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(54) **BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD**

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(58) **Field of Search** 424/464, 465, 424/468, 469, 470, 457, 484, 485, 486, 488, 472, 473

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,976,764	A	8/1976	Sumio et al.	
4,126,672	A	11/1978	Sheth et al.	
4,140,755	A	2/1979	Sheth et al.	
4,167,558	A	9/1979	Sheth et al.	
4,207,890	A	6/1980	Mamajek et al.	
4,357,469	A	11/1982	Schor	
4,369,172	A	1/1983	Schor et al.	
4,434,153	A	2/1984	Urquart et al.	
4,704,285	A	11/1987	Alderman	
4,711,782	A	12/1987	Okada et al.	
4,767,627	A	8/1988	Caldwell et al.	
4,828,836	A	5/1989	Elger et al.	
4,844,905	A	7/1989	Ichikawa et al.	
4,954,298	A	9/1990	Yamamoto et al.	
5,007,790	A	4/1991	Shell	
5,169,638	A	12/1992	Dennis et al.	
5,232,704	A	8/1993	Franz et al.	
5,374,430	A	12/1994	Newton et al.	
5,484,608	A	1/1996	Rudnic et al.	
5,575,987	A	11/1996	Kamei et al.	
5,582,837	A	12/1996	Shell	
5,645,858	A	7/1997	Kotwal et al.	
5,824,344	A	10/1998	Palepu et al.	
5,955,106	A	9/1999	Moeckel et al.	
6,099,859	A	8/2000	Cheng et al.	424/464
6,099,862	A	8/2000	Chen et al.	424/473
6,340,475	B2	1/2002	Shell et al.	
2001/0018070	A1	8/2001	Shell et al.	

FOREIGN PATENT DOCUMENTS

DE	4414544	C2	11/1994
EP	502642	A1	9/1992
EP	609961	A1	8/1994
FR	2594693		2/1987
WO	WO93/18755		9/1993
WO	WO94/27557		12/1994
WO	94/27589		12/1994
WO	WO 96/031996		3/1996
WO	WO97/18814		5/1997
WO	WO 98/55107		12/1998
ZA	95/7670		9/1995
ZA	957670	*	9/1995

OTHER PUBLICATIONS

Chem. Ab. 126:229547 M.P. Gouldson et al. 1997.*
Chem. Ab. 132:83528 Je Pinko et al. 1999.*
Noel, M., "Kinetic study of normal and sustained release dosage forms of metformin in normal subjects", Journal of International Biomedicl Information and Data, 1980, pp. 9–20.
Karttunen, P. et al, "The pharmacokinetics of metformin: a comparison of the properties of a rapid–release and a sustained–release preparation", Int. J. Clin. Pharmacology, Therapy & Toxicology, vol. 21, No. 1, pp. 31–36.
Vidon, N. et al, "Metformin in the digestive tract", Diabetes Research and Clinical Practice, 4 (1988) 223–229.
Pentikainen, P.J., "Bioavailability of metformin. Comparison of solution, rapidly dissolving tablet, and three sustained release products", Int'l Journal of Clin. Pharm., Therapy and Toxicology, 24, No. 4, 1986, 213–220.
Longer et al., Journal of Pharmaceutical Sciences, vol. 74, No. 4, pp. 406–411, Apr. 1985.
Davis et al., Pharmaceutical Research, vol. 3, No. 4, pp. 208–213, 1986.
Timmermans et al., Journal of Pharmaceutical Sciences, vol. 83, No. 1, pp. 18–24, Jan. 1994.

* cited by examiner

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(57) **ABSTRACT**

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 so that a dosing regimen of at least one gram metformin, once daily, may be achieved while providing effective control of plasma glucose. The delivery system 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.

50 Claims, No Drawings

BIPHASIC CONTROLLED RELEASE DELIVERY SYSTEM FOR HIGH SOLUBILITY PHARMACEUTICALS AND METHOD

REFERENCE TO OTHER APPLICATIONS

This is a continuation-in-part of U.S. application Ser. No. 09/044,446 filed Mar. 19, 1998, now abandoned.

FIELD OF THE INVENTION

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, so that a dosing regimen of at least one gram metformin once daily, may be achieved while providing effective control of plasma glucose, and to a method for treating diabetes employing such dosage form.

