APPLICATION FOR A PRODUCT LICENCE:

NIFEDIN DEXCEL 20 RETARD

(NIFEDIPINE)

ATTACHMENT NO. 5,
RELEVANT TO SECTION(S): 9,10,11,12,13,14,15

SUMMARY OF THE PRODUCT CHARACTERISTICS

(all information regarding the above sections is included)

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. TRADE NAME OF THE MEDICINAL PRODUCT

Nifedin DEXCEL 20 Retard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nifedipine 20.0 mg

3. PHARMACEUTICAL FORM

Modified release tablets

Clinical Particulars

4.1 Therapeutic indications

For the treatment of all grades of hypertension and the prophylaxis of angina pectoris.

4.2 Posology and method of administration

The recommended dose of Nifedin DEXCEL 20 Retard tablets is one tablet (20 mg) twice-daily swallowed with a little fluid, with subsequent titration of dosage according to response. The dosage may be adjusted within the range 10* mg twice daily to 40 mg twice-daily.

Nifedipine is metabolized primarily in the liver. It is therefore recommended that patients with liver dysfunction should commence therapy with 10* mg twice-daily, with careful monitoring. Patients with renal impairment should not require adjustment of dosage.

A slight alteration of the pharmacokinetics of nifedipine may be seen in the elderly. Lower maintenance doses of nifedipine may be required compared to younger patients. Nifedipine is not recommended for use in children. Treatment may be continued indefinitely.

*A 10 mg dosage of Nifedin DEXCEL Retard tablets is available.

4.3 Contra-indications

Nifedipine should not be administered to patients with known hypersensitivity to nifedipine, or other dihydropyridines because of the theoretical risk of cross-reactivity. Nifedipine should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

Nifedipine should not be used for the treatment of acute attacks of angina.

The safety of nifedipine in malignant hypertension has not been established. Nifedipine should not be used for the secondary prevention of myocardial infarction.

4.4 Special warnings and special precautions for use

Nifedipine should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed. Caution should be exercised in patients with severe hypotension.

Cardiac ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of nifedipine therapy. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur. Diabetic patients taking Nifedin DEXCEL 20 Retard may require adjustment of their control.

4.5 Interaction with other medicaments and other forms of interaction

Nifedipine may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Nifedipine will not prevent possible rebound effects after cessation of other antihypertensive therapy.

The antihypertensive effect of nifedipine may be potentiated by simultaneous administration of cimetidine.

When used in combination with nifedipine, serum quinidine levels have been shown to be suppressed regardless of dosage of quinidine. The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in the plasma digoxin level. Plasma digoxin levels should be monitored and, if necessary, the digoxin dose reduced.

Diltiazem decreases the clearance of nifedipine and hence increases plasma nifedipine levels. Therefore, caution should be taken when both drugs are used in combination and a reduction of the nifedipine dose may be necessary.

Nifedipine should not be administered concomitantly with rifampicin, since effective plasma levels of nifedipine may not be achieved owing to enzyme induction. As with other dihydropyridines, nifedipine should not be taken with grapefruit juice because bioavailability is increased.

4.6 Pregnancy and lactation

Nifedipine should not be administered to women capable of child-bearing, to pregnant women or to nursing mothers.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Most side-effects are consequences of the vasodilatory effects of nifedipine. Headache, flushing, tachycardia and palpitations may occur, particularly on commencement of treatment with nifedipine. Gravitational oedema not associated with heart failure or weight gain has been observed. Exacerbation of angina pectoris may occur rarely at the start of treatment with sustained release formulations of nifedipine.

Paraesthesia, dizziness, lethargy, and gastro-intestinal symptoms such as nausea and altered bowel habit may occur occasionally. There have been reports of skin reactions such as rash, pruritus and urticaria.

Other less frequently reported side-effects include myalgia, tremor and visual disturbances.

Increased frequency of micturition may occur. There are reports of gingival hyperplasia and, in older men on long-term therapy, gynaecomastia, which usually regress upon withdrawal of therapy. Mood changes may occur rarely.

Rare cases of hypersensitivity-type jaundice have been reported. In addition, disturbances of liver function such as intra-hepatic cholestasis may occur. These regress after discontinuation of therapy.

Side effects which may occur in isolated cases include photosensitivity, exfoliative dermatitis, systemic allergic reactions and purpura. Usually, these regress after discontinuation of the drug.

4.9 Overdose

Clinical effects: Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilatation, and tachycardia or bradycardia are the most likely manifestations of overdose.

Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo-or hyper-kalaemia. Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.

Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia and unconsciousness to the point of coma.

Treatment: As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardio-vascular conditions have priority. After oral ingestion, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Particularly in cases of intoxication with slow release products, elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. Activated charcoal should be given, 50 g for adults, 10-15 g for children. If a sustained release preparation has been taken, activated charcoal should be given in 4-hourly doses of 25 g for adults, 10 g for children. Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilatation should be treated with elevation of the feet and plasma expanders. If these measures are ineffective, hypotension may be treated with 10% calcium glucon10-20 ml intravenously over 5-10 minutes. If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition beta-sympathomimetics may be given, e.g. isoprenaline 0.2 mg slowly i.v. or as a continuous infusion of 5 µg/min. If an insufficient increase in blood pressureis achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

Pharmacological Properties

5.1 Pharmacodynamic properties

Nifedipine is a specific and potent calcium-channel blocker. Calcium-channel blockers inhibit the transmembrane influx of calcium ions into vascular smooth muscle.

In common with the other calcium blockers, nifedipine reduces peripheral vasodilatation and thus reduces peripheral vascular resistance and lowers blood pressure. Nifedipine is used as an anti-anginal agent because it both relieves coronary artery spasm, of particular importance in variant angina, and, more importantly, improves exertional angina by reducing vascular

peripheral resistance and thus myocardial oxygen demand. Compared with the other classes of calcium-channel blockers, nifedipine and similar dihydropyridines are more vasoselective. In other words, nifedipine exerts the least depressant effect on the myocardium and on the cardiac conduction in whole animals and in patients.

No negative inotropism or slowing of the sinus rate or AV conduction are observed with nifedipine. Nifedipine has no anti-arrhythmic activity.

5.2 Pharmacokinetic properties

Nifedipine is rapidly and fully (close to 100%) absorbed after oral administration, but has relatively low bioavailability (of 45%-68%) as a result of an extensive first pass effect. Nifedipine is highly bound to plasma proteins (90-98%), particularly to albumin. Nifedipine undergoes oxidation by hepatic cytochrome P-450 to form inactive metabolites. Studies on healthy volunteers have revealed that there is an intersubject variability when nifedipine is administered orally, whereas intraindividual variability is relatively small.

About 70-80% of the dose is eliminated in the urine. The elimination half- life of the drug after an oral dose varies between 6-11 hours. The half life of nifedipine in the plasma of healthy volunteers and in patients with normal liver function is about 2 hours. Liver disease reduces the clearance of nifedipine, while renal function does not participate significantly in nifedipine clearance.

