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HIGH-LEVEL ADVISORY ASSISTANCE TO STREAMLINE THE PROCESSING TECHNOLOGY OF "LITYAZOL CEMIL", A HERBAL PHARMACEUTICAL PRODUCED IN TURKEY

SI/TUR/93/801/11-01

TURKEY

Technical report: Findings, work performed and recommendations (second mission)*

Prepared for the Government of Turkey
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of M. B. Narasimha, chemical technologist

Backstopping Officer: T. De Silva
Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

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* This document has not been edited.

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ABSTRACT

The expert on mission (second and final mission) to the project SI/TUR/93/801/11-01, was briefed by the Backstopping Officer at Vienna during 12-14 April 1994 and given him the benefit of advise in the implementation of the final phase of the project. The Backstopping Officer also reviewed the progress made, during his visit to the project site during 27 to 28 April 1994 and tendered appropriate advise for the demonstration and training of the counterpart chemical engineer, in all aspects of the upgraded technology and quality control.

The old and obsolete processing methods being followed in the manufacture of "Lityazol Cemil" from the dried root bark of *Scolymus hispanicus*, at Dr. Cemil Sener Laboratory Ltd., Manisa, Turkey, was updated at the Medicinal Plants Research Centre (MPRC) under the technical guidance of the UNIDO expert during his first mission December 1993/January 1994.

Upon his arrival on 15 April 94 at the mission site (TBAM), he discussed and reviewed with NPD, the progress made during the intervening period.

The consultant visited the Factory at Manisa, near Izmir, accompanied by a counterpart engineer and discussed with the Managing Director and Commercial Manager of the company, the operational implementation of the updated production technology in the Company's Laboratory (Factory). The Laboratory's Managing Director indicated by letter (Annex 2) that "Since the implementation of the newly developed technology requires additional investment and because of the economic crisis in the country nowadays it is not possible for us to invest a large amount of money right now. But, as soon as, the crisis is overcome we clearly state that we will finance and implement the newly developed technology in our factory". However, he expressed his desire to train his technical staff "We will send our technical personnel to TBAM for the demonstration and training on the newly developed technology and quality control methods in the first half of May 1994".

This proposal was agreed to by the Backstopping Officer, Director of Medicinal Plants Research Centre and the expert on mission at a meeting held at MPRC on 27th April 94 with Mr. Rahit Karaosmanoglu, the Managing Director of Laboratory.

The consultant successfully demonstrated the updated processing technology for the production of "Lityazol Cemil" and trained a counterpart chemical engineer, in all aspects of the updated processing technology and quality control methods. The "hands on training" included lectures detailing the salient features of the updated technology and notes (Annex 3) covering the background information and details of the updated technology, description of pilot plant and quality control methods.

The results obtained confirms the conclusions drawn at the end of the expert's first mission, (Annex 4).

The pilot plant was modified incorporating pumps and in the piping manifold. As a result of these modifications, the pilot plant is truly working as a counter-current battery system.

With these modifications to the pilot plant, operational technique (maceration of the drug with ethanol 1:1 ratio), has further increased the extraction efficiency of *Scolymus hispanicus* and reduced one cycle time of percolation from about 9-10 to just 4 h. This meant that, as a result of updated processing technology of "Lityazol Cemil", the cycle operation time was reduced from 42 days to 4 hours, and higher yield of the product (extract) from 3 litres per 1 kg of the drug (first mission, prior to the modification) to 4 litres per kg drug without affecting the quality of the product.

The consultant also designed a commercial plant for the production of "Lityazol Cemil" based on updated technology.

This compactly designed plant can be easily accommodated in the existing building of the Dr.Cemil Sener Laboratory at Manisa without any modifications or additions.

The solvent recommended for the production of "Lityazol Cemil" is rectified spirit (95% ethanol).

The design drawings are in Annex 5.

He also designed and assisted in the fabrication of a continuous vacuum evaporator cum distillation unit of 50 litre/h capacity (evaporation).

This activity has resulted in not only considerable savings in the amount of money in foreign exchange, valuable time, but also highly valuable training and confidence afforded to a local fabricator, who is planning to diversify his production line to include fabrication of chemical plant and equipment. He is presently building tractor cabins in mild steel and glass.

INTRODUCTION

Dr. Cemil Sener Laboratory at Manisa, near Izmir, Turkey is reported to be the only company, producing "Lityazol Cemil" which is, an alcoholic extract of the root bark of the wild herb *Scolymus hispanicus*. The liquid extract is effectively used against "stone disorders" in the urinary track, and is being produced uninterruptedly since 1934. Since then the process technology and the equipment remained unchanged which have become obsolete and uneconomical.

The production of "Lityazol Cemil" is a batch operation which takes 42 days and results in about 83% solvent losses (96% ethyl alcohol).

The company is currently using about 2 tonnes of dried material and about 2630 litres of 96% ethanol a year to produce annually about 2000 litres of product to no known quality, since no quality control facilities and trained personnel are available, except pH, viscosity and specific gravity measuring instruments.

The UNIDO expert on mission to the current project No. SI/TUR/93/801/11-01 titled "High level advisory assistance to streamline the processing technology of "Lityazol Cemil", a herbal pharmaceutical produced in Turkey, was mandated to carry out the duties as given in the job description (Annex 1), specifically a detailed report outlining the improved technological process and quality specifications of "Lityazol" and recommendations on increasing production through:

- reduced batch operation period from 42 days to 1/4 of the present duration,
- reduced solvent losses from the current level of 83%,
- improve the economy of production and marketing for local and eventual foreign market.

The expert was specifically required to work in collaboration with counterpart staff at Sener Factory and Anadolu University in carrying out the following duties:

- Survey the site for Lityazol production and work out layout.
- Survey sources for equipment production.
- Prepare a list of required equipment after developing the process.
- Conduct pilot runs and testing on Lityazol products at Anadolu University.
- Develop process technology and process control parameters for the improvement of production of "Lityazol" at MPRC.

<u>Present Set - up</u>

The expert during the first mission, (December 93-January 94,) in collaboration with counterpart engineer and scientists streamlined the processing technology and up-dated the technology for the production of "Lityazol Cemil" from root bark of *Scolymus hispanicus* :

The following optimum conditions were established:

- coarsely powdered, dried root bark could be used
- one is to four ratio of solid to solvent
- rectified spirit (96% ethanol) be used as solvent
- three percolations for 3.5 hours each on counter-current principle on battery system
- solvent losses could be reduced to about 15%
- the time to complete one batch is about 9-10 h.
- the efficiency of the extraction is about 85-90%

The technology package developed consisted of design drawings of plant and equipment, analytical correlations and pharmacological studies for the activity of the ethanol extract.

2. ACTIVITIES

The expert on mission visited the Laboratory at Manisa accompanied by a counterpart engineer and discussed with the Managing Director and Commercial Manager of the Laboratory about the activities and the company's plans regarding the implementation of updated processing technology in the production of "Lityazol Cemil". The company director expressed his regret about the delay in implementation of the updated technology in his Laboratory, since it requires additional investment and because of the economic crisis in the country nowadays, it is not possible for him to invest large amounts of money right now. But, as soon as, the crisis is overcome, he will finance and implement the newly developed technology in the factory. He agreed to send his technical staff to Medicinal Plants Research Centre (MPRC) for demonstration and training on the newly developed technology and quality control methods (Annex 2).

The BSO, Director of the Medicinal Plants Research Centre (MPRC) and the expert agreed to this proposal at a meeting held at MPRC on 27th April 1994 with the Managing Director of the Laboratory.

The consultant successfully demonstrated and trained a counterpart chemical engineer (of Dr. Cemil Sener Laboratory), in the updated technology for the production of "Lityazol Cemil" a herbal pharmaceutical product produced in Turkey.

The training included (i) lectures detailing the salient features of the updated processing technology and written notes (Annex 3) covering theory of battery percolation system, background information, description of pilot plant with flow diagrams, operation procedure supported by two flow diagrams of the battery percolation system, quality control methods for the determination of water, ethanol extractable matter from the ethanolic extract and spectrophotometric measurements for the determination of total triterpenic compounds. (ii) hands on training at the pilot plant at MPRC, a battery percolation system. A total of nine battery cycles were performed during the training period. The battery system ensures counter-current flow of solvent through a battery of three percolators and the charge in any one percolator is treated by a succession of liquid of constantly decreasing concentration from stage to stage in a counter-current system.

The training covered all aspects of the processing technology at the pilot plant, operational techniques, process control parameters, quality control techniques and safety aspects of operating solvent extraction pilot and commercial plants. A note on safety aspects of solvent extraction plants is appended in Annex 7.

Also included in the training programme was the use of analytical instruments like UV spectrophotometer and interpretation of data in the determination of total dry matter and triterpenic compounds.

In addition, the consultant carried out the following activities:

1. Designed a commercial plant for the production of "Lityazol Cemil" based on updated technology.

The plant designed is a three stage battery percolation system to work continuously on a counter current principle, and can be operated for 24 h/day, 16 h/day or 8 h/day, and is capable of processing 37 to 45 tonnes per annum (tpa), 25 to 30 tpa and 12 to 15 tpa respectively.

This compactly designed plant can be easily accommodated in the existing building of the Dr.Cemil Sener Laboratory at Manisa without any modifications or additions.

Rectified spirit (ethanol of 96% concentration) was recommended as the solvent for the production of "Lityazol Cemil". However, if the management so desires to diversify its production line to other products (it is strongly recommended), needing the use of n-hexane as a solvent, the management can easily switch over to it, provided the following conditions are full-filled at the time of implementation.

- all the existing electrical wirings, light fittings, switches etc. in the plant building should be replaced with explosion proof type.
- the motors, starters, switches etc. should be of explosion proof type.
- the plant and support structure should be properly and adequately earthed so as to afford proper protection against static current.
- the building housing the plant should be well ventilated
- smoking in the entire building should be totally prohibited.

The design drawings are given in Annex 5.

2. Designed and assisted in the fabrication of a continuous evaporator cum distillation still, capacity 50 litre/h.

The design of a flash evaporator has been suitably modified to facilitate its use, not only as an evaporator but also for distillation operations, under vacuum.

Worked out details of all its components and drew detailed shop drawings of the following units:

- General assembly including water ring vacuum pump (30 m^3/h 3 kw motor)
- Calandria .. surface area .... 1.0 m^2
- Direct contact condenser
- Shell and tube condenser .... 1.3 m^2
- Receiver
- Interconnecting pipe lines
- Support structure and the specifications of the bought-out accessories.

Surveyed local engineering workshops and identified a potential fabricator of the unit under reference. This firm is already in the trade of manufacturing tractor cabins in mild steel and glass, but has basic infrastructure to undertake the fabrication of plant and equipment in stainless steel. The engineers and technicians of the firm expressed the need for proper guidance and supervision during fabrication of the pilot plant, since the firm had no prior experience in undertaking such jobs. Accordingly UNIDO expert who has wide experience in design and engineering including fabrication of chemical plants and equipment, extended appropriate guidance at the various stages of fabrication and assembly.

The unit has been reassembled in the pilot plant section of MPRC, successfully tested and commissioned.

This particular activity has resulted not only in considerable savings in the amount of money in foreign exchange and valuable time but highly valuable training and confidence afforded to a local fabricator who is planning to diversify his production line to include fabrication of chemical plant and equipment.

The design drawings are in Annex 6.

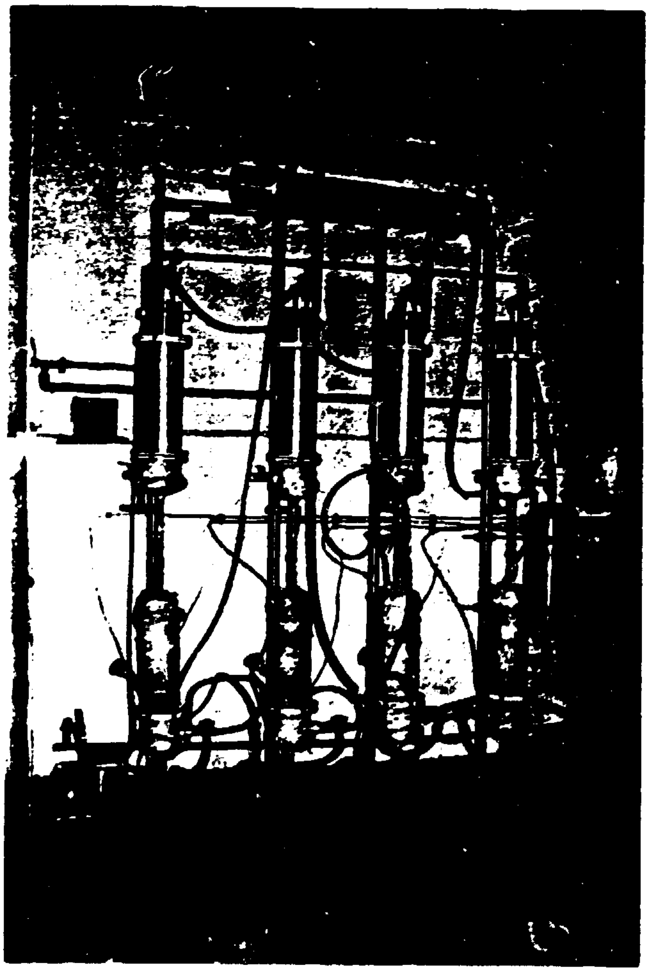
3. Modification of Battery Percolation System

The UNIDO expert during his first mission updated the processing technology, at a demonstration plant with limited facilities. The project authorities procured four stainless steel pumps from Germany, to the specifications provided by him.

The battery system set-up earlier at MPRC to UNIDO expert's design has been suitably modified with the addition of four stainless steel centrifugal pumps with flame proof motors and starters.

As a result of these modifications, the pilot plant is truly working as a counter-current battery system. Coupled with these modifications, the operational technique (maceration of crushed drug with ethanol (1:1 ratio), has further improved the extraction efficiency by cutting down, the time of percolation cycle from 9 hours to just 4 hours.

This meant that, as a result of updated processing technology of "Lityazol Cemil", the cycle operation time is reduced from 42 days to 4 hours, and the yield of the product (extract) was increased from 3 litres per 1 kg of the drug (first mission, prior to the modification) to 4 litres per kg drug without affecting the quality of the product. Flame proof quality motors and starters were chosen to broad base the functioning of the battery percolation system, to use volatile solvents viz., n-hexane etc. The pipeline manifolds were also been suitably modified to enable the battery system to function continuously and under a closed system.



Conclusions

As a result of studies conducted during the first and second missions, it is concluded that:

- it is technically feasible and economically viable to produce good quality "Lityazol" from the root bark of *Scolymus hispanicus* at the industrial level, based on updated processing technology.
- it is technically feasible to produce an ethanolic extract conforming to national and international standards.
- it is possible to reduce "batch operation period" from 42 days to 4 hours.
- it is possible to reduce solvent losses from 83% to about 15%. This can be reduced further to about 5% at the factory, in case the updated processing technology and plant designs are implemented.
- it is technically feasible to run the factory for 8 h/day, 16 h/day and 24 h/day as required.
- it is possible to produce an alcoholic extract containing higher concentrations of triterpenic compounds and alpha -amyrin acetate.
- the distillation and boiling of miscella operations, currently being followed by the factory at Manisa will become unnecessary.
- consequently the running costs of the new plant when implemented would be correspondingly reduced, thus increasing profitability.
- M/S Seker Makina of Eskisehir possesses extensive infrastructure and expertise to undertake fabrication of equipment in stainless steel. M/S sahlan Makina also from Eskisehir, who did a good job in fabrication of vacuum evaporator cum distillation unit to the designs and the guidance of the UNIDO expert and TBAM engineer, have acquired sufficient skills in the fabrication of the equipment in stainless steel. These two parties are capable of fabrication of the new plant to the design provided in this report.

