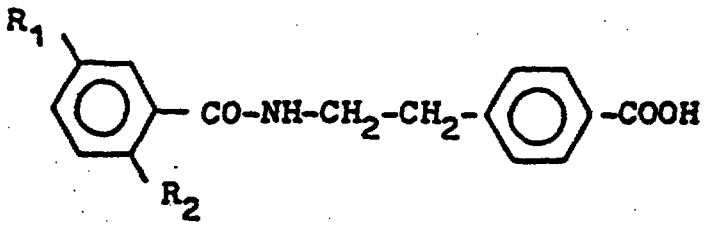
Orally administrable antidiabetic compositions

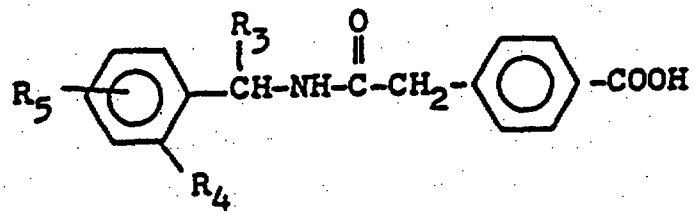
The invention relates to new orally administrable pharmaceutical compositions containing antidiabetic agents and processes for their preparation.

The said orally administrable compositions may contain as active substances sulphonylureas, such as gliquidone, or substituted phenylcarboxylic acids. Other preferred sulphonylureas include glibenclamide, glibornuride, glisoxepid, glipizide and gliclazide. Gliquidone is 1-cyclohexyl-3-[[p-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1H)-isoquinolyl)-ethyl]-phenyl]sulfonyl]urea, and exhibits a hypoglycaemic effect. However, other antidiabetic substances which may be used are 4-[2-(aroylamino)ethyl]benzoic acids of general formula (I)



(I)

wherein R_1 represents a halogen atom, preferably a chlorine atom, and R_2 represents an alkoxy group with 1 to 3 carbon atoms or a piperidin-1-yl or octamethyleneimino group, and also substituted 4-(aralkylaminocarbonylmethyl)-benzoic acids of general formula (II)



(II)

wherein R_3 represents an alkyl group with 1 to 4 carbon atoms (preferably an n-propyl group) or a phenyl group, R_4 represents a piperidin-1-yl, pyrrolidin-1-yl or hexamethyleneimino group and R_5 represents a hydrogen or halogen atom, preferably a chlorine or fluorine atom, or a methyl or methoxy group. However, mixtures of these active substances may also be used.

Micronised gliquidone is contained in a commercially available preparation consisting additionally of corn starch, lactose and magnesium stearate. This preparation containing gliquidone has already proved satisfactory as a reliable antidiabetic agent, with the great advantage that it is not contraindicated when there is restricted kidney function.

Generally, in the oral administration of substances which are difficultly soluble in the digestive fluids, and these include the substances mentioned above, the following problems arise: in many cases the active substance can only be partly reabsorbed and greatly fluctuating blood levels of the active substance may occur inter- and intra-individually. However, in oral antidiabetic agents, the start of the activity and the duration of the activity are also of particular importance since the activity should be matched to the blood sugar levels caused by the intake of food. This is not the case with the hitherto available preparations of antidiabetic

agents in which the effect of the substance and physiological insulin requirements in accordance with the intake of food cannot be reliably matched to one another in terms of time. The activity of the substance often occurs too late: frequently the maximum effect is only achieved at a time at which the blood glucose values are already dropping even without medication after the intake of food. Then the activity of the substance continues even when the blood glucose concentration has returned to its initial level (cf. Berger, in Pelzer and Froesch, Diabetische Enteropathie, Hypoglykämien, Verlag Hans Hüber, Bern-Stuttgart-Wien 1974).

Attempts have also been made to synchronise the hypoglycaemic activity of a sulphonylurea with the increase in blood sugar caused by food intake by taking the sulphonylurea at a suitable time before the meal. However, it was then found that administration of the active substance thirty minutes before the meal did not result in a satisfactory improvement in activity (cf. Sartor et al., Eur. J. Clin. Pharmacolog. 21, 403 to 408 (1982)), partly because of the longer duration of activity mentioned above. Furthermore, a specific time difference between the taking of the medicine and the taking of food can only be reliably monitored in a clinic.

