**Abstract:** The invention provides a controlled release pharmaceutical pellet composition comprising a drug having low solubility under acidic conditions, the said composition providing a release of at least 75% of the said drug within 45 minutes in phosphate buffer pH 6.8, further comprising a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the swellable polymer to the microcrystalline cellulose is above 5:100 and up to 30:100.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
CONTROLLED RELEASE PHARMACEUTICAL PELLET COMPOSITIONS FOR REDUCING SIDE EFFECTS OF DRUGS

The present invention is in the field of drug delivery systems and controlled release technology. Particularly, the invention is in the field of controlled release pharmaceutical pellet compositions. More specifically, the invention relates to compositions with low to moderate drug loading for immediate release of the drug in the small intestine, wherein the drug is preferably fewly soluble or nearly insoluble under acidic conditions, especially for instance a non-steroidal anti-inflammatory drug. In addition to controlled release pharmaceutical pellet compositions, this invention relates to solid shaped articles containing them, to a process for manufacturing them as well as to a method for reducing the side effects, including local irritation of the mucosa of a mammal, of a drug substance having low solubility in an acidic medium such as a non-steroidal anti-inflammatory drug.

BACKGROUND OF THE INVENTION

Non-steroidal anti-inflammatory drugs (hereinafter referred as NSAID) are used in humans and animals for the treatment of inflammatory and rheumatic disorders such as dysplasia of the hip, chronic arthritis, spondylitis and the like. As is well known to those skilled in the art, one of the most commonly signaled side effects of non-steroidal anti-inflammatory drugs is irritation of the gastrointestinal tract. This side effect can be attributed to local irritation due to the penetration of the drug in the gastric mucosal cells, but it can also be caused by enterohepatic recirculation, which extends the contact period of the non-steroidal anti-inflammatory drug with the mucosa, or by the inhibition of prostaglandin synthesis due to the inhibition of the cyclooxygenase enzyme. Similar side effects may also be attributed to certain other drugs, especially drug substances belonging to other therapeutic classes, which are not very water-soluble or nearly water-insoluble under acidic conditions, for instance having a low water-solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH
in the stomach. This is because the availability of a drug substance with respect to
entrance into the circulatory system is dependent on the presence of the said drug
on dissolved form as it is generally accepted that only dissolved substances are
capable of passing the mucous membranes in the gastro-intestinal tract.

In order to solve this problem of local irritation caused by certain drugs such
as non-steroidal anti-inflammatory drugs, it is desirable to provide a suitable drug
delivery system, for instance a system by which the said drug will not, or hardly,
come in contact with the gastric mucosa and/or by which high local drug
concentrations are avoided and/or by which the gastric emptying time will be less
variable than with the existing formulations.

Some general considerations relating to drug formulation are now provided
herein in order to understand both the applicable constraints which a technical
solution to the above problem faces and at the same time the kind of
pharmaceutical solid formulations to which the present invention may be applied.

Tablets and capsules are generally unsuitable for administering high doses
of biologically active ingredients such as non-steroidal anti-inflammatory drugs
since individual large dosage forms are difficult to swallow or necessitate the
administration of several tablets or capsules at a time, leading to impaired patient
compliance. Chewable tablets are usually not suitable with young children and
older people and are furthermore unsuitable for the incorporation of controlled-
release coated pellets which could get crushed upon chewing.

Oral liquid suspensions of pharmaceutical and veterinary ingredients are
designed for those experiencing difficulty in swallowing solid medication but are not
suitable for the incorporation of controlled-release particles into aqueous vehicles,
since this often results in premature release of the active ingredient into the
suspending media during storage. Efforts made to formulate controlled-release
susENSIONS include using ion-exchange resins in order to bind charged molecules
but this has limitations including low drug-loading capability and applicability to
ionic drugs only.
The formulation of a solid oral dosage form, whether tablet or capsule, which disintegrates rapidly in water to form an instantaneous homogenous suspension of adequate viscosity to be swallowed could circumvent the problems of administering large dosages without premature release from controlled-release particles while providing a ready measured dose. The key to the development of such a dosage form would be a rapidly disintegrating tablet which is able to disperse to form a viscous suspension. A delay in the development of a viscous gel would be essential for achieving disintegration of the tablet. On the other hand, a rapidly increasing viscosity would be necessary to provide adequate suspension properties.

The ideal solid oral dosage form should therefore contain a material which is able to increase viscosity on contact with water, an active ingredient for controlled release delivery and a filler conferring both a suitable compactibility and the capability to disintegrate quickly. However the inclusion of a viscosity increasing agent as a fine powder in the tablet matrix formulation without any processing would generally adversely interfere with the disintegration process and would result in the formation of a voluminous hydrophilic mass which is impossible to disperse. Thus until now it was believed necessary to incorporate such a viscosity increasing agent into the tablet as granules so that the disintegration process occurs before the viscosity increase. However prior art formulations have failed to design a suitable compromise between the kinetics of disintegration and viscosity increase.

Hard gelatin capsules are also known as a pharmaceutical dosage form. Their sizes have been standard since the start of industrial manufacture of drug compositions, ranging from 5 (corresponding to a volume of 0.13 ml) up to 000 (corresponding to a volume of 1.36 ml). Thus, when a large amount of ingredient is required for each dosage unit, depending on the bulk density of the formulation, it may be necessary to use large size capsules which are too large to swallow or, even worse, a size 000 capsule may be too small to receive the said amount. Pellets and coated pellets have often been filled into hard gelatin capsules to be used as conventional or controlled release dosage forms, however it is rather
difficult to manufacture controlled-release formulations while using a hard gelatin capsule as the dosage form and such attempts have found relatively limited use despite efforts to improve the engineering of such formulations. This is why tablets are generally recognized as the most popular pharmaceutical oral dosage form participating in the comfort of the patient. This is especially true of sustained-release tablets which are designed to release the drug slowly after ingestion. In this case, patient compliance is improved since the daily number of tablets and the frequency with which the patient has to take these tablets to obtain the desired effect are considerably reduced. With sustained-release tablets, drug activity can be extended to take effect throughout the night, so that the patient need not be awakened until morning, thus resulting in time saving for nurses in hospitals.