Recommendations

1. The effect of Lityazol Cemil on short-term, and long-term use needs further investigations.

2. A suitable delivery system needs to be developed for the ethanolic extract.

3. Collaboration with MPRC on a long range basis for implementation of the above two (2 and 3) recommendations as well as for "trouble shooting" in the production line, quality control and product diversification should be continued.

4. The company and MPRC may consider to diversify the products, to utilize the spare capacity, during the lean period.

5. A quality control laboratory has to be set up. To begin with the following instruments were procured for this purpose with the project funds:

   - Hand refractometer
   - UV - Visible spectrophotometer
   - Rotary evaporator.

6. The product obtained at MPRC during demonstration and training may be handed over to the company for clinical tests to be conducted through its normal channels.

7. To conserve naturally grown precious plants and to ensure steady supply of raw materials to the production unit, the plant *Scolymus hispanicus*, should be cultivated in earnest, so as to synchronize with the expanded production activity since it is known that this plant matures for harvest in two years of time after planting.

ACKNOWLEDGEMENTS

The author acknowledges with thanks the advise and generous help given by Dr.Tuley De Silva, Special Technical Adviser, Chemical Industries Branch, UNIDO, Vienna, Mr.Rahit Karaosmanoglu, Managing Director of Dr. Cemil Sener Laboratory, Manisa, Turkey, Prof.Dr. K.H.C.Baser, Director MPRC, who placed whole heartedly all the facilities, as well as the needed scientific and technical members of MPRC at his disposal. With his support it has been possible to achieve all the outputs including the updated technology development.

He also acknowledges with thanks the assistance of Doç.Dr.Nes'e Kirimer, Ms Zeynep Tunalier and Ms. Berrin Bozan in the development of quality control protocols and quality control analysis during the demonstration and training of the counterpart chemical engineer, Mr. Sedat Hakki Beis, the bright young chemical engineer during demonstration and training programme and in plant drawings and fabrication of equipment, Ms Nezihe Azcan in pilot plant operation and plant drawings, Prof Dr. Yusuf Öztürk, Mr. Süleyman Ayden and Ms. Rana Beis for pharmacological tests and Ms Berna Bozan for typing the report.

Annex 1

UNIDO

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

JOB DESCRIPTION

SI/TUR/93/801/11-01

Post Title:	Chemical Technologist (Plant Engineer)
Duration:	3.0 m/m (with split mission to assure follow-up to recommendations perhaps 6 months after initial mission)
Date Required:	ASAP
Duty Station:	Eskisehir and Manisa in Turkey, and travel in country as appropriate
Purpose of Project:	High level advisory assistance to streamline the processing technology of "Lityazol Cemil", a herbal pharmaceutical produced in Turkey.

Duties: The expert will be specifically required to work in collaboration with counterpart staff at Senel Factory and Anadolu University in carrying out the following duties:

1. Survey the site for Lityazol production and work out Layout.
2. Survey sources for equipment production.
3. Prepare a list of required equipment after developing the process.
4. Conduct pilot runs and testing on Lityazol products at Anadolu University.
5. Develop process technology and process control parameters for improvement of production of "Lityazol" at MPRC.
6. Introduce good manufacturing practices safety requirements, and marketing techniques

Finally, the expert will furnish a report embodying the progress made and outlining his recommendations to both UNIDO and the Government.

Qualifications:	Chemist/Pharmacist or chemical engineer with experience in the processing of essential and fixed oils from plant materials at pilot and industrial levels, and marketing experience is desirable
Language:	English

Dr. CEMİL ŞEN'ER
LABORATUARI LIMITED ŞİRKETİ
MANİSA

Telgraf : Dr. CEMIL ŞEN'ER
Telefon : 1023

22.April.1994
Tarih.22.Nisan.1994

21 ve 22 Nisan 1994 tarihinde UNIDO uzmanı Mr.M.B.Narasimha ile TBAM temsilcisi Kim.Yük.Müh. Sedat Beis'in Manisa'ya Dr.Cemil Şener Laboratuarı Ltd.Ştr.ne yaptıkları ziyaret sonucu; Şirket merkezinde görüşülmüştür. Görüşme esnasında projedeki görevinin birinci aşamasına ait Mr M.B.Narasimha tarafından gönderilen raporun memnuniyetle elde edilmiş olduğu belirtilmiştir. Görüşmelerimiz aşağıda ki şekilde gelişmiştir.

1- Dr.Cemil Şener Laboratuarı Ltd.Ştr.nin üretimi olan 42 günlük süreyi, 9-ilâ10 saate indiren ileri teknoloji çalışmasını Mr.M.B.Narasimha'nın teknik danışmanlığıda sonuca ulaşmasını sağlayan Anadolu Üniversitesi Tıbbi Bitkiler Araştırma Merkezi(TBAM) ve bu çalışmayı finansal ve personel ile destekleyen Birleşmiş Milletler Sınai Kalkınma Örgütü (UNIDO) nun ortak başarısı olduğu takdirle karşılanmıştır.

2- Sözü geçen ileri teknolojinin uygulanabilmesinin günümüz ekonomik koşullarında firmaya aşırı finans sıkıntısı getirmesi nedeniyle ; gerekli yatırımın hemen yapılamıyacağı, ancak içinde bulunulan ekonomik kriz atlatıldıktan hemen sonra; firmanın süratle finans sağlayıp yatırım yapacağı ve elde edilen ileri teknolojiye işlerlik kazandıracağımız beyan edilmiştir.

3- 27 Nisan 1994 tarihinde UNIDO teknik danışmanı Mr.De Silva'nın Eskişehir'e yapacağı ziyaretten istifade edilerek; Eskişehir'de,TBAM'da Prof.Dr.Hüsnü Can Başer, Mr.De Silva, Mr.Narasimaha ile Firma Temsilcisi M.Raşit Karaosmanoğlu'nun toplantı yaparak son defa bir durum değerlendirmesi yapacaktır.

4- Mayıs ayının ilk yarısı içinde de TBAM pilot tesisinde , Mr.Narasimha nın teknik danışmanlığında geliştirilen teknolojinin ve kalite kontrol yöntemlerinin uygulamalı eğitimi için firma yetkili [illegible]larını Eskişehir'de bulunduracağımızı bildiririz.

COMMENTS OF THE COMPANY MANAGEMENT ON THE NEW TECHNOLOGY DEVELOPED

On 21 and 22 April 1994, Mr.M.B.Narasimha, UNIDO expert, on mission to the project and Mr.Sedat Beis, Chem.Eng. TBAM and Mr.M.Raşit Karaosmanoğlu, Managing Director of the company held a meeting at the premises of the factory. We received a copy of report sent by Mr.Narasimha during the first part of his mission. The following are our comments.

I- Production period for the Lityazol Cemil drug produced by Dr.Cemil Şener Lâboratuarı Ltd.Şti.was reduced to 9-10 hours from 42 days per

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Tarih .

batch, reduced solvent losses and good quality product by the new technology developed at TBAM under technical guidance Mr. Narasimha. This highly developed technology and success made possible by UNIDO and TBAM efforts is highly appreciated.

2- Since the implementation of the newly developed technology requires additional investment and because of the economic crisis in the countr nowadays it is not possible for us to invest large amount of money right now. But, as soon as, the crisis is overcome we clearly state that we will finance and implement the newly developed technology in our factory.

3- By taking advantage of Prof. Dr.De Silva's visit to Eskişehir, I would like to hold a final meeting with Prof.Dr.K.H.C.Başer, Prof.Dr. De Silva and Mr.M.B.Narasimha to evaluate the present situation on 27.April.I994,in Eskişehir.

4- We will send our technical personnal to TBAM for the demonstration and training on the newly developed technology and quality control methods in the first half of May I994.

M.Raşit KARAOSMANOĞLU
Şirket Müdürü
Mg. Director of Company

Annex 3

Demonstration of Updated Processing Technology for Production of "Lityazol Cemil", a Herbal Pharmaceutical Product

Introduction

Demonstrated and provided comprehensive training to a counterpart Chemical Engineer on up-dated technology and quality control techniques developed at MPRC under technical guidance of UNIDO expert.

The following back-ground information was provided followed by a short lecture detailing the salient features of the updated technology in the production of the "Lityazol Cemil", from *Scolymus hispanicus*.

Background

The demonstration plant set up at MPRC consists of a set of four percolators having a volume of 10 litres and working capacity of 1.5 kg each. These are interconnected through a series of four centrifugal pumps and four pre-heaters in such a way that the miscella can be circulated from one percolator to any of the three remaining percolators and to preheat the solvent/miscella to the desired temperature.

Actually, three percolators are considered optimum for the extraction of *Scolymus hispanicus*, fourth one is provided to continue extraction operations uninterruptedly (ie.) the fourth one is put to use when one of the three is under steam stripping and evacuation.

This method ensures counter-current flow of solvent through a battery of percolators. Such a system is called an extraction battery. In such a battery, the solid is not moved physically from stage to stage, the charge in any one percolator is treated by a succession of liquid of constantly decreasing concentration from stage to stage in a counter-current system.

The raw material powder in the cell which is percolated twice with miscella of decreasing concentrations and finally with the fresh solvent is stripped of its adhering solvent by passing live steam through it. The resulting vapour mixture of ethanol and steam is condensed and the condensate rectified in a fractionating column to obtain ethanol of 96% concentration, for reuse.

The following optimum conditions have been established at pilot plant level during the first mission of the UNIDO expert:

- Coarsely powdered, dried root bark be used in commercial production.
- One is to four ratio of solid to solvent.
- Rectified spirit (96 % ethyl alcohol) be used as solvent.

- Three percolations for 3.5 h each at 45° - 50° C, on counter-current principle are adequate.
- The time to complete one batch is about 9-10 h.

The final miscella obtained after filtration has the following composition:

	Pilot Plant Product mg/ml	Lityazol Cemil (original) mg/ml
Total solids	1.38 - 2.48	10.5
Triterpenic compounds in total solids	38-50%	38.6%
alpha -amyrin acetate	0.19-0.23	0.01

The higher concentration of dry matter in the "Lityazol Cemil" is due to the presence of undesirable gums, tannins, polymerized substances etc.

The extract of the composition obtained as a result of the pilot plant studies has double the potency (as indicated by the pharmacological studies conducted at MPRC and Osman Gazi University Medical Faculty) to that produced in the factory under the name "Lityazol Cemil", thus rendering distillation and concentration operations currently being followed by the factory in Manisa redundant.

The following are the salient features of the updated technology developed:

1. Successfully optimized process conditions and up-dated technology.

2. Drastically cut down batch time from 42 days to about 9-10 hours.

3. Low solvent losses. About 15% compared to 83% losses at the factory. This can be reduced further to about 5% at the factory in the new set-up.

4. Higher yields of product; 3 litres per kg of root bark as against 1 litre/kg currently produced at the company.

5. Very high concentration of triterpenic compounds particularly a-amyrin acetate in the extract. Nearly 20 times higher concentration, compared to the company produced "Lityazol Cemil".

6. Higher efficiency of extraction about (85-90%).

7. Less impurities like tannins, gums, sugars etc., in the ethanol extract.

9. Two pharmacology teams, one from MPRC and another from Medical Faculty of Osmangazi University, who independently investigated the drug's activity have reported that two times dilution of the pilot plant extract has the same activity as that of the "Lityazol Cemil".

10. These reports clearly indicate that the ethanolic extract obtained from the percolators after removal of suspended solid particles in the filter press and diluting twice with distilled water is ready for use in the filling section. Therefore the operations of distillation of miscella and boiling the residue, that is currently practiced in the factory automatically become redundant.

11. Developed quality control specifications using analytical techniques and correlations, to calculate dry matter, Triterperic compounds (TTC) and a- amyrin acetate based on UV Spectrometry, Refractive Indices.

Pilot Plant

As mentioned in the introduction, the pilot plant consists of four percolators of 10 litre volume each made of stainless steel of quality AISI 304 (18 chromium and 8 nickel). Each one is fitted with a perforated false bottom and covered with a piece of muslin cloth to hold the coarsely crushed drug. Underneath the false bottom is a small chamber to receive the percolate. A single loop closed coil is fitted in the chamber to steam heat the percolate, a thermowell provided in it with a thermo-couple sensor and an indicator to facilitate easy reading of the temperature of the solvent/miscella that is to be pumped through a stainless steel centrifugal pump.

All the four percolators and pumps are interconnected generally as shown in the enclosed flow diagram (page 15) through a manifold of pipes and fittings so that the solvent/miscella can be circulated from one percolator to any of the three remaining percolators, through the preheaters.

Fitted at the top of the percolator battery assembly is a shell and tube condenser to serve all the four percolators to condense the solvent and steam vapour generated in these, one at any given time. Provision is made to collect the condensate. The condensate is rectified in the laboratory fractionating column.

Procedure

Initially before a pilot plant or a commercial plant gets into counter-current battery percolation system, it is necessary to use macerated drug in all the three cells or percolators. Generally the following procedure is followed (refer enclosed flow diagrams of battery percolation system I and II in pages 16-17).

Weigh 1.5 kg coarsely crushed *Scolymus hisponicus* root bark, macerate it with 1.5 litre of rectified spirit. Spread a clean muslin cloth over the perforated false bottom of the percolator. Charge the macerated bark powder into the percolator. Close the lid securely and pump in 6 litres of 96% ethyl alcohol into it. Let in steam slowly into the steam coil of the preheater. Switch on the pump. The piping network is adjusted in such a way that the miscella percolated and preheated is recycled back on to the top of the percolator in the form of a fine spray. The operation is continued for 3.5 hours while maintaining the miscella temperature between 45 - 50 °C.