Attempts were made to solve these problems in the case of substances which are difficultly soluble in the digestive fluids by attempting to optimise the dissolution rate of the active substance difficultly soluble per se in the development of the galenic preparations. This was done, for example, by increasing the surface area of the active substance. Thus, a pharmaceutical composition has been described (German Patent 2,348,334) in which the active substance (also a hypoglycaemic substance) is present with a particle surface area of from 3 to 10 m^2/g in

the presence of a wetting agent.

However, this objective was also supposed to be achieved by applying the active substance in dissolved form to a substrate or carrier with the largest possible surface area and then eliminating the solvent (cf. H. Rupprecht, Acta Pharm. Technol. 26/1, pages 13 ff. (1980)).

Furthermore, attempts have been made to improve the dissolution rate by adding salt forming agents (cf. German Offenlegungsschrift 31 24 090.9). Moreover, in order to improve the solubility and the dissolution rate, solid dispersions have also been produced. They consist of the active substance and one or more water-soluble carriers, possibly combined with surface-active substances. In order to prepare these dispersions, a homogeneous melt is prepared from the active substance or possibly a salt thereof and a carrier (cf. German Offenlegungsschrift 23 55 743). In another process, the active substance and carrier are dissolved in a common solvent and then the solvent is eliminated. The water soluble carriers used are, inter alia, polyvinylpyrrolidone or polyethylene glycols (cf. H.R. Merkle, Acta Pharm. Technol. 27/4, pages 193 ff. (1981) and W.L. Chiou and S. Riegelmann, J. Pharm. Sci. 60/9, 1281 ff. (1971)).

If the following methods described in the literature are used to produce preparations containing the compounds mentioned hereinbefore, a better dissolution rate for the active substance, e.g. the gliquidone, is scarcely obtained: the salt formation itself does not result in an increase in the dissolution rate (cf. Table 3, Example 6), and the application of active substance, e.g. gliquidone, to a carrier alone (cf. Example 1, comparison part) does not produce the desired result either. In corresponding tests, which will be described in more detail hereinafter, the dissolution rate was

(17)

determined and in the case of gliquidone it was found to be no greater than the dissolution rates shown by gliquidone-containing preparations known per se.

It has now been found that, surprisingly, pharmaceutical compositions according to the invention having a very rapid and total release of active substance can be produced by dissolving

(a) acidically reacting active substances by means of basic excipients,

(b) amphoterically reacting active substances by means of basic or acidic excipients or

(c) basically reacting active substances by means of acidic excipients

in a solvent in the presence of one or more solubilising substances. The solubilising substance used is polyvinylpyrrolidone and, optionally, other solubilising substances. The solution is evaporated to dryness and the product thereby obtained is, if required, processed further to produce the desired preparation. The molar ratio of active substance to basic or acidic excipient must be selected so that there is an excess of basic or acidic excipient.

Hence, according to one feature of the present invention there is provided a process for producing orally administrable pharmaceutical compositions containing antidiabetically active substances, wherein an acidically reacting active substance is dissolved in a polar solvent with the aid of at least one basic excipient, an amphoterically reacting active substance is dissolved in a polar solvent with the aid of at least one basic or acidic excipient or a basically reacting active substance is dissolved in a polar solvent with the aid of at least one acidic excipient, the said dissolution being effected in the presence of polyvinylpyrrolidone

and optionally other solubilising and/or emulsifying substances and the molar ratio of active substance to basic or acidic excipient being less than 1:1; the solution is evaporated to dryness; and the product thereby obtained is, if required, further processed optionally with the addition of further excipients to produce the desired pharmaceutical compositions.

Pharmaceutical compositions thereby obtained constitute a further feature of the present invention.

The invention includes within its scope processes for the preparation of pharmaceutical compositions as described herein containing mixtures of acidic, of basic or of amphoteric orally administrable antidiabetically active substances.

