TESTS

Viscosity (*2.2.9*): 45 mPa·s to 90 mPa·s for the apparent viscosity determined at 25 °C.

Dissolve 15 g, calculated with reference to the anhydrous substance, in 85 g of a mixture of 1 part of *water R* and 249 parts of *acetone R*.

Free acid: maximum 3.0 per cent, calculated as phthalic acid (anhydrous substance).

Shake 3.0 g for 2 h with 100 ml of a 50 per cent *V/V* solution of *methanol R* and filter. Wash the flask and the filter with 2 quantities, each of 10 ml, of a mixture of a 50 per cent *V/V* solution of *methanol R*. Combine the filtrate and washings, add *phenolphthalein solution R* and titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained. Carry out a blank titration.

1 ml of *0.1 M sodium hydroxide* is equivalent to 8.3 mg of free acid, calculated as phthalic acid.

Heavy metals (*2.4.8*): maximum 10 ppm.

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

Water (*2.5.12*): maximum 5.0 per cent, determined on 0.500 g.

Carry out the test using a mixture of 2 volumes of *methylene chloride R* and 3 volumes of *ethanol R*.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Phthaloyl groups. Dissolve 1.000 g in 50 ml of a mixture of 2 volumes of *acetone R* and 3 volumes of *alcohol R*. Add 0.1 ml of *phenolphthalein solution R* and titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained. Carry out a blank titration.

Calculate the percentage content of phthaloyl groups (*P*) from the expression:

$$\frac{14\,900n}{(100-a)(100-S)m} - \frac{179.5S}{(100-S)}$$

a = percentage content of water,

m = mass of the substance to be examined, in grams,

n = number of millilitres of *0.1 M sodium hydroxide* used,

S = percentage content of free acid (see Tests).

Acetyl groups. To 0.100 g add 25.0 ml of *0.1 M sodium hydroxide* and heat on a water-bath under a reflux condenser for 30 min. Cool, add 0.1 ml of *phenolphthalein solution R* and titrate with *0.1 M hydrochloric acid* until the colour is discharged. Carry out a blank titration.

Calculate the percentage content of acetyl groups from the expression:

$$\left[\frac{4300(n_2-n_1)}{(100-a)(100-S)m} - \frac{51.8S}{(100-S)}\right] - 0.578P$$

a = percentage content of water,

m = mass of the substance to be examined, in grams,

n_1 = number of millilitres of *0.1 M hydrochloric acid* used in the test,

n_2 = number of millilitres of *0.1 M hydrochloric acid* used in the blank titration,

P = percentage content of phthaloyl groups,

S = percentage content of free acid (see Tests).

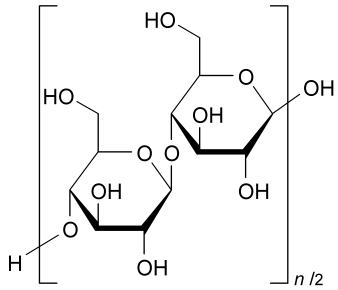
STORAGE

In an airtight container.

01/2008:0316
corrected 6.0

CELLULOSE, MICROCRYSTALLINE

Cellulosum microcristallinum



$C_{6n}H_{10n+2}O_{5n+1}$
[9004-34-6]

DEFINITION

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

CHARACTERS

Appearance: white or almost white, fine or granular powder.

Solubility: practically insoluble in water, in acetone, in anhydrous ethanol, in toluene, 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. The degree of polymerisation is not more than 350.

Transfer 1.300 g to a 125 ml conical flask. Add 25.0 ml of *water R* and 25.0 ml of *cupriethylenediamine hydroxide solution R*. Immediately purge the solution with *nitrogen R*, insert the stopper and shake until completely dissolved. Transfer an appropriate volume of the solution to a suitable capillary viscometer (*2.2.9*). Equilibrate the solution at 25 ± 0.1 °C for at least 5 min. Record the flow time (t_1) in seconds between the 2 marks on the viscometer. Calculate the kinematic viscosity (ν_1) of the solution using the following formula:

$$t_1\,(k_1)$$

where k_1 is the viscometer constant.

