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# IDENTIFICATION AND PREVENTION OF INSOLUBLE REACTION PRODUCTS FORMING AFTER DISSOLUTION OF EFFERVESCENT MULTI-VITAMIN TABLETS

A. P. Lötter, M. M. de Villiers, J.S. Handford & W. Liebenberg.
Institute for Industrial Pharmacy, Potchefstroom University, Potchefstroom, 2520, South Africa

## ABSTRACT

Two problems of an unacceptable nature were experienced during the formulation of effervescent multi-vitamin and mineral tablets. When tablets containing ascorbic acid, calcium carbonate and vitamins, combined with ordinary effervescent excipients and sodium benzoate as lubricant, were dissolved, fine needles formed during effervescence. These needles float on top of the solution, making the product unattractive. During effervescence of a second tablet containing magnesium oxide and calcium carbonate, combined with ascorbic acid, a flake-like sediment formed. Infrared spectrophotometry, differential scanning calorimetry and atomic absorption analysis showed that the needles were benzoic acid, while the flakes were citrates - mainly calcium citrate. These problems were overcome by substituting the benzoic acid with micronised polyethylene glycol 6000 and by not including citric acid during the granulation stage but to add coarse citric acid crystals to the dry granules - composed of the rest of the tablet ingredients.

## INTRODUCTION

Effervescent granules and tablets are popular dosage forms for multi-vitamin products[1]. In these products the effervescence is caused by the liberation of carbon dioxide, when sodium bicarbonate (and sodium carbonate) are reacted with citric, tartaric or ascorbic acid. In practice the components of an effervescent product are granulated by one of three wet granulation techniques[2]:

1. With the use of heat involving the release of water from hydrated formulation ingredients at a low temperature.
2. With the use of non-reactive liquids such as anhydrous ethanol, ethyl acetate and a range of other organic solvents. These liquids are inherently costly and require complicated solvent recovery processes.

3. With the use of a reactive liquid, usually water. The effervescent reaction is initiated by water and care must be taken to adequately control this process if the effervescent character of the finished product is to be maintained.

During the processing of effervescent products, low relative humidity and moderate to cool temperatures are required. In addition to the ingredients compounded into effervescent granules, a lubricant is one of the most important ingredients of effervescent tablets[2]. Effervescent granules are inherently difficult to lubricate due to the nature of the raw materials and because rapid tablet disintegration is required. If a clear solution is desired after disintegration of the tablet, the problem is even greater since most efficient lubricants are water insoluble. Powdered sodium benzoate and micronised polyethylene glycol (PEG 4000 and 6000) are efficient water soluble lubricants[3].

Overall, the processing of effervescent granules and tablets, although very similar to the processing of conventional granules and tablets, presents certain problems and employs methods which are not often found in the latter. The present study presents two problems of an unacceptable nature, with possible explanations and solutions, experienced during the formulation of multi-vitamin and vitamin-mineral containing effervescent granules and tablets.

## MATERIALS & METHODS

### Materials

Solvents and chemicals used were either HPLC or reagent grade. The ingredients used to make the effervescent tablets complied with either USP[4] or BP[5] standards.

### Tablet Manufacture

Granulates were prepared in a planetary type blender, screened through a 500 μm sieve and dried for 2 hours at 60 °C. Additional excipients were added to the dry granules and mixed in a V-blender for 20 minutes at 60 rpm. Tablets were compressed on a Manesty single punch tabletting machine using a 25 mm punch and die set.

### Isolation of Reaction Products

Effervescent solutions were allowed to stand for 15-20 minutes after effervescence was completed. The solutions were filtered through glass microfibre filters (Whatman, England). The filtrate was combined with the sediment left in the beaker and transferred to a porcelain crucible and then dried for 4 hours at 60 °C. The process was repeated in triplicate and the mean weight of the reaction products were determined. Mean values are listed in table 1.

