Incompatibilities in Prescriptions

V. The Use of Tribasic Calcium Phosphate and Silica Gel in Capsules to Prevent Liquefaction*

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In previous papers, Husa and Becker (1) reported on the value of different inert powders in capsules to prevent liquefaction due to deliquescence or the formation of an eutectic mixture. Among the inert powders they used were light magnesium oxide, heavy magnesium oxide, magnesium carbonate, talc, lactose and several different starches, both dried at 100° C. and undried. Since the publication of the above reports, two other substances, tribasic calcium phosphate and silica gel, have been studied similarly. In the present paper a report is made on the value of both of these substances as inert ingredients in capsules that liquefy. A comparison has likewise been made between these powders and light magnesium oxide and magnesium carbonate, which were found in the previous experiments to be most effective in preventing liquefaction of capsules.

The tribasic calcium phosphate was a fine, white powder of the grade specified in the monograph for Tribasic Calcium Phosphate in the Second Supplement to the U. S. P. XI. The silica gel used in the present investigation was a fine powder, very faintly pink in color, and was supplied through the courtesy of the Davison Chemical Company, Baltimore, Maryland. The other inert ingredients, light magnesium oxide and mangesium carbonate, as well as the ingredients of the capsule prescriptions, were of U. S. P. grade.

EXPERIMENTAL

PRESCRIPTION No. 1

℞	Camphor	gr. 1/4
	Salol	gr. iij

Fac tales capsulæ no. xx.
One capsule t. i. d. a. c.

When the ingredients of this prescription were triturated a pasty mass was formed. The prescription was compounded with varying quantities of the inert powders to determine the relative efficiency of each in preventing the difficulty. In each case the camphor was triturated with the inert powder; the salol was then added and the mixture triturated lightly. The temperature at the time of compounding was 71° F.; the relative humidity was 23–25%. The finished capsules were kept under observation for two weeks in open beakers as well as in closed capsule vials.

The addition of an inert powder obviously increases the size of the capsule to a certain extent depending on the quantity of powder used and its bulkiness. In the present investigation capsules larger than those ordinarily dispensed in prescription practice were used in some cases. This was done for purposes of uniformity in the experimental work. In many cases where the patients find it difficult to swallow the larger capsules it would be advisable to divide the material of the prescription into twice the number of capsules designated by the prescriber and to double the dose as to the number of capsules. The size of the capsule required in each case of the present study was recorded.

In all the tables of the present paper the following abbreviations are used: L = soft mass or liquid; P = dry powder; D = damp powder; S D = slightly damp powder; C M = cement-like mass. The quantity of inert powder is stated in grains per capsule.

Table I shows that magnesium carbonate was most effective in preventing liquefaction, 1 grain per capsule being sufficient to maintain the ingredients as a powder for four days. One grain of light magnesium oxide per capsule maintained the ingredients as a powder for two days. In the case of silica gel and also with calcium phosphate, 1 grain of the powder per capsule was not sufficient to keep the ingredients as a powder even during the period of compounding; 2 grains or more per capsule, however, were sufficient to maintain the ingredients as a powder for two weeks.

Table II shows that the results with the capsules stored in closed vials were similar to those with the capsules placed in open beakers. For this prescription at least 2 grains of one of the inert ingredients is indicated. Tight closure of the container seems to be without any distinct advantage.

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TABLE I.—PRESCRIPTION NO. 1 WITH INERT POWDERS

(Capsules Stored in Open Containers)

Inert Powder, Grains	Size of Capsule	Time in Days 0	1	2	4	14
Magnesium Carbonate						
1	2	P	P	P	P	D
2	1	P	P	P	P	S D
3	0	P	P	P	P	P
4	00	P	P	P	P	P
5	000	P	P	P	P	P
Light Magnesium Oxide						
1	2	P	P	P	S D	S D
2	0	P	P	P	P	P
3	00	P	P	P	P	P
4	000	P	P	P	P	P
Silica Gel						
1	3	S D	S D	S D	S D	D
2	2	P	P	P	P	P
3	1	P	P	P	P	P
4	0	P	P	P	P	P
5	00	P	P	P	P	P
Tribasic Calcium Phosphate						
1	3	S D	D	D	D	D
2	2	P	P	P	P	P
3	1	P	P	P	P	P
4	0	P	P	P	P	P
5	0	P	P	P	P	P

TABLE II.—PRESCRIPTION NO. 1 WITH INERT POWDERS

(Capsules Stored in Closed Containers)