5.3 Preclinical safety data

Nifedipine is a well-established drug for which there is adequate published safety data.

Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose, lactose, pregelatinized starch, colloidal anhydrous silica, polysorbate 20, magnesium stearate, Opadry OY-S-24932, carnauba wax.

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C, protected from light.

6.5 Nature and contents of container

The tablets are presented in aluminium/red-PVC blisters, strips of which are contained within a printed cardboard carton.

6.6 Instructions for use/handling

No specific statement

APPLICATION FOR A PRODUCT LICENCE:

NIFEDIN DEXCEL 20 RETARD

(NIFEDIPINE)

ATTACHMENT NO. 6,
RELEVANT TO SECTION(S): 16

ANALYTICAL METHOD OF EACH INGREDIENT

NIFEDIN DEXCEL 20 RETARD TABLETS

ANALYTICAL METHOD FOR EACH INGREDIENT

INDEX

NIFEDIN DEXCEL 20 RETARD TABLETS

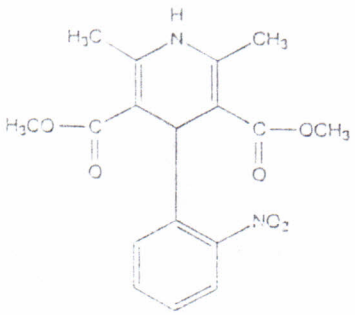
SECTION 16: ANALYTICAL METHOD OF EACH INGREDIENT

1. ROUTINE TESTING METHODS FOR THE RAW MATERIALS:

Constituent:	Complies with Monograph(s):	Data Enclosed on Page(s):
Nifedipine	PH.EUR.	98-99
Microcrystalline cellulose	PH.EUR.	100
Lactose	PH.EUR.	101
Pregelatinized starch	PH.EUR.	102
Colloidal anhydrous silica	PH.EUR.	103
Polysorbate 20	PH.EUR.	104
Magnesium stearate	PH.EUR.	105
Carnauba wax	PH.EUR.	106
Purified water	PH.EUR.	107
Opadry OY-S-24932	IN-HOUSE	108-110

NIFEDIPINE

Nifedipinum



$C_{17}H_{18}N_2O_6$ M_r 346.3

DEFINITION

Nifedipine contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate, calculated with reference to the dried substance.

CHARACTERS

A yellow, crystalline powder, practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol. When exposed to daylight and to artificial light of certain wavelengths, it readily converts to a nitrosophenylpyridine derivative. Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative. Prepare solutions immediately before use in the dark or under long-wavelength light (> 420 nm) and protect them from light.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 171 °C to 175 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *nifedipine CRS*. Examine the substances in the solid state.

C. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 10 mg of *nifedipine CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Apply separately to the plate 5 µl of each solution. Develop in an unsaturated tank over a path of 15 cm using a mixture of 40 volumes of *ethyl acetate R* and 60 volumes of *cyclohexane R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position, appearance at 254 nm and size to the principal spot in the chromatogram obtained with reference solution.

D. To 25 mg in a test tube, add 10 ml of a mixture of 1.5 volumes of *hydrochloric acid R*, 3.5 volumes of *water R* and 5 volumes of *alcohol R* and dissolve with gentle heating. Add 0.5 g of *zinc R* in granules and allow to stand for 5 min with occasional swirling. Filter into a second test tube, add 5 ml of a 10 g/l solution of *sodium nitrite R* to the filtrate and allow to stand for 2 min. Add 2 ml of a 50 g/l solution of *ammonium sulphamate R*, shake vigorously with care and add 2 ml of a 5 g/l solution of *naphthylethylenediamine dihydrochloride R*. An intense red colour develops which persists for not less than 5 min.

TESTS

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.200 g of the substance to be examined in 20 ml of *methanol R* and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 10 mg of *nifedipine impurity A CRS* in *methanol R* and dilute to 25.0 ml with the same solvent.

Reference solution (b). Dissolve 10 mg *nifedipine impurity B CRS* in *methanol R* and dilute to 25.0 ml with the same solvent.

Reference solution (c). Mix 1.0 ml of reference solution (a), 1.0 ml of reference solution (b) and 0.1 ml of the test solution and dilute to 20.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 10.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

- a stainless steel column 0.15 m long and 4.6 mm in internal diameter, packed with *octadecylsilyl silica gel for chromatography R* (5 µm),
- as mobile phase at a flow rate of about 1.0 ml per minute a mixture of 9 volumes of *acetonitrile R*, 36 volumes of *methanol R* and 55 volumes of *water R*,
- as detector a spectrophotometer set at 235 nm; the use of an electronic integrator is advisable.

Inject 20 µl of reference solution (c). When the chromatogram is recorded in the conditions described above, the substances elute in the following order: impurity A, impurity B and nifedipine; the retention time of nifedipine is about 15.5 min. The test is not valid unless in the chromatogram obtained with reference solution (c): the resolution between the peaks corresponding to impurity A and impurity B is greater than 1.5; the resolution between the peaks corresponding to impurity B and nifedipine is greater than 1.5; the peak corresponding to impurity A has a height not less than 20 per cent of the full scale deflection of the recorder. Inject separately 20 µl of the test solution and of reference

solution (c) and record the chromatograms for twice the retention time of nifedipine. In the chromatogram obtained with the test solution: none of the peaks apart from the principal peak and the peaks corresponding to impurity A and impurity B has an area greater than that of the peak corresponding to nifedipine in the chromatogram obtained with reference solution (c) (0.1 per cent); the areas of the peaks corresponding to impurity A and impurity B are not greater than the corresponding peaks in the chromatogram obtained with reference solution (c) (0.1 per cent); the total amount of related substances does not exceed 0.3 per cent. Disregard any peak whose area is less than 10 per cent of the area of the peak corresponding to nifedipine in the chromatogram obtained with reference solution (c).

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C for 2 h.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.1300 g in a mixture of 25 ml of *2-methyl-2-propanol R* and 25 ml of *perchloric acid solution R*. Titrate with *0.1 M ammonium and cerium sulphate* using 0.1 ml of *ferroin R* as indicator, until the pink colour disappears. Titrate slowly towards the end of the titration. Carry out a blank titration.

1 ml of *0.1 M ammonium and cerium sulphate* is equivalent to 17.32 mg of $C_{17}H_{18}N_2O_6$.

STORAGE

Store protected from light.