The concept of tableting coated active ingredient particles is therefore of interest. Attempts have been made to produce tablets comprising microcapsules because of the advantages resulting from the microencapsulated substance being protected from external influences and vice-versa, e.g. increased stability, reduced chances of irritations or undesirable reactions with other components in a mixture, ability to mask unpleasant tastes and smells, etc. However, compaction of coated beads (i.e. coated pellets) for making tablets encounters the following difficulties or problems. If the beads have been coated by a rate-controlling polymeric coating to sustain active ingredient delivery, cracking of the coating will cause the delivery system to change the rate of active ingredient delivery or release of the active dose. In "Design of an oral sustained release drug delivery system comprising polymer coated pellets compacted into tablet ", Dyer et al. describe the production of a tablet formed from pellets containing an active ingredient. The said pellets are coated with a polymer which forms a controlled release membrane and, on oral administration of the tablets, intact polymer coated pellets are released in which the controlled release membranes are preserved. These pellets are formed by extrusion-spheronization of a mixture of 80% ibuprofen and 20% microcrystalline cellulose. The spheres were subsequently coated with a film including triethyl citrate plasticizer. The pellets were then introduced into a tableting machine with a
mixture of excipients in a total amount adequate to fill the void volume. Release profiles of active ingredient from the tablets indicate that the film coat is damaged during the tableting procedure, resulting in an increased release rate. Scanning electron microscopy of the tablet showed that damage was incurred by pellets particularly at the tablet surface. Preventing cracking of the coating is therefore of utmost importance. Large amounts of carriers have been found necessary in most cases in order to overcome the tendency of microcapsules or coated beads to brittleness by preventing their rupture on compression, thus resulting again in unacceptably large tablets.

As is well known in the pharmaceutical industry, beads (or pellets) are quite distinguishable from granules. They can be defined as small, free-flowing spherical or sphere-like particulates manufactured by pelletization, i.e. the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. As opposed to the process of granulation, the production of beads by pelletization results in a larger average size and a narrower size-range distribution. The more spherical nature of beads, as compared to granules, provides better flow and significantly reduces segregation due to shape differences. Also, the surface morphology of beads is optimal for applying a functional coating.

Compaction of controlled release tablets containing coated pellets involves the following critical aspects. When such a dosage form is developed, the coated pellets must withstand the process of compaction without being damaged in order to prevent any undesirable or uncontrolled effects on the active ingredient release properties. The type and amount of coating agent, the size of the sub-unit, the selection of external additives and the rate and magnitude of the applied pressure must be carefully considered. The process of bead compaction involves the application of stress to polymer-coated spherical or sphere-like cores. The desirable mechanical properties of coated beads to be compacted into a tablet together with excipients should be such that they are strong, not brittle and have low elastic resilience. Investigation of the mechanical properties of both uncoated
and coated beads has demonstrated that the presence of a film coat applied by means of an aqueous polymeric dispersion of polymethacrylates influenced the crushing strength and the elastic properties of beads: increasing the polymer loading results in increasing the crushing strength of beads, whilst simultaneously enhancing bead resilience (characterized by a reduction in the elastic modulus).

Significant changes were observed between the compaction properties of the powder and pellet forms of the same formulations: powder formulations deformed plastically and produced stronger compacts, whereas their pellet corresponding forms exhibited elastic deformation and brittle fragmentation, which resulted in compacts of lower tensile strength. It was also observed that the active ingredient release rate from spheres coated with acrylate polymers increased with an initial increase in the applied pressure - this being attributed to the cracks in the coat that formed during compaction - but that further increase in pressure again retarded the release profile, possibly due to closer inter-particulate contacts within the tablet which partly compensated for the leaks of the pellet coats.

The selection of external additives is also of importance in the design of tablets since these additives are expected to prevent the occurrence of film cracking in the coated sub-units. Their compatibility with the active ingredient-loaded pellets, in terms of particle size, is also very critical since a non-uniform size distribution can cause segregation, again resulting in tableting problems such as weight variation, poor content uniformity, etc.

As previously mentioned, conventional highly compactible fillers like microcrystalline cellulose can be mixed with active ingredient-loaded beads and compressed into tablets. It is well known that beads made from microcrystalline cellulose are, by virtue of the inherent bonding capacity of this material, very hard and not easily deformed or broken. However due to particle size differences with active ingredient-loaded beads, segregation may occur and result in weight variation and content uniformity problems. Microcrystalline cellulose granules produced by dry or wet granulation techniques and having similar size as the active ingredient-loaded beads are able to minimize segregation due to size differences
and subsequent problems. However this advantage is then obtained to the
detriment of compactibility.

A certain number of specific formulations have been proposed in order to
overcome the above-mentioned difficulties. For instance, EP-A-686.392 deals with
the problem of batch homogeneity in the direct tabletting of low-melting active
compounds (in particular NSAID like ibuprofen and ketoprofen) which are
unsuitable for such production technique due to their unfavorable physico-chemical
properties. This problem is solved by melt extruding a mixture of the active
compound and the necessary auxiliaries at elevated temperature to give a
homogeneous non-agglutinating extrudate which is then comminuted to give
tabletable granules. Microcrystalline cellulose is among the auxiliaries mentioned
in this document, which nevertheless does not deal with the problem of controlled
drug release.

EP-A-403.383 faces the problem of optimizing a sustained release
composition containing ketoprofen in view of particulars of this active material
including rate of absorption, interaction with and between excipients, physical
properties and bioavailability. It provides a 40-90 weight% ketoprofen formulation
comprising granules, each comprising (i) a core comprising ketoprofen and
microcrystalline cellulose and (ii) a coating comprising both a water-soluble and a
water-insoluble cellulose derivatives, e.g. ethylcellulose and
hydroxypropylmethylcellulose respectively. This document teaches that the
ketoprofen sustained release depends on the respective proportions of the water-
soluble and water-insoluble cellulose derivatives in the coating. The cores of the
granules are made by mixing ketoprofen and microcrystalline cellulose, optionally
in the presence of less than 5 weight% sodium carboxymethylcellulose and
optionally in the presence of sufficient water to form cores by extrusion and
spheronization. The single example illustrates extrusion-spheronization of a
composition of 75 weight% ketoprofen and 25 weight% of a mixture comprising
3.5% sodium carboxymethylcellulose and 96.5% microcrystalline cellulose.

