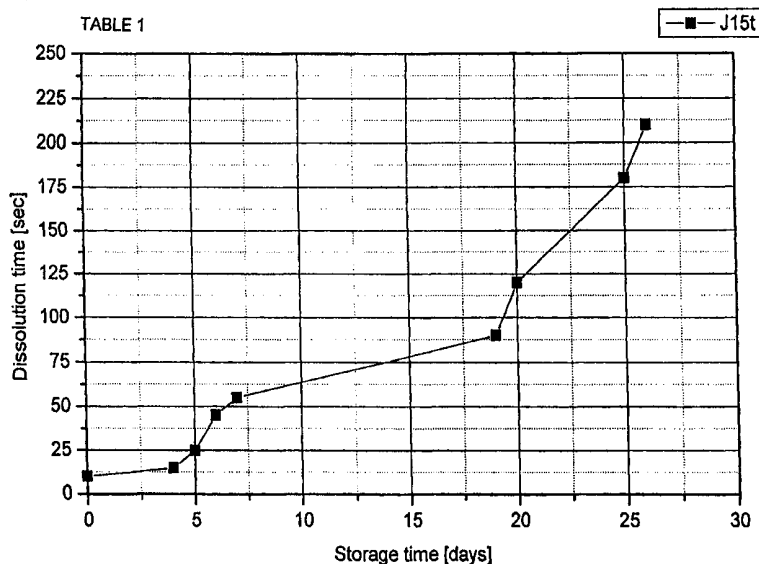




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(54) Title: EFFERVESCENT BASE



(57) Abstract

The effervescent base for the preparation of effervescent tablets and effervescent granules consists of at least one acidic and one gas-evolving component, the former of which is formed by a mixture of (predominantly) monosodium tartrate and (possibly) disodium tartrate, and optionally tartaric acid. The effervescent base is prepared by mixing tartaric acid with sodium bicarbonate and sodium carbonate containing water of crystallization and slowly reacting the mixture at a temperature increasing to about 50 °C, after which further sodium carbonate containing water of crystallization is admixed and is allowed to react up to a temperature of about 60 °C, and drying is then carried out, preferably in vacuo, the mixture is mixed with further, now anhydrous sodium carbonate and the product is optionally pressed to give tablets. The base may additionally comprise an acid sensitive or an alkali-sensitive pharmaceutically active substance.

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Effervescent base

It is known that particularly effervescent granules consisting of citric acid and sodium bicarbonate or sodium carbonate are relatively highly sensitive to atmospheric humidity. This is also true of systems in which sodium citrates are used with alkali metal bicarbonates and/or carbonates.

Effervescent systems which are prepared using monosodium tartrate with alkali metal bicarbonates and/or carbonates are known to have improved properties, especially with respect to the sensitivity to atmospheric humidity. On the other hand, monosodium tartrate is very expensive. Attempts have now been made to produce monosodium tartrate by reacting tartaric acid with sodium carbonate and bicarbonate by means of surface reactions.

Such surface reactions lead to mixed systems comprising monosodium tartrates and disodium tartrates. It has now surprisingly been found that relatively large amounts of monosodium tartrate are formed in surface reactions of this type, and it would have to be assumed that they give very slow effervescent systems.

On the other hand, it has been found that relatively substantial reaction of tartaric acid and resulting relatively large amounts of monosodium tartrate give very rapid effervescent systems which furthermore exhibit previously unknown stability to atmospheric humidity.

It was found, surprisingly, that the tartaric acid, which is converted to monosodium tartrate, with sodium bicarbonate gives surprisingly short dissolution times and in particular is stable to atmospheric humidity of 80% for 6 days or more.

The granules which are produced in the reaction of tartaric acid and sodium bicarbonate and sodium

carbonate were scientifically investigated in order to clearly find out which salts predominantly occur and what is the reason for the insensitivity to moisture.

The preparation principle is based on the fact that tartaric acid is reacted with sodium carbonates having different contents of water of crystallization and sodium bicarbonate at elevated temperatures, the tartaric acid being primarily converted into monosodium tartrate.

The reacted product is dried, preferably by means of vacuum, and although the system may contain a small amount of water of crystallization, it is extremely insensitive to atmospheric humidity with a dissolution time of 20 - 40 seconds. These effervescent granules which on the one hand are highly stable in relation to moisture while on the other hand have excellent dissolution properties were subjected to spectroscopic investigation and possible conclusions were drawn in regard to the reaction procedures.

