DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 7(1), 79-111 (1981)

EFFECT OF SCALING-UP AND FORMULATION FACTORS ON THE QUALITIES OF PREDNISONE TABLETS

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ABSTRACT

Four different tablet manufacturing techniques were scaled-up from a bench scale to a semi-large scale in order to study the effect of scaling-up on weight variation and content uniformity of prednisone tablets. One method was further scaled-up to a production scale, and the tablets obtained were tested for content uniformity. The effect of binders and lubricants on tablet hardness, disintegration, dissolution and chemical stability was investigated. It is shown that scaling-up of some techniques affect content uniformity of tablets. The various tablet parameters have been also found to be influenced by the type of binder and lubricant used and by aging of

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the tablets at normal and accelerated conditions. The presence or absence of intragranular starch as disintegrant appears to affect some of the tablet qualities.

INTRODUCTION

In a pervious report, Asker and associates (1) found that the method of preparation of tablets on a laboratory or bench scale, influenced the qualities of reserpine tablets including stability and in-vitro availability.

Scaling-up of batch size from a laboratory scale to a semi-large or a commerical scale has been reported to affect the qualities of the tablets (2,3). Moreover, evidence have been accumulating showing that tablet adjuvants incorporated as binders, diluents, disintegrants, absorbents and lubricants are not truly inert. They have been found to potentiate the chemical degradation of the active ingredients, cause the disintegration time and dissolution rate of tablets to change with storage, influence the therapeutic efficacy of the medicament, cause changes in the color of the tablets and affect other physical properties such as friability and hardness (4).

The objective of this investigation therefore, were to study the effects of scaling-up of some manufacturing procedures and of a number of selected binders and lubri-

cants on the qualities of prednisone tablets including drug stability and its in-vitro availability.

EXPERIMENTAL

Table 1 shows the various formulations of prednisone tablets studied.

Preparation of Tablets:

1. Semi-large scale: The techniques previously reported for the preparation of reserpine tablets on a bench scale (1), were scaled-up to a semi-large scale where a batch of 15,000 prednisone tablets was produced by each technique. These techniques are: slugging, partial granulation using a placebo carrier and wet granulation methods A, B and C. Wet method A requires the drug to be mixed with diluent and then the aqueous binder solution of polyvinylpyrrolidone is added to the powder mix and kneaded to form a coherent paste. In wet method B, the drug is dissolved in a mixture of equal volumes of alcohol and chloroform in which the binder has been dissolved, and the whole solution is then mixed with the diluent. In case of wet method C, the drug is suspended in an aqueous solution of the binder before being incorporated into the diluent.

Wet method B which was used to prapare reserpine tablets (1), could not be scaled-up to prepare prednisone tablets since prednisone did not dissolve in the

TABLE 1

Formulations of Prednisone Tablets

Ingredients in mg./Tablet	Dry Methods A	Dry Methods B	A	Wet Methods C I	II	III	IV	V	VI	VII	VIII
Prednisone	5	5	5	5	5	5	5	5	5	5	5
Lactose	80	80	80	80	80	82	60	60	62	57	60
Maize Starch (Intragranular Disintegrant)	---	---	---	---	---	---	20	20	20	20	20
Polyvinylpyrrolidone	5	5	5	5	---	---	5	---	---	5	5
Carbowax 6000	---	---	---	---	5	---	---	5	---	---	---
Gelatin	---	---	---	---	---	3	---	---	3	---	---
Magnesium Stearate	2	2	2	2	2	2	2	2	2	---	---
Stearic Acid	---	---	---	---	---	---	---	---	---	---	2
Talc	---	---	---	---	---	---	---	---	---	5	---
Maize Starch (Integranular Disintegrant)	8	8	8	8	8	8	8	8	8	8	8

organic solvent mixture. Moreover, attempts to use a suitable volume of an organic solvent that would dissolve both the drug and binder, without the formation of an over-wetted mass, were not successful.

In scaling-up the various techniques, mixing of dry powders was carried out in a double cone mixer for 20 minutes, whereas kneading the powder blend with the binder solution or drug suspension was done in the Drais Kneader for 10 minutes. Compression into tablets took place on a Kilian rotary tablet press using 7 mm punches.

2. Production Scale: The extension of batch size from a semi-large to a commercial or production scale was done using wet method C because of its inherent potential advantages over the other methods (1).

Production facilities offered by one of the pharmecutical firms were utilized in the scaling-up process. The fine powder of prednisone required tablets to prepare a batch of 400,000 tablets was treated as described under wet method C for prednisone tablets prepared on a semi-large scale. However, mixing was carried out in the double cone mixer for 30 minutes and kneading was done in the Drais Kneader for 30 minutes. The tablets were compressed on a Kilian rotary tablet press with 7 mm punches.