Inert Powder, Grains	Size of Capsule	Time in Days 0	1	2	4	14
Magnesium Carbonate						
1	2	P	P	P	P	D
2	1	P	P	P	P	P
3	0	P	P	P	P	P
4	00	P	P	P	P	P
5	000	P	P	P	P	P
Light Magnesium Oxide						
1	2	P	P	P	S D	S D
2	0	P	P	P	P	P
3	00	P	P	P	P	P
4	000	P	P	P	P	P
Silica Gel						
1	3	S D	S D	S D	S D	D
2	2	P	P	P	P	P
3	1	P	P	P	P	P
4	0	P	P	P	P	P
5	00	P	P	P	P	P
Tribasic Calcium Phosphate						
1	3	S D	D	D	D	D
2	2	P	P	P	P	P
3	1	P	P	P	P	P
4	0	P	P	P	P	P
5	0	P	P	P	P	P

PRESCRIPTION NO. 2

℞	Acetylsalicylic acid	gr. iiss
	Methenamine	gr. iiss

Ft. caps. d. t. d. no. xii.

In filling this prescription a damp powder resulted. After one day the contents of the capsules liquefied and on longer standing a light yellow color developed.

TABLE III.—PRESCRIPTION NO. 2 WITH INERT POWDERS

(Capsules Stored in Open Containers)

Inert Powder, Grains	Size of Capsule	Time in Days 0	1	2	4	14
Magnesium Carbonate						
1/2	2	P	C M	C M	L	L
1 1/2	1	P	C M	C M	L	L
2 1/2	0	P	S D	S D	D	L
3 1/2	00	P	P	P	S D	D
Light Magnesium Oxide						
1/2	1	P	C M	C M	C M	L
1 1/2	0	P	P	P	D	L
2 1/2	00	P	P	P	S D	D
3 1/2	000	P	P	P	P	S D
Silica Gel						
1/2	2	P	C M	C M	L	L
1 1/2	1	P	C M	C M	L	L
2 1/2	0	P	C M	C M	L	L
3 1/2	00	P	C M	C M	D	L
Tribasic Calcium Phosphate						
1/2	2	S D	C M	C M	L	L
1 1/2	1	P	C M	C M	L	L
2 1/2	0	P	C M	C M	L	L
3 1/2	00	P	S D	S D	D	L

TABLE IV.—PRESCRIPTION NO. 2 WITH INERT POWDERS

(Capsules Stored in Closed Containers)

Inert Powder, Grains	Size of Capsule	Time in Days 0	1	2	4	14
Magnesium Carbonate						
1/2	2	P	C M	C M	C M	C M
1 1/2	1	P	C M	C M	C M	C M
2 1/2	0	P	P	P	S D	D
3 1/2	00	P	P	P	P	S D
Light Magnesium Oxide						
1/2	1	P	P	C M	C M	C M
1 1/2	0	P	P	P	P	P
2 1/2	00	P	P	P	P	P
3 1/2	000	P	P	P	P	P
Silica Gel						
1/2	2	P	C M	C M	C M	C M
1 1/2	1	P	C M	C M	C M	C M
2 1/2	0	P	C M	C M	D	C M
3 1/2	00	P	C M	C M	D	C M
Tribasic Calcium Phosphate						
1/2	2	S D	C M	C M	C M	C M
1 1/2	1	P	C M	C M	C M	C M
2 1/2	0	P	C M	C M	C M	C M
3 1/2	00	P	S D	S D	C M	C M

Prescription No. 2 was filled with the addition of inert powders. The temperature at the time of compounding was 74° F.; the relative humidity was 24–27%. In each case the methenamine was mixed with the inert powder and the acetylsalicylic acid added, the final mixture being triturated lightly.

Table III shows that light magnesium oxide is the most effective powder in preventing liquefaction of the ingredients of the capsule. The ingredients of the capsule can be maintained as a powder for four days when stored in open containers

if 3½ grains of light magnesium oxide are added per capsule. Magnesium carbonate, silica gel and tribasic calcium phosphate are relatively inefficient as inert powders in this case since the ingredients of the capsules form a cement-like mass or liquefy even when larger quantities of these inert powders are added per capsule.

There is a slight advantage in storing the capsules of prescription No. 2 in closed containers. Table IV indicates that light magnesium oxide is the most effective powder in this case, 1½ grains per capsule being sufficient to maintain the ingredients of the capsule as a powder for fourteen days. Although magnesium carbonate is effective in some cases, silica gel and tribasic calcium phosphate are relatively ineffective.