### Microscopy

The recrystallised products removed by filtration was studied under a light microscope and with a scanning electron microscope (SEM). SEM samples were prepared as follows: Double-backed adhesive tape was attached to a SEM stub. The stub was lightly pressed in the powder sample. Any excess powder was removed by tapping the stub against a solid object. First a 10-20 nm thick carbon layer was affixed to the powder

**TABLE 1**

Weight of reaction product (sediment and other debris) isolated from effervescent solutions before and after the formulas were optimised.

| Multi-Vitamin Tablets | | Vitamin-Mineral Tablets | |
|---|---|---|---|
| Before (g) | After (g) | Before (g) | After (g) |
| 0.098 ± 0.023 | 0.012 ± 0.008 | 1.034 ± 0.218 | 0.025 ± 0.011 |

particles and then the particles were covered with a mixture of gold and palladium (60/40). The stubs were placed in a Cambridge Stereoscan 250 electron microscope and studied. Micrographs were taken with a camera attached to the microscope.

**Differential Scanning Calorimetry (DSC)**

DSC thermograms of the reaction products and standards were recorded with a Shimadzu DSC 50 combined with TA 50I system controller (Shimadzu, Japan). A heating rate of 10 °C.min$^{-1}$ was employed, 5 mg samples were placed in sealed aluminum pans and the cell was purged with nitrogen, 50 ml.min$^{-1}$. Thermograms were recorded from 30 - 350 °C.

**Infrared Spectrophotometry**

Potassium bromide discs containing approximately 2 % of the reaction products or standards were prepared and the spectra, from 400 - 400 cm$^{-1}$, were recorded on a Fourier Transform Infrared spectrophotometer (Shimadzu, FTIR 2400, Shimadzu, Japan).

**Atomic Absorption Spectrophotometry**

The amount of calcium present in the reaction product removed from the vitamin-mineral tablet solution were determined by atomic absorption spectrophotometry using a Varian AA 1275 atomic absorption spectrophotometer. A calcium standard was acquired from Varian and caesium chloride / lanthanum nitrate solution was used as a ion suppressant.

## RESULTS & DISCUSSION

In table 1 the amounts of reaction products isolated after effervescence are listed. Values represent the mean from five tablets plus standard deviation. The composition of the two effervescent tablets are given in table 2.

After disintegration and solution of effervescent tablets containing ascorbic acid, calcium carbonate, vitamins, effervescent excipients and the lubricant sodium benzoate

**TABLE 2**
Composition of the multi-vitamin and vitamin-mineral tablets

| FORMULA 1 Multi-Vitamin Tablets | | FORMULA 2 Vitamin-Mineral Tablets | |
|---|---|---|---|
| Ingredient | Amount per tablet (g) | Ingredient | Amount per tablet (g) |
| Ascorbic Acid | 0.300 | Magnesium oxide | 0.202 |
| Calcium Pantothenate | 0.025 | Sodium bicarbonate | 1.279 |
| Thiamine HCl | 0.020 | Ascorbic acid | 0.500 |
| Riboflavin | 0.020 | Thiamine HCl | 0.010 |
| Nicotinamide | 0.030 | Tartaric acid | 1.015 |
| Pyridoxine HCl | 0.020 | Sodium citrate | 0.615 |
| Biotin | 0.002 | Citric acid anhydrous | 1.045 |
| Cyanocobalamin | 0.001 | Calcium carbonate | 0.612 |
| Citric acid anhydrous | 1.750 | Sodium carbonate anhydrous | 0.172 |
| Calcium carbonate | 0.625 | Sweetener | 0.080 |
| Sodium carbonate anhydrous | 0.130 | Flavour | 0.060 |
| Sweetener | 0.330 | Colour | 0.010 |
| Flavour | 0.050 | | |
| Colour | 0.002 | | |
| *Lubricant* | 0.150 | *Lubricant* | 0.150 |
| Total Weight | 3.455 | Total Weight | 5.750 |

(formula 1, table 2), fine needles floated on top of the solution. To isolate and identify these needles a tablet was placed in a beaker containing 250 ml of distilled water. The mean weight of twenty tablets was 3.45 ± 12.8 g. After disintegration the effervescent solution was filtered, the filtrate dried for 4 hours at 60 °C and then analysed. Scanning electron microscopic evaluation, figure 1(a), showed these particles to be an elongated, bubble-like, recrystallised product. Infrared spectroscopy, figure 2, and differential scanning calorimetry, figure 3, identified the filtrate to mainly consist of benzoic acid. The melting points of the recrystallised product and benzoic acid was both 122 °C.