Dilute a suitable volume of *cupriethylenediamine hydroxide solution R* 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 following 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 following formula:

$$\nu_1/\nu_2$$

Determine the intrinsic viscosity ($[\eta]_c$) by interpolation, using the intrinsic viscosity table (Table 0316.-1).

Calculate the degree of polymerisation (P) using the following formula:

$$\frac{95\,[\eta]_c}{m\,[(100-b)/100]}$$

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

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*): 5.0 to 7.5 for the supernatant liquid.

Shake 5 g with 40 ml of *carbon dioxide-free water R* for 20 min and centrifuge.

Conductivity (*2.2.38*). The conductivity of the test solution does not exceed the conductivity of the water by more than 75 $\mu S \cdot cm^{-1}$.

Use as test solution the supernatant liquid obtained in the test for pH. Measure the conductivity of the supernatant liquid after a stable reading has been obtained and measure the conductivity of the water used to prepare the test solution.

Ether-soluble substances: maximum 0.05 per cent (5 mg) for the difference between the weight of the residue and the weight obtained from a blank determination.

Place 10.0 g in a chromatography column about 20 mm in internal diameter and pass 50 ml of *peroxide-free ether R* through the column. Evaporate the eluate to dryness. Dry the residue at 105 °C for 30 min, allow to cool in a dessicator and weigh. Carry out a blank determination.

Water-soluble substances: maximum 0.25 per cent (12.5 mg) for the difference between the mass of the residue and the mass obtained from a blank determination.

Shake 5.0 g with 80 ml of *water R* for 10 min. Filter through a filter paper with the aid of vacuum into a tared flask. Evaporate to dryness on a water-bath avoiding charring. Dry at 105 °C for 1 h and weigh. Carry out a blank determination.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulphated ash (*2.4.14*): maximum 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*).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient. This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for microcrystalline cellulose used as binder, diluent or disintegrant.

Degree of polymerisation: see Identification B.

Crystallinity (*2.9.33*).

Particle-size distribution (*2.9.31* or *2.9.38*).

Powder flow (*2.9.36*).

Table 0316.-1. – *Intrinsic viscosity table*

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}										
					$[\eta]_c$					
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
1.1	0.098	0.106	0.115	0.125	0.134	0.143	0.152	0.161	0.170	0.180
1.2	0.189	0.198	0.207	0.216	0.225	0.233	0.242	0.250	0.259	0.268
1.3	0.276	0.285	0.293	0.302	0.310	0.318	0.326	0.334	0.342	0.350
1.4	0.358	0.367	0.375	0.383	0.391	0.399	0.407	0.414	0.422	0.430
1.5	0.437	0.445	0.453	0.460	0.468	0.476	0.484	0.491	0.499	0.507
1.6	0.515	0.522	0.529	0.536	0.544	0.551	0.558	0.566	0.573	0.580
1.7	0.587	0.595	0.602	0.608	0.615	0.622	0.629	0.636	0.642	0.649
1.8	0.656	0.663	0.670	0.677	0.683	0.690	0.697	0.704	0.710	0.717
1.9	0.723	0.730	0.736	0.743	0.749	0.756	0.762	0.769	0.775	0.782
2.0	0.788	0.795	0.802	0.809	0.815	0.821	0.827	0.833	0.840	0.846

