

A NEW SUPPOSITORY BASE.*

BY JOHN C. BIRD.¹

The following is an account of preliminary investigations in connection with a suppository mass more suitably adapted to the use of certain medicaments than, and without the disadvantages of, the more usual media.

Hippocrates (460-370 B. C.) used cathartic suppositories of salt, nitre and colocynth in a base or matrix of soap and honey. This type of medication, however, although popular in Europe for the last 200 years was not used in this country before about 1852 when Taylor (1) of Philadelphia described an opium suppository made with honey plasticized to the correct consistency by continued heating, and also with oil of theobroma which he found eminently satisfactory for the purpose. Cacao butter was given official recognition in the U. S. P. of 1860 and suppository data in general appeared in the pharmacopœias around 1864.

Since that time a great many alternative materials have been suggested as suppository bases, most of the earlier ones being mixtures of fats, waxes, glycerin, gums and soaps. Martindale (2) in 1890 stated that the glycerin and gelatin suppositories of that time were frequently discharged intact after 12 hours and put forward a mixture of stearic and oleic acids varying the proportions according to local temperature conditions. Most of these excipients, however, seem to have been regarded as merely a convenient means of introducing drugs into the rectum with apparently no regard to the *modus operandi* or ultimate fate of the medicament.

These aspects were appreciated and investigated by Lewin and Eschbaum (3), who recorded that, to be really effective, a drug must not only be very finely subdivided and evenly distributed in the matrix, but—and this is the important point—it must be easily separable therefrom. They investigated several excipients and concluded that neutralized agar agar was superior in these respects to all others then available.

More recently Terrey (4) has recommended a mixture of kaolin and decoction of Irish moss, while "Astra fat" (5) a hydrogenated arachis oil—also "Lipositoria" (6) a complex of cholesterin and sugar and several others all claiming to promote resorption have appeared in Germany.

THEORETICAL CONSIDERATIONS.

The ultimate aim of suppository medication may be systemic or local, and attention should therefore be paid to the type of action required and the means of insuring it. For systemic action the drug must be presented in readily absorbable form and should come into close contact with the mucosa. Aqueous solutions are of course most desirable in this respect so that it would seem illogical to apply water-soluble drugs to a watery membrane to be carefully insulated therefrom by a coating of wax, fat or oil as must obviously be the case with cacao butter.

When local action is required, as in the treatment of hemorrhoids and other rectal conditions, absorption may be secondary to a prolonged and intimate contact of the drugs with a smaller specific area.

It would seem equally unsound to adopt the same means for local treatment, as an aqueous or oily liquid cannot be expected to remain in one particular portion of the lower bowel. Overlach (7) appreciated this point and observed that the occasional failure to obtain satisfactory results from glycerin suppositories might be due to their escape so far into the rectum as to lose a large measure of efficiency. He suggested that the suppository be attached to a string having a small wooden handle at the distal end by which the location and duration of the medication might

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be controlled. Such a device was actually patented in Germany although the extent of its practicability is not recorded.

Having these two main ideas of systemic and local actions in mind, much thought was given to the possibility of finding a suppository excipient which would most nearly fulfil both these requirements in addition to satisfying the many other minor but necessary conditions.

In view of the recent commercial availability of certain glyceryl and ethylene glycol esters of fatty acids with their excellent property of self emulsification, similar "synthetic fats" having free hydroxyl groups were investigated with a view to taking advantage of this characteristic.

Unfortunately the melting points of the mono glyceryl and ethylene glycol stearates and oleates were either much too high, or were of oily character, while admixture of other compatible low melting substances interfered largely with self emulsification and were unsatisfactory in other ways.

