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(54) Titre : PROCEDE DE REALISATION D'UNE MATRICE A ACTION PROLONGEE AMORPHE OU PARTIELLEMENT AMORPHE INSOLUBLE DANS L'EAU
 (54) Title: METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX

(57) **Abrégé/Abstract:**

The invention relates to a method for producing pharmaceutical forms or preliminary stages thereof by means of extrusion. The pharmaceutical form has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. The invention also relates to a pharmaceutical form which has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process, and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. Finally, the invention also relates to the use of said pharmaceutical form for producing granulates for tableting and filling capsules, for further processing using injection moulding techniques and as an auxiliary material for direct tableting and/or for producing monobloc pharmaceutical forms.





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<p>(54) Title: METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX</p> <p>(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG EINER WASSERUNLÖSLICHEN AMORPHEN ODER TEILAMORPHEN RETARDMATRIX</p> <p>(57) Abstract</p> <p>The invention relates to a method for producing pharmaceutical forms or preliminary stages thereof by means of extrusion. The pharmaceutical form has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. The invention also relates to a pharmaceutical form which has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process, and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. Finally, the invention also relates to the use of said pharmaceutical form for producing granulates for tableting and filling capsules, for further processing using injection moulding techniques and as an auxiliary material for direct tableting and/or for producing monobloc pharmaceutical forms.</p> <p>(57) Zusammenfassung</p> <p>Die Erfindung betrifft ein Verfahren zur Herstellung von Arzneiformen oder Vorstufen davon mittels Extrusion, wobei die Arzneiform eine den Wirkstoffgehalt im wesentlichen enthaltende Matrix aufweist, die in ihren wesentlichen Eigenschaften durch die Extrusion ausgebildet wird, und ein Polysaccharid und/oder ein Derivat davon und/oder einen Komplex davon und/oder eine beliebige Mischung der vorgenannten Substanzen mit anderen Substanzen und/oder Sacchariden und/oder Derivaten davon als wesentlichen Bestandteil der Matrix sowie mindestens eine pharmazeutisch wirksame Substanz umfasst. Die Erfindung betrifft weiterhin eine Arzneiform, welche eine den Wirkstoffgehalt im wesentlichen enthaltende Matrix, die in ihren wesentlichen Eigenschaften durch Extrusion ausgebildet ist, und ein Polysaccharid und/oder ein Derivat davon und/oder einen Komplex davon und/oder eine beliebige Mischung der vorgenannten Substanzen mit anderen Substanzen und/oder Sacchariden und/oder Derivaten davon als wesentlichen Bestandteil der Matrix sowie mindestens eine pharmazeutisch wirksame Substanz umfasst. Weiter betrifft die Erfindung die Verwendung der Arzneiform zur Herstellung von Granulaten für die Tablettierung und Kapselfüllung, zur Weiterverarbeitung mit Spritzgussverfahren, als Hilfsstoff bei der Direkttablettierung und/oder zur Herstellung von Monoblockarzneiformen.</p>		

Method for Producing a Water-insoluble Amorphous or Partially Amorphous Controlled-release Matrix

The invention relates to a method for producing pharmaceutical dosage forms or precursors thereof by means of extrusion.

The invention further relates to a pharmaceutical dosage form which may be produced by means of extrusion methods.

Extrusion is a widespread process, especially in the adhesive industry or in plastics processing for modifying polysaccharides, in particular starches. Extrusion is known in food technology for the production of starch-containing compositions, such as noodles, so-called peanut flips or various sweets. However, the production conditions of all of these products are selected in such a way that foamed, so-called popped products are obtained.

In pharmaceutical technology extrusion is used for the processing of waxes, fatty alcohols, fats and various thermoplastics and duroplastics. For example, extruded matrices from various polymer compounds are disclosed in EP-A2 0 240 904, EP-A2 0 240 906 and EP-A2 0 358 105. The processing of starch-containing mixtures into pharmaceutical products (capsules) by means of an injection-molding technique is described in EP-B2 0 118 240. In this context, it is not so well known how the polysaccharides used change during extrusion.

Extrusion methods for producing solid dispersions of an active agent in a polymeric carrier are known from EP-A 0 580 860. Among the raw materials which may be used are starch and starch derivatives mentioned in general. However, the method described therein is not suitable for preparations having starch as the main ingredient.

In pharmaceutical technology, orally administered dosage forms such as, for example, tablets, dragées or capsules are by far the most important. These also include the so-called controlled release (retard) dosage forms, which contain a relatively high dose of active agent and release this active agent in a controlled manner over a longer

period of time. For the patient, this means that the frequency of medication can be significantly reduced. From a medical-pharmacological point of view, the advantage of the controlled release dosage forms lies in a very uniform concentration of the active agent in the blood, producing a long-lasting effect with less side effects. When formulating controlled release dosage forms, the so-called matrix form is of fundamental importance. Matrix means a shaped body, such as, for example, a tablet or dragée made of inert adjuvants, which release the active agents into the gastrointestinal tract in a controlled manner. The release of the active agent generally occurs partly by diffusion, partly by slow degradation of the matrix.

In pharmaceutical technology such matrices are produced from synthetic polymers, such as polyacrylate or polyethylene. In this context, extrusion methods for the production of controlled-release forms from synthetic raw materials are also known.

One fundamental disadvantage of dosage forms produced hitherto by means of extrusion methods is the use of excipients such as plastics, waxes or even fatty alcohols. These adjuvants, which are not biologically degradable and in part environmentally harmful, such as residual monomers in the polymers used, are even up to the present day indispensable for dosage forms produced by means of extrusion methods and allowing a controlled and slow release of the active agent. Moreover, there is no known extrusion method for the production of dosage forms which allow a rapid release of the active agent.