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

	$[\eta]_c$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
2.1	0.852	0.858	0.864	0.870	0.876	0.882	0.888	0.894	0.900	0.906
2.2	0.912	0.918	0.924	0.929	0.935	0.941	0.948	0.953	0.959	0.965
2.3	0.971	0.976	0.983	0.988	0.994	1.000	1.006	1.011	1.017	1.022
2.4	1.028	1.033	1.039	1.044	1.050	1.056	1.061	1.067	1.072	1.078
2.5	1.083	1.089	1.094	1.100	1.105	1.111	1.116	1.121	1.126	1.131
2.6	1.137	1.142	1.147	1.153	1.158	1.163	1.169	1.174	1.179	1.184
2.7	1.190	1.195	1.200	1.205	1.210	1.215	1.220	1.225	1.230	1.235
2.8	1.240	1.245	1.250	1.255	1.260	1.265	1.270	1.275	1.280	1.285
2.9	1.290	1.295	1.300	1.305	1.310	1.314	1.319	1.324	1.329	1.333
3.0	1.338	1.343	1.348	1.352	1.357	1.362	1.367	1.371	1.376	1.381
3.1	1.386	1.390	1.395	1.400	1.405	1.409	1.414	1.418	1.423	1.427
3.2	1.432	1.436	1.441	1.446	1.450	1.455	1.459	1.464	1.468	1.473
3.3	1.477	1.482	1.486	1.491	1.496	1.500	1.504	1.508	1.513	1.517
3.4	1.521	1.525	1.529	1.533	1.537	1.542	1.546	1.550	1.554	1.558
3.5	1.562	1.566	1.570	1.575	1.579	1.583	1.587	1.591	1.595	1.600
3.6	1.604	1.608	1.612	1.617	1.621	1.625	1.629	1.633	1.637	1.642
3.7	1.646	1.650	1.654	1.658	1.662	1.666	1.671	1.675	1.679	1.683
3.8	1.687	1.691	1.695	1.700	1.704	1.708	1.712	1.715	1.719	1.723
3.9	1.727	1.731	1.735	1.739	1.742	1.746	1.750	1.754	1.758	1.762
4.0	1.765	1.769	1.773	1.777	1.781	1.785	1.789	1.792	1.796	1.800
4.1	1.804	1.808	1.811	1.815	1.819	1.822	1.826	1.830	1.833	1.837
4.2	1.841	1.845	1.848	1.852	1.856	1.859	1.863	1.867	1.870	1.874
4.3	1.878	1.882	1.885	1.889	1.893	1.896	1.900	1.904	1.907	1.911
4.4	1.914	1.918	1.921	1.925	1.929	1.932	1.936	1.939	1.943	1.946
4.5	1.950	1.954	1.957	1.961	1.964	1.968	1.971	1.975	1.979	1.982
4.6	1.986	1.989	1.993	1.996	2.000	2.003	2.007	2.010	2.013	2.017
4.7	2.020	2.023	2.027	2.030	2.033	2.037	2.040	2.043	2.047	2.050
4.8	2.053	2.057	2.060	2.063	2.067	2.070	2.073	2.077	2.080	2.083
4.9	2.087	2.090	2.093	2.097	2.100	2.103	2.107	2.110	2.113	2.116
5.0	2.119	2.122	2.125	2.129	2.132	2.135	2.139	2.142	2.145	2.148
5.1	2.151	2.154	2.158	2.160	2.164	2.167	2.170	2.173	2.176	2.180
5.2	2.183	2.186	2.190	2.192	2.195	2.197	2.200	2.203	2.206	2.209
5.3	2.212	2.215	2.218	2.221	2.224	2.227	2.230	2.233	2.236	2.240
5.4	2.243	2.246	2.249	2.252	2.255	2.258	2.261	2.264	2.267	2.270
5.5	2.273	2.276	2.279	2.282	2.285	2.288	2.291	2.294	2.297	2.300
5.6	2.303	2.306	2.309	2.312	2.315	2.318	2.320	2.324	2.326	2.329
5.7	2.332	2.335	2.338	2.341	2.344	2.347	2.350	2.353	2.355	2.358
5.8	2.361	2.364	2.367	2.370	2.373	2.376	2.379	2.382	2.384	2.387
5.9	2.390	2.393	2.396	2.400	2.403	2.405	2.408	2.411	2.414	2.417
6.0	2.419	2.422	2.425	2.428	2.431	2.433	2.436	2.439	2.442	2.444
6.1	2.447	2.450	2.453	2.456	2.458	2.461	2.464	2.467	2.470	2.472