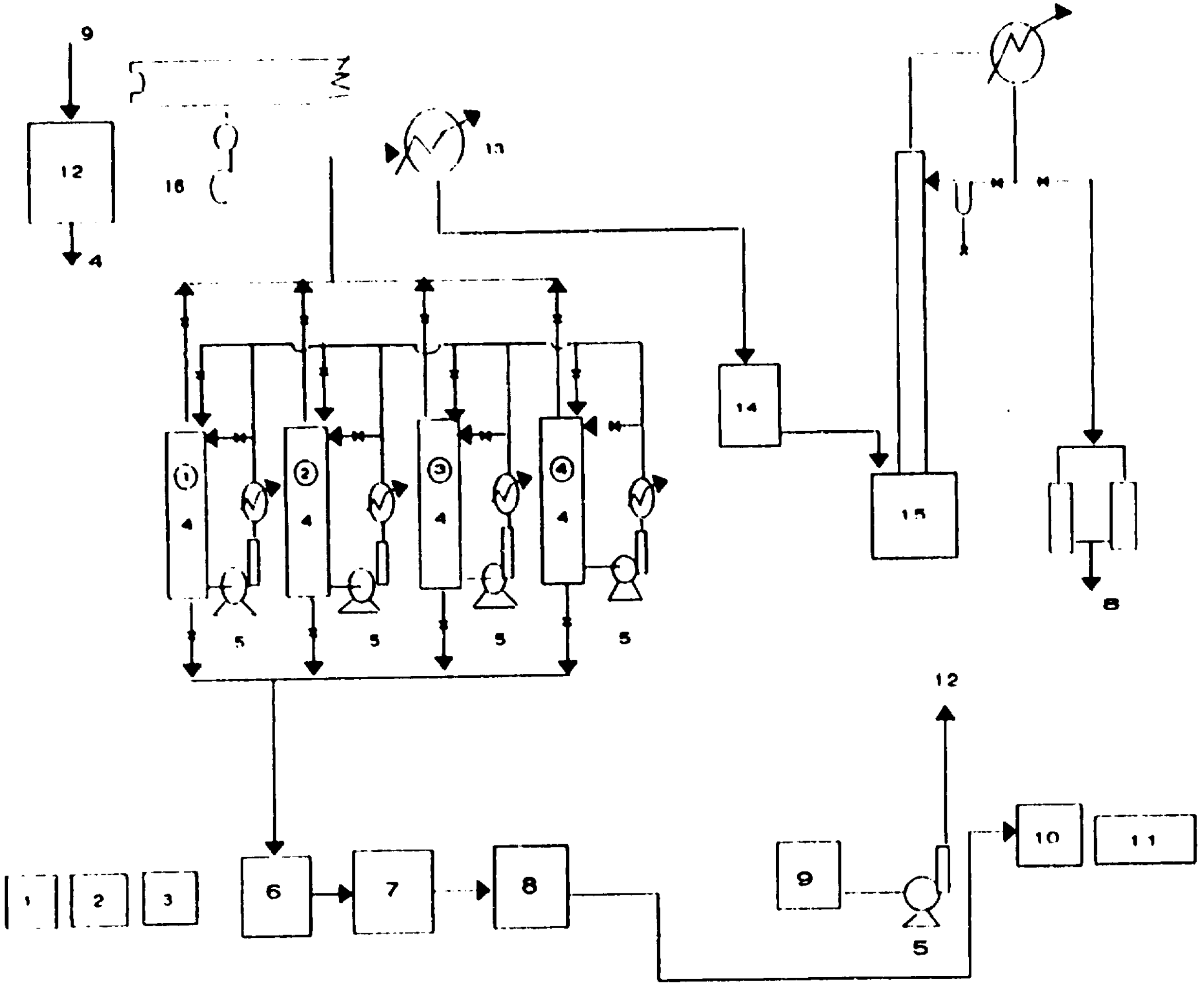
Drain the miscella S_3a into the miscella tank and then pump it on the percolator (2) which is filled with macerated drug (1.5 kg). Percolation is continued for 3.5 hours, maintaining the temperature around 45-50°C. During the period percolator (2) is under operation, percolator (1) is charged with fresh solvent and (FS_b) percolation is continued at 45-50°C for 3.5 hours. At the end of 3.5 hrs., the miscella (S_2a) from unit (2) is pumped into unit (3) kept ready with a charge of macerated drug (1.5 kg+1.5 litre ethanol) and miscella S_3b from unit (1) is pumped into unit (2) and a fresh batch of 6 litre ethanol (FS_c) is pumped into unit (1).

At the end of the extraction period, strong miscella S_1a from unit (3) is drained into a collection tank and set aside.

The marc in unit (1) is desolventised with steam. Condensate of dilute ethanol is collected. The marc is discharged from unit (1) and recharged with macerated drug (1.5 kg + 1.5 litre ethanol) The operations are continued as per the enclosed flow diagrams I and II which ensure counter-current flow of solvent through a battery of percolators (ie) the charge in any one percolator is treated by a succession of liquids of constantly decreasing concentration and finally with fresh solvent before being, desolventised and discharged and recharged with fresh drug.

During the period the system is functioning as a battery, samples of miscella S_1, S_2 and S_3, as well as marc and dilute ethanol are drawn and analyzed along with a sample of fresh drug for dry matter, TTC, alpha-amyrin acetate,ethanol and moisture content for material balance.

Experimentations made during the first mission, showed that filtered final miscella (S_1, has very high concentration of TTC and alpha-amyrin acetate, making further operations of distillation and concentration, currently being followed at the factory superfluous.

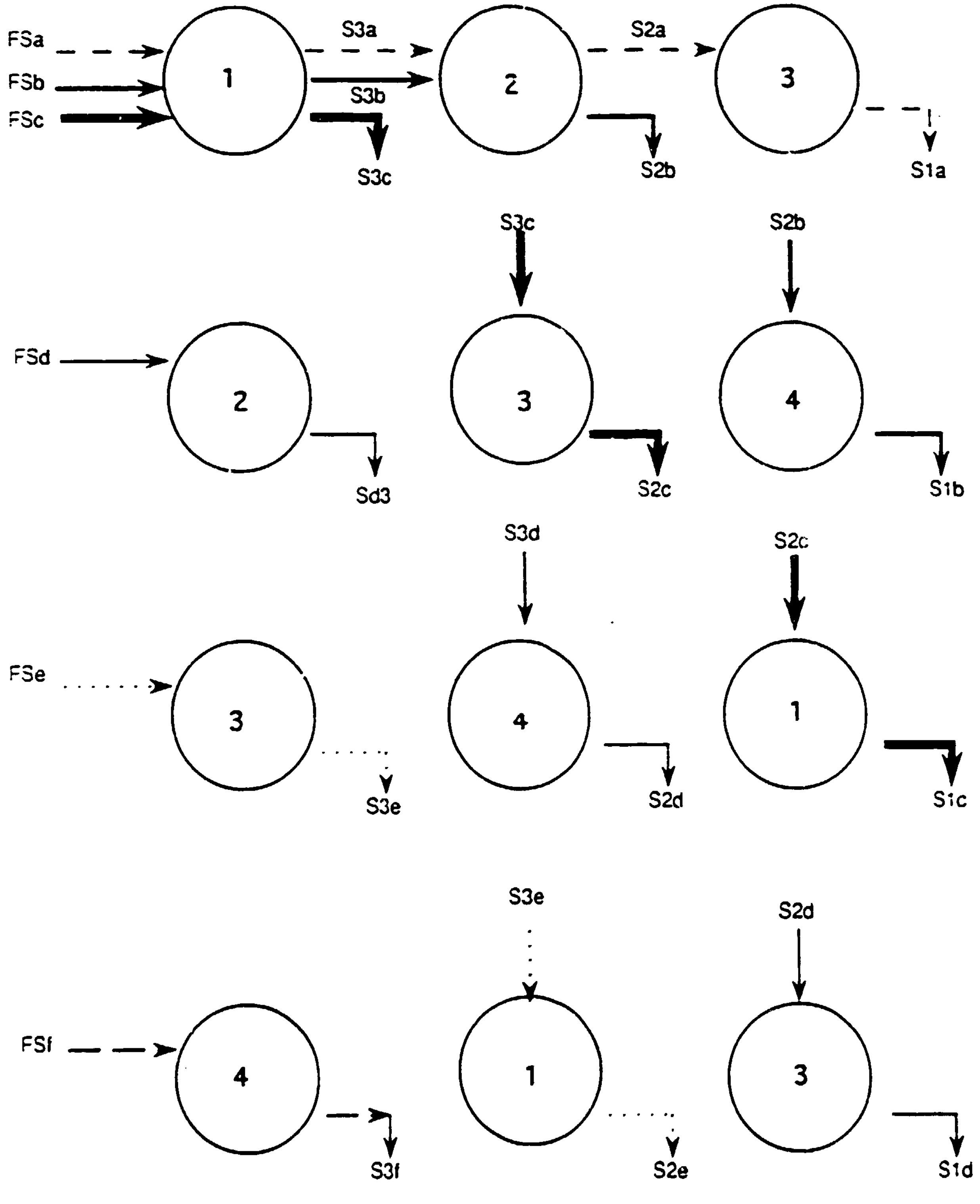


Item	Reqd.Nos.
16 Overhead Pully block	one
15 Rectification Column	one
14 Storage Tank (dil Ethanol)	one
13 Condenser	one
12 Ethanol (OH) Tank	one
11 Lityazol Bottling Packing	one
10 Lityazol Blender	one
9 Ethanol Storage	one
8 Filtered Miscella Tank	one
7 Sparkler Filter	one
6 Miscella tank	one
5 Pumps	five
4 Percolators	four
3 Platform Balance	one
2 Crusher. Siever	one
1 Dryer	one

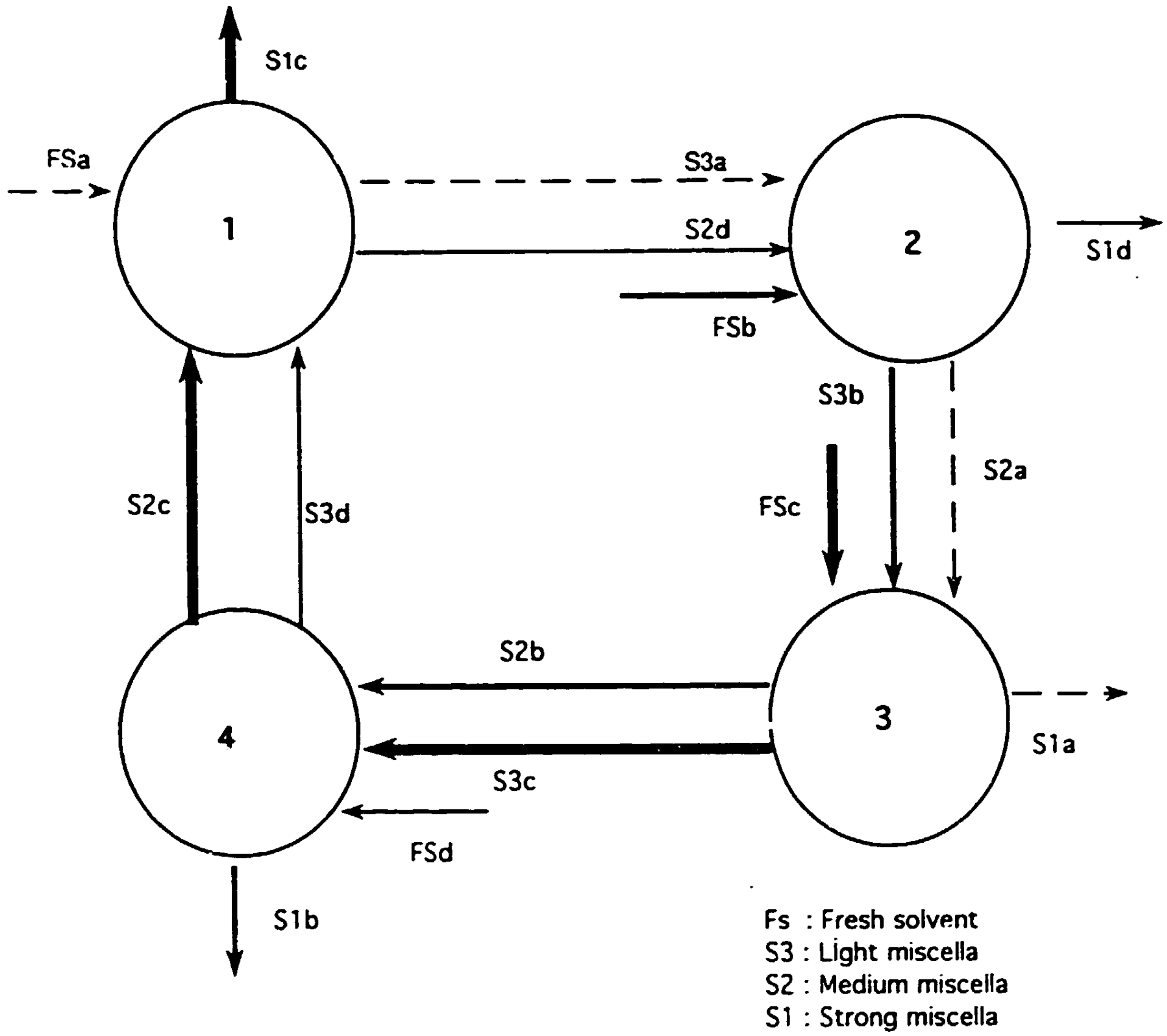
Capacity-100 kg/Batch

Flow diagram-Production of Lityazol Cemil from *Scolymus hispanicus*

Marla B. Narasimha UNIDO
Sedat H. Bels TBAM



FLOW DIAGRAM OF BATTERY PERCOLATION SYSTEM-I



Status of the battery at the time of charging fresh solvent (FSa) into unit (1)

Unit (1) already extracted twice, once with S2 and then S3
Unit (2) extracted once with S2
Unit (3) & (4) freshly filled with mascerated drug

At the end of the cycle, miscella S1a from Unit (3) withdrawn as product, miscella S2b from (3) charged into Unit (4), miscella S3b from (2) into Unit (3), fresh solvent FSb into Unit (2). The marc in Unit (1) is desolventized and discharged. Recharged with fresh mascerated drug. The cycle of extraction continues with out a break.

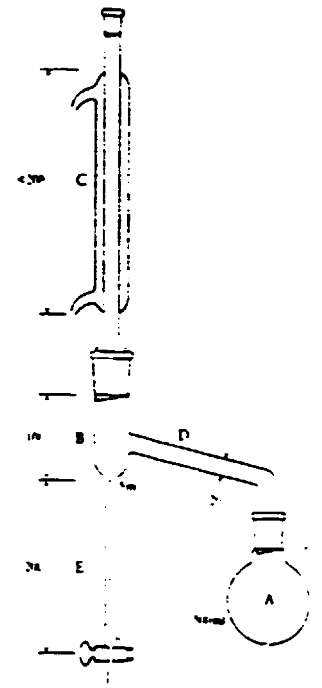
FLOW DIAGRAM OF BATTERY PERCOLATION SYSTEM-II

Laboratory experiments

Determination of the water content by volumetric method

Apparatus:

The apparatus as shown in the following figure consists of a glass flask (A) connected by a tube (D) to a cylindrical tube (B) fitted with a graduated receiving tube (E) and reflux condenser (C) (BP, 1988).



Method:

Place about 10 g powdered root bark into the glass flask, add approximately 100 ml xylene saturated with water. Distill for about 2 h. Allow to cool and read the water volume (ml).

Calculate the percentage of water in the substance being examined using the formula.

Water % = (Water volume (ml) / Weight of drug) x 100

Determination of the ethanol extractable matter from the drug

Place 25 g of powdered root bark and approximately 100 ml of 96% ethanol in a 250 ml flask fitted with reflux condenser. Allow to boil for four hours, then filter the extract immediately into a tared flask and remove the ethanol until the residue is dry using a rotary evaporator. Weigh the flask after it is dried. This solid amount is the ethanol extractable substances from 25 g of raw material.

Quality Control in Lityazol Cemil Production

1. Determination of total solid content in the ethanolic extract by a hand refractometer

Measure the Brix value (B_s%) of 96% ethanol using a hand refractometer.