IMPURITIES

A. Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (nitrophenylpyridine analogue),

B. Dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (nitrosophenylpyridine analogue).

* Column: Eurospher C18

** Mobile phase: Acetonitrile: Methanol: Water =
= 180 : 320 : 500.

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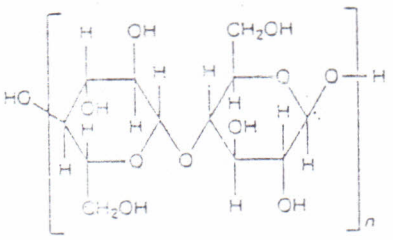
CELLULOSE, MICROCRYSTALLINE

Cellulosum microcristallinum



DEFINITION

Microcrystalline cellulose is a purified, partly depolymerised cellulose prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

CHARACTERS

A white or almost white, fine or granular powder, practically insoluble in water, in acetone, in ethanol, in toluene and in dilute acids and in a 50 g/l solution of sodium hydroxide.

IDENTIFICATION

A. Place about 10 mg on a watch-glass and disperse in 2 ml of *iodinated zinc chloride solution R*. The substance becomes violet-blue.

B. Transfer 1.300 g to a 125 ml conical flask. Add 25.0 ml of *water R* and 25.0 ml of *1 M cupriethylenediamine hydroxide solution*. Immediately purge the solution with *nitrogen R*, insert the stopper and shake until completely dissolved. Transfer 7.0 ml of the solution to a suitable capillary viscometer (*2.2.9*). Equilibrate the solution at 25 ± 0.1 °C for not less than 5 min. Record the flow time, t_1, in seconds, between the two marks on the viscometer. Calculate the kinematic viscosity ν_1 of the solution using the formula:

$$t_1(k_1),$$

where k_1 is the viscometer constant.

Dilute a suitable volume of *1 M cupriethylenediamine hydroxide solution* with an equal volume of *water R* and measure the flow time, t_2, using a suitable capillary viscometer. Calculate the kinematic viscosity ν_2 of the solvent using the formula:

$$t_2(k_2),$$

where k_2 is the viscometer constant.

Determine the relative viscosity η_{rel} of the substance to be examined using the formula:

$$\eta_1 / \eta_2$$

Determine the intrinsic viscosity, $[\eta]c$, by interpolation, using the Intrinsic Viscosity Table (Table 315-1 see Cellulose, powdered).

Calculate the degree of polymerisation P using the formula:

$$\frac{95[\eta]c}{m\left[\left(100-b\right)/100\right]}$$

where m is the mass in grams, of the substance to be examined and b is the loss on drying as a percentage.

The degree of polymerisation is not more than 350.

TESTS

Solubility. Dissolve 50 mg in 10 ml of *ammoniacal solution of copper tetrammine R*. It dissolves completely, leaving no residue.

pH (*2.2.3*). Shake 5 g with 40 ml of *carbon dioxide-free water R* for 20 min and centrifuge. The pH of the supernatant liquid is 5.0. to 7.5.

Ether-soluble substances. Prepare a column using 10.0 g in a tube about 20 mm in internal diameter. Pass 50 ml of *peroxide-free ether R* through the column. Evaporate the eluate to dryness. The residue weighs not more than 5.0 mg (0.05 per cent).

Water-soluble substances. Shake 5.0 g with 80 ml of *water R* for 10 min. Filter with the aid of vacuum into a tared flask. Evaporate to dryness on a water-bath and dry at 100 °C to 105 °C for 1 h. The residue weighs not more than 12.5 mg (0.25 per cent).

Starch. To 10 g add 90 ml of *water R* and boil for 5 min. Filter whilst hot. Cool and add to the filtrate 0.1 ml of *0.05 M iodine*. No blue colour is produced.

Heavy metals (*2.4.8*). 2.0 g complies with limit test C for heavy metals (10 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

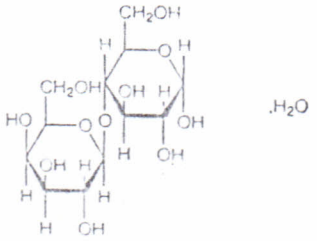
Loss on drying (*2.2.32*). Not more than 6.0 per cent, determined on 1.0 g by drying in an oven at 100 °C to 105 °C for 3 h.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^3 micro-organisms per gram and with a limit for fungi of 10^2 per gram, determined by plate-count. It complies with the tests for *Escherichia coli*, for *Pseudomonas aeruginosa*, for *Staphylococcus aureus* and for *Salmonella* (*2.6.13*).

LACTOSE MONOHYDRATE

Lactosum monohydricum



$C_{12}H_{22}O_{11},H_2O$ M_r 360.3

DEFINITION

Lactose monohydrate is the monohydrate of *O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose. It may be modified as to its physical characteristics and may contain varying proportions of amorphous lactose.

CHARACTERS

A white or almost white, crystalline powder, freely but slowly soluble in water, practically insoluble in alcohol.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *lactose CRS*.

B. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 10 mg of the substance to be examined in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (a). Dissolve 10 mg of *lactose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (b). Dissolve 10 mg each of *fructose CRS, glucose CRS, lactose CRS* and *sucrose CRS* in a mixture of 2 volumes of *water R* and 3 volumes of *methanol R* and dilute to 20 ml with the same mixture of solvents.

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[illegible] of each solution and thoroughly dry the starting points. Develop over a path of 15 cm using a mixture of 10 volumes of *water R*, 15 volumes of *methanol R*, 25 volumes of *anhydrous acetic acid R* and 50 volumes of *ethylene chloride R*, measured accurately since a slight excess of water produces cloudiness. Dry the plate in a current of warm air. Repeat the development immediately, after renewing the mobile phase. Dry the plate in a current of warm air and spray evenly with a solution of 0.5 g of *thymol R* in a mixture of 5 ml of *sulphuric acid R* and 95 ml of *alcohol R*. Heat at 130 °C for 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows four clearly separated spots.

C. Dissolve 0.25 g in 5 ml of *water R*. Add 5 ml of *ammonia R* and heat in a water-bath at 80 °C for 10 min. A red colour develops.

D. It complies with the test for water (see tests).

TESTS

Appearance of solution. Dissolve 1.0 g in *water R*, heating to 50 °C, dilute to 10 ml with the same solvent and allow to cool. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*Method II, 2.2.2*).

Acidity or alkalinity. Dissolve 6.0 g by boiling in 25 ml of *carbon dioxide-free water R*, cool and add 0.3 ml of *phenolphthalein solution R*. The solution is colourless. Not more than 0.4 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*). Dissolve 10.0 g in 80 ml of *water R*, heating to 50 °C. Allow to cool and add 0.2 ml of *dilute ammonia R1*. Allow to stand for 30 min and dilute to 100.0 ml with *water R*. The specific optical rotation is + 54.4° to + 55.9°, calculated with reference to the anhydrous substance.

Absorbance (*2.2.25*). Dissolve 1.0 g in boiling *water R* and dilute to 10.0 ml with the same solvent (solution A). The absorbance of the solution measured at 400 nm is not greater than 0.04. Dilute 1.0 ml of solution A to 10.0 ml with *water R*. Examine the solution from 210 nm to 300 nm. At wavelengths from 210 nm to 220 nm, the absorbance is not greater than 0.25. At wavelengths from 270 nm to 300 nm, the absorbance is not greater than 0.07.

