
Tetrahydropiperine

A Natural Topical Permeation Enhancer

Muhammed Majeed and Lakshmi Prakash
 Sabinsa Corporation
 Piscataway, New Jersey

7.1	Introduction	158
7.2	Historical Perspective	158
	7.2.1 The Spice Route and Black Pepper[29]	158
	7.2.2 Use of Black Pepper in Folk Medicine	159
	7.2.3 Discovery as a Delivery System	159
7.3	Concept Development	160
	7.3.1 Skin as a Delivery Conduit for Bioactives	160
	7.3.2 Black Pepper Extract as Bioavailability Enhancer for Nutraceuticals	162
	7.3.3 Tetrahydropiperine (THP): Unique Black Pepper Constituent Derived from Piperine	165
	7.3.4 Mechanism of Action	165
7.4	Scientific Basis for Efficacy	166
	7.4.1 Chemistry of Tetrahydropiperine (THP)	166
	7.4.2 Experimental Evidence for Topical Formation Enhancement Efficacy of THP	168
7.5	Safety Profile	172
	7.5.1 THP: Low Skin Irritation Potential	172
7.6	Enhancing Topical Delivery of Bioactives with THP	173
	7.6.1 Potential Skin and Hair Care Applications	173
7.7	Formulation Strategies	173
	7.7.1 Skin Care	173
	7.7.2 Hair Care	173
7.8	Summary	173
7.9	Formulations	174
	References	176

7.1 Introduction

The quest for novel topical delivery systems for bioactives, with emphasis on "natural" and "safe," is an area of dynamic research in the pharmaceutical, cosmetics, and nutritional fields. Tetrahydropiperine is a natural topical permeation enhancer for active compounds. Derived from black pepper fruit, the product is effective in very small quantities (0.01%–0.1% by weight in formulations containing actives). It has no irritant or sensitization side effects.

Prepared using a proprietary process, this branded ingredient is gaining popularity in a wide range of topical formulations. Its efficacy in enhancing the topical permeation and uptake of various classes of active compounds has been scientifically validated. The ingredient is compatible with commonly used formulation bases and does not adversely affect the sensory profile of cosmetic compositions.

A salient feature of tetrahydropiperine is that it is derived from black pepper fruit, a familiar culinary spice. Members of the botanical family Piperaceae, to which black pepper (*Piper nigrum*) and long pepper (*Piper longum*) belong, are believed to be among the first plants cultivated by humans for medicinal and food use. Black pepper and long pepper have a history of medicinal use in the Ayurvedic tradition. *Ayurveda* literally means the "science of life" and is comprised of a system of lifestyle recommendations, along with the use of specific herbs and minerals, in the management of disease conditions. Ayurvedic texts, dating back to three thousand years ago, recommend "Trikatu" or three acids, a mixture of black pepper, long pepper, and ginger in a wide range of formulations for optimal health and wellness.

In recent years, extensive research data on the phytochemistry and unique pharmacological actions of these plants have also become available. This has led to their popularity as nutraceutical ingredients. One branded black pepper extract is a clinically proven bioavailability enhancer. It improves the gastrointestinal uptake and utilization of orally administered nutrients by functioning as a thermoneutral. Several mechanisms of action have been proposed. These include augmented blood supply to the gas-

trointestinal tract, increased emulsifying content of the gut, and enhanced active-nutrient transport.

The skin shares many of the characteristics of the gastrointestinal epithelium. It is fitting, therefore, that a natural compound derived from black pepper fruit be used to enhance the topical permeation of actives into the skin. Tetrahydropiperine (THP) thus offers a natural solution to formulators challenged with poorly absorbed topical actives.

7.2 Historical Perspective

7.2.1 The Spice Route and Black Pepper^[29]

Black pepper (*Piper nigrum*) and long pepper (*Piper longum*) are the best-known species of the plant family Piperaceae. They are probably among the most recognized culinary spices in the world. Black pepper alone is reported to account for approximately 35% of the world's spice trade. By some chronicles, family Piperaceae was among the first plants cultivated by the early human. It is believed that the earliest European travelers who visited India found cultivated pepper vines on the Malabar Coast in southwestern India, over two thousand years ago.

As a matter of fact, the demand for Indian black pepper was so great that historical accounts of its trade often portray dramatic events. Some of these events altered the course of world history. Black pepper was among the Indian spices on which the Romans levied duty at Alexandria about 176 C.E. In the fifth century C.E., Roman writers reported that Attila the Hun demanded, among other things, three thousand pounds of pepper in ransom for the city of Rome.

Several centuries later, the high cost of pepper led the Portuguese to seek their own sea route to India, and this came to be called the "spice route." Successful in their mission, trade in this spice became a monopoly of the Crown of Portugal until the eighteenth century. In January 1793, an agreement was made between the Rajah of Travancore and the English. The Rajah was to supply large quanti-

ties of pepper to the Bombay government in return for arms, ammunition, and European goods. Historically, this agreement became known as the "Pepper Contract."

From the sixteenth to the eighteenth centuries, the struggle for control of spice-producing regions in the Far East led to a series of wars between Portugal, Holland, and England over this source of immense wealth. The United States entered the world spice trade towards the end of the eighteenth century, and began exchanging its salmon, flour, and soup for tea, coffee, and spices

One reason that spices in general, and pepper in particular, became so important in international trade was their popular culinary role. In those times, tough, heavily salted, long-stored meat was standard fare, and spice additives made these meats more palatable, while simultaneously masking off-flavors.

All of the commercial and political attention that black pepper has received throughout the centuries has been due to its pungency. The pungency of pepper evokes a familiar sensation of warmth in the mouth which, after a relatively short time, spreads throughout the body. This characteristic is primarily due to the presence of the alkaloid piperine, which was isolated at the beginning of the nineteenth century by the German scientist Derstad. A small quantity of tetrahydropiperine was recently isolated from long pepper (*Piper longum*),^[30] and is also reported to be present in black pepper oleoresin.^[31]

7.2.2 Use of Black Pepper in Folk Medicine^{[29][32][33][35]-[38]}

Piper species have been used in traditional medicine for reducing intermittent fevers and to promote the secretion of bile. They are also recommended for neurological, bronchopulmonary, and gastrointestinal disorders. These include dyspepsia, flatulence, constipation, and hemorrhoids. Some traditional applications employ black pepper in gargles for sore throat and in poultices for the topical management of inflammation and pain.

In Ayurveda, black pepper, long pepper, and ginger are often used together in equal proportions in a preparation known as "trikatu,"^[16] a Sanskrit word

meaning "three acrids." Out of 370 compound formulations listed in the *Handbook of Domestic Medicines and Common Ayurvedic Remedies*, 210 contain either trikatu or its individual ingredients.^[8] According to Ayurveda, the three acrids collectively act as "kapha-vata-pitta-haratwam" which means "correctors of the three biological humors (doshas) of the human organism." The sharp-tasting ingredients in trikatu are used to increase the protective gastrointestinal mucous secretion, a long-standing Ayurvedic treatment that has proven successful for both acute and chronic gastrointestinal conditions.

The advantage of utilizing black pepper (as opposed to the standard quinine) in the treatment of refractory intermittent fevers, (symptomatic of malarial infections), was first reported by Dr. C. S. Taylor in *The British Medical Journal*, September, 1886. Long pepper was also used for patients who had chronic malaria with splenomegaly (enlarged spleen). In traditional Chinese medicine, black pepper has been used for the treatment of epilepsy.^[34] Based on this traditional application, a new anti-epileptic drug called Antiepilepserine has recently been synthesized by Chinese researchers. Antiepilepserine is a chemical relative of piperine, the main alkaloid phytochemical found in plants of the family Piperaceae. In traditional Middle Eastern medicine, black pepper has been used as a nerve tonic.

7.2.3 Discovery as a Delivery System

Our research on tetrahydropiperine as a potential skin permeation enhancer for topical actives was based on the known bioavailability enhancement of nutrients and drugs by the parent compound piperine. Studies on piperine with rifampicin,^[23] piperine with isoniazid, pyrazinamide, and rifampicin,^{[21][22]} piperine with propranolol and theophylline,^[25] and piperine with phenytoin^[24] are reported in the literature.

Beta-carotene absorption has been shown to be variable among humans, with some individuals consistently absorbing it well, while others do not. Recently, an original bioavailability study showed that a standardized extract of black pepper (Bioperine[®]) increases gastrointestinal absorption of beta carotene in humans.^[39] Bioperine is about 98% pure piperine obtained from pepper through a proprietary

extraction process. A small amount of Bioperine (5 mg) combined with a formula containing 15 mg of beta carotene, given as a food supplement once a day, increased almost twofold the blood levels of beta carotene in human volunteers. These results suggest that Bioperine possesses the potential to increase the bioavailability of nutrients as well. Incidentally, the dose of piperine that increased the bioavailability of beta carotene was several times lower than the estimated amount of piperine consumed daily in the diet by an average individual in the USA.^[29] Coenzyme Q10,^[27] L(+)-selenomethionine, vitamin B₆, vitamin C (with propranolol hydrochloride), and herbal extracts such as curcumin showed enhanced bioavailability when co-administered with Bioperine.^[29] When 5 mg of Bioperine was added to a mixture of vitamin C with propranolol hydrochloride, the bioavailability of the nutrient was enhanced while the bioavailability of the drug remained unchanged.

Based on these properties, we tested a derivative of piperine (*viz.*, tetrahydropiperine) to determine if it had better bioavailability enhancement properties. Excellent results were obtained. This data provided a basis for a novel bioavailability-enhancing natural compound for topical use in personal care applications.