First of all, IR-spectra of the individual components such as tartaric acid, sodium hydrogen tartrate, di-sodium tartrate and sodium hydrogen carbonate, were measured, which were used for comparisons for the granule material. It was possible to find that the effervescent formulation primarily comprises sodium hydrogen tartrate (monosodium tartrate) and carbonates, that is to say the tartaric acid is almost completely converted into monosodium tartrate and only small amounts are reacted to form di-sodium tartrate under given manufacturing conditions.

In order to substantiate this, the tartaric acid content in tablets and granules was determined gravimetrically after extraction of the tartaric acid with diethyl ether. In the experiments, practically no free tartaric acid or only quite small amounts of it could be isolated, and tartaric acid was also no longer

to be found in the IR-spectra of the tablets and granules.

It is not only the conversion to monosodium tartrate but probably also crystal-chemical reasons that appear to be decisive aspects in terms of the stability of the system in effervescent tablets and the enhanced level of reactivity in regard to dissolution in water.

Preparation process:

370 parts of tartaric acid, 240 parts of sodium bicarbonate and 20 parts of sodium carbonate with 10 molecules of water of crystallization are mixed and are slowly reacted at a temperature increasing from 30°C to 54°C. On reaching about 54°C, a dried sample pressed to give tablets has a dissolution time of 300 seconds with a residual CO₂ content of 10% and a skeletal residue.

Another 25 parts of sodium carbonate with 10 molecules of water of crystallization are then introduced and reacted further up to a temperature of 55-60°C.

A dried sample, pressed to give tablets, has a dissolution time of 30 seconds with a residual CO₂ content of 5.50%. This low content of CO₂ furthermore indicates the very substantial conversion of tartaric acid into sodium tartrates.

After heating to 60°C, vacuum-drying is carried out. The dried mixture is furthermore mixed with anhydrous sodium carbonate in a ratio of 10:1 and has a pH of 4.5 in combination with dissolution times of 20-30 seconds.

The investigations of such tablets in a humidity chamber at 85% relative humidity and at a temperature of 22°C are then extremely surprising. Table 1 shows the change in the dissolution time of tartaric acid

effervescent system J15 according to the invention after storage in the humidity chamber. After 5 days, the dissolution time has scarcely changed and increases to about 100 seconds only after 20 days. It is only from 20 days onwards that the system dramatically slows down (Table 1).

Since the reactivity can also be determined by the change in tablet weight of tartaric acid effervescent system J15 according to the invention on storage in the humidity chamber, it is found that the tablet weight remains virtually unchanged for a storage time of 10 days or more and reaction occurs only after 15 days, the resulting CO₂ reducing the tablet weight (Table 2).

If such a system is compared with passivated citric acid (after preliminary reaction with bicarbonate and superficial conversion into monosodium citrate) in the humidity chamber, an increase in the dissolution time by a factor of about 4 is found after only one day, and the system decomposes after a longer time (Table 3).

The change in the tablet weight of a citric acid system on storage in the humidity chamber also shows the same trend, i.e. these systems are substantially more unstable than the tartaric acid/tartrate system (Table 4).

Furthermore, a comparison with a system consisting of monosodium tartrate and sodium bicarbonate has an initial dissolution time of about 50 seconds and relatively soon - after 2 days storage in the humidity chamber of about 80% relative humidity - of more than 250 seconds (Table 5).

In the humidity chamber at 80% relative humidity, too, the tablet of a sodium tartrate system M1 exhibits, as a result of a reaction and the CO₂

evolved thereby, weight loss and hence a relatively high sensitivity to atmospheric humidity (Table 6).

The use of the acid component according to the invention of an effervescent system mixed with alkali hydrogen carbonates and/or carbonates has also been found to be particularly advantageous for the incorporation of acid-sensitive active substances, such as for example H₂-blockers such as ranitidine and

famotidine. There was found to be a substantially lower tendency - especially also in a stress situation - on the part of the active substances to break down and to form decomposition products.

This system is also suitable for alkali-sensitive active substances in order to produce an effervescent tablet as it only requires small amounts of alkali hydrogen carbonates and/or carbonates in order to achieve rapid dissolution of the effervescent tablet.

Examples:

The effervescent system according to the invention may have a pH of 3.9 to 4.3. Owing to the high dissolution rate, further amounts of sodium bicarbonate and also anhydrous sodium carbonate can also be added in order to avoid residue formation and to achieve a less acid pH for the effervescent tablet.