Evaluation of the Qualities of Tablets:

(1) Weight Variation and Content Uniformity: The USP XIX (5) procedures were followed. Prednisone was assayed

in the individual tablets for content uniformity as follows: One tablet equivalent to 5 mg of prednisone was introduced into a 50-ml volumetric flask. Ten ml of distilled water was added and the flask was placed on a water bath at 50° for 10 minutes to allow the tablet to disintegrate. The flask was then cooled and 25 ml of ethanol was added. The flask was shaken for 20 minutes and then the mixture was completed to volume with ethanol. The mixture was filtered through Whatman filter paper No. 50 previously washed with ethanol, into a 50-ml volumetric flask. The filtrate was then adjusted to volume with ethanol. Five ml of the filtrate was accurately transferred into a 50-ml volumetric flask and the solution was completed to volume with ethanol. The absorbance of this solution was determined spectrophotometrically at 240 mμ using a standard solution prepared as follows: 50 mg of prednisone was accurately weighed and introduced into a 50-ml volumetric flask. Ethanol was added to dissolve prednisone and the solution was completed to volume. Five ml of this solution was accurately transferred into a 50-ml volumetric flask and the solution was completed to volume with ethanol. The adjuvants and the small amount of water used to aid in the disintegration of the tablet did not interfere with the spectrophotometric assay. The spectrophotometric assay of prednisone is used by the USP XIX (6) and by Campagna

TABLE 2

Weight Variation and Content Uniformity of Prednisone Tablets Prepared by the Various Techniques on a Semi-large Scale

Method	Weight Variation		Content Uniformity		Compliance With USP XIX
	Avg. Wt. (mg)	Standard Deviation	% Prednisone	Standard Deviation	Requirement for Content Uniformity
1. Slugging	98.88	1.2	102.41	4.79	Yes
2. Partial Granulation	100.55	2.28	92.46	22.16	No
3. Wet Granulation					
a. Method A	100.51	2.65	109.53	26.10	No
b. Method C	100.51	1.83	102.24	3.99	Yes

et al. (7) in the in-vitro dissolution of prednisone from tablets.

(2) Hardness: Twenty tablets were taken at random from each batch and tested for hardness using the Erweka hardness tester. Moreover, samples of tablets stored in polystyrene bottles at room conditions for 18 months were also subjected to hardness testing.

TABLE 3

Uniformity of Prednisone Content in Tablets Prepared by Wet Method C on a Production Scale

% Prednisone Per Tablet in Five Samples, Each of 10 Tablets				
(1)	(2)	(3)	(4)	(5)
102.0	105.9	103.2	98.9	101.4
100.0	104.0	102.3	101.5	106.0
103.5	109.0	101.0	105.0	103.0
104.9	103.0	108.0	103.4	104.0
103.7	107.0	105.9	102.0	104.0
101.4	105.7	104.0	99.5	101.5
100.2	104.0	102.3	104.0	102.0
103.9	101.0	100.7	101.4	103.5
105.0	100.0	102.4	103.9	106.5
100.7	103.4	101.0	100.0	100.0

Compliance with USP requirements for Content Uniformity for each Sample: Yes

Avg. % Prednisone content based on 50 tablets = 103.0%

Standard Deviation of Prednisone Content Based on 50 Tablets = 2.28

(3) Disintegration: Triplicate samples, each of six tablets were taken at random from each batch and subjected to the USP disintegration test. Samples of tablets stored at room conditions for 18 months were also tested for disintegration time.

(4) In vitro availability: Dissolution studies were carried out on freshly made prednisone tablets prepared acccording to formulae I, II, III, IV, V and VI. Moreover, samples of the tablets prepared according to formula IV, V and VI were stored at room conditions in polystyrene bottles for 18 months, and their dissolution patterns were then determined. The USP XIX dissolution procedure for prednisone tablets was followed. A cumulative correction was made for the previously removed samples in determining the total amount of prednisone dissolved according to the equation used by Sciarra and Patel (8).

(5) Chemical Stability:

a. Effect of Binder: Samples of prednisone tablets prepared by wet method C and containing polyvinylpyrrolidone, polyethylene glycol 6000 or gelatin as binders, were placed in loosely capped amber glass bottles. The bottles were stored at 50° and 83% RH, and at 70° and 96% R.H. for a period of seven weeks. The content of prednisone in the tablets was determined every week by the technique described by Wagner et al.

TABLE 4

Effect of type of Binder on Hardness of Fresh and Aged Prednisone Tablets Prepared by Wet Method C

Formula No and Binder Used	Fresh Tablets Hardness (Kg.) Range	Avg.	Aged Tablets Hardness (Kg.) Range	Avg.
I-PVP*	5.25-6.5	6.05	5.25-7.75	6.03
II-Carbowax 6000*	2.75-3.5	3.05	3.25-4.0	3.58
III-Gelatin*	3.5 -5.25	4.23	4.0 -6.25	4.98
IV-PVP	4.0 -5.5	5.0	5.25-6.0	5.33
V-Carbowax 6000	2.5 -3.5	2.93	2.5 -4.0	3.55
VI-Gelatin	3.25-4.25	3.75	3.0 -4.5	3.35

*No intragranular starch

TABLE 5

Effect of Type of Binder on Disintegration Time of Fresh and Aged Prednisone Tablets Prepared by Wet Method C

Formula No. and Bi er Used	Fresh Tablets Disintegrations Time (min) Range	Avg.	Age Tablets Disintegration Time (min) Range	Avg.
I-PVP*	9-11	9.83	20-30	22.16
II-Carbowax 6000*	8-11	9.5	15-16	15.16
III-Gelatin*	12-15	13.16	66-75	69.50
IV-PVP	4-5	4.66	5-6	5.6
V-Carbowax 6000	3-5	3.83	3.5-4	3.55
VI Gelatin	8-13	9.83	25-32	27.50

* No intragranular starch

(9) for the assay of prednisolone tablets using blue tetrazolium. The absorbance of solution was determined at 485 mμ on Unicam SP 600 spectrophotometer.

b. Effect of Lubricant: Samples of prednisone tablets prepared by wet method C and containing magnesium stearate, talc or stearic acid as lubricants were stored and subjected to the assay procedure mentioned under the effect of binders.