PRESCRIPTION NO. 3

℞ Methenamine gr. ij
Potassium acetate gr. ij

Prepare 30 such capsules.

When this prescription was compounded as written, a damp powder formed which liquefied in the capsules within a few days. Due to the removal of moisture from the gelatin capsules by the deliquescent potassium acetate, the capsules became brittle and cracked within a few minutes after filling. Storage of the capsules in closed vials maintained the powdered character of the ingredients over a period of two weeks; however, the capsules became brittle and cracked.

The prescription was compounded using various amounts of inert powders. In all cases of compounding, the methenamine was first triturated to obtain a fine powder and then the absorbent and potassium acetate were added in the order named. The temperature during compounding was 73–75° F.; the relative humidity was 21–23%.

Table V indicates that prescription No. 3 has a tendency to become damp or liquid, accompanied by brittleness and cracking of capsules, when stored in open containers, even when inert powders are added. Table VI shows that dampening and liquefaction of the capsules are retarded to a considerable extent when the capsules are stored in closed containers and when inert powders are added. Light magnesium oxide is the best inert powder in this case, followed in order by magnesium carbonate, tribasic calcium phosphate and silica gel.

TABLE V.—PRESCRIPTION NO. 3 WITH INERT POWDERS

(Capsules Stored in Open Containers)

Inert Powder, Grains	Size of Capsule	Time in Days: 0	1	2	4	14
Magnesium Carbonate						
1	2	P[a]	D[a]	L[a]	L[a]	L[a]
2	1	P	S D	S D	D[a]	L[a]
3	00	P	S D	S D	D[a]	L[a]
4	000	P	S D	P	S D	D[a]

(Table V continued in next column)

Inert Powder, Grains	Size of Capsule	Time in Days: 0	1	2	4	14
Light Magnesium Oxide						
1	2	P	S D	S D	D[a]	L[a]
2	0	P	P	P	S D	L[a]
3	00	P	P	P	S D	L[a]
4	000	P	P	P	P	D
Silica Gel						
1	2	S D[a]	D[a]	L[a]	L[a]	L[a]
2	1	P	S D	D[a]	L[a]	L[a]
3	0	P	S D	S D	D[a]	L[a]
4	00	P	P	S D	S D	L[a]
5	00	P	P	S D	S D	L[a]
Tribasic Calcium Phosphate						
1	2	S D	D[a]	L[a]	L[a]	L[a]
2	1	P	S D[a]	L[a]	L[a]	L[a]
3	0	P	S D[a]	D[a]	D[a]	L[a]
4	00	P	P	S D	D	D[a]
5	00	P	P	P	S D	D[a]

[a] Capsules became brittle and cracked.

TABLE VI.—PRESCRIPTION NO. 3 WITH INERT POWDERS

(Capsules Stores in Closed Containers)

Inert Powder, Grains	Size of Capsule	Time in Days: 0	1	2	4	14
Magnesium Carbonate						
1	2	P[a]	P[a]	P[a]	P[a]	P[a]
2	1	P	P	P	P	P
3	00	P	P	P	P	P
4	000	P	P	P	P	P
Light Magnesium Oxide						
1	2	P	P	P	P	P
2	0	P	P	P	P	P
3	00	P	P	P	P	P
4	000	P	P	P	P	P
Silica Gel						
1	2	S D[a]	S D[a]	S D[a]	S D[a]	S D[a]
2	1	P	P	P	P	S D
3	0	P	P	P	P	S D
4	00	P	P	P	P	P
5	00	P	P	P	P	P
Tribasic Calcium Phosphate						
1	2	S D	P	P	P	P
2	1	P	P	P	P	P
3	0	P	P	P	P	P
4	00	P	P	P	P	P
5	00	P	P	P	P	P

[a] Capsules became brittle and cracked.

PRESCRIPTION NO. 4

℞ Sodium iodide
Sodium nitrite, āā gr. iiss

Misce et ft. caps. no. xx.
Sig.: One t. i. d. as directed.

This prescription contains two deliquescent drugs. When it was compounded as written, the contents of the capsules turned yellow in color and liquefied after standing two days in open containers. Capsules placed in closed containers developed a light yellow color after standing two weeks and smelled strongly of iodine, but the contents of the capsules remained dry.

The prescription was compounded using various amounts of inert powders. In all cases, the sodium

iodide was first triturated with the inert powder and the sodium nitrite was then added. The temperature during compounding was between 65° and 67° F.; the relative humidity was 21–24%.

