these starches was also prepared. The results (Fig. 5) show that while the addition of an adsorbent starch reduced mottling, an almost identical reduction in mottling was obtained with a nonadsorbing starch.

Fuchs (13) showed that starch grains remain intact after tablet compaction. In the present study, it was noted that whereas calcium phosphate granules fragmented during determinations of granule crushing strength, those containing starch remained largely intact. It is thought, therefore, that starch can accommodate compressive forces by elastic deformation and thereby reduce the tendency of granules to fracture on compression. Thus, the present investigation confirmed the suggestion made by Zografi and Mattocks (12) that color uniformity can be improved by incorporating starch in the wet granulation. However, the mechanism by which mottling is reduced is not due to adsorption of the dye.

Effects of Dyes and Their Lakes on Mottling—Since dye migration is the primary cause of mottling, it may be expected that if the dye is bound to an insoluble substrate, *e.g.*, aluminum hydroxide, thereby giving the lake of the dye, migration and mottling should be reduced significantly.

Table III shows that, in the case of lactose granulated with povidone, mottling was reduced, although not abolished, when the dye lake was used. However, the lake had no effect on tablets made from calcium phosphate. This finding supports that of Goodhart *et al.* (11), who found that while lactose tablets colored with FD&C Red No. 3 lake exhibited uniform color, a high degree of mottling was observed with calcium phosphate and calcium sulfate.

It is well known that a dye can be leached from its lake by extremes of pH or by the presence of anions. It was found that FD&C Blue No. 1 was rapidly eluted from its lake at pH values greater than 6.4. Thus, while the elution in the presence of calcium phosphate can be accounted for by the pH of the medium, the elution in the presence of lactose was probably due to traces of anionic impurities such as chloride. Although chloride ions were found to be present in lactose only as trace impurities, the small amount of water present during the drying process resulted in relatively concentrated electrolyte solutions.

Hence, although in some circumstances the use of a lake will give a less mottled product than will the parent dye, the extent of the reduction is dependent on the pH of the system and the anions present.

CONCLUSIONS

The basic cause of mottling is dye migration in the granules on drying. None of the techniques reported in this paper successfully overcomes this problem. Nevertheless, in spite of the coarse granule size used, relatively uniformly colored tablets were prepared. The improvement in color uniformity was due to the effect of excipients on granule behavior on compression.

Tablet mottling occurred with each binding agent investigated, but was less apparent with acacia because that excipient reduced the overall tablet color. Mottling was also reduced initially by an increase in granule strength, but tablet mottling increased at high values due to the presence of a small number of extremely hard granules which did not fracture and appeared as dark patches on the tablet surface. The use of highly viscous binding solutions had no beneficial effect on tablet mottling.

Tablets prepared from lactose and mannitol granules, which deformed plastically and retained their integrity after compression, were relatively uniformly colored. In contrast, corresponding tablets prepared from dibasic calcium phosphate granules, which were brittle and dispersed into fragments on compression, were severely mottled. Incorporation of starch (20%) with dibasic calcium phosphate or lactose before wet granulation reduced the extent of granule fracture on compression and the degree of mottling. The starch grains are thought to reduce mottling by accommodating the compressive forces by deformation and, hence, resisting granule fracture.

Lactose tablets colored with FD&C Blue No. 1 lake were less mottled than corresponding tablets colored with an equivalent quantity of dye. However, dibasic calcium phosphate tablets colored with the lake were equally as mottled as those colored with the dye. The slight mottling observed in lactose tablets prepared with the lake is attributed to elution of dye from the lake, which may have been caused by chloride ions present as impurities in the tablet diluents. Severe elution of dye from FD&C Blue No. 1 lake also occurred in aqueous solutions with a pH in excess of 6.4. Hence, dye elution will also occur in the presence of those tablet excipients that raise the pH of the granulating fluid above 6.4.

As a result of the present investigation, the following general principles for the preparation of uniformly colored tablets are suggested:

1. Granules should be dried in such a manner (*e.g.*, with a fluid bed dryer) as to prevent intergranular solute migration.
2. No dye-deficient material should be visible before compression. Irrespective of the method of drying and the formulation used, the dye will migrate to the granule periphery, leaving the interior of the granule deficient of dye. Thus, compression should not be preceded, as is the custom, by a comminutive process; such a process exposes colorant-free zones of the granule interior.
3. As far as is commensurate with granule flow properties, the granule size used during compression should be as small as possible, so that the visible contrast between the granule interior and periphery is minimized.

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Constant Returns to Scale for Prescription Dispensing in U.S. Community Pharmacy

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Abstract □ By using data from a sample of 1767 community pharmacies, a total cost function was estimated by a polynomial regression of total cost on output. The Cobb–Douglas production function was estimated by a multiple linear regression of natural logarithmic transformations of output on natural logarithmic transformation of labor and capital. No economies of scale were found in prescription departments. Cost data led to a conclusion of constant marginal costs.

Keyphrases □ Prescription dispensing—community pharmacies, total cost function in relation to size, Cobb–Douglas production function □ Cobb–Douglas production function—community pharmacies, prescription dispensing, total cost in relation to size □ Pharmacies—total cost function in relation to size, prescription dispensing, Cobb–Douglas production function

The pervasive economic influence of the 1970's is inflation with an associated recession. The news media daily report on the state of the economy and profusely illustrate their conclusions by examples from agriculture and industry. These two sectors of the economy at least have the advantage of being well studied and somewhat understood.

The service industries are not so fortunate. Only one cost and scale study (of the U.S. Postal Service) was published in recent years (1). The health service industries have been subjected to some indepth studies. Most of these have concentrated on output specifications (2) and cost functions (3), resulting in seven hospital investigations reporting increasing returns to scale and three with constant returns. A production function was calculated (4) for medical office practice, but no economies of scale were calculated.

Many studies have concerned pharmacy and prescription costs (5–8). But there has been a dearth of studies concerning economies of scale in the health services and pharmacy practice generally. The purpose of this study was to find what, if any, economies of scale exist in the prescription dispensing operations of U.S. community pharmacies.

THEORETICAL

Economies of scale, or increasing returns to scale, may be defined as the proportional increase in output greater than the proportional increase in each input. If the proportional increase in output is less than the proportional increase in inputs, or equal to them, then the firm is experiencing decreasing returns to scale or constant returns to scale, respectively.

These economies of scale are due to the following factors (9):

1. Bulk transactions of materials—the ease of dealing with large quantities of materials reduces unit costs.
2. Pooled reserves—operating on a large scale reduces the cost of uncertainty through a spreading of the risk.
3. Multiples—the costs of personnel and machines fall with increasing size due to their indivisibilities.

The neoclassical theorists thought that diseconomies of scale would be manifest in the form of managerial inefficiencies with increasing size (10). In addition, the increasing division of labor might be taken so far that employees would become bored and inefficient with their highly specialized and repetitive tasks. On the other hand, it has been suggested that with the increasing usage of computers in large industry, the expected inefficiencies have not occurred, resulting in constant rather than decreasing returns to scale.

Economies of scale are closely related to both cost and production functions. Depending on the design of the study, economies of scale may be investigated by an examination of the shape of the marginal cost function or an examination of the parameters of the Cobb–Douglas production function.

The marginal cost is, mathematically, the derivative with re-