There is thus a great need for the provision of an extrusion method for the production of dosage forms having regulated, i.e. by choice delayed or even a more rapid release of the active agent, which overcomes the disadvantages of the prior art, and which particularly avoids the use of biologically non-degradable and to some extent even environmentally toxic excipients. Further objects can be gathered from the following description of the invention.

The solution of the objects relating to the method lies in the combination of features as set out herein.

Advantageous embodiments of the inventive method are hereinafter described.

According to the invention a method for producing of dosage forms or precursors thereof by means of extrusion is suggested, characterized in that the dosage form has a matrix which essentially comprises the active agent content, the essential features of which matrix are formed by the extrusion, and which comprises a biologically degradable polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as a constituent of the matrix and at least one pharmaceutically effective substance.

According to a preferred embodiment, the release of the active agent of the dosage form is regulated by the addition of adjuvants and/or by variation of the extrusion process parameters, such as temperature, geometry of the dies and/or the extrusion speed.

In a further preferred embodiment the matrix of the dosage form made according to the invention is amorphous or partially amorphous.

Furthermore, the invention in a preferred embodiment relates to a method, wherein the dosage form according to the invention comprises in the matrix starch or a derivative thereof, in particular amorphous or partially amorphous starch or a derivative thereof, as the polysaccharide.

In a further preferred embodiment the invention relates to a method of production wherein the dosage form comprises a water-insoluble and preferably a swellable matrix.

In a further preferred embodiment the invention relates to a method of production wherein the dosage form comprises a water-insoluble and preferably a swellable matrix.

According to an especially preferred embodiment, the dosage form according to the invention is a controlled release matrix.

Further preferred embodiments include a dosage form according to the invention showing a release of the active agent which essentially follows the lapidus function and which especially preferred shows a release of the active agent which is adjustable over 24 hours or longer.

A further essential object of the invention lies in the provision of a dosage form which essentially can function without biologically degradable ingredients.

According to the invention, this object is solved by a dosage form comprising a matrix in which the active agent is essentially contained, and whose essential properties are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent of the matrix, and at least one pharmaceutically effective substance.

Furthermore, the invention relates to the use of the inventive dosage form as adjuvant in direct tableting, for producing granulates for tableting and capsule-filling, for further processing using injection molding techniques and/or for producing monoblock pharmaceutical dosage forms.

During the extrusion process, i.e. while using or applying heat, shear forces and pressure, an amorphous or partially amorphous matrix is generated from the

crystalline or partly crystalline polysaccharides, in particular from starch or derivatives thereof, or from mixtures of these components. For the reproducible production of dosage forms based on the extrusion of polysaccharides and derivatives thereof, the extrusion conditions, such as temperature, die geometry and extrusion speed, are very important. For example, native starch may be completely plastified or vitrified under suitable extrusion conditions, so that homogeneous plastic-like shaped bodies are obtained.

When extruding starch, heating is only necessary at the beginning of the process. In the further course of the process, the heat generated by the strong shear and friction is preferably eliminated by cooling, in order to maintain a constant temperature. The formulations used in the inventive method are comprised of a mixture of polysaccharides and/or derivatives thereof, preferably of a mixture of starch and/or starch derivatives, there being various types of starch which are suitable. Furthermore, the mixture contains at least one pharmaceutically effective substance in an amount of up to 50% and preferably of up to 30%, based on the total weight of the formulation, and may additionally comprise further different substances. Water in concentrations of up to 15% should be added to the thoroughly mixed dry formulation. Where a forced conveying extruder is used, a lesser water content than 15% is sufficient.

After thoroughly mixing and the addition of water the obtained pre-blend should preferably be screened so that it is free of lumps, in order to ensure perfect conveyance through the screw feeder. Starting and cleaning of the extruder may for example be carried out using corn grit. When generating a matrix according to the inventive method, the temperature at the orifice of the extruder should not exceed 100°C under normal pressure, since at temperatures above 100°C the formation of a matrix free of pores will hardly be possible. The total energy fed into the process, in the form of shear forces, temperature, heat or pressure, should be as constant as possible and should be sufficient to achieve glass transition. The optimal screw speed and geometry of dies may be adjusted to the mixture comprised of the inventive

carrier and water. At extrusion temperatures below 100°C and suitable screw speeds transparent and completely amorphous products are obtained in most cases. The degree of plastification of the active agent/polysaccharide mixture and preferably of the active agent/starch mixtures is closely linked to the screw speed. While extrusion is no longer possible below the lowest speed, a screw speed which is too high causes the dosage form to "pop open".

Varying the extrusion process parameters allows the production of dosage forms according to the inventive method which show regulated release of the active agent. Within the meaning of the present invention "regulated" means that by the inventive extrusion method dosage forms with rapid as well as dosage forms with delayed release, so-called controlled-release dosage forms with release periods of up to 24 hours or longer, may be produced. Besides the process parameters already mentioned, also the processing temperature is of major importance in relation to the regulation of the release of the active agent. Dosage forms with rapid release may be obtained for example by extrusion below the temperature of gelatinisation of the polysaccharides used in each case. Since, among other things the density of the matrix influences the release of the incorporated active agents, corresponding dosage forms with controlled release may be produced by partial to complete vitrification, i.e. by transition into the amorphous state of the polysaccharide-containing mixture under suitable extrusion conditions. In contrast to previously described systems, such an amorphous or partially amorphous matrix according to the inventive method, which preferably is made of amorphous or partially amorphous starch or derivatives thereof or of mixtures of these components, is essentially not water-soluble, but instead preferably swellable and water-insoluble. The pharmaceutically effective substance or substances may be present in the matrix in dissolved, solid or liquid form.

Examples of starches which may be used in the inventive production method are tapioca starch, wheat starch, potato starch, starch 1500® (partially pregelatinized corn

starch, available from Colorcon), Waxylis® (wax corn starch from Roquette), Eurylon 7® (amylo corn starch available from Roquette), corn starch, acetylic starch.