According to a still further feature of the present invention there are provided orally administrable pharmaceutical compositions in solid form containing: an acidically reacting antidiabetically active substance together with a basic excipient, an amphoterically reacting antidiabetically active substance together with a basic or acidic excipient or a basically reacting antidiabetically active substance together with an acidic excipient; together with polyvinylpyrrolidone and optionally other solubilising and/or emulsifying substances and, if desired, one or more further excipients; the molar ratio of active substance to basic or acidic excipient being less than 1:1 and the active ingredient and polyvinylpyrrolidone being present as a molecular dispersion.

It is important that sufficient basic or acidic excipient is added to the active substance to ensure rapid and complete dissolution <u>in vivo</u>. This is only possible with a molar ratio of active substance to basic or acidic excipient of less than 1:1.

In order to dissolve 2.5 parts by weight of gliquidone, for example, in 50 parts by weight of water, 0.7 parts by weight of ethylenediamine.$1H_2O$, 3.0 parts by weight of N-methylglucamine or 3.5 parts by weight of diethanolamine are required. If we compare the molar ratios which are absolutely necessary for rapid and complete dissolution of the active substance, the following picture is obtained:

gliquidone (molecular weight 527.6): ethylenediamine.$1H_2O$ (molecular weight 78.1) is 1:1.89;
gliquidone: N-methylglucamine (molecular weight 195.21) is 1:3.24;
gliquidone: diethanolamine (molecular weight 105.14) is 1:7.03;
gliquidone: L-lysine (molecular weight 146.2) is 1:4.33.

This finding cannot be explained by mere salt formation of the gliquidone with the basic excipients in question; it appears that the excess base has an additional stabilising effect. The same phenomena also apply to the other active substances. This effect was not foreseeable even by someone skilled in the art.

The solutions are prepared with polyvinylpyrrolidone as solubilising agent; after evaporation, this substance also acts as carrier at the same time. It is not possible to incorporate the active substance and basic excipient directly in a melt of polyvinylpyrrolidone since this carrier decomposes even before reaching the melting point.

Suitable basic excipients include a number of inorganic or organic bases which are physiologically harmless at least in the dosage ranges used, such as sodium hydroxide solution, potassium hydroxide solution, ammonia, tert. sodium phosphate, diethanolamine, ethylenediamine, N-methylglucamine or L-lysine. The molar ratio of active substance to basic excipient or mixtures of excipients is preferably from 1:1.1 to 1:10, but a greater excess of base may be advantageous in some cases.

Suitable acidic excipients include sulphuric and phosphoric acid: the acid must be present in excess.

In order to stabilise highly concentrated solutions such as those which are clearly obtained

when using a preparation according to the invention, it is necessary to add solubilising and/or emulsifying substance. In addition, other such substances may be added, such as polyoxyethylene polyoxypropylene polymers, polyethylene glycol 4000 or 6000 , polyethoxylated sorbitan mono-oleates, sorbitol, glycerol polyethylene glycoloxy stearates and polyoxyethylene fatty alcohol ethers. Both the nature of the solubilising substance and also the proportions used are important in determining the dissolution rate of the active substance. The preferred ratio of active substance, e.g. gliquidone, to the total quantity of solubilising substances is from 1:1 to 1:10.

The solution of the active substance, basic or acidic excipients and solubilising and/or emulsifying substances is prepared primarily using water or other polar solvents such as lower alcohols, e.g. ethanol, isopropanol, ketones such as acetone or mixtures of these substances with water.

By using the method of solution according to the invention instead of the melting process known from German Offenlegungsschrift 23 55 743 for incorporating the active substance, the non-fusible solubilising substance polyvinylpyrrolidone can be processed in molecular dispersion together with the active substances.

The solution to the problem described above is surprising for the following reasons:

The methods for incorporation of substances which are difficultly soluble in the digestive fluids, described in the literature and listed hereinafter, do not result in a significant increase in the dissolution rate of the active substances when applied to the production of pharmaceutical compositions containing the above mentioned active substances; nor can they improve the dissolution rate found for the commercially available preparations which contain, for example, gliquidone. Some

relevant tests are described below. The dissolution rates were determined after 5 and 30 minutes by the USP XX Paddle Method in 900 ml of McIlvaine-Buffer, at pH 7.0, at 37°C and at 100 rpm. For each measurement, a quantity of preparation corresponding to 40.0 mg of active substance was used and each measurement was repeated twice and the average was calculated from the results obtained.

