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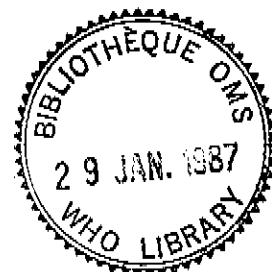
*Drug Stability
 Dosage forms
 Tropical climate 8656*

WHO/PHARM/86.531
 ENGLISH ONLY
 Distr. LIMITED

910.7. Pharmaceuticals Unit

ACCELERATED STABILITY STUDIES
 OF THE DRUGS IN PHARMACEUTICAL
 FORMS UNDER SIMULATED TROPICAL CONDITIONS

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1. Introduction

In continuation of earlier experiments of the stability of widely used pharmaceutical substances*, a further study has been undertaken on the degradation of 20 essential drugs in finished pharmaceutical forms.

The objective of the study is to provide some indications on relative stability of drug substances under simulated tropical conditions. Its results are valid for specific formulations tested (the qualitative composition is indicated in each case). It should be noted that other formulations of the same drug substance may have different stability patterns.

Each dosage form was tested twice; first in its original package (normally blister pack) and secondly without a package. Samples were maintained in an atmosphere of 100 % humidity at 50 °C for 10, 20 and 30 days (condition A), and then at 70 °C for 5 days (condition B).

The extent of degradation was assessed by the same methods as for drug substances.*

* (WHO/PHARM/86.529)

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A simple degradation test was developed to detect gross degradation and was added to degradable dosage forms.

The following comparison shows that pure drug substances and their dosage forms may have different stability characteristics, (d - degradable, nd - nondegradable).

<u>Tested drug</u>	<u>Drug substance</u>	<u>Dosage form</u>
acetylsalicylic acid (tablets)	d	nd
allopurinol (tablets)	nd	nd
amiloride hydrochloride (tablets)	nd	nd
atropine sulfate (injection)	nd	nd
charcoal, activated (powder)	nd	nd
colchicine (tablets)	nd	d
diazepam (injection)	nd	d
digoxin (tablets)	nd	nd
furosemide (tablets)	nd	nd
hydrochlorothiazide (tablets)	nd	nd
ibuprofen (tablets)	nd	nd
indometacin (capsules)	nd	nd
isoprenaline hydrochloride or sulfate (tablets)	d	nd
paracetamol (tablets)	nd	nd
phenytoin (tablets)	nd	nd
procainamide hydrochloride (tablets)	d	d
propranolol hydrochloride (tablets)	nd	nd
sodium nitrite (injection)	d	nd
sodium valproate (tablets)	-	d
spironolactone (tablets)	nd	nd

2. Index of dosage forms tested

acetylsalicylic acid tablets, uncoated and coated

allopurinol tablets

amiloride hydrochloride tablets

atropine sulfate injection

charcoal, activated powder

colchicine tablets

diazepam injection

digoxin tablets

furosemide tablets

hydrochlorothiazide tablets

ibuprofen tablets, coated

indometacin capsules

isoprenaline hydrochloride or sulfate tablets

paracetamol tablets

phenytoin tablets

procainamide hydrochloride tablets

propranolol hydrochloride tablets

sodium nitrite injection

sodium valproate tablets

spironolactone tablets, coated

3. Stability experiments

ACETYLSALICYLIC ACID TABLETS

Two types of tablets containing each 500 mg of acetylsalicylic acid:

- I - tablets with small amounts of pharmaceutical aids.
- II - coated tablets.

Pharmaceutical aids: cellacefate, diethyl or dioctyl phthalate, gelatin, magnesium stearate, polysorbate, polyoxymethylene paratolysulfamate (also known as scuro), starch, sugar, titanium dioxide.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

Formulation I shows no modification after conditions A and B.

The coating of formulation II darkens after heating and becomes more intensely coloured with time; the cores remain unchanged (white).

Thin-layer chromatography

Adsorbent: polyamide 60 F254.