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}

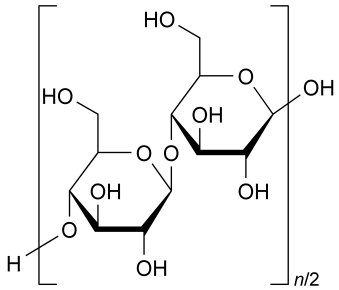
	$[\eta]_c$									
η_{rel}	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
6.2	2.475	2.478	2.481	2.483	2.486	2.489	2.492	2.494	2.497	2.500
6.3	2.503	2.505	2.508	2.511	2.513	2.516	2.518	2.521	2.524	2.526
6.4	2.529	2.532	2.534	2.537	2.540	2.542	2.545	2.547	2.550	2.553
6.5	2.555	2.558	2.561	2.563	2.566	2.568	2.571	2.574	2.576	2.579
6.6	2.581	2.584	2.587	2.590	2.592	2.595	2.597	2.600	2.603	2.605
6.7	2.608	2.610	2.613	2.615	2.618	2.620	2.623	2.625	2.627	2.630
6.8	2.633	2.635	2.637	2.640	2.643	2.645	2.648	2.650	2.653	2.655
6.9	2.658	2.660	2.663	2.665	2.668	2.670	2.673	2.675	2.678	2.680
7.0	2.683	2.685	2.687	2.690	2.693	2.695	2.698	2.700	2.702	2.705
7.1	2.707	2.710	2.712	2.714	2.717	2.719	2.721	2.724	2.726	2.729
7.2	2.731	2.733	2.736	2.738	2.740	2.743	2.745	2.748	2.750	2.752
7.3	2.755	2.757	2.760	2.762	2.764	2.767	2.769	2.771	2.774	2.776
7.4	2.779	2.781	2.783	2.786	2.788	2.790	2.793	2.795	2.798	2.800
7.5	2.802	2.805	2.807	2.809	2.812	2.814	2.816	2.819	2.821	2.823
7.6	2.826	2.828	2.830	2.833	2.835	2.837	2.840	2.842	2.844	2.847
7.7	2.849	2.851	2.854	2.856	2.858	2.860	2.863	2.865	2.868	2.870
7.8	2.873	2.875	2.877	2.879	2.881	2.884	2.887	2.889	2.891	2.893
7.9	2.895	2.898	2.900	2.902	2.905	2.907	2.909	2.911	2.913	2.915
8.0	2.918	2.920	2.922	2.924	2.926	2.928	2.931	2.933	2.935	2.937
8.1	2.939	2.942	2.944	2.946	2.948	2.950	2.952	2.955	2.957	2.959
8.2	2.961	2.963	2.966	2.968	2.970	2.972	2.974	2.976	2.979	2.981
8.3	2.983	2.985	2.987	2.990	2.992	2.994	2.996	2.998	3.000	3.002
8.4	3.004	3.006	3.008	3.010	3.012	3.015	3.017	3.019	3.021	3.023
8.5	3.025	3.027	3.029	3.031	3.033	3.035	3.037	3.040	3.042	3.044
8.6	3.046	3.048	3.050	3.052	3.054	3.056	3.058	3.060	3.062	3.064
8.7	3.067	3.069	3.071	3.073	3.075	3.077	3.079	3.081	3.083	3.085
8.8	3.087	3.089	3.092	3.094	3.096	3.098	3.100	3.102	3.104	3.106
8.9	3.108	3.110	3.112	3.114	3.116	3.118	3.120	3.122	3.124	3.126
9.0	3.128	3.130	3.132	3.134	3.136	3.138	3.140	3.142	3.144	3.146
9.1	3.148	3.150	3.152	3.154	3.156	3.158	3.160	3.162	3.164	3.166
9.2	3.168	3.170	3.172	3.174	3.176	3.178	3.180	3.182	3.184	3.186
9.3	3.188	3.190	3.192	3.194	3.196	3.198	3.200	3.202	3.204	3.206
9.4	3.208	3.210	3.212	3.214	3.215	3.217	3.219	3.221	3.223	3.225
9.5	3.227	3.229	3.231	3.233	3.235	3.237	3.239	3.241	3.242	3.244
9.6	3.246	3.248	3.250	3.252	3.254	3.256	3.258	3.260	3.262	3.264
9.7	3.266	3.268	3.269	3.271	3.273	3.275	3.277	3.279	3.281	3.283
9.8	3.285	3.287	3.289	3.291	3.293	3.295	3.297	3.298	3.300	3.302
9.9	3.304	3.305	3.307	3.309	3.311	3.313	3.316	3.318	3.320	3.321

