The Chemist

Subscription: $35 per year to members. $75 per year to non-members. Single copy, $25

The Chemist (ISSN: 0009-3025) is published quarterly by the American Institute of Chemists.

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E-mail: Publications@TheAIC.org
www.TheAIC.org
ISSN: 0009-3025

Volume 84, Issue 2
December 2007

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From the Editor………………

This issue of The Chemist includes an eclectic series of contributions. While we appreciate the support of all of the authors in this issue. I want to extended a personal thanks to Dr. Margot Hall who almost single-handedly kept the journal going in these last few issues. I know that everyone is faced with what has become known as multitasking, working smarter not harder and a number of other challenges but The Chemist needs the support of the membership. While research articles are of course nice, we would be delighted to include meeting reports, short columns, editorials of science related topics, technology items and book reviews. The book reviews can obviously be technical but we would also welcome reviews of books that members might find interesting such as The World is Flat or Einstein. I would welcome the chance to talk with you about suggestions for the journal and contributions.

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Formulating for Extruding Rigid PVC Fenestration Products

By Kenneth Abate, Ph.D., FAIC, CPC

In a single short paper, one cannot provide all the detailed information on the formulating of rigid polyvinyl chloride, PVC, or vinyl, as it is commonly called, for its many industrial uses or even for a specialty segment of the market like the window and door industry. Also, the author assumes that the reader understands the basics of the thermoplastic extrusion process, twin screw, both conical and parallel, and single screw.

In the last couple of years vinyl windows have become the number one selling product type sold in the residential market, around 31million annually, surpassing both wood and aluminum based products. (1) Because they are designed to conserve energy and serve a variety of structural requirements, vinyl window and door products will continue to increase their market share. Vinyl fenestration products are durable, not effected by rot, corrosion, cracking, flaking, or insect infestation, are recyclable, and are easy to maintain. They are resistant to fungus and mildew growth. Vinyl windows have excellent fire resistance properties, meeting most building codes for ignitability, flammability, heat released, burning rate, flame spread and smoke generated. Minor scratches do not require painting or repair, and the aesthetics are maintained by simply washing with a mild soap and water. When properly installed and maintained, vinyl window and door products will provide long lasting aesthetics, reliable performance, and continuing energy savings.

Being a good thermal insulator, not only does a vinyl window save money by conserving energy once installed, it is energy efficient in its manufacture. Salt and natural gas, petroleum, or coal are the main starting materials for PVC. PVC accounts for less than 0.3percent of the world's annual gas and oil consumption and about 10 percent of the annual salt consumption. One study indicates that vinyl windows require about one-third as much energy to manufacture as comparable aluminum windows. (2)

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Background:

PVC has been around since the late 19th century but did not come into general use until the 20th century when its commercial polymerization processes and the various post-polymerization processing techniques matured. Because of its basic properties (3) and the ability to be readily blended with other materials into "thermoplastic" systems or formulations that produce products ranging from rigid to very flexible, PVC has become commonplace. Its uses span from rigid materials like pipe to the various building products, where high strength to weight ratio, aesthetics, durability, and the ability to be recycled are important, to flexible products ranging from garden hoses, films for laminating, to medical tubing and bags.

The majority of PVC resins are produced commercially by the polymerization of vinyl chloride monomer, VCM. VCM can be produced via ethylene, processing natural gas or the cracking of oil/petroleum, or acetylene, the carbide process. The carbide process is based on the gasification of coal, has a different set of potential impurities than those of the ethylene route, and is used primarily in Asia (China).

Bulk PVC is produced at a number of different molecular weights by solution, suspension, or emulsion polymerization. The final product typically is "graded" by inherent viscosity differences and the number of gel particles allowed. Although suspension and emulsion polymerization at first glance appear to be the same, they are not and have a couple of important differences. In suspension polymerization the bulk phase is aqueous and the initiator is dissolved in the monomer phase. The kinetics of the reaction is the same as that of bulk polymerization. In emulsion polymerization, the initiator is in the aqueous phase, where the polymer particles produced are smaller than those produced in suspension polymerization, are highly dependent on the level and type of surfactant blend used, and higher molecular weights can be produced at a higher rate than with suspension polymerization. Among the various commercial producers of PVC resin, each may use a different surfactant stabilizer "package" during manufacture and because of differences in the drying technique once polymerization is complete, spray vs. coagulation/precipitation, the residuals differ. There are commercially available co-polymers of vinyl chloride with "acrylic" monomers and/or other vinyl monomers. These are either specialty resins or not readily available in the US unless imported.

PVC is chemically inert, resistant to water and environmental corrosion, is a good electrical and thermal insulator, and maintains its properties over a reasonably large temperature range. Because it is about 57% chlorine, it does not support combustion. It has a low degree of crystallinity, typically quoted around 7-8 % but literature values range from 5 to 12%, and is translucent. By adding other inorganic and organic ingredients, it can be formulated to yield a large variety of final properties and can be processed by all the typical thermoplastic processes commercially used today, extrusion, injection and blow molding, etc. It is also used in the paint and coatings industry to produce plastisols and organosols.

Recently, PVC has come under scrutiny because of potential health and safety concerns but many of these claims are misdirected because in actuality it is the various other materials which have been added to PVC formulations to be able to process for a particular use that are the problem. A good example would be that certain phthalate plasticizers commonly added to PVC to provide flexible materials have been shown to have adverse health effects. The plasticizers leaching out of the PVC are actually the cause of concern rather than the PVC itself. When other plasticizers are used, the concerns are eliminated. (4,5)

Another concern has been the use of Pb stabilizers, especially in products produced in Europe and Asia. As you will see later in this paper, there are other stabilizer options which totally eliminate the use of Pb.

Residual VCM remaining from the polymerization processes is a known carcinogen. With today's highly controlled manufacturing procedures, the residual VCM in commercially purchased PVC resins is extremely low, single digit or less parts per billion. After further processing into consumer goods, residual VCM is almost non-existent.

"Dioxins", which can be generated as a byproduct from PVC manufacture and/or the incineration of PVC materials, is a known health hazard because they persist in the environment, can travel long distances, and have been linked to a variety of health concerns. Dioxins are never produced intentionally but can be produced when anything containing chlorine is burnt. Forest fires, lightning, volcanoes, and activities such as burning wood and trash, diesel vehicle emissions and other manufacturing practices all can generate dioxins. The majority of dioxins generated today come from consumer incineration of garbage and scrap PVC materials, i.e., backyard burning. Global recycling would eliminate much of the dioxins being generated.(6)

Although more than a billion pounds of PVC materials were recycled in 1997(1), more extensive post consumer recycling of PVC is not done primarily due to the concomitant costs and inconvenience of waste PVC collection and reuse. Strong efforts are being made to encourage the collection and reuse of PVC materials rather than burning or simple throwing away but it is up to the consumer to decide the extent of recycling. Each and every one of us needs to make the commitment to recycle and become advocates of environmentally friendly practices.

Formulating:

Formulating blends of PVC resin with other ingredients or "compounding", as it is called in the industry, to produce rigid PVC building products has been going on for decades. A great deal of information is known about the effects of various ingredients and it is up to the formulator to decide what properties are most important and which ones are secondary. Rigid PVC or u-PVC, as it is sometimes referred to in Europe and other parts of the world, needs to be able to be extruded and then perform a specific task. Normally in the fenestration industry, the PVC formulator is concerned about a certain set of properties for ease of handling and extrusion, then another set of properties once the compound has been extruded into profiled product and will be further processed into complete windows or doors, and finally another once exposed to the environment as a window or door. All of these are important and as is the case with most things, not all of the desired properties are attainable without compromises. For example, one can increase strength but may lose the ability to extrude consistently, or perhaps increase brittleness to the point where the profile readily breaks or is very sensitive to impact temperature, or will pass all the required physical specifications but will badly discolor once exposed to the environment. It is not my intent to provide all the information required to enable the reader to become an expert formulator of PVC blends for the fenestration industry but to give you a general feel for the essential ingredients and what is possible. There is a lot of very good information available on the internet, from the various raw material suppliers, and in print today which the reader can refer to on their own. I have listed some in the bibliography.