Filter sample extract and measure its Brix (B_x%). The percentage of total solids (B_s%, g/100ml) is calculated by using the following formula.

$$B_m \% - B_e \% = B_s \% \qquad \text{(Equation 1)}$$

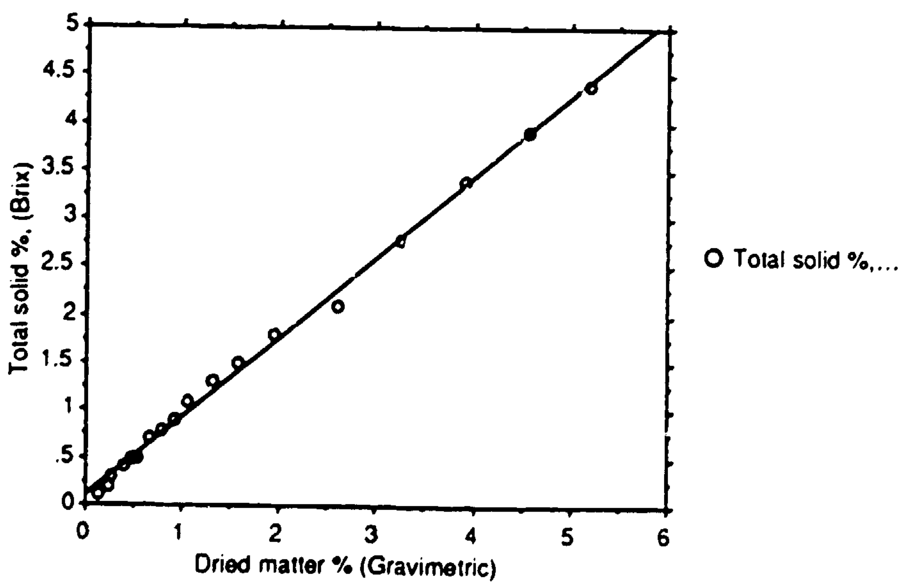
B_m %: Brix value of sample

B_e %: Brix value of 96 Ethanol

B_s %: Total solids percentage in the ethanolic solution (calculated)

The relationship between the percentage of dried matter calculated by evaporation and the percentage of total solids (B) calculated using Brix values is obtained graphically by the following equation.

$$y = 0.872\ x + 0.103 \qquad \text{(Equation 2)}$$



Using this equation dried matter percentage is calculated against Brix values.

y is total solid percentage (Brix).

x is dried matter in the ethanolic extract (g / 100 ml).

2. Spectrophotometric measurements

For the spectrophotometric measurements, some dilutions are recommended using the following Table:

Table 1.

Dried matter (g / 100 ml)	Dilutions range (ml/ml Ethanol)
0.2-0.6	5.0/25
0.6-1.5	2.5-25
1.5-2.0	1.5-25
2.0-3.0	1.0/25
3.0-4.0	0.5/25

a. Baseline correction is done against blank sample (EtOH: Conc.H_2SO_4, 1:2) at 490 nm.

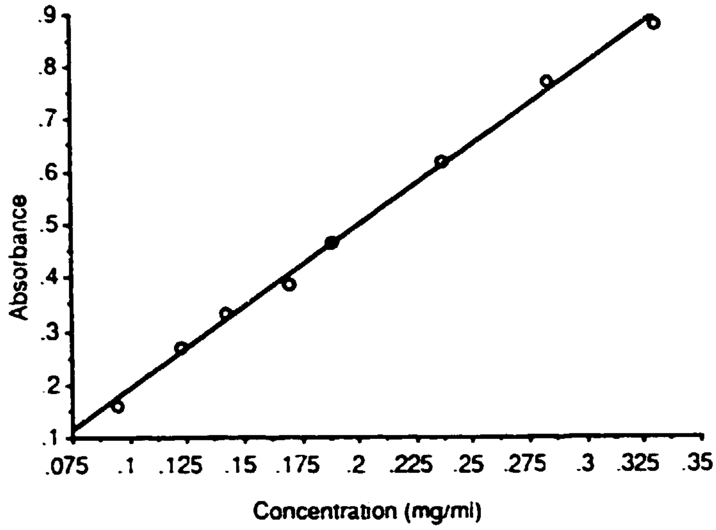
b. After baseline correction, diluted samples of 1 ml is pipetted into a test tube. 2 ml concentrated H_2SO_4 are added into the sample slowly in 30 sec and mixed by a vortex type mixer. Absorbance values of the samples has to be measured after mixing at 60th second at 490 nm.

Solid content (mg/ml) can be obtained from the following equation.

$$y = 3.0687\,x - 0.1171 \qquad \text{(Equation 3)}$$

y is absorbance value of the sample (at 490 nm)

x is TTC content in the ethanolic extract (mg/ml)



Example

Procedure	Exampled values
Take filtered sample from the production plant	S246.
Measure B% value of 96% EtOH	20.4
Measure B% value of the sample	23.7
Calculate the total solid percentage (Bs) using Equation 1.	3.3 (g / 100 ml)
Calculate the real dried matter content using Equation 2.	3.66 (g / 100 ml)
Dilute the sample into the suitable range given Table 1.	3.66 x (0.5 / 25)
Take 1 ml diluted sample and mix with 2 mL Conc.H_2SO_4	
Calculation of dilution effect	3.66 x (0.5/25) x (1/3) (g / 100 ml)
Convertion gram to miligram	= 0.0244 g / 100 ml x(1000 mg/1 g)
	= 0.244 mg / ml
Measure absorbance value at 490 nm	0.305
Calculate the TTC content (mg/mL) using Equation 3.	0.1375 mg / ml

0.244 mg dried extract contains 0.1375 mg TTC (ie) 56.35%

Annex 4

Results- Pilot plant demonstration cum training programme

The following results (Table 1) were obtained as the result of demonstration and training programme conducted to train the counterpart Chemical Engineer in the application of the updated technology developed at MPRC under the technical guidance of UNIDO expert.

From 10th May 94 to 14th May 94 a total of 9 extraction (cycles) of crushed *Scolymus hispanicus* with 96% ethanol were conducted on the battery percolation system, as per the procedure detailed under "Procedure" refer pages 16-17. This system set-up at MPRC has been modified in the pipeline manifold system to make the battery system function continuously.

Charge	:	1.5 kg
Macerated with	:	1.5 litres ethanol
Solvent	:	6 litres ethanol
Time of each percolation with in each cell	:	3.5 h
Temperature	:	45-50 °C
Number of percolations per charge in counter current method	:	3

The following samples of strong miscella S1 (product), medium miscella S2 and light miscella S3, have been obtained. For definition please refer flow diagrams of battery percolation system I.

10.5.94	S3a, S2a, S3b
11.5.94	S1a, S2b, S3c, S1b, S2c, S3d
12.5.94	S2d, S3e, S1d, S2e, S3f, S1e, S2f, S3g
13.5.94	S2f, S3g, S1f, S2g, S3h, S1g
14.5.94	S2h, S3i, S1h, S2i, S3j

Samples	Dried Matter (g/100 ml)	TTC (g/100ml) in the dried matter	TTC % in the (dried matter)
1a	2.76	1.38	50.0
1b	2.40	1.15	48.0
1c	1.71	0.96	55.9
1d	1.95	1.13	57.7
1e	1.72	1.06	61.8
1f	2.29	1.3	56.7
1g	2.63	1.28	48.6
1h	1.95	1.05	53.8
2a	-	-	-
2b	-	-	-
2c	-	-	-
2d	1.37	0.685	50.0
2e	1.26	0.60	47.6
2f	1.49	0.70	46.7
2g	1.37	0.65	47.8
2h	1.25	0.595	47.6
2i	1.49	0.656	44.0
3a	-	-	-
3b	-	-	-
3c	-	-	-
3d	-	-	-
3e	0.57	0.27	47.4
3f	1.37	0.63	45.7
3g	0.80	0.38	47.5
3h	0.80	0.352	44.4
3i	0.57	0.27	47.4
3j	0.57	0.25	44.7

<u>Laboratory scale</u>

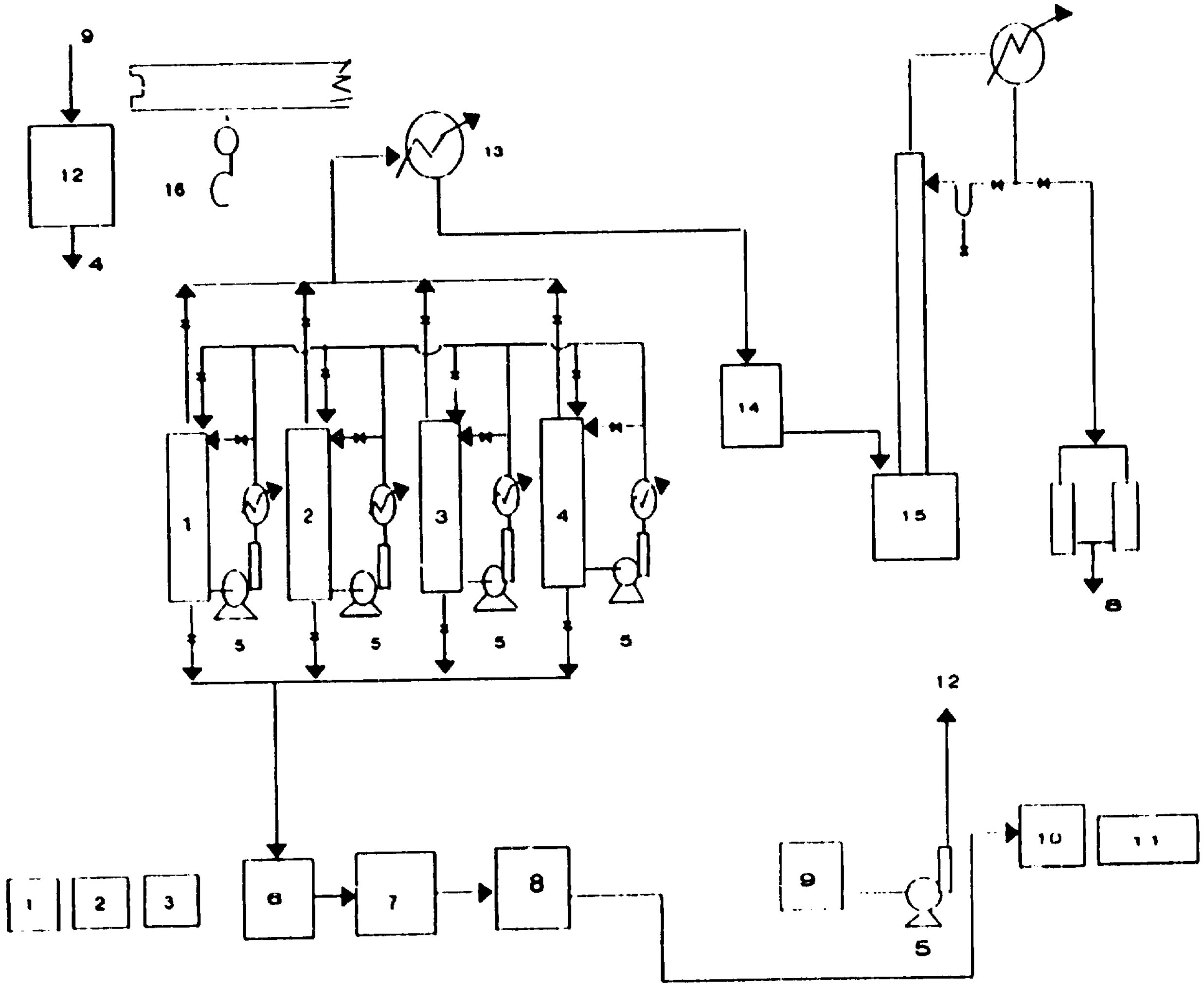
Extraction under reflux

1.	Drug amount	:	25 g
	Moisture	:	8.75 %
	Solvent	:	100 ml ethanol
	Extraction time	:	4 h
	Total ethanolic extract	:	81 ml
	Dried extract	:	1.52 g
	Extraction yield	:	6.67 % (MFB)
2.	Marc (from Pilot scale)	:	25.18 g
	Moisture	:	7.94 %
	Solvent	:	100 ml ethanol
	Extraction time	:	4 h
	Total ethanolic extract	:	82 ml
	Dried extract	:	0.45 g
	Extraction yield	:	1.94 % (MFB)

	Dried Matter	TC % in dried matter	a.a %
S1a	2.76	50	0.22
S1b	2.4	48	0.23
S1c	1.71	55.9	0.22
S1d	1.95	57.7	0.25
S1e	1.72	61.1	0.25
S1f	2.29	56.7	0.20
S1g	2.63	48.6	0.22
S1h	1.95	53.8	0.23
Lityazol	16	49.8	0.02

DESIGN DRAWINGS

"LİTYAZOL CEMİL" BASED ON UPDATED TECHNOLOGY

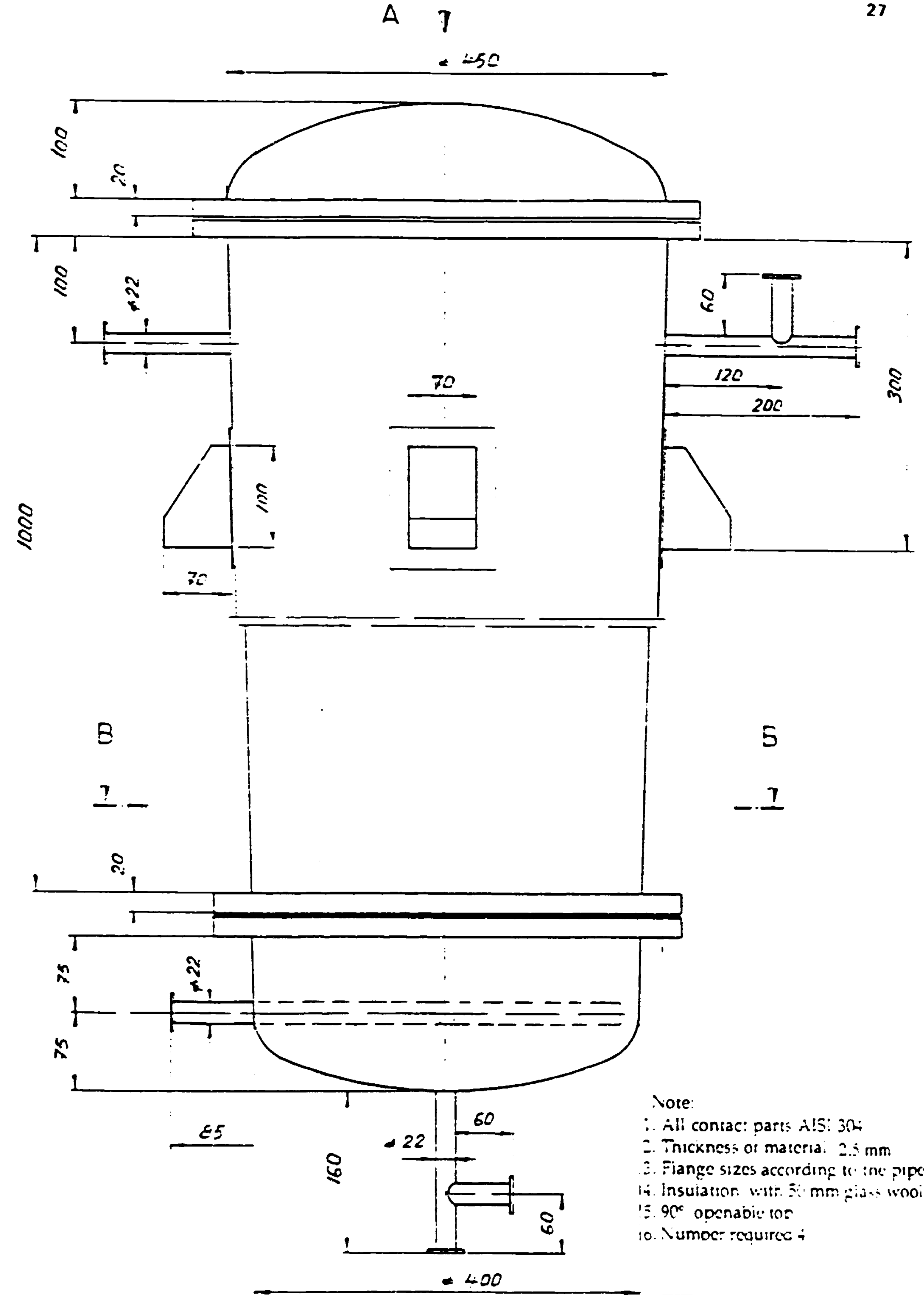


16	Overhead Pully block	one
15	Rectification Column	one
14	Storage Tank (dil Ethanol)	one
13	Condenser	one
12	Ethanol (OH) Tank	one
11	Lityazol Bottling Packing	one
10	Lityazol Blender	one
9	Ethanol Storage	one
8	Filtered Miscella Tank	one
7	Sparkler Filter	one
6	Miscella tank	one
5	Pumps	five
4	Percolators	four
3	Platform Balance	one
2	Crusher. Siever	one
1	Dryer	one
	Item	Reqd.Nos.

