

# Analytix<sup>Notes</sup>

 **Fluka**  
Riedel-deHaën®

## HYDRANAL<sup>®</sup> and the European Pharmacopoeia

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European Pharmacopoeia

Literature and Guides

Comparison Tests



**SIGMA-ALDRICH**

## HYDRANAL® ..... and the European Pharmacopoeia

### Introduction

Because moisture can affect the quality, activity and shelf life of many pharmaceutical products, it is important to have a reliable technique to measure moisture in a wide array of matrices from chemicals, powders and tablets to creams and lotions. Karl-Fischer titration is the method specified by European Pharmacopoeia (Ph. Eur.). However, current Ph. Eur. guidelines specify a Karl-Fischer reagent containing pyridine at a concentration not available in any commercial formulation. Additionally, many analysts prefer to use Karl-Fischer reagents where the pyridine and methyl glycol (2-methoxyethanol) have been replaced with safer, less toxic analogs. The Ph. Eur. makes the following statement regarding this substitution:

“The composition of commercially available iodophilous reagents often differs from that of the iodophilous reagent R by the replacement of pyridine with various other basic compounds. The use of these reagents must previously be validated, in order to verify, in each individual case, the stoichiometry and the absence of incompatibility between the substance and the reagent (IV.1 General Notices).” (Ph. Eur. V.3.5.6.-1).

Therefore, according to the Ph. Eur. analysts preferring to make this substitution and use a pyridine-free reagent are required to carry out these confirmatory tests themselves. Sigma-Aldrich has done this work for you by providing both pyridine-free Karl-Fischer reagents and verifying their suitability for the Ph. Eur. method.

### HYDRANAL® Pyridine-free Reagents Meet the Requirements of Ph. Eur. Guidelines

We compared the performance of HYDRANAL® pyridine-free Karl-Fischer reagents with the performance of reagents prepared following the Ph. Eur. procedure on many different pharmaceutical products. The following procedure to measure moisture content of polyethylene glycol 400 (PEG-400) serves as an example of the comparison titrations:

1. Prepare the pyridine-containing reagent according to Ph. Eur. method and determine titre.
2. Add methanol to the titration vessel as described in the Ph. Eur. and titrate to dryness.
3. Add approx. 2g PEG-400 sample, weighed precisely, to the vessel.
4. Titrate the water content of the sample.
5. Repeat titration steps 2 - 4.
6. At the end of the titration, add exactly 5.00mg water and titrate in the same manner.
7. Repeat this determination.

The same titration was carried out substituting the pyridine-containing reagent with HYDRANAL®-Composite 5 and steps 2-7 are followed exactly as above. The titrations were carried out using a regular titrator controlled by a PC. The printout of the protocol was generated automatically. The printed titration curve demonstrated the course of the titration with time and showed the end-point stability.

### Results of Comparison Titrations

The detailed protocols of both comparison titrations are enclosed (Enclosure 1 and 2). In the top section the reagents are described and the method follows. In the Samples section the sample weight, reagent volume and finally the titrated water content is presented. In the Water Added section the recovery of added water is documented.

The results of water content analysis for PEG-400 show that both titrations, using either the pyridine-containing Ph.Eur reagent or the HYDRANAL® pyridine-free reagent, gave the same results. This verifies that HYDRANAL® reagents satisfy the “stoichiometry and the absence of incompatibility” Ph. Eur. requirement. Additionally, the titration curves show that titration with HYDRANAL®-Composite 5 took only two minutes and gave a more stable end-point compared to the curve for the Ph. Eur. reagent.

### HYDRANAL® Reagents Provide Better Accuracy and Shorter Titration Time

The many compounds of pharmaceutical interest we compared are listed in the attached table. For most substances agreement between the two reagents was as good as the results achieved with the PEG-400 example. However, for several substances the pyridine-containing Ph. Eur. reagent gave erroneous results or had difficult or lengthy titration times. Some compounds where HYDRANAL® outperformed the Ph. Eur. reagent are:

- Acetone – The HYDRANAL®-Composite 5 gave correct results, but the Ph. Eur. reagent gave falsely high water content.
- Diethyl ether – The Ph. Eur. reagent had exceptionally long titration time, in excess of 15 minutes. Titration time was only a few minutes using HYDRANAL®
- Dimethyl sulphoxide – This compound gave decreasing values because the sample size recommended by the Ph. Eur. is too large.
- Hexetidine – Using the Ph. Eur. reagent resulted in delayed titrations with variable end-points and consequently erratic results.
- Disodium phosphate – This compound necessitated titration times of 40 minutes with Ph. Eur. reagents and decreasing results with the dimethyl formamide mixture specified as the Ph. Eur. solvent.