It is interesting to note that with most rigid compound formulations the ingredients are listed as "phr", parts per hundred parts of PVC resin, and then as percentages. One formulator talking with another will talk about usage levels as "parts". They are talking about phr.

PVC Resin (7):

In any formulation the largest ingredient by weight is PVC. The designation of the PVC used is a general purpose, homopolymer made by either suspension or bulk polymerization. (Emulsion resins are typically used in the manufacture of various paints, plastisols or organosols.) One needs to choose the grade of PVC that offers the best possible set of properties for the economics of the final product. The first choice is molecular weight.

Molecular weight is designated in different parts of the world differently. Here in the USA molecular weight is reported as Inherent Viscosity, IV, or K-value. The higher the IV or K-value the higher the molecular weight. In Europe and Asia, K-value is quoted more than IV and is calculated from relative viscosity. Because there are several different methods of calculating K-value yielding different results, one needs to be careful when using K-value globally. In general, the higher the PVC molecular weight the better the impact strength can be, and the more difficult it can be to get fusion and achieve polymer flow without excessive heat or shear. Typically, resins in the K-value range of 65-67 are used for rigid profile but somewhat lower molecular weights are not uncommon especially for foaming or capping formulations.

Other important properties are the number of allowed gel particles, called "fisheyes", residual VCM content, % moisture, bulk density, particle size distribution usually classified by sieve analysis, flow analysis, porosity, and resin heat stability. If one uses resin from different suppliers, comparing raw resin properties and base compound properties are a must. Not all resins supposedly the same IV but from different suppliers are the same and one can get very different extrusion and final product properties from the "same" molecular weight range resin from two different suppliers.

Exposure to temperatures above 70^{o}C and/or to ultraviolet light will degrade PVC. In air at elevated temperatures one will see a color change from translucent, almost colorless to yellow, then proceed to orange, brown, and, finally, black with a concomitant general decrease in the mechanical and electrical properties. Even if stored in the dark and in a cold environment, PVC can undergo degradation so the typical conditions for storing color standards cannot be relied upon for colored PVC formulations.

PVC is typically 70 to 80% of any formulation.

Processing Aids (8):

Processing aids function by promoting fusion of the PVC powdered blend into a molten mass that can be appropriately processed and by altering the melt rheology during extrusion. They assist with faster fusion, better mixing of the components as melting occurs, improving the strength of the melted PVC blend, controlling the die swell, reducing plateout, and achieving a smoother surface and higher production rates. Die swell is the term used to describe the volume increase or swelling that occurs immediately after the melted polymer blend leaves the die opening. Most processing aids today are "acrylic" polymers, i.e., containing acrylate and/or methacrylate monomers, with a variety of different compositions and molecular weights. They are always higher in molecular weight than is the PVC resin and because they are very compatible with the PVC resin, they assist with the interparticle mixing of the PVC particles at the beginning stages of fusion. Other high molecular weight polymer types, styrene derivatives and polyesters, have been promoted and evaluated commercially but they are not in common use today.

In general, the higher the molecular weight of the acrylic processing aid, the higher the die swell expected. Higher die swell can be a good thing if one is trying to make a foamed PVC material but is not good if one is making a solid profile and needs to carefully control dimensions. Acrylic process aids are usually used as a combination of different molecular weights and the polymers can have different monomer content. They also assist with impact strength improvement, weatherability, and there is some evidence that they reduce the crystallinity of the PVC. Acrylic processing aids are used at a 1 to 5 phr level depending on desired properties of the final product.

There is some evidence that fine particle size $CaCO_3$, less than 1 micron, can act as a process aid by increasing the friction during melting in the extruder. Other benefits are better heat transfer and increased productivity. Even though a fine particle $CaCO_3$ may act as a processing aid, it is usually considered a filler.

Impact Modifiers (8):

Impact modifiers are designed to improve the final product's toughness and the ability to not crack and shatter during subsequent manufacturing operations such as cutting with a saw, or punching or routing holes in the profile. They function by absorbing energy and/or dissipating the energy of a propagating crack and can increase the yield of the extruded PVC formulation by acting somewhat like a lubricant. Impact modifiers fall into three very broad categories: "core-shell particulate" polymers, semi-compatible polymers, and fine particulate inorganics.

Core-Shell:

The "core-shell particle" type of technology is where the mechanism of improved impact resistance or toughening is the dispersion of a very small particle with an incompatible, rubbery core and a more compatible outer shell throughout the PVC compound. This technology is used to toughen many other polymeric matrixes across different industries. Chemically, the impact modifiers are based on co-polymers such as methacrylate/butadiene/styrene (MBS), all "acrylics", acrylate/butadiene/methacrylate, and acrylonitrile/butadiene/styrene (ABS). All have a highly crosslinked, incompatible, rubbery inner core with a grafted, compatible, outer polymeric shell or shells. Obviously, the ability to uniformly disperse the particle within the melted mass is very important for this approach to work. In this approach it is also important to have a small particle size, so as to provide numerous sites for stress/crack control, to be able to readily disperse the particles throughout the bulk matrix, to have compatibility of the outer shell with the PVC, and to minimally influence the overall system's other physical and weathering properties. With a blunt impact, the decrease in brittleness allows the PVC to flex and not break. Once a crack does initiate, the tip of the crack with its high concentration of shear energy running through the matrix will encounter a rubbery particle that will absorb and dissipate the crack propagation energy and minimize or stop crack propagation. It is important that the outer shell favorably interacts with the PVC so that effective energy transfer occurs between the rubber particle and the surrounding matrix. In general, there is an increase in fusion rate when particulate impact modifiers are used.

Semi-compatible Polymers:

In the semi-compatible polymer approach, the polymer at lower but elevated temperatures is compatible and is dispersed readily as a melt between the PVC primary particles. Polymers of chlorinated polyethylene (CPE) and ethylene-vinyl acetate (EVA) fall into this general category.

With CPE as fusion continues, and the temperature increases, the CPE becomes less soluble and forms a discrete particulate phase. Once the mix is cooled after extrusion, the PVC product now has finely dispersed particles of the lower T_g CPE dispersed within the PVC matrix. (9, 10)

CPE is manufactured by chlorinating high-density polyethylene. Typical grades of CPE contain 25 or 36 % chlorine so as to be compatible with PVC. CPE with less than 25% chlorination are incompatible with PVC and provide no impact enhancement. Theoretically, the dispersed particles of CPE after PVC extrusion should be spherical but in actuality become flattened and somewhat distorted in the direction of extrusion flow. Because it melts at a low temperature, initially coating the PVC and inorganic particles, and acts like a lubricant as the remainder of the PVC compound is being fused, fusion is delayed with the use of CPE impact modifiers and their use may require adjustments in the lubrication portion of the formulation. Depending on the total formulation, CPE based materials are not as light stabile as the acrylic based impact modifiers and tend to yellow a bit more. CPE is typically used in the 3-5phr level.

EVA polymers with vinyl acetate content of around 40% are used primarily in Europe as impact modifiers. They are used at quite high levels, 5-15 %, and although impact, and thermal stability is improved, modulus, strength, and heat deflection temperature decrease. The mechanism of impact improvement is the formation of an elastomeric honeycomb network within the PVC matrix. EVA impact modifiers are supplied primarily as pellets as their powders tend to agglomerate. This causes blending and handling difficulties. EVA modified formulations weather close to those modified with the acrylics.

Other polymers have been tried as impact modifiers. Among them are terpolymers of ethylene / vinyl acetate / carbon monoxide, ethylene/propylene/carbon monoxide, polymers of olefins with acrylates, various copolymers of butadiene with acrylonitrile, methacrylates or other rubbers, and even polysiloxane enhanced materials. Although they improve impact resistance, most are not in common usage for a variety of reasons.

Inorganic particles:

The mechanism of improving impact resistance by the use of a hard, very small particle sized inorganic material has been called the cavitation mechanism. It has been described as one in which once the hard particles are very well dispersed throughout the polymer matrix, they will dissipate the impact energy striking them over the total surface of the hard particle such that in any direction the energy transmitted is less than necessary to initiate cracking or to continue crack propagation.