Heavy metals (*2.4.8*). Dissolve 4.0 g in *water R* with warming, add 1 ml of *0.1 M hydrochloric acid* and dilute to 20 ml with *water R*. 12 ml of the solution complies with limit test A for heavy metals (5 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*). 4.5 per cent to 5.5 per cent, determined on 0.50 g by the semi-micro determination of water, using a mixture of 1 volume of *formamide R* and 2 volumes of *methanol R* as the solvent.

Sulphated ash. Not more than 0.1 per cent. To 1.0 g add 1 ml of *sulphuric acid R*, evaporate to dryness on a water-bath and ignite to constant mass.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^2 micro-organisms per gram, determined by plate-count. It complies with the test for *Escherichia coli* (*2.6.13*).

STORAGE

Store in an airtight container.

STARCH, PREGELATINISED

p. 882 - 883

Amylum pregelificatum

DEFINITION

Pregelatinised starch is starch, apart from wheat starch, that has been mechanically processed in the presence of water, with or without heat to rupture all or part of the starch granules and subsequently dried. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics.

CHARACTERS

A white or yellowish-white powder, swelling in cold water.

IDENTIFICATION

A. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R* it presents irregular, translucent, white or yellowish-white flakes or pieces with an uneven surface. Under polarised light (between crossed nicol prisms), starch granules with a distinct black cross intersecting at the hilum may be seen.

B. Disperse 0.5 g in 2 ml of *water R* without heating and add 0.05 ml of *iodine solution R1*. A reddish-violet to blue colour is produced.

TESTS

pH (*2.2.3*). Shake 5.0 g with 25.0 ml of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min. The pH of the solution is 4.5 to 7.0.

Iron (*2.4.9*). Shake 0.75 g with 15 ml of *dilute hydrochloric acid R*. Filter. The filtrate complies with the limit test for iron (20 ppm).

Oxidising substances (*2.5.30*). It complies with the test for oxidising substances.

Sulphur dioxide (*2.5.29*). Not more than 50 ppm.

Foreign matter (*2.8.2*). Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R*, not more than traces of cell walls and of cytoplasmic residues are present.

Loss on drying (*2.2.32*). Not more than 15.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulphated ash (*2.4.14*). Not more than 0.6 per cent, determined on 1.0 g.

Microbial contamination. Not more than 10^3 bacteria and not more than 10^2 fungi per gram, determined by plate-count (*2.6.12*). It complies with the test for *Escherichia coli* (*2.6.13*).

STORAGE

Store in a well-closed container.

LABELLING

The herbal origin of starch, pregelatinised is stated.

Ph. Eur, p. 1469
3d. add.

1997:0434

SILICA, COLLOIDAL ANHYDROUS

Silica colloidalis anhydrica

SiO_2 M_r 60.1

DEFINITION

Colloidal anhydrous silica contains not less than 99.0 per cent and not more than the equivalent of 100.5 per cent of SiO_2, determined on the ignited substance.

CHARACTERS

A light, fine, white, amorphous powder, with a particle size of about 15 nm, practically insoluble in water and in mineral acids except hydrofluoric acid. It dissolves in hot solutions of alkali hydroxides.

IDENTIFICATION

About 20 mg gives the reaction of silicates (*2.3.1*).

TESTS

pH (*2.2.3*). Shake 1.0 g with 30 ml of *carbon dioxide-free water R*. The pH of the suspension is 3.5 to 5.5.

Chlorides (*2.4.4*). To 1.0 g add a mixture of 20 ml of *dilute nitric acid R* and 30 ml of *water R* and heat on a water-bath for 15 min, shaking frequently. Dilute to 50 ml with *water R* if necessary, filter and cool. 10 ml of the filtrate diluted to 15 ml with *water R* complies with the limit test for chlorides (250 ppm).

Heavy metals (*2.4.8*). Suspend 2.5 g in sufficient *water R* to produce a semi-fluid slurry. Dry at 140 °C. When the dried substance is white, break up the mass with a glass rod. Add 25 ml of *1 M hydrochloric acid* and boil gently for 5 min, stirring frequently with the glass rod. Centrifuge for 20 min and filter the supernatant liquid through a membrane filter. To the residue in the centrifuge tube add 3 ml of *dilute hydrochloric acid R* and 9 ml of *water R* and boil. Centrifuge for 20 min and filter the supernatant liquid through the same membrane filter. Wash the residue with small quantities of *water R*, combine the filtrates and washings and dilute to 50 ml with *water R*. To 20 ml of the solution add 50 mg of *ascorbic acid R* and 1 ml of *concentrated ammonia R*. Neutralise with *dilute ammonia R2*. Dilute to 25 ml with *water R*. 12 ml of the solution complies with limit test A for heavy metals (25 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Loss on ignition. Not more than 5.0 per cent, determined on 0.200 g by ignition in a platinum crucible at 900 °C for 2 h. Allow to cool in a desiccator before weighing.

ASSAY

To the residue obtained in the test for loss on ignition add 0.2 ml of *sulphuric acid R* and sufficient *alcohol R* to moisten the residue completely. Add 6 ml of *hydrofluoric acid R* and evaporate to dryness on a hot-plate at 95 °C to 105 °C, taking care to avoid loss from sputtering. Wash down the sides of the dish with 6 ml of *hydrofluoric acid R* and evaporate to dryness. Ignite at 900 °C, allow to cool in a desiccator and weigh.

The difference between the mass of the final residue and the mass of the residue obtained in the test for loss on ignition gives the amount of SiO_2 in the quantity of the substance to be examined used.

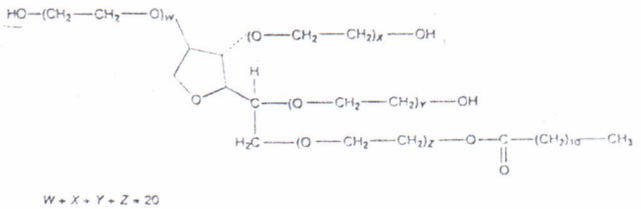
אושר ע"י מנהלת המעבדה
חתימה
23.12.97 תאריך

Eur. Ph. 3rd ed. 1997 - pages: 1353-1354

1997:0426

POLYSORBATE 20

Polysorbatum 20



$W + X + Y + Z = 20$

DEFINITION

Polysorbate 20 is a mixture of partial lauric acid esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. The lauric acid used for the esterification may contain other fatty acids.

CHARACTERS

An oily, yellowish or brownish-yellow, clear or slightly opalescent liquid, miscible with water, with ethanol, with ethyl acetate and with methanol, practically insoluble in fatty oils and in liquid paraffin.