The compounds we used to compare the HYDRANAL® and Ph. Eur. reagents appear in the attached list. The titrations followed the protocol outlined in this report.

## Enclosure 1 .....


**Riedel-de Haën®**

 Hydranal®-Laboratory  
 D-30926 Seelze

 Water determination by Karl Fischer Titration  
 Comparison HYDRANAL®-Composite with Reag.Ph.Eur.II / DAB10

Product: Polyethylene Glycol 400

Date of titration: 07.09.04

**Titrant**

 HYDRANAL®-Composite 5  
 Titer: 5.085 mg/ml

**Working medium**

30ml methanol

**Sample handling**

 The sample is administered with a plastic syringe without a needle.  
 Weigh by difference.

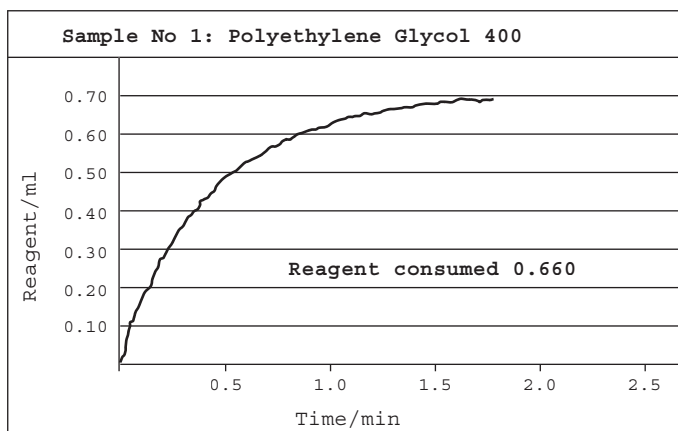
**Procedure**

The working medium is placed in the titration cell and titrated to dryness with the titrant. The sample is then added and titrated in the same way to a stable end-point.

**Recovery of water added**

After achieving the end point a measured amount of water is added and titrated in the same way.

	Samples		Water added	
Sample size (g)	2.166	1.974		
Water added (mg)			5.000	5.000
Reagent consumed (mL)	0.6600	0.6080	0.9830	0.9830
Titration time (min)	1.8	1.9	1.7	1.6
Water found (mg)	3.356	3.092	4.998	4.998
Water content (per cent)	0.1549	0.1566		



## Enclosure 2 .....



Hydranal®-Laboratory  
D-30926 Seelze

Water determination by Karl Fischer Titration  
Comparison HYDRANAL®-Composite with Reag.Ph.Eur.II / DAB10

Product: Polyethylene Glycol 400

Date of titration: 08.09.04

#### Titrant

Karl Fischer Solution according Reag.Ph.Eur.II / DAB10  
Titer: 5.802 mg/ml

#### Working medium

30ml methanol

#### Sample handling

The sample is administered with a plastic syringe without a needle.  
Weigh by difference.

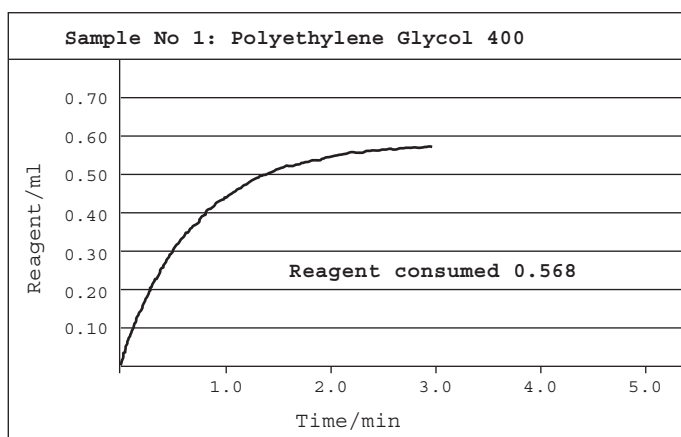
#### Procedure

The working medium is placed in the titration cell and titrated to dryness with the titrant. The sample is then added and titrated in the same way to a stable end-point.

