DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(3), 213-235 (1980)

EFFECT OF PROCESSING FACTORS ON THE QUALITIES OF RESERPINE TABLETS

A. F. Asker*, M. M. Abdel-Khalek and I. Machloof

ABSTRACT

Reserpine tablets were made by five different processing techniques. The tablets were tested for weight variation, content uniformity, hardness, friability and disintegration. The stability of reserpine in the compressed tablets was evaluated at accelerated conditions of 50^0 and 83% R. H. for a period of 6 months and at room conditions for 18 months. In-vitro availability studies were conducted on the tablets produced by the various techniques. It is shown that the method of preparation of tablets influences their properties in cluding stability and in-vitro availability.

*School of Pharmacy, Florida A&M University, Tallahassee, Florida 32307

INTRODUCTION

Although a limited amount of information on interactions of drugs with various adjuvants in solid dosage forms is available, little work has been published on the influence of tablet processing factors, such as granulation techniques on the qualities of tablets including drug stability and/or availability.

Recent publications have pointed out wide variations in drug absorptoin from tablets produced by various manufactures (1,2). Failure to maintain uniform dosage and bioavailability due to poor product design and improper manufacturing techniques accounts for these variations. Maintenance of uniform drug content and its full availability appears to be difficult when low levels of drugs such as reserpine, digoxin and prednisone are required.

The objectives of this investigation therefore, were to study the influence of various granulation techniques on the qualities of reserpine tablets including drug stability and its in-vitro availability.

EXPERIMENTAL

Reserpine tablets having the following formula, were prepared by the various techniques:

	mg/tab.
Reserpine	2

Lactose, anhydrous (Diluent)	83
Polyvinylpyrrolidone (Binder)	5
Maize starch (Disintegrant)	8
Magnesium stearate (Lubricant)	2

Reserpine was first ground in a mortar and screened through a sieve of 0.1 mm mesh. All the other ingredients were similarly screened and the tablets were prepared by the following methods:

(1) Slugging (Dry Method A):

The fine powder of reserpine required to make 1000 tablets was mixed with lactose, polyvinylpyrrolidone and half the quantity of the lubricant by geometric dilution in the Turbula mixer for a total of 10 minutes. The mixture was then slugged on the Erweka single-punch tablet press using a 20-mm flat punch. The slugs were ground in the Erweka granulator using a screen of 1-mm mesh. The moisture content of the granules was determined by the Ultramat moisture balance and maintained within 1.8 ± 0.05±. The granules were mixed with the disintegrant and the remainder of the lubricant in the Turbula mixer for 10 minutes. The mixed granules were then compressed on the Erweka tablet press using a 7-mm flat punch.

(2) Partial Granulation (Dry Method B)

A placebo granulation was first prepared as follows: Lactose was kneaded with an aqueous solution of

polyvinylpyrrolidone in a mortar. The wet mass was passed through the granulator with a 5-mm mesh screen. The granules were dried in a tray dryer with circulating air at 40° for 8 hours. The moisture content was then determined and maintatined within 1.8 ± 0.05%.

(3) Wet Granulation:

a. Wet Method A: Reserpine was mixed with lactose by geometric dilution in the Turbula mixer for a total of 10 minutes. The aqueous solution of the binder was added to the powder and kneaded in a mortar to produce a coherent mass which was then passed through the granulator using a 5-mm mesh screen. The granules were dried in a tray dryer with circulating air at 40° for 8 hours. The moisture content was determined and maintained within 2.1 ± 0.1%. The dried granules were ground, mixed with the desintegrant and lubricant and then compressed into tablets as described before.

b. Wet Method B: The same procedure as that described under wet method A was followed, except that reserpine was dissolved in a mixture of equal volumes of alcohol and chloroform in which the binder had been dissolved.

c. Wet Method C: The tablets were prepared as described under wet method A, but reserpine was suspended in an aqueous solution of the binder.

Evaluation of the Qualities of Tablets:

(1) Weight Variation and Content Uniformity: The USP XIX (3) procedure was followed, but reserpine was assayed in the individual tablets by the method reported by Brochmann-Hanssen and Medina (4). In case of content uniformity determination, three samples each of 10 tablets were subjected to the test. The results are shown in Table 1.

