Sustained-Action Tablets Prepared by Employing a Spray-Drying Technique for Granulation

SAUL S. KORNBLUM

Abstract □ A spray-drying technique has been investigated which provides a free-flowing powder with decreased dissolution rate for the medicinal agent when compressed into tablets. The fine powder (10–150 μ) obtained by this process has proved to possess excellent drug distribution and when tableted offers good reproducibility of drug release for consecutive batches. The consistency of the drug-release pattern is tabulated and the drug-release phenomena discussed. The effect of aging on the release rate of the sustained-action tablets has been investigated.

Keyphrases □ Sustained-action tablets—spray-drying technique □ Spray-dried powder—sustained-action matrix □ Particle-size determination—spray-dried powder □ Dissolution rates, tablets—spray-dried powder effect

Spray drying has been utilized pharmaceutically for many years for the preparation of free-flowing microparticles which are used in the manufacture of solid dosage forms. Previous researchers (1, 2) have described the utility of the process including the varied formulations and operational techniques that must be considered for the successful employment of spray drying. Newton (3) has provided an excellent review wherein the physical characteristics of spray drying are elucidated as well as specific practical considerations.

Spray drying has been employed for the manufacture of drug matrices that are subsequently processed into various solid-dosage forms; however, no report exists that has utilized the many advantageous physical properties of spray-dried powder in the development of a sustained-action tablet dosage form. Uniformity of drug distribution in the matrix and ease of reproducibility are two major factors comprising the utility of spray drying in this matter.

The purpose of this study was to determine the suitability of a spray-drying technique in the manufacture of a drug matrix that would possess sustained action when compressed into tablets. Major emphasis has been directed to the reproducibility of the drug-release rate for consecutive batches.

EXPERIMENTAL

Materials—Isobutylallylbarbituric acid was combined with various proportions of ethylcellulose, low viscosity,[1] and methylcellulose 60 HG, 50 cps.,[2] employing a spray-drying technique so that the rate of dissolution of the barbituric acid derivative would be reduced.

[1] Marketed as Ethocel, Dow Chemical Co., Midland, Mich.

Table I—Determination of Particle-Size Distribution of Spray-Dried Powders Employing Sieve Analysis

Sieve Size, Mesh	Av. Diam. of Particles, μ	% by Wt. Retained by Sieve[a]
100	149	12.5
120	125	5.2
200	74	27.4
325	44	11.6
>325	<44	43.3

[a] Average determined by comparing five batches.

An example of the solids composition of the slurry for spray drying that was determined most suitable from a drug-release standpoint is described below:

	% w/w
Isobutylallylbarbituric acid	24.0
Ethylcellulose, low viscosity	4.5
Methylcellulose 60 HG, 50 cps.	1.0
Calcium sulfate dihydrate	65.6
Alginic acid	4.9

Preparation of Slurry—The isobutylallylbarbituric acid and ethylcellulose, low viscosity, were placed in a stainless steel vessel containing 1,000 ml. of special denatured alcohol (90% ethanol:10% methanol). A propeller-type mixer was employed to stir until the solids were dissolved. In another vessel, 200 ml. of purified water was heated to boiling and the methylcellulose 60 HG, 50 cps., slowly added to the vortex formed by the propeller mixer until the synthetic gum was completely dispersed. The hydrated methylcellulose was then slowly added to the alcoholic solution. Finally, the calcium sulfate dihydrate and alginic acid were added and mixed until a uniform smooth slurry was obtained. Each batch manufactured contained 1 kg. of solids.

Spray-Drying Technique—A portable laboratory spray dryer[3] equipped with a centrifugal atomizing wheel functioning from air-turbine drive with a velocity of about 40,000 r.p.m. was employed in this study. The heated chamber of the spray dryer was maintained at 150–160° and the outlet temperature at 90–100°. The slurry must be maintained uniform throughout the spray-drying process by use of a propeller mixer. The slurry was introduced to the atomizing wheel employing a pump[4] which maintained the flow at the rate of 45 g./min. A cyclone collector was employed to separate the spray-dried powder from the solvent.

Spray-Dried Powder Particle-Size Determination—The particle-size distribution of the spray-dried powder was determined using a sonic sifter[5] (Table I). The validity of the data obtained using the

[2] Marketed as Methocel, Dow Chemical Co.

[3] Nerco-Niro, distributed by Nichols Engineering & Research Corp., New York, N. Y.

[4] Sigmamotor, Inc., Middleport, N. Y.