Neither the binders nor the lubricants used interfered with the spectrophotometric assay.

DISCUSSION OF RESULTS

Effect of Scaling-up of Various Techniques on Weight Variation and Content Uniformity:

Table 2 summarizes the results of anlysis of five samples of each of the four batches of prednisone tablets prepared on a semi-large scale by slugging, partial granulation and wet methods A and C. Compared with the results previously reported (1) for reserpine tablets that were produced on a bench scale, it is evident that as a result of extending the batch size from a bench scale to a semi-large scale, there was generally an increase in the value of standard deviation of drug content. Tablets prepared by slugging and wet method C maintained their compliance with the USP XIX requirements for content uniformity through scaling-up. On the

TABLE 6

Effect of Aging on Dissolution of Prednisone Tablets Prepared With Various Binders

Formula No. and Binder Used	Fresh Tablets			Aged Tablets		
	Avg.% Drug Dissolved in 20 minutes	Dissolution Range(%)	C.V.*	Avg.% Drug Dissolved in 20 minutes	Dissolution Range(%)	C.V.*
IV-Polyvinyl-pyrrolidone	96.49	89.5-100	3.82	83.81	80.46-89.7	3.82
V-Carbowax 6000	92.59	86.67-97.78	5.18	90.25	84.44-93.76	4.85
VI-Gelatin	72.78	70.41-75.54	2.92	32.64	23.25-40.7	1.84

*Coefficient of Variance

TABLE 7

Effect of Type of Lubricant on Disintegration Time of Fresh and Aged Prednisone Tablets Prepared by Wet Method C

Formula No. and Lubricant Used	Fresh Tablets Disintegration Time (min) Range	Avg.	Aged Tablets Disintegration Time (min) Range	Avg.
IV-Mg. Stearate	4-5	4.6	5-6	5.33
VII-Talc	3.5-5	3.94	4-6	4.66
VIII-Stearic Acid	2-4	3.17	3.5-5.75	3.88

TABLE 8

Effect of Type of Lubricant on Hardness of Fresh and Aged of Prednisone Tablets Prepared by Wet Method C

Formula No. and Lubricant Used	Fresh Tablets Hardness (Kg) Range	Avg.	Age Tablets Hardness (Kg) Range	Avg.
IV-Mg. Stearate	4-5.5	5.0	5.25-6	5.33
VII-Talc	4-6	5.25	5-7	6.13
VII-Stearic Acid	4.5-6.5	5.4	5-7.25	6.33

other hand, tablets made by partial granulation or wet method A deviated substantially from the official requirements as a result of scaling-up. However, prednisone tablets prepared by any of the techniques were found to comply with the USP XIX requirements for weight variation.

The difference in results obtained through scaling-up of batch size is not entirely unexpected.

In partial granulation technique the factors responsible for non-uniformity of drug content on a bench scale previously reported (1), were also involved when the tablets were made on a semi-large scale. However, the problem was more pronounced as indicated by an increase in the values of standard deviation. This may be attributed to demixing which would occur during handling of the powders prior to compression or during flow of powders in the hopper of the tablet press as a result of its vibrations. Lachman et al. (10), have stated "The most critical factor involving scale-up of dry blends for direct compression is uniform distribution of small quantities of active ingredients, often representing less than 5% of the total tablet weight".

In case of wet method A, a substantial deviation from the USP XIX requirements for content uniformity was observed. Geometric dilution and the mixing procedure followed for such a small quantity of prednisone, appeared to be unsatisfactory when the batch size was

extended. It appears that when the binder solution is added to the previously mixed powders, there is a possibility that this solution may disturb the already mixed bed of powders by mechanically dislocating the drug particles from their random distribution and having them held in another location. Uniform redispersion of the dislocated drug particles would appear to be difficult in view of the increasing consistency and cohesiveness of the mass as mixing continues, and of the presence of a very small amount of the active drug.

Therefore, from the standpoint of content uniformity of tablets prepared on either a bench scale or a semi-large scale, method C can be considered the best followed by the slugging technique. This conclusion is also supported by the results obtained when wet method C was extended to a production scale. The tablets produced demonstrated the lowest value of standard deviation as shown in Table 3.