Capacity-100 kg/Batch

Flow diagram-Production of Lityazol Cemil from *Scolymus hispanicus*

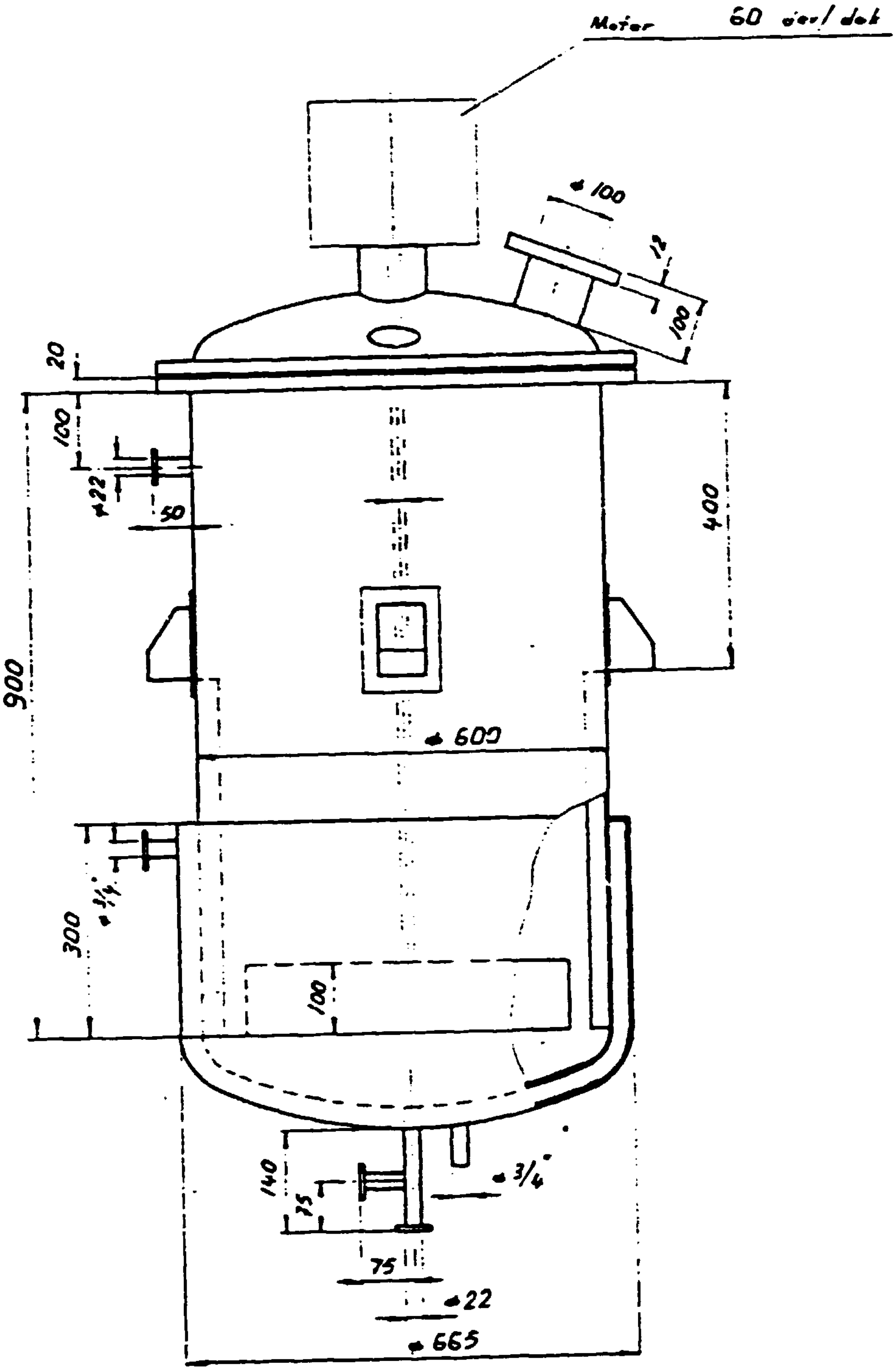
Marla B. Narasimha UNIDO
Sedat H. Beis TBAM



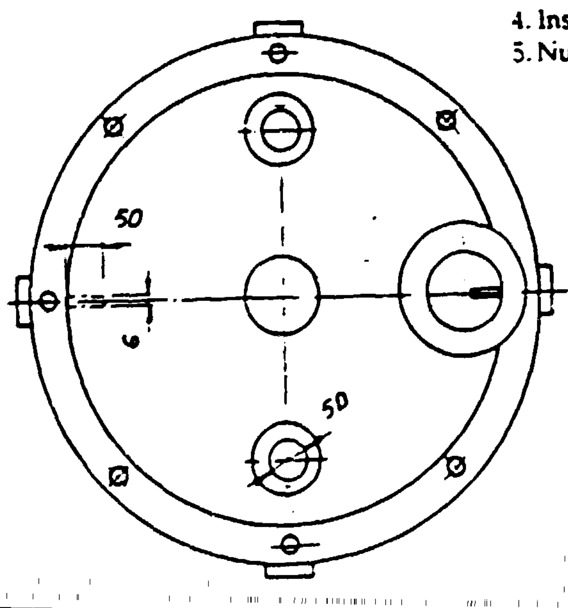
Note:

1. All contact parts AISI 304
2. Thickness of material 2.5 mm
3. Flange sizes according to the pipe
4. Insulation with 50 mm glass wool
5. 90° openable top
6. Number required 4

LITYAZOL CEMIL PERCOLATOR
Design: M.B.NARASIMHAN NIDO
Drawn: [illegible]
Date: [illegible]

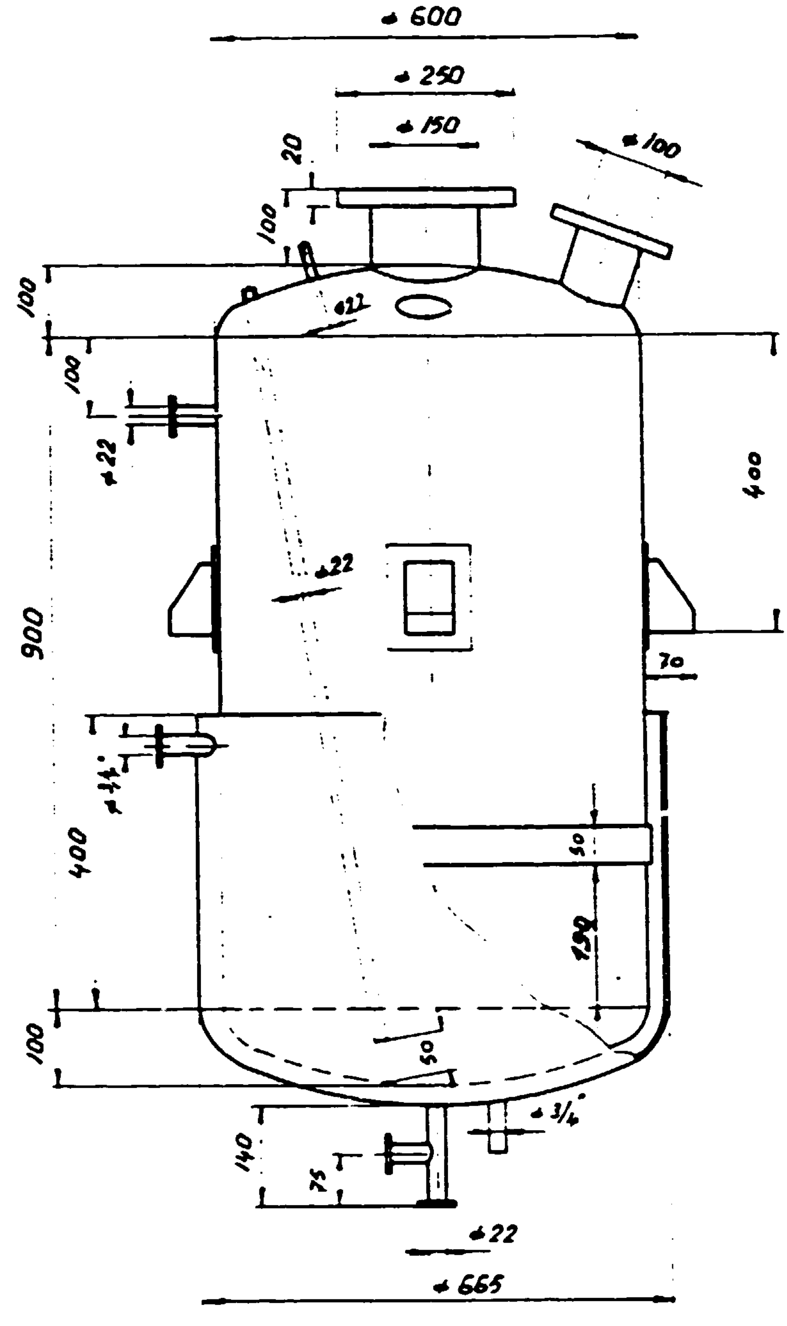


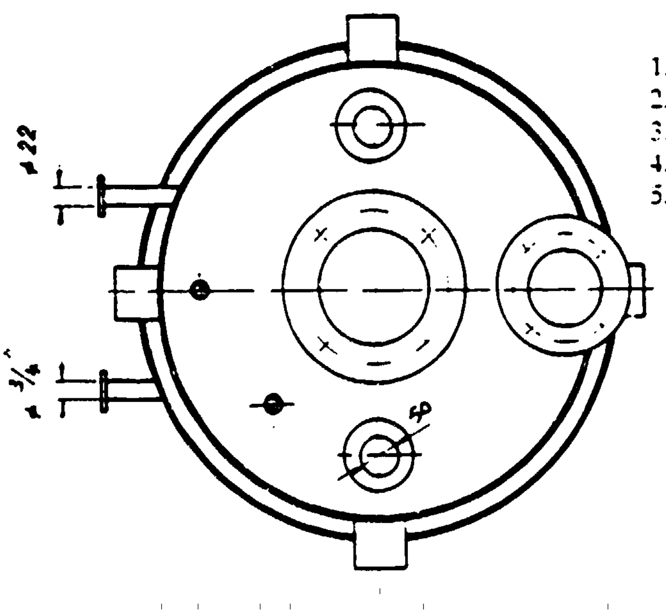
Note:
1. All contact parts AISI 304
2. Thickness of material 2.5 mm
3. Flange sizes according to the pipe di
4. Insulation with 50 mm glass wool
5. Number required 1



LITYAZOL CEMIL
BLENDER

Design: M.B.NARASIMHA.UNIDO
Drawn: S.H. BEIS. TBAM
Date:25.04.1994, Eskişehir



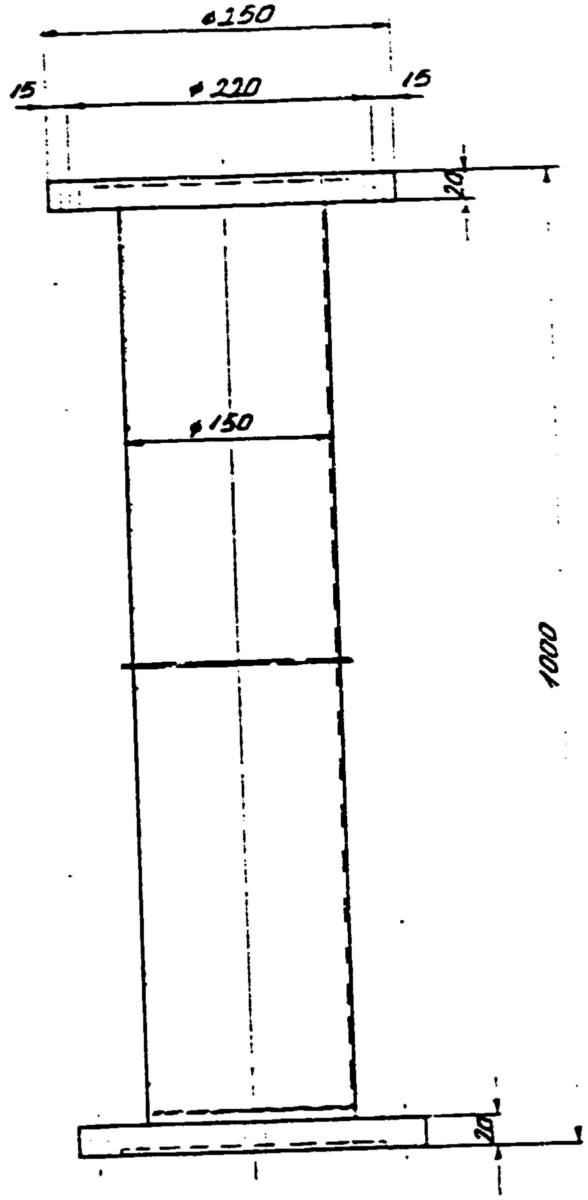


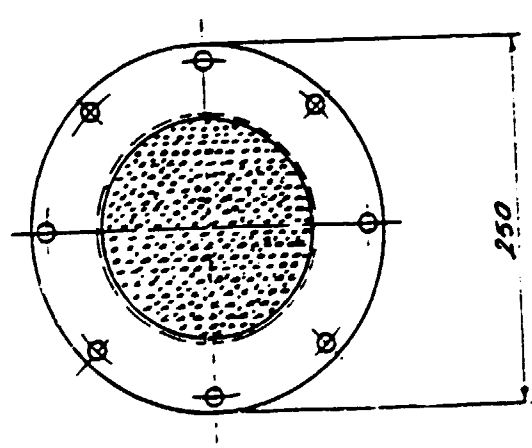
Note:
1. All contact parts AISI 304
2. Thickness of material 3 mm
3. Flange sizes according to the pipe c
4. Insulation with 50 mm glass wool
5. Number required 1