(2) Hardness: A sample of 10 tablets was taken at random from each batch and tested for hardness using the Erweka hardness tester.

(3) Friability: A sample of about 10 grams of tablets was taken at random from each batch and allowed to rotate in the Roche friabilator at 25 rpm for 15 minutes. The intact tablets were brushed with a camel hair brush to remove any adhering powder and weighed. The average percentage friability was then calculated for two samples

(4) Disintegration: A sample of 6 tablets was taken at random from each batch and subjected to the USP XIX disintegration test without the use of disks (5).

The reseults on hardness, friability and disintegration are shown in Table 2.

(5) In-Vitro Availability: The USP XIX, does not include in the monorgraph on reserpine tablets a dissolution requirement. Therefore, in order to determine the in-vitro availability of reserpine tablets, the following procedure was followed:

TABLE 1

Weight Variation and Content Uniformity of Reserpine Tablets Prepared by the Various Techniques

Method	Weight Variation		Content Uniformity	
	Avg. Wt.(mg)	Standard Deviation	% Reserpine	Standard Deviation
1. Slugging	97.455	1.34	99.830	3.628
2. Partial Granulation	97.970	1.47	92.420	13.410
3. Wet Granulation				
a. Method A	101.780	0.78	101.067	6.129
b. Method B	101.735	0.86	99.670	9.705
c. Method C	99.950	1.83	97.930	3.172

TABLE 2

Hardness, Friability and Disintegration Time of Reserpine Tablets Prepared by the Various Techniques

	Slugging	Partial Granulation	Wet Method A	Wet Method B	Wet Method C
Hardness range (Kg)	2.3-2.8	4.5-7	5-6.5	4-6.5	5.3-6.3
% Friability	5	0.85	0.75	0.9	0.8
Disintegration time range (minutes)	1-4	8-13	9-12	10-12	9-11

Five tablets were taken at random from each batch prepared by the method in question. Each individual tablet was placed in the rotating basket of the USP XIX dissolution apparatus. The basket was immersed in a 150-ml beaker containing 100 ml of 10% w/v phosphoric acid (pH=1.2). The temperature of the batch was maintained at 37^{0}, and the basket was allowed to rotate at 100 rpm at a distance of 2 cm from the bottom of the beaker. Five ml of the dissolution medium was withdrawn by a filtering pipet containing a plug of filter paper at 15 minute intervals. The solution was again filtered through Whatman No. 50 filter paper. An equal volume of 10% w/v phosphoric acid was introduced into the beaker to keep the volume of the dissolution medium constant. The concentration of reserpine was determined spectrophotomerically at 268 mμ from a calibration curve using 10% w/v phosphoric acid as a blank. The adjuvants used were found not to interfere with the spectrophotometric assay. A cumulative correction was made for the previously removed samples in determining the total amount of reserpine dissolved according to the equation used by Sciarra and Patel (6).

The same test was carried out on tablets prepared by wet method C, but using 0.005 N acetic acid (pH=3.5) and 0.6% w/v HCl (pH=1.5) as the dissolution media, in order to study the influence of dissolution medium on

reserpine release. This appears to be of interest in view of the fact that no dissolution test is included in the USP. The results are shown in Table 3 and Figure 1.

(6) Chemical Stability of Reserpine Tablets: Samples of tablets prepared by dry method A, wet method B and wet method C were placed in loosely capped amber glass vials and stored at 50° and 83% R.H. for a period of 6 months. This storage environment was maintained by placing a saturated solution of potassium chloride in a desiccator that was kept in a incubator maintained at 50°. The content of reserpine was determined montly using the USP xVIII (7) assay method for reserpine tablets. The data are represented by Fig. 2.