A final formulation for ranitidine hydrochloride is then as follows:

171 parts by weight of ranitidine hydrochloride,
2443 parts by weight of tartaric acid system according to the invention,
205 parts by weight of sodium bicarbonate,
128 parts by weight of sodium carbonate,
13 parts by weight of aspartame,
10 parts by weight of sodium chloride and
30 parts by weight of solid flavoring agent
are pressed to give tablets having a tablet weight of 3 g.

It must be noted that this dry mixture can be pressed to give hardnesses up to 10 kp, whereas systems which were based on monosodium tartrate can scarcely be pressed with hardnesses above 3 kp without granulation.

The dissolution time is about 60 seconds and the pH 4.5.

Example 2 - Famotidine effervescent tablet

40 parts by weight of famotidine,
1056 parts by weight of tartaric acid effervescent
system according to the invention,
89 parts by weight of sodium bicarbonate,
55 parts by weight of sodium carbonate,
30 parts by weight of sodium cyclamate,
3 parts by weight of saccharin sodium,
87 parts by weight of mannitol and
40 parts by weight of solid flavoring agent
are pressed to give tablets having a tablet weight of
1200 mg.

Dissolution time: about 40 seconds, pH: about
4.5

CLAIMS

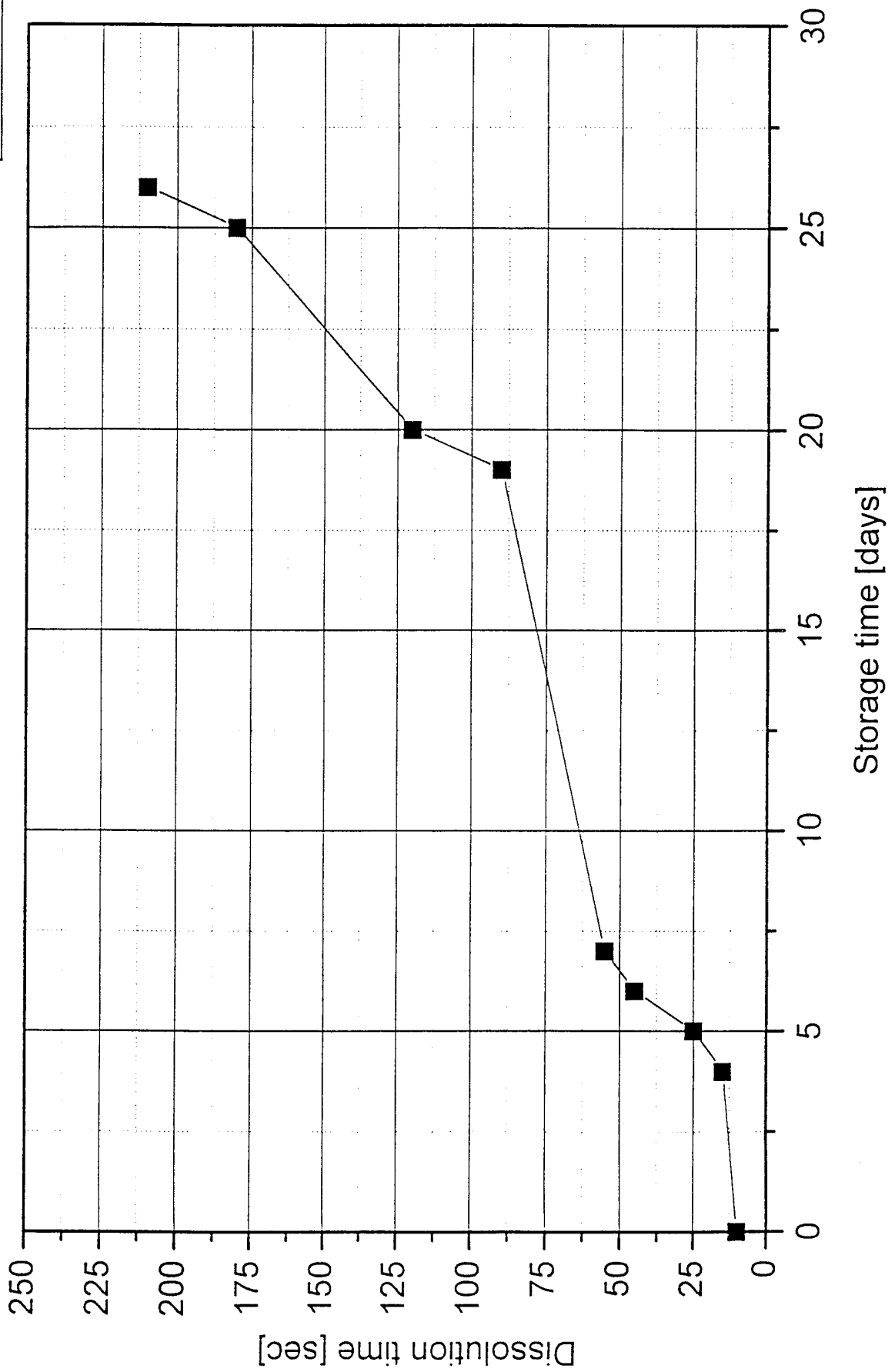
1. An effervescent base for the preparation of effervescent tablets and effervescent granules, consisting of at least one acidic and one gas-evolving component, wherein the acidic component is formed by a mixture of (predominantly) monosodium tartrate and (possibly) disodium tartrate, and optionally tartaric acid.

