potential employ spinning membranes or vibrating modules.

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Dialysis in Medical Separations

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Introduction

Although haemodialysis (HD) as a therapy for uraemia (kidney failure) was first described early in the 1900s, its widespread use did not occur until the 1950s. At this time, Travenol Laboratories (now Baxter International) unveiled the 'coil' dialyser ('artificial kidney') in which tubes composed of cellophane membranes were wound around a support structure and immersed in a recirculated dialysis solution. Relative to contemporary models, the mass transfer efficiency of this type of dialyser was extremely poor, due to high mass transfer resistances in all three compartments (blood compartment, membrane, and dialysate compartment). In the early 1960s, solution mass transfer resistances were decreased with the introduction of parallel flow dialysers, in which sheet membranes were formed in a stacked configuration. The improvement in dialysate-side mass transfer with these dialysers was particularly large because the dialysis solution contacted the membrane under flow conditions as opposed to the semi-batch operation of the coil dialyser. In addition, the membranes used in these devices were thinner in structure, providing less diffusive resistance than earlier versions. Although the earliest manufactured parallel flow dialysers were not disposable, design improvements permitted the production of disposable units by the late 1960s.

The last truly major development in haemodialysers occurred more than 30 years ago when the hollow fibre artificial kidney was developed. Blood compartment mass transfer was reduced further with this design due to the high shear rate that could be achieved in the annular space of the hollow fibre. Additional benefits of the hollow fibre artificial kidney included an enhanced ability to control transmembrane pressure (see below) and a lower extracorporeal blood volume. This type of dialyser is now used in virtually all HD treatments.

On a global basis, approximately 800 000 patients receive chronic haemodialysis therapy for the treatment of end-stage renal disease (ESRD) and this population is growing at a rate of 8–10% per annum. This figure represents approximately 85% of the ESRD population, with the remaining patients receiving peritoneal dialysis. Numerous dialysis membrane and haemodialyser manufacturers are situated around the world, with the vast majority based in the three largest markets: United States, Western Europe and Japan.

The Haemodialysis Procedure

In addition to the dialyser, the other fundamental component of a HD system is a dialysis machine, which serves a number of purposes. First, it is equipped with a roller pump that delivers blood, usually at a rate of 200–500 mL min^{-1}, from the patient to the dialyser and back to the patient. Second, the dialysis machine prepares dialysate by mixing ('proportioning') water and a concentrated bicarbonate solution in such a ratio that the dialysis fluid produced is the same as that prescribed by a physician to meet the needs of an individual patient. The typical dialysate flow rate is 500–800 mL min^{-1} and its major constituents are sodium, potassium, calcium and bicarbonate. The pathophysiology of uraemia is such that during the period between dialysis treatments, potassium levels in the plasma rise while calcium and bicarbonate levels fall. Consequently, the concentration of potassium in the dialysate is typically lower than that in the plasma at the beginning of the procedure while dialysate calcium and bicarbonate concentrations are typically higher. The third major function of the dialysis machine is to provide an accurate measurement of transmembrane pressure (TMP) in the dialyser, which is defined as the difference between the average pressure in the blood and

dialysate compartments. Fluid removal requirements are quite patient-specific in this patient population such that both the rate and total volume of plasma water ultrafiltration need to be controlled accurately. Accurate control of ultrafiltration is achieved by continuous monitoring of dialyser TMP, which essentially is an ultrafiltration surrogate for a membrane of specific hydraulic permeability. Finally, monitoring components of the dialysis machine safeguards against potentially catastrophic events, such as air embolism or a massive blood leak related to a membrane defect.

Classification of Uraemic Solutes

In the properly functioning human kidney, plasma water and blood solutes are removed by ultrafiltration and convection, respectively. Solutes of molecular mass less than approximately 40 000 Da have essentially unrestrained passage through the glomerulus, the kidney's filtration unit. As such, the clearance of these solutes approximates to the plasma water ultrafiltration rate, which is about 120 mL min^{-1} for humans of normal size. By definition, ESRD is associated with absent or minimal native kidney function. As a result, blood solutes normally removed by the above filtration mechanism are retained in the blood stream with a resultant several-fold increase in their plasma concentrations.