It has a relative density of about 1.10.

IDENTIFICATION

A. Dissolve 0.5 g in *water R* at about 50 °C and dilute to 10 ml with the same solvent. The solution produces a copious foam on shaking. Add 0.5 g of *sodium chloride R* and heat the solution to boiling. The resulting cloudiness disappears during cooling to about 50 °C.

B. To 4 g add 40 ml of a 50 g/l solution of *potassium hydroxide R* and boil under a reflux condenser in a water-bath for 30 min. Allow to cool to about 80 °C, add 20 ml of *dilute nitric acid R* and boil under a reflux condenser for about 10 min to break the emulsion. Fatty acid separates on the surface as an oily liquid. Allow to cool to room temperature. Transfer the fatty acid to a separating funnel with the aid of 50 ml of *light petroleum R*, avoiding vigorous shaking. Wash the organic layer with three quantities, each of 5 ml, of *water R*. Evaporate the organic layer to dryness on a water bath. The acid value (*2.5.1*) of the residue is 245 to 300, determined on 0.30 g.

C. Dissolve 0.1 g in 5 ml of *chloroform R*. Add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R*. Stir with a glass rod. The solution becomes blue.

TESTS

Acid value (*2.5.1*). Not more than 2.0, determined on 5.0 g dissolved in 50 ml of the prescribed mixture of solvents.

Hydroxyl value (*2.5.3*). 96 to 108, determined on 2.0 g (Method A).

Iodine value (*2.5.4*). Not more than 5.0.

Saponification value (*2.5.6*). 40 to 50, determined on 2.0 g. Use 15.0 ml of *0.5 M alcoholic potassium hydroxide* and dilute with 50 ml of *alcohol R* before carrying out the titration.

Reducing impurities. Dissolve 2.00 g in 25 ml of hot *water R* and add 25 ml of *dilute sulphuric acid R* and 0.1 ml of *ferroin R*. Titrate with *0.01 M ammonium and cerium nitrate*, shaking continuously, until the colour change from red to greenish-blue persists for 30 s. Carry out a blank titration. Not more than 2.0 ml of *0.01 M ammonium and cerium nitrate* is required.

Heavy metals (*2.4.8*). 2.0 g complies with limit test C for heavy metals (10 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*). Not more than 3.0 per cent, determined on 1.00 g by the semi-micro determination of water.

Sulphated ash (*2.4.14*). Not more than 0.2 per cent. To 2.00 g in a silica or platinum crucible add 0.5 ml of *sulphuric acid R* and heat on a water bath for 2 h. Carefully ignite at a low temperature until thoroughly charred. Add to the carbonised mass 2 ml of *nitric acid R* and 0.25 ml of *sulphuric acid R*, cautiously heat until white fumes are evolved and ignite at 600 °C until all black particles have disappeared. Allow to cool, weigh and repeat the ignition for periods of 15 min to constant mass.

STORAGE

Store in an airtight container, protected from light.

1997:0229

MAGNESIUM STEARATE

Magnesii stearas

DEFINITION

Magnesium stearate [$(C_{17}H_{35}COO)_2Mg$; M_r 591.3] may contain varying proportions of magnesium palmitate [$(C_{15}H_{31}COO)_2Mg$; M_r 535.1] and magnesium oleate [$(C_{17}H_{33}COO)_2Mg$; M_r 587.2]. It contains not less than 3.8 per cent and not more than 5.0 per cent of Mg, calculated with reference to the dried substance.

CHARACTERS

A white, very fine, light powder, greasy to the touch, practically insoluble in water, in ethanol and in ether.

IDENTIFICATION

A. The residue obtained in the preparation of solution S (see Tests) has a freezing point (*2.2.18*) not lower than 53 °C.

B. 1 ml of solution S gives the reaction of magnesium (*2.3.1*).

TESTS

Solution S. To 5.0 g add 50 ml of *ether R*, 20 ml of *dilute nitric acid R* and 20 ml of *distilled water R* and heat under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with two quantities, each of 4 ml, of *distilled water R*. Combine the aqueous layers, wash with 15 ml of *ether R* and dilute to 50 ml with *distilled water R* (solution S). Evaporate the organic layer to dryness and dry the residue at 100 °C to 105 °C.

Appearance of solution. Solution S is not more intensely coloured than reference solution Y_6 (*Method II, 2.2.2*).

Appearance of solution of fatty acids. Dissolve 0.5 g of the residue obtained in the preparation of solution S in 10 ml of *chloroform R*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*Method II, 2.2.2*).

Acidity or alkalinity. To 1.0 g add 20 ml of *carbon dioxide-free water R* and boil for 1 min with continuous shaking. Cool and filter. To 10 ml of the filtrate add 0.05 ml of *bromothymol blue solution R1*. Not more than 0.05 ml of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Acid value of the fatty acids (*2.5.1*). 195 to 210, determined on 0.200 g of the residue obtained in the preparation of solution S dissolved in 25 ml of the prescribed mixture of solvents.

Chlorides (*2.4.4*). 2 ml of solution S diluted to 15 ml with *water R* complies with the limit test for chlorides (250 ppm).

Sulphates (*2.4.13*). 0.3 ml of solution S diluted to 15 ml with *distilled water R* complies with the limit test for sulphates (0.5 per cent).

Heavy metals (*2.4.8*). 1.0 g complies with limit test D for heavy metals (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 6.0 per cent, determined on 1.00 g by drying in an oven at 100 °C to 105 °C.

ASSAY

To 0.750 g in a 250 ml conical flask add 50 ml of a mixture of equal volumes of *butanol R* and *ethanol R*, 5 ml of *concentrated ammonia R*, 3 ml of *ammonium chloride buffer solution pH 10.0 R*, 30.0 ml of *0.1 M sodium edetate* and 15 mg of *mordant black 11 triturate R*. Heat to 45 °C to 50 °C and titrate with *0.1 M zinc sulphate* until the colour changes from blue to violet. Carry out a blank titration.

1 ml of *0.1 M sodium edetate* is equivalent to 2.431 mg of Mg.

מאושר ע"י מ[illegible] המעבדה:
חתימה.........
תאריך. 15/1.98

Ph. Eur. 3rd addit. p. 578-579

1997:0597

CARNAUBA WAX

Cera carnauba

DEFINITION

Carnauba wax is the purified wax obtained from the leaves of *Copernicia cerifera* Mart.

CHARACTERS

Pale-yellow or yellow powder, flakes or hard masses, practically insoluble in water and in alcohol, soluble on warming in ethyl acetate and in xylene.

It has a relative density of about 0.97.

IDENTIFICATION

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 0.10 g of the substance to be examined with warming in 5 ml of *chloroform R*. Use the warm solution.

Reference solution. Dissolve 5 mg of *menthol R*, 5 µl of *menthyl acetate R* and 5 mg of *thymol R* in 10 ml of *toluene R*.