In addition, dosage forms are obtainable according to the inventive extrusion method which have regulated release of the active agent due to the addition of adjuvants. For accelerating release of the active agent by formation of pores in the matrix, the following substances may be added, for example:

- hydrophilic or amphiphilic solids, water-soluble substances, such as sodium chloride, lactose, surface-active substances, such as for example sodium lauryl sulfate, silica (colloidally dispersed and/or as xerogel),
- hydrophilic or amphiphilic liquids, polyglycols, such as for example glycerol, polyethylene glycol, surface-active substances, such as for example polysorbate,
- gases, such as for example nitrogen, carbon dioxide.

A reduction in the release of the active agent by inhibiting the diffusion may for example be effected by the addition of the following adjuvants:

- lipophilic or amphiphilic adjuvants of natural, synthetic and/or partially synthetic origin, such as for example fats, fatty acids, waxes in solid or liquid state,
- saturated or unsaturated hydrocarbons,
- metal soaps, such as for example magnesium stearate.

Furthermore, a reduction in the release of the active agent may be achieved by the formation of stoichiometric or non-stoichiometric complexes, such as for example iodine-starch complex, miltefosin-amylose complex.

Moreover, the release of the incorporated active agents can be influenced by the use of suitable blends of the components of the matrix, preferably by using blends of different starches and/or derivatives thereof. Further factors which can also influence the release of the active agent are the outer surface of the shaped body of the dosage form and its particle size, or the distribution of the active agent(s) within the particle.

An examination of the course of the release of the active agent shows that the release of the active agent is preferably controlled by diffusion and follows the so-called lapidus rule, as shown in the tests described below. The course of the release does not change, even after storage of the dosage forms over several months.

The dosage forms produced according to the inventive method may be used to produce granulates for tableting and filling capsules, may be used as adjuvants for direct tableting, for further processing by means of extrusion molding techniques and/or as mono-block dosage forms, where the extrudate is formed by means of a suitable arrangement at the extrusion die – similar to the case of soap production. The inventive method allows the production and use of mono-block forms, in the process of which an extrude is created that is vitrified only at the surface and includes the active substance/carrier mixture in an unchanged state in its interior. In order to achieve the desired bio-pharmaceutical properties of the dosage form, all adjuvants known for producing solid forms may be used.

Drying of the dosage form can take place merely through the frictional heat that is created, so that a final drying step is not necessary. In a production extruder, preferably a twin screw extruder, especially preferred in a forced conveying twin screw extruder, all process steps, such as dosing, moistening, mixing, extruding and forming can be carried out continuously. The inventive method is thus able to combine the processes of mixing, granulating and drying, for which no additional energy has to be expended, in one piece of equipment.

According to the invention, also the number of possible incompatibilities is reduced, since the dosage form comprises for example only one excipient, preferably starch or a derivative thereof, and one pharmaceutically effective substance. The matrix made according to the inventive method further prevents a possible unintended demixing.

The following examples show that the degree of retardation of the active agent is best regulated by the process or the process parameters, the type of polysaccharide or the addition of further adjuvants. The examples serve to illustrate the invention only and do not represent any limitations to certain embodiments or applications. Rather, further embodiments within the scope defined by the attached claims are conceivable.

Examples

In the following examples, which have been carried out according to the inventive method, various polysaccharides with the addition of caffeine as a model active agent were used. The extrusion experiments were carried out with a Brabender one-screw extruder type 811201. This device has three segments which may be tempered independently of each other, the feed area, the screw area and the die. A conveyor screw was used without compression, having a screw length of 22 cm, a screw diameter of 19 mm, a core diameter of 16 mm and a pitch of 15 mm. Dies with different diameters between 2.5 and 7 mm were used.

The batch size in the experiments was between 350 and 600 grams. Active agent and starch were thoroughly mixed in a Stephan mixer, moistened with 15% water; this pre-blend was then screened until free of lumps.

Temperatures of about 65°C in the feed area of the extruder, of about 80°C in the screw area and of about 98°C at the die have proven to be a suitable choice of temperature for carrying out the inventive method.

The proof of the transition of the crystalline or partially crystalline structures of the polysaccharides into amorphous or partially amorphous structures may be carried out with the aid of different techniques.

By means of differential scanning calorimetry (DSC) the transition of the crystalline or partially crystalline starch into the amorphous state can be detected. Under suitable extrusion conditions the starch becomes completely vitrified, i.e. changes into the amorphous state. By way of example, a test with tapioca starch as the polysaccharide and caffeine as the active agent was carried out. The thermogram of the pre-blend is shown in Fig. 1a, consisting of 90% tapioca starch and 10% caffeine with the addition of water, shows the typical endothermic peaks in the range of about 65°C.

After the extrusion carried out according to the invention, no peaks in the decisive temperature range are detectable. It has to be concluded that the starch has been completely vitrified, which means that it has turned into the amorphous state (see Fig. 1b).

The transition from the crystalline or partially crystalline into the amorphous or partially amorphous state may also be detected with the aid of x-ray diffraction. For the following exemplary test, a sample consisting of 80% potato starch and 20% caffeine was used. The x-ray diffraction pattern of the potato starch-caffeine pre-blend shown in Fig. 2 shows the signals of the crystalline part of the starch in the range of around 20°C. After application of the inventive method, the x-ray diffraction pattern of the corresponding extrudate does not have any signals anymore, which indicates a crystalline portion of the starch.

In this context it is once again pointed out that the degree of destructurezation into the glass state is decisive for the kinetics of the release of the active agents. Checking of the release of the active agent was done in a paddle agitator model according to USP in the liquids of 0.1 N hydrochloric acid (artificial gastric fluid having a pH value of

1) and in phosphate buffer pH 7.2 (artificial intestinal fluid). In this context it has again to be pointed out that the extrudates did not dissolve in the test, but merely a swelling of the extrudes was observed. In the following exemplary test to determine the quantitative release of the active agent, a sample consisting of a commercially available starch Eurylon 7® (amylo corn starch available from Roquette) and a 30% portion of caffeine was used. The diagram in Fig. 3 shows the quantitative course of the release of the active agent. For comparative purposes, the release of pure caffeine, not retarded and filled in a capsule has been drawn in.

