7. Production of Water for Injection by Membrane Process

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ABSTRACT:

Reverese osmosis or ultrafiltration systems have generally been regarded as hard to validate about WFI production.
Though the Japanese and US Pharmacopoeias have allowed distillation and RO to be applied to WFI production process, only water stills, especially multiple effects have practically been employed for parenteral water production.
On the other hand, the latest analysis has shown that even distillate contains such volatile organic matters as trihalomethanes and traces of heavy metals at a little higher concentration than supposed.
The JP requires TOC to be monitored in WFI process based on RO or UF systems to control the concentration below 300ppb, but very few monographs or papers have so far been published about the concentrations of organic volatile matters in distillate. (See table 1-1)
Therefore, this paper proposes a new applicable WFI systems based on the result of purified water analysis with some membranes used in the process.
A well combined membrane system with other units could be expected to provide less amount of impurities in membrane-treated water than in distillate.

KEY WORDS: JP, WFI, Membrane-treated Water, Highly Pure Water, Water Quality, Heavy Metal, TOC, Nonvolatile matter, Volatile Organic Substances

INTRODUCTION:

High purity is required for water used for the pharmaceutical injection process.
Water for Injection abbreviated to "WFI" is a typical example, for which distillation has predominantly been used in the production equipment.
Membrane systems, however, have generally been applied to such process as pretreatment for distillation or flushing and final rinsing.
The author has experienced in a wide range of high purity WFI production systems including distillation and membrane methods in the pharmaceutical industry as well as the semiconductor industry.
No virtual difference in water quality has been found between the above two kinds of methods, when some quality items required for WFI were analysed by us.
A subtle difference may be detected, if more detailed analysis is performed about impurities.
From this viewpoint, water quality was scrutinised in feed water and distillate respectively at five WFI plants, all of which have been supplied by Nomura Micro Science Co. to the relevant industry in Japan.

On the other hand, highly pure water is used to wash impurities off wafers in the various steps of the semiconductor process.
Various kinds of pure waters are manufactured by membrane systems in the industry.
The water quality items required for washing wafers are not quite the same as in WFI, but the lowest possible concentration must be prepared to reduce the impurities of TDS.
Therefore, the above water analysis should precisely be made, and so the analytical method has been applied to measuring impurities in WFI, too.
As the result of this analysis, a particular matter is detected in distillate distinct from water treated by membrane systems.
Further interesting data obtained are described below.
The way to remove impurities for WFI is also reviewed in comaprison with water for washing wafers.

1. Items and Methods to Evaluate Water Quality

As endotoxins are the most important factor, which is not evaluated in highly pure water for the semiconductor field, the endotoxin level is analysed for WFI evaluation.
TOC is a common quality in WFI and semiconductor water as well.
Nonvolatile particulates are an item recently regulated for automatic in-line control with a highly sensitive monitoring unit, so it is included for analysis.
Silica analysis is also adopted to examine the correlation with nonvolatile matters for WFI quality control.
Metals are quantified in each element, and volatile organic matters are analysed to find out what exist in TOC.

Table 1-1 WFI Quality Standards of Japanese Pharmacopoeia

Control Items		Distillate	Membrane-Treated Water	
			Action Level	Alert Level
Conductivity			<1μ s/cm	<0.2μ s/cm
Live Microbes			<10cfu/100ml	<10cfu/1000ml
Endotoxin(by Limulus Test)		<0.25EU/ml	0.25 EU/ml	<0.1 EU/ml
Insoluble Particulate	over 10 μ m	<20 p./ml	<20 p./ml	<1 p./10ml
	over 25 μ m	<2 p./ml	<2 p./ml	<1 p./100ml
TOC in line			<300 ppb	<100 ppb
off line			<500 ppb	

Remarks: 1. TOC is applied to membrane systems.
2. cfu is the abbreviation of colony forming unit.
3. 1 EU nearly equals 0.1 ppb.