Apply separately to the plate as bands 20 mm by 3 mm, 30 µl of the test solution and 10 µl of the reference solution. Develop over a path of 10 cm using a mixture of 2 volumes of *ethyl acetate R* and 98 volumes of *chloroform R*. Allow the plate to dry and spray with a freshly prepared 200 g/l solution of *phosphomolybdic acid R* in *alcohol R*, using about 10 ml for a plate 200 mm square and heat at 100 °C to 105 °C for 10 min to 15 min. The chromatogram obtained with the reference solution shows in the lower part a dark blue zone (menthol), above this zone a reddish zone (thymol) and in the upper part a dark blue zone (menthyl acetate). The chromatogram obtained with the test solution shows a large blue zone (triacontanol = melissyl alcohol) at a level between the thymol and menthol zones in the chromatogram obtained with the reference solution. Further blue zones are visible in the upper part of the chromatogram obtained with the test solution, at levels between those of the menthyl acetate and thymol zones in the chromatogram obtained with the reference solution; above these zones further zones are visible in the chromatogram obtained with the test solution; the zone with the highest R_f value is very pronounced. A number of faint zones are visible below the triacontanol zone and the starting point is coloured blue.

TESTS

Appearance of solution. Dissolve 0.10 g with heating in *chloroform R* and dilute to 10 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than a 0.05 g/l solution of *potassium dichromate R* (*Method II, 2.2.2*).

Melting point (*2.2.15*). 80 °C to 88 °C. Melt the substance carefully on a water-bath before introduction into the capillary tubes. Allow the tubes to stand at a temperature not exceeding 10 °C for 24 h or at 0 °C for 2 h.

Acid value. 2 to 7. To 2.000 g (m g) in a 250 ml conical flask fitted with a reflux condenser add 40 ml of *xylene R* and a few glass beads and heat until the substance is completely dissolved. Add 20 ml of *alcohol R* and 1 ml of *phenolphthalein solution R1* and titrate the hot solution with *0.5 M alcoholic potassium hydroxide* until a pink colour persists for at least 10 s (n_1 ml). Carry out a blank test (n_2 ml). Calculate the acid value from the expression:

$$\frac{28.05(n_1 - n_2)}{m}$$

Saponification value. 78 to 95. To the titrated solution from the determination of the acid value, add 20.0 ml of *0.5 M alcoholic potassium hydroxide* and boil under a reflux condenser for 3 h. Add 1 ml of *phenolphthalein solution R1* and titrate the hot solution immediately with *0.5 M hydrochloric acid* until the red colour disappears. Reheat the solution to boiling and continue the titration, if necessary, until the red colour disappears; repeat the heating and titration until the colour no longer reappears on heating (n_3 ml). Carry out a blank test (n_4 ml). Calculate the saponification value from the expression:

$$\frac{28.05(n_4 - n_3)}{m} + \text{acid value}$$

Total ash (*2.4.16*). Not more than 0.25 per cent, determined on 2.0 g.

STORAGE

Store protected from light.

מאושר ע"י מנהלת המעבדה
רשימה
תאריך 28/7/97

Pr. amp. sa add 1723-1724

1997:0008

WATER, PURIFIED

Aqua purificata

H_2O M_r 18.02

DEFINITION

Purified water is water for the preparation of medicinal products other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised.

PRODUCTION

Purified water is prepared by distillation, by ion exchange or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

CHARACTERS

A clear liquid, colourless and tasteless.

TESTS

pH *(2.2.3)*. Examine a solution containing 0.3 ml of a saturated solution of *potassium chloride R* per 100 ml of purified water. The pH of the solution is 5.0 to 7.0.

Oxidisable substances. To 100 ml add 10 ml of *dilute sulphuric acid R* and 0.1 ml of *0.02 M potassium permanganate* and boil for 5 min. The solution remains faintly pink.

Chlorides. To 10 ml add 1 ml of *dilute nitric acid R* and 0.2 ml of *silver nitrate solution R2*. The solution shows no change in appearance for at least 15 min.

Nitrates. Place 5 ml in a test-tube immersed in iced water, add 0.4 ml of a 100 g/l solution of *potassium chloride R*, 0.1 ml of *diphenylamine solution R* and, dropwise with shaking, 5 ml of *sulphuric acid R*. Transfer the tube to a water-bath at 50 °C. After 15 min, any blue colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 4.5 ml of *nitrate-free water R* and 0.5 ml of *nitrate standard solution (2 ppm NO_3) R* (0.2 ppm).

Sulphates. To 10 ml add 0.1 ml of *dilute hydrochloric acid R* and 0.1 ml of *barium chloride solution R1*. The solution shows no change in appearance for at least 1 h.

Ammonium. To 20 ml add 1 ml of *alkaline potassium tetraiodomercurate solution R*. After 5 min, examine the solution down the vertical axis of the tube. The solution is not more intensely coloured than a standard prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution R* to a mixture of 4 ml of *ammonium standard solution (1 ppm NH_4) R* and 16 ml of *ammonium-free water R* (0.2 ppm).

Calcium and magnesium. To 100 ml add 2 ml of *ammonium chloride buffer solution pH 10.0 R*, 50 mg of *mordant black 11 triturate R* and 0.5 ml of *0.01M sodium edetate*. A pure blue colour is produced.

Heavy metals *(2.4.8)*. Heat 150 ml in a glass evaporating dish on a water-bath until the volume is reduced to 15 ml. 12 ml of the concentrated solution complies with limit test A for heavy metals (0.1 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Aluminium *(2.4.17)*. If intended for use in the manufacture of dialysis solutions, it complies with the test for aluminium. To 400 ml add 10 ml of *acetate buffer solution pH 6.0 R* and 100 ml of *water R*. The solution complies with the limit test for aluminium (10 µg/l). Use as the reference solution a mixture of 2 ml of *aluminium standard solution (2 ppm Al) R*, 10 ml of *acetate buffer solution pH 6.0 R* and 98 ml of *water R*. To prepare the blank, use a mixture of 10 ml of *acetate buffer solution pH 6.0 R* and 100 ml of *water R*.

Residue on evaporation. Evaporate 100 ml on a water-bath and dry in an oven at 100 °C to 105 °C. The residue weighs not more than 1 mg (0.001 per cent).

Microbial contamination. Total viable aerobic count *(2.6.12)* not more than 10^2 micro-organisms per millilitre, determined by membrane filtration, using agar medium B.

Bacterial endotoxins *(2.6.14)*. If intended for use in the manufacture of dialysis solutions without a further appropriate procedure for the removal of bacterial endotoxins, not more than 0.25 I.U. of endotoxin per millilitre.

STORAGE

Store in a well-closed container that does not alter the properties of the water.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

מאושר ע"י מנהלת המעבדה
חתימה .....
תאריך 11/99 .....