#### Recovery of water added

After achieving the end point a measured amount of water is added and titrated in the same way.

	Samples		Water added	
Sample size (g)	2.126	2.209		
Water added (mg)			5.000	5.000
Reagent consumed (mL)	0.5680	0.5850	0.8620	0.8620
Titration time (min)	2.7	2.7	2.4	2.2
Water found (mg)	3.296	3.394	5.002	5.002
Water content (per cent)	0.1550	0.1537		



## Comparison Tests HYDRANAL®-Composite 5 ..... with reagent Ph.Eur.

### How to Obtain Sample Protocols from the HYDRANAL® Team

All of the comparative protocols and detailed results cited in this report are available for your review by simply contacting us. Indicate which specific sample protocols that you are interested in and request it to us.

Also, if you have a sample that you would like to be analyzed by the same comparison procedure, please contact our Karl-Fischer Help Lines:

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<input type="checkbox"/> Acetone	<input type="checkbox"/> Fluticasone propionate	<input type="checkbox"/> Polyethylene glycol 400
<input type="checkbox"/> Adenosine triphosphate disodium	<input type="checkbox"/> Folic acid	<input type="checkbox"/> Polyethylene glycol 4000
<input type="checkbox"/> Almond oil	<input type="checkbox"/> D(-)-Fructose	<input type="checkbox"/> Polyethylene glycol 6000
<input type="checkbox"/> Ammonium glycyrrhizate	<input type="checkbox"/> Gentamicin sulfate	<input type="checkbox"/> Polyoxyl 40 hydrogen castor oil
<input type="checkbox"/> Amoxicillin trihydrate	<input type="checkbox"/> D(+)-Glucose	<input type="checkbox"/> Polysorbate 20
<input type="checkbox"/> Ampicillin sodium	<input type="checkbox"/> Glucose monohydrate	<input type="checkbox"/> Polysorbate 60
<input type="checkbox"/> Ampicillin trihydrate	<input type="checkbox"/> Glycerol	<input type="checkbox"/> Polysorbate 80
<input type="checkbox"/> Atropine sulfate	<input type="checkbox"/> Glycerol monooleate	<input type="checkbox"/> Polyvinyl pyrrolidone 25
<input type="checkbox"/> Benserazid hydrochloride	<input type="checkbox"/> Glyceryl monostearate	<input type="checkbox"/> Potassium citrate
<input type="checkbox"/> Benzalkonium chloride	<input type="checkbox"/> n-Hexane	<input type="checkbox"/> Potassium Clavulanate
<input type="checkbox"/> Betamethasone sodium phosphate	<input type="checkbox"/> Hexetidine	<input type="checkbox"/> 1,2-Propanediol
<input type="checkbox"/> 1-Butanol	<input type="checkbox"/> Isomalt	<input type="checkbox"/> Quinoline sulf./Potassium sulf.
<input type="checkbox"/> 2-Butanol	<input type="checkbox"/> Isopropanol	<input type="checkbox"/> Saccharin sodium
<input type="checkbox"/> Castor oil	<input type="checkbox"/> Isopropyl acetate	<input type="checkbox"/> tri-Sodium citrate-2-hydrate
<input type="checkbox"/> Cellulose Acetate Phthalate	<input type="checkbox"/> D(+)-Lactose monohydrate	<input type="checkbox"/> di-Sodium hydrogen phosphate-12-hydrate
<input type="checkbox"/> Chlorobutanol-hemihydrate	<input type="checkbox"/> Lidocaine hydrochloride	<input type="checkbox"/> Sodium nitroprusside
<input type="checkbox"/> Citric acid-1-hydrate	<input type="checkbox"/> L(+)-Lysine-1-hydrate	<input type="checkbox"/> Sorbic acid
<input type="checkbox"/> Citric acid anhydrous	<input type="checkbox"/> Macrogol cetostearyl ether	<input type="checkbox"/> Sorbitan monooleate
<input type="checkbox"/> Crospovidon	<input type="checkbox"/> Macrogol stearate	<input type="checkbox"/> Sorbitan monostearate
<input type="checkbox"/> Cyclophosphamide	<input type="checkbox"/> Magnesium aspartate tetrahydrate	<input type="checkbox"/> D(-)-Sorbitol
<input type="checkbox"/> Dexpanthenol	<input type="checkbox"/> Magnesium chloride hexahydrate	<input type="checkbox"/> Soya oil refined
<input type="checkbox"/> Dextrometorphan hydrobromide	<input type="checkbox"/> Maleic acid	<input type="checkbox"/> Sulfacetamide Sodium
<input type="checkbox"/> Dibutylphthalate	<input type="checkbox"/> D-Mannitol	<input type="checkbox"/> Tetrahydrofuran, stabilized
<input type="checkbox"/> Dichloromethane	<input type="checkbox"/> Methanol	<input type="checkbox"/> Tetrahydrofuran
<input type="checkbox"/> Diethylether	<input type="checkbox"/> Methotrexate	<input type="checkbox"/> Theophylline-Ethylene diamine
<input type="checkbox"/> Di-isopropylether	<input type="checkbox"/> Methyl-iso-butylketone	<input type="checkbox"/> Theophylline-Monohydrate
<input type="checkbox"/> N, N-Dimethyl formamide	<input type="checkbox"/> Nikethamide	<input type="checkbox"/> Thiamine hydrochloride
<input type="checkbox"/> Dimethyl sulfoxide	<input type="checkbox"/> Octyl dodecanole	<input type="checkbox"/> Toluene
<input type="checkbox"/> Doxycycline hyclate	<input type="checkbox"/> Olive oil	<input type="checkbox"/> Triamcinolone acetonide
<input type="checkbox"/> Erythromycin ethyl succinate	<input type="checkbox"/> Oxytetracycline hydrochloride	<input type="checkbox"/> Triethyl citrate
<input type="checkbox"/> Esculin	<input type="checkbox"/> Peanut oil	<input type="checkbox"/> Triglyceride (medium-chained)
<input type="checkbox"/> Ethanol (absolute)	<input type="checkbox"/> Penicilline G procaine	<input type="checkbox"/> Valerian root extract dried
<input type="checkbox"/> Ethyl acetate	<input type="checkbox"/> Poloxamere	