Table 1-2 Evaluation Items and Measurement Methods

Analysis Items	Measurement Methods	Quantitative Lower Limit
Endotoxins	Limulus Test	0.01EU/mℓ
TOC	NDIR(Nondifussed Infrared Gas Analysis by OI-700)	30μg/ℓ
Nonvolatile Matter	HPM (High Pure Monitor ᴿ)	1 μg/ℓ
Silica	Molybdate Blue Absorptiometric Analysis	5 μg/ℓ
Metals	GF-AAS or ICP-MS	0.01 - 1μg/ℓ
Volatile Organic Matters	PT-GC-MS	

2. Points Sampled at Five Pharmaceutical WFI Plants and One Semiconductor Plant

System A: Supply Water ----→ M.B.-○→ R.O.-○→ Distillation --○→

System B: Supply Water ----→ A.C.----→ M.B.----→ Distillation --○→
○→ U.F. ----------○→

System C: Supply Water ----→ R.O.----→ A.C.----→ M.B.-○→ Distillation --○→
---→ U.F. --------○---→

System D: Supply Water ----→ R.O.-○→ M.B.-○→ Distillation --○→

System E: Supply Water ----→ A.C.-○→ M.B.-○→ Distillation --○→
--→ U.F. -----------→

System F: Industrial Water ----→ R.O.------→ 2B3T -----→ M.B. --○→ R.O. ---┐
(for semiconductor) ←--○-- U.F. ←---- M.B. ←○-- U.V. ←○--┘

○ mark : Sampling Points M.B.: Mixed Bed Deionizer R.O.: Reverse Osmosis
A.C.: Activated Carbon U.F.: Ultrafiltration
2B3T: Two Beds Three Towers Deionisation Unit U.V.: Ultraviolet Radiation (185 nm)

Note: The use points are followed at each System end.

Fig. 1 Process Flows of Respective Systems Examined by Sampling

3. Water Qualities before and after Distillation

Feed waters to stills and distilled waters were analysed as follows;

3.1 Endotoxins

The endotoxin concentrations in the respective samples from System A to System E were 0.1 EU/ml or below the lower limit in feed waters and below the lower limit in distillates, all of which were far below the maximum endotoxin limit of 0.25 EU/ml for WFI specified in the pharmacopoeias.

3.2 TOC

The removal rates of TOC by distillation were 19% and 61% for the first and second samplings at System A , and 16% at System E, but 0% at Systems B, C, and D.

The data shows that distillation may not be expected to remove organic matters related to TOC at a lower concentration than 100ppb, depending on feed water quality.

3.3 Nonvolatile Matters

The data shows that distillation will provide a very high removal rate.

The feed of System D shows an abnormally high concentration of nonvolatile matters due to extremely saturated ionexchange resins which need to be immediately regenerated, but its concentration was drastically reduced from over 1,000ppb to 12ppb after distillation.

3.4 Silica

Though a variety of silica concentrations were found in feed waters of the systems A to E, distillates' silica concentrations were 5 $\mu g/l$ to 8$\mu g/l$.

As a comparatively high correlation is found between nonvolatile matters and silica concentrations., a large part of nonvolatile matters in the feed water is supposed to be silica.

3.5 Metals

Traces of heavy metals were detected in all the distillates except System E.

The structural material of water stills is stainless steel AISI 316 or 316L, which main elements are composed of Fe, Cr, Ni, and Mo (316L), so they should have been dissolved in water through distillation heating.

The other elements of Na, Al, Cu, and Co were found and appeared to be originated from the other source than stainless steel materials.

4 . Qualities of Waters Treated with Membranes

4.1 Endotoxins

The system A's RO achieved an endotoxin romoval rate over 99%, but no removal rate was obtained with the UFs of systems B, C, and F, because feed-in waters were far below the lower quantitative limit of 0.01 EU/ml.

The feed waters to UF may be well ion-exchanged as well as good quality water supplied to each deioniser.

Anyway, all the membrane-treated waters of systems A, B, C, and F were proved to contain far less amount of endotoxins than 0.25 EU/ml.