In order to determine the dissolution rate with an increase in the surface area of gliquidone, 30 parts by weight of the active substance was dissolved in 150 parts by weight of methylene chloride and the solution was applied to 210 parts by weight of a tablet carrier. After drying, the treated tablet carrier was compressed to form tablets and the dissolution rate of the gliquidone from these tablets was determined; 5% of the active substance dissolved after 5 minutes and 7% dissolved after 30 minutes. In the case of micronised gliquidone with no excipients, 0% dissolved after 5 and 30 minutes. When the micronised gliquidone was compressed to form tablets (see the comparison preparation in Example 1) 5.8% of active substance dissolved after 5 minutes and 7.2% after 30 minutes.

No better dissolution rate was obtained by forming gliquidone salts. 5.0 parts by weight of gliquidone was dissolved in an aqueous solution of 1.9 parts by weight of ethylenediamine.$1H_2O$, with heating and stirring; this solution was dried <u>in vacuo</u> in a rotary evaporator and the solid product was passed through a 1.0 mm mesh screen. This product also yielded a quantity of only 4% of dissolved active substance after 5 minutes and 30 minutes.

Not even the use of a gliquidone-containing dispersion produced any better dissolution rates. Analogously to the method described in German Offenlegungsschrift 23 55 743, 1.47 parts by weight of gliquidone

was dissolved in a melt consisting of 79.1 parts by weight of polyethylene glycol 4000 and 5.0 parts by weight of polyoxyethylene-40-stearate and then 14.43 parts by weight of potassium bicarbonate was dispersed therein. The solidified melt was rubbed through a screen with a mesh size of 1.0 mm. The measurement of the dissolution rate gave a result of 10% of active substance after 5 minutes and 7% after 30 minutes.

A further series of tests was carried out to check whether the use of gliquidone salts in the process described in German Offenlegungsschrift 23 55 743 leads to better dissolution rates. Again, a melt consisting of 79.1 parts by weight of polyethylene glycol 4000 and 5.0 parts by weight of polyoxyethylene-40-stearate was used, in which a saturated solution of the gliquidone salt in question was prepared. Then 14.43 parts by weight of potassium hydrogencarbonate was dispersed in this solution. The solidified melt was passed through a screen with a mesh size of 1.0.

TABLE

Gliquidone Salt containing	Maximum active substance (calculated as base) soluble in melt consisting of PEG 4000 and Polyoxy-ethylene-40-stearate:	Quantity of solidified melt required for a 30 mg dose of gliquidone:
Ethylenediamine	0.65%	4.6 g
NH_4OH	2.40%	1.25 g
N-Methylglucamine	0.54%	5.54 g
Piperidine	2.15%	1.395 g
NaOH	1.99%	1.51 g

(PEG 4000 = polyethylene glycol 4000)

It is easy to see from these results that the quantity of melt required for a 30 mg dose of gliquidone cannot be contained in a disintegrating tablet which can be swallowed. Thus, the process according to German Offenlegungsschrift 23 55 743 is unsuitable for gliquidone salts and also for the similarly added salts of the other active substances mentioned hereinbefore.

It is not therefore possible to achieve rapid and total dissolution of the active substances using the known methods which are described as suitable for such purposes, as can be seen from the tests described above.

When developing pharmaceutical preparations, optimisation is carried out using <u>in vitro</u> methods. The release and dissolution of the active substance are determined using dissolution tests. In order to create conditions comparable to those which obtain <u>in vivo</u>, these tests are normally carried out in an acidic medium at pH 1.2. If this pH is used with the preparations according to the invention, no measurable release rates are obtained.

In vitro dissolution tests must therefore be carried out at pH 7 (or above). This is due to the fact that the solubility of the active substance is no longer sufficient at pH levels below 7. It would therefore be expected that there would be only a slight release of active substance in vivo in the acidic range of the intestinal tract. The rapid and total reabsorption of the active substance even in the upper region of the intestinal tract is therefore surprising to anyone skilled in the art. It is also surprising that, despite the difference between in vivo conditions and those conditions which are created for the measurement of the dissolution rate in vitro, there is considerable concord between the in vitro and in vivo results. This is shown by a comparison of the dissolution rates of Example 2 in Table 1 with the curve in Fig. 1, on the one hand, and by a comparison of the curve for a preparation according to the present invention (Example 2) with the curves for the preparations of Examples 6 and 8, which are not according to the present invention, on the other hand.