According to in vitro tests, this formulation show an extended, approximately linear
release rate for ketoprofen at typical physiological pH’s, indicating that they are able to sustain a therapeutic level of ketoprofen in the body over a period of time.

WO-A-99/12524 deals with the problem of providing NSAID formulations to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. This is achieved by an oral modified release multiple-units NSAID composition wherein the unit dosage form comprises at least (i) a first fraction being able to release at least 50% of the NSAID substance within the first 20 minutes of a certain dissolution method, and (ii) a second fraction for delayed and extended release of the NSAID substance. The multiple-units of the first fraction may be coated pellets, uncoated pellets or granulates but, as detailed herein-after, they should be granulates, unless a surfactant is added to their formulation, in order to achieve the required fast release. Formulation of the first fraction depends on the specific drug but typically includes wet-granulation and an antacid-like or other alkaline substance was found to have a pronounced increasing effect on the release rate. Also, examples in this document clearly demonstrate an increased release rate when the first fraction consists of uncoated pellets obtained by extrusion-spheronization and containing a non-ionic surfactant like a polysorbate. Example 9 of this document further demonstrates that, in the absence of a surfactant, preparing the first fraction by compression of a granulate (particulate) composition makes it possible to achieve a faster drug release than from pellets. Apart from the alkaline substance or surfactant having a strong impact on the drug release rate, the formulation may further comprise conventional excipients such as microcrystalline cellulose.

WO-A-99/17748 deals with the problem of masking the disagreeable (bitter) taste of a pharmaceutically active agent (such as ibuprofen, ketoprofen, carprofen, fenoprofen calcium or naproxen) in a chewable tablet with an extremely high drug loading (70-90 weight%). This problem is solved by the physical form of a composition when small amounts (10-30 weight%) of a microcrystalline cellulose composition are wet granulated with the active agent and then formed into
substantially spherical particles having an average particle size of not more than 1 mm. Suitable microcrystalline compositions for this purpose include blends of microcrystalline cellulose with various hydrocolloids, including methylcellulose, hydroxyalkylcellulose and carboxymethylcellulose sodium in a ratio of microcrystalline cellulose to hydrocolloid of 80:20 to 99:1. A coprocessed aggregate of microcrystalline cellulose and methylcellulose is preferred for the purpose of taste masking, as demonstrated in example 7 of this document.

Thus a first problem to be addressed by the present invention is the design of a drug delivery system with low to moderate drug loading which is suitable for suppressing or at least extensively decreasing the side effects, including local irritation of the gastric mucosa, caused by certain drugs with low water-solubility in an acidic medium such as non-steroidal anti-inflammatory drugs. Another problem is the design of a drug delivery system based on pellets with low to moderate drug loading which is able to provide a controlled release of a sparingly water-soluble drug such as a non-steroidal anti-inflammatory drug. Yet another problem is the design of a drug delivery system based on pellets with low to moderate drug loading which is able to provide such a fast drug release without the need to include a surfactant and/or an alkaline substance such as an alkaline-earth metal phosphate salt into the pellet composition and consequently without the corresponding drawbacks of such adjuvants.

**SUMMARY OF THE INVENTION**

The present invention is based on the unexpected observation that the above-identified problems may be solved by incorporating a low to moderate amount of a drug having low solubility under acidic conditions, e.g. a non-steroidal anti-inflammatory drug, into a pharmaceutical pellet composition further comprising a suitably selected combination of a microcrystalline cellulose and a suitable adjuvant, more precisely comprising suitable respective amounts of a microcrystalline cellulose and a swellable polymer. More specifically, the invention first provides a controlled release pharmaceutical pellet composition based on at least one drug having low solubility under acidic conditions, wherein the drug
constitutes at least 0.5% by weight and less than 40% by weight of the composition, the said pellet composition being able to provide a release of at least 75% of the said drug within 45 minutes in phosphate buffer pH 6.8, and the said composition further comprising a blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose in the blend is above 5 : 100 and up to about 30 : 100. Preferably, the swellable polymer is an uncrosslinked carboxyalkylcellulose metal salt such as sodium or calcium carboxymethylcellulose.

According to another embodiment, the present invention further provides a controlled release pharmaceutical pellet composition such as above defined and further comprising a drug dissolution enhancing agent such as a cyclodextrin or a cyclodextrin derivative, the weight ratio of the said drug dissolution enhancing agent to the microcrystalline cellulose being preferably up to about 50 : 100.

The present invention additionally provides solid shaped articles, such as for instance tablets optionally comprising a coating, including a controlled release pharmaceutical pellet composition such as previously defined.

The present invention also provides the use of a blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose in the blend is above 5 : 100 and up to about 30 : 100 for the manufacture of a medicament, preferably a pharmaceutical pellet composition based on at least one drug having low solubility under acidic conditions, wherein the drug constitutes at least 0.5% by weight and less than 40% by weight of the composition, the said pellet composition being able to provide a release of at least 75% of the said drug within 45 minutes in phosphate buffer pH 6.8. The relevant drug preferably is an analgesic or non-steroidal anti-inflammatory drug and the said medicament is preferably for the treatment of inflammatory diseases and rheumatic disorders such as dysplasia of the hip, chronic arthritis, spondylitis and the like.
The present invention further provides a method for reducing side effects, including local irritation of the gastric mucosa, of a drug having low solubility under acidic conditions, e.g. a non-steroidal anti-inflammatory drug, comprising providing a dosage form including a controlled release pharmaceutical pellet composition such as above defined and administering said dosage form to a human or mammal orally.