BACKGROUND OF THE INVENTION

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).

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 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 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).

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".

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.

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 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 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 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 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 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 undesireable variable burst can occur.

Studies by Vidon et al (1) strongly suggest that there is permeability limited absorption of metformin. Perfusing drug into the jejunum via an intubation technique showed a 2.5 fold greater area under the plasma concentration-time profile (a measure of the quantity of drug absorbed) compared with similar introduction of drug into the ileum. Drug was not detectable in plasma when drug was perfused into the colon. Drug will transit down the small intestine following dissolution from an ingested dosage form and, if absorption rate is slow, it is possible that drug can reach regions of poor permeability before absorption of a given dose is complete. In such a case, increasing the given dose may be predicted to result in a reduction in the percentage of administered dose absorbed.

Improvements in the therapeutic regimes employing metformin might be achieved by a dosage form that allows a reduction in dosing frequency, providing patient convenience that would probably improve compliance. Conventional extended release formulations have been demonstrated to invariably compromise the availability of metformin (2), (2A), and (2B). This is probably because the dosage form carries a significant proportion of the drug

content remaining to be released, as the dosage form is carried to regions of the gastrointestinal tract with very poor permeability to the drug. To reduce dosing frequency, the rate of release from the dosage form must be such as to extend effective plasma levels, but the potential for effective delivery at this rate is compromised by the combined influences of the significant reduction in permeability to the drug in passing from the proximal small intestine down to the colon and the limited residence time in the regions of the gastrointestinal tract where the drug is well absorbed. That transit time down the "useful" region of the gastrointestinal tract is only likely to be of the order of a few hours.

Maintained or even improved bioavailability from an extended release dosage form that releases metformin at a rate likely to provide the desired plasma levels of drug for an extended time period might, however, be possible from a dosage form that has extended residence time in the upper gastrointestinal tract, resisting mechanisms that promote normal transit time for solid materials. That this principle might work in practice was demonstrated in an in-house study where metformin was co-administered with propantheline, an agent that reduces gastrointestinal motility. Compared with giving metformin alone, the combination provided an increased AUC, a delayed tmax and an extended time period over which therapeutically beneficial plasma levels of drug were maintained.

Giving a drug such as metformin for the treatment of diabetes with a further drug, such as propantheline, not used for the treatment of diabetes and where the sole intent of using the second agent is to achieve extended residence time in the upper GI tract, has many disadvantages although it is likely to allow effective extended delivery of metformin to an optimal absorption site. The co-administered drug may have other undesirable pharmacological effects or side effects deleterious to the patients well being and detract from the improved quality of life offered by the treatment for their diabetes. Furthermore, it may be difficult or impossible to appropriately co-formulate the two agents due to chemical compatibility issues or solubility differences, the latter preventing the required release rate of agent influencing residence time in the upper GI tract. Thus, the patient could be required to take separate, multiple medications to achieve the desired effect. The timing of taking the two medications would be critical to effective delivery of the drug with the limited window of absorption and many patients may thus fail to take their medication correctly resulting in ineffective treatment of their diabetes.

Prior Art Gastro-Retentive Systems

It would be desirable to provide a dosage form that inherently has the property of extended gastric residence, possessing some resistance to the pattern of waves of motility present in the gastrointestinal tract that serve to propel material through it. There have been many attempts to provide for this, with varying degrees of success.

Possible approaches described in prior art include:

(1) Floating or buoyant systems:

These are designed to have a low density and thus should float on gastric contents after administration until the system either disintegrates (and presumably the resultant particles empty from the stomach) or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

(2) Bioadhesive systems:

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened for example by continuing hydration of the outer layer of the device or by the persistent application of shear.

(3) Swelling and expanding systems:

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (for example, less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet). On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach.

Re: (1) Buoyant/floating Systems

Buoyant systems designed to float on the gastric contents have been designed where buoyancy is created by low density of the formulation components. For example, Watanabe et al (3) used low density shells such as spherical polystyrene foam particles in which polymer and drug layers were loaded. Such a system has the required low density and will not need to disintegrate into small pieces to empty from the stomach, but may not have a controlled loss of density alternatively required for it to eventually exit from the stomach. It also has limited capacity for loading with drug in the thin layers that can be applied around the polystyrene shells. It would be difficult to also layer large amounts of polymer on such a system to retard the release of very water soluble drugs.