Intrinsic viscosity $[\eta]_c$ at different values of relative viscosity η_{rel}										
					$[\eta]_c$					
η_{rel}	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
10	3.32	3.34	3.36	3.37	3.39	3.41	3.43	3.45	3.46	3.48
11	3.50	3.52	3.53	3.55	3.56	3.58	3.60	3.61	3.63	3.64
12	3.66	3.68	3.69	3.71	3.72	3.74	3.76	3.77	3.79	3.80
13	3.80	3.83	3.85	3.86	3.88	3.89	3.90	3.92	3.93	3.95
14	3.96	3.97	3.99	4.00	4.02	4.03	4.04	4.06	4.07	4.09
15	4.10	4.11	4.13	4.14	4.15	4.17	4.18	4.19	4.20	4.22
16	4.23	4.24	4.25	4.27	4.28	4.29	4.30	4.31	4.33	4.34
17	4.35	4.36	4.37	4.38	4.39	4.41	4.42	4.43	4.44	4.45
18	4.46	4.47	4.48	4.49	4.50	4.52	4.53	4.54	4.55	4.56
19	4.57	4.58	4.59	4.60	4.61	4.62	4.63	4.64	4.65	4.66

01/2008:0315
corrected 6.0

CELLULOSE, POWDERED

Cellulosi pulvis



$C_{6n}H_{10n+2}O_{5n+1}$

DEFINITION

Purified, mechanically disintegrated cellulose prepared by processing alpha-cellulose obtained as a pulp from fibrous plant material.

CHARACTERS

Appearance: white or almost white, fine or granular powder.

Solubility: practically insoluble in water, slightly soluble in a 50 g/l solution of sodium hydroxide, practically insoluble in acetone, in anhydrous ethanol, in toluene, in dilute acids and in most organic solvents.

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. The degree of polymerisation is greater than 440.

Transfer 0.250 g to a 125 ml conical flask. Add 25.0 ml of *water R* and 25.0 ml of *cupriethylenediamine hydroxide solution R*. Immediately purge the solution with *nitrogen R*, insert the stopper and shake until completely dissolved. Transfer an appropriate volume of the solution to a suitable capillary viscometer (*2.2.9*). Equilibrate the solution at 25 ± 0.1 °C for at least 5 min. Record the flow time (t_1) in seconds between the 2 marks on the viscometer. Calculate the kinematic viscosity (ν_1) of the solution using the following formula:

$$t_1 \, (k_1)$$

where k_1 is the viscometer constant.

Dilute a suitable volume of *cupriethylenediamine hydroxide solution R* 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 following 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 following formula:

$$\nu_1 / \nu_2$$

Determine the intrinsic viscosity ($[\eta]_c$) by interpolation, using the intrinsic viscosity table (Table 0315.-1).

Calculate the degree of polymerisation (P) using the following formula:

$$\frac{95 \, [\eta]_c}{m \, [(100 - b) / 100]}$$

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

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*): 5.0 to 7.5 for the supernatant liquid.

Mix 10 g with 90 ml of *carbon dioxide-free water R* and allow to stand with occasional stirring for 1 h.