Effect of Binders on Dissolution Profiles of Fresh and Aged Prednisone Tablets Using Lactose and Lactose-Starch as Tablet Matrix:

a. Fresh Tablets: From Figure 1, the $T_{60\%}$, i.e., the time required for 60% of the contained drug to dissolve was found to be 27.5 minutes, 26 minutes and 37.5 minutes for tablets made with Carbowax 6000, polyvinylpyrrolidone and gelatin respectively. These results

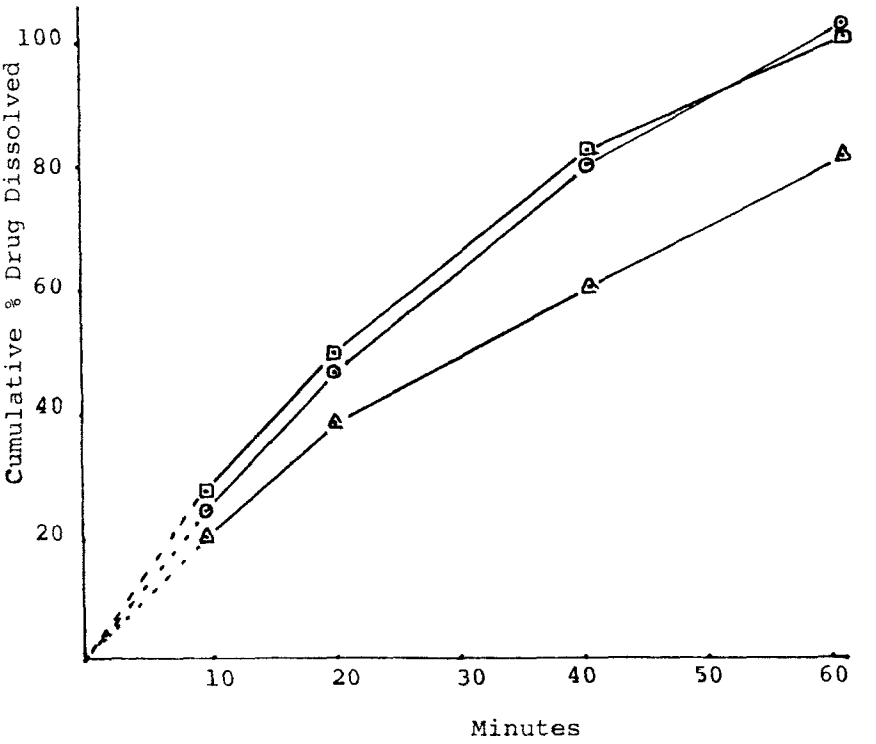

FIGURE 1. Dissolution Profiles of Fresh Prednsione Tablets Prepared with Various Binders Without Intragranular Starch

△-Gelatin

⊙-Carbowax 6000

⊡-Polyvinylpyrrolidone

indicate therefore, that dissolution rate is influenced by the type of binder used as previously reported (11, 12).

The increase in dissolution time of tablets prepared with gelatin over those prepared with Carbowax

6000 or polyvinylpyrrolidone may be attributed to the formation of a thin film of gelatin around the powder particles or granules. This film could be converted into a mucilogenous viscous barrier when the tablets and breakup fragments contacted the dissolution medium. Huber et al. (13), have reported that gum-type binders may form a gel barrier around the tablet to inhibit disintegration with subsequent delay in drug release. Furthermore, the temperature encountered in drying and during tableting could cause melting of asperities of the tablet matrix made with gelatin. This would result in the formation of stronger adhesive bonds between the particles, thereby affecting dissolution of the active ingredient from the tablet. This view was expressed by York and Pilpel (14).

Although tablets prepared with Carbowax 6000 or polyvinylpyrrolidone gave better dissolution profiles than those prepared with gelatin, yet all the three batches failed to comply with the USP requirement for dissolution of prednisone from tablets. The USP requires that not less than 60% of the tablet content must be in solution within 20 minutes. This failure of compliance is probably due to the absence of intragranular starch, thus resulting in the formation of a more compact and cohesive lactose matrix. The addition of starch before and after granulation has been described as the most effective technique to accom-

plish fast disintegration (15). Moreover, starch has been reported in the review by Lowenthal (16) to increase the pore diameter and porosity of tablets. The effect of starch on porosity of the tablet may be due to its poor ability to bond and compress. Consequently, the incorporation of intragranular starch in the formulations was found to enhance dissolution rate of prednisone as can be seen from Figure 2. Improvement of dissolution is indicated by the values of the average concentration of prednisone released in 20 minutes. These values as shown in Table 6 are 72.78 for gelatin, 92.59 for Carbowax 6000 and 96.49% for polyvinylpyrrolidone thus complying with the USP requirement for dissolution of prednisone tablets.

b. Aged Tablets: It can be seen from Figure 3, that aging of the tablets at room conditions for 18 months, resulted in a substantial decrease in the amount of prednisone released at various times from the tablets made with gelatin. However, tablets prepared with polyvinylpyrrolidone showed a less pronounced change in dissolution profile, whereas tablets made with Carbowax 6000 demonstrated a practically negligible change.