Solution applied to the plate: 10 µl of 1% solutions in water.

Solvent system: chloroform..... 100 volumes
toluene..... 20 volumes
formic acid..... 2 volumes

Detection: UV light at 254 nm.

Results: Below the principal spot, a very weak spot appears corresponding to salicylic acid.

Determination of salicylic acid

Colorimetrically: reaction with iron(III) nitrate.

Results: The content is evaluated at less than 1 %.

Conclusion

With the adopted experimental conditions acetylsalicylic acid tablets are nondegradable, in spite of the darkening of the coating.

ALLOPURINOL TABLETS

Tablets containing 100 mg of allopurinol.

Pharmaceutical aids: corn starch, lactose, magnesium stearate, polyvidone.

The study was performed with samples in the package of origin (bottle) and without the package.

Visual appearance

No modification after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in sodium hydroxide (0.1 mol/l).

Solvent system: butanol saturated with ammonia (5 mol/l).

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of allopurinol

Spectrophotometrically at 250 nm.

Results: The absorption maximum shows no modification and the content is evaluated between 98 and 102 % of the labelled amount.

Conclusion

With the adopted experimental conditions allopurinol tablets are nondegradable.

AMILORIDE HYDROCHLORIDE TABLETS

Tablets containing 5 mg of amiloride hydrochloride.

Pharmaceutical aids: dibasic calcium phosphate, corn starch, lactose, magnesium stearate, tartrazine.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in methanol.

Solvent system: dioxan..... 90 volumes

ammonia (3 mol/l)..... 12 volumes

Detection: UV light at 366 nm followed by the exposure to iodine vapours.

Results: No secondary spots are detected.

Determination of amiloride hydrochloride

Spectrophotometrically: spectrum and absorption at 285 nm of a solution in methanol.

Results: The three absorption maxima show no modifications and the content is evaluated between 100 and 104 % of the labelled amount.

Conclusion

With the adopted experimental conditions amiloride hydrochloride tablets are nondegradable.

ATROPINE SULFATE INJECTION

Injectable solution containing 1 mg of atropine sulfate per ml of a suitable vehicle and made isotonic with sodium chloride.

The study was performed with samples in ampoules of 1 ml.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: Silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions.

Solvent system: acetone..... 90 volumes

water..... 7 volumes

conc. ammonia..... 3 volumes

Detection: Spraying first with iodobismuthate reagent and then with a sodium nitrite solution.

Results: No secondary spots are detected.

Determination of atropine sulfate

Gas-liquid chromatography determined directly on the injectable solution.

Results: No secondary peak is detected. The content is evaluated between 96 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions atropine sulfate injection is nondegradable.

CHARCOAL, ACTIVATED POWDER

Powder of activated charcoal containing 25 % water.

The study was performed with samples without the package.

Visual appearance

No modifications after conditions A and B.

Adsorbing power

Adsorption of phenazone in aqueous medium and after filtration iodometric determination of the nonabsorbed phenazone.

Results: No modification is observed.

Conclusion

With the adopted experimental conditions activated charcoal powder is nondegradable.

COLCHICINE TABLETS

Tablets containing 1 mg of colchicine.

Pharmaceutical aids: erythrosine, lactose, magnesium stearate, polyvidone, sugar.

The study was performed with samples in the package of origin (blister).

Visual appearance

During the study the tablets appear humid and after conditions A and B they become soft and deformed.

Thin-layer chromatography

Adsorbent: 1) alumina F254.
2) silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.05 % solutions in ethanol.

Solvent system: 1) dichloroethane 10 volumes
acetone..... 20 volumes
conc. ammonia..... 0.4 volumes
2) butanol..... 6 volumes
acetic acid..... 2 volumes
water..... 2 volumes

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of colchicine

Extraction with hydrochloric acid (0.1 mol/l) - spectrophotometrically:
spectrum and absorption at 352 nm.