2. An effervescent base according to claim 1, characterized in that it additionally comprises an acid sensitive or an alkali-sensitive pharmaceutically active substance.

3. A process for the preparation of an effervescent base for the preparation of effervescent tablets and effervescent granules, consisting of at least one acidic and at least one gas-evolving component, wherein tartaric acid is mixed with sodium bicarbonate and sodium carbonate containing water of crystallization and slowly reacted at a temperature increasing to about 50°C, after which further sodium carbonate containing water of crystallization is admixed and is allowed to react up to a temperature of about 60°C, and then drying is carried out, preferably in vacuo, the mixture is mixed with further, now anhydrous sodium carbonate and the product is optionally pressed to give tablets.

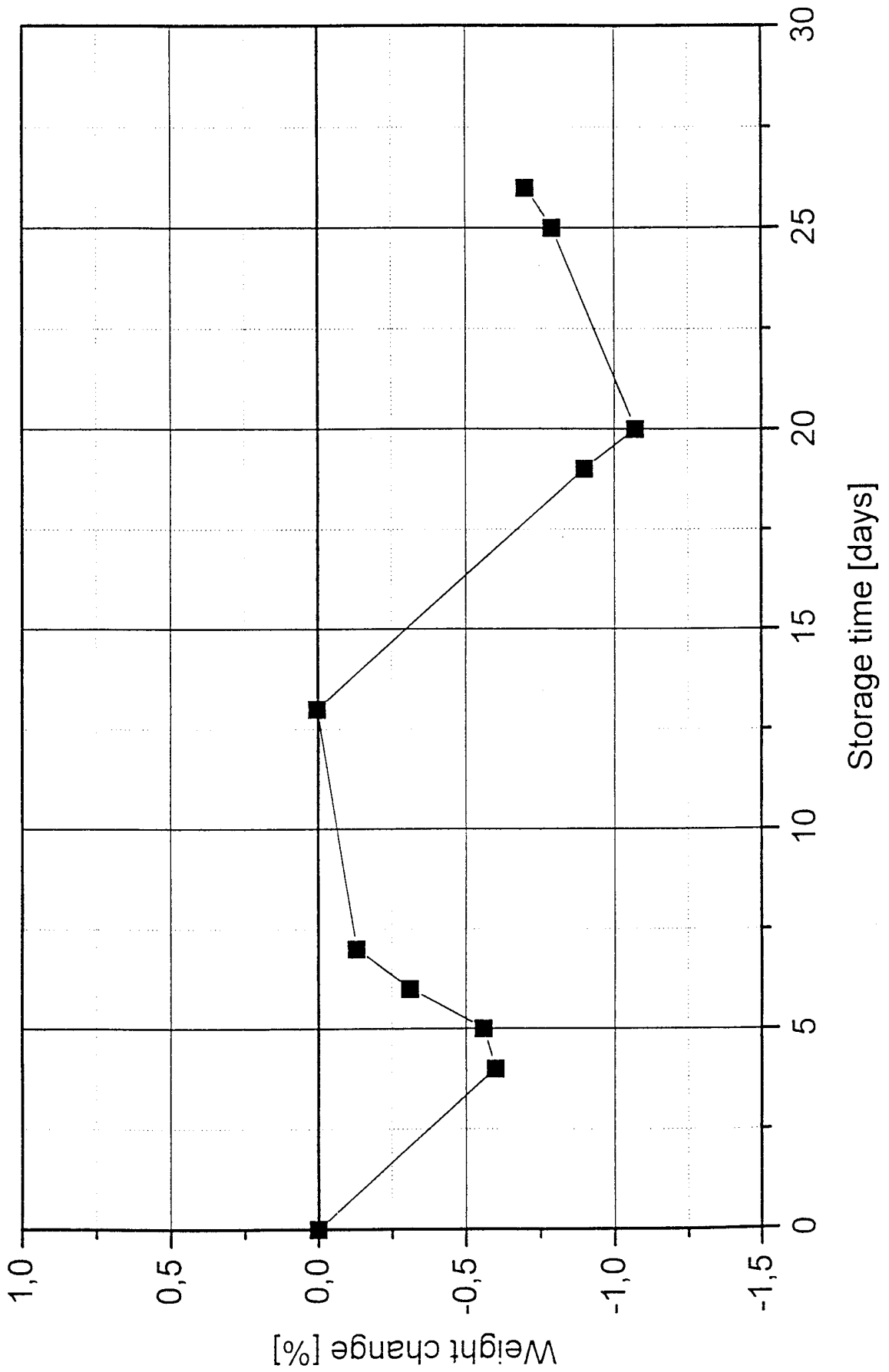
—■— J15t

TABLE 1



—■— J15W

TABLE 2



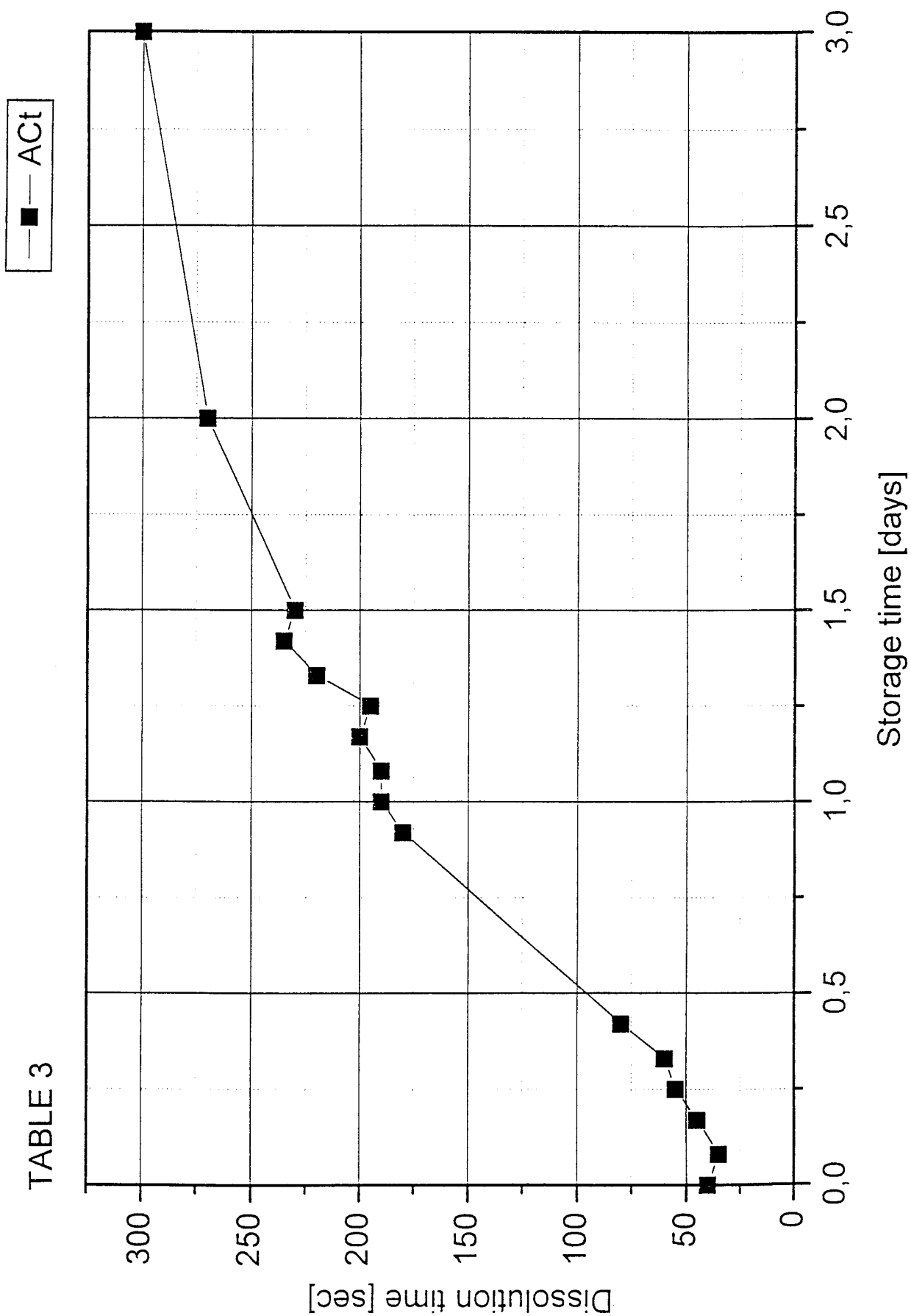
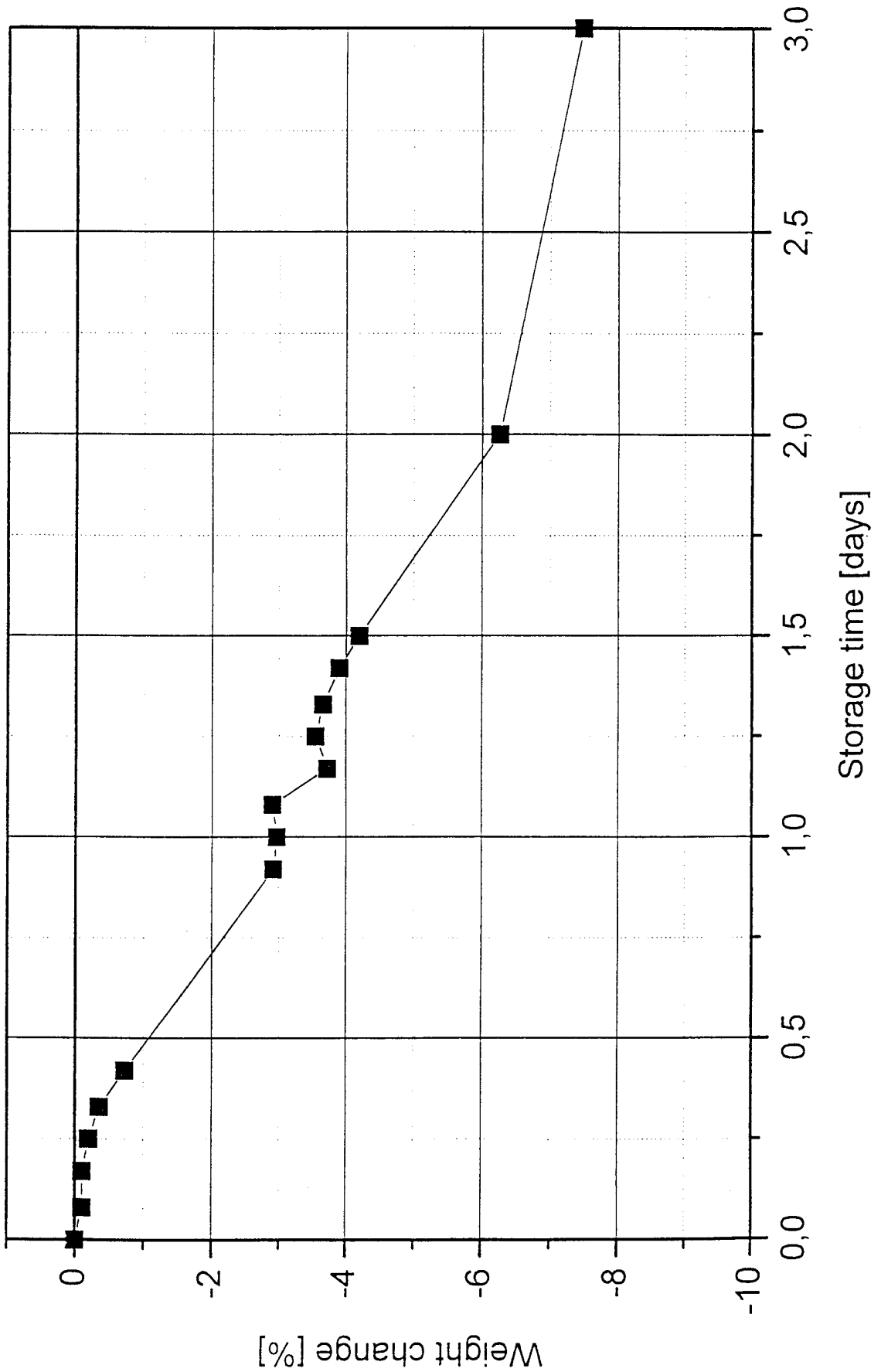
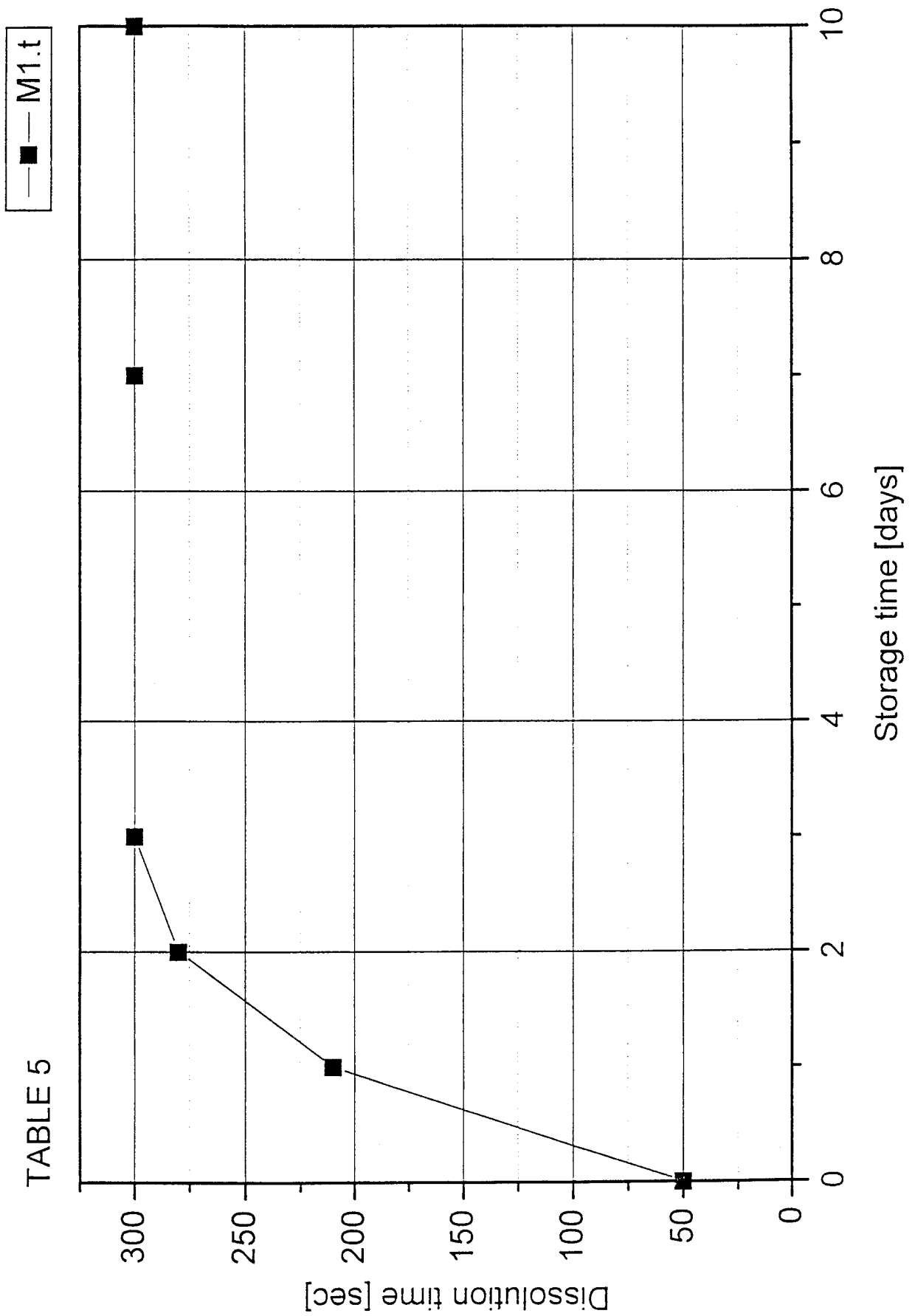