4.2 TOC

The system A's RO gave about 50 - 65% TOC removal rate, but UFs of Systems B and C gave 0% because of too low TOC concentrations in their feed waters.
The actual concentrations in the system F, however, have been reported to be less than 1 μ g/l by the analysis on the operation.

4.3 Nonvolatile Matters

The system A's RO gave 53% removal rate, but the system B's UF had no effect on removal.
Moreover, System F showed a far lower concentration than 1μ g/l as feed water to UF, so that two stages RO treatment could contribute to higher reduction of nonvolatile matters.

4.4 Silica

The system A's RO gave about 50 - 60 % removal rate, but UF systems of B and C had naturally no effect on silica removal.
The system F had the similar data as shown in the nonvolatile matters.
All the data of silica has also shown a correlation with nonvolatile matters, which may prove that nonvolatile matters are mostly composed of silica.

4.5 Metals

All the metals were found at very low concentrations less than 1 μ g/l except Na in the first sampling water of system A.
Na in the system A is supposed to come from the deioniser due to incomplete rinsing after regeneration.

5 . Monitoring Traces of Nonvolatile Matters in Process Water

High Pure Monitor ^{R} is a continuous-measurement unit to quantify a ten ppt order of nonvolatile matters in water and applicable in line.
A conventional measurement device can generally provide a detection limit up to a ppm order by a resistivity metre, but HPM allows nonions including endotoxins to be detected.
As good membrane systems will highly reduce an amount of endotoxins in water, HPM will be an important monitoring unit by detecting all nonvolatile matters, which may involve silica, metals, high molecular organic substances such as pyrogens.
This idea is supported by the analysis data, in which silica was found as a main or a single substance of nonvolatile matter in each water level.
The measurement results are shown in Fig.2 and Fig.3.
Though what substances are included in TOC is not clearly found out, HPM is proved very useful to monitor and detect total nonvolatile matters or silica.

6. Proposal for Improvement in WFI quality

As described before, such impurities as nonvolatile matters and volatile organic substances were shown to exist in water treated by either distillation or membrane systems, which are RO or UF.
Traces of heavy metals and TOC are found in distillate, and silica and TOC are in membrane-treated water.
On the other hand, all the above impurities were undetectable in highly pure water for the semiconductor application.
The reasons why the difference is developed in quality between pharmaceutical and semiconductor waters should be considered as follows;

6.1 Heavy Metals

Traces of metals were detected in distillate and other treated waters except Na in System A and Fe in System D.
Traces of heavy metals are considered originated from stainless steel material of AISI 316 used for the tanks, piping, and water stills.
Some other metals may have been due to imcomplete deionisation by membranes.
On the other hand, all metal in System F water was under the lower quantitative limit, so no metal detection is considered to be due to the entire impurities removal system, which was constructed with piping and tanks made of polymer materials.

6.2 TOC

Though deionisation, RO, and UV are usually aaplied as effective means to remove TOC, deionisation and RO as well as distillation are insufficient as shown in Table 2.
Therefore, WFI could naturally contain an amount of TOC in a range from 10 to 100ppb.
TOC-UV with a wave length of 185nm is generally applied to ionise organic substances in the semiconductor purified-water.
Actual composition in TOC, however, is not clarified.
Original raw feed waters are supposed to contain traces of many organic matters, which include volatile matters.
The organic volatile matters were analysed in the sampled process waters by System E and System F, and the results are shown in Figs.4 -7.
Chloroform is detected in them as follows;

System E: 14ppb in deionised water and 7ppb in distillate
System F: about 70ppt in deionised water and about 3ppt in TOC-UV treated water

6.3 Nonvolatile matters and Silica

As nonvolatile matters were found to consist mostly of silica, TOC will contain very little nonvolatile matters; in other words, TOC level can nearly equal organic volatile matters concentration.
The data shows that a single RO stage should be insufficient to remove nonvolatile matters at a higher rate than 90%.

CONCLUSION

The water treatment system for the semiconductor industry has proved to produce highly pure water in comparison with WFI, so that the following proposal (Fig. 8) could be applied to WFI production system instead of distillation.