The classification of uraemic solutes is typically based on molecular mass and three well accepted classes currently exist (**Table 1**). The first category, simply called 'small solutes', is comprised of nitrogenous compounds of molecular mass less than 200 Da. These solutes are by-products of protein metabolism and include the compounds urea (molecular mass 60 Da) and creatinine (113 Da), which are commonly measured in clinical medicine. The second category, referred to as 'middle molecules', consists of a diverse group of molecules in the 200 to 2000 Da range. Although this class has been widely studied from an experimental perspective, a representative solute, which is clinically measurable, has not yet been identified. Low molecular mass peptides and proteins (molecular masses 2000 to 40 000 Da) are the most recently identified class of uraemic toxins. The plasma concentrations of these compounds are typically increased 50–100-fold in ESRD. Recently, a specific toxin in this class, β2-microglobulin (β2M: molecular mass 11 800 Da), has been identified as a causative factor in the development of dialysis-related amyloidosis, a deposition disorder specific to the ESRD population.

Table 1 Classification of ureamic solutes

Solute class	*Molecular mass range (Da)*	*Examples*
Small solutes	< 200	Urea Creatinine
Middle molecules	200–2000	Appetite suppressant Osteoblast inhibitor
Peptides/proteins	2000–40 000	AGE-peptides β2-Microglobulin Parathyroid hormone

Source: Vanholder R and De Smet R (1999).

Dialyser Specifications

Contemporary hollow fibre dialysers have nominal surface areas ranging from 1.0 to 2.2 m^2, although the trend in clinical practice is to use devices at the upper end of this range. Both the length (approximately 23 cm) and inner diameter (i.d.: usually 200 μm) of hollow fibres used for clinical HD are fairly standard. The i.d. parameter represents a compromise between the desirable characteristics of a short diffusive pathlength and high shear rate with a small i.d., and a low axial pressure drop and hydraulic resistance with a large i.d. fibre. On the other hand, the variation in wall thickness is considerable, with values ranging from 6 to 55 μm. (See below for an expanded explanation.) Based on the surface area of the dialyser, the total number of fibres comprising the dialyser ranges approximately from 7000 to 12 000.

Extracorporeal Therapy Modes Used in ESRD Patients (Figure 1)

In a typical haemodialysis procedure, although transmembrane mass transfer occurs predominantly by diffusion, a modest degree of convective mass transfer is also achieved in association with the ultrafiltered plasma water. However, the recent recognition of β2M and other low molecular mass proteins as important uraemic toxins has prompted interest in using dialytic therapies with increased convective removal capabilities for these poorly diffusible solutes. In haemodialysis, the total ultrafiltration volume and net ultrafiltration rate are determined by the degree to which a patient's plasma volume needs to be reduced and the duration of the treatment. (The total ultrafiltration requirement is dictated by the amount of fluid ingested by the patient in the period between dialysis treatments.) The total volume of plasma water ultrafiltered is approximately 3–4 L, resulting in a typical net ultrafiltration rate of 15–20 mL min^{-1}.

As a means to augment convective solute removal, haemofiltration (HF) was developed by Henderson,

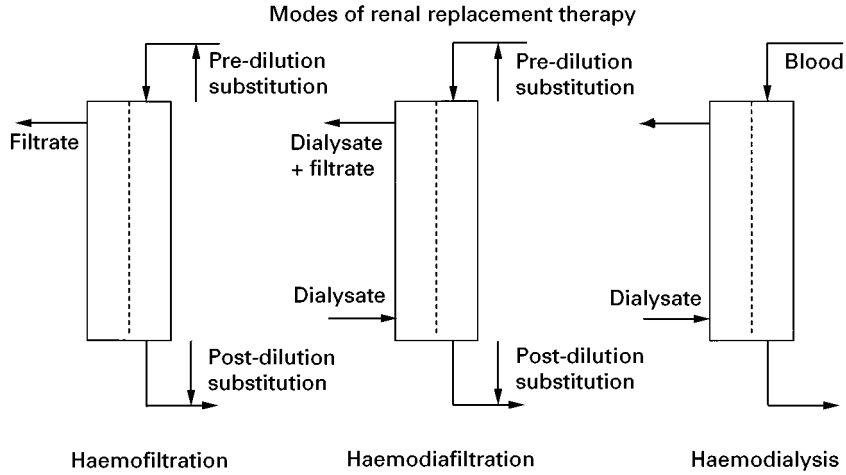

Figure 1 Extracorporeal therapy modes used in end-stage renal disease.