Since the skilled person knows from EP-A-403.383 that (i) the ketoprofen release rate of a high drug loading formulation is mainly governed by tailoring the composition of the coating and (ii) a coated formulation including microcrystalline cellulose blended with 3.5% sodium carboxymethylcellulose in the core and an ethylcellulose/hydroxyalkylcellulose blend in the coating is one showing an extended, approximately linear release rate for ketoprofen at typical physiological pH's, therefore the skilled person is taught away from using sodium carboxymethylcellulose for the purpose of increasing the drug release rate. Since the skilled person knows from WO-A-99/12524 that a faster drug release rate is achieved when replacing an extruded-spheronized pellet composition with a compressed granulate composition, unless a surfactant or an alkaline substance is present in the formulation, this teaching being opposite to that of the present invention provided that a carboxyalkylcellulose metal salt is suitably incorporated into the drug pellet formulation, the skilled person is also taught away from the invention by this document. Furthermore there was no reason for the skilled person to suspect any (increased or decreased) drug release rate function for an uncrosslinked carboxyalkylcellulose metal salt, due to the fact that WO-A-99/17748 considers it as a hydrocolloid equivalent to the ethylcellulose or hydroxyalkylcellulose which are also known from EP-A-403.383 to contribute to an extended, approximately linear drug release rate.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 represents the release, as a function of time, of piroxicam from a comparative pellet composition and from a pellet composition according to the invention.
Figure 2 represents the release, as a function of time, of piroxicam from a comparative pellet composition and from various pellet compositions including sodium carboxymethylcellulose according to the invention.

Figure 3 represents the release, as a function of time, of piroxicam from a comparative pellet composition and from yet other pellet compositions including a synergistic mixture of sodium carboxymethylcellulose and hydroxypropyl-β-cyclodextrin according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

For a detailed understanding of the present invention, the nature of the ingredients of the pharmaceutical pellet compositions and of their manufacturing methods are explained as follows.

Microcrystalline cellulose, in particular a pharmaceutical grade thereof, is well known in the art of pharmaceutical industry for its high surface porosity and its outstanding capillary character. It is available from a variety of commercial sources, e.g. Avicel ® PH 101 (FMC Corporation, Philadelphia, Pennsylvania), Emcocel ® (Mendell), Vivocel ® (JRS) and the like. Microcrystalline cellulose is a partially purified depolymerized form of cellulose and is obtained by treating pulps derived from fibrous plant material with mineral acid. The acid preferentially attacks the less ordered or amorphous regions of the cellulose polymer chain, thereby exposing and freeing the crystalline sites which form cellulose crystallite aggregates. The reaction mixture is washed to remove the degraded byproducts, the resulting wet-cake is freed of water and the dried cellulose crystallite aggregates, or more commonly microcrystalline cellulose, recovered. Microcrystalline cellulose is a white, odorless, tasteless, relatively free-flowing powder, insoluble in water, organic solvents, dilute alkalies and dilute acids.

A swellable polymer suitable for use in the present invention may be defined herein preferably as an ionic hydrocolloid polymer which is easily miscible with microcrystalline cellulose and which, on its own, is able to form a colloidal suspension in an aqueous environment, the colloidal particles e.g. forming a three-dimensional network or grid-like structure throughout the liquid phase. Suitable
examples of such polymer include pharmaceutical grades of sodium carboxymethylcellulose such as commercially available under the tradenames Nymcel®, Tilose® and Blanose® (Aqualon). Preferably, the swellable polymer is a low molecular weight and/or low viscosity polymer. For instance when the swellable polymer is an uncrosslinked carboxyalkylcellulose metal salt, it should preferably have sufficient unsubstituted hydroxyl groups in order to hydrogen bond to the microcrystals of the microcrystalline cellulose upon drying and the substituent groups should have ability to impart water-solubility. The degree of substitution of the carboxyalkylcellulose should preferably not exceed about 0.9 and more preferably be within a range of 0.5 to 0.9. Also, the viscosity of a 2% aqueous solution of the swellable polymer at 20°C should preferably be below 1,000 mPa.s, more preferably within a range from about 20 to 800 mPa.s.

The swellable polymer and the microcrystalline cellulose may be afforded separately at the time of making the pharmaceutical pellet compositions of the present invention or they may be present in the form of a coprocessed blend.

A coprocessed blend of the swellable polymer together with microcrystalline cellulose is readily available, e.g. as Avicel® RC 581 and Avicel® CL 611 (FMC Corporation), both well known in the art in the form of pharmaceutical grades. This cellulosic blend may be prepared by bringing the two blend components into intimate contact under suitable conditions, for instance by subjecting the washed filter cake containing microcrystalline solids from the acid degradation of cellulose to intense attritive forces, thus resulting in a further break up of the cellulose crystallite aggregates and an increase in submicron particles. As the attrition proceeds, a sufficient amount of the swellable polymer (e.g. sodium carboxymethyl cellulose) is added to the aqueous mixture in order to at least partially coat the individual microcrystals of the microcrystalline cellulose. Upon completion of the attrition, the blend is dried and recovered. The dried product is readily redispersible in aqueous media to give gels. Important for its effectiveness in the present invention is the fact that this blend is a non-disintegrating water-insoluble water-dispersible powder before it is granulated in admixture with a drug in the presence
of a granulating fluid. Preferably at least about 1% by weight and more preferably at least about 30% by weight of the powder particles have an average size not greater than about 1.0 μm as determined by electron microscopic examination.

Without wishing to be bound by theory, it is believed that the efficiency of both (coprocessed and non-coprocessed) embodiments of the invention on the drug release rate may well be explained by different mechanisms of action. The effect of the coprocessed embodiment may derive from diffusion of the drug through the hydrogel formed in the presence of water under acidic conditions. The effect of the non-coprocessed embodiment may be explained by a specifically good wetting ability of the swellable polymer within the composition.