One can see that embedding the caffeine in a polysaccharide matrix leads to a substantial delay in release, in the present case from about 15 minutes to about 8 to 10 hours for the total dose of 25 mg.

A diagram of the amount released against the square root of time according to the lapidus rule shows an almost straight lined course of the curves, which indicates that the release of the active agent is controlled by diffusion (see Fig. 4).

As already described, the release rate of the active agent may also be regulated by the kind of polysaccharide or the polysaccharide mixture. In the following example, a pre-blend consisting of potato starch and 10% caffeine was used for a quantitative investigation of the release of the active agent. Changing the type of starch, together with a lower dose of the active agent leads to a significant slowdown in the release of the active agent. The diagram shown in Fig. 5 indicates that the extrudate prepared according to the inventive method provides a release of the active agent over a period of 24 hours.

The graph shown in Fig. 6 according to lapidus rule indicates that the release of the active agent is controlled by diffusion.

As already described above, the duration and course of the total release of the active agent can be regulated. Very long active agent release times, such as 24 hours in the above-mentioned example, are regarded as advantageous in view of the development of a new retardation principle, since in such a way "reserves" for extremely good water-soluble active agents are obtained. Release of the active agent may be selectively influenced, as already described several times, by the polysaccharides or corresponding derivatives and mixtures thereof, by the addition of corresponding adjuvants and/or by the extrusion process parameters.

According to the inventive method, faster release times of the active agents may also be achieved. The table shown below shows by way of example that a process parameter change, which for example leads to an incomplete vitrification, results in the possibility of regulating the release times of the active agent over a wide range.

Table

Polysachharide	Active agent	Concentration of active agent	Period in which 50% of the active agent is released [min]	Period in which the active agent is theoretically released [hours]
Tapioca starch	Caffeine	10% (50 mg)	240	16
Tapioca starch	Caffeine	10% (50 mg)	120	8
Corn starch	Caffeine	30% (50 mg)	195	13
Corn starch	Caffeine	30% (50 mg)	55	3.7

As can be seen from this table, for identical types of starch relatively short release times of the active agent as well as release times of the active agent falling into the range of controlled release dosage forms may be achieved solely by varying the process parameters.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Method for producing pharmaceutical dosage forms or precursors thereof by means of extrusion,

characterized in that the dosage form has an amorphous matrix whose essential properties are formed by extrusion and which comprises starch, derivatives of starch or complexes of starch or a combination thereof as an essential constituent, and at least one pharmaceutically active agent, wherein the release of the active agent of the dosage form is regulated by variation of the extrusion process parameters, and wherein the method comprises the following steps:

- (a) producing a dry formulation by mixing at least one pharmaceutically active agent in an amount of up to 50 wt.-% based on the total weight of the formulation with starch, derivatives of starch or complexes of starch or a combination thereof, and
- (b) producing the matrix by extruding the formulation into a shaped body, wherein the temperature at the orifice of the extruder does not exceed 100°C under normal pressure.

2. Method according to claim 1,

characterized in that the release of the active agent of the dosage form is additionally controlled by the addition of adjuvants.

3. Method according to any one claims 1 or 2,

characterized in that the matrix is water-insoluble.

4. Method according to any one of claims 1 to 3,

characterized in that the matrix is a sustained release matrix.

5. Method according to any claims 1 to 4,
characterized in that the release of the active agent of the dosage form substantially follows the lapidus function.
6. Method according to any one of claims 1 to 5,
characterized in that the release of the active agent of the dosage form may be adjusted over a period of up to 24 hours or longer.
7. Method according to any one of claims 1 to 6,
characterized in that at least one pharmaceutically active agent is present in the matrix in dissolved, solid or liquid form.
8. Pharmaceutical dosage form, comprising an amorphous or partially amorphous matrix, which is obtained by means of extrusion and which comprises starch, derivatives of starch or complexes of starch or a combination thereof as an essential constituent of the matrix, and at least one pharmaceutically active agent, and which is obtainable by the method for producing pharmaceutical dosage forms according to any one of claims 1 to 7, wherein the release of the active agent of the dosage form is controlled by variation of the extrusion process parameters.
9. Dosage form according to claim 8,
characterized in that the release of the active substance is additionally regulated by the addition of adjuvants.
10. Dosage form according to any one of claim 8 to 9,
characterized in that the matrix is water-insoluble.
11. Dosage form according to any one of claims 8 to 10,
characterized in that the matrix is a sustained release matrix.
12. Dosage form according to any one of claims 8 to 11,
characterized in that the release of the active agent substantially follows the lapidus function.