Lysaght and colleagues in the early 1970s. This is a purely convective therapy in which no dialysate is used but an ultrafiltration rate that far exceeds the net ultrafiltration requirements of the patient is employed. As plasma water is typically ultrafiltered at an absolute rate of at least 100 mL min^{-1} (6 L h^{-1}) in HF, the much lower net ultrafiltration rate required for fluid removal from the patient is achieved by 'replacing' most of the ultrafiltrate with a bicarbonate-based solution. For the large volume of intravenous-quality 'replacement fluid' that is required, the filtrate produced by sequential ultrafiltration of dialysate is used. This 'on-line' mechanism, in which the dialysate precursor of the replacement fluid is produced by the same HD machine that performs the HF treatment, allows very high volumes of ultrafiltrate to be produced. In HF, only dialysers with very high hydraulic permeability (see below) are used.

Although HF is a significant improvement over HD with respect to relatively large sized uraemic toxin removal, the absence of diffusion renders it only a marginal therapy with respect to small solute removal. To overcome this deficiency of HF, Canaud and colleagues approximately 15 years ago first employed online haemodiafiltration (HDF). As its name implies, this therapy is essentially a HD/HF hybrid in which both dialysate flow and high ultrafiltration rates are used. At present, HDF offers the broadest solute removal spectrum of all dialytic therapies.

Permeability Classification of Dialysis Membranes

Although numerous classification schemes have been proposed, HD membranes are traditionally classified according to water flux. The clinical parameter used to characterize the water permeability of a dialyser is the ultrafiltration coefficient (K_{UF}: mL h^{-1} mmHg). In fact, the only dialyser classification scheme recognized by the United States Food and Drug Administration is based on water permeability, with low and high permeability dialysers having K_{UF} values of < 8 and ≥ 8 mL h^{-1} mmHg, respectively. The water permeability of a dialyser is usually derived from *in vitro* experiments in which bovine blood is ultrafiltered at varying transmembrane pressure. Based on a commonly used model which assumes that a membrane is composed of parallel cylindrical pores, the flux of plasma water through each pore is dependent on the fourth power of the radius so that small changes in mean pore size have a very large effect on water permeability.

A common misconception relating to dialyser performance is the assumption that a membrane's solute removal capabilities are necessarily correlated with its water permeability. Based on a model in which a membrane has N (straight) cylindrical pores (per unit surface area) of radius r, diffusive solute flux can be expressed as:

$$\phi = \lambda D \rho \Delta C / t \qquad [1]$$

where λ is the solute partition coefficient, D is solute diffusivity, ρ is membrane porosity, ΔC is the transmembrane concentration gradient, and t is membrane thickness. (While the partition coefficient is essentially unity for solutes such as urea and creatinine, larger solutes with incomplete access to the membrane pores have λ values that are less than one.) Membrane porosity is a function of both pore size and number:

$$\rho = N\pi r^2 \qquad [2]$$

For all dialysis membranes, small solutes such as urea and creatinine have free pore access ($\lambda = 1$). Therefore, small solute transport is highly dependent on membrane porosity. As eqn [2] indicates, one membrane with a large number of relatively small pores and a second membrane with a small number of relatively large pores can have equivalent porosities. Although the small solute transport properties of these two hypothetical membranes would be equivalent, the flux (water permeability) properties would greatly differ. This difference is explained by the strong dependence of ultrafiltrate flux on membrane pore size, described above.

Polymeric Composition of Dialysis Membranes

From a relatively simplistic perspective, dialysis membranes can be divided into those comprised of cellulose-based material and those comprised of synthetic materials.