If the hypoglycaemically active substances mentioned hereinbefore are formulated by the processes according to the present invention described hereinbefore, pharmaceutical compositions are obtained wherein the action of the active substance is matched to the physiological requirement of the patient for this medicament. These special pharmaceutical products ensure rapid and complete reabsorption of the active substance. Rapid reabsorption shortens the time which must elapse between taking the medicament and taking a meal in order to synchronise the hypoglycaemic activity of the sulphonylurea with the increase in blood sugar caused by food intake. Rapid and total reabsorption reduces intra- and inter-individual fluctuations in the blood glucose level, minimizes the dependence of reabsorption

on the state of the gastrointestinal tract or on the nature or quantity of food taken and thus ensures the correct metabolic pattern and consequently a correct insulin release. The disadvantages described above relating to the preparations known at present are avoided by using the process according to the invention.

Trials on humans (see Fig. 1) demonstrate the rapid onset of activity of the preparation according to the invention (Example 2) and the slight activity of Examples 6 and 8, which are not according to the invention. It is also found that the values obtained in vitro and in vivo correspond well.

The findings mentioned above show that the medical objective:

a) avoiding a non-physiological rise in blood sugar after the intake of food and

b) avoiding a massive drop in blood sugar some hours after food intake,

is achieved with the preparations according to the invention.

The methods of measuring used will now be described:

Determining the blood glucose

The blood sugar was measured in whole venous blood. 50 ul of blood were freed from protein with 500 ul of 0.32 M perchloric acid. After centrifuging, the glucose in the supernatant was measured by the hexokinase method using an automatic substrate.

Human trials

Blood samples were taken through long-term catheters with heparinised disposable syringes.

After a preliminary period of 15 minutes in which the course of the blood sugar level and of the insulin level without any medicament was measured, the preparation was administered in the form of a granulate or in tablet form in the appropriate dosage with 70 ml of water.

The essence of the invention will be investigated more closely hereinafter in a discussion of the results obtained in the tests described in the Examples.

Table 1 shows the correlation between the quantity of polyvinylpyrrolidone and the dissolution rate.

Table 2 shows that the presence of a basic excipient is absolutely necessary not only for dissolving the gliquidone but also for obtaining rapid release of the active substance. In order to achieve an equally high dissolution rate solely by using the solubilising carrier Kollidon 25 (R) and without using a basic excipient, the quantity of Kollidon 25 (R) in this Example would have to be increased by approximately a power of 10. However, such a high proportion of polyvinylpyrrolidone is impossible for practical reasons (the preparations would no longer be manageable as oral preparations and in any case such forms would not be viable from the point of view of manufacture and cost).

The Examples on which these observations are based now follow, with precise numerical data:
In the Examples:
Kollidon 25 (R) is a poly-N-vinylpyrrolidone (-2),
PEG 4000 = polyethylene glycol 4000
Pluronic F 68 (R) is a polyoxyethylene polyoxypropylene polymer,
Avicel (R) is a microcrystalline cellulose,
Explotab (R) is sodium carboxymethyl starch and

Amberlite IRP 88 is the potassium salt of a polymer of methacrylic acid with divinylbenzene.

PLURONIC, AVICEL, EXPLOTAB and AMBERLITE are registered Trade Marks.

Examples 1 to 3

Table 1 contains Examples 1 to 3 with their dissolution rates.

Table 1:

Examples 1 to 3 have the following compositions in common:

5mg of gliquidone, 1.9mg of ethylenediamine.$1H_2O$

Example	Kollidon 25(R) mg	Dissolution Rate in percent of the active substance which has gone into solution after 5 and 30 minutes	
1	10	91	93
2	30	95	97
3	60	92	96

The pharmaceutical compositions in the Examples were produced as follows:

The basic excipient is dissolved in 100 parts by weight of water at 70°C with stirring. The active substance is added; the mixture is stirred until the latter is completely dissolved. Polyvinylpyrrolidone is dissolved in this solution. The solution is evaporated to dryness in vacuo with stirring and the product is rubbed through a screen with a mesh size of 1 mm.