[5] Allen-Bradley Co., Milwaukee, Wisc.

Table II—Physical Specifications and Properties of Tablets Prepared from the Spray-Dried Powder

	Batch No. 1	2	3	4	5
Theoretical wt., mg.	255	255	255	255	255
Actual wt., mg.	253	256	254	255	254
Tablet diam., mm.	8	8	8	8	8
Thickness, mm.	3.15	3.20	3.20	3.15	3.20
Hardness, Strong-Cobb apparatus	11	11	11	11	11
Friability, Roche friabilator: 100 drops	no loss	no loss	no loss	no loss	no loss

sieve method was substantiated by photomicroscopic analysis. The microscopic method clarified the absence of significant electrostatic aggregation of the fine powder that is often encountered when using a sieve method for particle-size analysis.

Tablet Manufacture from Spray-Dried Powder—The formula and procedure used in preparing the tablets from the spray-dried powder is as follows:

	mg./tablet
Isobutylallylbarbituric acid spray-dried powder	250.0
Magnesium stearate	5.0

The magnesium stearate was bolted through 100-mesh screen and placed with the spray-dried powder in a blender.[6] The powders were blended for 5 min. The blended powders were then compressed into tablets using a single-station machine[7] employing 8-mm. flat, bevel-edge punches. The physical specifications and properties of tablets prepared from the five batches discussed in this study are tabulated in Table II.

Dissolution-Rate Study—An *in vitro* method was designed to be utilized in determining the decreased dissolution rate of the spray-dried powder as compared to pure isobutylallylbarbituric acid and the sustained action of the compressed tablets. The dissolution-rate method and chemical analysis employed for the powders and tablets is outlined below.

The dissolution rates of isobutylallylbarbituric acid during the first, second, third, and fourth hours, were determined for the tablets at the time of manufacture and after 16-months' normal storage.

The results obtained, when comparing the dissolution rate for 250 ml. spray-dried powder *versus* 60 mg. pure isobutylallylbarbituric acid, demonstrated an insignificant retarding effect for the concentration of water-insoluble materials employed in this study. The pure isobutylallylbarbituric acid and the spray-dried powder were determined to be completely in solution within 5 min. after treatment outlined below.

Pipet 50.0 ml. of simulated gastric fluid (prepared without pepsin) into a 75-mg. amber-glass bottle. Place one tablet or powder in the bottle and agitate on rotating-bottle apparatus (40 rotations/min.) for 1 hr. at 37°. At the end of the first hour, remove 25.0 ml. of solution by means of a filter-tip pipet. Assay this solution by taking a 2.0-ml. aliquot and dilute to volume in a 100-ml. volumetric flask with 0.1 *N* NH_4OH. Add 25.0 ml. fresh gastric fluid and return bottle to apparatus and rotate for the second hour. At the end of the second hour, withdraw a 25.0-ml. sample and assay this solution in the same manner as was performed for the first-hour sample. Add 25.0 ml. of intestinal fluid to the bottle and rotate for the third hour. At the end of the third hour, take a 25.0-ml. sample by means of a filter-tip pipet and assay as before. Add 25.0 ml. fresh intestinal fluid and rotate for the fourth hour. At end of the fourth hour, take 25.0 ml. of solution and assay.

Carefully decant the remaining 25 ml. while leaving behind all the residue. Pipet 50.0 ml. of 0.1 *N* NH_4OH into the bottle and then crush the remaining tablet. Rotate the contents for 15 min. Subsequently, filter the entire contents into a volumetric flask and bring the volume to 100 ml. with the 0.1 *N* NH_4OH washings. Dilute a 5.0-ml. aliquot of the filtrate to 50.0 ml. with 0.1 *N* NH_4OH. Determine the absorbance at 240 mμ using a spectrophotometer. Calculate the percent of isobutylallylbarbituric acid released during the specific time segment employing the outlined formulas below:

1st hr.
$A_{240}/1.056 \times 100 =$ % isobutylallylbarbituric acid released.

2nd hr.
$A_{240} - 0.5$ (A_{240} of 1st hr.)$/1.056 \times 100 =$ % isobutylallylbarbituric acid released.

3rd hr.
$A_{240} - 0.5$ (A_{240} of 2nd hr.)$/1.056 \times 100 =$ % isobutylallylbarbituric acid released.

4th hr.
$A_{240} - 0.5$ (A_{240} of 3rd hr.)$/1.056 \times 100 =$ % isobutylallylbarbituric acid released.

Residue
$A_{240}/2.640 \times 100 =$ % isobutylallylbarbituric acid in residue.