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Suuply Water -----→ Deionisation ----→ RO ----→ TOC-UV + Deioniser -----┐
                                         Use point ←--- UF ←-------------┘
                                                          Heating at 80 ℃
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Fig. 9 Proposed Ideal Flow

A combination of the deioniser and RO system should be variable to meet supply water quality in order to desalinate at a high rate.
The RO is to be applied for removing organic matters, pyrogens, and traces of residual ions.
The TOC-UV combined with a deioniser is to decompose organic matters into ionisation and to be deionised .
Finally, heated highly pure water is passed through UF to be fed to use points.
Sterilisation can be made at UF because of pure water heated at 80℃ .
This total system can possibly provide highly pure water including traces of nonvolatile matters at a concentration of 50ppt or lower.
Silica is proved to be a main substance in the nonvolatile matters, so a new version of High Pure Monitor^{R} can be applied as an endotoxins monitoring unit, because 0.25EU/ml will correspond to about 0.05 μg/l, that is 50 ppt.
The above system will allow endotoxins to be monitored by controlling an extremely low concentration of nonvolatile matters with High Pure Monitor as well as TOC metre in-line, with which the total system can be validated.

Table 2 Water Quality Analysis By Various System

Item		Unit	System A (1)			System A (2)			System B		
			RO in	RO out	Still out	RO in	RO out	Still out	UF in	UF out	Still out
Endotoxins		EU/mℓ	8.8	<0.01	<0.01	13	<0.01	<0.01	<0.01	<0.01	<0.01
TOC		μg/ℓ	100	36	<30	100	48	<30	30	<30	30
N.V.M (*)		μg/ℓ	145	68	2	—	—	3	143	155	5
Silica		μg/ℓ	200	81	<5	13	6	<5	140	180	5
Metals	Na	μg/ℓ	13	7.0	<0.01	0.73	0.66	<0.01	1.1	0.32	0.73
	Fe	μg/ℓ	—	—	—	—	—	—	—	—	—
	Cr	μg/ℓ	<1	<1	<1	<1	<1	<1	<1	<1	<1
	Ni	μg/ℓ	<0.1	<0.1	0.2	<0.1	<0.1	0.2	0.3	<0.1	0.4
	Mo	μg/ℓ	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.07
	Mn	μg/ℓ	0.1	0.05	<0.05	0.08	<0.05	<0.05	1	1	0.06
	Al	μg/ℓ	1	0.2	<0.1	1	0.1	<0.1	<0.1	<0.1	<0.1
	Cu	μg/ℓ	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.3	<0.05	<0.05
	Co	μg/ℓ	<0.05	<0.05	0.2	<0.05	<0.05	0.2	<0.05	0.08	<0.05

Item		Unit	System C			System D		System E		System F	
			MB out	UF out	Still out	Still in	Still out	Still in	Still out	UF in	UF out
Endotoxins		EU/mℓ	<0.01	<0.01	<0.01	<0.01	<0.01	0.10	<0.01	<0.01	<0.01
TOC		μg/ℓ	<30	<30	<30	84	81	120	100	<1	<1
N.V.M (*)		μg/ℓ	>100	>100	7	>1000	12	—	—	<1	<1
Silica		μg/ℓ	100	100	<5	8600	8	9	<5	<0.1	<0.1
Metals	Na	μg/ℓ	0.30	0.32	<0.05	<0.05	0.23	0.16	0.01	<0.01	<0.01
	Fe	μg/ℓ	<0.1	<0.1	<0.1	<0.10	12	0.44	<0.01	<0.1	<0.1
	Cr	μg/ℓ	<0.1	<0.1	<0.1	<0.1	0.5	0.1	<0.1	<0.1	<0.1
	Ni	μg/ℓ	<0.05	<0.05	0.37	<0.05	0.27	0.07	<0.05	<0.05	<0.05
	Mo	μg/ℓ	<0.01	<0.01	0.05	<0.01	0.02	<0.01	<0.01	<0.01	<0.01
	Mn	μg/ℓ	<0.01	<0.01	0.06	0.05	0.15	0.05	<0.01	<0.01	<0.01
	Al	μg/ℓ	<0.05	<0.05	<0.05	1.0	0.14	0.03	0.01	<0.05	<0.05
	Cu	μg/ℓ	<0.02	<0.02	0.02	<0.02	<0.02	0.08	<0.02	<0.02	<0.02
	Co	μg/ℓ	<0.01	<0.01	0.01	0.19	0.01	<0.01	<0.01	<0.01	<0.01