Furthermore, samples of tablets placed in tightly capped amber glass vials were stored at room conditions

TABLE 3

Average Cumulative Percentage Reserpine Dissolved in 10% w/v Phosphoric Acid From Tablets Prepared by Various Techniques

Time	Slugging		Partial Granulation		Wet Method A		Wet Method B		Wet Method C	
(min)	Avg%	S.D.	Avg%	S.D.	Avg%	S.D.	Avg%	S.D.	Avg%	S.D.
15	100.5	3.6	84.56	15.2	83.3	10.3	93.8	9.5	96.9	4.2
30	102.9	3.9	103.29	13.8	102.1	4.8	103.0	8.9	101.0	2.8
45	104.2	3.2	113.45	12.7	108.5	3.2	107.2	9.9	102.5	3.6

*Values based on 5 individual tablets

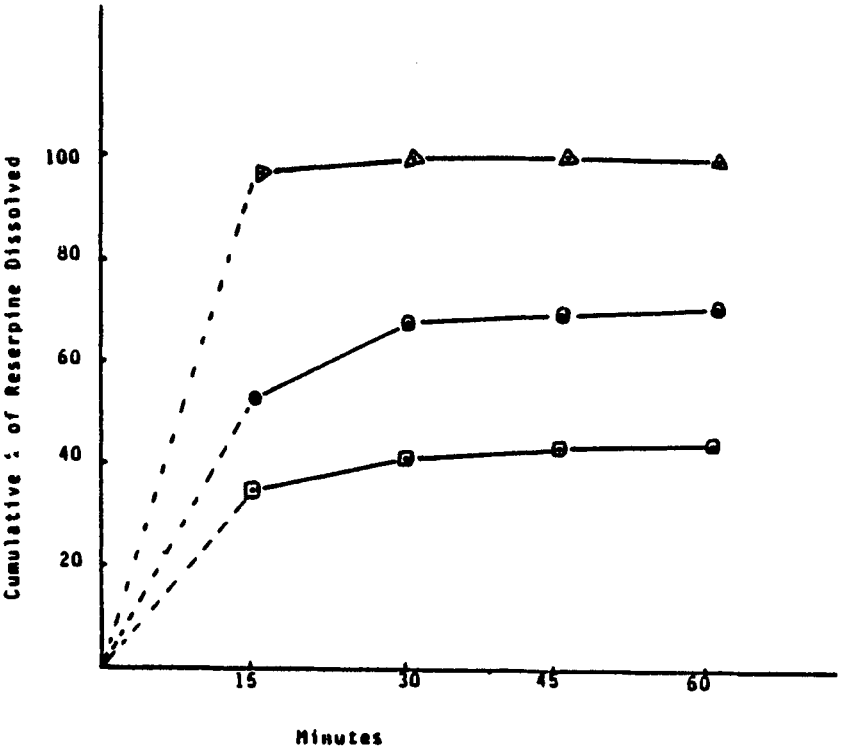

FIGURE 1. Dissolution of Reserpine in Various Media from Tablets Prepared by Wet Method C

▲ 10% w/v Phosphoric Acid
● 0.005 N Acetic Acid
■ 0.6% w/v Hydrochloric Acid

for a period of 18 months. The concentration of reserpine was determined at the end of this period. The results are shown in Table 4.

(7) Discoloration of Reserpine Tablets During Storage: Samples of tablets prepared by dry method A, wet method B and wet method C were stored at 50° and 83% R.H. in