We developed a novel process to convert natural piperine in black pepper oleoresin to tetrahydropiperine and then tested its biological activity. Three interesting observations came to light in preliminary studies. Tetrahydropiperine, at very low levels in formulations, enhances the bioavailability of bioactive molecules (with potential applications in the topical delivery of drugs and nutrients), increases topical permeation of bioactive molecules (with potential cosmeceutical, cosmetic applications) and increases the dermal penetration of insecticides (with potential applications in pesticides, anthelmintics, and insecticides).

The discovery that tetrahydropiperine can be used to enhance active-molecule penetration through the skin in topical applications, as well as for the penetration of pesticides, fungicides, herbicides, and foliar fertilizers applied to pests or plants, formed the subject of our patent application.^[28] Derivatives of tetrahydropiperine were also included in the patent application.

7.3 Concept Development

7.3.1 Skin as a Delivery Conduit for Bioactives

The skin is the largest organ in the body. It has far-reaching functions such as being a barrier to the environment and an interface with the outside world, and the capability to accentuate aesthetic appeal and beauty. The skin also participates in nourishing and healing the body. It contains actively metabolizing cells that constantly imbibe nutrients and facilitate their transport to the underlying tissues and organs in the body. Simultaneously, with the "intake" processes, metabolic wastes are excreted through perspiration.

Conventional nourishment is conveyed through the skin from environmental sources such as light, moisture, and sensory stimuli. These inputs affect neurohormones. Noxious substances in the environment trigger the immune response. Deliberately applied substances and stimuli that can potentially heal, renew, and revitalize the body can be similarly conveyed through the skin. It is not surprising, therefore, that pharmacologists and cosmetologists alike look to the skin as a potential conduit for nutrients and drugs. By analogy, the skin functions quite like the gastrointestinal tract.

Although easily accessible, the skin presents unique opportunities and challenges when it comes to the delivery of pharmaceuticals, nutritional compounds, nutraceuticals, and cosmeceuticals. The skin and its appendages (*i.e.*, sweat glands, sebaceous glands, hair, hair follicles, and nails) constitute a dynamic metabolic system with intricate functions. An active compound applied to the skin needs to be absorbed through the protective five-layered epidermis, transported into the dermis and, thereafter, enter the metabolic cycle by absorption into the blood microcirculation.

The outermost layer of the epidermis, the stratum corneum, is made of cornified or keratinized cells. It is in a state of dynamic shedding and renewal. This layer is a consequence of maturation of keratinocytes. These are cells that originate four layers down from the outermost stratum corneum layer in the bottom (basal) layer of the epidermis (stratum basale). Looking outward from this layer, a layer

just above the basal layer, the stratum spinosum, produces "waterproofing" material (a mixture of lipids and glycoproteins) that regulates skin permeability. This is topped by the stratum granulosum, which manufactures keratohyalin, an amino acid complex believed to be metabolized into eleidin in the layer above it (the stratum lucidum). Eleidin is converted to keratin, the tough protective protein of the skin, hair, and nails, in the stratum corneum. The epidermis is also home to several specialized cells. These include, for example, Merkel cells, which play a role in an early warning system against noxious stimuli to the skin. Langerhans cells, which function as immune cells, and melanocytes, which provide protection against excess UV light with potential influence on the circadian rhythms, are also part of the epidermis.

Underlying the epidermis is the dermis. It is comprised of a cushion-like network of elastic fibers (collagen), capillary blood vessels and lymphatic vessels, fine-touch receptors (Meissner's corpuscles), pressure receptors (Pacinian corpuscles), temperature sensors and pressure receptors (Krause's end bulbs). It also contains bundles of smooth muscles attached to hair follicles (when activated giving an appearance of "goose bumps"), eccrine sweat glands (the "sex" glands), wax glands and sebaceous glands. By analogy with the gastrointestinal tract, this complex array of specialized cells and structures permits the skin to communicate with the outside world by selectively permitting nutritious stimuli into the body, while at the same time preventing the entry of noxious stimuli. It also provides for the evacuation of metabolic waste material (by way of the sweat, sebaceous, and wax glands).

A variety of therapeutic molecules such as corticosteroids, steroid hormones, and nonsteroidal anti-inflammatory agents (NSAIDs) have been typically delivered topically. Their efficacy and availability has been assessed by monitoring the biological effects or levels of actives in the plasma. However, attempts to optimize/maximize the delivery of such bioactive compounds is an area of dynamic research. By contrast, other nutrients and drugs, whether protein or peptide in nature, present unique delivery problems of their own, since factors such as molecular size and the charge present in the compound can have a major impact on their ability to be delivered.

A number of different pathways exist for the penetration of actives through skin. These include: intercellular penetration between stratum corneum (mainly hydrophobic, lipid soluble materials), transcellular (through the stratum corneum and consisting primarily of small water-soluble molecules), and via hair shafts and follicles as well as via sebaceous glands.^[1]

It is generally assumed that hydrophobic molecules of molecular weight less than five hundred can easily penetrate the stratum corneum, although the penetration through the deeper layers of the epidermis and dermis is questionable.^{[1][54]} However, for proteins with molecular weight higher than five hundred, as well as charged molecules, even penetration through the stratum corneum is doubtful. For these materials, and for delivery of actives into the blood stream, several strategies have been attempted.

A variety of "chemical penetration enhancers" have been used in the past to increase penetration of drugs into and through the skin. These include: solvents such as DMSO, ethanol, and other alcohols and glycols such as propylene glycol, etc. Fatty acids such as oleic acid and others have been used, as well as trans fatty acids that disrupt the lipid bilayer structure of the stratum corneum. Still other examples include detergents such as sodium lauryl sulfate, polyoxyethylene lauryl ethers, chaotropic agents such as thioglycolate, urea, mercaptoethanol, and many others.^[1] Most of these agents increase penetration of certain drugs; they also have the potential to cause damage to the stratum corneum and to increase the probability of irritation. Most of these agents work by perturbation of the intercellular lipid bilayers present in the stratum corneum.^[2]

Several other strategies have also been used to deliver drugs through the skin. Designing *prodrugs* that can be cleaved enzymatically within the skin has been one such strategy. The prodrug is designed to improve skin penetration by initially increasing the hydrophobicity, or by neutralizing the charge on the molecule, until it is cleaved enzymatically. This strategy can utilize parameters such as lipid solubility, partition coefficient, and molecular volume.^[3]

A third strategy for increasing penetration is entrapment of the drug, nutraceutical, or cosmeceutical inside liposomes, or other skin penetrable vesicles.^[4] Liposomes have been extensively stud-

ied and suggested as a vehicle for topical delivery systems. It has also been suggested that liposome size makes a difference in the rate of penetration of the drug through the skin.^[5] Penetration efficacy has been found to be inversely proportional to the size of the liposomes. Liposomes modified with hyaluronic acid have been suggested as better carriers of topical drug delivery, especially for delivering drugs for wound healing.^[6] In addition, liposomes also accelerate delivery of materials via both pilosebaceous units^[7] and a follicular route.^[11]

Various formulation strategies have been applied to induce delivery of actives into the skin. Skin penetration of alpha tocopherols can be greatly enhanced by formulating them in hydroalcoholic gels.^[8] Microemulsions are suitable carriers to stabilize and deliver ascorbic acid derivatives and estradiol into skin.^{[9][10]}

The nutraceutical industry has begun to use this strategy to deliver nutraceuticals via the skin as an alternative to oral supplements. Skin permeation enhancement technologies also include the use of phospholipid vesicles and cyclodextrins as delivery vehicles, as well as the use of essential oils, fatty acids, squalene, alcohols, and other compounds.

Two natural ingredients derived from black pepper extract have been demonstrated to enhance the gastrointestinal and topical absorption of nutrients. Both these ingredients are patented by Sabinsa Corporation.^{[12]-[15][28]}

7.3.2 Black Pepper Extract as Bioavailability Enhancer for Nutraceuticals^{[12]-[15]}

Do all nutritional supplements consumed, or all topically applied products, provide optimal health benefits? Typically, the answer to this question depends upon how well they are absorbed along their delivery route. *Bioavailability* encompasses availability, absorption, retention, and utilization of nutrients. Absorption in the body is a key factor for the nutrient to be biologically effective. Black pepper extract, or to be more precise, its active alkaloid component piperine, has been shown to enhance bioavailability when co-administered with nutrients.

The spicy or "hot" taste of pepper when sprinkled on food is well known. The perception of heat is stronger when fresh pepper is used. This heat is, in fact, a manifestation of the biological activity of some of the active compounds found in pepper, the most notable of these being piperine.

Black and long peppers stimulate the skin as well as the tongue. They have, therefore, also found wide use in topical applications. These peppers have been found to have broad antimicrobial, antiparasitic, and insecticidal properties. Peppers have been traditionally used as local anesthetics, but the mechanism of this analgesic (pain-relieving) action has only recently been described.^[17] It is believed that piperine, the active constituent in black pepper and long pepper, acts in a similar (but not identical) way to capsaicin, another well-known pungent phytochemical, found in cayenne peppers (*Capsicum annum*). Black and various red peppers, including cayenne, chili, and paprika, are all spicy but are not related botanically.