(*) Nonvolatile Matters

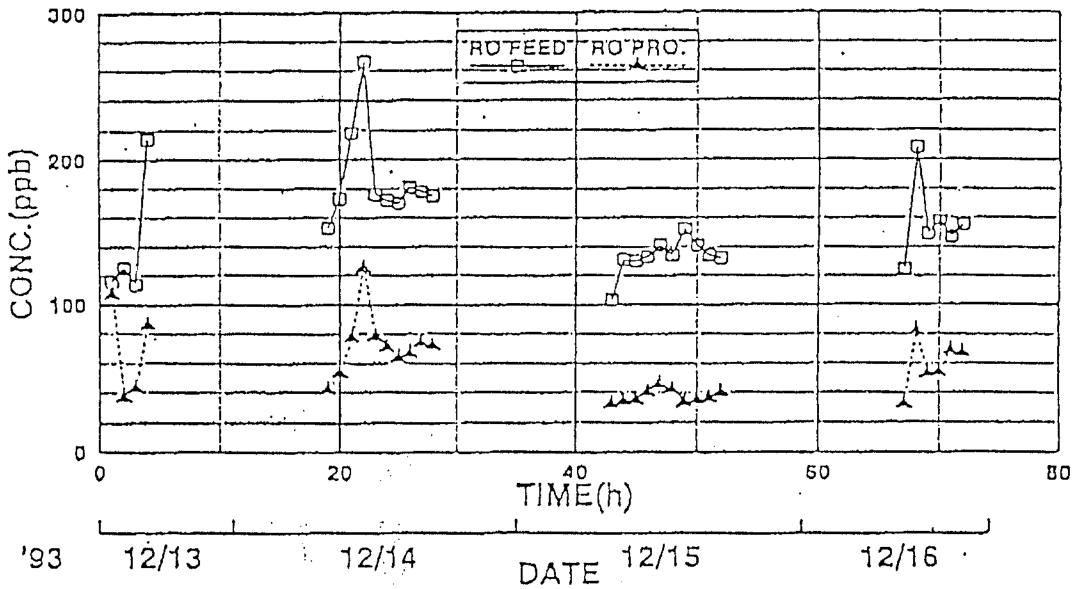

Fig.2 Concentrations of Nonvolatile Matters before and after RO at System A

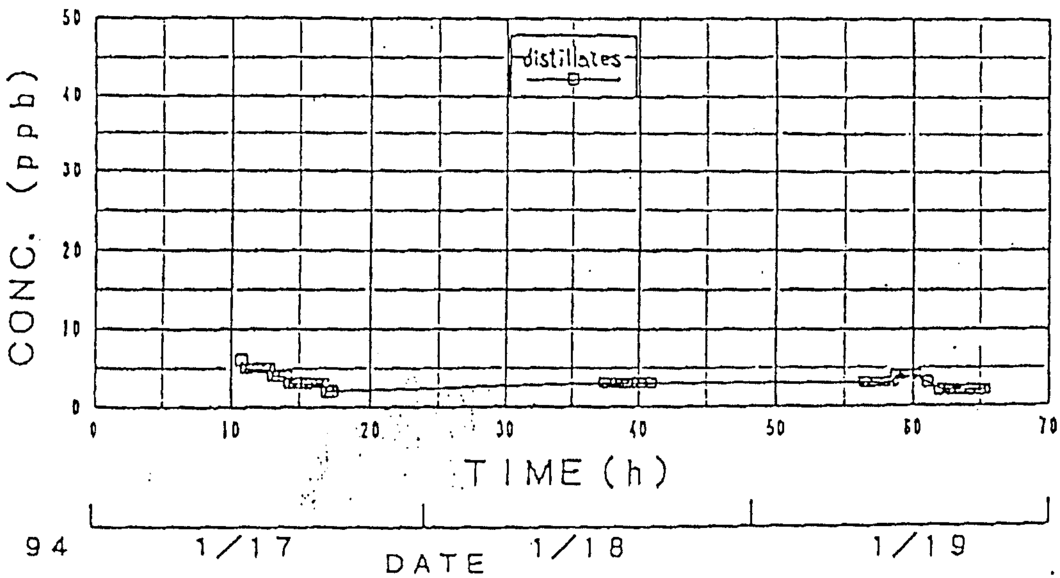

Fig.3 Concentrations of Nonvolatile Matters ~~before and~~ after