It was found, however, that the stearyl esters of α -propylene glycol possessed lower melting points and other favorable properties which rendered possible their adaptation to the purpose in view. By condensing the α -chlorhydrin of α -propylene glycol with sodium stearate the pure mono stearate is obtained after some manipulation. For larger scale production, however, the simpler method of direct condensation of the glycol with stearic acid is used. By using an excess of glycol and controlling the conditions the formation of distearate is kept at a minimum. The melting point of the pure distearate, however, is about 40° C. so that the presence of small quantities is of assistance rather than hindrance, the resultant melting point being just in the desirable range. A close check may be kept upon the progress of the esterification by frequent titration of samples with alcoholic potash, and the standardization is such that the characters of successive batches of material are practically identical. For convenience the term mono stearic ester of propylene glycol has been shortened to "monolene."

PROPERTIES OF "MONOLENE."

The stearic acid ester of α -propylene glycol as prepared for use as a suppository mass and using the best grade of commercial stearic acid is an ivory-colored, somewhat translucent wax-like solid, smooth and unguentous but not greasy to the touch, and with an agreeable odor reminiscent of cocoanut. It is of good consistency, amorphous when freshly prepared and cuts like firm cheese. It gradually changes in physical state on keeping, becoming more brittle and assuming a crystalline structure particularly evident upon fracture. This physical change common to many of the natural waxes and fats is accompanied by a rise in melting point.

The melting point of the fresh substance is from 33° to 34° C. rising after 24 hours or so to 35° C. On continued storage a maximum of 37° C. is reached in about three weeks after which no further change has been noticed during a period of six months. The congealing point of the aged material is 36° C.

It is soluble in the common organic solvents, *e. g.*, alcohol, chloroform, ether, acetone, benzol, etc., and in mineral and vegetable oils. It is immiscible with glycerin and the glycols.

The substance itself is hydrophilic in character, absorbing water to some extent. This property, as with the glyceryl esters, is enhanced by the presence of small quantities of the soaps of organic or inorganic bases. The melting point is but little affected by the addition of say 1-2% of sodium or ethanalamine stearate while the resulting product swells considerably in cold water, becoming completely self emulsified with the liquid as the continuous or external phase. The pH of a 10% emulsion lies between 7 and 8.

As a suppository matrix it possesses several advantages. It congeals much more readily than cacao butter and may be "poured" at a higher temperature. Molds do not require nearly as much chilling while the shapes are removable with the greatest ease without external lubrication. The molded forms are of particularly fine and clean appearance having a firm bright surface of smooth lubricant quality, without sense of greasiness. This lubricant quality is greatly increased by slight wetting, thus rendering insertion of the suppository particularly simple and free from the objectionable features attendant upon cacao butter bases. Suppositories made from "Monolene" withstand warm weather better than cacao butter and do not give rise to as much spoilage in storing.

In contact with considerable water *in vitro* "Monolene" absorbs the liquid, swelling to several times its original size, eventually forming a soft creamy mass which on shaking or stirring becomes a hydrophilic plastic ointment (Fig. 1). This action is independent of temperature, for such swelling and ointment formation take place in ice water.

At body temperature the substance melts but at once emulsifies with any fluid present, such action being intensified under conditions of use by body or muscular movement. In the rectum or rectal canal the voluminous mass so formed may be expected to extend to the more inaccessible crypts and rugæ, or at least to provide more efficient contact with the mucosal walls (Fig. 2).

Being hydrophilic, such a substance should admit of the penetration and diffusion of aqueous fluids and consequent extraction of water-soluble medicaments more readily than would be possible from fats like cacao butter (Fig. 3). Absorption and efficiency of such drugs should be enhanced, while it is obvious that actual melting of the base is not essential to obtain the medication (Fig. 4).

A further advantage lies in the possibility of localizing certain insoluble drugs used in rectal treatment. Such drug particles are held by the mass in intimate contact with the walls in the desired area and are not widely distributed as with a free flowing non-emulsified fat, thus prolonging or-intensifying treatment.