Results: The spectrum shows no modification and the content is
evaluated between 95 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions no degradation of the drug
substance is determined. Though, colchicine tablets become humid in an
atmosphere saturated with water and are therefore, considered degradable.

Degradation test

Colchicine tablets must be hard, dry and not deformed.

DIAZEPAM INJECTION

Injectable solution containing 10 mg of diazepam in 2 ml of a suitable vehicle.

Pharmaceutical aid: benzoic acid, benzyl alcohol, ethanol, propylene
glycol, sodium benzoate, sodium hydroxide

The study was performed with samples in ampoules of 2 ml.

Visual appearance

During the study the solution remains clear but becomes yellow and more
intensely coloured with time.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.
Solution applied to the plate: 5 µl of 0.5 % solutions.
Solvent system: ethyl acetate..... 1 volume
 hexane..... 1 volume
Detection: UV light at 254 nm
Results: Secondary spots appear during the study.

Determination of diazepam

Gas-liquid chromatography using Bondapak C18 as an adsorbent.
Results: Two secondary peaks are detected. The content is evaluated between 95.5 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions diazepam injection is degradable.

Degradation test

The colour of diazepam injection must not be modified.

DIGOXIN TABLETS

Tablets containing 0.25 mg of digoxin.

Pharmaceutical aids: lactose, starch, talc.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.
Solution applied to the plate: Five times 10 µl of 0.01 % solutions in a mixture of equal volumes of ethanol and chloroform.
Solvent system: ethyl acetate..... 80 volumes
 methanol..... 5 volumes
 water..... 5 volumes

Detection: Spraying with a mixture of 15 volumes of a 25 % solution of trichloroacetic acid in ethanol and 1 volume of a 3 % aqueous solution of chloramine, and heating of the plate at 105 °C for 10 minutes. UV light at 366 nm.

Results: No secondary spots are detected.

Conclusion

With the adopted experimental conditions digoxin tablets are nondegradable.

FUROSEMIDE TABLETS

Tablets containing 40 mg of furosemide.

Pharmaceutical aids: corn starch, magnesium stearate, lactose, talc.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 1 % solutions in acetone.

Solvent system: chloroform..... 90 volumes
methanol..... 10 volumes
acetic acid..... 5 volumes

Detection: UV light at 254 and 366 nm, followed by the exposure to iodine vapours.

Results: No secondary spots are detected.

Determination of furosemide

Extraction with sodium hydroxide (0.1 mol/l) and dilution with sodium hydroxide (0.02 mol/l) - spectrophotometrically: spectrum and absorption at 271 nm.

Results: The spectrum shows no modification and the content is evaluated between 97 and 102 % of the labelled amount.

Conclusion

With the adopted experimental conditions furosemide tablets are nondegradable.

HYDROCHLOROTHIAZIDE TABLETS

Tablets containing 25 mg of hydrochlorothiazide.

Pharmaceutical aids: lactose, magnesium stearate, colloidal silica, talc, wheat starch.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.25 % solutions in methanol.

Solvent system: ethyl acetate 98.5 volumes
water..... 1.5 volumes

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of hydrochlorothiazide

Extraction with acetone, hydrolysis in sodium hydroxide (2 mol/l) and colorimetric reaction of the nitrite ion in acid medium with N-(1-naphthylethylenediamine). Absorption at 518 nm.

Results: Taking experimental errors into consideration the content is found to be uniform of the labelled amount.

Conclusion

With the adopted experimental conditions hydrochlorothiazide tablets are nondegradable.

IBUPROFEN TABLETS

Coated tablets containing 400 mg of ibuprofen.

Pharmaceutical aids: acacia, calcium sulfate dihydrate, carmellose sodium, carnauba wax, corn starch, soluble corn starch, erythrosine, ink for inscription, polyvidone, shellac, colloidal silica, stearic acid, sucrose.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.2 % solutions in methanol.