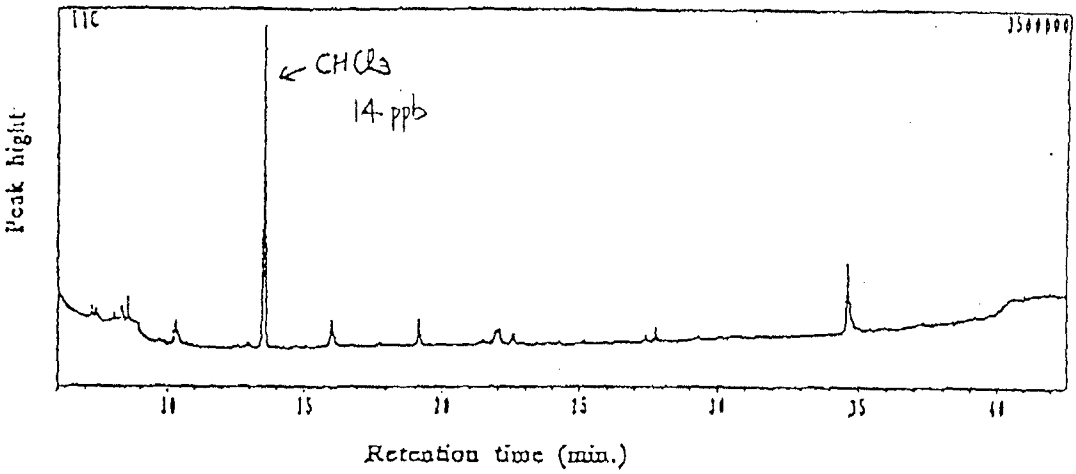

Fig. 4 Organic Volatile Matters in Water befor Distillation at System E

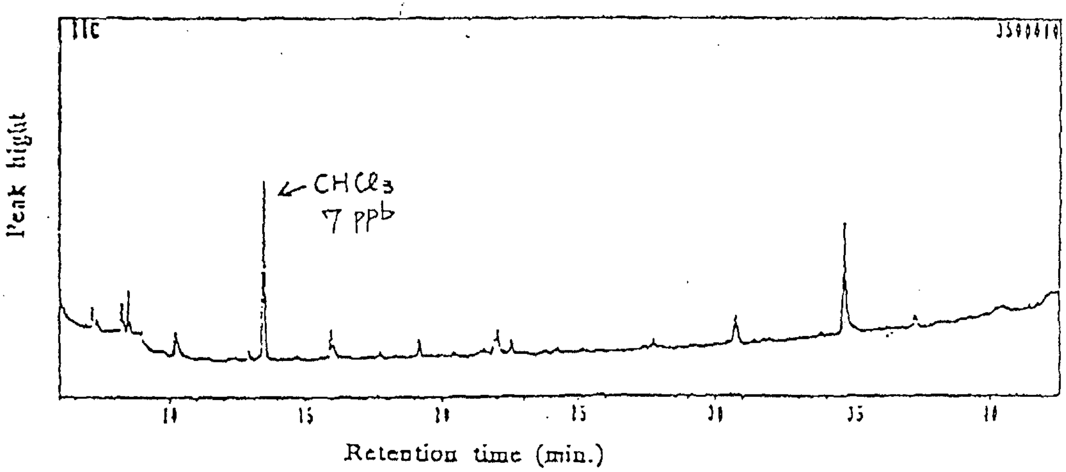

Fig. 5 Organic Volatile Matters in Water after Distillation at System E