Cellulosic Dialysis Membranes

The monomeric subunit of cellulosic membranes is cellobiose, a naturally occurring saccharide found in plants. Chemically, cellobiose is a ringed structure richly endowed with hydroxyl groups. The interaction of complement cascade products with these hydroxyl groups is felt to be responsible, at least partly, for the relatively pronounced complement activation observed when unsubstituted cellulosic membranes contact blood. For the past several years, a major objective among manufacturers has been the development of modified (substituted) cellulosic membranes in which a certain fraction of these hydroxyl groups are replaced with other moieties. The substitution groups diminish the degree of complement activation by at least three different mechanisms. One mechanism is the replacement of a large percentage of the hydroxyl groups with acetate groups. In the first substituted cellulosic membrane, cellulose (di)acetate, approximately 70–80% of the hydroxyl groups on the cellulosic backbone were replaced with an acetate group. Most likely because this modification eliminates a large fraction of the active surface sites for interaction with complement components, an attenuation of the intense complement activation seen with unmodified cellulosics was achieved. This membrane modification also resulted in a moderate increase in pore size, yielding a slightly higher water permeability and broader solute removal spectrum for cellulose acetate in comparison to unsubstituted cellulosic membranes of similar surface area. Extrapolation of this process to total replacement of the hydroxyl groups resulted in the cellulose triacetate fibre characterized by further attenuation of complement activation and higher water permeability.

A second cellulosic substitution mechanism is the replacement of a relatively small percentage (less than 5%) of the hydroxyl groups with a bulky chemical group, which sterically reduces the degree of interaction between complement activation products and the membrane. Examples for which this strategy is employed are Hemophan® (tertiary amine substitution) and synthetically modified cellulose (SMC; benzyl substitution group).

The evolution in cellulosic membranes has resulted in a wide spectrum of biocompatibility and flux profiles. If complement activation and neutropenia are used as the major biocompatibility criteria, regenerated cellulose is the least biocompatible while cellulose triacetate is the most biocompatible, with the other modified cellulosic membranes having intermediate profiles. However, characterization of the flux properties of these membranes is not as straightforward. For dialysers of comparable surface area, a simplistic approach is to report K_{UF} values in the following ascending order: regenerated cellulose < Hemophan®, synthetically modified cellulose < cellulose acetate < cellulose triacetate. In this simplistic scheme, a 1.5 m^2 dialyser having a regenerated cellulose, Hemophan®, or SMC membrane generally falls in the low flux category ($K_{UF} < 8$ mL h^{-1} mmHg) while comparably sized dialysers having cellulose acetate and cellulose triacetate membranes fall in the midflux (K_{UF} 10–20 mL h^{-1} mmHg) and high flux ($K_{UF} > 20$ mLh^{-1} mmHg) categories, respectively. However, this simplistic categorization scheme breaks down in several respects. High flux cellulose acetate membranes have now been produced and cellulose triacetate dialysers of low water permeability (K_{UF} 9.5 mL h^{-1} mmHg) are also available. Finally, the recent development of unmodified cellulosic and cellulose acetate membranes having relatively low water permeability but solute removal capabilities that include β2M further confounds this classification scheme and provides additional examples of a dissociation between water and solute flux.

Synthetic Dialysis Membranes

The monomeric subunits of the various synthetic membranes individually vary and all differ significantly from cellobiose. The absence of surface hydroxyl groups on synthetic membranes is one factor responsible for the reported differences in complement activation between synthetic membranes and either unsubstituted cellulosic membranes or modified cellulosic membranes of low permeability.

Subsequent to the introduction of the AN69® (sulfonated polyacrylonitrile) membrane in the early 1970s, numerous additional synthetic membranes have been introduced for clinical use. Similar to AN69®, polysulfone and polyamide were brought to the market for use in both high flux HD and haemofiltration. One obvious reason accounting for the use of these membranes in a haemofiltration mode is their significantly larger pore size and hydraulic permeability than regenerated cellulose membranes. The other reason relates to the structural differences between the synthetic and unsubstituted cellulosic membrane groups. Cellulosic membranes have relatively thin walls (generally in the 6–15 μm range) which have a uniform (symmetric) composition across their entire thickness. Although the relative thinness of cellulosic membranes is desirable with respect to diffusive solute transport, this same characteristic renders many cellulosic membranes unable to withstand the high transmembrane pressures required to perform convective therapies employing high ultrafiltration rates. The synthetic membranes have thicker walls (20 μm or more) which may be structurally symmetric (e.g. AN69®, polymethylmethacrylate (PMMA)) or asymmetric (e.g. polysulfone, polyamide, polyethersulfone). In the latter category, a very thin 'skin' (less than 5 μm) contacting the blood compartment lumen acts primarily as the membrane's separative element with regard to solute removal while the remaining thickness (stroma) imparts mechanical strength. In turn, the composition of the stroma layer is quite variable for the various synthetic membranes. For the Fresenius polysulfone membrane, the stroma is relatively homogeneous with a sponge-like structure while the Gambro polyamide membrane has, adjacent to the skin, a sponge-like stroma layer which has progressively larger pores ('macrovoids' with a finger structure) in the radially outward direction. Finally, a new synthetic (polyethersulfone) membrane developed by Membrana GmbH (formerly Akzo Nobel) has a novel configuration consisting of a sponge-like stroma layer interposed between skin layers on both the inner (blood-side) and outer (dialysate-side) aspects.