Solvent system: hexane..... 75 volumes
ethyl acetate..... 25 volumes
acetic acid..... 5 volumes

Detection: UV light at 254 nm followed by spraying with a 1 % solution of potassium permanganate in sulfuric acid (1 mol/l), heating at 105 °C and UV light at 366 nm.

Results: No secondary spots are detected.

Determination of ibuprofen

Extraction of the cores with chloroform, titration with sodium hydroxide (0.1 mol/l).

Results: The content is evaluated between 97 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions ibuprofen tablets are nondegradable.

INDOMETACIN CAPSULES

Capsules containing 25 mg of indometacin.

Pharmaceutical aids: lactose, lecithin, magnesium stearate, colloidal silica.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

The content of the capsules show no modifications after conditions A and B, except of a hint of brown coloration after condition B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in ethanol.

Solvent system: chloroform..... 7 volumes
 methanol..... 3 volumes

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of indometacin

Extraction of the content of the capsules with ethanol -
spectrophotometrically: spectrum and absorption at 318 nm.

Results: The spectrum shows no modification and the content is
evaluated between 96 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions indometacin capsules are
nondegradable.

ISOPRENALINE HYDROCHLORIDE

Tablets containing 10 mg of isoprenaline hydrochloride.

Pharmaceutical aids: acacia, lactose, saccharin sodium, sodium sulfite,
starch, talc.

The study was performed with samples in the package of origin (bottles)
and without the package.

Visual appearance

Samples in the package of origin show no modifications after conditions
A and B, whereas the samples in an open dish develop a brown colour that
become more intensely coloured with time.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in methanol.

Solvent system: n-butanol..... 6 volumes
 acetic acid..... 2 volumes
 water..... 2 volumes

Detection: Spraying with a 5 % solution of iron(III) chloride in
ethanol.

Results: No secondary spots are detected.

Determination of isoprenaline hydrochloride

Extraction with water - spectrophotometrically: spectrum and absorption at 279 nm.

Results: The spectrum shows no modification and the content is evaluated between 97 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions isoprenaline hydrochloride tablets are nondegradable.

PARACETAMOL TABLETS

Tablets containing 500 mg of paracetamol.

Pharmaceutical aids: lactose, starch, talc.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.2 % solutions in methanol.

Solvent system: chloroform..... 6 volumes
acetone..... 4 volumes

Detection: UV light at 254 nm followed by spraying with Folin reagent and exposure to ammonia vapours.

Results: No secondary spots are detected.

Determination of paracetamol

Extraction with methanol and hydrochloric acid - spectrophotometrically: spectrum and absorption at 249 nm.

Results: The spectrum shows no modification and the content is evaluated between 98 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions paracetamol tablets are nondegradable.

PHENYTOIN TABLETS

Tablets containing 100 mg of phenytoin.

Pharmaceutical aids: magnesium stearate, mannitol, polyvidone, wheat starch.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 5 µl of 0.2 % solutions in methanol.

Solvent system: chloroform 7 volumes

methanol..... 3 volumes

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of phenytoin

Liquid chromatography using Bondapak C18 as an adsorbent.

Results: No secondary peaks are detected. The content is evaluated between 99 and 103 % of the labelled amount.

Conclusion

With the adopted experimental conditions phenytoin tablets are nondegradable.

PROCAINAMIDE HYDROCHLORIDE TABLETS

Tablets containing 250 mg of procainamide hydrochloride.

Pharmaceutical aids: corn starch, lactose, magnesium stearate, polyvidone, saccharose, stearic acid.

The study was performed with samples in the package of origin (bottles) and without the package.

Visual appearance

During the study yellow-brown spots appear on the surface of the tablets, the size of which increases with time. The edges of the breakline become light yellow veined with brown.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.25 % solutions in methanol.

Solvent system: methanol..... 100 volumes
 conc. ammonia..... 1.5 volumes

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of procainamide hydrochloride

Extraction with sodium hydroxide (0.01 mol/l) - spectrophotometrically: spectrum and absorption at 273 nm.