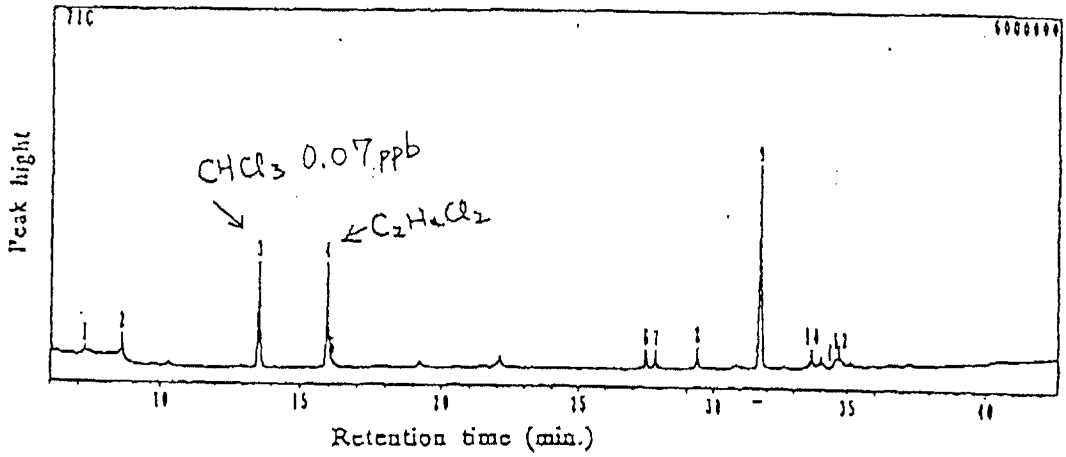

Fig. 6 Organic Volatile Matters in Water
Deionized at System F

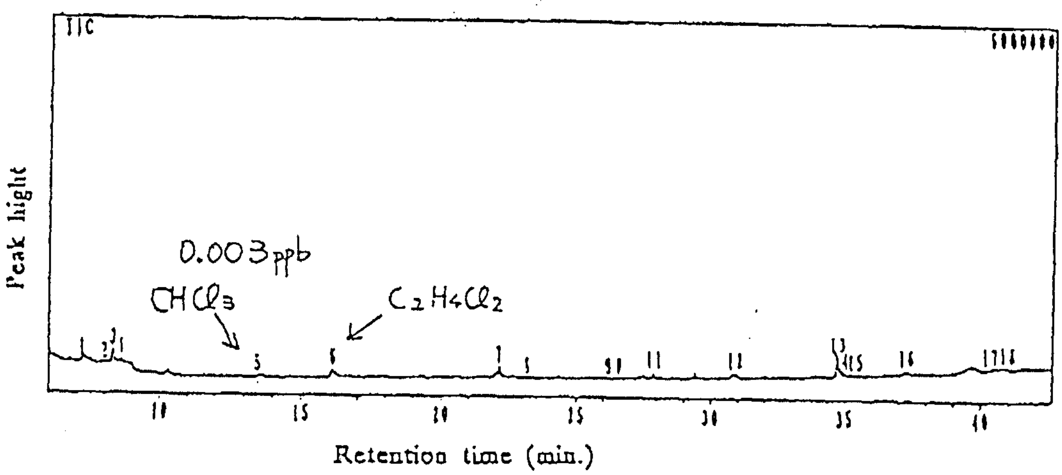

Fig. 7 Organic Volatile Matters in Water
Treated by TOC–UV at System F