The reason for this reaction occurring was that sodium benzoate apparently reacted with ascorbic acid to form poorly soluble benzoic acid. The reaction is illustrated in scheme 1. Sodium benzoate reacted with ascorbic acid because the reaction product was not present when ascorbic acid was eliminated from formula 1. Theoretically 0.15 g sodium benzoate should have reacted with 0.18 g ascorbic acid to form 0.13 g benzoic acid. As expected this did not correspond to the amount of reaction product removed from the effervescent solutions, table 1, because the reaction depended also on the solubility of the two substances in and the distribution of the granulating fluid in the powder mix. Through elimination it was found that the needles were absent when sodium benzoate was omitted from the formula or replaced with micronised PEG 6000 as lubricant. This is illustrated by the small amount of reaction product, table 1, removed after optimisation of formula 1.

In effervescent granules, destined for making tablets (formula 2, table 2), containing 0.202 g magnesium oxide and 0.612 g calcium carbonate per 5.6 g dosage, prepared by controlled effervescence, a sediment of flake-like crystals formed in solution. Scanning electron microscopic evaluation, figure 1(b), showed the sediment to be agglomerates of particles. When water was used as the granulating liquid these flakes formed during granulation and drying of the granules. To isolate and identify the flakes a dosage of 5.6 g of the prepared granules, without the lubricant, was placed in a beaker containing 250 ml of distilled water. After effervescence the solution was filtered, the filtrate dried for 4 hours at 60 °C and then analysed. Infrared spectroscopy, figure 2, and differential scanning calorimetry, figure 3, identified the filtrate to mainly consist of calcium citrate. According to atomic absorption analysis the filtrate contained 82.5 % (0.85 g) calcium citrate.

Apparently calcium carbonate reacted with citric acid to form poorly soluble calcium citrate, scheme 2. Theoretically 0.612 g calcium carbonate should have reacted with 0.782 g citric acid to produce 1.016 g tri calcium dicitrate. This corresponds well with the amount of reaction product removed from the solutions, table 1. The problem was overcome, with varying degrees of success, by one of three methods. Firstly, without granulation the sediment was absent, but due to the nature of the ingredients granulation proved essential for the production of a free flowing product. Secondly, granulation with anhydrous ethanol also produced granules without a sediment but because of the high cost involved it did not prove economically viable. Finally, the most successful and economic solution was to granulate all the ingredients, except citric acid, with water. Then relatively coarse citric acid crystals were mixed with the dried granules. This reduced the