DEXON LTD. IN - HOUSE MONOGRAPH

OPADRY OY - S-24932 PINK (RAW MATERIAL)	REF No.	PAGE 1
	1337800008	OF 3
	DATE	REPLACES
	9.1.96	

PREPARED BY		QA		QC MANAGER* (for QC methods)	
SIGNATURE		SIGNATURE		SIGNATURE	
DATE	20.02.96	DATE	20.02.96	DATE	20.2.96

* This IN - HOUSE MONOGRAPH is not valid for QC testing without the approval of the QC manager in the space above.

DEXON LTD. IN - HOUSE MONOGRAPH

OPADRY OY - S-24932 PINK (RAW MATERIAL)	REF No. 1337800008	PAGE 1 OF 3
	DATE 9.1.96	REPLACES

1. APPEARANCE

Pink powder.

2. COLOR DIFFERENCE

Conforms to the color of the in-house standard.

3. SULPHATED ASH

3.1 REAGENTS

Sulphuric acid - Analytical grade.

3.2 APPARATUS

Balance AE-240 or equivalent.
Muffle furnace.

3.3 PROCEDURE

Previously ignite a crucible to constant weight at 800°C and weigh accurately after cooling.

Take approximately 1 g of sample, transfer into the ignited container and weigh it accurately. Moisten with 1 ml of sulphuric acid. Ignite gently and then ignite at 800 +25°C to constant weight. Use a dessicator for the cooling.

DEXON LTD. IN - HOUSE MONOGRAPH

OPADRY OY - S-24932 PINK (RAW MATERIAL)	REF No. 1337800008	PAGE 1 OF 3
	DATE 9.1.96	REPLACES

4. CALCULATION

$$\% \text{ sulphated Ash} = \frac{W3 - W1}{W2 - W1} \times 100$$

where,

W1 = weight of crucible, g
W2 = weight of crucible with substance before ignition, g
W3 = weight of crucible with substance after ignition, g

5. REQUIREMENT

20% - 30%

6. REFERENCE

Colorcon.

4. ROUTINE TESTING METHODS FOR INTERMEDIATE PRODUCTS:

Not applicable.

5. ROUTINE TESTING METHODS FOR THE FINISHED PRODUCT:

A monograph of Release Analytical Test Methods of the finished product is given on pages 112-122.

6. ROUTINE TESTING METHODS FOR ADMINISTRATION DEVICES:

Not applicable.

DEXON LTD. ANALYTICAL METHOD

	Product No.	PAGE 1
NIFEDIPINE AT 10 and 20 mg SR COATED	1155480035 1155480042 1155470031 1155470013	OF 10
	DATE	REPLACES
	02/03/98	29/05/97

ANALYTICAL DEVELOPMENT MANAGER		QA		QC MANAGER* (for QC methods)	
SIGNATURE		SIGNATURE		SIGNATURE	
DATE	2/3/98	DATE	02.03.98	DATE	2/3/98

* This analytical method is not valid for QC testing without the approval of the QC manager in the space above.

DEXON LTD. ANALYTICAL METHOD

NIFEDIPINE AT 10 and 20 mg SR COATED	Product No.	PAGE 2 OF 10
	1155480035 1155480042 1155470031 1155470013	
	DATE	REPLACES
	26/02/98	29/05/97

1. ASSAY

1.1 SPECIFICATIONS

95 - 105% of the claim of Nifedipine per tablet

1.2 OUTLINE OF THE METHOD

Extraction of the active ingredient with methanol and content determination by HPLC using the external standard method.

NOTE: This procedure should be performed in the dark or under golden fluorescent or other low-actinic glassware.

1.3 SPECIAL SAFETY PRECAUTIONS

Acetonitrile and methanol are highly flammable. Toxicity can occur by inhalation, on contact with skin or when swallowed. Keep away from heat, sparks and open flames. Avoid breathing vapors and contact with eyes, skin and clothing.

1.4 REAGENTS

Methanol - HPLC grade
Water - HPLC grade
Acetonitrile - HPLC grade
Methanol - HPLC grade
Nifedipine in house standard of known content

DEXON LTD. ANALYTICAL METHOD

NIFEDIPINE AT 10 and 20 mg SR COATED	Product No.	PAGE 3 OF 10
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1.5 EQUIPMENT AND WORKING CONDITIONS

Apparatus:	Varian system or equivalent
Pump:	Varian 9010
Detector:	Varian 9050
Integrator:	Varian 9050 module 03
Auto-sampler:	Varian 9100
Wavelength:	235 nm
Column:	Lichrospher RP 18, 5µm (125 x 4 mm) or equivalent
Mobile phase:	A mixture (V/V) of Acetonitrile : Methanol : water 25 : 25 : 60
Flow:	1 ml per minute
Temperature:	Room temperature
Sample size:	10 µl

1.6 STANDARD SOLUTION PREPARATION

Accurately weigh about 20 mg of Nifedipine in house standard of known content into a 200 ml volumetric flask. Dissolve and dilute to volume with methanol.

1.7 SAMPLE SOLUTION PREPARATION

Weigh accurately 20 tablets and determine the average weight. Grind them to a very fine powder and weigh a quantity equivalent to 20 mg Nifedipine into a 200 ml volumetric flask. Dissolve with about 100 ml methanol, sonicate for 15 minutes and shake on a mechanical shaker for an additional 30 minutes. Dilute to volume with methanol.

1.8 PROCEDURE

Filter through 0.45 µ filter and separately inject standard and sample solution preparation solutions into the HPLC system. Record the areas of the principal peaks using the electronic integrator and calculate the content according to the external standard method.

DEXON LTD. ANALYTICAL METHOD

NIFEDIPINE AT 10 and 20 mg SR COATED	Product No.	PAGE 4 OF 10
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1.9 **CALCULATION**

Calculate the Nifedipine content using the following equation:

$$\text{Nifedipine mg/tablet} = \frac{As \times Wst \times Wt \times Cst}{Ast \times Ws}$$

As = Peak area of the sample solution
Ast = Peak area of the standard solution
Wst = Weight of Nifedipine in house standard in mg
Ws = Weight of sample in mg
Wt = Average weight of the tablets in mg
Cst = Content of Nifedipine in house standard (in case of 100% P=1)

2. IDENTIFICATION

2.1 **ACTIVE INGREDIENT**

Nifedipine

2.1.1 Method:
by HPLC (see assay method 1.2)

2.1.2 Requirement:
In the assay the exhibition of the retention time of the sample solution is the same as the retention time of the standard solution.

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2.2 COLORING MATERIAL

2.2.1 IDENTIFICATION OF TiO2 (E 171)

2.2.1.1 Procedure

Wash the coating of 20 tablets with 15 ml water into a porcelain crucible. Evaporate to dryness. Add 2 ml of concentrated sulfuric acid and ignite at 800°C about 1 hour until the residue is white and cool. Add 3 g of $KHSO_4$ and heat again at 800°C for 1-2 minutes (to complete melting) and cool. Add a few drops of H_2O_2 30%.