[6] Twin-Shell, Patterson-Kelley Co., East Stroudsburg, Pa.
[7] Stokes E Tablet Press, Warminster, Pa.

Table III—Uniformity of Drug Distribution for Spray-Dried Powder

Powder Sample	Actual % by Wt. Isobutylallylbarbituric Acid[a]
1	94.9 ± 1.1
2	92.8 ± 0.7
3	93.5 ± 0.3
4	94.3 ± 0.3
5	93.6 ± 0.9

[a] Average of two assays for Batch No. 2.

RESULTS AND DISCUSSION

A spray-drying technique for the manufacture of a sustained-action tablet offers some advantages when compared with the process using water-insoluble matrices, *i.e.*, fatty acids, fatty esters, waxes, and cellulose derivatives that were previously described (4). The last reference has employed a conventional wet-granulation technique which does result in certain manufacturing problems such as drug distribution and uniformity of drug release for consecutive batches. Previous literature (1, 3) has indicated certain advantages of the spray-drying process as related to the wet-granulation method, *i.e.*, improved color distribution in a tablet matrix, limited exposure to high temperatures for heat-sensitive drugs, excellent flowability of the powder for high-speed tableting, and absence of residual granulating solvents in the powder. The present study concerning sustained-action tablets has demonstrated the attainment of uniformity of drug distribution and consistency of drug release for consecutive batches of tablets with the employment of spray drying for granulation.

If comparison is drawn, it appears apparent that spray drying does offer some improvement or reduction of effort when compared with the conventional wet method. It was proved that a noteworthy reduction of water-resisting agents necessary to accomplish sustained action exists with the spray-drying method. In the present study 5.5% by weight of the water-resistant components of the tablet was proved suitable for sustained action. A previous investigator (4) using similar water-resistant agents required generally about 15% of this material in order to achieve similar sustained-action tablets. In general, water-resistant agents have been known to increase tablet hardness after normal storage, and it was felt that by reducing their content, the extent of the physical change could possibly be diminished.

The slurry preparation offers excellent homogeneity between the drug and the water-insoluble component since they are both dissolved in the solvent system. The solids content of the slurry has been found suitable in a range from 50 to 60% by weight (3). The solvent system employed must solubilize the drug and the water-insoluble component; however, the inert drug carrier should be insoluble. The calcium sulfate dihydrate was employed as the inert drug carrier. The methylcellulose 60 HG and ethylcellulose, low viscosity, provided the necessary water-insoluble retardants which associated in intimate dispersion with the drug. The drug and cellulose derivatives coat the calcium sulfate dihydrate particles. The spray-drying process rendered spherical particles in the 10–150-μ range. The great variation in particle size of the spray-dried powder

Table IV—Cumulative Release Rate for the Isobutylallylbarbituric Acid Sustained-Action Tablets

Batch No.	% by Wt. of Cumulative Release of Isobutylallylbarbituric Acid, hr.[a] 1	2	3	4	Residual
1	44.6	63.1	70.0	75.7	21.3
2	40.6	61.8	69.0	75.7	18.2
3	42.7	62.5	67.6	73.5	20.0
4	35.6	60.9	65.2	72.0	27.3
5	41.8	67.1	73.0	80.4	16.5

[a] Dissolution-rate method and analytical procedure outlined under *Experimental.*

Table V—Cumulative Release Rate for the Isobutylallylbarbituric Acid Sustained-Action Tablets Stored Under Normal Conditions for 16 Months

Batch No.	% by Wt. of Cumulative Release of Isobutylallylbarbituric Acid, hr.[a] 1	2	3	4	Residual
1	40.6	58.9	70.2	75.5	23.4
2	30.8	52.3	64.4	68.2	27.3
3	26.4	46.5	60.2	64.3	30.1
4	28.7	57.1	71.4	77.6	20.9
5	29.2	52.3	66.9	72.0	23.7

[a] Each cumulative percent is an average of five individual tablets.

appeared to be a result of the varied particle-size distribution of the calcium sulfate dihydrate, perhaps as a result of not employing a colloid mill when preparing the slurry. The uniformity of particle-size distribution remained quite constant for consecutive batches.

The uniformity of the drug distribution for spray-dried powder containing 60 mg. drug/250 mg. drug matrix was exceptionally good (see Table III). The powder samples for Batch No. 2 were withdrawn at 30-min. intervals during the spray-drying process. Only Batch No. 2 was handled in this manner in order to establish consistent drug distribution throughout the process. In the case of the other batches, two powder samples were taken from the total yield of spray-dried powder so that the drug content could be established.