The drastic change in dissolution profile obtained as a result of aging prednisone tablets prepared with gelatin, caused the tablets to fail to comply with the USP requirement for dissolution. Only 32.64% of the contained drug was released in 20 minutes. On the other

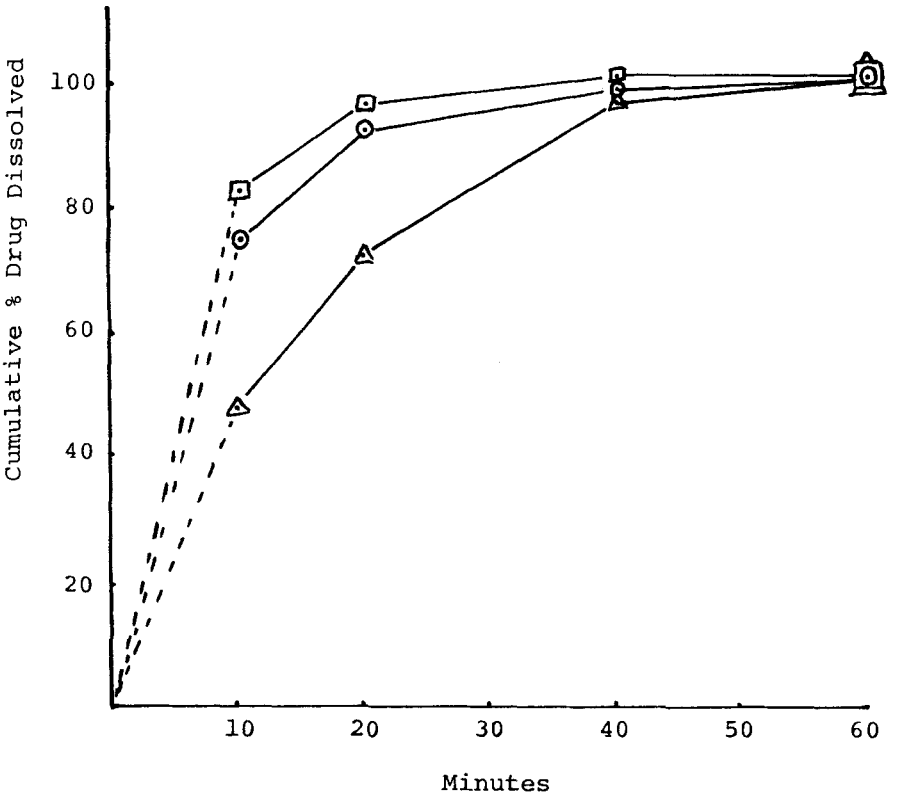

FIGURE 2. Dissolution Profiles of Fresh prednisone Tablets Prepared with Various Binders and Contained Intragranular Starch

△-Gelatin

●-Carbowax 6000

□-Polyvinylpyrrolidone

hand, aged tablets made with polyvinylpyrrolidone or Carbowax 6000 complied with the official dissolution requirement since 83.81% and 90.25% respectively were released in 20 minutes as shown in Table 6.

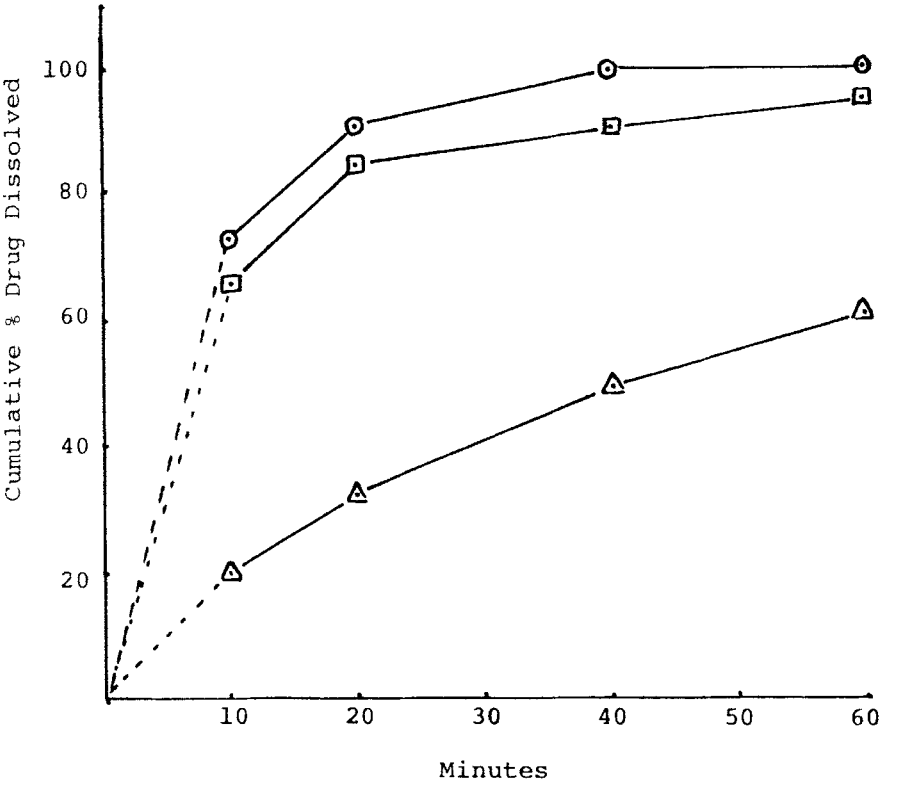

FIGURE 3. Dissolution Profiles of Aged Prednisone Tablets Prepared with Various Binders and Contained Intragranular Starch

▲ - Gelatin

● - Carbowax 6000

■ Polyvinylpyrrolidone

The decrease in dissolution rate of prednisone from the aged tablets made with gelatin is probably due to slow polymerization of gelatin that would take place during storage. This polymerization process would

result in hardening and increasing rigidity and cohesiveness of the tablet matrix, thus delaying disintegration and dissolution time. Aged tablets made with gelatin were found in this study to have a longer disintegration time than those made with polyvinylpyrrolidone or Carbowax 6000 as shown in Table 5. Evidently, this is reflected in the low dissolution rate obtained for tablets made with gelatin.