According to one hypothesis, piperine may cause depletion of the neurotransmitter called "Substance P,"^[29] from the sensory nerves. Substance P's appearance and concentration is correlated with the experience of pain. This action may cause local desensitization to pain stimuli. It has been proposed that Bioperine acts through thermoreceptors, both locally in the skin nerve endings, and systemically, throughout the nervous system. This action, in turn, interferes with pain stimulus transmission and causes desensitization of pain receptors.^[29]

The proposed mechanism for pain reduction through thermoreceptors (sensors of heat energy) in the body may provide clues to the mechanism of thermogenic (heat-generating) action of pepper and piperine. The thermogenic effect of piperine and other components of spices such as capsaicin, gingerol, and shogaol is now broadly discussed as a new application of spices traditionally known for their ability to regulate body temperature. Thermogenesis is scientifically linked to the metabolic processes in the body and the metabolic rate. The higher the metabolic rate, the greater is the heat energy produced by the body. Could it be that thermoregulation by piperine is a mechanism through which metabolism can be regulated, including the absorption and utilization of nutrients and drugs? In light of the profound effects of piperine on nutrient absorption when given orally in a dose as small as a few milligrams,

the compound deserves to be called a "supernutrient." In view of its possible thermogenic effect in the body, it could also be dubbed a *thermo-nutrient* [18]

The concept of thermogenesis is not documented in Ayurveda, the ancient Indian system of medicine. However, its texts describe the empirical use of certain combinations of herbs and minerals specifically targeted to improve the digestibility of food. Recent experimental evidence shows that piperine has anti-inflammatory and antioxidant properties [19]. Piperine may thus facilitate nutrient absorption by reducing inflammation at the site of active molecule absorption. The mechanisms underlying the beneficial action of piperine, as one of the principal ingredients of numerous formulas for digestive health and respiratory support employed by Ayurveda, certainly requires further investigation. Particular attention needs to be paid to the traditional understanding that restoring optimal gastrointestinal function is an effective means of preventing disease and improving overall nutrition through improved nutrient absorption. Black pepper and long pepper are thus potentially useful herbs in the management of a variety of gastrointestinal and related problems.

Future research on pepper and its constituents may further explore the origin, evolution, and effects of its pungency, a property that has attracted attention since ancient times. Pliny commented some two thousand years ago: "It is quite surprising that the use of pepper has come so much in fashion, its only desirable quality being a certain pungency; and yet it is for this that we import it all the way from India!" [20]

The pungency of pepper is now understood to be an offshoot of the biological properties of piperine. This compound can, in fact, regulate neurohormones, and thereby increase thermogenesis, or the production of heat by the body. Scientific research has now revealed that the "hot" pepper taste is due to the production of heat energy. The thermogenic effect is also attributed to the ability of piperine to stimulate the thyroid gland and increase the action of thyroid hormones. The biological mechanism of piperine is thus clearly linked to its hot taste, further validating its representation as a nutraceutical or "functional food."

The biological properties of piperine have been extensively studied only in recent years [21][22]. The proposed mechanism for the increased bioavailability of drugs co-administered with piperine is attributed to the interaction of piperine with enzymes that participate in drug metabolism. Examples of these are mixed function oxidases found in the liver and intestinal cells. Interaction with the synthesis of drug chelating molecules in the body such as glucuronic acid has also been proposed. Piperine may also interact with the process of oxidative phosphorylation, or the process of activation/deactivation of certain metabolic pathways, thereby slowing down the metabolism and biodegradation of drugs. This action of piperine results in higher plasma levels of drugs, thereby rendering them more available for pharmacological action.

One of the first scientific experiments to confirm that pepper could enhance the bioavailability of drugs was performed in the late 1970s by Atal and coworkers at the Regional Research Laboratory, Jammu-Tawi in India [21]. These experiments revealed that *Piper longum* orally co-administered to rats with the drugs vasicine and sparteine increased the blood levels of vasicine by 232% and sparteine by more than 100% as compared to control animals who did not receive *P. longum*. In subsequent experiments, piperine has been proven to enhance the bioavailability of a number of drugs including rifampicin, phenytoin, propranolol, and theophylline [22][23][25].

The successful use of piperine to increase bioavailability of certain drugs has created interest in its use for nutrient and food absorption. Nutritional deficiencies due to poor gastrointestinal absorption are an increasing problem in developing countries as well as in Western nations; therefore, the use of piperine represents an opportunity to alleviate these deficiencies. While overall gross malnutrition may be the culprit for this problem in developing countries, incidence of poor gastrointestinal absorption is increasing in Western nations due to a larger percentage of aging baby boomers in the population. Nutritional deficiencies in Western nations are further exacerbated by "junk food diets," allergies, gastric ulcers, and chronic yeast infections (Candidiasis).

Bioperine® is a standardized extract manufactured by Sabinsa Corporation from the fruits of *Piper nigrum* L. (black pepper) or *Piper longum* L. (long

pepper) It contains a minimum piperine content of 95% compared to the 3%–9% and 3%–5% found in raw forms of *Piper nigrum* and *Piper longum*, respectively. Bioperine may be co-administered with various nutrients to produce improvements in both human and animal health.^{[12]–[15]}

When optimal oral delivery of nutrients is required, Bioperine may be co-administered in low amounts (5 mg) with the nutrients to increase absorption and bioavailability. The efficacy of Bioperine in this regard is supported by clinical data as shown in Figs. 7.1–7.4.

Nutritional materials which may be co-administered with Bioperine, include the following groups:

- Herbal extracts
- Water-soluble vitamins
- Fat-soluble vitamins
- Antioxidants
- Amino acids
- Minerals

Bioperine was effective in increasing nutrient absorption with a dose several times lower than that

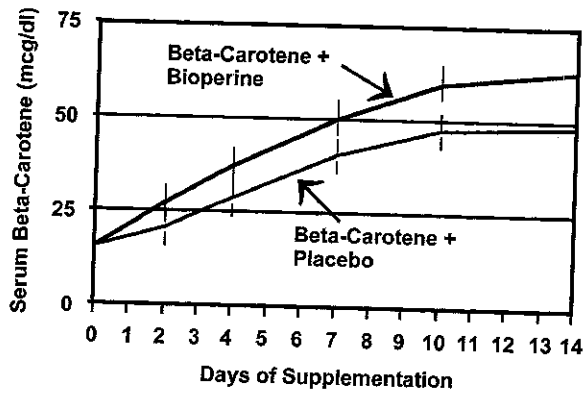


Figure 7.1 Effect of Bioperine® on the mean serum beta carotene levels during a fourteen-day supplementation trial.

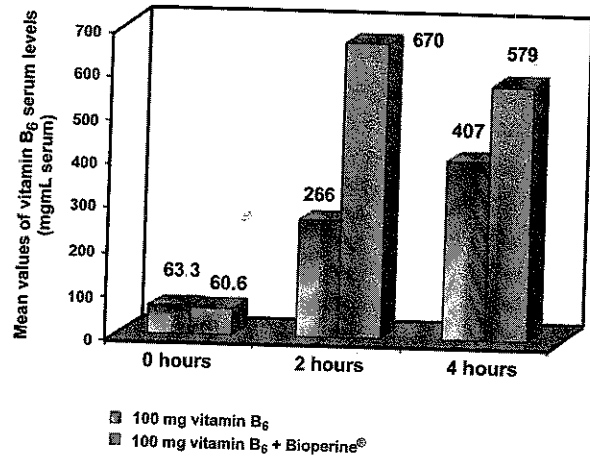


Figure 7.3 Efficacy of Bioperine® on the bioavailability of vitamin B₆ absorption in human volunteers.

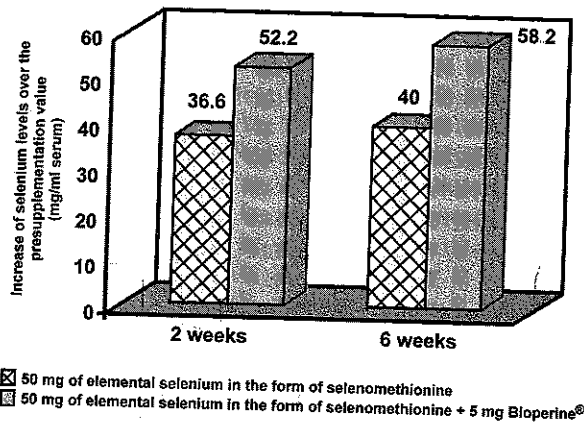


Figure 7.2 Effect of Bioperine® on the mean serum selenium levels during a six-week supplementation trial.

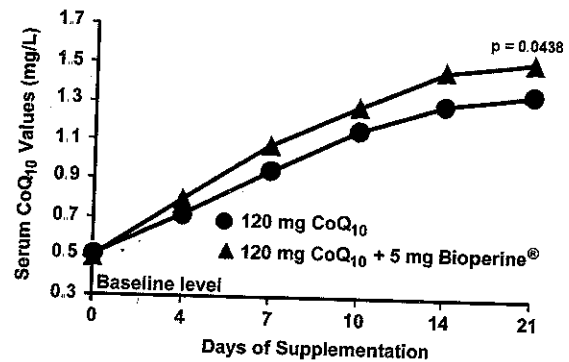


Figure 7.4 Effect of Bioperine® on the mean serum CoQ₁₀ levels during a twenty-one day supplementation trial.

commonly used to bioenhance blood levels of a drug. Incidentally, the dose of piperine, which increased the bioavailability of beta carotene,^[26] was several times lower than the estimated amount of piperine consumed daily in the diet by an average individual in the USA.^[29] Similar bioavailability enhancement was observed on co-administration of other nutrients including coenzyme Q10,^[27] L(+)-selenomethionine, vitamin B₆, vitamin C (with propranolol hydrochloride) and herbal extracts such as curcumin with Bioperine.^[29] These experimental results provide strength to the concept that nutrient delivery through the skin could similarly be enhanced by piperine and related compounds.

7.3.3 Tetrahydropiperine (THP): Unique Black Pepper Constituent Derived from Piperine

Tetrahydropiperine, a compound present in small amounts in black pepper and long pepper extracts, can be commercially prepared from piperine by using a proprietary process. This process produces a concentrate containing pure tetrahydropiperine in the form of a light tan powder. The material is suitable for use in cosmetic formulations and topical delivery systems for drugs, nutrients, and other bioactives. When added in low amounts (0.01–0.1%) to such formulations, this product enhances the skin uptake and bioavailability of actives in the formulations.

