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Nürnberg et al.

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[54] **MEMANTINE-CONTAINING SOLID PHARMACEUTICAL DOSAGE FORMS HAVING AN EXTENDED TWO-STAGE RELEASE PROFILE AND PRODUCTION THEREOF**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[6] **A61K 9/38**; A61K 9/64; A61K 37/16

[52] **U.S. Cl.** **514/775**; 530/360; 424/465; 424/469; 424/470

[58] **Field of Search** 424/465, 469, 470; 514/775; 530/360

[56] **References Cited**

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Pharmaceutical Technology 9, 360–374 (1990), "Influence of Sodium Caseinate on the Dissolution Rate of Hydrochlorothiazide and Chlorothiazide", F. C. Millar, et al.

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[57] **ABSTRACT**

The present invention provides solid pharmaceutical compositions in dosage form containing an active ingredient or principle, preferably memantine, which exhibit an extended two-phase release profile and which are characterized by the presence of both a water-soluble and a water-insoluble salt of casein, preferably sodium and calcium caseinate, in the matrix thereof, in broad proportions and in a total amount between 5 and 98% by weight of the composition, and with a process for the production thereof.

22 Claims, 3 Drawing Sheets

FIG. 1

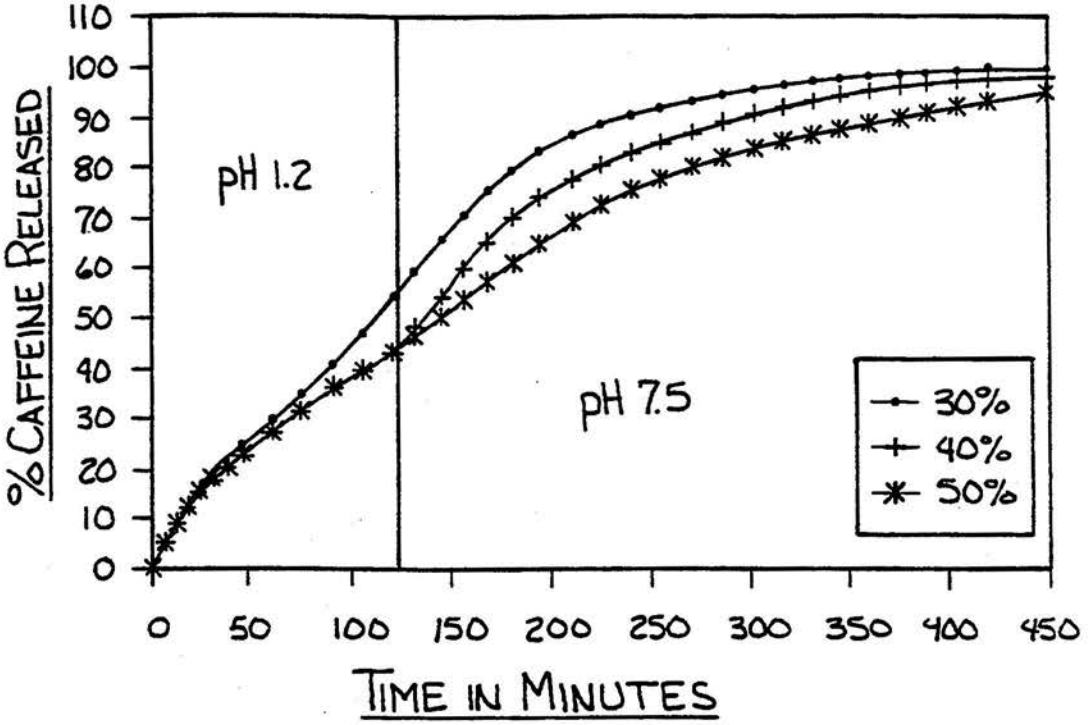


FIG. 2

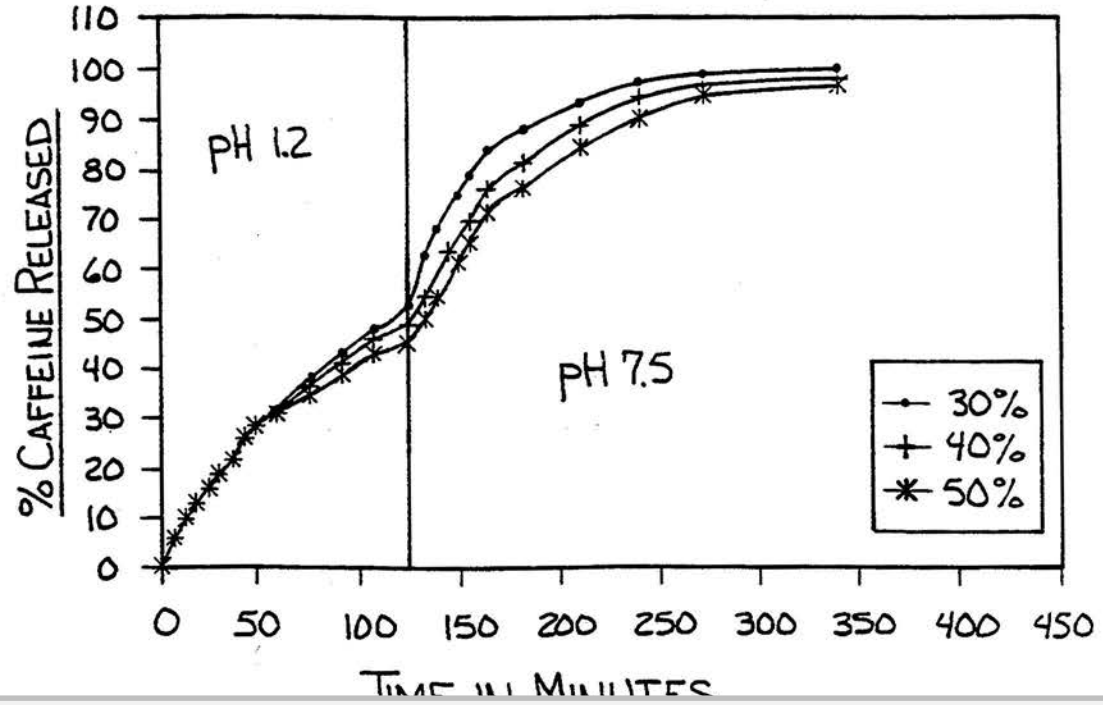


FIG. 3

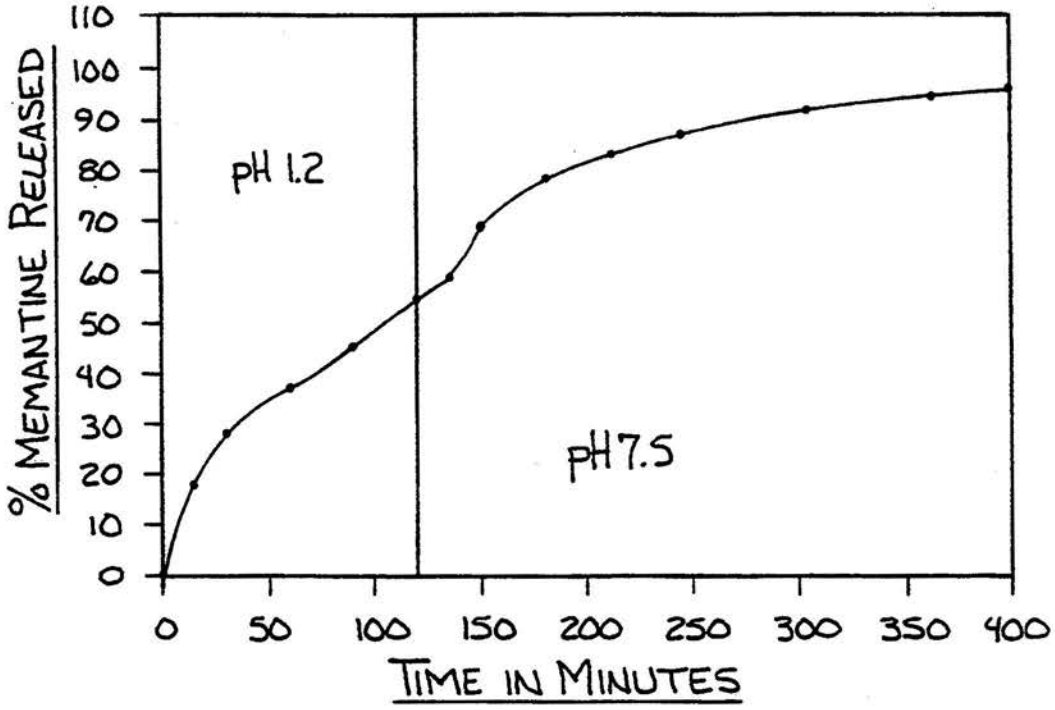


FIG. 4

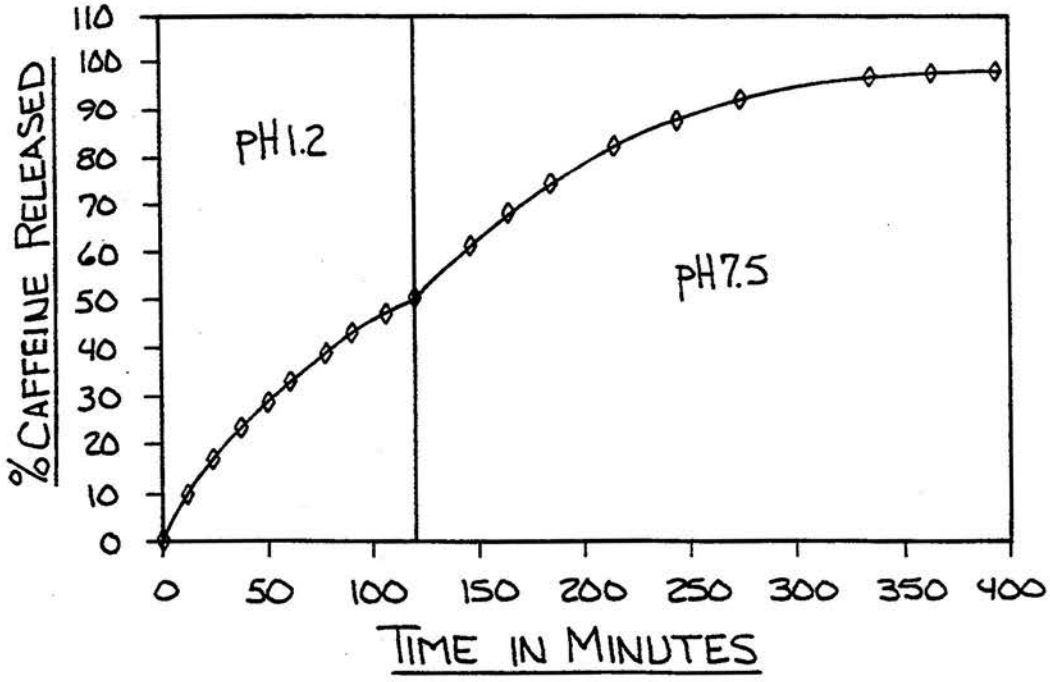
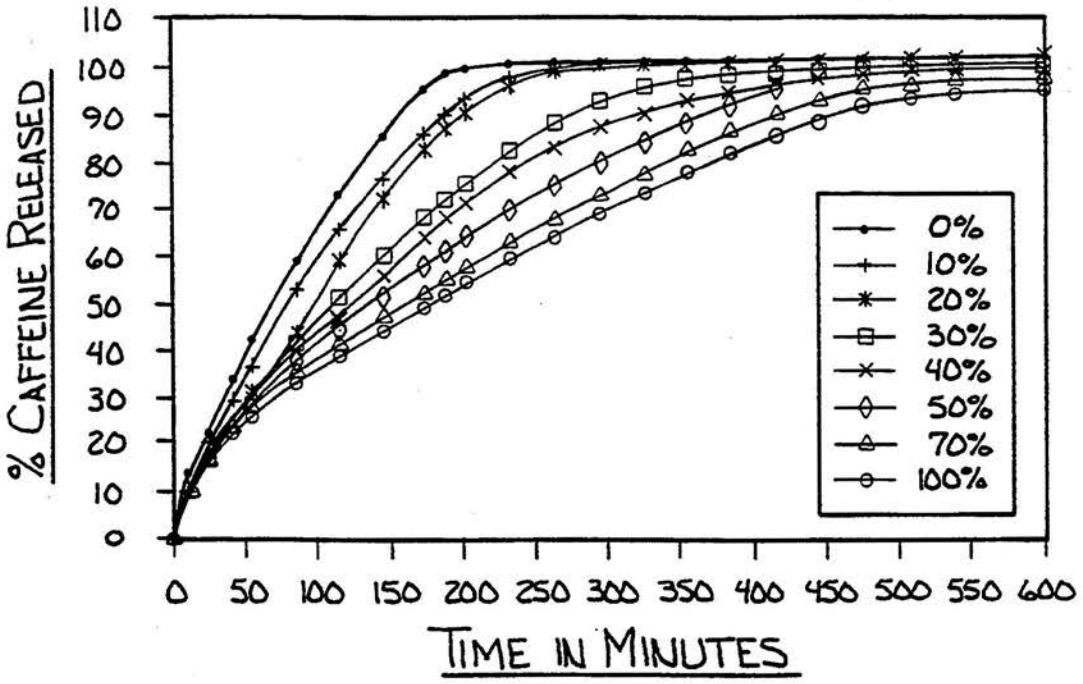


FIG. 5



MEMANTINE-CONTAINING SOLID PHARMACEUTICAL DOSAGE FORMS HAVING AN EXTENDED TWO-STAGE RELEASE PROFILE AND PRODUCTION THEREOF

BACKGROUND OF THE INVENTION

1. Field of Invention

The present invention is concerned with solid pharmaceutical compositions in dosage form which exhibit an extended matrix-controlled two-phase release profile and which are characterized by the presence in the matrix of both a water-soluble and a water-insoluble salt of casein, preferably sodium and calcium caseinate, respectively, in a total amount between 5 and 98% by weight of the composition, and with a process for the production thereof. A part or all of the insoluble casein salt may be replaced by a salt or solution of a polyvalent including bivalent cation, e.g., the calcium cation, adapted to form the water-insoluble casein salt in situ. The invention is particularly suitable for the provision of solid pharmaceutical dosage forms in which the active substance or principle is memantine.