Ultrafine, coated, precipitated $CaCO_3$ has been found to improve low temperature impact resistance and increase UV stability in rigid PVC products. (11) A variety of organic surface treatments are available but stearic acid or its derivatives are most common. Careful control of the very fine particle size, less than 1 micron, and complete dispersion within the PVC blend are critical. Use levels of from 5 to 20 phr are recommended depending on the application.

More recently, the incorporation of synthetic amorphous silica has been described as improving impact resistance. (12) The particle size, about 150 nm, and surface area are carefully controlled. These materials are used in the 4-8 phr level and may require adjustments in the lubrication to get proper fusion. One of the cautions is that the particles need to be very well dispersed and this may require additional processing steps to do effectively. Silica is also used to provide improved flow with certain PVC formulations and to reduce the surface gloss. The use level is very low and even very low levels of silica in a formulation can contribute to wear to both the compound blending and the extrusion equipment.

Fillers:

Solid fillers are incorporated into the formulation primarily to reduce cost. Although one can get very involved with providing the proper definition of what a filler is, the author will simply state that it is a solid material which does not change its state during extrusion and maintains, for the most part, its shape during extrusion. To correctly use a filler, one should understand its effect on the overall properties of formulation. One needs to balance cost reduction, use level, and processing changes that may occur with the use of a specific filler versus final product properties desired. PVC fillers can be classified as extender or functional.

Extender fillers are low in cost, have the appropriate size and shape to pack well, are chemically inert within the formulation, compatible with the process, and have an acceptable color, refractive index, and specific gravity. Functional fillers provide some processing or final product advantage. Since it is not always easy to determine which is which, the following are commonly used as fillers:

Limestone, $CaCO_3$, is a natural occurring mineral. If mined, it can contain small impurities of Mg, Si, Al, and Fe. Mined and then ground to a specific particle size range, it is inexpensive and you get whatever was in the ground. One should evaluate carefully the use of any naturally occurring material to make sure that it fits one's needs. Limestone from the same company but from different mines may differ significantly in impurities.

$CaCO_3$ also can be manmade, precipitated, and the impurities and particle size can be more controlled. Precipitated cost more than mined material and is considered to be a functional filler by many. Commonly, $CaCO_3$ is surface treated with a stearate to improve its hydrophobicity, and the flow properties. When $CaCO_3$ is treated with stearic acid the surface of the particle chemically reacts to form a monolayer of calcium stearate. This surface treatment also can be beneficial by reducing the lubricant level required, and improving impact.

Kaolin clay is a mineral with the approximate chemical formula $Al_2O_3{\cdot}2SiO_2{\cdot}2H_2O$. It is a mined mineral with several different plate-like structures. Because of the platy structure aligning with the direction of extrusion, one can obtain an increase in stiffness.

Talc is hydrated magnesium silicate with an idealized formula of $3MgO{\cdot}4SiO_2{\cdot}H_2O$. The actual composition varies somewhat in the Mg to Si ratio. It is mined across the country and is associated with a variety of other minerals. It is very soft and is plate-like in its structure. The surface of talc is active so it is commonly surface treated with an organic material. With talc's platy structure, one typically can achieve improved strength with its incorporation into a formulation. Because of impurities, one needs to be careful of the source of talc to avoid discoloration and inconsistencies during processing.

Mica is potassium/aluminum silicate, is platy, and very similar to talc. It is harder than talc and softer than $CaCO_3$. It can be used in PVC formulations to improve flexural strength, increase heat deflection temperature, and dimensional stability.

Wollastonite, calcium metasilicate, is typically used as a high aspect ratio mineral for improved stiffness and deflection temperature. It can be abrasive to equipment.

Lubricants:

Lubricants are used in small amounts. They are to function by reducing the resistance to flow of the polymer chains and other ingredients in the formulation, and should not dramatically effect the other bulk properties of the formulation once it has been extruded. Essentially lubricants act as processing aids but processing aids do not act as lubricants. With PVC formulations lubricants are described as being external or internal lubricants. Although this distinction is made, the difference between materials is not as clean as the names imply. Some materials act as both depending on the use level and extrusion conditions.

If a material provides improved flow of the hot compound through the equipment and is found after extrusion primarily on the outer surface, it is classified as an external lubricant or a metal release aid. During discussions about lubrication, one will hear the phrases, "metal release" and "slip agent". These mean that the lubricant tends to go to the surface and allow the hot plastic extrudate to flow through the metal, vacuum calibrators without sticking and causing chattering.

If after extrusion the lubricant can be found throughout the part, it is classified as an internal lubricant. Internal lubricants provide a reduced melt viscosity. When used at too high a level, they can start to act as an external lubricant, which can cause other problems, typically referred to as "plate out". Plate out is when the lubricants required for processing are squeezed out of the hot bulk plastic as the extrudate is leaving the die and/or going through the vacuum calibrators and either plugs the calibrator's vacuum slots preventing good surface contact between the hot extrudate and the calibrators or collects at the exit of the die and drips. Neither of these is good. In the first instance the surface of the part deteriorates, dimensions may be hard to control, and one will need to shut the line down and clean the vacuum calibrator section. In the latter case, in addition to plugging the calibrators the hot, dripping lubricants make a mess and are safety hazards.

On the surface lubricants and plasticizers might appear to serve the same purpose. The major difference is that plasticizers are used in very much higher use levels than are lubricants. Rigid PVC formulations typically do not contain plasticizers.

There are several chemically different types of lubricants. Each needs to be carefully balanced to maximize the processing improvements and minimize adverse formulation effects. Almost always a combination of lubricant types is used rather than a single material.

Hydrocarbons called paraffin waxes are the most commonly used external lubricant, and are used in very low use levels, less than 1%, with good metal release properties. When these waxes are oxidized under carefully controlled conditions, they are called oxidized polyethylene, OPE. Because of the carboxylic acid groups, OPE has increased solubility, is used at very low levels, and can have a dramatic effect on fusion.

Various long chained carboxylic acids, their esters, amides, and salts are used to assist with lubrication of PVC systems. They are not used alone but as internal lubricants in conjunction with waxes. Stearic acid derivatives are most common but other long chain, saturated, aliphatic acids are used. Derivatives based on montanic acid, octacosanoic acid, can and have been used.(13) Calcium stearate is commonly used as an internal lubricant as not only will it act as an internal lubricant but also the calcium portion can act as a secondary heat stabilizer. In large amounts calcium stearate starts to act as an external lubricant and can quickly lead to plate out issues.

Esters typically can have both internal and external lubricant properties. Glycerol monostearate (GMS) is frequently used and is relatively inexpensive. Esters based on other multifunctional alcohols are also available and are many times blended with GMS to get improved properties. In general, esters have better heat stability than the corresponding amides. Amides are and can be used as lubricants but because they can discolor more readily than esters, their use is limited.

At times long aliphatic chain alcohols have been used as lubricants. They are inexpensive but do not lubricate as well as acids or esters. In some instances esters and alcohols have been used to increase surface gloss. The use level would be low.

The above-described lubricants can be used from less than 1 to 5 % depending on formulation. Lower levels and blends are most common.

Stabilizers:

Two kinds of stabilizers are used by the rigid PVC industry. The first and probably the most important are heat stabilizers and the second are UV stabilizers. PVC resin when exposed to elevated temperatures degrades by the elimination of HCl and the formation of conjugated unsaturation along the PVC chain. The liberated HCl will accelerate further degradation. The unsaturation formed within the PVC chain leads to colored moieties. As a very general rule of thumb, from 1 to 5 conjugated double bonds, the colors are in the UV and therefore not readily noticeable. From 5 to 10 the colors imparted are yellow to orange, and from 10 upward the colors proceed to go through red-brown to purple. The conjugation seems to stop on its own at about 19. Although there is some speculation about the exact mechanism of degradation, in order to thermally process PVC and retard degradation as much as possible, heat stabilizers are required. (14, 15)

Depending on global location and extruded product end use, the commonly used heat stabilizer systems are Pb based, or dialkyltin compounds, or mixed metal stabilizers, or all organic systems. In Europe, an extruder may use several different systems depending on the end market. This can present production contamination concerns so switching back and forth may not be as easy as simply cleaning the equipment.