Sheth described hydrodynamically balanced systems including both capsules and tablets (4,5,6) which had low density to enable floating on the stomach contents and which slowly eroded after administration, losing buoyancy and being expelled from the stomach.

Buoyancy can also be combined with control of drug release at different pH values to make for a device with better control in case of drugs with very marked dependency of solubility on pH (7); hence dissolution of contained drug depending on environment pH.

These approaches may be applicable to many drugs dosed in doses of up to a maximum of a few hundred milligrams per day but may not be applicable to similar or higher dose levels of highly water soluble drugs. Where large amounts of polymer are needed to retard drug release as in the case of use of high water soluble drugs a capsule dosage form may not be possible on grounds of size. Furthermore, the relatively homogenous distribution of drug in the tablet versions of this technology would not readily control the burst effect seen with a very water soluble drug.

A bilayer tablet approach (8) where the buoyancy generation comes from a separate layer to the drug containing layer having a release rate controlling property might overcome some of the problems seen with the hydrodynamically balanced systems, but this type of system would probably only be able to carry low drug payloads due to size constraints.

Approaches involving in situ gas generation within the system, where the gas is trapped within the dosage form on generation, encouraging buoyancy, might offer improved control over degree, onset time and persistence of buoyancy. Ichikawa (9) described such a device with a drug loaded core surrounded by the gas generating layer, which in turn was

surrounded by a polymeric layer responsible for controlling drug release from the system.

Such floating or buoyant dosage forms seem to have met with limited clinical success due to the requirement that such dosage forms be taken with a suitable amount of fluid (normal gastric contents could be as little as a few tens of milliliters so that the total amount of fluid thus available would not be conducive to performance of such systems even when taken with a draught of water). Davis et al (10) found no benefit of floating formulations over non-floating formulations when studied in vivo. Their performance may also be posture dependent. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach (11). The physical size of such dosage forms seems to be as important if not more important as ability to float in encouraging prolonged gastric residence. Hence, floating/buoyant dosage forms might be expected to only have limited applications.

Re: (2) Bioadhesive Systems

Polycarbophil has been identified as a suitable polymer for encouraging adhesion of orally administered dosage forms to the gastric mucosa, thereby prolonging residence time for a system designed to slowly deliver drug to absorptive sites in the proximal small intestine (Longer et al, J. Pharm. Sci., 74, 406–411 (1985)). The success seen in animal models with such systems has been found not to translate to human subjects due to differences in mucous amounts, consistency and turnover between animals and humans. Bioadhesive systems allow dosage forms to adhere to mucous, not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage forms would not appear to offer a solution for extended delivery of drug over a period of more than a few hours to the upper small intestine in humans.

Re: (3) Swelling/Expanding Systems

Other solutions to encouraging prolonged gastric residence have included dosage forms that unfold rapidly within the stomach to a size that resists gastric emptying. Such systems retain their integrity for an extended period and will not empty from the stomach at all until breakdown into small pieces occurs. Caldwell (12) describes a cross shaped device made of erodible polymer and loaded with drug which is folded and inserted into a hard gelatin capsule. Following oral administration the gelatin shell disintegrates and the folded device opens out. With a minimum size of 1.6 cm and a maximum size of 5 cm it will not pass from the stomach through the pylorus until the polymer erodes to the point where the system is sufficiently small that it can be passed from the stomach. Such a system may in fact obstruct the pylorus or even open earlier or later than intended possibly causing obstruction in the esophagus or small intestine. As such, it may represent a potential hazard to the patient.

An alternate approach to using size to modulate gastric residence of a dosage form is to use a hydrophilic erodible polymer system that is of a convenient size for administration to humans. On imbibing fluid the system swells over a short period of time to a size that will encourage prolonged gastric retention, allowing sustained delivery of contained drug to absorption sites in the upper gastrointestinal tract. Because these systems are made of an erodible and hydrophilic polymer or polymer mixture, they readily erode over a reasonable time period to pass from the stomach. The time period of expansion is such that this will not occur in the esophagus and if the system passes into the intestine in a partially swollen state, the erodibility and elastic nature of the hydrated polymer will eliminate the chance of intestinal obstruction by the device.