The amount of the swellable polymer used in the pharmaceutical pellet compositions of this invention, especially in the blend present therein, is critical with respect to the amount of microcrystalline cellulose in order to achieve the desired release rate of at least 75%, preferably at least 80% and more preferably at least 90%, of the drug or pharmaceutically-active ingredient (preferably a non-steroidal anti-inflammatory drug) within 45 minutes in phosphate buffer pH 6.8, and consequently to reduce the well known side effects, namely local irritation of the gastrointestinal tract, of such a drug. When the coprocessed blend embodiment of the invention is contemplated, it may be used as the single release-modifying adjuvant of the pharmaceutical pellet composition or alternatively it may be admixed with pure microcrystalline cellulose if desired for an easier manufacture. For optimal efficiency, the weight ratio of the said swellable polymer to the microcrystalline cellulose in the pharmaceutical pellet composition, respectively in the (coprocessed) blend as above defined, should be above 5 :100 and up to about 30 :100, preferably between 7 :100 and 20 :100. Preferably the combined amounts of microcrystalline cellulose and of the swellable polymer represent from about 20% by weight to about 98% by weight of the pharmaceutical pellet composition, depending on the amounts of the other excipients (fillers) optionally present therein.
Drug dissolution enhancing agents such as cyclodextrins and cyclodextrin derivatives, in particular their pharmaceutical grades, which may be further used in an alternative embodiment of the present invention, are well known in the art and are available from a variety of commercial sources. They may be collectively referred as starch cyclic degradation products containing 6 to 8 glucose residues, or alternatively as cyclic oligosaccharides composed of L-glucose molecules linked by α or β osidic bonds having a toric form. A suitable representative embodiment of such a cyclodextrin derivative enhancing agent consists of hydroxypropyl-β-cyclodextrin. Surprisingly these agents were found able to provide a synergistic effect, in combination with the blend of a microcrystalline cellulose and a swellable polymer, in increasing the drug release rate in phosphate buffer pH 6.8, especially for drugs having low solubility under acidic conditions. Specifically, drug release rates of at least 95% and up to 100% were observed after 45 minutes in phosphate buffer pH 6.8 were observed with such synergistic combinations.

Drugs having low solubility (i.e. water-solubility) under acidic conditions (i.e. in an acidic medium having a pH of from about 1 to about 4) or sparingly water-soluble acidic drugs considered within the framework of the present invention is a category of drugs well recognized in the art, as shown for instance in U.S. Patent No. 6,231,890. As used herein, the term "low solubility" refers to any of the following definitions:

- a drug belonging to Class II (poorly soluble, highly permeable) or Class IV (poorly soluble, poorly permeable) of the Biopharmaceutical Classification System according to G. Amidon et al. in Pharm. Res. (1995) 12:413-420.
- a drug with an aqueous solubility lower than 1 mg/mL, preferably lower than 0.2 mg/mL, more preferably lower than 0.05 mg/mL under acidic conditions.
- a drug with a pKₐ value higher than gastric pH, e.g. higher than about 4, preferably higher than 3.

As a few examples of such drugs, there may be cited atovaquone, carbamazepine, danazol, glibenclamide, griseofulvin, ketoconazole, troglitazone, chlorothiazide and furosemide.
Non-steroidal anti-inflammatory drugs considered within the framework of the present invention constitute a well-known class of therapeutic agents including sub-groups such as aminoarylcarboxylic acid derivatives, arylcarboxylic acid (especially arylpropionic acid) derivatives, pyrazoles, pyrazolones, thiazine carboxamides, and stereochemically isomeric forms thereof. Specific examples of such drugs include aceclofenac, acemetacin, aclclofenac, amfenac, bromfenac, bufexamac, cinmetacin, clopironac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, fuflenamic acid, glucametacin, ibufenac, indomethacin, isofezolac, isozepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac, bumadizon, butibufen, fenbufen, xenbucin, clidanac, ketorolac, tinoridine, alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, loxoprofen, mefenamic acid, naproxen, oxaprozin, pikeprofen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximopronen, zaltoprofen, difenamizole, epirizole, apazone, benzpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone, pipebuzone, propylphenazone, ramifenazone, suxibuzone, thiazolinobutazone, aspirin, benorylate, bromosaligenin, calcium or lysine acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, salacetamide, salsalate, sulfasalazine, ampiroxicam, drocxicam, isoxicam, lornoxicam, piroxicam, tenoxicam, meloxicam and the like.

The term “stereochemically isomeric forms” as used herein defines all the possible isomeric forms, including all diastereomers and enantiomers of the basic molecular structure, which the said drug may possess. Pure stereoisomeric forms of the said drugs are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term “stereoisomerically pure” refers to drugs having a stereoisomeric excess of at least 80% (i.e. at least 90% of one isomer and at most 10% of the other possible
isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

The amount of drug having low solubility under acidic conditions, e.g. a non-steroidal anti-inflammatory drug, used in the pharmaceutical pellet compositions of the invention should be above 0.5% by weight, preferably at least 2% by weight, and less than 40% by weight, preferably not above 30% by weight, of the said composition.

The pharmaceutical pellet compositions of the invention may further optionally comprise one or more pharmaceutically acceptable excipients or fillers of the type usually present in a drug formulation for oral administration. The term "pharmaceutically acceptable filler" as used herein is intended to denote any material which is inert in the sense that it does not have any therapeutic and/or prophylactic effect *per se* but does not interfere with the therapeutic or prophylactic property of the drug or pharmaceutical active ingredient. The nature and amount of such fillers are not critical to the present invention. They include for instance binding agents such as starch, gelatin, glucose, alginic acid, sodium and calcium alginates, water-soluble acrylic (co)polymers, polyvinylpyrrolidone, polyaminoacids, ethylene-vinyl acetate copolymers and the like; natural and synthetic mineral fillers or glidants such as fumed (colloidal) silica (e.g. commercially available under the tradename Aerosil ©), magnesium silicates such as talc, diatomaceous earth, aluminium silicate such as kaolinite, montmorillonite or mica, magnesium aluminium silicate such as attapulgite and vermiculite, carbon such as charcoal, sulphur and highly dispersed silicic acid polymers; water-soluble diluents such as lactose, sorbitol and the like. Preferably however, the pharmaceutical pellet compositions of the invention are devoid of the presence of a surfactant and/or an alkaline substance such as an alkaline-earth metal phosphate or other salts such as calcium carbonate, sodium bicarbonate or sodium hydrogenocarbonate.
In view of manufacturing the pharmaceutical pellet compositions of the invention, it is preferred to make use of an extrusion-spheronization process which may comprise the steps of:

(a) granulating a mixture of a drug having low solubility under acidic conditions and a blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose in the blend is above 5:100 and up to about 30:100 and optionally a drug dissolution enhancing agent, and further optionally conventional additives (such as fillers) in the presence of a granulating fluid, and then

(b) extruding the wet mass from step (a) by means of an extruder and then spheronizing the resulting extrudate by means of a spheronizer.