Commonly used for a long time, Pb based stabilizers offer several extrusion advantages but are very toxic and are sensitive to other chemicals, i.e., the formation of PbS in the presence of sulfur containing environments, etc. Because of its toxicity, Pb based materials are being eliminated globally.

Organo-tin stabilizers are commonly used in the USA. Most are dimethyl, dibutyl, dioctyl Sn based with organic ligands, i.e., carboxylates such as laurates or maleates, which can assist with either preventing or destroying conjugation in the PVC chain. In addition to carboxylic acid ester based dialkyltin stabilizers, dialkyltin mercaptides and reverse esters based on fatty acid esters of mercaptoethanol are used today. These are considered to be a better stabilizer as the mercaptide ligand is a better nucleophile than the carboxylate for replacing labile chlorines along the PVC chain and the reverse esters are less expensive to manufacture. (16) Of importance with Sn stabilizers are the percentage of Sn, the alkyl ligand(s), and whether or not the material is a mixture of dialkyl moieties or the same alkyl groups. Tin stabilizers are used in the 1-2phr range.

Other materials evaluated as PVC stabilizers have been the antimony analogs of the tin mercaptides, cadmium in conjunction with barium and/or zinc, and all organic materials. The antimony materials do not have as good a stabilization effect as does Sn. Both Cd and Sb are toxic, which limits their use. The all-organic materials are not strong enough to be used in light colored profile but are being used in pipe formulations.

A lot of work is going into the development of a Ca/Zn stabilizer system for weatherable profiles today. In addition to closely controlling the ratio of Ca to Zn, a blend of other ingredients such as epoxies, phosphites, polyols, antioxidants, beta-diketones, and uracil derivatives as well as lubricants are typically formulated as a system. Some of these materials are liquids and are easier to handle as a premixed system by the compounder rather than as separate ingredients. These systems are being used in Europe today where the weathering demands might be less severe than in the southern US.

In some cases organic epoxies have been used effectively as HCl scavengers to assist with PVC stabilization. One must watch the chemical type and the overall use levels with epoxies so as to not plasticize the rigid formulation or get migration of the material as objectionable plateout, or exudate.

With mixed metal stabilizers and epoxies, organic phosphites are sometimes used. It is assumed that they act as both cheleators of the mixed metal to improve compatibility and possibly act as ligands in the labile chlorine displacement reaction.

UV stabilizers typically do not assist with heat stabilization. Various “classical” UV stabilizers, hindered amines, phenols, etc., have been incorporated into weatherable PVC formulations to retard degradation due to sunlight. The ability to withstand the high processing temperatures, the potential chemical reactivity, and cost of these materials limits their use. In addition, since only the surface weathers and the UV stabilizer is throughout the total PVC layer, most of the protection afforded by a UV stabilizer goes to waste as it is not on the surface where degradation occurs. My experience is that a good UV stabilizer can prolong initial degradation but once “used up” fast discoloration occurs.

Pigments:

Pigments are used to provide color. In general, ceramic pigments are required for exterior durability with rigid PVC formulations. Because of this, the color range attainable is limited. The most commonly used example is titanium dioxide for white colors but various metallic oxides are used to provide the color ranges seen today. All need to be high temperature, anhydrous HCl, and environmentally stabile. For non-weathering or less weathering applications, certain organic pigments can be used but, again, they need to be high temperature and HCl stabile.

The pigmentation of any PVC formulation strongly contributes to Heat Build Up values (HBU) of the final product. Simply stated, HBU is the temperature difference between ambient temperature and that of a sample exposed to “sunlight” and allowed to equilibrate at the upper temperature. Because of this, IR reflective pigments are commonly used to keep the HBU as low as possible. HBU is a major contributor to the exterior durability of any rigid PVC for every time the temperature of the profile is elevated, additional degradation occurs, and the higher the temperature, the more the degradation.

TiO_2 is the most commonly used pigment with PVC. TiO_2 provides a very white color and also assists with mitigation of UV light degradation by both blocking the penetration and reflecting the light. With TiO_2, the surface treatment and UV driven reactivity are important. Pure TiO_2 can and does act as a photo/redox-catalyst for the degradation of organic materials, which leads to chalking if not controlled. To control this catalytic activity, TiO_2 can be surface treated with a variety of things but commonly silica or alumina surface treatments are used. (17) As a general rule, the more the inorganic surface treatment and better its uniformity, the less photo-active is the TiO_2 particle and therefore the less chalking that will occur. For this reason you will hear discussions in the industry about chalking and non-chalking grades of TiO_2. For colored compounds, a non-chalking grade should be used. For a white colored profile, controlled chalking may assist with color retention.

Pigments containing Fe should be avoided with PVC. Fe has a large affinity for chloride ions and Fe containing materials catalyze the degradation of PVC materials especially at elevated temperatures.

Comments:

Examples of starting formulations can be obtained from most suppliers of PVC resin, processing aids, impact modifiers, stabilizers, and the various additives. In addition, there are several detailed books or series of books available that give much more detail about the materials discussed and their properties. (18, 19) For the novice and for the skilled formulator, these can be a ready reference source but the technology is changing daily so one should establish a good relationship with the various suppliers in order to take advantage of the latest technologies.

Recently an extensive technical assessment by the U.S. Green Building Council has been made addressing the overall performance of PVC based building materials and how PVC based materials should be included in its Leadership in Energy and Environmental Design (LEED) rating system. (20) After all the data had been gathered and reviewed by all the technical and environmental personnel, and finally by the public, it was concluded that the evidence comparing the life-cycle assessment and the environmental risk assessment of rigid PVC building products were at least comparable to the alternate materials. This assessment indicates that based on its properties and overall performance, rigid PVC is a good material to use as a "green" building product material.

Formulating rigid PVC is not difficult, but it is not simple. The need to balance blending, storage, and handling of the compound with the need for a robust processing window for extrusion against the overall cost and performance of the profile once extruded and fabricated into commercial products and finally in the environment, is a series of compromises. Sometimes not all the desired requirements can be attained but formulation with PVC is a good candidate with which to start one's evaluation. Globally, PVC is a very useful and beneficial plastic. Because of its durability and ability to be recycled, its contribution to the fenestration industry should continue to evolve and grow.

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Endocrine Function in Eating Disorders Associated with Weight Gain and Weight Loss

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Abstract

The objective of this paper is to give a brief review of the endocrinology of eating disorders leading to excessive weight gain and excessive weight loss in humans. Normal and abnormal hormonal control are discussed and some clinical laboratory tests are cited.

Key Words: Clinical Chemistry/Biochemistry

Introduction

The balance of energy in the body is dependent upon a complex system of pathways that control hunger and satiety as well as rate of energy expenditure. Many hormones are released into the circulation to signify hunger and satiety. These hormones act as signals to the central nervous system, most notably to the hypothalamus, to trigger central neuropeptides to modulate appetite. In people with normal eating habits, this system is tightly regulated to maintain hunger and satiety and energy expenditure; however, in people with eating disorders that lead to excessive weight gain or loss, this system may be altered. A normal balance of energy consumption and energy expenditure is needed to sustain a constant body weight, and signals that trigger hunger and satiety allow the body to do that. Neuronal circuits are responsible for maintaining energy homeostasis, and they regulate hunger and satiety via neuropeptides. An important regulator of energy homeostasis is the arcuate nucleus (ARC). It incorporates two populations of neurons, one that stimulates the intake of food and one that inhibits the intake of food. The neural circuit that stimulates food intake does so by expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP). In addition, the hormone ghrelin is orexigenic and communicates with the hypothalamus to promote increased food intake and decreased energy expenditure. The neural circuit that inhibits food intake does so by expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART).[1] Other signals that are anorexigenic and thus suppress food intake and increase energy expenditure are leptin, insulin, glucagon, cholecystokinin (CCK), and corticotropin-releasing hormone (CRH). Thyroid hormones also play a role in energy expenditure. In addition, the balance between energy intake and expenditure affects the deposition of energy stores. Energy is stored in white adipose tissue (WAT), which is regulated in part by cortisol and insulin, and brown adipose tissue (BAT), which is regulated by thermogenin.[2]

Hormones Associated with Weight Gain and Weight Loss

Hormones and Obesity:

NPY, a neurotransmitter composed of thirty-six amino acids, is very abundant throughout the brain, and the level of NPY in the hypothalamus is important for long-term energy homeostasis.[3] The level of NPY rises during periods of fasting and falls after a person eats; thus, a rise of NPY levels leads to increased food intake and decreased energy expenditure. The NPY interacts with the ipsilateral paraventricular nucleus (PVN), and the release of NPY in the PVN triggers feeding episodes. It has been demonstrated that when NPY is injected intracerebroventricularly (ICV) into the PVN over a period of time, hyperphagia results. It has also been demonstrated that central administration of NPY causes a decrease of energy expenditure and thus reduced brown adipose tissue (BAT) thermogenesis.[1] Rodent models of obesity have shown that overactivity of the projection of NPY to the PVN contributes to the hyperphagia and reduced energy expenditure that eventually results in obesity in the rodents. On the contrary, when obesity is induced by the diet rather than overactivity of the ARC-PVN projection, the levels of hypothalamic mRNA decrease and non-NPY receptors in the lateral

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hypothalamic area (LHA) become up-regulated. It appears that the hyperphagia leading to dietary-induced obesity is not caused by the activity of ARC NPY, suggesting that the decreased levels of NPY observed in dietary-induced obesity may be due to a compensatory mechanism by ARC NPY to try to limit hyperphagia and weight gain.[3]

Ghrelin, a twenty-eight amino acid gastric peptide, is an unusual gut hormone because it stimulates hunger rather than satiety, as the other gut hormones do. It increases appetite and food intake, and its levels are highest during periods of negative energy balance (i.e. fasting) and lowest following a meal. It also stimulates the secretion of growth hormone and, to a lesser extent, enhances the release of insulin. Ghrelin mediates its orexigenic effects via the ARC NPY and AGRP.[4] c-Fos expression within these neurons increases after ghrelin is administered peripherally, while surgical removal of the ARC results in the failure of ghrelin to stimulate food intake.[1] Studies on animals have demonstrated that administration of ghrelin both centrally and peripherally increases caloric intake, and the injection of antibodies to ghrelin prevents feeding brought on by fasting. In addition, one study showed that when ghrelin is given intravenously to humans prior to a meal, there is a 28% increase in the intake of food.[5] In people with eating disorders, the concentration of ghrelin is altered. In patients with binge eating disorder and obesity, the fasting plasma ghrelin level is decreased relative to that seen in patients with anorexia nervosa but equal to or higher than that observed in control subjects, suggesting that there may be a time frame and/or resistance factor involved with ghrelin and these diseases.[6] In addition, the binge eating obese patients also lack the post-prandial suppression of ghrelin secretion, which may be partly responsible for their eating habits and excessive weight gain. Similarly, morbidly obese patients suffering from Prader-Willi syndrome have significantly increased ghrelin concentrations, which may play a role in the severe hyperphagia seen in these patients.[3]

Another hormone whose levels in the body are altered in obesity is growth hormone (GH), or somatotropin. GH is a 190-amino acid protein hormone that is secreted by somatotroph cells in the anterior pituitary. GH increases the rate of energy expenditure by stimulating the metabolism of protein, carbohydrate, and fat. It causes the anabolism of protein in many tissues, helps maintain normal blood glucose levels, and stimulates adipocytes, or fat cells, to break down triglycerides and inhibits their ability to uptake circulating lipids.[7] Normally, the secretion of GH is highest during periods of fasting and the levels quickly drop post-prandially, following the same pattern as ghrelin. In the obese individual, however, this pattern is not seen because the secretion of GH is greatly diminished.[8] This decrease in growth hormone secretion leads to reduction in the rate of energy expenditure.

Many anorexigenic signals are in place to induce satiety and suppress the appetite. Leptin is a 146-amino acid peptide hormone that is synthesized mostly by adipocytes of white adipose tissue (WAT), although it may also be secreted to a lesser extent by brown adipose tissue (BAT), the placenta, the stomach, breast tissue, and skeletal muscle.[3] The amount of circulating leptin is proportional to the amount of adipose tissue. It acts as a signal to the areas of the brain that regulate feeding behavior by signaling the mass of the adipose tissue, and is therefore an indicator of both food intake and energy stores. In people of normal body weight, a decrease in the level of circulating leptin is a signal of the need for food intake, while an increase of leptin inhibits feeding via inhibition of the NPY/AgRP neurons.[1] In people with hyperphagia and obesity, leptin is over-secreted and the counter-regulatory activity of leptin appears to be lost. It is believed that patients who suffer from hyperphagia and obesity experience leptin resistance, similar to the insulin resistance seen in patients with hyperinsulinemia. This would prevent the patient from receiving the signal by leptin that would inhibit eating, thus contributing to the increased caloric intake.[3]

The first adiposity signal to be characterized was insulin, a major metabolic hormone that is secreted by the pancreas. Insulin is similar to leptin in that the concentration of insulin in the plasma is proportional to changes in adiposity, meaning that the amount of plasma insulin is higher during periods when the energy balance is positive and lower when the energy balance is negative.[1] It provides a mechanism of negative feedback in order to maintain constant body weight and fat mass.[4] However, insulin is different from leptin in that the secretion of insulin increases rapidly post-prandially while leptin concentration is relatively unaffected by short term caloric intake. Once inside the brain, insulin exerts its anorexigenic signal to decrease energy consumption and body weight.[1] Insulin's role in the regulation of food intake has been demonstrated in laboratory mice. When receptors of insulin in the brain are selectively inactivated, hyperphagia and obesity results.[4] In patients with eating disorders and subsequent obesity, insulin levels are elevated and insulin resistance often develops. Insulin resistance prevents the negative feedback mechanism of insulin, leading to further caloric intake and increased body weight.

The first hormone of the gut that was shown to be anorexigenic was cholecystokinin (CCK). It is a hormone that is expressed throughout the gastrointestinal tract, but is mostly found in the duodenum and jejunum.[5] CCK is involved in short-term energy regulation by initiating satiety and meal termination.[9] Following food consumption, intraluminal levels of long-chain fatty acids cause the release of CCK from the gut. CCK exerts its actions by activating the vagal fibers and sending satiety signals to the hypothalamus. It has been demonstrated that intravenous administration of CCK to levels equal to physiological post-prandial concentrations causes the decrease of hunger and lowers the intake of food.[4] Studies have demonstrated that genetic deletion of CCK receptors in the hypothalamus of rats leads to hyperphagia and obesity.[1] Therefore, in patients with eating disorders leading to obesity, it is possible that the CCK receptors are defective, or the secretion of CCK post-prandially is impaired. CCK may also take part in long-term energy regulation by acting synergistically with leptin. When leptin is administered centrally, the action of CCK is enhanced, and the use of CCK with leptin leads to more weight loss during the same time period than with leptin alone.[9] On the other hand, when CCK antibodies and antagonists to CCK receptors are administered to rodents, weight gain results.[1] The overall effect of CCK is to decrease the amount of food intake and increase the rate of energy expenditure.[3]

Another anorexigenic hormone is corticotropin-releasing hormone (CRH). CRH is a 41-amino acid peptide neurohormone that is produced by the hypothalamus and causes the release of corticotropin from the anterior pituitary. CRH has many biological functions, one of which is the regulation of energy homeostasis. CRH is part of the CRH system, a neuronal energy balance circuit that causes a decrease of food intake and an increase of energy expenditure. Studies have demonstrated that obese individuals have reduced amounts of CRH. In obese rats, the infusion of CRH into the brain results in decreased energy gain (reduced weight gain), supporting the theory that obesity in rats is due to decreased levels of CRH. In another experiment, the injection of an inhibitor ($CRH_{(6\text{-}33)}$) to the CRH-binding protein (CRH-BP, a protein that can inactivate CRH), results in a reduction of weight gain in obese Zucker rats.[10]

Pancreatic glucagon is believed to be a satiety hormone and has demonstrated the ability to inhibit food intake. Glucagon stimulates the release of glucose from stores in the liver, thus increasing the level of circulating glucose. As with other satiety hormones in eating disorders that lead to weight gain, the ability of glucagon to induce satiety is blunted. The level of glucagon following a meal is dependent upon the type of food consumed: a meal high in protein leads to an increase in the level of glucagon, but a meal high in carbohydrates leads to a decrease in the level of glucagon. The decrease in glucagon after a carbohydrate-rich meal likely leads to a decrease in the satiety signal and thus a higher intake of food.[11]