Mamajek et al, U.S. Pat. No. 4,207,890, describes a system wherein a drug release rate controlling (metering) component and a swelling component are mixed with drug enclosed within a membrane. The swelling component draws in fluid through the membrane, which maintains system integrity during its functioning, and the drug metering component controls the rate of drug release through the membrane.

Urquart (13) describes a different approach which consists of a matrix of hydrogel that imbibes fluid to swell the system so that it reaches a size encouraging prolonged gastric retention. This matrix surrounds a plurality of tiny pills consisting of drug with a release rate controlling wall of fatty acid and wax surrounding each of the pills.

Shell (14,15,16) has described systems for delivering drugs for the treatment of diseases of the upper gastrointestinal tract or for delivering drugs that might be irritating or injurious to the gastrointestinal mucosa. A swelling hydrogel polymer has embedded within it drug particles that dissolve once the hydrogel matrix is hydrated. The swollen matrix is of a size to encourage gastric retention but only dissolved drug reaches the mucosa and this can be delivered in a sustained manner. Such a system thus does not insult the mucosa with solid particles of irritant drug and is suitable for delivering drug to upper gastrointestinal tract. These systems only apply in case of drugs of limited water solubility.

In the case of metformin, it is desirable to provide a dosage form that allows extended delivery of the drug and has a prolonged gastric residence via swelling of the system rather than unfolding or expanding of a folded device, and that may be manufactured on a commercial scale. The prolonged gastric residence time is required due to the window of absorption seen with metformin.

Another problem for extended delivery of metformin is its very high water solubility. High levels of polymer would be needed if many prior art approaches to provide the required release rate are employed. This could result in a rapid and variable initial release (burst) of drug from an extended release dosage form. The latter will thus give rise to difficulty in providing a true control of drug release and minimal inter-patient variability in drug plasma levels (arising from the possibility of variable burst of drug from tablets given to different patients).

Prior Art Controlled Release Systems for Very Soluble Drugs

Typical prior art techniques for creating a controlled release oral dosage form would involve either matrix systems or multi particulate systems. Matrix systems may be formulated by homogeneously mixing drug with hydrophilic polymers, such as hydroxypropylmethylcellulose, hydroxypropylcellulose, polyethylene oxide, carbomer, certain methacrylic acid derived polymers, sodium alginate, or mixtures of components selected from these, and compressing the resultant mixture into tablets (employing some other excipients where needed). Hydrophobic polymers, such as ethyl cellulose, certain polymeric methacrylic acid esters, cellulose acetate butyrate, poly(ethylene-co-vinyl-acetate) may be uniformly incorporated with the above materials to give additional control of release. A further alternative involves embedding drug within a wax based tablet, by granulation or simply mixing of drug with a wax, such as carnauba wax, microcrystalline wax or commercially available purified fatty acid esters. As noted above, it may not be possible to use these approaches with very highly water soluble drugs.

Multi particulate systems consist of a dosage form based on a plurality of drug loaded spheres, prepared by layering drug onto a core, usually a sugar-starch mixture sphere of around 0.8 mm diameter, until a sufficient level is reached, and then providing a drug release barrier around the drug-loaded sphere. Drug-loaded spheres can also be made by wet massing a mixture of drug and excipients, forcing the wet mass through a perforated screen to form short strands which are rounded in a spheronisation apparatus before drying and having the drug release barrier applied. The drug release barrier can be a wax, such as carnauba wax or glyceryl fatty acid esters, or a polymeric barrier, such as a mixture of ethyl cellulose and hydroxypropylmethylcellulose. These work well for moderately soluble drugs with doses in the units of milligrams to less than a few hundred milligrams per day.

In several examples, prior art systems seem to provide a controlled release formulation of a very water soluble drug by improving the multi particulate system approach. Fisher discloses a multi particulate system for highly soluble drugs especially opiate agonists (17) based on drug containing cores surrounded by a drug release controlling barrier which has the property of being partially soluble at a highly acidic pH.

Hansraj (18) coats drug loaded cores with methacrylic or acrylic acid derived polymers whose properties are modified by inclusion of at least one anionic surfactant. In such a system, drug release of highly water soluble drugs is controlled without having to resort to the use of thick coatings on the release rate controlling layer.