In the production of synthetic membranes made of primarily hydrophobic polymers (polysulfone, polyamide, polyethersulfone), a hydrophilic additive (polyvinylpyrrolidone: PVP) acts as a polymer alloy. PVP is used to impart sufficient hydrophilicity to the membrane to allow clinical use and, as a wetting agent, modulates surface tension and viscosity within the pore structure during membrane formulation. This latter feature explains PVP's importance in determining the overall pore size distribution of synthetic membranes.

Although synthetic membranes are employed for both haemofiltration and high flux HD, it is in the latter mode that these membranes have found their widest application. Another synthetic membrane formulation was reported in the late 1980s with the introduction of low flux versions. Low flux polysulfone and PMMA have been used clinically for several years and recently a low flux version of a polyamide/polyethersulfone copolymer has been introduced.

Effect of Membrane Composition and Structure on Dialytic Solute Removal

Small Solute Removal

Small solute removal during HD occurs almost exclusively by diffusion. To quantify a particular membrane's diffusive capabilities, its mass transfer resistance is frequently used:

$$R_O = R_B + R_M + R_D$$

In the above equation, the overall resistance to diffusive mass transfer of a particular solute (R_O) has three components: blood compartment resistance (R_B), resistance due to the membrane itself (R_M) and dialysate compartment resistance (R_D). Minimizing the mass transfer resistance in the blood compartment primarily requires the use of relatively high flow rates (i.e. shear rates) that decrease unstirred layers. Dialysate-side mass transfer resistance is likewise decreased by increasing flow rate but optimal dialysate perfusion of fibre bundles is also a consideration. Although increasing dialysate flow rate may itself improve fibre bundle perfusion (see below), another mechanism by which this can be achieved is the inclusion of spacer yarns. These devices are spacing filaments placed external to the fibres and are designed to facilitate dialysate distribution and reduce channelling. The resistance related to the membrane itself actually has two components:

$$R_M = X_M/D_M$$

where X_M is the effective diffusion pathlength for a solute and D_M is the solute-specific membrane diffusivity. This equation indicates that a decrease in membrane resistance can be achieved either by a decrease in membrane thickness or an increase in membrane diffusivity, the latter of which is influenced strongly by membrane porosity.

Middle Molecule Removal

Vitamin B_{12} (molecular mass 1350 Da) is commonly used for *in vitro* characterizations of dialysers. However, due to its extensive binding to plasma proteins, this compound is not useful *in vivo*. In fact, the removal of uraemic solutes having molecular masses which fall in the classic middle molecule category has been difficult to quantify due to the lack of an easily measured *in vivo* surrogate molecule (cf. urea and creatinine for the small solute category). Because recent evidence suggests that uraemic appetite suppression is mediated by the retention of solute(s) in this size range, an understanding of removal mechanisms for middle molecules is important. Based on dialysis practices used in the 1960s and early 1970s (i.e. relatively low flow rates and thick, low permeability cellulosic membranes), diffusive middle molecule removal was so limited that any convective removal contributed relatively substantially to total removal. However, the situation is vastly different in contemporary HD, in which higher flow rates and dialyser membranes of significantly greater diffusive permeability for middle molecules are employed.

