Animal Injectables Lab

Fats, Oils and Fatty Chemicals for the Pharmaceutical Industry

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ALTHOUGH ITS ORIGIN dates back to the mid-1800's, the U. S. pharmaceutical industry really did not come into its own until after World War II. This industry has experienced a five-fold increase in ethical drug sales between 1946 and 1961, sales increasing during this period from $428 million in 1946 to $2.147 billion in 1961. This growth is not only impressive by any measure or standard, it is also unique to the chemical industry as a whole since it is coupled with a very enviable profit record. This industry has averaged a net income after taxes as a percent of sales of 11.3% for the 1946–1961 period, an earnings ratio that can never be more than a delightful pipe-dream to industries like our own, whose business structure is built about the manufacture and sale of commodity fats and oils and chemical derivatives and by-products derived therefrom.

This difference in the profit picture does not preclude, however, that we and the pharmaceutical industry are incompatible, or that we, as the low member on the totem pole, are to be considered as untouchables by our lofty superiors. In fact, their growth has opened, and will continue to open, new areas of applications for fats, oils, and specialties that are sure to give us an opportunity to enhance our own earnings picture.

The pharmaceutical industry is now on the threshold of a new era of federal and state control and subject to intense public scrutiny because of several unfortunate circumstances with which we are all familiar. The Drug Amendments of 1962 (the Kefauver-Harris bill) will seriously affect pharmaceutical research, manufacturing, and distribution. The new regulations being promulgated by the Food and Drug Administration that are related to the control of experimental drug testing will also put additional costly burdens on the pharmaceutical manufacturer. There is no question, however, that this industry is now of sufficient stature to take these problems in stride and to eventually arise from its present harried state with only a temporary dip in its sales and profits as a lasting scar of the battle. It is predicted by most knowledgeable observers and economic experts that this industry will still meet its projected sales goal of $4.7 billion by 1970. It behooves our industry, therefore, to work closely with this growing giant as a means of finding new and increasing outlets for fats and fatty chemicals.

Pharmacy and medicine are intimately linked together by both definition and practice, for both deal with ways and means of preventing and combatting disease, with investigations of the normal body functions of digestion, metabolism, absorption, etc. Since fats represent a high percentage of our normal diet and since many human diseases and ailments are due to certain malfunctions of the body in digesting, absorbing, and utilizing fats, it is only natural that many ethical drugs and drug preparations are designed to counteract and correct these body deficiencies. This role of fats and oils in nutrition gives our industry a close fundamental link with pharmacy and medicine, but the second and more important link to our industry as a whole is in the use and consumption of fats, oils, and fatty chemicals as formula ingredients for both ethical and proprietary drug preparations. These range from the simple use of natural and synthetic triglyceride oils as liquid carriers and solvents for vitamins, hormones and antibiotics for intramuscular injections, to the more complex fatty chemical derivative that is specifically designed to impart specific characteristics to a formulated pharmaceutical aerosol product. The various potential applications of fats, oils, and fatty chemicals will be further expanded during the course of this article.

The use of fats and oils as emollients and medicaments dates back to biblical times. We probably all remember the New Testament account by St. Luke of the Good Samaritan's merciful aid to the poor traveler who had been set upon by robbers, sorely beaten, and left to die. In St. Luke's words, we are told that "He went up to him and bound up his wounds, pouring on oil and wine." Up through the ages there are many other references to be found on the use of natural fats and oils as poultices and salves to heal the wounds of battle, and as the basic ingredients for medications that were designed for the treatment of dermatological disorders. The science and technology of the use of fats, oils, and fatty chemicals in the preparation of ethical and proprietary drug products has progressed at a rapid rate over the last twenty years and the following section of this article will attempt to point up a number of areas within the pharmaceutical industry that currently represent a good potential for our industry's products.