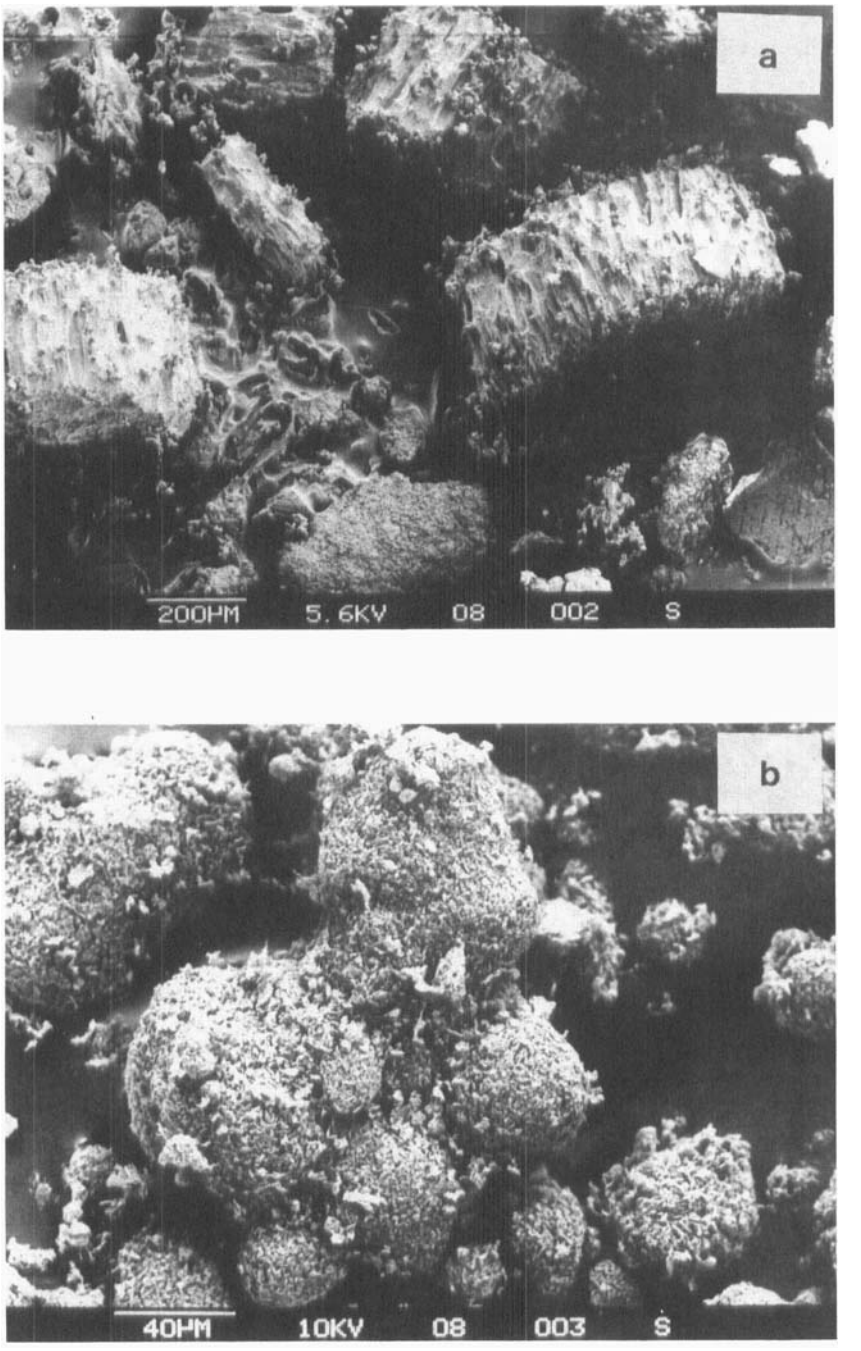



**FIGURE I**
SEM micrographs of recrystallised products: (a) the elongated, bubble-like product isolated from formula 1 and (b) agglomerates isolated from formula 2.