In this study a colorant was not used; however, previous researchers (1) have described the excellent color uniformity that may be obtained if color is desired. The alginic acid has provided a swelling property to the compressed tablets that permitted necessary water penetration for drug-dissolution purposes. During the 4-hr. *in vitro* dissolution-rate analysis, the compressed tablets remained intact and did not fall apart or disintegrate upon being exposed to alimentary fluids.

If high concentrations of the ethylcellulose were employed in preparing the spray-dried powder, it resulted in a significant decrease in the drug-release rate. When the ethylcellulose content was reduced to 2.5% by weight, about twice the amount of drug was released during the first hour as compared to the reported data. Therefore, this process does provide an opportunity to obtain varied release patterns with slight variation of the water-insoluble components.

The drug is released from the compressed tablet by means of a combined dissolution and diffusion process. The tablet upon first exposure to gastric fluid hydrates and swells, thus permitting water diffusion into the interior of the tablet matrix. A dynamic phenomenon of both dissolution of the drug in alimentary fluids and subsequent diffusions from the tablet matrix into the alimentary canal results in sustained action. As pointed out previously, the concentration of the cellulose derivatives required to provide this sustained action is considerably less than that required when employing the wet-granulation process. With the spray-dried powder, there is most probably more intimate contact between the drug and water-insoluble cellulose derivatives thus decreasing the amount of methyl and ethylcellulose needed to retard dissolution.

The spray-dried powder combined with a lubricant was readily compressed into hard tablets with a minimum-pressure adjustment of the tablet machine. The weight variations of the tablets manufactured from the spray-dried material were within ±1.5% of the average tablet weight.

The cumulative release data from five similar batches of isobutylallylbarbituric acid sustained-action tablets are tabulated in Table IV. The cumulative release data for each batch represent the average of two tablets. The cumulative release percentages calculated were derived from individual values which in all cases did not exceed a 3.7% difference.

The release data demonstrate good consistency of available drug for consecutive batches. As previously described, the release pattern can be altered by varying the ethylcellulose content of the spray-dried powder. The release rate pattern obtained in this study typifies published data concerning sustained-action solid dosage forms (4, 5). It appears obvious with the advent of the biopharmaceutic approach that *in vivo* testing of such tablets would be required before accepting the proposed dosage form as possessing desirable characteristics for sustained action.

It is a well-known fact that certain characteristics of the dosage-form matrix such as hardness, crystalline structure of the retardant, and moisture content, can vary upon normal storage and cause alteration of the original release pattern. The five tablet batches reported in this study were stored in tightly closed glass containers for 16 months at room temperature and the cumulative release percentages of this study are tabulated in Table V. The cumulative release percentages calculated were derived from individual values which in all cases did not exceed a 4.4% difference.

The cumulative release data when compared with data in Table IV indicate a decrease in the drug available during the first hour from the sustained-action tablets stored for 16 months under normal conditions. It is interesting to note that during the second and third hour in Tables IV and V the cumulative release does adequately compare. The tablet hardness increased from 11 to 15 kg. after 16 months storage and is possibly the cause for decreased dissolution during the first hour.

SUMMARY

A spray-drying method has been described for the manufacture of a drug matrix which possesses sustained action when compressed into tablets. The method possesses the advantages of uniformity of drug distribution and reproducibility of drug release pattern for consecutive batches which provides greater ease of manufacture than by prior methods employing the same water-insoluble retardants. The effect of aging the sustained-action tablets under normal conditions has not invalidated the practical application of the proposed method.

REFERENCES

(1) A. Raff, M. J. Robinson, and E. V. Svedres, *J. Pharm. Sci.*, **50**, 76(1961).

(2) M. W. Scott, M. J. Robinson, J. F. Pauls, and R. J. Lantz, *ibid.*, **53**, 670(1964).

(3) J. M. Newton, *Mfg. Chemist Aerosol News*, **37**, 33(1966).

(4) W. E. Gaunt, U. S. pat. 3,148,124 (Sept. 8, 1964).

(5) M. S. Vora, A. J. Zimmer, and P. V. Maney, *J. Pharm. Sci.*, **53**, 487(1964).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 13, 1968, from the *Pharmacy Research and Development Department, Sandoz Pharmaceuticals, Hanover, NJ 07936*

Accepted for publication October 15, 1968.

The technical assistance of D. Murdock and C. Still is gratefully acknowledged.