Laboratory studies with betamethasone dipropionate (BMDP), a steroidal anti-inflammatory agent that is commonly used in topical anti-inflammatory formulations, revealed faster absorption of the drug when combined with tetrahydropiperine.

Similar enhanced permeation was observed in studies with other active materials including *Coleus forskohlii* extract (forskolin, green tea extract [polyphenols]) and tetrahydrocurcuminoids (derived from tumeric root extract). For example, the permeation of forskolin was enhanced when the concentration of tetrahydropiperine was 5% of forskolin concentration. Similarly, about 30% improvement in bioavailability of the other botanical extracts was observed when they were co-administered with tetrahydropiperine.

In view of these properties, tetrahydropiperine is a potential transdermal bioavailability enhancer when co-administered topically with nutrients or other active compounds. Improved absorption of topically beneficial nutraceuticals is expected for carotenoids, ascorbic acid, vitamin A, mineral nutrients, 7-keto DHEA, herbal extracts, amino acids, and other topically beneficial nutraceuticals and cosmeceuticals.

With regard to safety, tetrahydropiperine does not irritate the skin when used in cosmetic formulations, as revealed by occlusive patch testing performed on human volunteers.^[55]

7.3.4 Mechanism of Action

Based on clinical experimentation with its parent compound piperine, tetrahydropiperine is a potentially versatile adjuvant for nutrient and cosmeceutical delivery into the skin. As discussed previously, piperine in oral dosage forms is reported to enhance the gastrointestinal absorption of drugs and nutrients in animals and humans. Compounds successfully studied include drugs such as vasicine, pyrazinamide, rifampicin, isoniazid, propranolol, theophylline, and phenytoin. Similar action has been seen for nutrients such as fat-soluble beta carotene, water-soluble vitamin B₆, vitamin C, coenzyme Q10 and the mineral selenium in the form of L-selenomethionine.^[29]

In vitro studies with tetrahydropiperine, using systems that simulate dermal absorption showed promising results. An application analogous to gastrointestinal bioavailability enhancement by piperine is therefore likely. This result presents exciting alternative inroads for new directions in nutrient delivery. Effective topical delivery of essential nutrients could provide an accessible and affordable means of disease prevention and sustaining good health.

This above stated rationale is based upon the physicochemical factors that influence skin permeation of topically applied substances, and the mode of action of known permeation and bioavailability enhancers. Selective nutrient absorption is an important physiological property of the skin. The process begins at outermost epidermal layer, the stratum corneum, the barrier against the external environment.^[44] This barrier function is effected by the

unique composition of the lipid moieties in the epidermis.^{[45]-[48]} Lipids produced by actively metabolizing keratinocytes are released into the intercellular spaces, where they undergo enzymatic processing to produce a lipid mixture consisting of ceramides, cholesterol, and fatty acids. These intercellular lipids are organized to form a selectively permeable barrier. These intercellular lipids mediate transdermal delivery of both lipophilic and hydrophilic molecules.^[49]

Fatty acids in epidermal lipids play a pivotal role in regulating nutrient bioavailability because they are important components of cell membranes and form the hydro-lipid skin surface film.^[50] It is known that topical application of certain fatty acids can lead to changes in permeation of co-administered topical bioactives. Fatty acids may restore a damaged stratum corneum barrier, or enhance nutrient and drug transport through the skin, by increasing cell membrane fluidity. Increased cell membrane fluidity results in a better fit for the bioactive molecule and translates to increased uptake.

Research shows that regulating the composition of intracellular lipids in the skin can increase or decrease the bioavailability of topically applied actives. It is known that a diet deficient in essential fatty acids, repeated exposure to organic solvents, or prolonged topical application of agents that interfere with lipid synthesis can reduce the barrier function of the skin, rendering it more porous.^[47] Examples of these agents include lovastatin, fluvastatin, and cholesterol sulfate. This decrease in barrier function would trigger increased synthesis of lipids, DNA, and relevant types of epidermal cells to compensate for the deficiency in the protective barrier. These natural defense mechanisms serve to restore the integrity of the skin barrier and its functions. It should also be noted that providing an artificial barrier, for example, by applying a topical sealant, blocks the natural defense mechanisms that serve to repair the skin structure.^[47] This observation indicates that the epidermal lipid composition might be able to be modified sufficiently in order to permit the entry of beneficial molecules.

In studies with drug molecules, it has been observed that supersaturation of the active ingredient could effect enhanced permeability. Alternatively, when the skin is viewed as a delivery conduit, it can

contain ingredients that may decrease the diffusional (electrostatic) resistance of the lipid bilayer to the active molecule. Topical liposome preparations are a good example of such materials. They function as effective penetration enhancers for the delivery of certain co-applied drugs and biological compounds, (e.g., interferon). The mechanism of action is believed to be due to their role in increasing cell membrane fluidity.^{[52][53]}

It is also known that an increase in blood supply to the skin can enhance the absorption of topically delivered nutrients.^[51] In the case of tetrahydro-piperine, the increase in skin permeation/bioavailability effected could be due to a synergistic combination of all the modes discussed above.^[43]

While more experimental data are needed to further elucidate the bioenhancing mechanism of tetrahydro-piperine, data from experiments done both in vitro and in vivo with the parent compound piperine indicate that the compound may be influencing either of two events favorably:

1. Membrane fluidity
2. Affinity of nutrient/drug to the cell membrane

Another aspect to be considered is that tetrahydro-piperine, which is a lipophilic compound, may increase solubilization of the intracellular lipid moiety in the skin. This, in turn, would help to enhance the permeation of topically applied active compounds.

7.4 Scientific Basis for Efficacy

7.4.1 Chemistry of Tetrahydro-piperine (THP)

Tetrahydro-piperine is an arylpentanamide found naturally in small amounts in *Piper nigrum* and *Piper longum*. It can be synthesized from piperine by controlled hydrogenation in methanol using palladium carbon catalyst. This indicates that enzymes responsible for the biochemical transformation (hydrogenation) of piperine do occur in nature in low amounts. Table 7.1 describes the chemistry of THP.

Table 7.1. Chemistry of Tetrahydropiperine (THP)

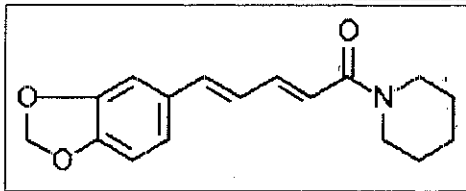
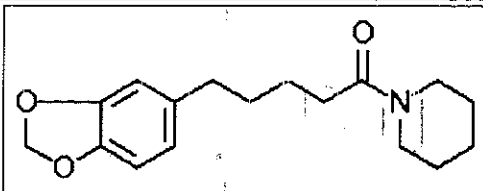
Piperine		Tetrahydropiperine	
			
Chemical Name	1-[5-(1, 3-Benzodioxol-5 yl)-1-oxo - pentanoyl]-Piperidine		
Molecular formula	C ₁₇ H ₂₃ NO ₃		
Molecular weight	289.36		
Percentage composition	C: 70.56%, H: 8.01%, N: 4.84%, O: 16.59%		
Specifications of Tetrahydropiperine			
Description	Off-white, low melting solid with characteristic odor.		
Solubility	Soluble in alcohols (ethanol, methanol, sparingly soluble in propylene glycol), insoluble in water.		
Melting point	41°C–42°C		
Assay by HPLC	Minimum 99.5%		
Chromatographic impurities	Not more than 0.5%		
Spectral characteristics	(See Fig. 7.5.)		

Figure 7.6 shows the HPLC chromatogram of pure tetrahydropiperine. The procedure is summarized here.

Mobile Phase

Mix acetonitrile and water in the ratio of 50:50, filter and degas.

Standard Preparation

Weigh 50 mg of the standard and transfer into a 50 ml volumetric flask. Add 25 ml of methanol to dissolve and dilute the volume, mix.

Sample Preparation

Weigh 50 mg of the sample and transfer into a 50 ml volumetric flask. Add 25 ml of methanol to dissolve the sample and dilute to volume, mix.

Chromatographic System

The liquid chromatograph is equipped with 230 and 241 nm UV detector and a 250 × 4.6 mm column that contains the packing C18 or ODS (Sigma Aldrich column is used). The flow rate is 1.0 ml per min. The relative standard deviation for replicate injections of standard preparation should not be more than 1.0%.