As mentioned hereinabove, the microcrystalline cellulose/swellable polymer blend used in step (a) may be a coprocessed one.

Spheronization was first disclosed in U.S. Pat. No. 3,277,520 and equipment design change has been minimal since then. The spheronizer consists basically of a grooved horizontal plate rotating at high speed within a stationary vertical cylinder fitted with a door to allow release of the pellets. Although extrusion is usually regarded as a continuous process, spheronization equipment design limits the extrusion-spheronization process to a batch process or multiple batch process. There are five unit operations involved in the extrusion-spheronization process: blending or mixing the ingredient powders, wet granulation, extrusion, spheronization and drying. The moistened pre-compact mass is extruded into strands, which are then rounded into pellets in a spheronization machine, dried and subjected to further processing. The granulating fluid may be water or an aqueous solution containing a lower alcohol, such as ethanol or propanol. The amount of granulating fluid used influences the mechanical properties (porosity, density, friability and compactibility) of the pellets produced. The amount of granulating fluid used depends on the composition of the powder mixture used in step (a) and is generally such as to provide a final solids concentration, of about 20 to 80% by
weight. The granulating fluid content and the composition of the powdery mixture granulated in step (a) must be carefully selected in order that a suitable plastic deformability (extrudability) is obtained. The particle size distribution of the pellets obtained is also primarily determined by the extrudate density and granulating fluid content. However, individual process parameters such as the pressure at which the granulate of step (a) is extruded, the rotation speed of the spheronizer, the aperture size of the extruder screen of the spheronizer, the size and texture of the friction plate of the spheronizer and the spheronizer residence time are not critical to the present invention. The drying unit operation is usually effected by fluid bed, tray or freeze-drying and carried out at temperatures below the freezing point of the product, thus producing highly porous and compactible pellets.

Other pelletization processes such as solution layering, suspension layering or powder layering (collectively referred as a layering process), such as briefly discussed in Encyclopaedia of Pharmaceutical Technology (1995), volume 11, chapter "Pelletization techniques", may be used alternatively.

The term "solid shaped article" as used herein means any article being in a hard solid state at temperatures not exceeding about 60°C and having a definite geometrical shape, such as for instance ordinary tablets, effervescent tablets, pills, lozenges and other compressed dosage forms.

The term "pellets" as used herein means spherical beads having a diameter preferably ranging from above 0.7 to about 2.0 mm, more preferably from above 0.7 to 1.4 mm and most preferably from 0.8 to 1.2 mm and a narrow size range distribution, i.e. preferably a ratio of the greater diameter to the smaller diameter ranging between about 1.0 and 1.6.

The solid shaped articles of the present invention may further optionally contain additives typically used in the formulation of such articles, for instance flavoring agents (such as anethole, benzaldehyde, vanillin, ethyl vanillin, ethyl acetate, methyl salicylate and the like), lubricants (such as magnesium stearate), sweeteners (such as sucrose, mannitol, aspartame, saccharin and its salts), colorants and/or buffering agents.
Optionally, a coating material may be applied, preferably by means of the film-coating process, to the pellets of the composition for further controlling the release properties of the drug or pharmaceutically active ingredient or for taste masking or for imparting resistance to gastric fluid. Film coating of a tablet involves the deposition, usually by spraying, of a thin film of polymer surrounding the tablet core. The coating solution contains a polymer in a suitable liquid solvent and optionally mixed together with other ingredients such as plasticizers, pigments and/or colorants. After spraying, the drying conditions permit to remove substantially all of the solvent.

The particular coating material used is not critical to the present invention, and depends upon the purpose of the coating material, e.g. the release profile, the ability to stay intact and/or to withstand the mechanical stress of compaction without cracking and so on. Examples of coating polymers useful for controlling the release properties of the active ingredient and/or taste masking are well known in the art and include derivatives of cellulose such as methylcellulose, hydroxypropylmethylcellulose and ethylcellulose (such as those marketed under the tradenames Surelease® and Aquacoat®), polyvinylpyrrolidone (e.g. as marketed under the tradenames Polyvidon®, Kollidon® and Polylablone®) and aminoalkylmethyacrylate copolymers. Examples of coating polymers useful for imparting resistance to gastric fluid include shellac, cellulose acetate phthalate (Aquateric®), cellulose acetate trimellicate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate (Coateric®), hydroxypropyl methylcellulose acetate succinate; carboxymethylethylcellulose, styrene/acrylic acid copolymers, methacrylic acid copolymers, maleic anhydride copolymers and the like. Examples of plasticizers which may be mixed together with the coating polymer include, without limitation, polyethylene glycol, glycerol, phtalate esters, triethylcitrate, etc.

The thickness of the coating layer used is not critical to the present invention. It depends upon the desired release profile of the active ingredient and typically is in the nanometer to micron ranges. Alternatively, the above-listed polymers and optionally plasticizers can be incorporated into a matrix system
together with the active ingredient-loaded pellets to sustain its action, e.g. during
dry powder mixing prior to granulation, or in the granulation solution prior to
extrusion-spheronization, or within the other techniques conventionally used to
produce pellets. In such a case, the amount of polymers and optionally plasticizers
is not critical to the present invention, as long as they do not interfere with the
desired release profile of the active ingredient.

Preferably, the applied coating is a film of a polymeric gastro-resistant and
enterosoluble material, in order to allow activation of the pharmaceutical pellet
composition only after it has reached the duodenal-intestinal tract, i.e. more
preferably, in order to release the active ingredient in the last part of the duodenal-
intestinal tract. Cellulose acetophthalate, cellulose acetopropionate, cellulose
trimellitate, acrylic and methacrylic polymers and copolymers having different
molecular weight and solubility depending on pH values may be used for this
purpose.

The following examples are provided solely for the purpose of illustrating
various embodiments of the invention, and without any intention of limiting the
scope thereof.