Aged tablets made with Carbowax 6000 showed only a very slight change in either the overall dissolution profile or in the percentage of drug released in 20 minutes. This can be attributed to the relative ease with which Carbowax 6000 dissolves in the dissolution medium without appreciably affecting its viscosity as in the case of gelatin. Polyethylene glycols have been reported to cause the tablet to dissolve rather than disintegrate (17). Moreover, apparently no polymerization of Carbowax 6000 is likely to occur during aging.

The change in dissolution profile of aged tablets made with polyvinylpyrrolidone may be due to slow cross-linking that would increase rigidity and cohesiveness of the tablet matrix thus causing some delay in drug release. These findings are in accordance with those reported by Alam and Parrott (4) who found polyvinylpyrrolidone to cause a slight increase in dissolution time after 1 year of storage at room temperature.

It can be concluded from this study therefore, that from the standpoint of in-vitro availability of prednisone and its maintenance during storage without an appreciable change, polyvinylpyrrolidone and Carbowax 6000 are preferred to gelatin as binders.

Effect of Binders on Disintegration Times of Fresh and Aged Prednisone Tablets:

It can be seen from Table 5 that disintegration times of fresh and aged tablets made with the various binders were longest with gelatin and shortest with Carbowax 6000 regardless of the presence or absence of intragranular starch.

Variation in disintegration time is apparently due to the difference in the rate of dissolution of the individual binders and not due to difference in hardness, since tablets prepared with polyvinylpyrrolidone gave the longest disintegration time. This is in accordance with findings of other workers (18,19) who have reported that disintegration time is not always related to the hardness of the tablet.

In tablets made with polyvinylpyrrolidone, the formation of a hard crust of the polymer during drying of the tablet granulations could prolong disintegration time as previously reported (20).

All batches of fresh tablets made with the various binders were found to comply with the USP general disin-

tegration requirement whether the tablets contained intragranular starch or not. These results are not reflective of those obtained in the dissolution study, since tablets containing no intragranular starch failed to comply with the official dissolution requirement. These findings therefore, emphasize that disintegration times are not always correlated with dissolution times as previously reported (21-23).

All tablets containing no intragranular starch showed noticeable increase in disintegration time during storage regardless of the type of binder used. Disintegration times of aged tablets containing no intragranular starch and prepared with either Carbowax 6000 or polyvinylpyrrolidone were within the official limits. On the other hand, tablets made with gelatin demonstrated disintegration time of 66-75 minutes, thus failing to comply with the USP requirements as can be seen from Table 5.

The increase in disintegration time as a result of aging of tablets prepared with various binders and containing no intragranular starch, may be due to absorption of some moisture by the tablets. This moisture would tend to dissolve a portion of the lactose matrix, increasing its cohesiveness and thus prolonging disintegration time.

The incorporation of intragranular starch substan-

tially decreased disintegration times of all freshly made tablets regardless of the type of binder used. The reason for this can be attributed to a more porous and less compact tablet matrix due to the intragranular starch present as discussed earlier under dissolution.

Aging of tablets containing intragranular starch resulted in a substantial increase of disintegration time of tablets made with gelatin, whereas in tablets made with polyvinylpyrrolidone, the effect of aging on disintegration time was very slight and practically negligible. Aged tablets made with Carbowax 6000 showed no change or little lowering of disintegration time. This effect is probably due to the absorption of moisture by tablets made with Carbowax 6000. This moisture would tend to render the tablets softer and less compact especially in the presence of intragranular starch.

It can be concluded from this study therefore, that from the standpoint of disintegration time and its maintenance without as appreciable change during storage, polyvinylpyrrolidone and Carbowax 6000 are preferred to gelatin as tablet binders.

Effect of Binders on Hardness of Fresh and Aged Prednisone Tablets:

It can be observed from Table 4 that tablets prepared with polyvinylpyrrolidone are harder than those prepared with gelatin or Carbowax 6000, whether when

freshly made or after storage. The reason for tablets made with polyvinylpyrrolidone or gelatin giving higher hardness values than those obtained with Carbowax 6000, is apparently due to the adhesive or gummy characteristics of the former binders. Such an adhesiveness would tend to firmly bond together the particles of the tablet matrix, thus increasing tablet hardness.

The inclusion of intragranular starch appears to change the hardness values of fresh and aged tablets prepared with various binders, to values lower than those obtained when intragranular starch was not included. This is probably due to the poor ability of starch to bond and compress as previously reported (16).

