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<b>(21) International Application Number:</b> PCT/US99/05233 <b>(22) International Filing Date:</b> 10 March 1999 (10.03.99) <b>(30) Priority Data:</b> 09/044,446                      19 March 1998 (19.03.98)                      US <b>(71) Applicant:</b> BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). <b>(72) Inventors:</b> TIMMINS, Peter; 5 Heathbank Avenue, Irby, Merseyside L61 4XD (GB). DENNIS, Andrew, B.; 7 Pear Tree Close, Barnston, Merseyside L60 1YD (GB). VYAS, Kiren, A.; 34 Adisham Green, Sittingbourne, Kent ME10 2SR (GB). <b>(74) Agents:</b> RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD  <b>(57) Abstract</b>  A biphasic controlled release delivery system for pharmaceuticals which have high water solubility, such as the antidiabetic metformin HCl salt, is provided which provides a dosage form that has prolonged gastric residence and includes (1) an inner solid particulate phase formed of substantially uniform granules containing a pharmaceutical having a high water solubility, and one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, and (2) an outer solid continuous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout, the outer solid continuous phase including one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, which may be compressed into tablets or filled into capsules. Methods for forming the so-described biphasic controlled release delivery system and using such biphasic controlled release delivery system for treating diabetes are also provided.		

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BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM  
FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD

Field of the Invention

5           The present invention relates to a new dosage form  
for highly water soluble medicaments, such as the  
antidiabetic metformin, which provides for extended release  
of the drug and also for prolonged gastric residence which  
enables efficient delivery of drugs normally absorbed in  
10 the upper gastrointestinal tract, and to a method for  
preparing such dosage form.

Background of the Invention

15           Metformin is an antihyperglycemic agent of the  
biguanide class used in the treatment of non-insulin  
dependent diabetes mellitus (NIDDM). It is usually  
marketed in the form of its hydrochloride salt as  
Glucophage® (TM-BMS).

20           Metformin hydrochloride has intrinsically poor  
permeability in the lower portion of the gastrointestinal  
tract leading to absorption almost exclusively in the upper  
part of the gastrointestinal tract. Its oral  
bioavailability is in the range of 40 to 60% decreasing  
with increasing dosage which suggests some kind of  
25 saturable absorption process, or permeability/transit time  
limited absorption. It also has a very high water  
solubility (>300 mg/ml at 25°C). This can lead to  
difficulty in providing a slow release rate from a  
formulation and problems in controlling the initial burst  
30 of drug from such a formulation. These two difficulties  
are further compounded by the high unit dose, 500 mg per  
tablet, usually required for metformin hydrochloride (1997-  
PDR).

35           Drugs that have absorption limited to the upper  
gastrointestinal tract coupled with poor absorption in the  
distal small intestine, large intestine and colon are  
usually regarded as inappropriate candidates for

formulation into oral controlled delivery systems. This limitation on absorption (for example, in the upper gastrointestinal tract) is referred to as the "absorption window".

5           The gastrointestinal tract functions to propel ingested material from the stomach (where digestion takes place) into the small intestine (where absorption principally occurs) and on to the large intestine (where water is absorbed/secreted as part of body fluid regulation processes). Residence time for non-digestible materials in the stomach depends on whether one is dealing with a fed or a fasted subject. Typical gastric emptying times for particulate material (greater than a few millimeters in diameter) varies from a few tens of minutes in the fasted state to a few hours in the fed state. Transit times through the small intestine are consistently of the order of 3 to 4 hours.

          Oral controlled release delivery systems function by releasing their payload of drug over an extended period of time following administration. Thus, controlled release dosage forms may only spend a relatively short period in the regions of the gastrointestinal tract where good absorption of certain drugs can occur. The dosage form will pass on to regions of the intestine where absorption of certain drugs is poor or non-existent, still releasing its contained drug albeit with a significant percentage of its payload still to be delivered. Drug when released from the dosage form in the circumstances described will not be absorbed. Thus, administration of a drug subject to a window of absorption in a conventional controlled release delivery system can lead to subtherapeutic blood levels and ineffective treatment of the disease state for which the drug was intended.

          Drugs with very high solubility in water (for example, greater than 100 mg/ml) can be difficult to formulate into a controlled release oral dosage form. Solubility is a driving force for a drug substance to

dissolve in water; the greater the solubility the greater the rate of dissolution when all other factors are maintained constant.

5 In a controlled release dosage form, the formulator  
tries to reduce the rate of dissolution by, for example,  
embedding the drug in a polymeric matrix or surrounding it  
with a polymeric barrier membrane through which drug must  
diffuse to be released for absorption. To reduce the rate  
of release of drug from the dosage form to an appropriate  
10 level consistent with the blood level profile desired for a  
drug possessing very high water solubility, very large  
amounts of polymer would be required for the matrix or  
barrier membrane. If the total daily dose of drug to be  
delivered is of the order of only a few milligrams this may  
15 be feasible, but many drugs having the solubility  
properties described require total daily doses of the order  
of many hundreds of milligrams. Whilst it is possible to  
create oral controlled release dosage forms for such  
products by use of large amounts of polymer, an  
20 unacceptably large dosage form may result.

A further problem with highly water soluble drugs  
formulated into a controlled release dosage form is that a  
significant and variable "burst" of drug can occur from  
these systems. The burst of highly water soluble drug is  
25 the initial rapid release of drug that occurs from oral  
controlled release dosage forms when first contacting  
fluid, such as gastric fluids, prior to release controlling  
mechanisms of the dosage form establishing themselves and a  
stable release rate being provided. Hydration of any  
30 polymer matrix used to formulate the dosage form is a pre-  
requirement of establishing a stable release rate. Thus, a  
readily hydrating polymer is required to establish the  
desired stable release rate. However, if the polymer used  
is slow to hydrate, then an undesirable variable burst can  
35 occur.

Studies by Vidon et al (1) strongly suggest that  
there is permeability limited absorption of metformin.

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