2.2.1.2 Requirement

A yellow-orange color is produced.

2.2.2 IDENTIFICATION OF IRON OXIDE RED (E-172)

2.2.2.1 Procedure

Shake 20 tablets on a mechanical shaker with 20 ml warm water. Centrifuge the mixture and keep the supernatant (1). Heat the residue with 5 ml HCl concentrate, centrifuge and obtain the supernatant (2). Mix the supernatant (1) and (2) and add 2 drops of H_2O_2 30%. Evaporate the solution by heating, to obtain 2 ml and dilute with water to 4 ml. Add a few drops of potassium thiocyanate 10% and mix.

2.2.2.2 Requirement

A red color should develop. After adding a few crystals of mercuric (II) chloride reagent the color fades.

3. PURITY TEST

3.1 SPECIFICATIONS

Nitrophenylpyridine analog (V1)	NMT 1.0%
Nitrosophenylpyridine analog (V2)	NMT 0.5%
Individual unidentified impurities	NMT 0.2%
Total unidentified impurities	NMT 0.5%
Total impurities	NMT 1.5%

DEXON LTD. ANALYTICAL METHOD

NIFEDIPINE AT 10 and 20 mg SR COATED	Product No	PAGE 6 OF 10
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3.2 **OUTLINE OF THE METHOD**

Nifedipine and the related compounds are extracted from sample test and the content of related compounds is determined by HPLC method.

3.3 **SPECIAL SAFETY PRECAUTIONS**

Same as for assay method (see 1.2).

3.4 **REAGENTS**

Methanol - HPLC grade
Water - HPLC grade
Acetonitrile - HPLC grade
Methanol - HPLC grade
Nitrophenylpyridine analog impurity standard
Nitrosophenylpyridine analog impurity standard
Nifedipine in house standard of known content

3.5 **EQUIPMENT AND WORKING CONDITIONS**

Use the same instrument conditions as for the assay procedure with a run time of at least 30 minutes.
Note: This procedure should be performed in the dark or under golden fluorescent or other low-actinic light. Use low-actinic glassware.

3.6 **IMPURITIES STANDARD SOLUTION PREPARATIONS**

3.6.1. V1 and V2 Standard Stock Solutions
Weigh 10 mg of each impurity (V1 and V2) into separate 100 ml volumetric flasks. Dissolve and dilute to volume with methanol.

3.6.2 V1 and V2 Standard Solutions
Transfer 2 ml of V1 stock solution and 1 ml of V2 stock solution into separate 20 ml volumetric flasks. Dilute to volume with methanol.

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3.6.3 Nifedipine Standard Solution for unknown impurity

Weigh 20 mg of Nifedipine in house standard into a 50 ml volumetric flask. Dissolve and dilute to volume with methanol. Transfer 1 ml of this solution into a 200 ml volumetric flask. Dilute to volume with methanol.

3.7 SAMPLE SOLUTION PREPARATION

Weigh 20 tablets and determine the average weight. Grind them to a very fine powder. Weigh a quantity equivalent to 20 mg of Nifedipine into a 20 ml volumetric flask. Dissolve with about 10 ml methanol and shake on a mechanical shaker for 30 minutes. Dilute to volume with methanol.

3.8 PROCEDURE

Filter through 0.45 µm filter and separately inject standard and sample solution preparation into the HPLC and record the chromatograms.

3.9 CALCULATIONS

Calculate the content in percent of the impurity according to the following equation:

$$\% \text{ impurity} = \frac{As}{Ast} \times \frac{Wst}{Ws} \times \frac{D}{K} \times Wt \times 100$$

where:

As = impurity peak area of the sample solution
Ast = standard peak area of the appropriate impurity
Ws = weight of sample in mg
Wst = weight of impurity standard in mg
D = dilution factor
K = claim of the Nifedipine tablet
Wt = average weight of the tablets in mg
100 = conversion factor to percent

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4. DISSOLUTION

4.1 SPECIFICATION

After 1 hour	10 - 35 %
After 4 hours	47 - 72%
After 8 hours	65 - 90%
After 12 hours	NLT 75%

4.2 OUTLINE OF THE METHOD

The determination of the amount of Nifedipine released in 0.1N HCl is carried out by the use of flow through dissolution tester.
NOTE: This procedure should be performed in the dark or under golden fluorescent or other low-actinic light.

4.3 SPECIAL SAFETY PRECAUTIONS

None

4.4 REAGENTS

Hydrochloric acid - grade
Methanol - analytical grade
Nifedipine in house standard

4.5 EQUIPMENT

Dissolution Tester: Sotax CH - 4008 Basel
UV Detector: Unicam 8620 Spectrophotometer

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4.6 **CONDITIONS**

Apparatus:	USP apparatus 4
Medium:	0.1N HCl
Flow rate:	10 cc/min. cross cell ± 5%
Temperature:	37°C ± 0.5°C
Time:	16 hours
Intervals:	Every 10 minutes
Optical length:	1 cm
Wavelength:	237 nm
Cell diameter:	12 mm
Filter:	GF/D 2.7 µm
Specified volume:	10 ml x 10 min. = 100 ml
Decontamination:	Continuous with helium

4.7 **STANDARD SOLUTION PREPARATION**

Prepare 3 standard solutions with Nifedipine in house standard and perform a calibration curve.
Standard 1) Weigh accurately about 200 mg Nifedipine into a 100 ml volumetric flask. Dissolve and fill up to volume with methanol. Dilute 1 ml of this solution to 200 ml with 0.1N HCl. This is the standard solution of Nifedipine with a concentration of 0.01 mg/ml. Proceed in the same way to obtain 0.005 mg/ml and 0.0025 mg/ml.

4.8 **PROCEDURE**

After assembly of the dissolution apparatus according to the instructions, introduce by pump the dissolution medium warmed to 37°C ± 0.5°C. Check the flow rate of the medium to obtain flow 10 ml/min cross cell ± 5%. Place one tablet in each of the six cells. Enter in computer the program time of dissolution test. The recording and evaluation of the measurements are carried out by the computer.

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4.9 ACCEPTANCE CRITERIA

In accordance to BP 93 Addendum 96 (p. A514).

5. HARDNESS

5.1 SPECIFICATIONS

NLT 25 N for 10 mg tablets
NLT 40 N for 20 mg tablets

5.2 EQUIPMENT AND WORKING CONDITIONS

Apparatus: Schleuninger Hardness tester or equivalent
No. of tablets: 5

6. MICROBIOLOGICAL TEST

6.1 SPECIFICATION

Acc. to European Pharmacopoeia
Execution: One batch out of every five batches

7. REFERENCE

1. In house method
2. Ph.Eur. 3rd edition