Results: The spectrum shows no modification and the content is evaluated between 98 and 101 % of the labelled amount.

Conclusion

In spite of the important change observed in the visual appearance of procainamide hydrochloride tablets no degradation is determined of the drug substance. Though the modification of the appearance renders the tablets degradable with the adopted experimental conditions.

Degradation test

Procainamide hydrochloride tablets must be of a uniform white colour.

PROPRANOLOL HYDROCHLORIDE TABLETS

Tablets containing 40 mg of propranolol hydrochloride.

Pharmaceutical aids: alginic acid, gelatin, magnesium stearate, mannitol, stearic acid.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in methanol.

Solvent system: chloroform..... 90 volumes
 methanol..... 10 volumes
 acetic acid..... 5 volumes

Detection: Spraying with a mixture composed of

 p-anisaldehyde..... 0.5 volumes
 acetic acid..... 10 volumes
 methanol..... 85 volumes
 sulfuric acid..... 5 volumes

and heating at 105 °C.

Results: No secondary spots are detected.

Determination of propranolol

Extraction with hydrochloric acid (0.1 mol/l), then after addition of sodium hydroxide extraction into heptane - spectrophotometrically: spectrum and absorption at 293 nm.

Results: The spectrum shows no modification and the content is evaluated between 96 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions propranolol hydrochloride tablets are nondegradable.

SODIUM NITRITE INJECTION

Injectable solution containing 30 mg of sodium nitrite per ml of a suitable vehicle.

The study was performed with samples in ampoules of 10 ml.

Visual appearance

No modifications after conditions A and B.

Determination of sodium nitrite

Colorimetric reaction with iron(II) sulfate - brown colour.

Results: positive, no foreign colour.

Diazo reaction with sulfonamide and naphthylethylenediamine.

Results: The content is evaluated between 94 and 100 % of the labelled amount.

Conclusion

With the adopted experimental conditions sodium nitrite injection is nondegradable.

SODIUM VALPROATE TABLETS

Tablets containing 200 mg of sodium valproate.

Pharmaceutical aids: calcium silicate, cellacefate, corn starch, diethyl phthalate, magnesium stearate, polyoxyethylene glycol 400, polyvidone, talc, titanium oxide.

The study was performed with samples without the package.

Visual appearance

During the study the tablets absorb humidity and the separation of a viscous liquid phase is observed.

Gas-chromatography

Adsorbent: Silanized siliceous earth and impregnated with polyethylene glycol 20000.

Results: No secondary peaks are detected.

Conclusion

With the adopted experimental conditions no degradation was determined of the drug substance. Though in a water saturated atmosphere sodium valproate tablets become humid and their appearance is completely changed, therefore they are considered degradable.

Degradation test

Sodium valproate tablets must be firm and of a white colour.

SPIRONOLACTONE TABLETS

Coated tablets containing 100 mg of spironolactone.

Pharmaceutical aids: acacia, carnauba wax, gelatin, lactose, magnesium stearate, methylpolysiloxane, rice starch, sodium laurilsulfate, spermaceti, sugar, talc, titanium oxide, white wax.

The study was performed with samples in the package of origin (blister) and without the package.

Visual appearance

No modifications after conditions A and B.

Thin-layer chromatography

Adsorbent: silica gel 60 F254.

Solution applied to the plate: 10 µl of 0.1 % solutions in chloroform.

Solvent system: cyclohexane..... 1 volume
ethyl acetate..... 1 volume

Detection: UV light at 254 nm.

Results: No secondary spots are detected.

Determination of spironolactone

Extraction of the cores with toluene, evaporation and dissolving in toluene - spectrophotometrically: spectrum and absorption at 238 nm.

Results: The spectrum shows no modification and the content is evaluated between 96 and 101 % of the labelled amount.

Conclusion

With the adopted experimental conditions spironolactone tablets are nondegradable.

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