Procedure

Separately inject equal volumes (20 µl) of the standard preparation and sample preparation into the chromatograph, record the peak responses obtained for the major peaks, and calculate the percentage as follows:

$$\frac{\text{Area of Sample} \times \text{Standard Concentration} \times \text{Standard Strength}}{\text{Area of Standard} \times \text{Sample Concentration}}$$

7.4.2 Experimental Evidence for Topical Formation Enhancement Efficacy of THP

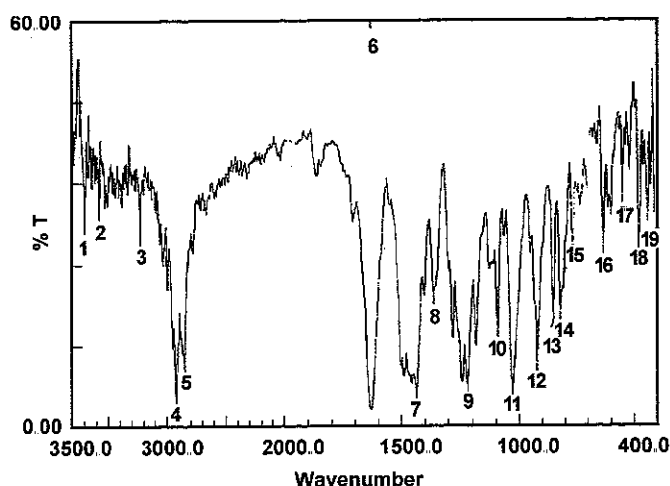
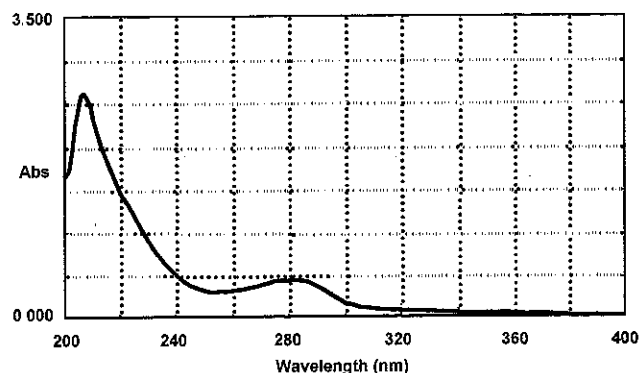


Figure 7.5 Spectral characteristics of tetrahydropiperine.

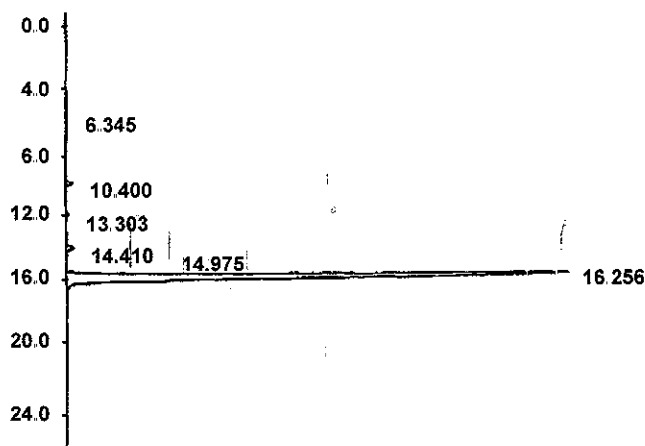


Figure 7.6 HPLC chromatogram of tetrahydropiperine.

Three sample botanical extracts used as cosmeceutical ingredients were tested for bioavailability enhancement by tetrahydropiperine: green tea extract (polyphenols rich, a well known antioxidant), *Coleus forskohlii* extract (providing forskolin, a skin conditioning agent) and tetrahydrocurcumin (derived from curcuminoids extracted from tumeric root, a potent antioxidant).^[56]

The permeation of green tea extract and forskolin in the presence and absence of tetrahydropiperine was studied in a Franz diffusion cell system, and carried out across a hydrated skin substitute. The bioenhancing potential of tetrahydropiperine was similarly evaluated in experiments with the steroidal anti-inflammatory drug betamethasone dipropionate (BMDP), and an anthelmintic, fenvalerate. The antioxidant effect of tetrahydrocurcumin in the presence and absence of tetrahydropiperine, was also evaluated.

In the experiment involving BMDP, the skin preparation was mounted in a Franz diffusion cell in two compartments: "donor" and "receptor." The drug (100 mcg/ml) was applied with 0.1% (active sample) or without (control sample) of tetrahydropiperine in the donor compartment. Subsequently, the absorbances of the fluid in the receptor compartment for the presence of BMDP and THP were measured in time intervals of 5, 10, 15, 20, 30, 45, and 60 minutes. The active sample resulted in 100% diffusion of the BMDP within the first 10 minutes. The control sample resulted in 29% diffusion of BMDP after 45 minutes and only 54% diffusion after 60 minutes.^[40]

Example 1: Increased efficacy of an anti-inflammatory agent (BMDP).

Materials. A Franz diffusion cell was utilized in the experiment. The test drug, BMDP, with or without tetrahydropiperine (control), was applied on one side of the skin (donor compartment). The drug's transport to the receptor side of the skin was estimated using a UV spectrophotometer at predetermined time intervals.

Instruments. Franz diffusion cell (fabricated); capacity of receptor compartment: 36 ml; area of skin mounted: 10.18 sq cm.; UV/VIS spectrophotometer (Jasco V-530); FTIR spectrophotometer (Jasco 5300).

Chemicals Betamethasone dipropionate (Nucron Pharmaceuticals, Ltd); sodium chloride; Tween 20; propylene glycol. All chemicals were of analytical grade.

Standard BMDP solution (100 µg/ml). In a volumetric flask of 100 ml, 10 mg of BMDP was taken and dissolved in 50 ml saline with Tween 20 solution and volume was made up with the same.

Tetrahydropiperine solution (1% w/v). In a volumetric flask of 25 ml, 0.25 g of tetrahydropiperine was made up with propylene glycol.

Methods. Hydrated skin was mounted on the Franz diffusion cell with the shaved surface facing the donor compartment. The receptor fluid (saline with Tween 20 solution) was maintained at $37 \pm 0.5^\circ\text{C}$ and stirred continuously at 200 rpm. The experiments conducted are described below.

Control. Propylene glycol, 0.5 ml, was applied to the mounted skin and kept for one hour. The receptor fluid was removed and replaced with fresh receptor fluid. BMDP solution, 0.5 ml (50 µg), was applied and sampling was carried out for a period of three hours. The sample volume was 2 ml each time, which was replaced by fresh receptor fluid. Absorbance of each sample was measured by UV spectrophotometer at the wavelength of 256 nm.

Test. Tetrahydropiperine solution, 0.5 ml, was applied to the mounted skin and kept for one hour. The receptor fluid was removed and replaced with fresh receptor fluid. BMDP solution, 0.5 ml (50 µg), was applied and sampling was carried out for a period of three hours. The sample volume was 2 ml each time, which was replaced by fresh receptor fluid. Absorbance of each sample was measured by UV spectrophotometer at the wavelength of 256 nm.

UV absorption spectra of BMDP solutions show absorption at 238 nm when prepared in saline with Tween 20 solution. We selected 256 nm as the wavelength of analysis for the following reasons:

- Tetrahydropiperine showed absorbance at 228 nm and 275 nm.

- The absorbance of tetrahydropiperine was minimum at 256 nm while it was good for BMDP. The difference in the absorption value at λ_{256} is the maximum.
- The calibration curve was prepared using receptor fluid to simulate the conditions for BMDP, present in test solution (Table 7.2)

Considering that absorbance is an additive property, the concentration of BMDP in the permeation study was determined by exploiting the curve subtraction facility of software V500 provided by Jasco. The absorbance at 256 nm was obtained by subtracting the curve of the spectrum of tetrahydropiperine from the spectrum of BMDP with tetrahydropiperine. The percentage of drug diffused in control and test are given in Table 7.3.

Table 7.2. Calibration Curve for Betamethasone Dipropionate in Saline with Tween 20 (0.05%); λ_{256} nm

Conc. (µg/ml)	Absorbance
5	0.090
10	0.12
15	0.147
20	0.197
25	0.248
30	0.310

Table 7.3. Effect of Tetrahydropiperine on Transdermal Diffusion of BMDP

Time (min)	Percent Diffuse	
	Control	Test
5	--	95.06
10	--	102.55
15	--	--
20	--	--
30	--	--
45	29.05	--
60	53.847	--

Table 7.3 shows that, in the first thirty minutes, the amount of drug diffused in the control is undetectable. However, in the presence of tetrahydropiperine, all the drug has diffused within ten minutes. This demonstrates the increased permeation of BMDP in the presence of tetrahydropiperine (Fig. 7.7).

Example 2: Bioavailability enhancement of antioxidant botanical extracts. Two sample botanical extracts used as "cosmeceutical" ingredients were tested for bioavailability enhancement by tetrahydropiperine: green tea extract (polyphenols rich)^{[41][56]} and tetrahydrocurcumin (derived from curcuminoids extracted from tumeric root)^[40]

Materials. Franz diffusion cell (Permegear #4G-01-00-09-05), Permegear station stirrer (Permegear #V6), egg shell membrane, buffer (50 mM phosphate buffer, pH 6.8), green tea extract (containing 70% polyphenols), DMSO, tetrahydropiperine.

Method.^[42] Green tea extract, dissolved in the buffer in 3 mg/ml concentration, was used as the stock solution. A blank solution (B) was prepared from the green tea stock solution containing 0.2% DMSO, and a test solution (I) was prepared from the green tea stock solution containing 1% THP in 0.2% DMSO. Fresh membrane was removed from the egg shell, washed five to six times with the buffer, and kept in the buffer for twenty minutes for stabilization. The receiving chamber had 5 ml of the buffer.

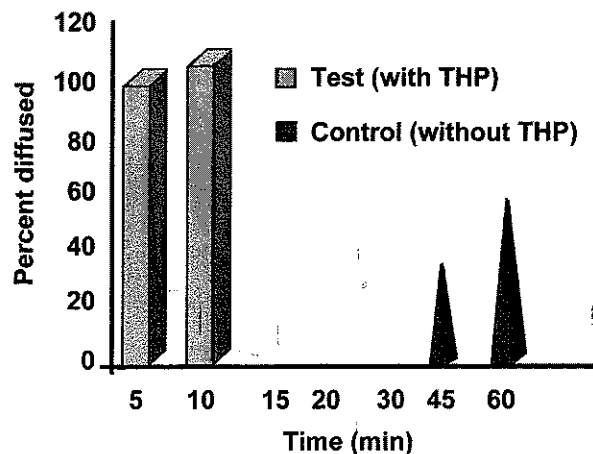


Figure 7.7 Transdermal absorption study with betamethasone dipropionate (BMDP).