The change in the hardness values of tablets prepared with the various binders as a result of aging at room conditions, appears to be only slight. However, aging caused a more pronounced change in disintegration and dissolution times. These findings are in accordance with those of Horhota et al. (18), who have reported that hardness and disintegration are not always related when aged tablets are evaluated.

Effect of Lburicants on Disintegration Time and Hardness of Fresh and Aged Prednisone Tablets:

It appears from Tables 7 and 8 that the type of lubricant in the concentrations used in this study, did not have an appreciable effect on either hardness

or disintegration time of fresh and aged prednisone tablets. This may be due to the relatively low concentrations of lubricants which would not appreciably modify the mechanical strength of the tablet. Such mechanical strength is predominantly determined by the binder. Moreover, the relatively high concentration of the intergranular starch used, would substantially dilute the potential effect of any lubricant on tablet hardness. This interagranular starch would also greatly minimize the effect of hydophobic lubricants on tablet disintegration and hence drug dissolution.

Effect of Binders on Chemical Stability of Prednisone Tablets:

Figure 4 indicates that tablets prepared with Carbonwax 6000 exhibited the most drastic decrease in prednisone content at any of the two storage conditions used. Evidently storage at higher temperature and humidity resulted in a more pronounced decrease in prednisone content. The most common type of prednisone degradation has been reported to be the oxidation of the C-17 side chain (24). Therefore, degradation of prednisone tablets prepared with Carbowax 6000 may be attributed to the presence of peroxide in the wax. This peroxide was detected by its decolorization of an acid potassium permanganate solution. The presence of per-

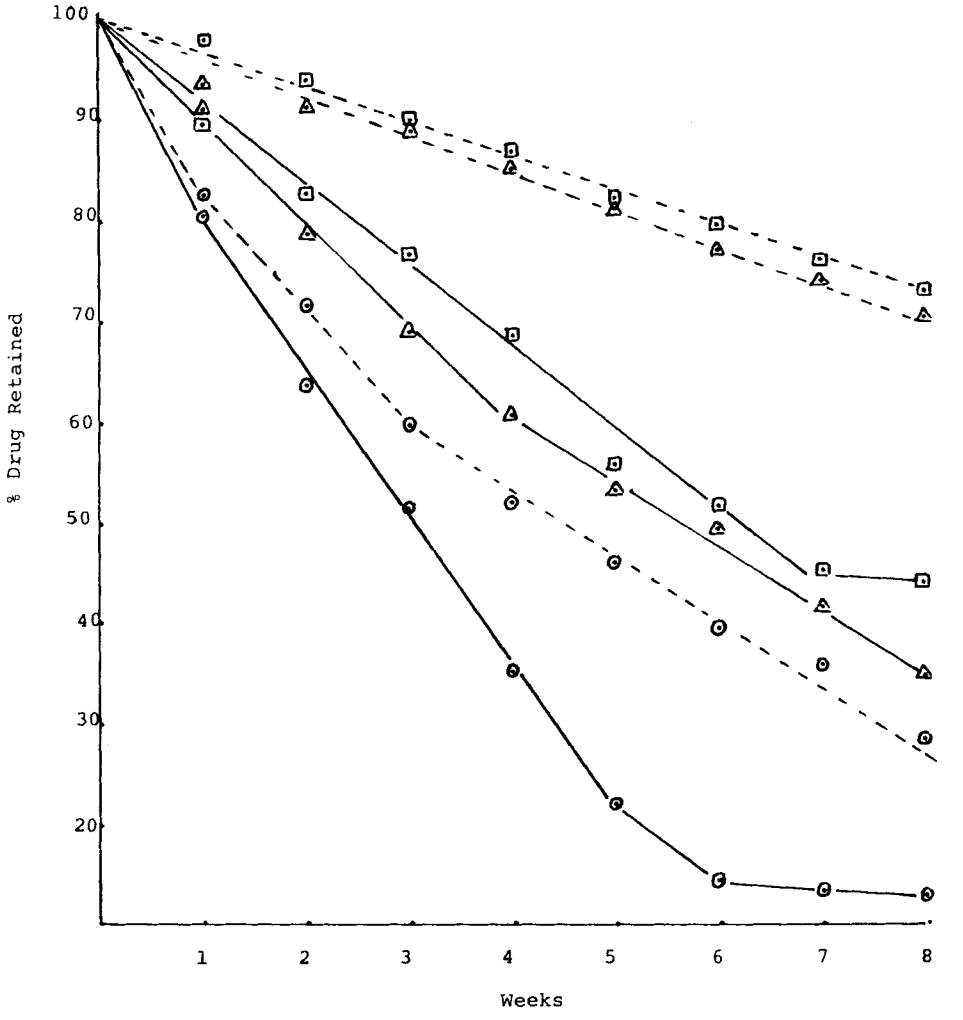

FIGURE 4. Effect of Binders on Chemical Stability of Prednisone Tablets Stored at 50° and 83% R.H. (-----)and at 70° and 96% R.H. (——)

△- Gelatin

⊙ - Carbowax 6000

⊡ -Polyvinylpyrrolidone

oxide has been reported to enhance the inactivation of chloramphenicol and tetracycline hydrochloride in tablets made with Carbowax 6000 (25). Similar findings were reported by Coates et al. (26) in their study on the stability of some antibiotics incorporated in polyethylene glycol mixtures in ointments. Moreover, McGinity et al. (27), have reported that traces of peroxide present in macrogols would decrease the stability of a corticosteroid in cream. Another possible cause of prednisone degradation is the formation of a less stable complex with Carbowax 6000, especially in view of the fact that prednisone is a polyfunctional molecule.