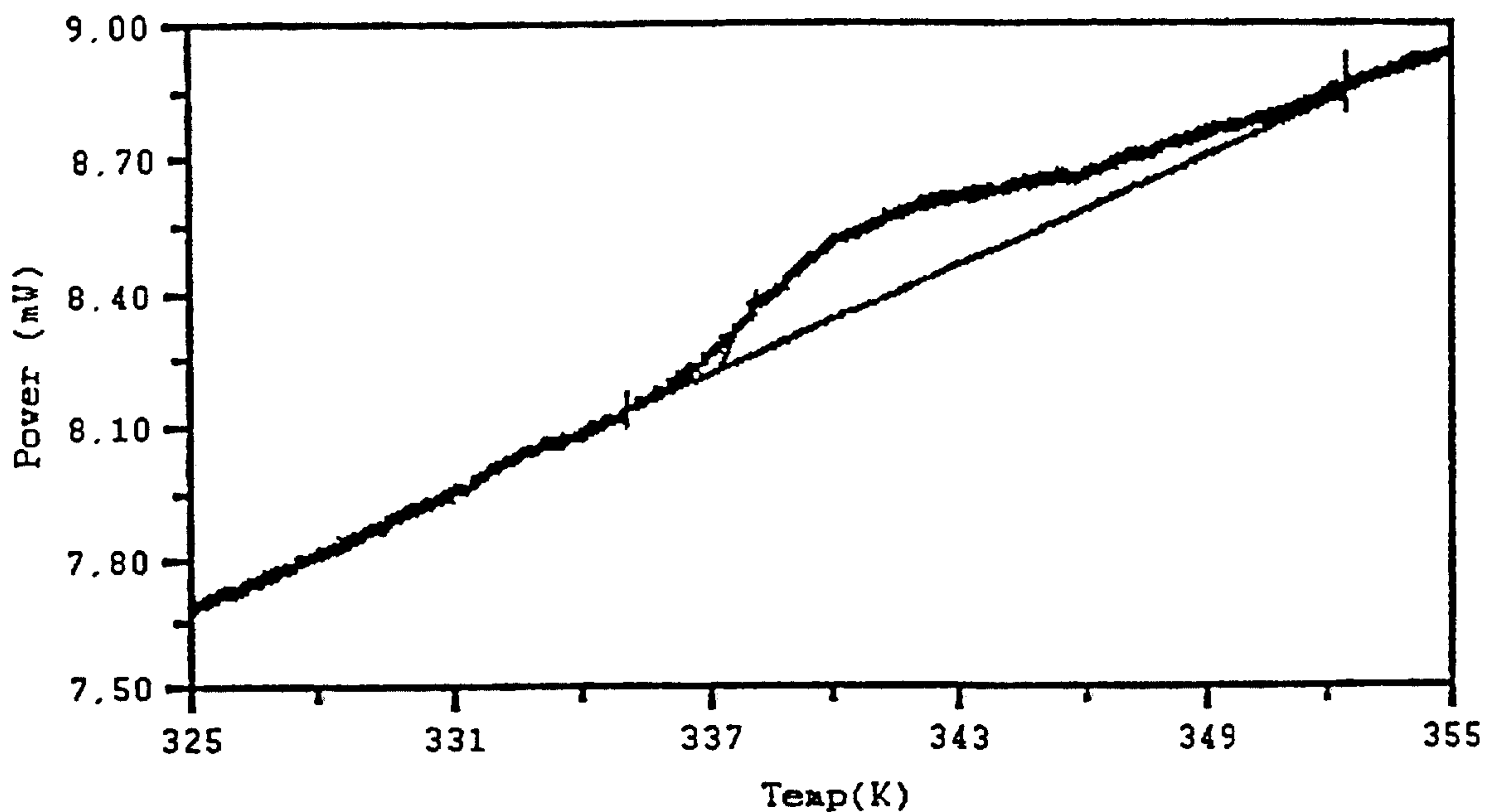
13. Dosage form according to any one of claims 8 to 12,
characterized in that the release of the active agent is adjusted over a period of up to 24
hours or longer.

14. Dosage form according to any one of claims 8 to 13,
characterized in that at least one pharmaceutically active agent is present in the matrix
in dissolved, solid or liquid form.

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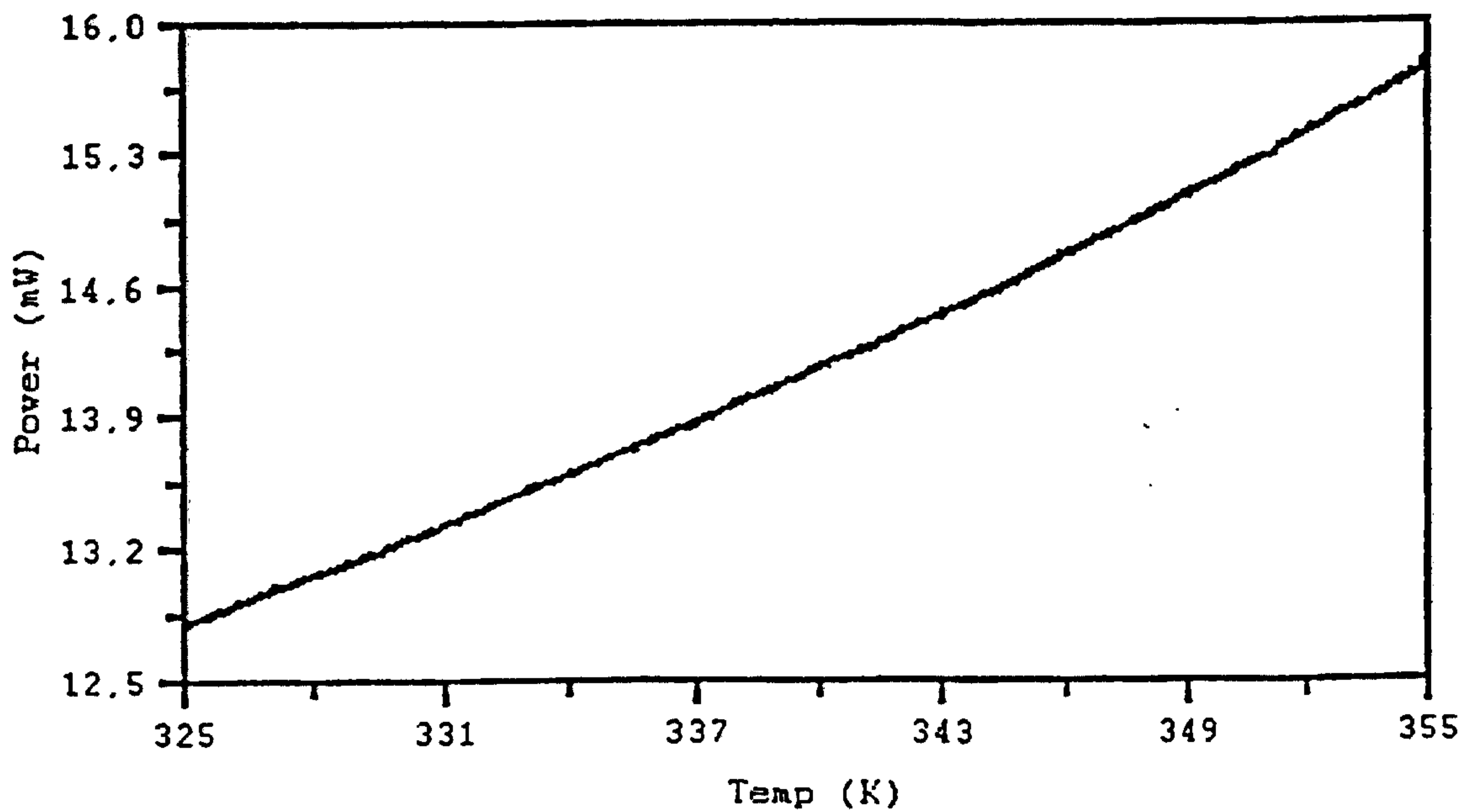
DSC data of extrudable mixture made of 90% tapioca starch and 10% caffeine