Additional hormones that are affected during weight gain are the thyroid hormones. A function of the thyroid hormones is the stimulation of energy expenditure. They are very important to the regulation of many metabolic processes. In obese individuals, the concentration of thyroid hormones is decreased, leading to decreased metabolism and energy expenditure.[12]

Excessive weight gain due to eating disorders results from an intake of energy in excess of energy expenditure. Excess energy is stored in adipocytes as triglycerides. Triglycerides are the body's primary form of energy reserve. Lipoprotein lipase (LPL) hydrolyzes triglycerides and regulates their uptake by fat cells. LPL activity and expression is controlled mainly by insulin and cortisol, and it is important for the deposition of triglycerides among different tissues in the body. Insulin promotes the storage of triglycerides by stimulating LPL activity in adipose tissue, increasing the uptake of glucose, inhibiting the breakdown of lipids, and stimulating the differentiation of adipocytes. Cortisol's effect on energy storage actually promotes weight gain and obesity, possibly via a synergistic effect with insulin on the stimulation of LPL in adipose tissue.[13]

The majority of adipose tissue in adults is white adipose tissue (WAT). WAT actually functions as an endocrine organ. Adipocytes secrete many substances, including leptin, resistin, estrogen, and tumor necrosis factor-α. In adults with obesity, the number of adipocytes can be up to four times greater than that of lean adults. Obese individuals can develop the metabolic or insulin resistance syndrome. Some of the features of this syndrome are insulin resistance, hyperinsulinemia, impaired glucose tolerance, impaired insulin-mediated glucose disposal, and dyslipidemia. Another complication of obesity possibly related to the metabolic syndrome is the deposition of triglycerides in nonadipose tissue.[13]

The other form of adipose tissue is brown adipose tissue (BAT). It is where most of the thermogenesis takes place in infants, but there is very little BAT in adults. BAT contains a large concentration of mitochondria with thermogenin, a mitochondrial uncoupling protein that enhances thermogenesis.[14] Studies have suggested that BAT can play a role in the development of obesity. Mice that are bred to demonstrate a deficiency of BAT exhibit hyperphagia and obesity. When new BAT is synthesized, the obesity resolves.[15]

Some diseases that are often associated with obesity include: Type 2 diabetes mellitus with insulin resistance, cardiovascular disease and stroke, hypertension, pulmonary dysfunction, gallstones, and endocrine abnormalities.[13] The obesity may be causal, may aggravate the condition, or may be the result of a common underlying defect. When working up a patient with unexplained obesity, one should include tests for these diseases as part of the differential diagnosis. Timed blood glucose and blood insulin tests will confirm or rule out diabetes mellitus. A lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides will be useful when assessing potential cardiovascular disease and stroke. Renal function and other causes of hypertension can be evaluated with blood and urine levels of creatinine and urea, and blood levels of angiotensin, sodium and potassium, and osmolality. Tests for pulmonary dysfunction should include blood gases and electrolytes. Gallstones and liver disease could require testing for bile acids, bilirubin, and liver enzymes such as aspartate transaminase [AST] and alanine transaminase [ALT]. Among the more common endocrine abnormalities associated with obesity are Type 2 diabetes mellitus (mentioned above), hypothyroidism, and Cushing's syndrome. Thyroid status can be assessed with a total thyroxine (total T_4) test and a thyroid stimulating hormone (TSH) test. Most hypothyroid patients have primary disease and present with an abnormally decreased T_4 and abnormally increased TSH. A few patients will have central hypothyroidism (pituitary or hypothalamic disease) and present with both low T_4 and low TSH. More exotic forms such as the inability to convert T_4 to T_3 do exist but are very rare. Cushing's syndrome can be assessed with blood cortisol levels and these should be timed samples to verify the presence or absence of a circadian rhythm. Tests for adrenocorticotropic hormone (ACTH) and a dexamethazone suppression test will help establish the source of the excess cortisol. Inappropriately low testosterone in an obese male may be a symptom of genetic disease, trauma, or infection and deserves further workup. Abnormally elevated estradiol and inappropriate hormonal rhythm in an obese female may signal a neoplasia and deserves further workup. Tests for hormones such as NPY, ghrelin, and leptin require specialized collection and are currently performed in a research/reference laboratory. They should be ordered only after the more obvious tests have failed to diagnose the problem.[16]

Hormones and Anorexia Nervosa:

Anorexia nervosa is an eating disorder characterized by self-starvation that is manifested by extreme anxiety about body weight and size. It is a serious eating disorder and mental health condition that can have significant health consequences and can become life-threatening. The vast majority of Americans who suffer from anorexia nervosa are girls and women. It typically begins during early to mid-adolescence and is one of the most commonly diagnosed mental health conditions in young American women. Anorexia nervosa also has one of the highest death rates of all mental health illnesses, resulting in the deaths of 5-20% of individuals who suffer from it.[17]

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association, there are four primary criteria for diagnosis of anorexia nervosa: refusal to maintain at least the minimum body weight considered normal for age and height, extreme fear about gaining weight or becoming "fat" despite being underweight for age and height, having a distorted image about one's body size or being in denial about the possible severe consequences of being underweight, or amenorrhea for three consecutive menstrual cycles in postmenarcheal females. The diagnosis of anorexia nervosa is based on many tests and exams, including a physical exam, psychological evaluation, and laboratory tests.[18]

Physical examination involves several measurements, including checking height and weight. A person with anorexia presents with a body weight about 15% lower than what is expected for the patient's height, age, and physical activity. The vital signs are also checked, which may reveal hypotension, bradycardia, or hypothermia. The patient may also demonstrate mid-systolic click of mitral valve prolapse upon physical examination. In addition, the patient may also present with peripheral edema, thinning hair, lanugo, dry skin, poor skin turgor, or obvious emaciation.[19]

A psychological examination is performed with suspected cases of anorexia nervosa to gain insight into of the patient's thoughts, feelings, and eating habits. [18] Several psychological characteristics can indicate anorexia nervosa. The patient may be preoccupied with her weight, dieting, food, caloric intake, and the number of fat grams she eats. She may make comments about feeling "fat" even after becoming underweight. She may withdraw from family and friends, deny hunger, make excuses to avoid mealtimes or other situations in which food is present, or she may develop food rituals. In addition, she may adopt a very excessive exercise routine that she adheres to even during illness, injury, or fatigue.[17]

No specific laboratory test exists to diagnose anorexia nervosa, but there are a plethora of tests available to indicate anorexia nervosa and determine health status of the patient. A chemistry panel may indicate hyponatremia due to excess water consumption; it may also indicate low serum phosphorus levels. Although liver function tests may be a little elevated, the levels of albumin and protein are usually normal. Leukopenia and thrombocytopenia may be demonstrated with a complete blood count.[19] The endocrinology of a patient with anorexia nervosa may also be altered. This includes the hormones of the hypothalamus and pituitary gland, thyroid hormones, adrenal hormones, and hormones of the ovary in females and testis in males.