LITYAZOL CEMIL
REBOILER

Design: M.B.NARASIMHA.UNII
Drawn: S.H. BEIS. TBAM
Date 25.02.1994 Eskisehir

1 ADET



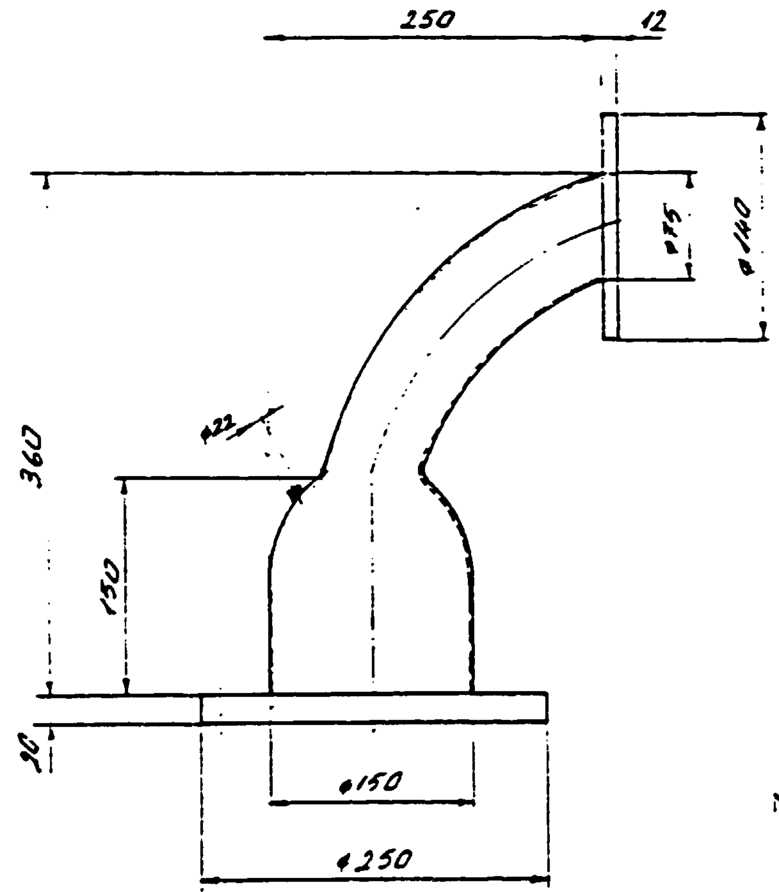


Note:

1. All contact parts AISI 304
2. Thickness of material 2.5 mm
3. Flange sizes according to the pipe
4. Insulation with 50 mm glass wool
5. Number required 1
6. Internal packing Ø 13x13 pall rings

LITYAZOL CEMIL
DISTILLATION COLUMN

Design: M.B.NARASIMHA.UNIL
Drawn: S.H. BEIS. TBAM
Date:25.04.1994. Eskişehir

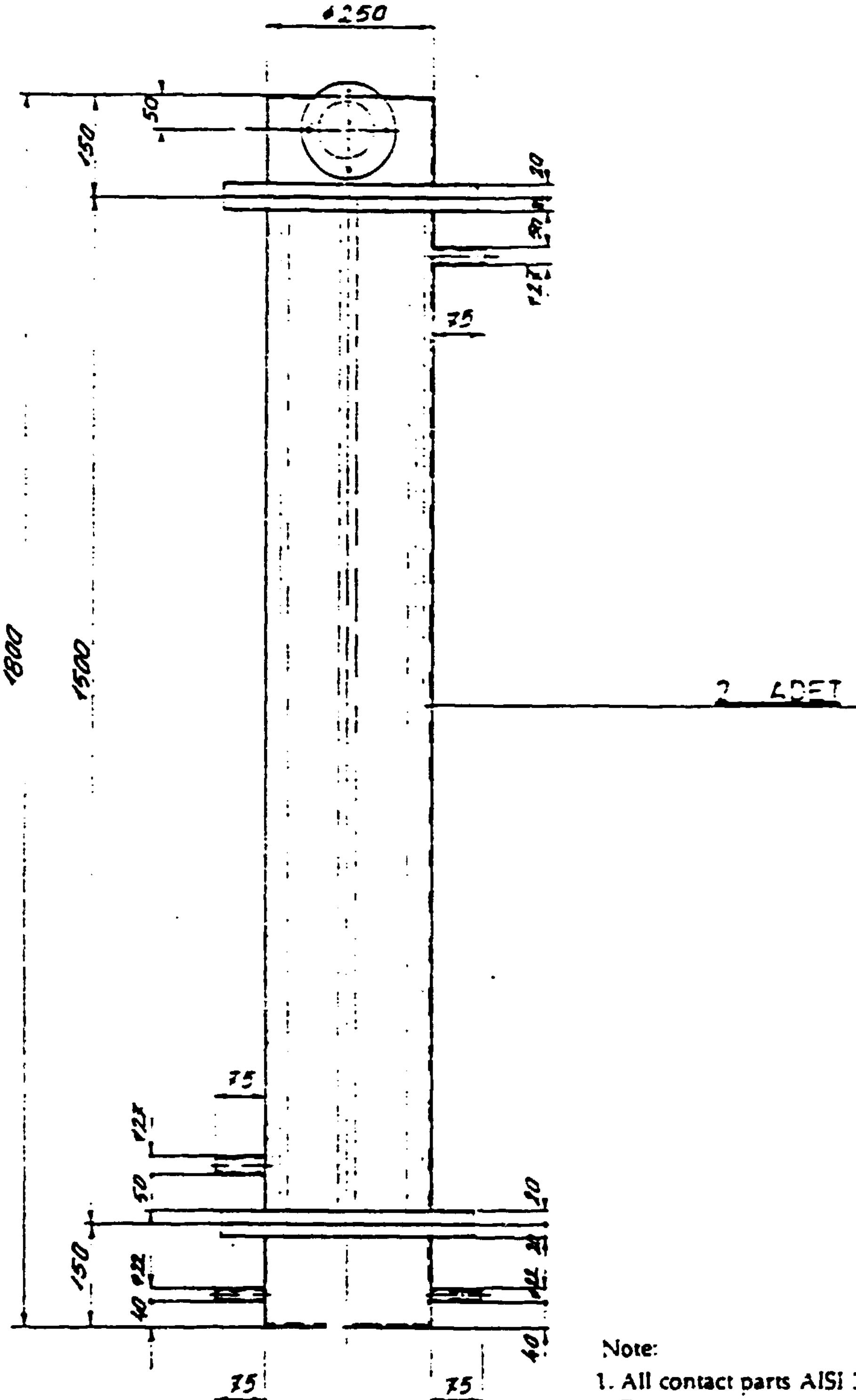


1 ADET

Note:
1. All contact parts AISI 304
2. Thickness of material 2.5 mm
3. Flange sizes according to the pipe di
4. Insulation with 50 mm glass wool
5. Number required 1

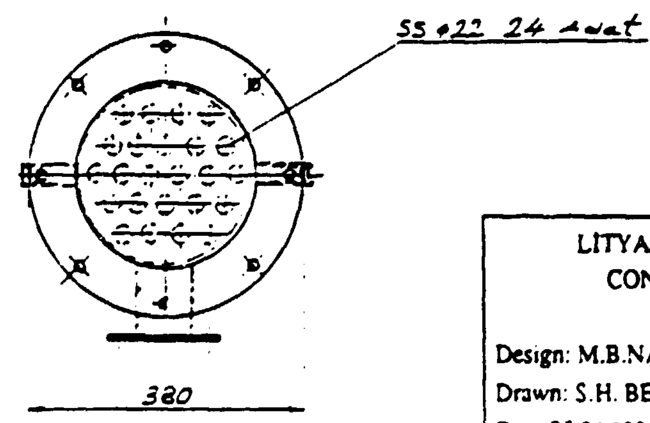
LITYAZOL CEMIL
VAPOUR LINE

Design: M.B.NARASIMHA.UNIDO
Drawn: S.H. BEIS. TBAM
Date:25.04.1994. Eskisehir



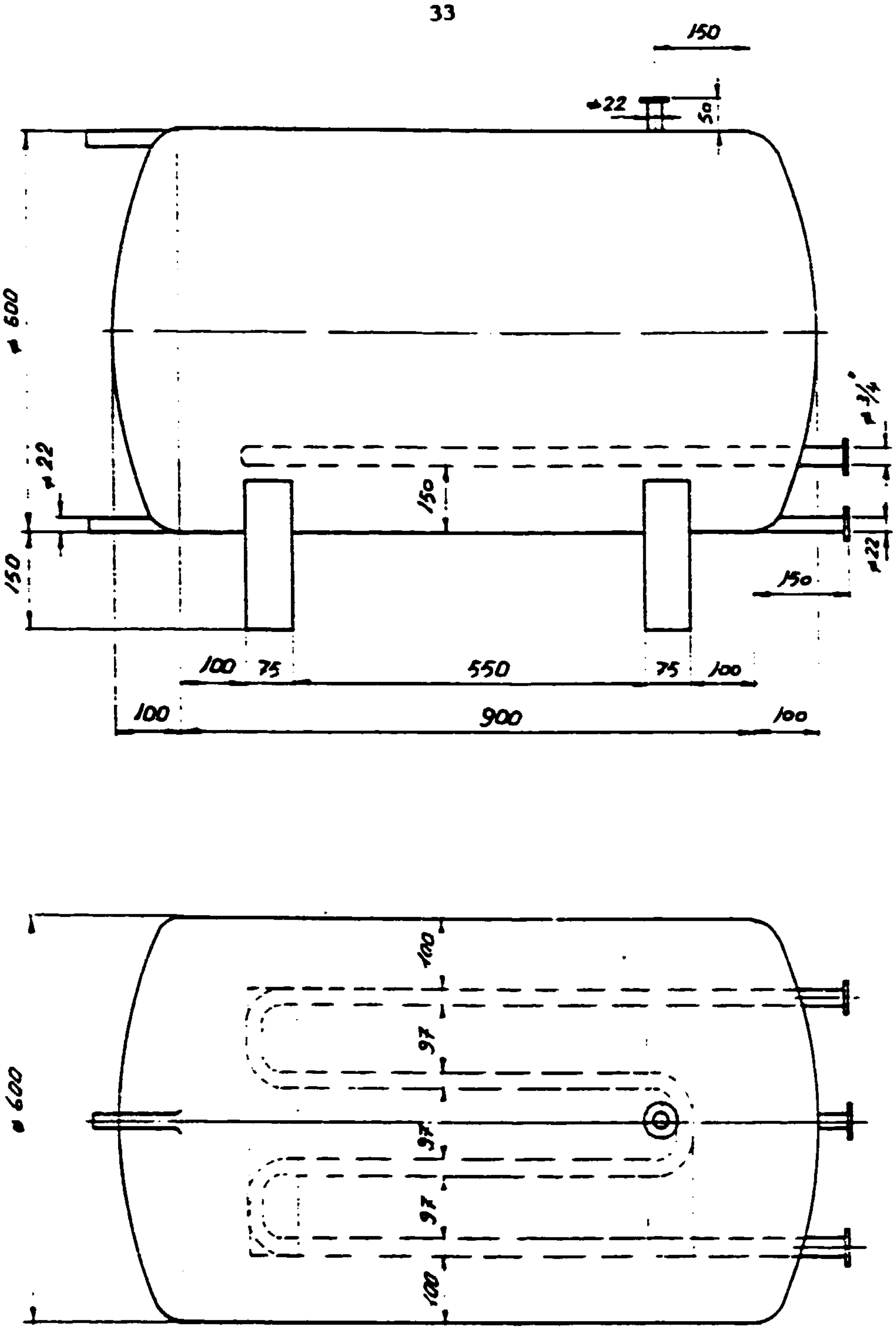
Note:

1. All contact parts AISI 304
2. Thickness of material 2.5 mm
3. Flange sizes according to the pipe di
4. Tubes AISI 304, seamless.
5. Number required-2



LITYAZOL CEMIL
CONDENSER

Design: M.B.NARASIMHA. UNIDC
Drawn: S.H. BEIS. TBAM
Date: 25.04.1994. Eskişehir



Note: 1. All contact parts AISI 304
2. Thickness of material 3 mm
3. Flange sizes accordingly to the pip-
4. Number reruired 4