Fig. 1a

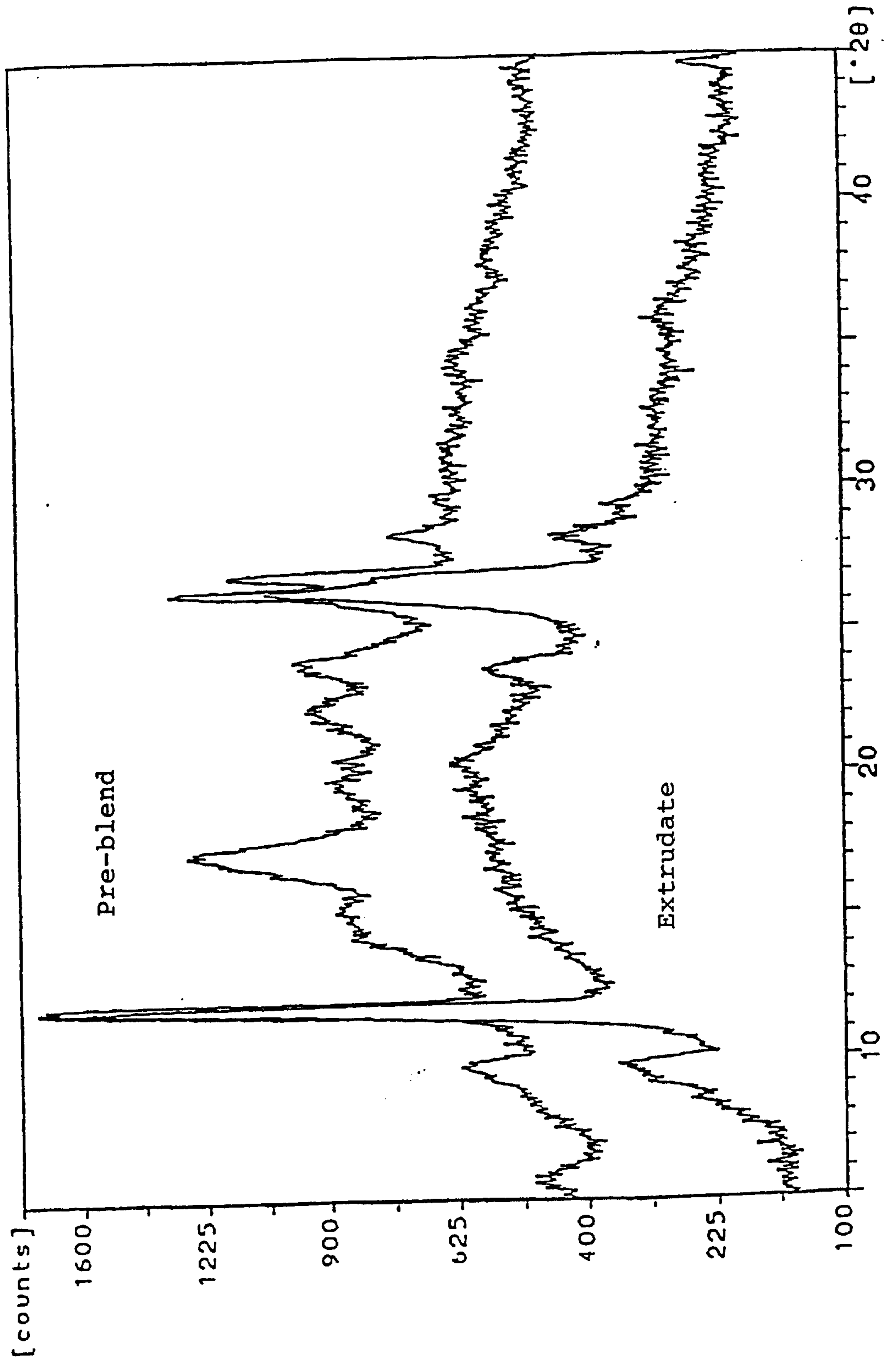


DSC data of the extrudate made of 90% tapioca starch and 10% caffeine

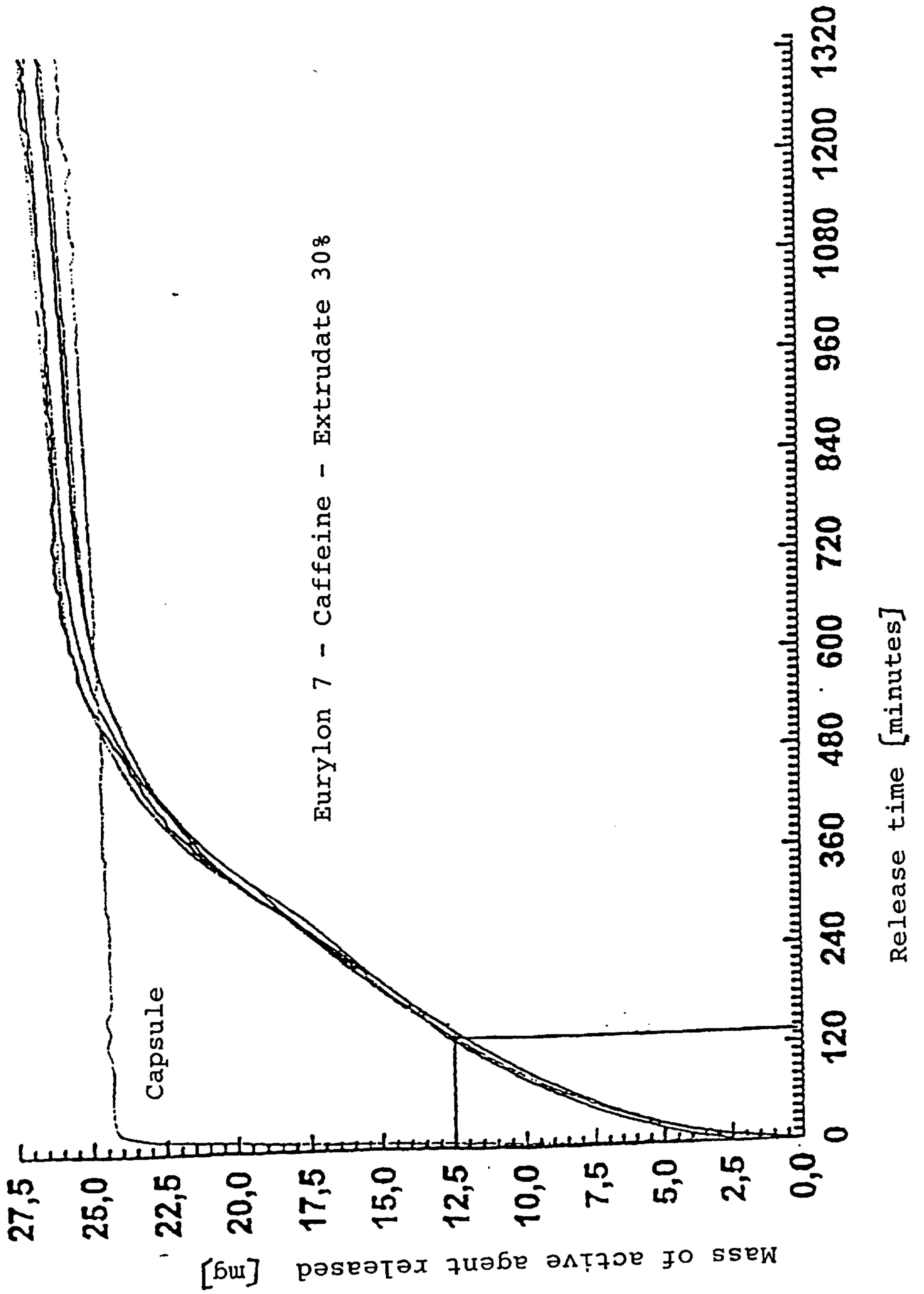