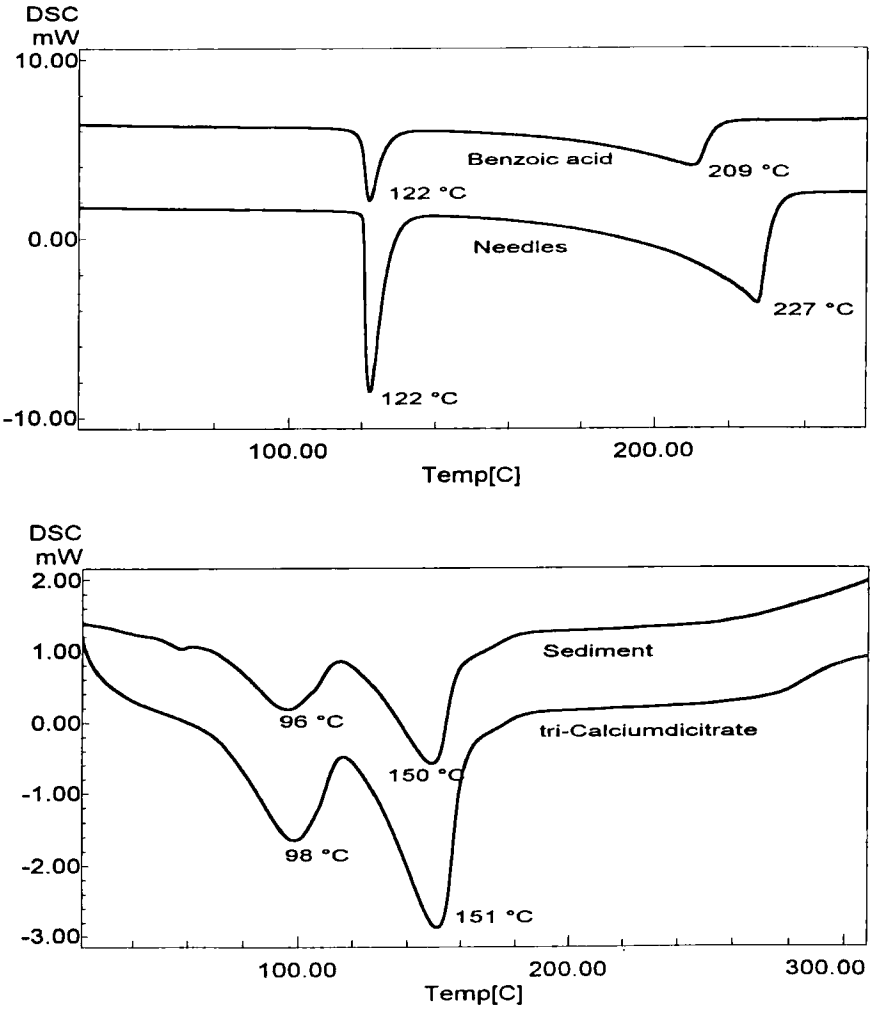



**FIGURE 2**
IR spectra of the reaction products removed from the effervescent solutions.

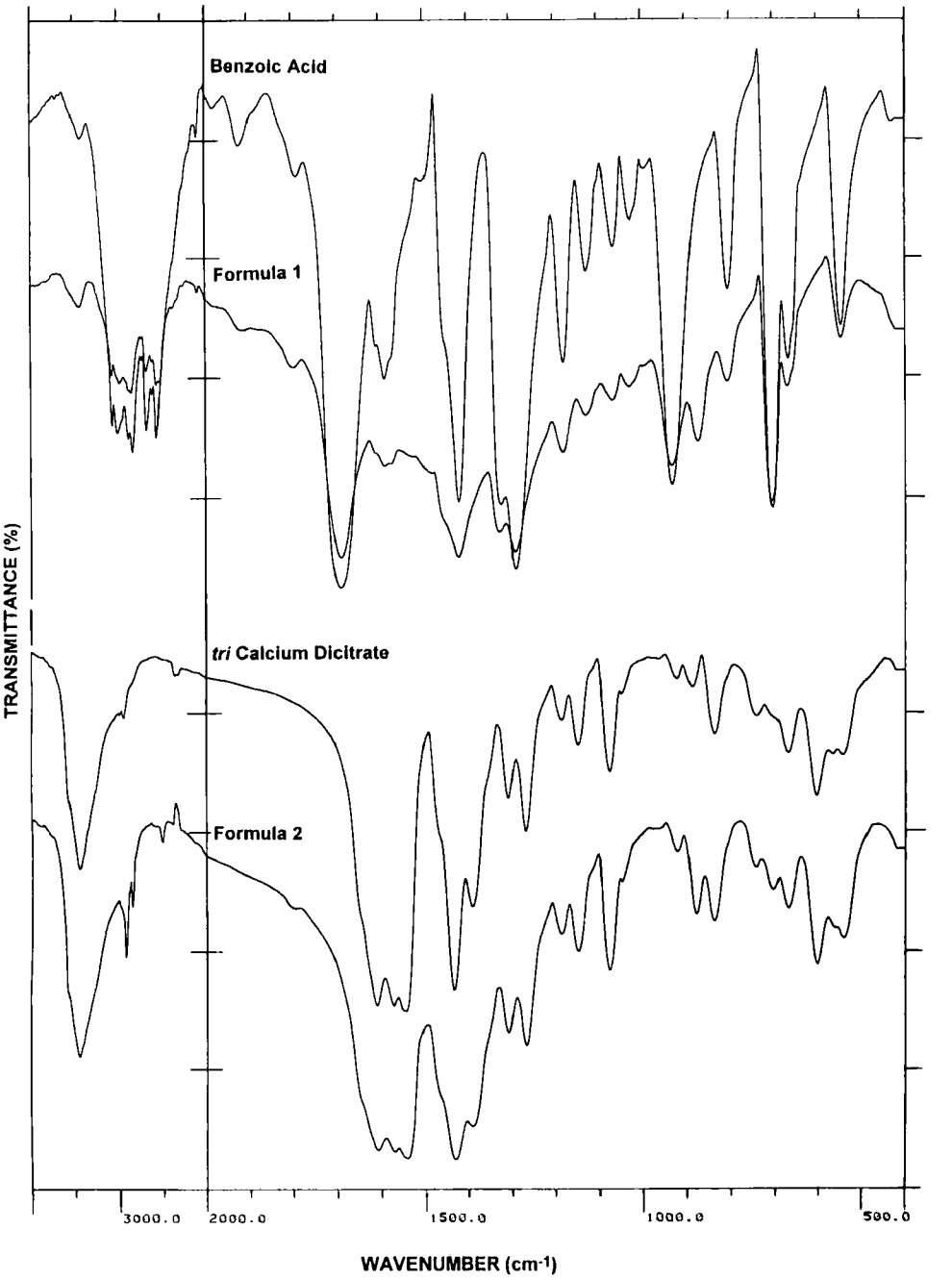
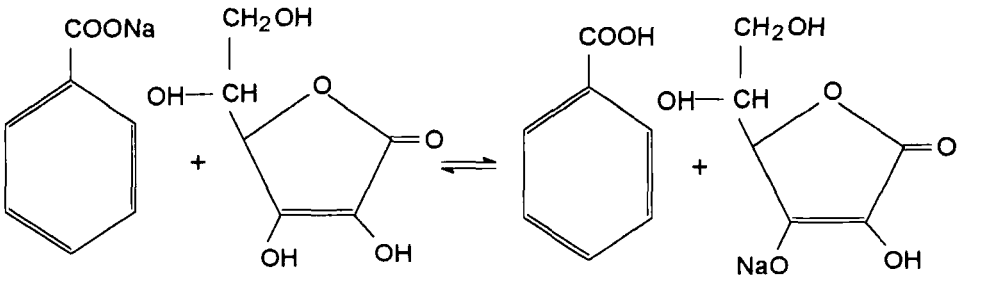
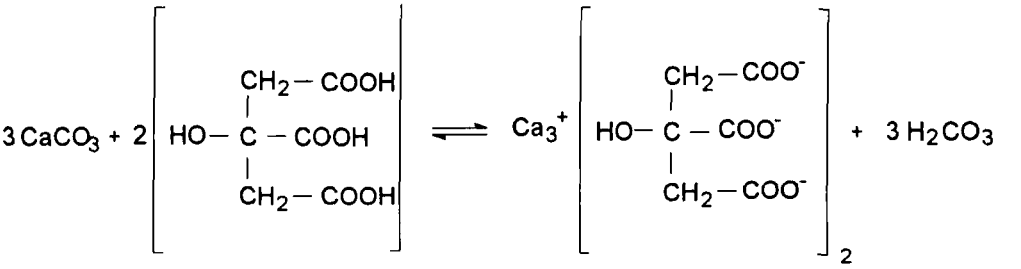