Low Molecular Mass Protein Removal

Recent interest in increasing the extracorporeal removal of β2M has provided insight into the general mechanisms mediating the removal of low molecular mass proteins. A number of studies published in the past 15 years support several general conclusions. First, β2M removal by low flux unsubstituted cellulosic membranes is usually negligible, although certain exceptions do exist. Second, the primary mechanism by which β2M is removed during high flux HD varies widely among membranes. For certain membranes, such as AN69® and particularly PMMA, removal is achieved predominantly or solely by adsorption. At the other end of the spectrum is the cellulose triacetate membrane, for which adsorption is minimal and removal occurs primarily by diffusion. High flux polysulfone and unsulfonated PAN membranes have intermediate adsorptive characteristics and achieve transmembrane β2M removal by a combination of diffusion and convection. Third, at least for the high flux synthetic membranes, use of convection-based therapies (HF and HDF) increases β2M removal relative to standard (diffusion-based) HD. Although many clinicians consider β2M to be surrogate for the low molecular mass protein class of uraemic solutes, this assumption has not been conclusively proved. Nevertheless, it is reasonable to use the abundant transport data available for β2M to provide insight into the transport characteristics of other low molecular mass proteins, such as complement activation products and cytokines.

Interaction Between Biocompatibility and Flux

Measurement of complement pathway by-products is one technique used to assess the inflammatory response elicited by exposure of blood to a dialysis membrane. However, numerous previous studies have failed to account for the fact that the clinically measured complement components (C3a and C5a) are low molecular mass proteins. Therefore, the concentration of these inflammatory mediators represents the net result of the simultaneous processes of generation and any dialytic removal that may occur. In this regard, complement activation products are similar to most uraemic solutes, for which the plasma concentration is determined by both generation and net removal. The corollary of this observation is that the permeability properties and not just the polymeric composition of a dialysis membrane must be considered when evaluating complement activation data. Recent data indicate that the relatively low levels of complement activation associated with high permeability synthetic membranes is at least partially related to their ability to remove, either by adsorption or transmembrane transport, the generated inflammatory mediators.

It is simplistic to limit the discussion about membrane biocompatibility to complement activation as a number of agents have been identified as potential inflammatory mediators in chronic HD patients. A list of these putative mediators appears in **Table 2**. Some of these compounds, such as Lipid A and LPS fragments, potentially have their origin in dialysate, a nonsterile fluid. Due to their relatively low molecular mass, these inflammatory mediators may undergo transmembrane passage and induce cytokine

Table 2 Inflammatory mediators

Mediator	*Molecular mass (kDa)*
Lipid A	2–4
Lipopolysaccharide (LPS) fragments	< 8
C3a	8.9
Granulocyte inhibitory peptide (GIP) II	9.5
C5a	11
Interleukin-1	17
Tumour necrosis factor (monomeric)	17
Factor D	23
Granulocyte inhibitory peptide (GIP) I	28
Tumour necrosis factor (trimeric)	55
Lipopolysaccharide (LPS)	> 100

Source: Lonneman G (1993).

production in the blood stream, either directly via an effect on mononuclear cells or indirectly via an effect on the alternative complement pathway. Conversely, the majority of the mediators that are potentially elicited in the blood, such as C3a and IL-1, may be simultaneously eliminated during high flux therapies by an adsorptive or transmembrane mechanism, as discussed above. Other investigations have confirmed that adsorption is also important in the removal of other inflammatory mediators, such as Factor D and cytokines.

Summary

Dialysers used in contemporary HD are equipped with a wide variety of membranes and within both the cellulosic and synthetic classes, water and solute flux properties vary widely. For small and middle-sized solutes, abundant clinical data point to the importance of membrane thickness in diffusive mass transfer. The removal of low molecular mass proteins may occur largely by adsorption for some high flux membranes, particularly those of hydrophobic synthetic composition. Because many of the mediators of inflammation in dialysis patients fall in this low molecular mass protein category, the biocompatibility of a particular membrane must be interpreted in conjunction with its permeability properties.

See Colour Plate 47.

See also: **II/Membrane Separations:** Membrane Bioseparations. **III/Membrane Preparation:** Hollow Fibre Membranes; Interfacial Composite Membranes.

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Diffusion Dialysis

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Introduction

Diffusion dialysis is a separation process in which an ion exchange membrane separates a source solution and a receiving solution, usually water. Anion exchange membranes are notoriously permeable to acids, and diffusion dialysis exploits this property to separate acids from salts. A common application of diffusion dialysis is recovery of acids from waste metal pickling solutions, the strong acid solutions that are used to remove oxide coatings from metal parts before they are painted, galvanized or