## Helpful HYDRANAL® Literature and Contacts .....

### HYDRANAL® Manual

A 128-page manual containing theory & practical advice on Karl Fischer Titration

### HYDRANAL®-Multimedia Guide CD

This Guide covers nine different subjects, and features a video-assisted description of volumetric and coulometric titration and a complete product listing. Over 500 applications and 400 laboratory reports on specific samples, detailed instructions designed according to ISO 9000, comparative analyses with pyridine-containing reagents and advice on disposal of spent reagents are included.

### Contact Information: For technical help, please contact our Karl Fischer Help Lines:

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Table 1 ..... Volumetric Karl Fischer titration – One-component reagents

Cat. No.	Brand	Product	Description	Pack Size
34827	Riedel-de Haën	HYDRANAL®-Composite 1	One component reagent, titer: 1 mL ~ 1 mg water	500 mL, 1 L
34806	Riedel-de Haën	HYDRANAL®-Composite 2	One component reagent, titer: 1 mL ~ 2 mg water	500 mL, 1 L, 2.5 L, 5 L
34805	Riedel-de Haën	HYDRANAL®-Composite 5	One component reagent, titer: 1 mL ~ 5 mg water	500 mL, 1 L, 2.5 L, 5 L
34816	Riedel-de Haën	HYDRANAL®-Composite 5K	One component reagent for titration of aldehydes and ketones, Titer: 1 mL ~ 5 mg water	500 mL, 1 L, 2.5 L
34734	Riedel-de Haën	HYDRANAL®-CompoSolver E	Methanol-free working medium	1 L, 2.5 L
34697	Riedel-de Haën	HYDRANAL®-Solver (Crude) Oil	To use with HYDRANAL®-Composite for titration of oils	1 L, 2.5 L
37855	Riedel-de Haën	HYDRANAL®-LipoSolver CM	To use with HYDRANAL®-Composite for titration of non-polar substances	1 L
37856	Riedel-de Haën	HYDRANAL®-LipoSolver MH	To use with HYDRANAL®-Composite for titration of non-polar substances, fats and oils	1 L
34738	Riedel-de Haën	HYDRANAL®-KetoSolver	To use with HYDRANAL®-Composite 5 K for titration of aldehydes and ketones	500 mL, 1 L
34698	Riedel-de Haën	HYDRANAL®-Medium K	To use with HYDRANAL®-Composite 5 K for titration of aldehydes and ketones	1 L
34817	Riedel-de Haën	HYDRANAL®-Working Medium K	To use with HYDRANAL®-Composite 5 K for titration of aldehydes and ketones	1 L
34741	Riedel-de Haën	HYDRANAL®-Methanol dry	Solvent, max. 0.01 % water	1 L, 2.5 L
37817	Riedel-de Haën	HYDRANAL®-Methanol Rapid	Solvent for a fast Karl-Fischer titration, max. 0.02% water	1 L, 2.5 L

Table 2 ..... Volumetric Karl Fischer titration – Two-component reagents