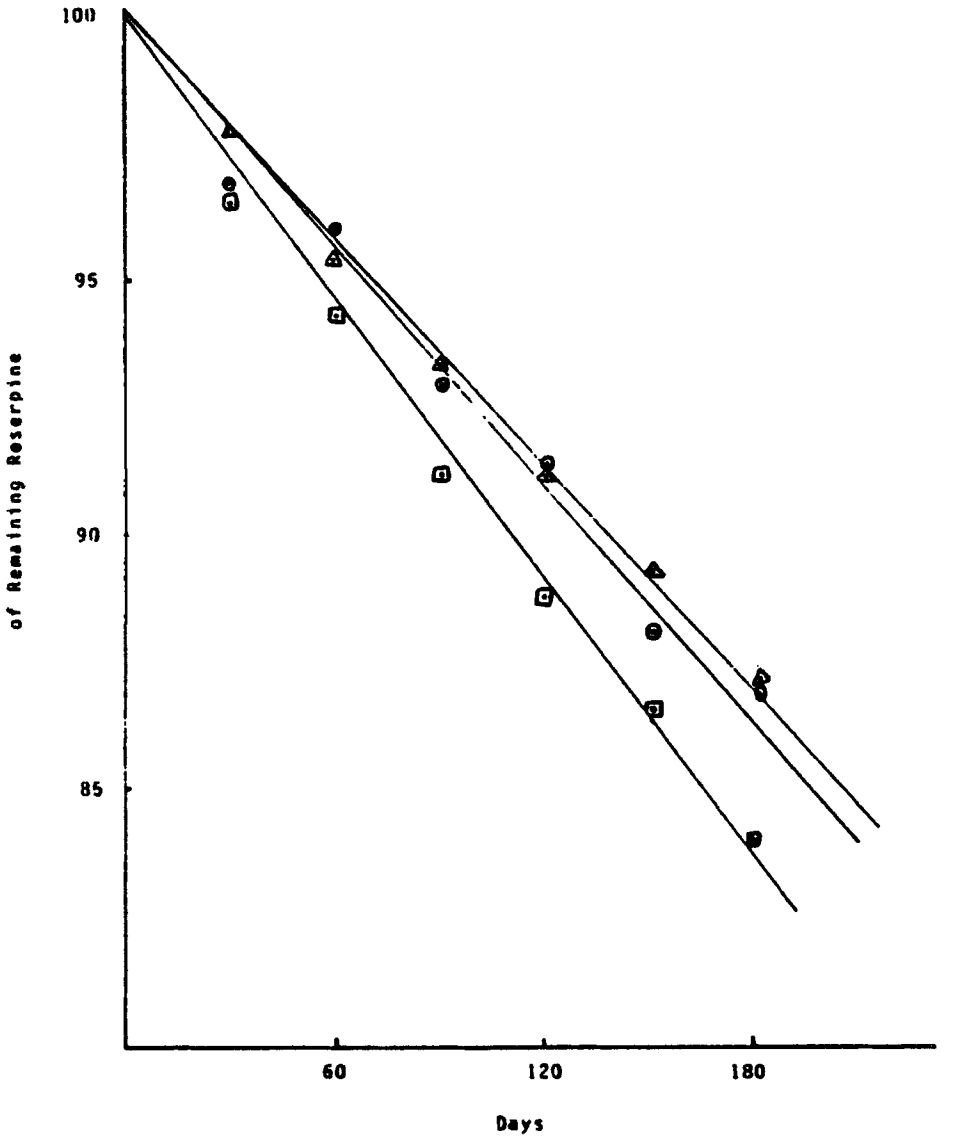

FIGURE 2. Degradation of Reserpine in Tablets Prepared by Various Techniques and Stored at 50° and 83% R. H.

▲ Dry Method A

■ Wet Method B

● Wet Method C

TABLE 4

Chemical Stability of Reserpine Tablets Prepared by Three Different Methods and Stored at Room Conditions for 18 Months

Methods	% of Reserpine Remaining in 3 Samples After Stoarage for 18 Months at Room Conditions			
	(1)	(2)	(3)	Average
Slugging	90.48	93.33	94.10	92.64
Wet Method B	83.33	84.52	84.52	84.12
Wet Method C	85.71	88.10	89.29	87.70

loosely capped amber glass vials for 6 months. The yellow color developed on the tablets was periodically determined using the following method: Ten tablets were taken from each batch, ground in a small mortar. The powder was quantitatively transferred into a small beaker using 7 ml of ethyl alcohol. The solution was then filtered through Whatman filter paper No. 50, previously washed with ethyl alcohol, into a 10-ml volumetric flask. The residue in the beaker was mixed with a small portion of ethanol and the mixture was passed through the filter paper. The filtrate was adjusted to volume with ethyl alcohol and its optical density was measured at 375 mμ, using placebo tablets treated similarly to serve as a blank. The data were shown in Table 5.

TABLE 5

Comparative Discoloration of Reserpine Tablets Prepared by Three Different Techniques

Method	Absorbance of the Yellow Color Developed in Reserpine Tablets During Storage at Various Conditions for 12 MOnths									
	Initial		2 Months		4 Months		6 Months		12 Months	
	R.C.	A.C.	R.C.	A.C.	R.C.	A.C.	R.C.	A.C.	R.C.	A.C.
Slugging	0	0	0	0.016	0.005	0.024	0.023	0.144	0.07	0.28
Wet Method B	0.015	0.015	0.185	0.40	0.345	0.604	0.415	0.834	0.67	0.97
Wet Method C	0	0	0	0.08	0.015	0.174	0.035	0.264	0.11	0.36

R.C. = Room Conditions

A.C. = Accelerated Conditions of 50° and 83% R.H.