There was a practically negligible difference in the assay data between prednisone tablets made with polyvinylpyrrolidone and those prepared with gelatin. Both batches of tablets demonstrated substantial decrease in prednisone content at the end of the 8-week storage period. The resemblance in results may be attributed to the fact that polyvinylpyrrolidone shows resemblance in reactions to gelatin and protein of natural plasma. Therefore, there is a possibility of interaction between prednisone and each of these two binders, with the formation of a less stable compound. Methylprednisolone has been found to bind with the protein components of human tears (28).

Degradation of prednisone from the various tablets during the 8-week storage period, appears to follow a

zero-order rate. This is expected for tablets containing insoluble drugs especially in the presence of moisture (29).

It can be concluded from this study therefore, that the use of gelatin or polyvinylpyrrolidone as tablet binder, produced more chemically stable prednisone tablets than those made with Carbowax 6000.

Effect of Lubricants on Chemical Stability of Prednisone Tablets:

It is evident from Figure 5 that tablets made with magnesium stearate as lubricant, had undergone more degradation then those made with talc or stearic acid. This may be due to the alkalinity imparted by the lubricant which would catalyze oxidation of prednisone. Guttman and Meister (30), have reported that degradation of prednisolone in aqueous solutions is catalyzed by alkali. Moreover, Bornstein and Lach (31) in their diffuse reflectance studies of solid-solid interactions have indicated interaction between prednisone and magnesium-containing adjuvants.

Tablets made with stearic acid as lubricant appeared to be the most stable at 50^{o} and 83% R.H., and at 70^{o} and 96% R.H. These results are in accordance with those reported in the diffuse reflectance studied by Bornstein and Lach (31). These authors reported

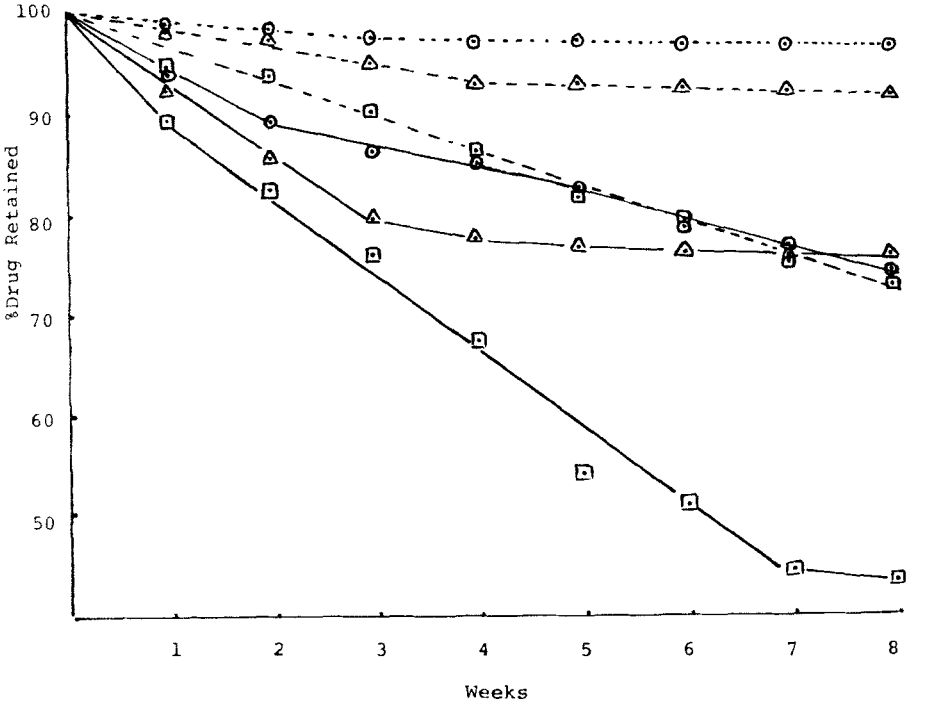

FIGURE 5. Effect of Lubricants on Chemical Stability of Prednisone Tablets Stored at 50° and 83% R.H. (-----) and at 70° and 96% R.H. (——)

⊡ - Magnesium Stearate

△ - Talc

⊙ - Stearic Acid

lack of any interaction between prednisone and stearic acid.

The decrease in prednisone content of tablets made with talc especially during storage at 70° and 96% R.H., is probably due to traces of heavy metal impurities pre-

sent in talc. Magnesium and aluminum-containing adjuvants of which talc is one, have been found by a diffuse reflectance study, to interact with prednisone (31).

In can be concluded from this study therefore, that talc and stearic acid are preferred to magnesium stearate as tablet lubricants, from the standpoint of prednisone stability in tablets.

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