Oil-soluble medicaments, moreover, are applied in fine subdivision in the disperse phase of the emulsion. Schroff (8) recently showed that cacao butter emulsified with lecithin enabled absorption of water-soluble drugs to take place from the external water phase almost as quickly as by injection. By reversing the phases of the emulsion by cholesterol, more prolonged local action was possible.

PHARMACOLOGY.

Preliminary pharmacological tests have been directed toward ascertaining irritant or other undesirable effects of the base. Blank suppositories of small size were all retained by rabbits (starved for 24 hours previously) with no defecations until several hours later. Feces were soft, well formed and somewhat unctuous. No diarrhea, hyperemia or irritation of any kind was observed. These points were also confirmed by human tests.

Investigations as to drug absorption are still proceeding. Substances which give a recognizable effect upon blood pressure and respiration have been incorporated in "Monolene" and tests upon anesthetized animals recorded.

Observations to date show that water-soluble drugs are readily absorbed from this base—the effect of Sodium Alurate for example, in dosage sufficient to cause narcosis, exerted its effect in about 90 minutes. The same dose in an entirely fatty base took about 50% longer.

It is possible, of course, that differences in other cases may be less marked, and unqualified general superiority is by no means claimed as yet. It would seem, however, that in "Mono-

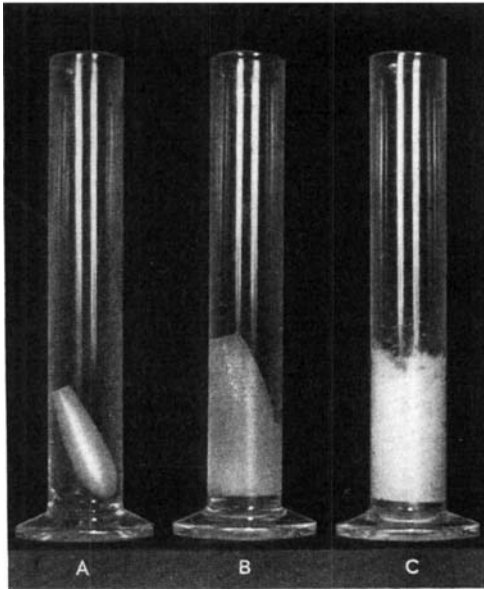


Fig. 1.—Water Imbibition at Room Temperature.

- A. "Monolene" control—original size.
- B. Suppository swollen in water.
- C. Creamy mass after agitation.

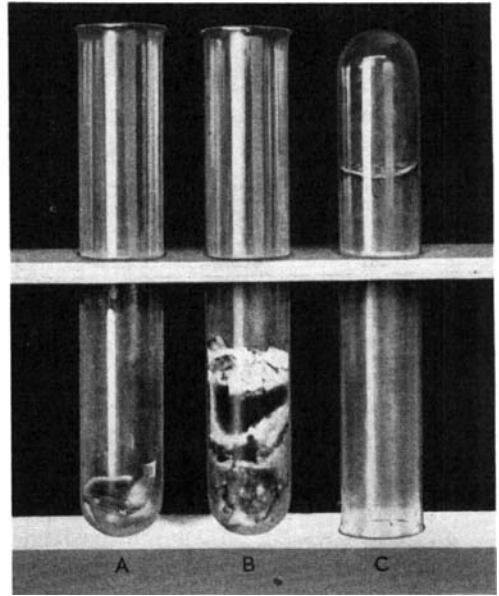


Fig. 2.—Action at Body Temperature.

- A. Melted control.
- B. Swollen mass in presence of water.
- C. Showing firm but soft consistency.