2. Background of the Invention and Prior Art

Solid oral drug compositions or preparations having a retarded release, so-called retarder or extended-release preparations, are products from which the active ingredient is released over an extended period of time and hence exhibit a prolonged effect, with resultant plasma levels being adapted to therapeutic requirements. Also, a polyphase release profile can be employed to attain the desired therapeutic objectives. However, this does not necessarily mean that long-lasting effective blood level concentrations are consistently achieved. Moreover, systemic side effects and undesirable local effects within the gastrointestinal tract due to excessive local concentrations and resulting erratic plasma levels, respectively, are to be avoided.

In conventional procedures for the preparation of solid pharmaceutical dosage forms having an extended-release profile or pattern, the active substance in the majority of cases is either given extended-release properties by the application of various coatings or by being embedded in a macromolecular substance from which it is slowly released.

The most important control procedures for the release of an active pharmaceutical from a solid dosage form are the film-coating and the matrix procedures. In film coating procedures, film-forming polymers are employed to provide sustained release of the active substance in a diffusion-controlled manner. However, such an approach is disadvantageous if, during ingestion of the oral dosage form, the film is prematurely breached, as by chewing or abrasion, thereby releasing an excessive amount of active ingredient, which can result in undesirable effects from such excessive single-shot drug release.

In the matrix-controlled release approach, lipophilic substances, e.g., higher alcohols, waxes, or insoluble thermoplasts, are employed, it being a disadvantage that synthetic polymers not only generally contain varying amounts of undesirable monomers but that moreover a complete release of drug from the matrix is frequently not effected in practice.

The U.S. Pat. No. 4,665,081 describes a nifedepin formula for oral administration, which contains casein and inorganic additives selected from magnesium silicate, oxide, or aluminatemetasilicate, synthetic hydrotalc and magnesium aluminum oxide, thereby ensuring that the active substance—provided that a gastric juice-resistant auxiliary agent is included—is not released in the stomach but is rather rapidly released in the intestine. Such formulation will cause, on the one hand, a retarded release relative to the time of administration but, on the other hand, due to the rapid dissolution in the intestine, a high plasma concentration which is likely to result in undesirable side effects.

Pharm. Acta Helv. 66, No. 4, 120–124 (1991) describes an ibuprofen formula containing casein or gelatine which causes an elevated rate of dissolution and release, respectively, of the active substance.

Pharmaceutical Technology 9, 360–374 (1990) examines the influence of the presence of sodium caseinate on the rate of release of an active substance. Here, too, an enhanced dissolution, in particular, of chlorothiazide and hydrochlorothiazide, is reported.

The EP-A 0 447 100 Patent discloses formulations permitting controlled release in the stomach and in the intestine in response to the enzymes contained therein. For this purpose, a gel matrix, e.g., of alginate or carboxymethyl cellulose, carragheenin, or the like is employed, which contains imbedded therein a protein, such as calcium caseinate, and which comprises a further drug or food substance which is bondable to the protein. Although a controlled release is enabled thereby, such effect is achieved by the incorporation of protein in a surrounding matrix-forming gel.

GB-A 2 207 353 also describes formulations with a controlled release, containing calcium-free mixtures of alginic acid salts and caseinate. The protracted release is, however, based on a surrounding gel-matrix principle of the type referred to above.

It is apparent to one skilled in the art that the available technology for effective and reliable extended release, especially multistage release pharmaceutical dosage forms, still leaves much to be desired.

OBJECTS OF THE INVENTION

It is accordingly an object of the present invention to provide a pharmaceutical dosage form which is characterized by an extended controlled-release profile such that the active substance can be conveniently and reliably released over an extended period in at least two (2) stages and a process for the production thereof. Other objects of the invention will become apparent hereinafter, and still others will be obvious to one skilled in the art to which the present invention pertains.

SUMMARY OF THE INVENTION

The invention then, comprises the following, inter alia, separately or in combination:

A solid pharmaceutical composition in dosage form having a matrix-controlled extended two-stage release profile comprising an effective amount of at least one pharmaceutically-active ingredient or principle, wherein the matrix consists essentially of a combination of a water-soluble salt of casein and a water-insoluble salt of casein, the total water-soluble and water-insoluble casein salt content comprising between 5% and 98% of the total weight of the pharmaceutical composition, all salts and cations being pharmacologically acceptable; such a

composition wherein the water-soluble and water-insoluble casein salts comprise between 10% and

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