**FIGURE 3**
DSC thermograms of the reaction products removed from the effervescent solutions. Top Formula 1 and bottom Formula 2.




Sodium Benzoate MW = 144.11 | Ascorbic acid MW = 176.12 | Benzoic acid Mw = 122.12 | Sodium ascorbate MW = 198.12

**SCHEME 1**
Possible reaction between sodium benzoate and ascorbic acid.




Calcium carbonate MW = 100.1 | Citric acid MW = 192.12 | *tri* Calcium dicitrate MW = 498.44

**SCHEME 2**
Possible reaction between calcium carbonate and citric acid.

sediment formed significantly as shown by the amount of reaction product, table 1, present after optimisation of formula 2.

## CONCLUSIONS

When sodium benzoate is used as a lubricant in effervescent tablets, especially where ascorbic acid is included, the manufacturing process and formula must be as such that sodium benzoate can still exist. Otherwise benzoic acid will precipitate forming needles that float on top of the drink. The problem was overcome by substituting sodium

benzoate with another soluble lubricant, micronised polyethylene glycol (PEG) 6000. Where controlled effervescence was used as a means of granulation of granules containing magnesium oxide and a large amount of calcium carbonate, calcium citrate was formed, which precipitated. The problem was overcome by not including citric acid during the granulation stage but to add it to the dry granules.

## REFERENCES

1. V. Bühler, "Vademecum for vitamin formulations", Wissenschaftlichte Verlagsgesellschaft, Stuttgart, 1988.
2. R. Mohrle, in "Pharmaceutical dosage forms : tablets, volume 1", H.A. Lieberman, L. Lachman, and J.B. Schwartz, eds., Marcel Dekker, New York, 1989, p.285-328.
3. A.H. Rau and H. Yorozu, *Cosmet. Toilet.*, 107, 55 (1992).
4. United States Pharmacopoeia XX11 (USP), Mack, Easton, Pa., 1990.
5. British Pharmacopoeia (BP), Her Majesty's Stationary Office, London, 1988.