Fig. 1b



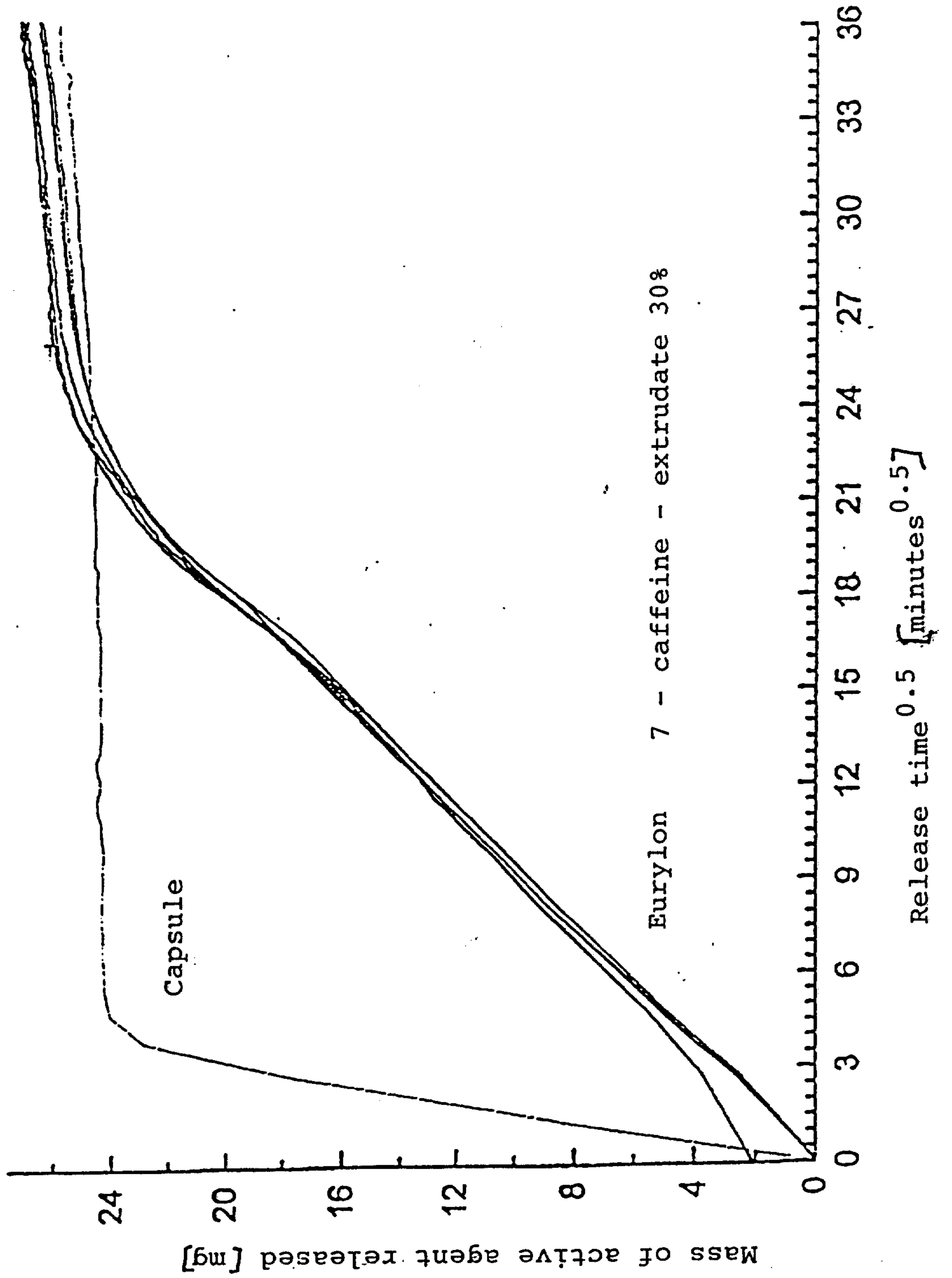
X-ray diffraction pattern of the pre-blend and the extrudate made of 80% potato starch and 20% caffeine