Membrane of uniform thickness was cut and placed between the receiving chamber and the donor chamber. One milliliter each of the solutions B and I were added to the respective receiving chambers of the Franz diffusion cells at constant temperature with stirring. Samples were collected from the receiving chambers after 5, 10, 20, and 40 minutes from both the B (without THP) and I tests (series with THP).

The samples were analyzed for the total polyphenol contents based on the reaction of polyphenols with phosphomolybdotungstic acid, forming a blue-colored complex, and the absorbance was measured at 760 nm. Tetrahydropiperine enhanced the permeation of green tea polyphenols across the egg membrane by about 30% on average (Fig. 7.8).

In another similar experiment, the bioenhancing potential of tetrahydropiperine on the free-radical scavenging properties of topically applied tetrahydrocurcuminoids (THC) was evaluated. In this *in vitro* DPPH radical scavenging method, the ability of an antioxidant to bind and inactivate the 1,1-diphenyl-2-picrylhydrazyl radical, or DPPH, was measured. DPPH is considered an example of a very stable free radical. The control sample contained 0.01% of THC while active samples contained 0.01% of THC with tetrahydropiperine concentrations ranging from 0.1%–0.0001%. Additionally, controls containing various concentrations of tetrahydropiperine alone were also tested for DPPH binding.

While tetrahydropiperine by itself did not show any significant antioxidant properties, together with THC it was shown to enhance the antioxidant properties of THC by up to 30% compared with THC used alone (Fig. 7.9). Even in its highest dilution of 0.0001 mg/mL, tetrahydropiperine still displayed some beneficial bioenhancing activity with THC.^[40]

Example 3: Enhanced permeation of forskolin, a skin-conditioning agent.^[41] *In vitro* permeation studies of forskolin, a diterpenoid compound which has various therapeutic effects (bronchodilation, prevents platelet aggregation, anti-hypertensive, anti-glaucoma, anti-inflammatory, weight management, and cellulite care support) were performed. Fabricated Franz diffusion cells of capacity 67 and 69 ml were used for the study. Hydrated skin was used as the membrane for permeation studies.

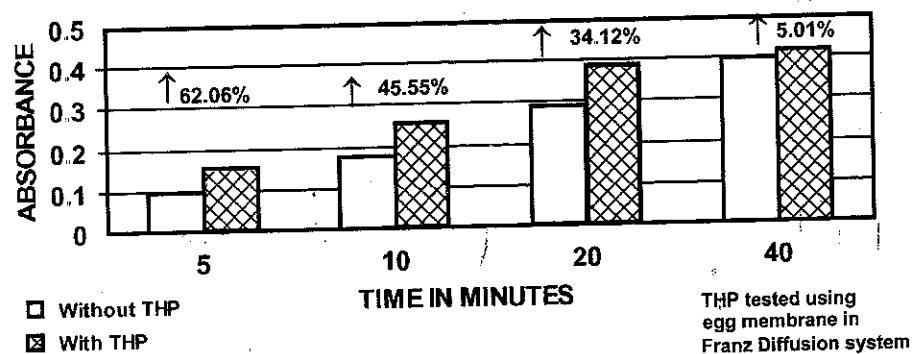


Figure 7.8 Effect of THP on penetration of green tea polyphenols across egg membrane.

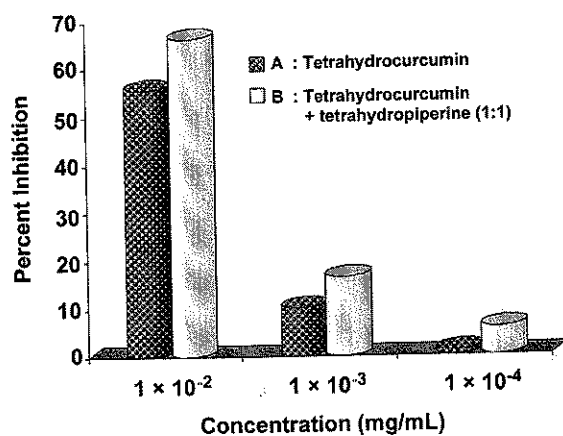


Figure 7.9 Bioavailability enhancement of tetrahydrocurcumin by tetrahydropiperine.

Apparatus. Fabricated Franz diffusion cells with receptor compartments of 67 and 69 ml capacities.

Materials. Solutions used in the study:

- 2.5% forskolin in methanol.
- 0.05% tetrahydropiperine in 2.5% forskolin in methanol.
- 0.1% tetrahydropiperine in 2.5% forskolin in methanol.

Methods.

Procedure. Hydrated skin was mounted on the Franz diffusion cell with the outer layer of the skin facing the donor compartment. The receptor fluid was maintained at 35°C using a thermostatic magnetic stirrer.

The study was conducted by replacing the medium in the receptor compartment with methanol instead of phosphate buffer. In both the receptor and donor compartments, methanol was used as the medium in the permeation studies.

Test. In the donor compartment, 2 ml of methanol containing 50 mg of forskolin and tetrahydropiperine (5% forskolin conc.) was taken. The receptor compartment consisted of 69 ml of methanol maintained at 35°C. The permeation study was carried out for a period of one hour. Samples were withdrawn at 15-, 30-, and 60-minute intervals and the amount of forskolin present was analyzed by HPLC.

Control. In the donor compartment, 2 ml of methanol containing 50 mg of forskolin was taken. The receptor compartment consisted of 65 ml of methanol maintained at 35°C. The permeation study was carried out for a period of one hour. Samples were withdrawn at 15-, 30-, and 60-minute intervals and the amount of forskolin present was analyzed by HPLC.

Results Fig. 7.10 shows the transdermal permeation of forskolin in the presence and absence of tetrahydropiperine (5% forskolin conc.) Table 7.4 gives a comparative release data of forskolin in the presence and absence of tetrahydropiperine.

The permeation of forskolin was enhanced when the concentration of tetrahydropiperine was at a level of 5% forskolin concentration. The phenomenon appears to be concentration-dependant since at a lower tetrahydropiperine of 2% (forskolin concentration), enhanced permeation was not observed.

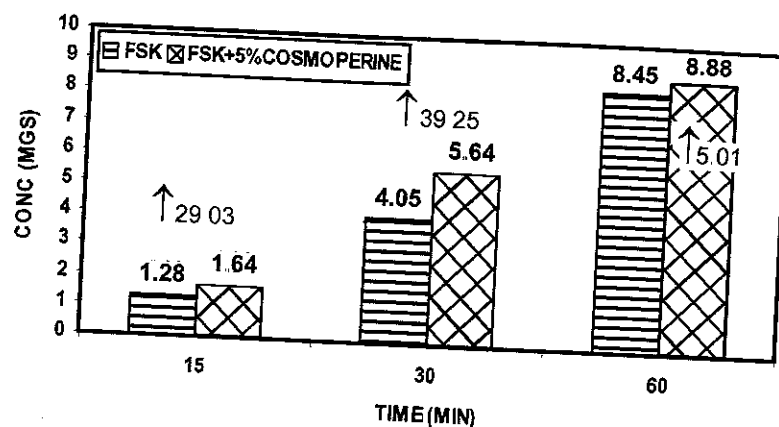


Figure 7.10 Effect of THP on the dermal penetration of Forskolin.

Table 7.4. Transdermal Release/Permeation of Forskolin

Time (minutes)	Forskolin Release Control	Forskolin Release with THP	Increase in release (% of Forskolin)
15	1.28	1.64	28.12
30	4.05	5.64	39.25
60	8.45	8.88	5.09

7.5 Safety Profile

Safety is of prime concern in selecting a suitable topical delivery system. Although tetrahydropiperine is based on a pungent principle, it is non-irritant and interacts with the skin in a manner different from other pungent principles such as capsaicin from cayenne pepper.

Capsaicin is recognized by the US FDA as an OTC counterirritant and topical pain reliever in a dose of 0.025%. However, besides the pain relieving action this dose provides, it often causes skin reddening due to vascular engorgement as well as a slight skin tingling sensation. This reaction to capsaicin can occur within minutes or a few hours after topical application. The reaction usually lasts from half an hour to several hours from the moment it occurs. It tends to subside with regular, sustained use of topical capsaicin in a pain-relieving dose. Tetrahydropiperine, derived from the pungent compound piperine, does not irritate the skin when used at therapeutically significant levels.

7.5.1 THP: Low Skin Irritation Potential

Determination of skin irritation potential—patch test in human volunteers.^[55] A study was conducted to determine whether tetrahydropiperine at levels of 0.01% and 0.1% (an effective dose range for the compound) would produce symptoms of topical irritation.^[57] A skin patch test using tetrahydropiperine in a petrolatum vehicle was conducted on fifty healthy volunteers for 48 hours and the results were read after 48 hours and 72 hours. Neither dose caused skin irritation at the time of clinical evaluation of the study subjects. The supervising physician, a practicing dermatologist, reported the irritation score as 0. This study was conducted by the US FDA accredited BioScreen Testing, Inc., laboratory. These results indicate that tetrahydropiperine does not act as a skin irritant in a dose range considered effective for topical nutrient delivery. Details of this study are presented below.

The 48-hour Repeat Insult Patch Test was used to evaluate skin irritation potential of the test compound.

Fifty male or female subjects between ages 18 and 87 years participated in the study. Five male and 41 female subjects completed the study. The subjects were in good health and were not using any medications for thirty days prior to the commencement of the study.