DISCUSSION OF RESULTS

Weight Variation and Content Uniformity:

Data of Table 1 indicate the values of standard deviation for weight variation were in the range of 0.78-1.83 and all batches prepared by the various techniques were found to comply with the USP requirements for weight variation. However, not all the batchs fulfilled the official requirements for content uniformity. Partial granulation technique and wet method B produced tablets that did not comply with the USP requirements for content uniformity. These results were reflected by the high values of standard deviation obtained with these 2 methods. These findings support the conclusion of previous works that tablet weight variation is not always an indication of content uniformity especially when dealing with small quantities of active ingredients (4, 8,9).

The compliance of the tablets made by slugging with the official requirements for content uniformity may be attributed to a more efficient mixing of the active ingredient and the adjuvants due to homogenity of the particle size of the mixture. Moreover, the apparent free flowability of the granules during final compression resulted in the production of tablets of more uni-

form weight which would generally contribute to better content uniformity.

Failure of the tablets made by partial granulation to comply with the USP requirements for content uniformity with a high value of standard deviation may be attributed to segregation of the powder drug-placebo granules mixture due to wide difference in prticle size of the drug and the placebo granules. An attempt was made to overcome this problem by reducing the particle size of the placebo granules. However, this resulted in a mixture lacking suitable compressibility. Tablets prepared by precompression have been reported to be more uniform in content of active ingredient than tablets made by the process of mixing two or more separate granulations that would tend to separate in the feeding devices (10).

In case of wet granulation techniques, methods A and C produced tablets that complied with the USP requirements for content uniformity, while method B failed to do so. Method C gave better content uniformity than either wet method A or dry method A as evidenced by its lowest value of standard deviation for content uniformity.

In preparing tablets by wet method C, the binder solution acts as a carrier for the finely divided suspended drug particles, and therefore effecting a homogenous distribution of the drug. The use of a suspension

or a solution of an active drug in a nonaqueous carrier has been suggested to ensure uniform distribution of small quantities of active ingredients in dry blend for direct compression (11).

Wet method B was expected to provide uniformity of drug content in view of the fact that the drug was dissolved in the solution of the binder in the organic solvent mixture. However, the tablets produced by this method demonstrated the highest value of standard deviation. Moreover, the tablets failed to comply with the USP requirements for content uniformity. The reason for this may be attributed to migration of the drug during drying of the tablet granules in the tray dryer. This would result in variation of drug content at various levels in the granulation bed. The migrated drug would concentrate into the upper layer of the granules. These results are in accordance with the findings of Chaudry and King (12) who have shown intergranular migration of sodium warfarin in a tray-dried granulations to cause such variation in compressed tablets that only 12% of those sampled were within the USP limits. A second possibility of lack of content uniformity in these tablets might be that a normal batch of granules would have a wide distribution of granule sizes and porosities; consequently, the larger granules having more void spaces will upon drying contain more drug than the finer granules

which will only have a surface coating. This observation has been reported by Cox et al. (13) and Nicholson and Enever (14).

In case of wet method A, the tablets were found to comply with the USP requirments for content uniformity although two tablets out of thirty demonstrated the upper permissible limit for drug content. These results would suggest that conditions of wet method A appear to be critical and they may result in the production of tablets lacking content uniformity. This was found to be true when the method was scaled up since the tablets produced on a semi-large scale by this method, were found to deviate substantially from the official limits of content uniformity (15).

Hardness, Friability and Disintegration Time: It can be seen from Table 2, that the technique used in making tablets influences their physical properties.

Compared with all the other techniques studied, slugging was found to produce tablets having the highest friability value and the lowest values for hardness and disintegration time. This can be attributed to lack of sulfficient cohesiveness in the dry blend since the dry binder used is not as effective as a binder solution in reaching and wetting each of the particles within the mass of powders (16). Moreover, the lactose used as diluent in this study will partially dissolve in the

binder solution and then recrystallize upon drying the tablet granulation forming solid bonds that would contribute to the strength of the granules. This view has been expressed by Harwood and Pilpel (17), and Hunter and Granderton (18). Tablets prepared by precompression have been reported by Chalmers and Elworthy (19) to disintegrate more rapidly than those prepared by wet granulation presumably also due to weakness of the cohesive bonds that hold the tablet together.