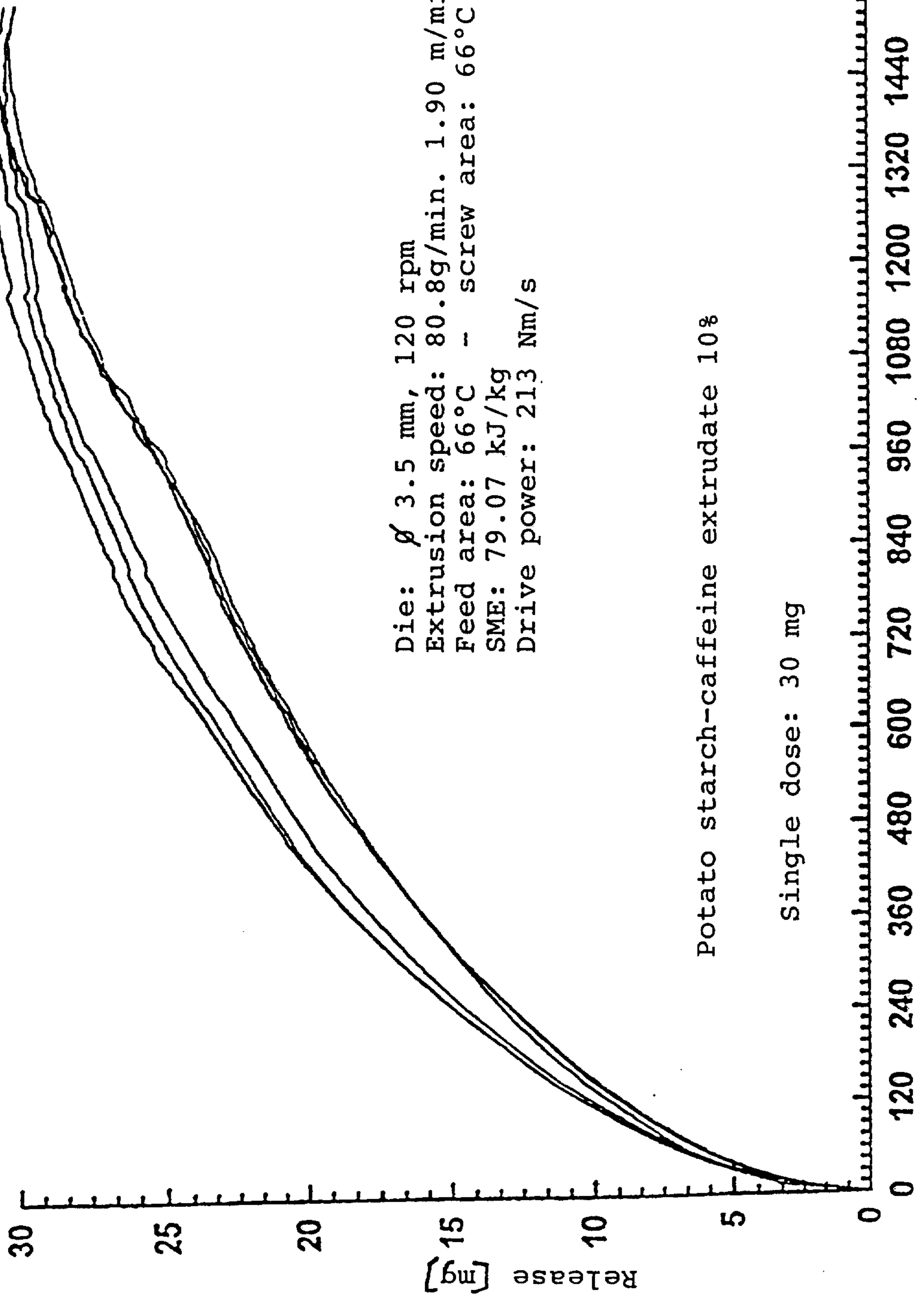
Quantitative course of active agent release of an extrudate made of Eurylon 7 and 30% caffeine



Lapidus graph of the active agent release of an extrudate made of Eurylon 7 and 30% caffeine



Quantitative course of active agent release of an extrudate
made of potato starch and 10% caffeine



Time [min.]

Lapidus graph of the active agent release of an extrudate made of potato starch and 10% caffeine