**EXAMPLE 1 — production of a pellet composition**

Pellets are produced by means of extrusion-spheronization comprising the
steps of:
- dry mixing powders of the composition ingredients in a planetary mixer for 10
  minutes at a rotation speed of 60 rpm,
- granulating the mixture in the planetary mixer with water for 5 minutes at a
  rotation speed of 60 rpm,
- extruding the wetted mass by means of a Dome extruder (available from Fuji
  Paudal Co., Tokyo, Japan; Dome die with perforation diameter 1 mm) operated
  at 45 rpm,
- spheronizing the extrudate by means of a spheronizer (Caleva, Dorset, United
  Kingdom) for 5 minutes at 1000 rpm followed by 10 minutes at 1250 rpm, and
- tray drying (35°C till constant weight) or fluid bed drying (using a dryer from Glatt, Bilzen, Germany; inlet temperature 50°C, outlet temperature 35°C).

**EXAMPLE 2 – Controlled release evaluation of the pellet composition**

Drug release profiles were obtained by using the U.S. Pharmacopeia 23 paddle dissolution test, using the following settings of the dissolution parameters:

- Method: Paddle
- Speed: 100 rpm
- Medium: phosphate buffer pH 6.8
- Sample time points: 5' 10' 15' 20' 30' 45' 60' 90' 120' 150'
- Sample volume: 5 ml
- Replacement medium: phosphate buffer pH 6.8
- Detection: UV spectrophotometer
- Wavelength: 353 nm

Results are expressed as the cumulative amount of drug released (in %) as a function of time.

**EXAMPLE 3 (comparative)**

200 g of a pellet composition is produced, according to the method of example 1, from 5 g of piroxicam and 195 g of a microcrystalline cellulose available from FMC Corporation under the tradename Avicel® PH 101. The composition is then evaluated according to the method of example 2. Results of evaluation are reported on figures 1 to 3 for comparison purposes with the pellet compositions of the present invention. The release of piroxicam from these pellets is rather slow, amounting to only 30% after 45 minutes in phosphate buffer pH 6.8.

**EXAMPLES 4 to 11**

200 g of various pellet compositions are produced, according to the method of example 1, from 5 g of piroxicam and 195 g of a mixture of pellet components as indicated in the table below (all amounts expressed in grams).
<table>
<thead>
<tr>
<th>Example</th>
<th>Avicel PH 101</th>
<th>Swellable polymer-containing component</th>
<th>Drug-dissolution enhancing agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0</td>
<td>195 (Avicel RC 581)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>97.5</td>
<td>97.5 (Avicel CL 611)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>130 (Avicel CL 611)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>48.75</td>
<td>146.25 (Avicel CL 611)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>195 (Avicel CL 611)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>155</td>
<td>0</td>
<td>40 (HPCD)</td>
</tr>
<tr>
<td>10</td>
<td>38.75</td>
<td>116.25 (Avicel CL 611)</td>
<td>40 (HPCD)</td>
</tr>
<tr>
<td>11</td>
<td>173</td>
<td>22 (Blanose 7MF)</td>
<td>0</td>
</tr>
</tbody>
</table>

Avicel RC 581 (available from FMC Corporation) is a swellable polymer-containing coprocessed blend consisting of 86.2 to 91.7 % by weight of microcrystalline cellulose and 8.3 to 13.8% by weight of sodium carboxymethylcellulose.

Avicel CL 611 (available from FMC Corporation) is a swellable polymer-containing coprocessed blend consisting of 81.2 to 88.7% by weight of a microcrystalline cellulose and 11.3 to 18.8% by weight of sodium carboxymethylcellulose.

HPCD is an abbreviation for hydroxypropyl-β-cyclodextrin.

Blanose 7MF (available from Aqualon) is a sodium carboxymethylcellulose with a degree of substitution in the range 0.65-0.9 and with a viscosity (2% aqueous solution at 20°C) of 450 mPa.s.

All compositions are then evaluated according to the method of example 2. Results of evaluation are reported on figures 1 to 3 respectively. All compositions according to the invention demonstrate a release of at least 75% of piroxicam within 45 minutes in phosphate buffer pH 6.8.

As will be readily understood, example 9 is for comparative purpose. Further, example 10 demonstrates the synergistic effect achieved by hydroxypropyl-β-cyclodextrin in combination with the coprocessed blend of a
microcrystalline cellulose and sodium carboxymethylcellulose, with a release of 100% of piroxicam within 45 minutes in phosphate buffer pH 6.8.

The release rate of piroxicam in phosphate buffer pH 6.8 for the composition of example 11 (figure 2) is quite outstanding, being 87% within 20 minutes and 100% within 45 minutes.
CLAIMS

1. A controlled release pharmaceutical pellet composition based on at least one
drug having low solubility under acidic conditions, wherein the drug constitutes
at least 0.5% by weight and less than 40% by weight of the composition, the
said composition being able to provide a release of at least 75% of the said
drug within 45 minutes in phosphate buffer pH 6.8, and the said composition
further comprising a blend of a microcrystalline cellulose and a swellable
polymer in respective amounts such that the weight ratio of the said polymer to
the microcrystalline cellulose in the blend is above 5:100 and up to 30:100.

2. A controlled release pharmaceutical pellet composition according to claim 1,
wherein the polymer in the blend is an uncrosslinked carboxyalkylcellulose
metal salt.

3. A controlled release pharmaceutical pellet composition according to claim 1 or
claim 2, wherein the polymer in the blend is uncrosslinked sodium or calcium
carboxymethylcellulose.

4. A controlled release pharmaceutical pellet composition according to any of
claims 1 to 3, wherein the viscosity of a 2% aqueous solution of the polymer at
20°C is below 1,000 mPa.s.

5. A controlled release pharmaceutical pellet composition according to any of
claims 2 to 4, wherein the degree of substitution of the carboxyalkylcellulose
does not exceed 0.9.

6. A controlled release pharmaceutical pellet composition according to any of
claims 1 to 5, further comprising a drug dissolution enhancing agent.
7. A controlled release pharmaceutical pellet composition according to claim 6, wherein the drug dissolution enhancing agent is a cyclodextrin or a cyclodextrin derivative.