The results on the capsules stored in open containers were as follows:

Magnesium Carbonate.—Capsules varying in size from 2 to 000 and containing from 1 to 5 grains of magnesium carbonate per individual dose, although white powders when compounded, turned yellow after several days of standing. Although the absorbent powder prevented liquefaction in most cases, the gelatin capsule itself became soft and sticky.

Light Magnesium Oxide.—Capsules varying in size from 2 to 000 and containing from 1 to 4 grains of light magnesium oxide per individual dose, although white powders when compounded, turned yellow on standing. With small quantities of the absorbent, liquefaction occurred; with larger quantities of the absorbent, the contents of the capsules remained dry, but the gelatin capsule itself became soft and soggy.

Silica Gel.—Capsules varying in size from 3 to 00 and containing 1 to 5 grains of silica gel per individual dose, although white or faintly yellow when compounded, discolored rapidly and resulted in a black-colored capsule on standing two weeks. With 1 grain, 2 grains and 3 grains of silica gel per capsule the contents of the capsules became liquid at the end of two weeks' standing. When 4 or 5 grains of silica gel was added per capsule, the contents of the capsules were powders at the end of two weeks, but there was black discoloration and the capsules themselves were soft and soggy.

Tribasic Calcium Phosphate.—Capsules varying in size from 3 to 00 and containing from 1 to 5 grains of tribasic calcium phosphate per individual dose, although white powders when compounded, discolored rapidly on standing for two weeks, becoming either yellow liquids or yellow-speckled powders contained in soft, soggy capsules.

The results on capsules stored in closed containers were as follows:

Magnesium Carbonate, Silica Gel and Tribasic Calcium Phosphate.—Capsules containing up to 5 grains of the absorbents per individual dose turned yellow and smelled strongly of iodine after standing a few days. The contents remained dry over a period of two weeks.

Light Magnesium Oxide.—Capsules varying in size from 2 to 000 and containing 1 to 4 grains of light magnesium oxide per individual dose discolored only slightly after two weeks' standing. Capsules containing 4 grains of light magnesium oxide per individual dose remained white powders after the two-week standing period. It is possible that the discoloration was retarded or entirely prevented in the case of light magnesium oxide because magnesium oxide will take up moisture to form magnesium hydroxide, which in turn is capable of neutralizing the traces of free nitrous acid liberated during the decomposition of sodium nitrite. The neutralized nitrous acid is incapable of liberating iodine from sodium iodide, and hence discoloration is prevented.

In summarizing the effects of inert powders on prescription No. 4, it may be said that none of the inert powders prevent discoloration and deterioration of capsules stored in open containers. The prescription can be satisfactorily compounded using one or more grains of light magnesium oxide per capsule and dispensing in a closed capsule vial.

DISCUSSION OF RESULTS

In a study of the effects of several inert powders in preventing liquefaction of capsules due to the formation of an eutectic mixture, light magnesium oxide and magnesium carbonate, both of which are light, fluffy powders, were most effective. This was also the conclusion reached by Husa and Becker (1). Silica gel and tribasic calcium phosphate are both effective in preventing liquefaction in some cases, especially when the capsules are stored in closed containers. Nevertheless they are inferior to light magnesium oxide and magnesium carbonate as inert powders. One explanation for this may be that both silica gel and tribasic calcium phosphate are heavier powders than light magnesium oxide and magnesium carbonate, hence not as bulky. Silica gel and tribasic calcium phosphate are not effective in preventing the formation of cement-like masses in capsules.

The results show that liquefaction of capsules containing deliquescent ingredients may be prevented in most cases by the addition of an inert powder and by storage in closed capsule vials. As to relative efficiency of the various powders studied, light magnesium oxide and magnesium carbonate were best, tribasic calcium phosphate ranked next, and silica gel was poorest.

Deterioration and discoloration of capsules containing sodium iodide and sodium nitrite in equal parts is most effectively prevented by the addition of light magnesium oxide as an inert powder and by storage in closed capsule vials. Magnesium carbonate, silica gel and tribasic calcium phosphate are not effective.

SUMMARY

A study was made of the efficiency of silica gel and tribasic calcium phosphate as compared with light magnesium oxide and magnesium carbonate when used as inert powders in capsules that liquefy due to deliquescence or the formation of an eutectic mixture. In general, both light magnesium oxide and magnesium carbonate are superior to silica gel and tribasic calcium phosphate as inert ingredients in capsules.

REFERENCES

(1) Husa, W. J., and Becker, C. H., JOUR. A. PH. A., 29 (1940), 78, 136.