Materials and methods. The test material was applied occlusively, 0.1% w/w diluted in petrolatum. Two-tenths gram or 0.2 cc of the test material was dispensed into the skin of the upper back. Paper tape such as 3M Micropore® or Kendall Tenderskin® was used for fixation after preparation of the surrounding skin with an adhesion enhancer such as Mastitol®. The subject was instructed to avoid exposure to water or to direct sunlight during the 48-hour observation period. The tape was removed at the test facility at the end of the exposure period and evaluated by trained personnel under the supervision of the principal investigator.

Reactions were scored based on the appearance of erythema or edema immediately following removal of the patch and again at twenty-four hours following removal. Subjects were instructed to report any delayed reactions occurring after the final reading.

Results. No erythema or edema reactions were observed in any of the subjects after forty-eight hours' exposure of the skin to the test material.

Conclusion. The test material when tested as described under 48-hour occlusive patch testing on fifty subjects appears not to produce primary (contact) irritation. Therefore, tetrahydropiperine has low skin irritation potential.

7.6 Enhancing Topical Delivery of Bioactives with THP

7.6.1 Potential Skin and Hair Care Applications

In recent years, the role of topically delivered nutrients has been of great interest to personal care formulations. This is especially true with the emerging significance of "cosmeceuticals" in cosmetics and dermatological formulations. The rapidly evol-

ing anti-aging skin care market is one area where the versatile tetrahydropiperine finds many applications. When co-administered with antioxidant herbal extracts, amino acids, and other nutrients, tetrahydropiperine is expected to effectively enhance their permeation and bioavailability.

Skin care formulations that would benefit from use of tetrahydropiperine are expected to be lotions, creams, gels, massage oils, sun protection formulations containing natural herbal extracts, minerals, growth factors, enzymes, and other nutrients. Hair care formulations that will benefit include hair oils, creams, treatment products, conditioners, styling gels, and other compositions that contain nutrients to support healthy hair.

7.7 Formulation Strategies

7.7.1 Skin Care

Suggested levels of usage in formulations range from 0.01%–0.1% in skin creams and lotions. A typical skin cream formulation is shown in Formulation 1 (see end of chapter). This formulation includes "bioprotectant" tetrahydrocurcuminoids, a colorless product derived from the yellow curcuminoids extracted from tumeric root. This material functions as a versatile antioxidant, with potential applications in anti-aging, UV protection, and skin tone lightening compositions. In addition, the formulation contains another active ingredient, a freeze-dried coconut water composition to support skin texture and effect moisturization. This extract is rich in amino acids, enzymes, and growth factors that nourish and soothe tired skin.

7.7.2 Hair Care

A base formula for a nourishing hair treatment is shown in Formulation 7.2 (see end of chapter). Herbal extracts may be included as desired. The formulation contains a freeze-dried coconut water composition to support healthy hair growth and effect moisturization. This extract is rich in amino acids, enzymes and growth factors that nourish and soothe.

7.8 Summary

The quest for novel topical delivery systems for bioactives, with emphasis on "natural" and "safe" is an area of dynamic research in the pharmaceutical, cosmetics, and nutritional fields. Tetrahydropiperine is a natural topical permeation enhancer for active

compounds. Derived from black pepper fruit, the product is effective in very small quantities (0.01%–0.1% by weight in formulations containing actives), with no irritant or sensitization side effects. The evolution of this ingredient, from concept development to its applications in formulations, is described in this chapter.

7.9 Formulations

Formulation 7.1: A Typical Skin Cream

Phase	Ingredients	Function	% w/w
A	Paraffinum liquidum	Emollient/Solvent	10.0
	Petrolatum	Emollient	1.5
	Acetylated lanolin	Emollient	2.2
	Lanolin alcohol	Emollient	1.4
	Laneth-10	Viscosity control	0.5
	Glyceryl monostearate SE	Emulsifying agent	3.0
B	Carbomer (Carbopol 940, BF Goodrich)	Viscosity modifier	0.1
	Sodium methylparaben	Preservative	0.2
	Sodium propylparaben	Preservative	0.02
	Sodium hydroxide (10%)	Buffering agent	2.5
	Water (<i>aqua</i>)	Solvent	qs 100.0
C	Tetrahydrocurcuminoids	Active	0.5%
	Tetrahydropiperine (Cosmoperine [®] , Sabinsa Corporation)	Active	0.1%
D	Coconut (<i>Cocos nucifera</i>) fruit juice (Cococin [™] , Sabinsa Corporation)	Active	2.0 (25% colloidal suspension in 1,4-butylene glycol)

Blend Phase A ingredients maintaining temperature at 80°C. Separately blend Phase B ingredients at 80°C. Add Phase C ingredients to blended Phase A, maintaining the temperature at 80°C, with agitation, and mix the blended Phases A + C with Phase B in a homogenizer until thoroughly emulsified.

Adjust the pH to neutral with citric acid solution. Cool to 50°C. Add Phase D slowly with homogenization. Cool to desired fill temperature.

Formulation 7.2: A Base Formula for a Nourishing Hair Treatment

Phase	Ingredient	Function	Weight Percent
A	Deionized water	Solvent	82.10
	Xanthan gum	Stabilizer	0.60
B	Caprylic/capric triglyceride	Emollient/Solvent	3.00
	Myristyl myristate	Emollient	3.00
	Cetyl alcohol	Emollient/solvent	1.50
	Emulsifying wax NF	Emulsifying agent	2.50
	Sodium methylparaben	Preservative	0.2
	Sodium propylparaben	Preservative	0.1
	Tetrahydropiperine (Cosmoperine [®] Sabinsa Corp)	Active	0.1
C	Coconut (<i>Cocos nucifera</i>) fruit juice (Cococin [™] , Sabinsa Corp)	Active	5.00 25% colloidal suspension in 1,4 butylene glycol
	Cyclomethicone	Antistatic agent	3.00

Heat water from Phase A to 50°C and sprinkle in xanthan gum, mixing well, and then heat mixture to 75°C. Combine ingredients of Phase B with mixing and heat to 75°C. Add Phase B to Phase A using agitation, mix for 20 minutes and maintain temperature at 70°C–75°C. Cool to 40°C, add Phase C with mixing and cool to desired fill temperature.

References

1. Goldsmith, L A , ed , Cutaneous pharmacology, pathophysiology and dermal biology, in: *Physiology, Biochemistry and Molecular Biology of the Skin*, Vol. II, Oxford University Press, New York (1991)
2. Potts, R O , Mak, V H., et al , Strategies to enhance permeability via stratum corneum lipid pathways, in: *Advances in Lipid Research*, Vol 24 (Elias, P M., ed), Academic Press (1991)
3. Sloan, K B , Wasdo, S., Designing for topical delivery: pro-drugs can make the difference., *Med. Res. Rev.*, 23:763-793 (2003)
4. Verma, D. D., Verma, S., Blume, G., Fahr, A., Liposomes increase skin penetration of entrapped and non-entrapped hydrophilic substances into human skin: a skin penetration and confocal laser scanning microscopy study, *Eur. J. Pharm. Biopharm.*, 55:271-277 (2003)
5. Verma, D D , Verma, S., Blume, G., Fahr, A., Particle size of liposomes influences dermal delivery of substances into skin, *Int. J. Pharm.*, 258:141-151 (2003)
6. Yerushalmi, N., Arau, A., Margalit, R., Molecular and cellular studies of hyaluronic acid-modified liosomes as bioadhesive carriers for topical drug delivery in wound healing, *Arch Biochem Biophys.*, 313:267-273 (1994)
7. Bieb, L. M., Ramachandran, C., Egbaria, K., Weiner, N., Topical delivery enhancement with multilamellar liposomes into pilosebaceous units, *J. Investig. Dermatol.*, 99:108-113 (1992)
8. Rangarajan, M , Zatz, J. L., Effect of formulation on the topical delivery of alpha tocopherol, *J. Cosmet. Sci.*, 54:161-174 (2003)
9. Spiclin, P, Homar, M, Zupancic, A , Gasperlin, M , Sodium ascorbyl phosphate in topical microemulsions, *Int. J. Pharm.*, 256:65-73 (2003)
10. Peltola, S., Saarinen-Savolainen, P., et al., Microemulsions for topical delivery of estradiol, *Int. J. Pharm.*, 254:99-107 (2003)
11. Ciotti, S N., Weiner, N., Follicular liposomal delivery systems, *J. Liposome Res.*, 12:143-148 (2002)
12. Majeed, et al., Use of piperine to increase the bioavailability of nutritional compounds, United States Patent No. 5,536,506 (1996)
13. Majeed et al., Use of piperine as a bio-availability enhancer, United States Patent No. 5,744,161 (1998)
14. Majeed, et al., Use of piperine as a bio-availability enhancer, United States Patent No. 5,972,382 (1999)
15. Majeed, et al., Process for making high purity piperine for nutritional use, United States Patent No. 6,054,585 (2000)
16. Johri, R. K , Zutshi, U., An Ayurvedic formulation 'Trikatu' and its constituents, *J Ethnopharm.*, 37:85-91 (1992)
17. Szallasi, A , Vanilloid (capsaicin) receptors in health and disease, *Am. J. Clin. Pathol.*, 118(1):110-121 (Jul, 2002)
18. Walker, M., Piperine in black pepper: one of a newly recognized class of thermonutrients, *Health Foods Business* (April, 1997)
19. Lee, E. B., et al., Pharmacological study on piperine, *Arch. Pharmac. Res.*, 7:127-132 (1984)
20. Dymock, W, Warden, C J. H , Hooper, D , Piper nigrum: pharmacographia Indica, published by The Institute of Health & Tibbi Research under auspices of Hamdard National Foundation, Pakistan, Vol III, 372-374 (1972)
21. Atal, C. K., Zutshi, U., Rao, P. G., Scientific evidence of the role of Ayurvedic herbals on bioavailability of drugs, *J. Ethnopharm.*, 4:229-233 (1981)
22. Atal, C. K., et al., Biochemical basis of enhanced drug availability by piperine: evidence that piperine is a potent inhibitor of drug metabolism, *J. Pharmacol. Exptal Therap.*, 232:258-262 (1985)
23. Zutshi, U., et al., Influence of piperine on rifampicin blood levels in patients with pulmonary tuberculosis, *J. Assoc. Physicians India*, 33:223-224 (1984)
24. Bano, G., et al., The effect of piperine on the pharmacokinetics of phenytoin in healthy volunteers, *Planta Medica*, 53:568-570 (1987)