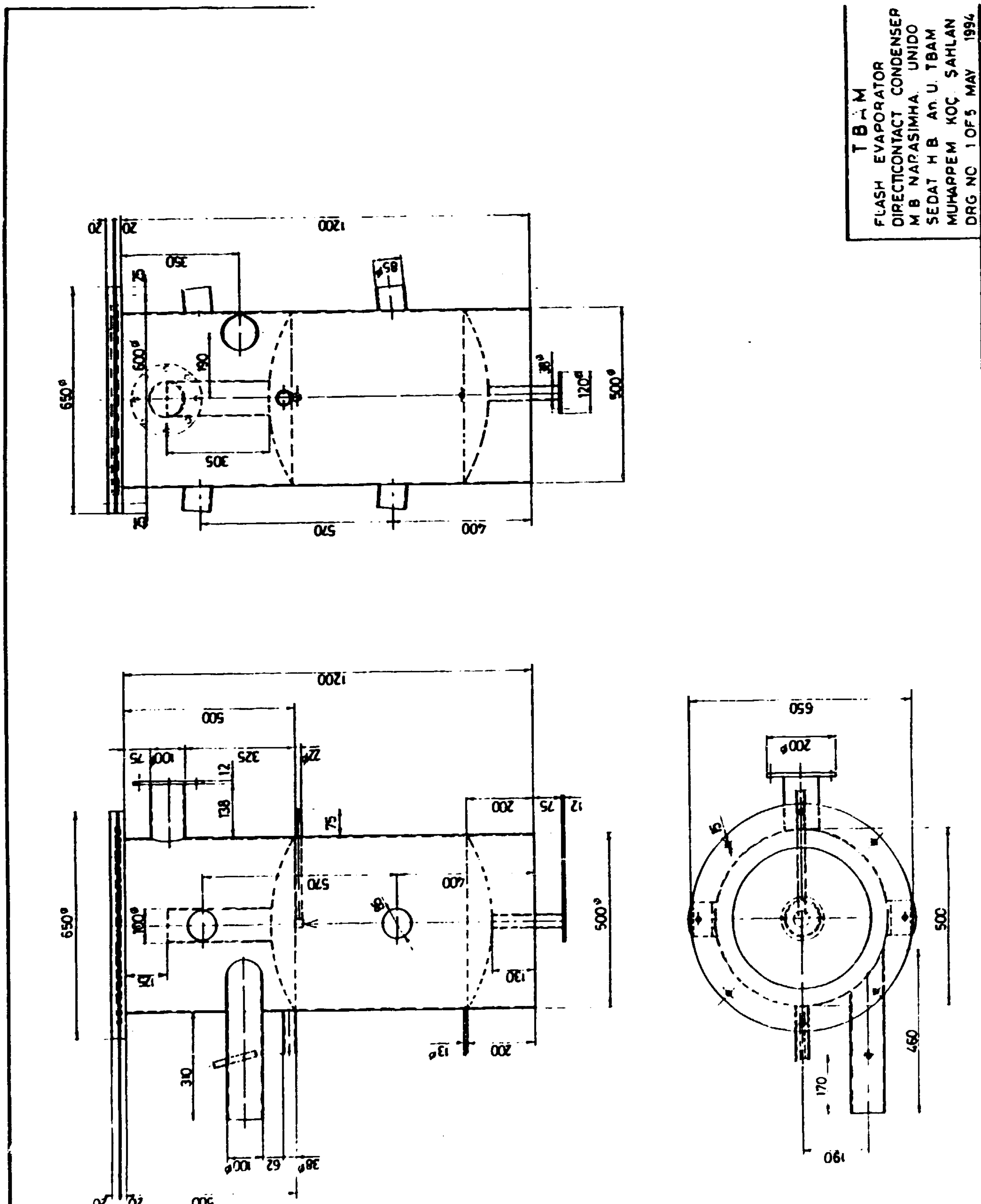
LITYAZOL CEMIL
RECEIVER

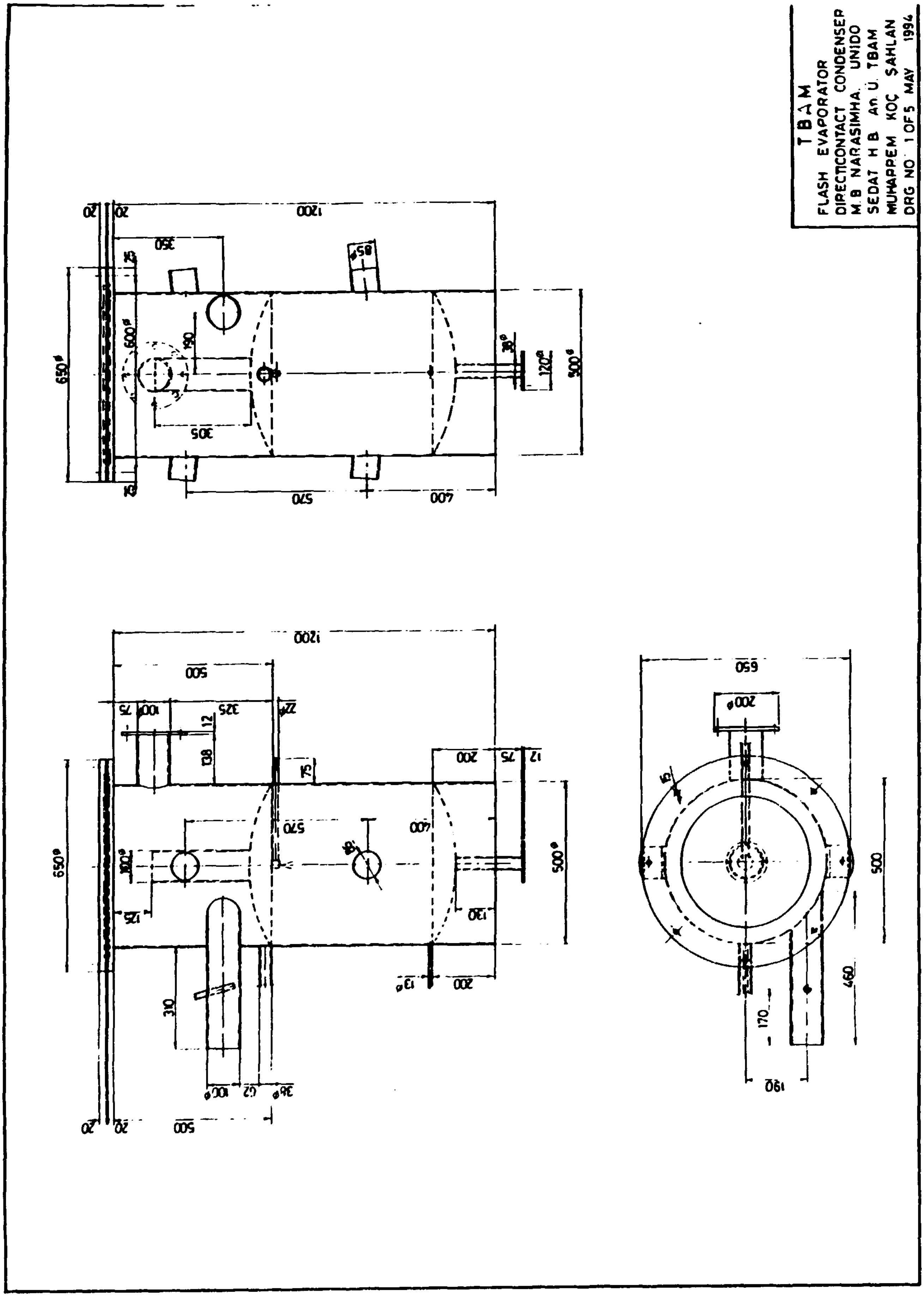
Design: M.B.NARASIMHA.UNIDO
Drawn: S.H. BEIS. TBAM
Date:25.04.1994. Eskisehir

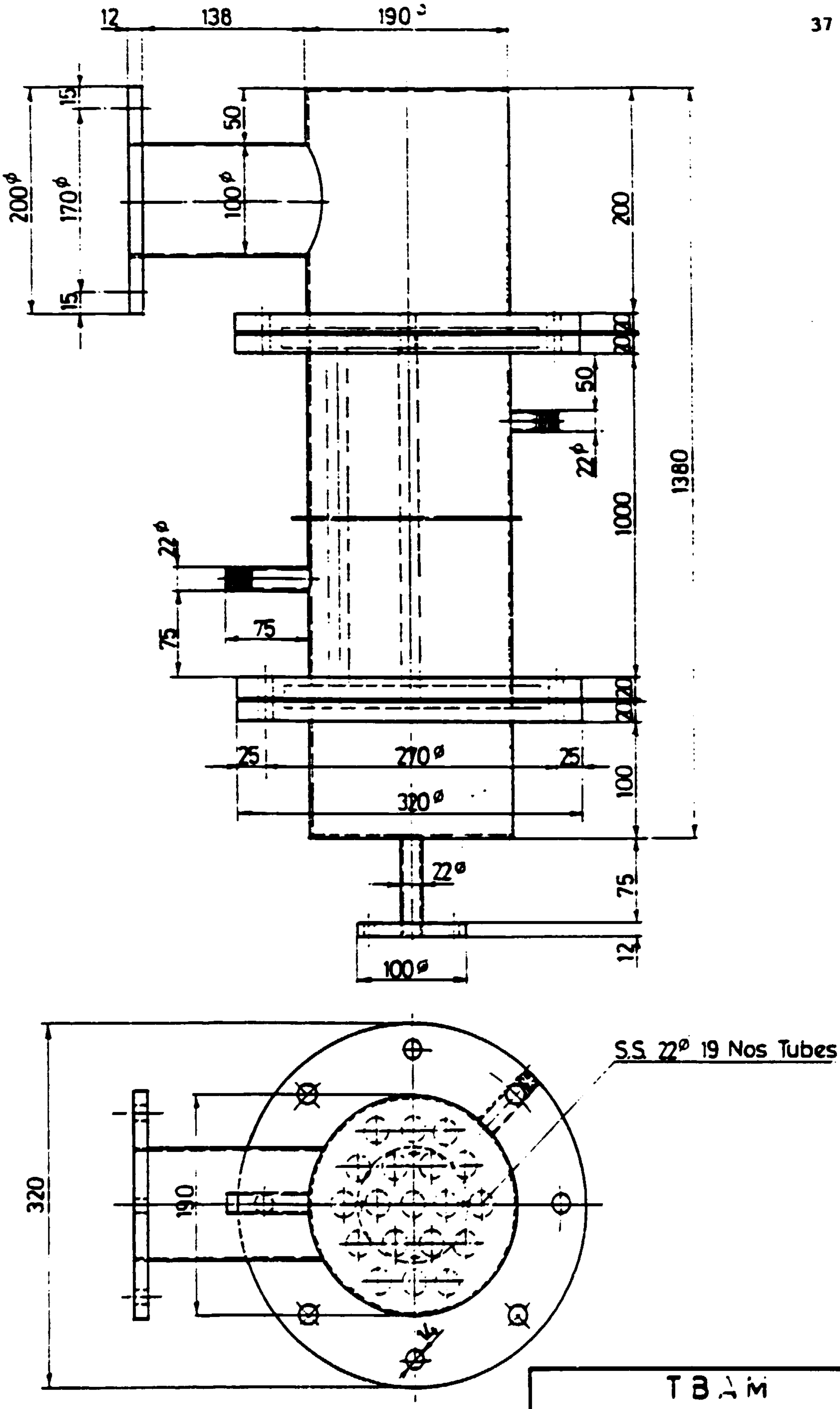
DESIGN DRAWINGS

CONTINUOUS VACUUM EVAPORATOR CUM DISTILLATION UNIT

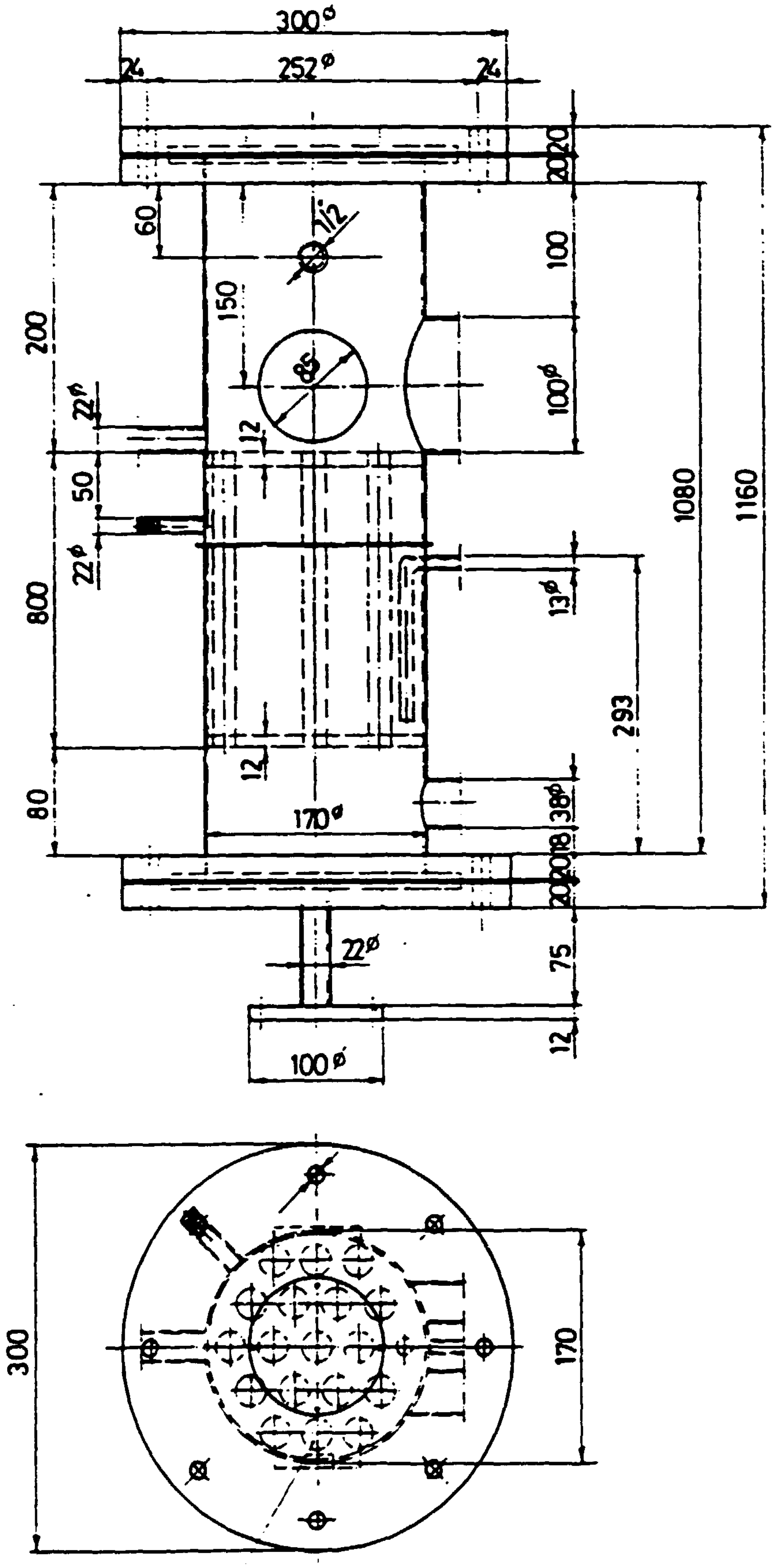
(FLASH EVAPORATOR)


TBAM
FLASH EVAPORATOR
DIRECTCONTACT CONDENSER
M B NARASIMHA UNIDO
SEDAT H B An. U. TBAM
MUHARREM KOÇ SAHLAN
DRG NO 1 OF 5 MAY 1994


T B A M
FLASH EVAPORATOR
DIRECTCONTACT CONDENSER
M.B NARASIMHA. UNIDO
SEDAT H B An Ü TBAM
MUHARREM KOÇ SAHLAN
DRG NO 1 OF 5 MAY 1994

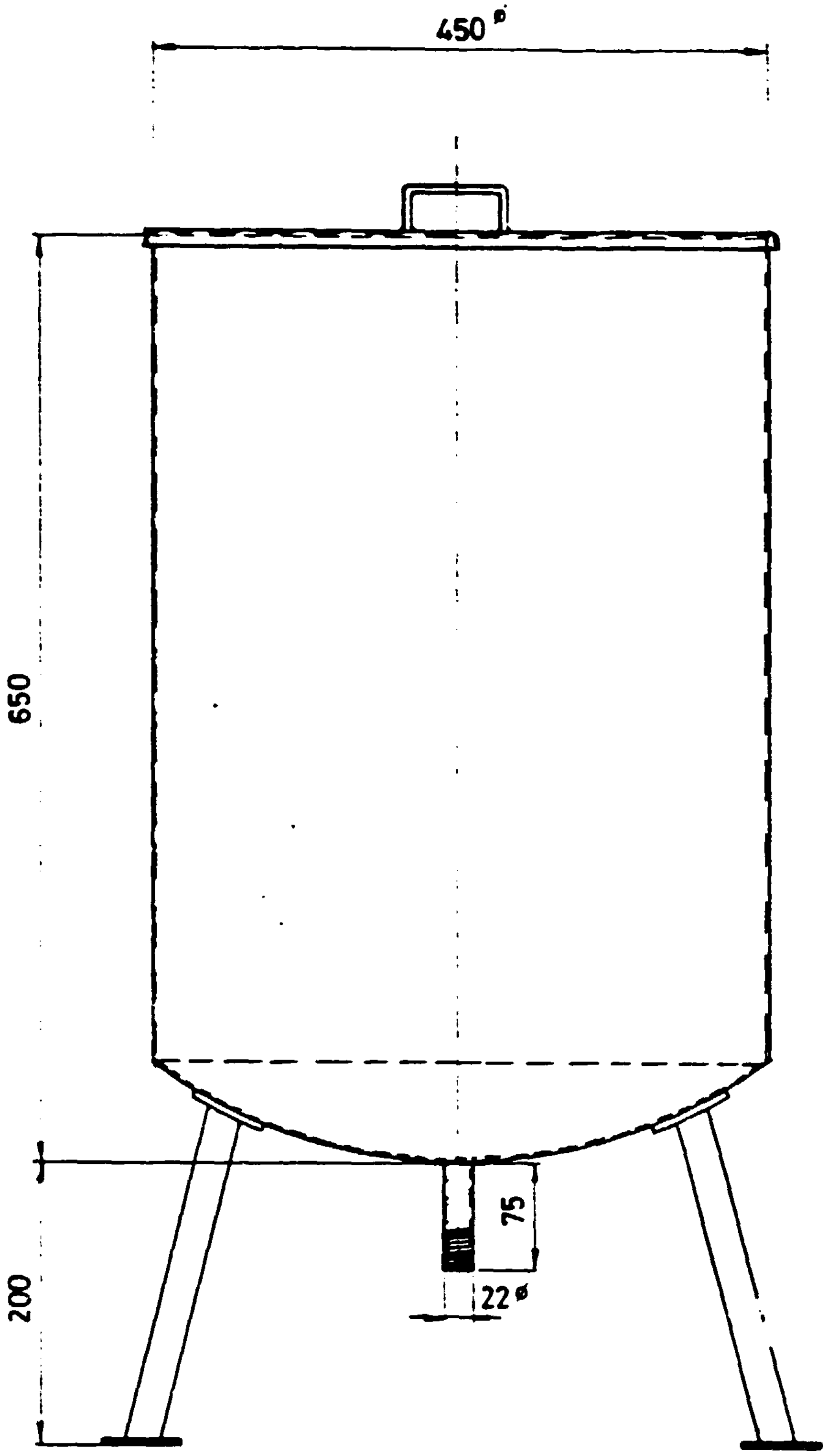


T B A M
FLASH EVAPORATOR
SHELL AND TUBE CONDENSER
M.B. NARASIMHA. UNIDO
SEDAT H. B An. U. TBAM
MUHARREM KOÇ. ŞAHLAN
DRG NO: 2 OF 5 MAY 1994