A comparison with a known gliquidone-containing preparation of the following composition:

micronised gliquidone	30 parts by weight
corn starch	75 parts by weight
lactose	132 parts by weight
magnesium stearate	3 parts by weight

showed the following dissolution rate:

after 5 minutes : 5.8% gliquidone

after 30 minutes : 7.2% gliquidone

Examples 4 and 5

The pharmaceutical compositions shown in Table 2 which follows comprise, in addition to 5 mg of gliquidone, increasing quantities of polyvinylpyrrolidone (Kollidon 25 (R)) but no basic excipient and no carrier. A useful dissolution rate is achieved only with upwards of 12 times the quantity of Kollidon 25 (R).

The pharmaceutical compositions in these Examples were produced by dissolving the active substance and solubilising substance together in ethanol; the solution was then evaporated to dryness and the product was rubbed through a screen with a mesh size of 1 mm.

Table 2:

Example	Kollidon 25 (R) mg	Dissolution Rate in percent of the active substance which has gone into solution after 5 and 30 minutes	
4	10	24	44
5	60	90	93

Examples 6 to 8

The pharmaceutical composition in Example 7 was prepared as described in Example 1. The

pharmaceutical compositions in Examples 6 and 8 were produced analogously to the method described in Examples 4 and 5.

Table 3 shows the compositions and the dissolution rates measured. As can be seen from Table 3, the presence of a basic excipient alone does not lead to a useful dissolution rate nor does the sole presence of a solubilising substance (without a basic excipient and a carrier) lead to a product with a useful dissolution rate. This shows that the combination of gliquidone with a basic excipient and solubilising agent in the presence of a soluble carrier yields the best results in terms of rapid and fullest possible dissolution of the active substance.

Table 3:

Example	Gliquidone mg	Basic Excipient mg	30 mg of Kollidon 25 (R)	Dissolution Rate in per cent of the active substance which has gone into solution after 5 and 30 minutes	
6	5	1.9) Ethylene	no	4	4
7	25	6.5) diamine .$1H_2O$	yes	88	94
8	25	-	yes	12	24
9	30	36.0 L-lysine	yes * *(Kollidon 25 + Pluronic F 68)	91	

Example 9

1 Tablet contains:

30.0 mg gliquidone
36.0 mg L-lysine
20.0 mg Kollidon 25
24.0 mg Pluronic F 68

Processing analogously to Examples 1 to 3, but with the solution being evaporated in a spray dryer.

The following are added per tablet:

105.0 mg	Avicel
105.0 mg	Explotab
320.0 mg	

From this mixture round biconvex tablets weighing 320 mg and measuring 10 mm in diameter are compressed and coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: after 5 minutes : 91%.

Example 10

Film-coated tablets containing 4-[(1-(2-piperidinophenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Example 10a:

1 Tablet contains:

30 mg 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

134 mg	Amberlite IRP 88
134 mg	Avicel
2 mg	magnesium stearate
300 mg	

The tablet constituents are mixed together, compressed to form round biconvex tablets weighing 300 mg and measuring 10 mm in diameter and then coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: after 5 minutes: 25.6%
after 30 minutes: 36.3%

Example 10b:

Granulate of active substance.

30 mg of the active substance of Example 10a
36 mg L-lysine
30 mg Kollidon 25
24 mg Pluronic F 68

Processing is carried out analogously to Examples 1 to 3. The following are added to this granulate:

90 mg Avicel
90 mg Amberlite IRP 88
300 mg

Round biconvex tablets weighing 300 mg and measuring 10 mm in diameter are compressed from this mixture and coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: after 5 minutes : 48.7%
after 30 minutes : 81.3%

Example 11 - Film-coated tablets containing 4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

Example 11a:

1 Tablet contains:

30 mg of active substance
134 mg Amberlite IRP 88
134 mg Avicel
2 mg magnesium stearate
300 mg

The tablet ingredients are mixed together, compressed to form round biconvex tablets weighing 300 mg and measuring 10 mm in diameter and coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: 15.8% after 5 minutes
20.9% after 30 minutes

Example 11b:

Granulate of active substance

30 mg of active substance of Example 11a
30 mg L-lysine
30 mg Kollidon 25
24 mg Pluronic F 68

Processing analogously to Examples 1 to 3.