25. Bano, G., et al., The effect of piperine on the bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers, *European J Clin Pharm.*, 41:615-618 (1991)
26. Badmaev, V., et al., Piperine, an alkaloid derived from black pepper, increases serum response of beta-carotene during 14 days of oral beta-carotene supplementation, *Nutrition Research*, 19(3):381-388 (1999)
27. Badmaev, V., et al., Piperine derived from black pepper increases the plasma levels of coenzyme q10 following oral supplementation, *J. Nutritional Biochemistry*, 11(2):109-113 (2000)
28. Majeed, et al., Method of increased bioavailability of nutrients and pharmaceutical preparations with tetrahydropiperine and its analogues and derivatives, United States Patent No. 6,849,645 (2005)
29. Majeed, M., et al., Bioperine®: Nature's own therrmonutrient and natural bioavailability enhancer, Nutriscience Publishers Inc. Piscataway, NJ (1999)
30. Madhusudan, P., Vandana, K. L., Tetrahydropiperine the first natural aryl pentanamide from Piper longum, *Biochemical Systematics and Ecology*, 29:537-538 (2001)
31. Loder, J. W., Moorhouse, A., and Russel, G. B., Tumor Inhibitory plants, *Australian J. Chem.*, 22:1531-1538 (1969)
32. Satyavati, G. V., Gupta, A. K., and Tandon, N., eds, *Medicinal plants of India*, Indian Council of Medical Research, New Delhi, India, 426-456 (1987)
33. Nadkarni, A. K., *Indian Materia Medica*, Popular Book Depot, Bombay, India (1954)
34. Pei, Y. Q., A review of pharmacology and clinical use of piperine and its derivatives and uses, *Epilepsia*, 24:177-181 (1983)
35. Perry, L. M., *Medicinal Plants of East and Southeast Asia Attributed Properties and Uses*, MIT Press, Cambridge (1980)
36. Charaka, et al., *Charaka Samhita*, 3rd ed., Nirnaya Sagar Press Bombay, India [in Sanskrit] (1941)
37. Vagbhat, *Ashtang Hridaya*, Chowkhamba Sanskrit Series, Varanasi, India [in Sanskrit] (1962)
38. Kaviraj, K. B., *Sushruta Samhita*, Vol. 3, 2nd ed., Chowkhamba Sanskrit Series, Varanasi, India [in Sanskrit] (1963)
39. Research Report, Sabinsa Corporation (April 2000)
40. "Studies on Transdermal Penetration Enhancement Activity of RD/TP/09" Research Report, Sami Labs Ltd. (April, 2000)
41. Research Report, Sami Labs Ltd. (May, 2000)
42. Barry, B. W., Dermatological Formulations: Percutaneous Absorption, *Drugs and the Pharmaceutical Sciences*, Vol. 18, Marcel Dekker, New York (1983)
43. Badmaev, V., and Majeed, M., Skin as a delivery system for nutrients, nutraceuticals and drugs; THP, a natural compound with the potential to enhance the bioavailability of nutrients and drugs through the skin, *Agro-Industry Hi-Tech.*, 6-10 (Jan/Feb, 2001)
44. Marjukka, S. T., Bouwstra, J. A., Urtti, A., Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations, *J. Controlled Release*, 59(2):149-161 (May 20, 1999)
45. Prokosch, F., Prokosch, E., Regulation of the epidermal permeability barrier by lipids and hyperproliferation, *Hautarzt*, 43(6):331-338 (June, 1992)
46. Wertz, P. W., Lipids and barrier function of the skin, *Acta Derm. Venereol. Suppl.*, (Stockh) 208:7-11 (2000)
47. Proksch, E., Holleran, W. M., Menon, G. K., Elias, P. M., Feingold, K. R., Barrier function regulates epidermal lipid and DNA synthesis, *Br. J. Dermatol.*, 128(5):473-482 (May, 1993)
48. Prokosch, E., The epidermis as metabolically active tissue: regulation of lipid synthesis by the barrier function, *Z. Hautkr.*, 65(3):296-300 (Mar, 1990)
49. Tsai, J. C., Guy, R. H., Thornfeldt, C. R., Gao, W. N., Feingold, K. R., Elias, P. M., Metabolic approaches to enhance transdermal drug delivery; 1. Effect of lipid synthesis inhibitors, *J. Pharm Sci.*, 85(6):643-648 (Jun. 1996)

50. Schneider, I. M., Wohlrab, W., Neubert, R., Fatty acids and the epidermis, *Hautarzt* 48(5):303-310 (May, 1997)
51. Hadgraft, J., Passive enhancement strategies in topical and transdermal drug delivery, *Int J. Pharm.*, 184(1):1-6 (Jul. 5, 1999)
52. Golden, G. M., McKie, J. E., Potts, R. O., Role of stratum corneum lipid fluidity in transdermal drug flux, *J. Pharm. Sci.*, 76(1):25-28 (Jan. 1987)
53. Short, S. M., Rubas, W., Paasch, B. D., Mrsny, R. J., Transport of biologically active interferon-gamma across human skin in vitro, *Pharm. Res.*, 12(8):1140-1145 (Aug. 1995)
54. Bos, J. D., Meinardi, M. M., The 500 Dalton rule for the skin penetration of chemical com-

DELIVERY SYSTEM HANDBOOK FOR PERSONAL CARE AND COSMETIC PRODUCTS

Technology, Applications, and Formulations

Edited by
Meyer R. Rosen

NEW SERIES: Breakthroughs in Personal Care and Cosmetic Technology

DESCRIPTION

Novel delivery systems designed to facilitate the use of "fountain of youth" and other functional actives is an idea whose time has come. In a rapidly growing global market eager for products that really work, accelerating market pull and technology push forces have set the stage for this Foundation text. This "must have" book is the first volume of a new series entitled "Breakthroughs in Personal Care and Cosmetic Technology." It has been carefully designed for training, development, and the empowerment of synergistic technology transfer across the personal care, cosmetic, and pharmaceutical industries.

This book is intended to cause a breakthrough in effective communication and interaction among technology and marketing functions. It is a showcase for understanding, using, and marketing the technology of why and how delivery systems work, as well as current, emerging/potential applications and working formulations. Each chapter is written by one or more experts in the field. A wide range of companies serving the global marketplace are represented. These companies offer numerous types of delivery systems containing highly desirable functional actives, delivery system technology development services, and opportunities for technology licensing, mergers, and acquisitions. A unique feature of the book is the use of **Mind Map™ technology** to capture and present the essence of the inner-thinking of **over 80 authors** in a **Book-at-a-Glance Executive Overview** section. This section has been specifically designed to powerfully impact decision making leading to the development of innovative product differentiation in a global context.

AUDIENCE

This book is designed to be of high interest to the entire team responsible for creating and bringing to market novel Personal Care, Cosmetic, and Pharmaceutical products. This includes scientists and technologists as well as those involved in market development and business management. It will also be of interest to those who use products that contain delivery systems, such as dermatologists, academic researchers, and pharmaceutical scientists.

ABOUT THE EDITOR

Meyer R. Rosen is President of Interactive Consulting, Inc. (www.chemicalconsult.com). Among his many distinctions, he is a Fellow of the American Institute of Chemists; a Fellow of the Royal Society of Chemistry (London), and a Fellow of the American College of Forensic Examiners. Mr. Rosen holds national certifications as both a professional chemist and professional chemical engineer. He has been Technical Advisor and Moderator for the HBA Global Beauty Expo, Chemical Week's Global Beauty Congress, and moderator for the PCITX product development conferences. His firm provides management and technology solutions such as custom market research, "out of the box" ideation sessions, and market/applications development services. Product areas served include consumer, household, personal care, cosmetic, industrial, pharmaceutical, and medical. Mr. Rosen has published over 40 technical papers and holds over 20 patents. He has written numerous articles for *Chemical Market Reporter*, *DCI*, *Global Cosmetic Industry*, *HAPPI* magazine, and *Specialty Chemicals (UK)*. Mr. Rosen is the coauthor of the *Rheology Modifiers Handbook: Practical Use and Application* from William Andrew Publishing.

BREAKTHROUGHS IN PERSONAL CARE AND COSMETIC TECHNOLOGY – A NEW BOOK SERIES

This new series of books is intended for scientists, engineers, technicians, business managers, and marketing personnel. It focuses on the technologies used in the personal care and pharmaceutical industries and highlights the value of technology transfer among them. The intention of the series is to mentor, educate, and act as a catalyst for the generation of new ideas and applications yet to come. The books will cover technology, formulations, ingredients, labeling, manufacturing, equipment, processing, and packaging. They will balance the practical and theoretical with a clear emphasis on the practical. The range of book topics will include, but not be limited to: fundamental and practical aspects of delivery systems, bioengineering, and fermentation processes, biocides, and emulsifying agents. It will also include surface and interfacial science and technology, naturals and botanicals, fragrances, cosmeceuticals, and legal/regulatory and testing topics.



13 Eaton Avenue
Norwich, NY 13815
www.williamandrew.com

ISBN 0-8155-1504-9