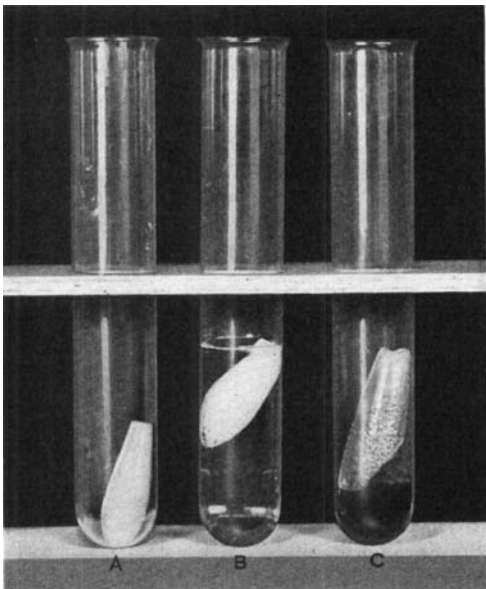


Fig. 3.—Extraction of Medicament by Diffusion.

- A. "Monolene" control.
- B. Cacao butter containing Congo Red powder, immersed in water.
- C. "Monolene" under same conditions. Note extraction of dye, while cacao butter is impervious.

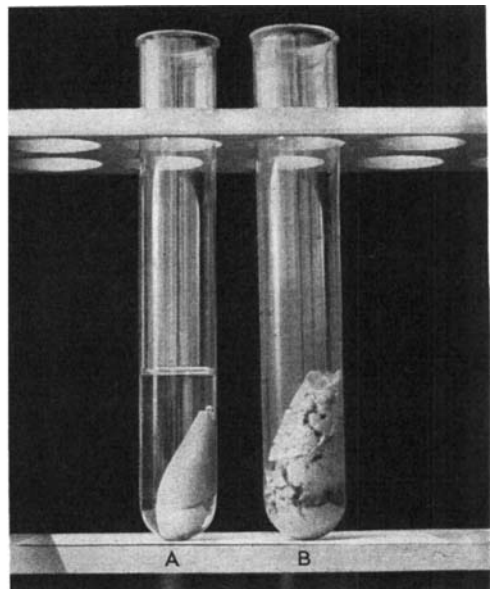


Fig. 4.—Action at Lowered Temperatures.

- A. Cacao butter suppository in ice water in refrigerator several hours remains intact.
- B. "Monolene" suppository disintegrates independent of temperature.

lene" we have a suppository medium whose physical properties render more likely the fulfilment of theoretical considerations of this type of medication, while providing many minor points of distinct advantage to both maker and user.

SUMMARY.

A new suppository base is suggested—propylene glycol stearate. The substance melts within body temperature range, is self emulsifying in water, forming soft, bulky, unguentous, hydrophilic and non-irritant emulsions particularly suitable for rectal treatment.

Its properties allow of medicament diffusion and absorption of water-soluble drugs irrespective of melting range, while insoluble substances are emulsified and kept in intimate local contact with mucosal tissue.

Other advantages include freedom from greasiness and leakage in use, while retaining firmness, ease and rapidity of molding, and better storage qualities.

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THE USE OF CETYL ALCOHOL AS AN ENTERIC COATING MATERIAL.*¹

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The first reference to the passage of pills through the stomach undissolved was made by Proctor (1), in 1862, who ascribed the occasional failure of the pills to disintegrate either to the condition of the patient or the composition of the pill, rather than the nature of the coating. Wruble (2), in 1930, did some work on enteric coating materials; he stated, as a practical specification that an enteric coated tablet should withstand the gastric fluids for a period of four hours and then be deprived of its coat within one-half hour after entering the intestinal tract. Lozenski and Diver (3), used the fluoroscopic method to determine the point of disintegration. In their work they gave one tablet of barium sulfate and another of sodium salicylate, both having the same enteric coating. It was assumed that both tablets left the stomach at the same time; later this was shown to be a fallacy by Bukey and Brew (4).

The purpose of this study was to determine the value of cetyl alcohol, cetyl alcohol and shellac, and cetyl alcohol and mastic as possible enteric coating materials. Cetyl alcohol was chosen because of its similarity to some other coating materials which have been previously used with some success.

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