Gonadotropin-releasing hormone (GnRH), also known as luteinizing-hormone releasing hormone (LHRH), is a hormone of the hypothalamus that controls sexual development and reproduction. GnRH acts on the anterior pituitary by binding gonadotroph receptors and stimulating the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The malnutrition that accompanies anorexia nervosa causes a decline in GnRH activity at the level of the pituitary, which results in a dramatic decrease in the numbers of GnRH receptors on the pituitary gonadotrophs.[2] The reduced secretion of GnRH in anorexia nervosa causes a decline in the secretion of LH and FSH. FSH is responsible for the development of the ovarian follicle in women, and FSH and LH both cause the secretion of estrogen from the follicle. LH is also responsible for ovulation and the production of progesterone from the ovary. FSH and LH are secreted in different amounts during the menstrual cycle. In men, FSH stimulates testicular growth and aids in spermatogenesis. LH acts on the Leydig cells of the testes to stimulate testosterone production.[20] Anorexia nervosa can disrupt the natural secretion patterns of LH and FSH in women, leading to primary or secondary amenorrhea and decreased levels of estradiol.[21] Decreased circulating estradiol in turn leads to decreased fat deposition. In men, decreased secretion of FSH and LH results in decreased blood levels of testosterone which is associated with decreased male secondary sexual characteristics.[16]

Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and controls thyroid function. It acts on the anterior pituitary to stimulate the release of thyroid-stimulating hormone (TSH). During periods of starvation, such as anorexia nervosa, the blood[2] and cerebrospinal fluid[22] levels of TRH are depressed. This leads to a reduction in TSH.[2] TSH acts at the level of the thyroid to release the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). The thyroid hormones are important to the metabolism of the cells of the body. The starvation associated with anorexia nervosa results in decreased levels of T_3 and slightly decreased levels of T_4, while the levels of TSH are relatively unchanged [normal to slightly decreased].[23] Two significant features of anorexia nervosa are the increased conversion of T_4 to reverse T_3 with concomitant diminution of the T_4 to T_3 pathway, and the delayed response of the pituitary to endogenous and exogenous TRH infusion.[24] TRH also acts at the level of the pituitary to stimulate the release of prolactin.[2] The hormones of the serotonin pathway and vasoactive intestinal peptide (VIP) also serve to stimulate the release of prolactin. However, the major regulator of prolactin secretion is dopamine, which acts to inhibit its release.[25] Prolactin is the hormone responsible for the initiation of lactation in women. The levels of prolactin have been reported to be low, normal and increased in anorexia nervosa.[2, 25, 26] Decreased circulating prolactin in anorexia nervosa could be the result of decreased TRH secretion. Arguments have been presented that the cause of the increased prolactin in anorexics is increased stress (hypoglycemia), increased exercise, hypothyroidism, or decreased dopamine due to generalized hypothalamic failure.[24, 25] The increased levels of prolactin perpetuate the hypogonadism seen in anorexia by inhibiting GnRH pulsatile secretion.[26]

Corticotropin-releasing hormone (CRH) is a hormone of the hypothalamus that responds to internal and external environmental stresses. It also acts on the anterior pituitary to stimulate the release of adrenocorticotropic hormone (ACTH) from corticotroph cells. ACTH is responsible for stimulating cortisol secretion from the adrenal glands. Cortisol, a glucocorticoid, causes the release of glucose for use in response to stress. In patients with anorexia nervosa, CRH and cortisol levels are both increased.[27] However, the levels of ACTH do not change. The response of ACTH to CRH is actually repressed.[28] The increase in CRH depresses the reproductive aspects of the patient. CRH hinders the release of GnRH, and cortisol and other glucocorticoids inhibit the release of GnRH at the level of the hypothalamus, the release of LH at the level of the pituitary, and the release of estrogen and progesterone at the level of the ovaries and testosterone at the level of the testes.[27]

Growth hormone releasing hormone (GHRH) is a hormone of the hypothalamus that stimulates the release of growth hormone (GH) from somatotroph cells in the anterior pituitary. GH plays a major role in several physiological processes, most notably growth and metabolism. Its chief role is to induce the secretion of IGF-I from the liver and other tissues, which then acts on chondrocytes to stimulate bone growth.[7] In patients with anorexia nervosa, the secretion of GH is increased, although the secretion of IGF-I is decreased. GH also has an increased response to GHRH.[28]

The hormone responsible for maintaining normal plasma osmolality is antidiuretic hormone (ADH), also known as vasopressin. It is secreted by the posterior pituitary and stimulates the reabsorption of water at the level of the kidney. Anorexia nervosa can cause inappropriate secretion of ADH, resulting in hyponatremia.[29]

The serum concentration of leptin in anorexia nervosa patients is abnormally decreased reflecting the low weight and low body fat content of these women. Following alimentary supplementation, blood leptin levels increase and this leads to a subsequent increase in gonadotropins, demonstrating the tie between leptin and the reproductive hormones.[24]

Anorexia nervosa is a serious and sometimes life-threatening disease. It is, however, not the only cause of weight loss. Diseases often associated with extreme weight loss include: Type 1 diabetes mellitus, alcoholism, inflammatory bowel disease, starvation, cancer, renal disease, tuberculosis and/or pneumonia, and parasitic diseases. Such illnesses may be part of the differential diagnosis in someone with anorexia nervosa, and must be ruled out to establish a definitive diagnosis. One of the characteristics of a person with Type 1 diabetes mellitus is weight loss. Diabetes mellitus can be ruled out with the oral glucose tolerance test. If a patient has diabetes mellitus, the oral glucose tolerance test would reveal hyperglycemia, but an anorexia nervosa patient would demonstrate hypoglycemia (low blood glucose levels) due to dietary restriction.[30, 31] One laboratory test that can be used to indicate alcoholism is acetaldehyde-modified hemoglobin (HAA). When alcohol is metabolized, it forms acetaldehyde that can irreversibly bind hemoglobin, called HHA. In patients with alcoholism, HAA is increased. Because the HAA test has such high specificity and sensitivity for alcoholism, HAA levels are not likely to be increased in an anorexia nervosa patient.[32] Inflammatory bowel disease (IBD) may be suspected in cases of weight loss. The detection of certain antibodies can help a physician rule out IBD. Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) are autoantibodies that have a sensitivity for IBD of around 71% when used together, and help rule out IBD in patients with non-specific symptoms.[33] A patient with anorexia nervosa would not demonstrate these autoantibodies. While anorexia nervosa is self-starvation, it may be possible to distinguish between voluntary and involuntary starvation by examining a stool specimen for the presence of excess fat, which could indicate starvation due to malabsorption. The fecal fat test allows one to quantitate the degree of steatorrhea. In an anorexia nervosa patient, fat would likely not be present in the stool. Similarly, the fecal occult blood test could demonstrate the presence of a bleeding ulcer with resultant malabsorption.[16] One test that can be used to rule out cancer is a test for calcium levels. In ten to twenty percent of cancers, patients experience hypercalcemia.[34] In contrast, the patient with anorexia nervosa would likely demonstrate a deficiency in calcium. In addition, imaging for tumors and tests for tumor markers can help rule out cancer if such tests are negative, which should be the case for a patient with anorexia nervosa. A urinalysis could be done to help rule out renal failure. A patient with renal failure may demonstrate granular or tubular casts in his urine, while an anorexia nervosa patient would not likely present with such casts. Additionally, a creatinine clearance test and a serum blood urea nitrogen should prove informative. A chest x-ray and microbiological tests for organisms such as *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* will confirm or rule out tuberculosis and pneumonia. Following a confirmed diagnosis of anorexia nervosa, laboratory tests to assess the general health status of the patient should be performed. Included in the general chemistry profile should be an assessment of the calcium status of the patient since many of these patients present with bone loss and psychiatric effects of low calcium.[16, 24]

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Thoughts on the Implementation of Analytical Determinations in Plant Environments I

By W. Jeffrey Hurst, PhD

The definition of in-line or at-line tends to be dependent on the organization. There is substantial analytical technology that can migrate from the laboratory to the manufacturing footprint and technically provides excellent data, there is one issue that has not yet been addressed. That issue relates to the implementation of the analytical determinations in the plant environment and there are several items that should be considered before progressing. The focus of this column is to provide you with some general thoughts but it will not be a “how to” column since that is technique and organization dependent. Items that one needs to consider include assay requirements, technical development, funding and support, personnel and continuing activities. In this installment of the column, I will discuss initial assay requirements and technical development with the discussion of the other issues continuing in another column. Finally, this column is being presented from the perspective of an internal analytical group who has this as one of their charters not a group with this as their primary objective.