The most fundamental source for determining wherein lies the market for fats, oils, and fatty chemicals in the pharmaceutical industry is the U. S. Pharmacopeia. This "bible" of pharmacy had its beginning in 1820 and has been revised and published at five-year intervals since that date. The Pharmacopeia reflects with fidelity the best practices of medicine and pharmacy in providing standards of purity for ingredients of pharmaceutical preparations. Of the many products for which definitions and standards have been established and which appear in the latest issue of the

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U. S. Pharmacopeia, the following is the list of those that are either natural triglycerides or chemical derivatives of the fatty components of natural fats and oils:

Aluminum Monostearate	Wool Fat
Benzalkonium Chloride	Chloriodized Oil
Celypyridinium Chloride	Cottonseed Oil
Castor Oil	Erythromycin Estolate
Chloramphenicol Palmitate	Glycerin
Corn Oil	Iodized Oil
Erythromycin Stearate	Oleic Acid
Hexachlorophene Liquid Soap	Synthetic Oleovitamin A
Magnesium Stearate	Peanut Oil
Oleovitamin A	Polysorbate 80
Olive Oil	Medicinal Soft Soap
Polyoxyl 40 Stearate	Sodium Stearate
Propyliodone Oil Suspension	Stearic Acid
Sodium Lauryl Sulfate	Theobroma Oil
Spermaceti	Zinc Stearate
Stearyl Alcohol	

In addition to the above materials, U. S. Pharmacopeia lists standards and specifications for the following preparations that contain glyceride oils, fatty acids, or fat derived chemicals:

Coal Tar Ointment
Coal Tar Solution
Flexible Collodion
Glycerine Suppositories
Hydrophilic Ointment
Hydrophilic Petrolatum

The above two lists represent a portion of the potential that is present in the field of ethical drugs for use of fats, oils, and fatty chemicals. In addition to these products that require definition, fats and oils have many other potential uses as excepients or inert ingredients and extenders in ethical drug products. This usage is even more extensive in the field of proprietary products that are sold on over-the-counter, non-prescription basis. Water-in-oil emulsifiers derived from natural fats and oils find wide usage as absorption bases for cream and ointment preparations. The more hydrophilic types such as the glycerol, glycol, and polyglycol partial esters are used quite extensively as the basic emulsifiers for the preparation of oil-in-water cream and liquid pharmaceutical emulsions. The sorbitan esters and polyoxyethylene sorbitan esters are employed both as emulsifiers and as solubilizers in many pharmaceutical preparations. Polysorbate 80, U.S.P., or polyoxyethylene (20) sorbitan monooleate is the preferred solubilizing agent for water soluble vitamin oil preparations and this fatty chemical has FDA approval for this use.

Hydrogenated fats and high melting saturated fatty acids are employed not only as thickening agents for creams, lotions, and ointments, but also as coatings in tabletting operations. The high melting edible grades of hydrogenated fatty products are finding use as coatinngs for delayed action pills and tablets. These coatings can withstand the acid environment of the stomach without disintegrating and will only break down and liberate the active medication when the alkaline enzymatic intestinal tract is reached.

The pharmaceutical industry also represents a fine potential for the essential oils and flavors industry. Some essential oils possess medicating and healing properties, per se, but the biggest potential by far, for these raw materials lies in their ability to mask and flavor the objectionable flavors and odors of many ethical drug products. Your doctor can now prescribe your favorite antibiotic or vitamin preparation in any one of six delicious flavors and aromas. It is a far cry from the old sulfur and molasses and the raw castor oil days. Most children actually look forward to those raspberry flavored, chewable vitamin tablets and enjoy them as much as we savor that first cup of morning coffee. This is real progress by any standard of measure.

The low calorie diet preparations also represent areas where special fats, oils, and edible emulsifiers may be used to advantage. Coconut oil and its hydrogenated, interesterified and chemically modified forms are the preferred fatty components here because of their lower calorific value. Their saturated nature also offers advantages in shelf-life characteristics under conditions where proprietary products may occupy shelf space in the corner drug store over a period of several months.