TABLE 4

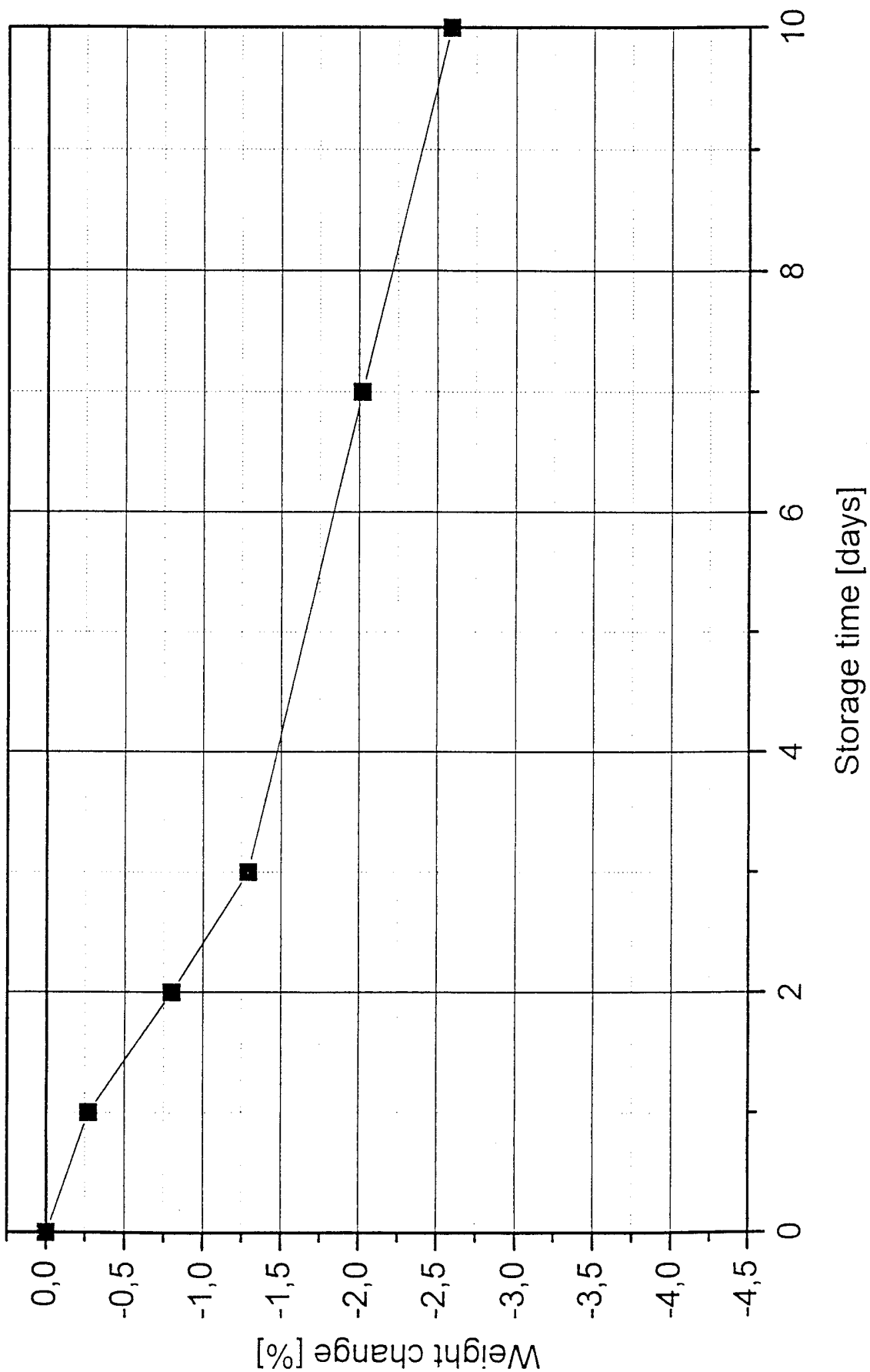
■ ACW





—■— M1.w

TABLE 6



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06663

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 474 040 A (BAYER AG) 11 March 1992 see claims 1,2,11 see example 8 ---	1,2
A	GB 1 269 620 A (WARNER-LAMBERT) 6 April 1972 see the whole document ---	3
A	US 5 415 870 A (GERHARD GERGELY) 16 May 1995 see the whole document ---	3
A	US 5 527 540 A (GERHARD GERGELY) 18 June 1996 see the whole document ---	3
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 603 920 A (DAVID E. RICE) 18 February 1997 see the whole document -----	1,2

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Information on patent family members

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