One of the first issues when evaluating requests is the assay requirements. This items is the linchpin for this type of determination since this is where much can be clarified and many items that can cause confusion can be eliminated. One should first inquire as the reason for the assay. For example, is it to replace any existing manual method or is this a new process that needs monitored? If it is to replace an existing manual process, it can be extremely useful to inquire as to why since if the data requirement is only for 1 sample an hour and the current manual assay only takes 15 minutes, then maybe it is more useful to improve on the current method rather than embark on potentially costly new method. As in some of the early laboratory automation projects, there are some that feel it important to perform in/at line determinations because it seemed like the thing to do. Should this be some of the reasoning this should be vigorously fought against since these projects like their lab automation predecessors tend to be fraught with frustration and likely faulty implementation. Other issues that must be addressed in this phase of the project include requirements for data such as precision, accuracy, calibration intervals and calibration standard. Additionally, one should determine what final form is required for the data. Will it be used as is? Will it be sent to a LIMS, plant data information system or used as an input to a PLC? Will it be imported or exported to a local Excel spreadsheet or Oracle databases? When one has the answer to these questions, they will obviously beget others. One of the other items that are critical is the development of a timetable for the project. This is agreed upon by all involved and should include periodic update briefings that can address issues that could alter the final timetable and the efficient delivery of the application. Finally, in this discovery phase of the project, ensure that the process is iterative since a partnership is critical to a successful implementation.

Once agreement has been reached that there is indeed a true need for this assay, one can begin the work in earnest in technical developments although it is likely many of these activities will be accomplished in a parallel fashion since in the initial phase, there should be discussions about potential measurement alternatives. By the time one reaches this phase of the project, the technical requirements for the determination should have been established. This is not to indicate that there cannot be changes but major alterations in the matrix or method should not occur at this time. Based on earlier discussions, one will be able to ascertain whether the instrumentation will be purchased off the shelf and used as is, purchased off the shelf and modified or custom made. Each of these alternatives has its own set of concerns with the most straightforward of the choices being to use off the shelf instrumentation in an established application. This has the advantage of a straightforward implementation, vendor documentation, vendor support, likely less costly and more timely. In the second case, where one modifies an off the shelf instrument, the implementation can be less “clean” since one likely will need to develop a new application either with vendor support or internally depending on a number of factors including number of instruments purchased, complexity of application and final timetable. In this case, one ends up with a compromise since there may be additional costs associated with the application development of potentially instrument modifications if these activities have been performed with a vendor. Should these items be accomplished internally, the amount of vendor support will likely be less and depending of the avenue chosen the laboratory partner can be more directly involved than in the first case. The third of the alternatives is the most challenging of the three since in this case one is embarking on an ambitious activity that will be more expensive than the first two and will likely require more “hand holding” than the other two options. In another column, I will continue with some additional thoughts on this topic.

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Implementation of Analytical Determinations in Plant Environments II

By W. Jeffrey Hurst, PhD

There are a number of issues that should be considered when implementing method in the plant environment. Previously I discussed assay requirements, timetable and some equipment considerations. I had hoped that those involved in these kind of implementations were well aware that it was not as simple as taking an method or instrumentation developed in the laboratory and moving it to a manufacturing footprint but based some comments from colleagues that is not the case. To apply this same logic, one could take a synthesis developed in the laboratory and then apply some conversion factor or in the home environment, try taking a recipe for a family of four and making enough to serve 100. Obviously this kind of misstep is a recipe for disaster and should be avoided at all costs. During this next installment on the topic, I will briefly remark on regulatory methods, environmental and siting concerns, management commitment communications, and personnel issues.

In the previous column, I had some comments about methods and potential choice of methods but failed to address some issues related to those in regulated industries where methods need approval by some governmental agency since this could limit the options available. For those not in this area, a method/instrument chosen for a plant environment would likely need to be reviewed by an internal review group to ensure all involved in agreement.

After the choice of a technology or instrumentation one needs to determine if there are any special siting or environmental concerns that need to be fulfilled. These might included conditioned power, uninterrupted power through the use of a UPS, temperature requirements for components which may mean air conditioning or even a dedicated phone line that could be used for remote troubleshooting and potentially remote operations. One should also review siting issues. For example, if all the equipment's cleaned with steam each shift will the instrumentation stand up to this type of treatment?

Management commitment is a critical linchpin to the successful implementation of method or technology since without it again the activity is destined to fail. It may be appropriate to provide a management overview of the technology chosen since some tend to use terms like NMR, NIR, FTIR and others without thinking about their meaning but to one who doesn't use these everyday, they may resemble a foreign language. This review doesn't need to be in excruciating detail but should be sufficient so those involved are informed. This has two complimentary benefits with the first of this being that there should be no surprises to management and those directly involved will likely have an umbrella of support. To paraphrase an old Holiday Inn ad, "The best surprise is no surprise at all"

Communications is another on of the items that if no done well can create substantial problems for a project. My recommendation is to err on the side of providing too much information since the opposite approach is fraught with problems. With respect to communications, not only should there be sufficient in quantity but one should ensure they are of sufficient quality since one doesn't want the GIGO syndrome. One final comment related to communication is that it should be 360-degree communications ranging from the instrument operator to the project manager and above.

As in every project, people make the difference and this type of implementation is no different. The choice of those involved in the project team needs to be carefully accomplished since it needs to be the correct mix of those familiar with the method and instrumentation and those familiar with plant operations. For example, is the method going to be an at-line or in-line method? While both types of methods occur in the manufacturing area, one type might need a small laboratory while the other is performed in a production stream. These choices would obviously have been made early in a project but can impact some of the personnel choices. In the previous column, I addressed the issue of data and where it might it be used and that would impact the personnel requirements. After these questions have been answered, one can then determine does the individual need to be a trained scientist or would a better approach be to train a member of the operations staff? There are pros and cons to both approaches and that discussion is beyond this modest column but these are points for consideration. In a similar vein, one should also address the type of training that is going to be required such as on-site. off-site, Internet or some hybrid of these since one needs to again get management commitment to ensure the training can be accomplished in a timely manner and is not looked upon as a "spare time" activity. Finally under this topic, one should ascertain what type of follow up training is going to be required.

On final item in this second installment is to ensure what type of follow up will be required. For example, regular phone calls and emails are a given but what else might be appropriate. Should someone on the project team visit the installation on a regular basis and if so, what is the best timeframe? While some of these issues have likely already been decided earlier, ensure that this activity is accomplished and yes! This is a part of the 360-degree communications.

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BOOK REVIEWS

Green Chemistry and Catalysis

Authors: RA Sheldon; I Arends; U Hanefeld
Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 978-3-527-30715-9
Price: $175

As stated by the authors in the preface, the book is aimed at researchers, in industry or academia, who are involved in developing processes for the manufacture of chemicals. The focus of the book is to share the available information concerning the use of more “green” chemical processes to manufacture materials and to provide real examples of comparisons of the different methodologies enabling the chemist to manufacture materials in a more environmentally acceptable and sustainable fashion. Throughout the book it is stressed that key to the future of being more “green” and being able to sustain the sources of raw materials is the application of homogenous, heterogeneous, and enzymatic catalysis to future processes.

The book is well written, and assumes a good working knowledge of industrial organic synthetic chemistry from which comparisons are made between presently used, standard chemical processes and “green”, sustainable chemical and biocatalytic processes. The book is written by concerned chemists for working chemists and those who will be chemical professionals and is not for the novice or casual “green” advocate. The authors hope the book is useful to those presently working in process development and as a textbook for upper undergraduate and graduate coursework.

The subjects covered include acid and base catalysis, catalytic oxidations and reductions, carbon-carbon bond formation reactions, hydrolysis reactions, reactions in novel media, i.e., solvents, super critical fluids, ionic liquids, and the use of renewable raw materials. Numerous examples are presented of how more “green” processes can be and have been successful and, also, encouragement is given to those doing process development to look for environmentally better solutions rather than to just stick with conventional chemical methodologies. It is evident that the authors believe that integrating advances in biotechnology, materials science, and reaction and process design are essential to a sustainable future chemical industry. Although traditional chemistry is discussed, the use of bio/enzymatic catalysis over conventional catalysis is frequently emphasized which to one not familiar to this technology may be a hindrance to fully understanding some of the subject matter.

In the extensive list of references included at the end of each chapter, the authors attempt to provide the principal literature through 2006. The numerous equations, charts and tables are well done and readily understood. The overall quality of the book is high. I would have expected the publisher would have used recycled paper, etc. to reinforce the green theme of the book but they did not. Although a bit pricey, I would recommend this book to all process development chemists and chemists in general.

Reviewed by : Kenneth Abate, PhD, FAIC, CPC

* * *

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