Another dietary link of natural fats and oils to the pharmaceutical industry is the important connection between the polyunsaturated fats and their ability to control cholesterol levels in the human circulatory system. A vast amount of medical research has been carried out in this area and results do indicate that the soft unsaturated oils, in contrast to the hardened saturated varieties, actually do retard the formation and accumulation of cholesterol in the blood vessels. Although it is generally known that there are several factors other than dietary control that seriously influence the cholesterol levels that cause hardening of the arteries, the advertising groups of several vegetable oil producers immediately employed these medical findings as copious copy for successful sales promotional programs that were centered about the benefits to be derived from the use of soft oils in our diet as a means of avoiding and controlling arteriosclerosis. This inflated bubble has already burst and is evidenced by the declining safflower oil market. Vast acreages of safflowers were planted and harvested in expectation of a continued and increasingly high consumption of safflower oil by virture of its medical dietary nature, but the novelty of the sales promotional gimmicks have now worn off and additional medical research has somewhat lessened the role of the polyunsaturates in controlling cholesterol levels. In fact, there has been some interesting work recently published which showed that a synthetic liquid triglyceride derived from coconut oil and completely saturated in nature has the ability to not only control cholesterol levels in approximately the same degree as corn oil, but also controls the deposition of cholesterol in the liver, arteries, and heart. All of these factors have gradually lowered the safflower oil market from its pedestal position to its present level where it is now competing with soybean oil in several industrial applications where commodity prices prevail.

Fats and oils have other specialized uses in pharmaceuticals and one of the more important in this area is is in the formulation of suppositories. Suppositories have been employed for many years as a means of introducing medicaments to the human body and this mode of medication is most often employed when the active ingredient is extremely distasteful and causes nausea or when the medication is designed specifically to treat a disorder in the lower abdominal or urinary tracts. The preferred fatty base for this type of medication has been cocoa butter, owing to the fact that this natural fat has a melting point that is very close to body temperature. Cocoa butter, however, has a low incipient melting point and a wide melting range and will very often produce suppositories that are not sufficiently firm when incorporated with liquid medicaments. Several firms are currently manufacturing a group of synthetic triglycerides derived from coconut oil that offer several advantages over cocoa butter as fatty suppository bases designed for slow release of a

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medication. These synthetic products are produced via hydrogenation and interesterification of coconut oil with other natural oils or by reesterification of fractionated coconut fatty acids with glycerin followed by hydrogenation or interesterification. There is also a patented process whereby the low molecular weight fatty acids are displaced from coconut oil to produce modified oils with higher and sharper melting points than the natural product. These specialty oils can be tailored to meet specified melting point requirements and their saturated and higher purity configurations give them better storage and oxidative stability than cocoa butter along with very sharp melting characteristics that allow the suppositories to retain their firm character until body temperature is reached. These synthetic coconut oil products are finding increasing usage as replacements for cocoa butter in suppository preparations that are designed for slow release. The incorporation of glycerol monostearate or propylene glycol monostearate into formulations of this type will yield products with increasing release rate properties that will be proportional to the amount of monoester employed. In contrast to the fatty based, slow release suppositories, many medications of this type are designed for instant release of the medicament and this type of formulation often employs a water soluble polyethylene glycol ester as its basic ingredient. Polyoxyl 40 Stearate, U.S.P., is often employed in quick release suppositories. This base represents the reaction product of 40 moles of ethylene oxide on stearic acid and its consistency and water solubility meet the necessary requirements for a quick release base.

Another interesting group of fatty chemical derivatives that are ideally designed for use by the pharmaceutical industry in a variety of applications is the polyglycerol esters. A wide variety of these fatty chemicals have been approved by FDA as food additives and are, therefore, of tremendous interest these days to the pharmaceutical formulator who must necessarily be very much concerned with the FDA status of each ingredient. The polyglycerol esters represent reaction products of polymerized glycerols with a variety of fractionated fatty acid products. Many combinations are possible and the resultant products vary from oil soluble to water soluble derivatives with hydrophilic/lipophilic balances ranging from 2–13.