Rollet (19) achieves prolonged release of a drug from a multi particulate formulation based on fine particles of hydrophilic and hydrophobic silicas or silicates. Presumably, this system would function for drugs of high water solubility.

Multi particulate systems are usually filled into capsules to provide unit dose forms because of the damage caused to such particles in trying to compress them into tablets. Total dose contained in a single unit is constrained by the loading possible in a hard gelatin capsule of easily swallowable size and is usually not more than a few hundred milligrams.

Single unit controlled release systems applicable to highly water soluble drugs include the application of multiple layers around a dose form as described by Howard (20). Where coating is not employed, special mixtures of polymers or formation of a complex with the drug have been used. Macrae (21) uses mixtures of polyethylene oxide and hydroxypropylmethylcellulose with optional enteric polymers to produce a constant release rate for highly water soluble drugs. Belenduik (22) combines the highly water soluble drug with a hydrophilic polymer based on acrylic acid and disperses this in a hydrophobic matrix.

Variations of Alza osmotic systems have been described suitable for highly water soluble drugs such as venlafaxine hydrochloride (23). These systems need two layers, a drug layer and an osmotically driven displacement layer all surrounded by a water permeable/drug impermeable membrane with an exit passage in this membrane for the drug.

Granules of highly water soluble clavulanate were prepared (24) having to employ a barrier layer of a hydrophobic waxy material in order to provide for controlled release of this material when co-formulated with controlled release amoxycillin trihydrate granules in capsule or compressed tablet.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, a novel way has been found of formulating drug with high water solubility and a limited window of absorption such as metformin or a salt thereof which has a window of absorption in the upper gastrointestinal tract, to provide a dosage form that inherently has prolonged gastric residence. This is accomplished (a) without need for co-administration of a drug such as propantheline, and (b) without need for low density formulation or gas generation within the formulation. The formulation of the invention (a) achieves extended gastric residence by virtue of size but will degrade in vivo so as not to have potential for causing gastric or intestinal obstruction, and (b) controls drug release adequately where the initial burst of drug is under control. The formulations of the invention will provide for an extended release formulation of drug with minimal interpatient variability in pharmacokinetic parameters.

In the case of metformin, the formulation of the invention allows a patient a dosing regimen of at least one gram metformin, once-daily, preferably from about 1 to about 3 grams, once daily, in the form of one or more tablets and/or one or more capsules, while providing effective control of plasma glucose. The metformin formulations of the invention may be administered once daily at the above dosages to effectively treat diabetes while avoiding problems which may be associated with high plasma metformin levels as may be encountered with conventional metformin formulations, while providing optimum therapeutic control.

The invention is applicable to all drugs having high water solubility and a limited window of absorption.

The biphasic controlled release delivery system of the invention is a heterogeneous two phase system which includes (1) an inner solid particulate phase in the form of individual granules or particles containing (a) drug which has a high water solubility, preferably, metformin or a salt thereof, and a limited window of absorption (such as in the upper gastrointestinal tract), and (b) an extended release material formed of one or more hydrophilic polymers, and/or one or more hydrophobic polymers, and/or one or more other type hydrophobic materials (such as one or more waxes, fatty alcohols and/or fatty acid esters), and (2) an outer solid continuous phase in which granules or particles of inner solid particulate phase are dispersed and embedded, the outer solid continuous phase which primarily is formed of an extended release material formed of one or more hydrophilic polymers, and/or one or more hydrophobic polymers, and/or one or more other type hydrophobic materials (such as one or more waxes, fatty alcohols and/or fatty acid esters).

The biphasic controlled release formulation of the invention is particularly adapted for delivery of high water soluble drugs, such as metformin and pharmaceutically acceptable salts thereof, in controlled and extended manner without significant initial burst of drug, and wherein release of drug (liberated from the individual dispersed particles forming the inner solid particulate phase) is effectively controlled. Drug upon being released from the particles of the inner phase, in effect, migrates through the outer solid continuous phase and then is released from the formulation into the upper gastrointestinal tract to be available for absorption.

As indicated, the inner solid particulate phase will be formed of individual discrete particles or granules each of which contains drug and one or more polymeric materials and/or other hydrophobic-type materials. In effect, the components of the inner solid particulate phase are in particulate association without having a barrier layer around the individual particles or granules.

The outer solid continuous phase is preferably a continuous phase or matrix having the particles or granules includ-

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