Cat. No.	Brand	Product	Description	Pack Size
34800	Riedel-de Haën	HYDRANAL®-Solvent	To use with HYDRANAL®-Titrant E or HYDRANAL®-Titrant	1 L, 2.5 L
34811	Riedel-de Haën	HYDRANAL®-Titrant 2	To use with HYDRANAL®-Solvent E or HYDRANAL®-Solvent Titer: 1 mL = 2.00 ± 0.02 mg water (20°C)	500 mL, 1 L, 2.5 L
34801	Riedel-de Haën	HYDRANAL®-Titrant 5	To use with HYDRANAL®-Solvent E or HYDRANAL®-Solvent Titer: 1 mL = 5.00 ± 0.02 mg water (20°C)	500 mL, 1 L, 2.5 L
34730	Riedel-de Haën	HYDRANAL®-Solvent E	Methanol free solvent to use with HYDRANAL®-Titrant E or HYDRANAL®-Titrant	500 mL, 1 L, 2.5 L
34723	Riedel-de Haën	HYDRANAL®-Titrant 2 E	Methanol free titrant to use with HYDRANAL®-Solvent E or HYDRANAL®-Solvent Titer: 1 mL = 2.00 ± 0.02 mg water (20°C)	1 L
34732	Riedel-de Haën	HYDRANAL®-Titrant 5 E	Methanol-free titrant to use with HYDRANAL®-Solvent E or HYDRANAL®-Solvent Titer: 1 mL = 5.00 ± 0.02 mg water (20°C)	500 mL, 1 L, 2.5 L
34812	Riedel-de Haën	HYDRANAL®-Solvent CM	To use with HYDRANAL®-Titrant for titration of fats and oils	1 L, 2.5 L
34749	Riedel-de Haën	HYDRANAL®-Solvent Oil	To use with HYDRANAL®-Titrant for titration of oils	1 L

Table 3 ..... Coulometric Karl Fischer titration

Cat. No.	Brand	Product	Description	Pack Size
34807	Riedel-de Haën	HYDRANAL®-Coulomat A	Anolyte for cells with diaphragm reagent contains chloroform	500 mL
34836	Riedel-de Haën	HYDRANAL®-Coulomat AG	Anolyte suitable for cells with and without diaphragm	500 mL, 1 L
34810	Riedel-de Haën	HYDRANAL®-Coulomat AD	Reagent for cells without diaphragm	500 mL
34843	Riedel-de Haën	HYDRANAL®-Coulomat AG-H	Anolyte for titration of long-chained hydrocarbons free of halogenated hydrocarbons	500 mL
34820	Riedel-de Haën	HYDRANAL®-Coulomat AK	Anolyte for titration of ketones	500 mL
34739	Riedel-de Haën	HYDRANAL®-Coulomat AG Oven	Anolyte for determination with a KF-oven	500 mL
34829	Riedel-de Haën	HYDRANAL®-Coulomat AF-7	Anolyte suitable for coulometer AF 7	1 L
34726	Riedel-de Haën	HYDRANAL®-Coulomat E	Ethanol based reagent to be used as anolyte and catholyte	500 mL
34840	Riedel-de Haën	HYDRANAL®-Coulomat CG	Catholyte, free of halogenated hydrocarbons 25 mL bottle resp. 10 x 5 mL ampoules	25 mL, 50 mL
34821	Riedel-de Haën	HYDRANAL®-Coulomat CG-K	Catholyte for titration of ketones contains 10 ampoules of 5mL	50 mL
34868	Riedel-de Haën	HYDRANAL®-Coulomat Oil	Anolyte for titration of oils	100 mL, 500 mL