The slightly higher amount of residual moisture in the granulations obtained by partial granulation and wet methods A, B and C, would be also linked to the high values of hardness and disintegration time and the low friability value. This residual moisture would contribute to the cohesiveness of the tablet matrix.

It also appears from Table 2, that no or only a negligible difference is observed in the values of hardness, friability and disintegration time of tablets prepared by partial granulation and any of the wet methods. This can be expected in view of the fact that wet granulation was also followed in the preparation of the placebo granulation required for the partial granulation technique. Moreover, reserpine was incorporated into the placebo granulation in a too small quantity to confer any effect on the properties of this granulation.

In-Vitro Availability

Table 3 shows the percentage concentration of reserpine released into 10% w/v solution of phosphoric acid at various time intervals. The data indicate that the initital percentage of reserpine released during the first 15 minutes was in the following descending order: slugging > wet method C > wet method B > wet method A or partial granulation. This order can be considered with experimental error, to correspond with that obtained from the results of the effect of techniques on disintegration time. The same type of argument used earlier to explain variation in disintegration time is also applicable here. No substantial difference was noted in the percentage of drug released at the later time intervals among the tablets produced by the various techniques. This is probably due to the powerful solvent action on phosphoric acid on reserpine.

The highest value of standard deviation for the percentage of reserpine dissolved at the various time intervals was demonstrated by tablets prepared by partial granulation, and then followed tablets made by wet method B. Tablets prepared by either slugging or wet method C, on the other hand appeared to give the lowest values of standard deviation. These reflect the results of variation in reserpine content uniformity previously determined for the various batches of reserpine tablets.

The release of reserpine from tablets made by partial granulation was very erratic in regard to tablet-to-tablet content variation. These results also support previous conclusions made by Morris et al. (20), who emphasized the importance of predetermination of content uniformity before bioavailability is considered.

In view of the fact that no dissolution test is included in the USP XIX for reserpine tablets, a preliminary investigation was undertaken to study the effect of some dissolution media on reserpine release from tablets prepared by wet method C. The dissolution media tested were 10% w/v phosphoric acid, 0.005 N acetic acid and 0.6% w/v hydrochloric acid. Figure 1 shows that the percentage of reserpine released at any time interval in various dissolution media was in the following ascending order: phosphoric > acetic > hydrochloric. It also appears that dissolution of reserpine from the tablets in independent of the pH of the dissolution media tested, but is rather influenced by the anionic species of the acid that is capable of forming salts with reserpine which is a weakly basic compound. However, a more comprehensive study is needed to support this conclusion.

Chemical Stability of Reserpine Tablets:

Figure 2 reveals that reserpine degraded according to a zero-order rate when the tablets were stored at 50° and 83% R.H. for a period of 6 months. This rate order is unexpected in view of the reported results

on degradation of insoluble drugs in solid dosage forms. It has been indicated that in the presence of moisture, degradation of drugs in solid dosage forms follows a zero-order rate since the decomposition kinetics are indicated by the rates in saturated solutions (21).

The highest percentage of reserpine degradation under the exaggerated conditions used in this study was less than 20%. Therefore, it appears that a more comprehensive kinetic study for a longer period of time and/or at more accelerated conditions, is needed for a more meaningful interpretation of the kinetic study in terms of long-term stability prediction. However, the results obtained from this study would provide preliminarey information as to the comparative effects of the various manufacturing techniques on the stability of reserpine tablets.

From Figure 2, it can be seen that the values of $t_{0.9}$ for tablets prepared by wet methods B anc C and dry method A are 100, 127 and 131 days respectively. The reason for the slugging method giving a slightly higher value of $t_{0.9}$ is that because the technique does not subject the drug to moisture or heat which would enhance hydrolytic as well as oxidative degradation of reserpine (22, 23).