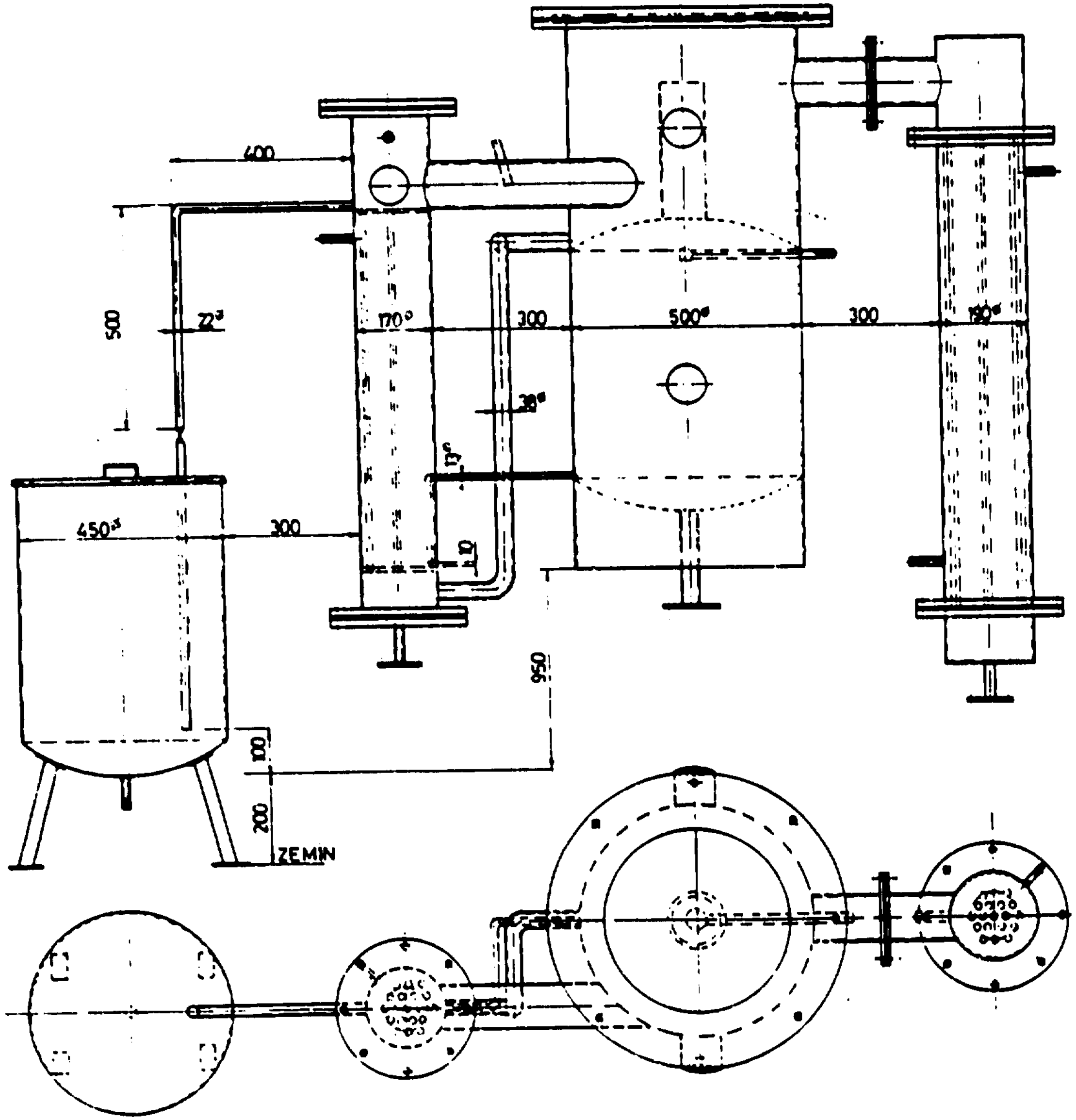


SS 22Ø 18 Nos Tubes

T3 - M
FLASH EVAPORATOR
CALANDRIA
M.B. NARASIMHA. UNIDO
SEDAT H.B. An.Ü. TBAM
MUHARREM KOÇ. ŞAHLAN
DRG NO 3 OF 5 MAY 1994



TBAM
FLASH EVAPORATOP.
FEED TANK
M. B NARASIMHA, UNIDO
SEDAT H.B An. Ü TBAM
MUHARREM KOÇ ŞAHLAN
DRG NO: 4 OF 5 MAY 199



TBAM
FLASH EVAPORATOR
GENERAL ASSEMBLY
M.B. NARASIMHA, UNIDO
SEDAT H.B An U TBAM
MUHARREM KOÇ SAHLAN
DRG NO 5 OF 5 MAY 1994

Annex 7

A note on safety aspects of solvent extraction plants

Marla B. Narasimha

The solvent extraction operation is employed to extract "concretes" and "absolutes" from essential oil bearing materials (also fixed oils) by treatment with a solvent. When so treated, the solvent diffuses into the cells of the material and dissolves the essential oils. A solution of oil in the solvent known as miscella is obtained. The miscella is then separated into its components viz., solvent and oil by simple distillation. The large difference in the boiling points of the two components facilitates the separation.

Normal hexane of high purity equivalent to food grade quality is generally used in the extraction of "concretes" from Rose petals, Jasmine flowers etc., at all the stages of process/product development viz., bench scale, pilot plant and commercially, since it has properties most suitable for extraction purposes. However, the high inflammability of n-hexane makes it necessary that the design and operation of solvent extraction plants should aim at elimination of fire hazard.

Inflammability indicates the rate at which a material undergoes combustion. Combustion is a chemical reaction by which the oxygen combines with the elements of the combustible materials forming mostly carbon-dioxide. The reaction is highly exothermic and in the case of highly inflammable materials the heat of combustion is very high so much so, that once the reaction is set in by application of external heat, the heat of combustion itself will provide enough heat for further ignition and the heat of reaction is released as fire. The heat of combustion of n-hexane is 21,000 Btu/lb. and the reaction start at an ignition temperature of 260 °C.

Hence for a solvent to catch fire, two conditions are to be simultaneously fulfilled. These are:

- there should be a correct amount of air
- there should be enough heat to bring the temperature to 260°C to start the combustion reaction.

Absence of any one of these conditions renders the solvent extraction safe. The design of extraction plants should aim at the elimination of both of these conditions required for starting the combustion of the solvent to ensure perfect safety.

The mixture of air and hexane may not always be flammable unless proportionate amount of oxygen and hexane vapour is present in the mixture. The flammable limits for n-hexane is 1.2% by volume minimum and 6.9% by volume maximum in air, in other words any mixture containing less then 1.2% and more then 6.9% hexane vapour is considered safe.

The sources of ignition in an extraction plant can be of two types:

- mechanical
- electrical.

In the extraction plant area metal to metal impact should be avoided.

All the electrical equipment such as starters, cables, light fittings, motors, etc., required in the extraction plant are necessarily to be flame proof type equipment, any spark occurring is confined inside a perfectly air tight casing, so that it is impossible for the spark to come into contact with the outside atmosphere.

An electrical spark can be set off, due to static electricity generated in the equipment, due to friction between various parts of the extraction plant. To avoid such a contingency it is necessary to ensure the electrical continuity between any two points in an extraction plant and earth the entire plant, so that statically generated electricity is transferred to the earth as and when produced. Lightning arresters grounded to the earth are also installed at suitable points so that in case of lightning in the solvent extraction area it is immediately grounded.

All heating operations in the extraction plant are carried out by steam heating only to ensure that the temperature in the plant at any point does not reach the ignition temperature of 260°C. Temperature of steam at a pressure of 150 psig is only 185°C.

Under abnormal conditions, solvent can find way out of the equipment and likely to create hazardous situation. To avoid such abnormal conditions the following general safety design features are to be incorporated.

Solvent vapours from distillation as well as desolventisation sections are lead to a system of condensers and then the uncondensed gases are lead through a "breather" or an oil absorber or through a chilled condenser, a cold trap and then vented into the atmosphere. Under normal operation conditions the gases vented out contains traces of solvent vapours much below the flammable limits. But in the case of failure or inadequacy of cooling water in the condensing system the gas will consist mainly of solvent vapours, hexane vapour being three times heavier than air would settle in the extraction area creating a very hazardous atmosphere. It therefore becomes necessary that the person in charge of the plant must be alerted in advance of such a situation occurring so that he can take immediate preventive action. For this purpose a vent thermostat is installed in the vent line. The function of this thermostat is to actuate an electrical contact as soon as the temperature of the vent reaches 45°C, an alarm is set off thus warning of the impending danger. For further precaution, this electrical contact is installed in sequence with an electrically operated steam valve installed in the main steamline. As soon as this contact is activated the main steam valve is automatically closed, thus cutting off the supply of steam, so that no further evaporation of solvent occurs in the extraction plant.

In case of power failure, the main steam valve is automatically shut off thus cutting off the steam supply.

Live steam is used for final stripping of the oil and this is condensed along with the solvent vapours and is separated from the solvent in a separator.

The vent of exhaust gases of the extraction plant must be located at a minimum height of 7 meters, so that traces of solvent vapour present in the gas gets diluted with atmospheric air below the flammable limits and does not settle down near the floor.

Solvent extraction plant area should be well ventilated so that concentration of vapours due to any leaks in the equipment does not take place.

BIPHASIC (CONTRACTILE & RELAXANT) EFFECTS OF "LITYAZOL CEMIL" ON RAT ILEUM IN VITRO[1]

	Contraction (Mean)	Relaxation (Mean)
Acetylcholine	42.00 ± 4.18 (n=10)	0*
Lityazol Cem	5.33 ± 1.20 (n=5)	2.66 ± 0.33 (n=5)
P1 (Not diluted)	6.44 ± 1.30** (n=9) F=3.52 P>0.10	2.66 ± 0.53*** (n=9) F=7.5 P>0.10
P2 (1/2 diluted)	4.44 ± 0.40** (n=5) F=0.1846 P>0.10	2.00 ± 0.31*** (n=5) F=1.5 P>0.10

*Rat ileum was standardized according to the contractile responses to acetycholine, as it has only contractile response on this tissue

Statistical differences between the responses to Lityazol Cemil and those to pilot plant products, which were diluted two-times with water, were evaluated by the Student's t-test (P values) and Analysis of variance (F values).

According to the results of the statistical comparison, there were no differences between Lityazol Cemil and diluted and not diluted pilot plant products. This finding suggests that the samples tested are equally active when compared with Lityazol Cemil.

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1 Methodological reference: Altan, V.M., Öztürk, Y., Yıldızoğlu-Arı, N., Nebigil, C., Lafcı, D., Özcelikay, A.T.: Insulin action on different smooth muscle preparations., Gen. Pharmacol. 20(4): 529-535 (1989).

Annex 9

ACUTE TOXICITIES OF LITYAZOL CEMIL & PILOT PLANT PRODUCT PRODUCED BY TBAM IN MICE[2].

SAMPLE	Doses (ml/kg)	Mortality
Lityazol Cemil	0.02 (Therapeutic dose)	0/3
	0.2	0/3
	2.0	0/3
	LD_{50}>2.0 ml/kg i.p.	
Pilot Plant Product	0.02 (Therapeutic dose)	0/3
	0.2	0/3
	2.0	0/3
	LD_{50}>2.0 ml/kg i.p.	

The findings obtained in this test clearly indicate that both Lityazol Cemil and pilot plant product prepared by TBAM have very low toxicities on mice.

2 <u>Methodological reference:</u> Lorke, D. (1983). A new approach to practical acute toxicity testing. Arch. Toxicol. 54, 275-287.

Annex 10

LIST OF PERSONS CONTACTED

1. Mr. Adalat Khan	Dy. Resident Representative UNDP, Ankara
2. Mr. Rasit Karaosmanoglu	Managing Director Dr. Cemil Sener Lab. Manisa
3. Mr. M.Hikmet Taygon	Director, Finance Dr.Cemil Sener Lab. Manisa
4. Ms Asuman Pulat	Chemical Engineer Dr.Cemil Sener Lab. Manisa
5. Prof.Dr.K.H.C.Baser	Director, TBAM Eskisehir
6. Prof.Dr.Yusuf Öztürk	Professor of Pharmacology Faculty of Pharmacy A.Ü., Eskisehir
7. Doç.Dr.Nes'e Kirimer	Faculty of Pharmacy A.Ü., Eskisehir
8. Mr. S.H. Beis	TBAM
9. Ms Zeynep Tunalier	TBAM
10. Ms Berrin Bozan	TBAM
11. Ms Nezihe Azcan	TBAM
12. Mr. Süleyman Aydin	TBAM
13. Ms Rana Beis	TBAM
14. Mr. Adnan Kürkçüoglu	M/S Sahlan Makina Eskisehir

Annex 11

Backstopping Officer's Technical Comments based on the work of Mr. M. Narasimha, SI/TUR/93/801/11-01

The report contains a detailed account of the work carried out by the consultant. He has improved the production technology of "Lityazol Cemil", substantially to save the costs of production and to produce a high quality product. In fact the processing time has been drastically reduced, the recovery of the expensive solvent has been made very efficient, the quality of the product has been improved and the strength of the product has been doubled. Hence the consultant has made a very significant contribution for the improvement of the product and the process of production. He has trained the counterpart staff and submitted the designs for a commercial plant. Quality control specifications have been developed. In addition to the tasks in his job description, the consultant has designed and supervised the fabrication of a vacuum evaporator which could be used to diversify the products of the company. Backstopping officer hopes that the company will soon use the technology developed and improve the quality of the product so that a significant contribution could be made to the health care of people.