8. A controlled release pharmaceutical pellet composition according to claim 6 or claim 7, wherein the weight ratio of the drug dissolution enhancing agent to the microcrystalline cellulose is up to 50:100.

9. A controlled release pharmaceutical pellet composition according to any of claims 1 to 8, characterized by the absence of a surfactant and/or an alkaline substance.

10. A controlled release pharmaceutical pellet composition according to any of claims 1 to 9, further comprising one or more pharmaceutically acceptable fillers.

11. A controlled release pharmaceutical pellet composition according to claim 10, wherein the pharmaceutically acceptable fillers are selected from binding agents, glidants, lubricants and diluents.

12. A controlled release pharmaceutical pellet composition according to any of claims 1 to 11, wherein the drug having low solubility under acidic conditions is a non-steroidal anti-inflammatory drug.

13. A controlled release pharmaceutical pellet composition according to any of claims 1 to 12, wherein the drug is selected from the group of aminoarylcarboxylic acid derivatives, arylcarboxylic acid derivatives, pyrazoles, pyrazolones, thiazine carboxamides, and enantiomers thereof.
14. A controlled release pharmaceutical pellet composition according to any of claims 1 to 13, wherein the pellets have a diameter ranging from above 0.7 up to 1.4 mm.

15. A controlled release pharmaceutical pellet composition according to any of claims 1 to 14, wherein the pellets have a narrow size range distribution, the ratio of their greatest size to their smallest size being from 1.0 to 1.6.

16. A controlled release pharmaceutical pellet composition according to any of claims 1 to 15, wherein the pellets are obtained by an extrusion-spheronization process.

17. A controlled release pharmaceutical pellet composition according to any of claims 1 to 15, wherein the pellets are obtained by a layering process.

18. A controlled release pharmaceutical pellet composition according to any of claims 1 to 17, being able to provide a release of at least 80% of the drug within 45 minutes in phosphate buffer pH 6.8.

19. A controlled release pharmaceutical pellet composition according to any of claims 1 to 18, being able to provide a release of at least 90% of the drug within 45 minutes in phosphate buffer pH 6.8.

20. A controlled release pharmaceutical pellet composition according to any of claims 1 to 19, wherein pellets further comprise a coating.

21. A controlled release pharmaceutical pellet composition according to claim 20, wherein the coating is a film of a polymeric gastroresistant and enterosoluble material designed to allow activation of the pharmaceutical pellet composition only after it has reached the duodenal-intestinal tract.
22. A solid shaped article comprising a controlled release pharmaceutical pellet composition according to any of claims 1 to 21.

23. A process for manufacturing a controlled release pharmaceutical pellet composition according to any of claims 1 to 21, comprising the steps of:
   (a) granulating a mixture of a drug having low solubility under acidic conditions and a blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose in the blend is above 5:100 and up to 30:100, in the presence of a granulating fluid, and
   (b) extruding the wet mass from step (a) by means of an extruder and then spheronizing the resulting extrudate by means of a spheronizer.

24. A pharmaceutically acceptable blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose is above 5:100 and up to 30:100, for use in the manufacture of a pharmaceutical pellet composition based on at least one drug having low solubility under acidic conditions, wherein the drug constitutes at least 0.5% by weight and less than 40% by weight of the composition, the said composition being able to provide a release of at least 75% of the said drug within 45 minutes in phosphate buffer pH 6.8.

25. A pharmaceutically acceptable blend according to claim 24, wherein the polymer in the blend is an uncrosslinked carboxyalkylcellulose metal salt.

26. A pharmaceutically acceptable blend according to claim 24 or claim 25, wherein the polymer in the blend is uncrosslinked sodium or calcium carboxymethylcellulose.
27. A pharmaceutically acceptable blend according to any of claims 24 to 26, wherein the viscosity of a 2% aqueous solution of the polymer at 20°C is below 1,000 mPa.s.

28. A pharmaceutically acceptable blend according to any of claims 25 to 27, wherein the degree of substitution of the carboxyalkylcellulose does not exceed 0.9.

29. A pharmaceutically acceptable excipient composition comprising:
   - a blend of a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose is above 5:100 and up to 30:100, and
   - a cyclodextrin or a cyclodextrin derivative
     in respective proportions such as to provide a synergistic effect in increasing the release rate of a drug having low solubility under acidic conditions.

30. A pharmaceutically acceptable excipient composition according to claim 29, wherein the polymer in the blend is an uncrosslinked carboxyalkylcellulose metal salt.

31. A pharmaceutically acceptable excipient composition according to claim 29 or claim 30, wherein the polymer in the blend is uncrosslinked sodium or calcium carboxymethylcellulose.

32. A pharmaceutically acceptable excipient composition according to any of claims 29 to 31, wherein the viscosity of a 2% aqueous solution of the polymer at 20°C is below 1,000 mPa.s.
33. A pharmaceutically acceptable excipient composition according to any of claims 30 to 32, wherein the degree of substitution of the carboxyalkylcellulose does not exceed 0.9.

34. A pharmaceutically acceptable excipient composition according to any of claims 29 to 33, wherein the cyclodextrin derivative is hydroxypropyl-β-cyclodextrin.

35. A pharmaceutically acceptable excipient composition according to any of claims 29 to 34, wherein the weight ratio of the cyclodextrin or cyclodextrin derivative to the microcrystalline cellulose is up to 50:100.

36. Use of a pharmaceutically acceptable excipient composition according to any of claims 29 to 35 for providing a release of at least 95% of the drug within 45 minutes in phosphate buffer pH 6.8.

37. A method for reducing the side effects of a drug having low solubility under acidic conditions, comprising providing a dosage form including a controlled release pharmaceutical pellet composition according to any of claims 1 to 20 and administering said dosage form to a human or a mammal orally.
Fig. 1

- Ex. 3
- Ex. 4

Cumulative release (in %)

Time (in min)
Fig. 3

Cumulative release (in %)

Time (in min)

- Ex. 3
- Ex. 9
- Ex. 7
- Ex. 10