Both wet methods B and C subject reserpine to thermal effect in the drying process. However, tablets prepared by wet method C were found to retain a higher

percentage of reserpine content than those prepared by wet method B. This may be due to the effect of chloroform used in the granulating liquid in wet method B. Chloroform has been reported to accelerate oxidative degradation of reserpine (22). As a result of this effect, reserpine tablets prepared by wet method B showed more discoloration than those made by any of the other methods as shown in Table 5.

The values of $t_{0.9}$ obtained for the various techniques are also reflective of the amount of reserpine remaining in the various batches of tablets at the end of the storage period of 6 months.

Data on the stability of reserpine tablets prepared by the various techniques and stored at room conditions for 18 months indicate the same order of preference as that obtained from the accelerated stability study.

Discoloration of Reserpine Tablets:

It is evident from Table 5, that regardless of the manufacturing technique used, all batches of tablets demonstrated less discoloration when stored at room conditions than when stored at 50^{o} and 83% R.H. This is of course attributed to the enhanced degradation of reserpine at elevated temperatures.

Tablets prepared by slugging showed the least extent of discoloration followed by those made by wet

method B. These results are reflective of those of chemical stability of reserpine previously discussed. The same explanation given for the effect of manufacturing techniques on chemical stability of reserpine are also applicable here. The more intense discoloration was exhibited by tablets prepared by wet method B due to the effect of residual cholorform. Tablets prepared by wet method C and stored at room conditions showed a slight discoloration, whereas those prepared by slugging and stored at the same conditions remained almost colorless.

Therefore, from the standpoint of chemical and color stability of reserpine tablets, the various manufacturing techniques can be arranged in a descending order of preference as follows: slugging > wet method C > wet method B.

REFERENCES

(1) J. Lindenbaum, M. H. Mellow, M. O. Blackstone and U. P. Butler, Jr., New Eng. J. Med., 285, 1344 (1971).

(2) D. L. Sorby and T. N. Tozer, Drug Intel., 7, 78 (1973).

(3) "United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, PA, 1975, p. 671.

(4) E. Brochmann-Hanssen and J. C. Medina, J. Pharm. Sci., 52, 630 (1963).

(5) "United States Pharmacopeia," op. cit., p. 650.

(6) J. J. Sciarra and S. P. Patel, J. Pharm. Sci., 65, 1519 (1976).

(7) United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, PA, 1970, p. 589.

(8) R. E. Moskalyk, L. G. Chatten, C. E. Fox, and M. Pernarowski, J. Pharm. Sci., 50, 651 (1961).

(9) J. M. Airth, D. F. Bray, and C. Radecka, Ibid., 56, 233 (1967).

(10) "Dispensing of Medication," 7th ed., E. W. Martin, Ed., Mack Publishing Co., Easton, PA, 1971, p. 790.

(11) L. Lachman, H. Lieberman, and J. Kanig, "The Theory and Practice of Industrial Pharmacy," Lea and Febiger, Philadelphia, PA, 1970, p. 649.

(12) I. A. Chaudry and R. E. King, J. Pharm. Sci., 61, 1121 (1972).

(13) P. H. Cox, T. J. G. Ambaum, and H. P. Wijnand, J. Pharm. Pharmacol., 20, 238 (1968).

(14) G. L. Niclson and R. P. Enever, ibid., 26, 420 (1974).

(15) To be published.

(16) "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA., 1975, p. 1578.

(17) C. F. Harwood and N. Pilpel, J. Pharm. Sci., 57, 478 (1968).

(18) B. M. Hunter and D. Ganderton, J. Pharm. Pharmac., 24, Suppl., 17P (1972).

(19) A. A. Chalmers and R. H. Elworthy, ibid, 28, 234 (1976).

(20) R. M. Morris, J. L. Stowers, S. W. Mundy, and F. L. Hicks Jr., Current Therap. Res., 20, 103 (1976).

(21) J. T. Carstensen and P. Pothisiri, J. Pharm. Sci., 64, 37 (1975).

(22) A. F. Leyden, E. Pomerantz and E. F. Bouchard, J. Am. Pharm. Ass., Sci., Ed., 45, 771 (1956).

(23) J. W. Warren Jr., and E. J. Rowe, Can. J. Pharm. Sci., 10, 40 (1975).