Table 4 ..... Standards for Karl Fischer titration

Cat. No.	Brand	Product	Description	Pack Size
34849	Riedel-de Haën	HYDRANAL®-Water Standard 10.0	Standard for volumetric Karl Fischer titration 1 g contains 10.0 mg = 1.00 % water contains 10 glass ampoules of 8 mL Traceable to NIST SRM 2890	80 mL
34828	Riedel-de Haën	HYDRANAL®-Water Standard 1.00	Standard for coulometric Karl Fischer titration 1 g contains 1.00 mg = 0.10 % water contains 10 glass ampoules of 4 mL Traceable to NIST SRM 2890	40 mL
34847	Riedel-de Haën	HYDRANAL®-Water Standard 0.10	Standard for coulometric Karl Fischer titration 1 g contains 0.10 mg = 0.01 % water contains 10 glass ampoules of 4 mL Traceable to NIST SRM 2890	40 mL
34748	Riedel-de Haën	HYDRANAL®-Water Standard KF-Oven	Solid standard for control of Karl Fischer ovens assay of water: 5.55 ± 0.05 %	10 g
34813	Riedel-de Haën	HYDRANAL®-Standard 5.00	Non hygroscopic standard for volumetric Karl Fischer titration	100 mL, 500 mL
34803	Riedel-de Haën	HYDRANAL®-Standard-sodium tartrate-2-hydrate	Primary standard for volumetric Karl Fischer titration assay of water: 15.66 ± 0.05 %	100 g
34696	Riedel-de Haën	HHYDRANAL®-Standard-sodium tartrate-2-hydrate	Traceable to NIST SRM 2890	25g

Table 5 ..... Other products

Cat. No.	Brand	Product	Description	Pack Size
34802	Riedel-de Haën	HYDRANAL®-Water-in-methanol Standard 5.00	Standard for volumetric back titration, water content: 5.00 ± 0.02 mg/mL	1 L
34804	Riedel-de Haën	HYDRANAL®-Buffer Acid	Buffer capacity: 5 mmol acid/mL	500 mL
37859	Riedel-de Haën	HYDRANAL®-Buffer Base	Buffer substance, max. 0.03 % water	500 mL, 1 L
34741	Riedel-de Haën	HYDRANAL®-Methanol dry	Solvent, max 0.01% water	1 L
37863	Riedel-de Haën	HYDRANAL®-Chloroform	Solubilizer, max. 0.01 % water	1 L
34724	Riedel-de Haën	HYDRANAL®-Formamide dry	Solubilizer, max. 0.02 % water	1 L
37864	Riedel-de Haën	HYDRANAL®-Imidazole	Buffer substance, max. 0.1 % water	500 g
34788	Riedel-de Haën	HYDRANAL®-Humidity Absorber	Drying agent for air and gases with indicator	500 g, 1 kg
34241	Riedel-de Haën	HYDRANAL®-Molecular Sieve 0.3nm	Molecular sieve suitable for Karl Fischer applications	250g, 1kg
37866	Riedel-de Haën	HYDRANAL®-Xylene	Solubilizer, max. 0.01 % water	1 L
37865	Riedel-de Haën	HYDRANAL®-Salicylic acid	Buffer substance, max. 0.2 % water	500 g
37862	Riedel-de Haën	HYDRANAL®-Benzoic acid	Buffer substance, max. 0.01 % water	500 g

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