The following are added to this granulate:

93 mg Avicel
93 mg Amberlite IRP 88
300 mg

Round biconvex tablets weighing 300 mg and measuring 10 mm in diameter are compressed from this mixture and coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: after 5 minutes: 58.4%
after 30 minutes: 93.4%

Example 12 - Film-coated tablets containing 4-[2-(5-chloro-2-octamethyleneimino-benzoyl-amino)ethyl]-benzoic acid

Example 12a:

1 Tablet contains:

30 mg of active substance
134 mg Amberlite IRP 88
134 mg Avicel
2 mg magnesium stearate
300 mg

The tablet ingredients are mixed together, compressed to form round biconvex tablets weighing 300 mg and measuring 10 mm in diameter and then coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: 18.4% after 5 minutes
27.2% after 30 minutes

Example 12b:

Granulate of active substance

30 mg of active substance of Example 12a
36 mg L-lysine
30 mg Kollidon 25
24 mg Pluronic F 68

Processing is carried out analogously to Examples 1 to 3.

The following are added to the granulate:

90.0 mg Avicel
90.0 mg Amberlite IRP 88
300.0 mg

Round biconvex tablets weighing 300 mg and measuring 10 mm in diameter are compressed from this mixture and coated with hydroxypropylmethylcellulose to mask the flavour.

Dissolution rate: 96.2% after 5 minutes
99.9% after 30 minutes

There now follows an Example of the production of a pharmaceutical composition.

Example 13

Capsules

A quantity of granulate from Example 1 corresponding to 10 mg of gliquidone is mixed with a corresponding quantity of corn starch and magnesium stearate and then packed into size 5 hard gelatine capsules.

* C L M S *

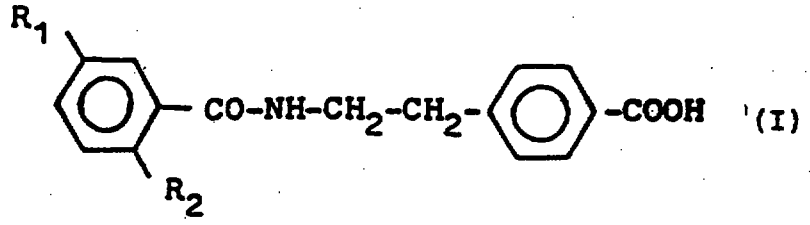
Claims:

1. A process for producing orally administrable pharmaceutical compositions containing antidiabetically active substances, wherein an acidically reacting active substance is dissolved in a polar solvent with the aid of at least one basic excipient, an amphoterically reacting active substance is dissolved in a polar solvent with the aid of at least one basic or acidic excipient or a basically reacting active substance is dissolved in a polar solvent with the aid of at least one acidic excipient, the said dissolution being effected in the presence of polyvinylpyrrolidone and optionally other solubilising and/or emulsifying substances and the molar ratio of active substance to basic or acidic excipient being less than 1:1; the solution is evaporated to dryness; and the product thereby obtained is, if required, further processed optionally with the addition of further excipients to produce the desired pharmaceutical compositions.

2. A process as claimed in claim 1, wherein the active substance comprises an orally administrable antidiabetically active sulphonylurea.

3. A process as claimed in claim 1, wherein the active substance comprises at least one substance selected from:

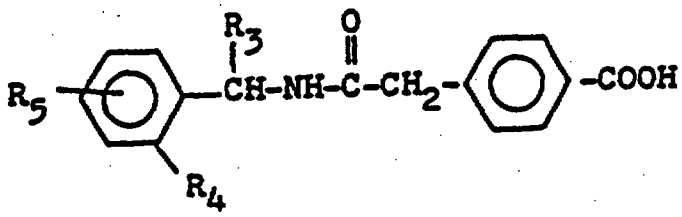
a) 4-[2-(aroylamino)ethyl]-benzoic acids of general formula (I)



(I)

(wherein R_1 represents a halogen atom and R_2 represents an alkoxy group with 1 to 3 carbon atoms or a piperidin-1-yl or octamethyleneimino group) and

b) substituted 4-(aralkylaminocarbonylmethyl)-benzoic acids of general formula (II)



(II)

(wherein R_3 represents an alkyl group with 1 to 4 carbon atoms or a phenyl group, R_4 represents a piperidin-1-yl, pyrrolidin-1-yl or hexamethyleneimino group and R_5 represents a hydrogen or halogen atom or a methyl or methoxy group).