Their properties are such as to suggest their use as emulsifiers for ointment bases, creams, and lotions as well as solubilizers and bases for controlled release tablets and suppositories. This group of products is unique from the standpoint that polyglycerols are found in nature and they also hydrolyze in the body to yield glycerol and the fatty component as the end products of hydrolysis in the same manner that natural fats and oils are broken down and assimilated by the body. The absence of the ethylene oxide stigma, plus the manner in which these esters are assimilated, have been the main reasons for quick acceptance by FDA of this line of naturally derived products. The polyglycerol esters should find many additional applications in a variety of pharmaceutical formulations in the years to come.

The modified coconut oils that are supplanting cocoa butter in suppositories and the polyglycerol products that represent a fine potential for many pharmaceutical applications cover only two of the many areas in which the fat and oil industry could cooperate and grow with this new industrial giant. A third example that demonstrates how our own technical skills can be of mutual benefit to the pharmaceutical industry is the use of synthetic liquid triglycerides as replacements for several U.S.P. vegetable oils as solvents and carriers for vitamins, hormones, antibiotics, and other medicaments in formulations that are designed for either oral or injectable preparations. These synthetic triglycerides are also derived from coconut and palm kernel oils and represent glycerol triesters of eutectic mixtures of the short chain fatty components of these oils. They are very fluid liquids, completely saturated in character and they possess enhanced solvent characteristics for many of the more difficultly soluble drugs. These synthetic oils are completely edible, extremely bland, and readily assimilated by the human body. Their saturated nature precludes the need for antioxidants.

The synthetic oils described above exemplify the manner in which our skills in fats and oils technology can be gainfully employed to produce tailor-made compounds that are more beneficial from a performance standpoint than the natural products that were previously employed by the pharmaceutical industry for specialized applications. As we become better acquainted with the needs and requirements of this industry, it is sincerely felt that the synthetic oils will find wider usage in pharmaceutical preparations whereby product improvement and greater product acceptance will be realized.

The discovery of penicillin opened up a vast new area of drug preparations via the fermentation route and one of the first problems that accompanied the transfer of this type of process to a full plant production scale was the proper control of the foam that developed during the aerobic oxidation of the nutrient solution. It was soon discovered that the addition of small quantities of formulated oil-based products would control the foam in the reactors so that greater capacities could be realized and better housekeeping conditions maintained. The formulation and composition of these defoamers is quite varied, some being simple combinations of oils including mineral, vegetable, and silicone oils, while others are more technical in nature and could include fatty alcohols plus a sufficient amount of surfactant to spread the fatty base over the surface of the fermentation vessel. In formulated products of this type, however, it is very important that the surfactant employed has the ability to lower surface tension in the nutrient solution without adversely affecting the activity of the bacteria strain. Many types of surfactants will poison and kill the bacteria strain and halt the fermentation cycle. The amount of this type of product that is consumed by the pharmaceutical industry is quite substantial and, as a result, prices on these items are highly competitive, being handled more as commodities than as specialty chemicals.

In summarizing the relationship of the fats and oils industry with the ethical and proprietary drug industries, therefore, it can be repeated that several close ties do exist that are related to man's dietary need for fats and oils as necessities for health and growth. Natural fats and oils represent a most abundant and economical source of building blocks to the pharmaceutical industry and surpass petroleum products in this regard, since the latter class of products cannot be considered as nutritious, nor can they be absorbed and utilized by the human body. The healing nature and unctuous character of fats and oils make them ideally suited as bases for many types of pharmaceutical preparations. Numerous fatty-derived surfactants are employed as the basic detergents, emulsifiers, and solubilizers for standardized ethical drug products. The use of synthetic triglycerides derived from natural fats and oils in pharmaceutical formulations is constantly growing and has an unlimited potential in this area. The rapid pace of pharmaceutical and medical research will open new outlets for fats, oils, and fatty chemicals as formula ingredients for new drug preparations. All of the above facts indicate that there are many advantages to be gained through a sincere and earnest marketing effort by our industry to better acquaint our pharmaceutical allies with the wide variety of fatty based oils and chemicals that are currently available to them for the development of new and improved pharmaceutical products.