4. A process as claimed in claim 3 wherein the active substance comprises at least one compound of formula I in which R_1 represents a chlorine atom.

5. A process as claimed in claim 3 wherein the active substance comprises at least one compound of formula II in which R_3 represents an n-propyl group.

6. A process as claimed in claim 3 or claim 5 wherein the active substance comprises at least one compound of formula II in which R_5 represents a fluorine or chlorine atom.

7. A process as claimed in claim 2 wherein gliquidone is used as the active substance.

8. A process as claimed in claim 3 wherein 4-[2-(5-chloro-2-octamethyleneimino-benzoylamino)ethyl]benzoic acid is used as the active substance.

9. A process as claimed in claim 3 wherein 4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid is used as the active substance.

10. A process as claimed in claim 3 wherein 4-[[1-(2-piperidino-phenyl)-1-butyl]-aminocarbonylmethyl]-benzoic acid is used as the active substance.

11. A process as claimed in any one of the preceding claims wherein mixtures of acidic, of basic or of amphoteric orally administrable antidiabetically active substances are used.

12. A process as claimed in any one of the preceding claims wherein a basic excipient is used and the molar ratio of active substance to basic excipient is from 1:1.1 to 1:10.

13. A process as claimed in any one of the preceding claims wherein a mixture of basic excipients is used.

14. A process as claimed in any one of the preceding claims wherein the ratio of active substance or mixture of active substances to the total quantity of solubilising substances is from 1:1 to 1:10 parts by weight.

15. A process as claimed in any one of the preceding claims, wherein the other solubilising and/or emulsifying substance(s) used is/are selected from polyoxyethylene polyoxypropylene polymers, polyethylene glycols, polyethoxylated sorbitan mono-oleates, sorbitol, glycerol polyethylene glycoloxy stearates, polyoxyethylene fatty alcohol ethers and mixtures of these substances.

16. A process as claimed in any one of the preceding claims wherein the solvent used is water or is a lower alcohol or ketone or a mixture thereof with water.

17. A process as claimed in any one of the preceding claims wherein at least one basic excipient selected from sodium hydroxide solution, potassium hydroxide solution, ammonia, tert. sodium phosphate, diethanolamine, L-lysine, ethylenediamine or N-methylglucamine is used.

18. A process as claimed in claim 1 wherein at least one acidic excipient selected from sulphuric acid and phosphoric acid is used.

19. A process as claimed in claim 1 substantially as herein described.

20. A process as claimed in claim 1 substantially as herein decribed in any one of the Examples.

21. A process as claimed in claim 1 substantially as herein described in any one of Examples 1 to 3, 7 and 13.

22. Pharmaceutical compositions whenever prepared by a process as claimed in any one of the preceding claims.

23. Pharmaceutical compositions prepared by a process as claimed in claim 7 or claim 21.

24. Orally administrable pharmaceutical compositions in solid form containing: an acidically reacting antidiabetically active substance together with a basic excipient, an amphoterically reacting antidiabetically active substance together with a basic or acidic excipient or a basically reacting antidiabetically active substance together with an acidic excipient; together with polyvinylpyrrolidone and optionally other solubilising and/or emulsifying substances and, if desired, one or more further excipients; the molar ratio of active substance to basic or acidic excipient being less than 1:1 and the active ingredient and polyvinylpyrrolidone being present as a molecular dispersion.

25. Pharmaceutical compositions as claimed in claim 24 containing an antidiabetically active sulphonylurea together with a basic excipient.

26. Pharmaceutical compositions as claimed in claim 24 substantially as herein described.

27. Pharmaceutical compositions as claimed in claim 24 substantially as herein described in any one of Examples 1 to 3, 7, 9, 10b, 11b, 12b and 13.

28. Pharmaceutical compositions as claimed in claim 24 substantially as herein described in any one of Examples 1 to 3, 7 and 13.