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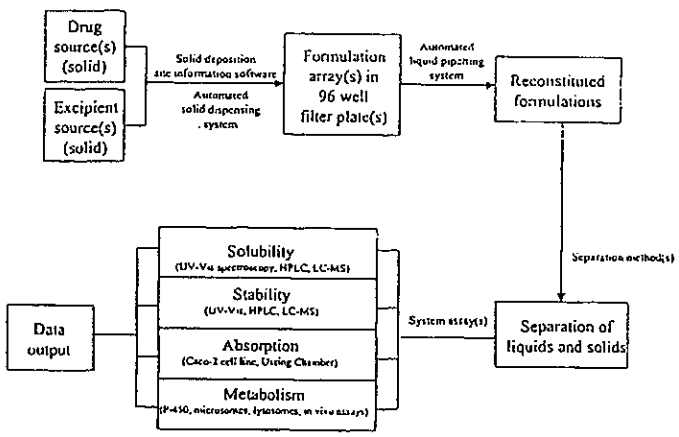
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(57) Abstract

Methods have been developed which use high throughput combinatorial formulation technologies, preferably in combination with nanotechnology and microarrays, to improve one or more properties of materials used as components of, or in the manufacture or use of, health care products, consumer products, agricultural products, nutraceutical products, veterinary products, products for use in manufacturing or processing industries, military applications, and research reagents. In a preferred application, the bioavailability and pharmacokinetics of the drugs, especially small molecule pharmaceuticals, are optimized by making many new formulations and selecting those formulations based on one or more physical or chemical properties such as solubility in an aqueous solution, without compromising selectivity or potency. Systems employing these technologies have been designed to rapidly, systematically and cheap identify optimal compositions for a desired purpose. In one preferred embodiment, new formulations are prepared and tested for bioequivalence to a formulation that is approved or commercially available. In another embodiment, the formulations are initially optimized *in vitro* for their pharmacokinetics, such as absorption through the gut (for an oral preparation), skin (for transdermal application), or mucosa (for nasal, buccal, vaginal or rectal formulation), solubility, degradation or clearance by uptake into the reticuloendothelial system ("RES"), metabolism or elimination, then tested *in vivo*.

FORMULATION ARRAYS AND USE THEREOF

Background of the Invention

This invention is generally in the field of methods and systems for developing optimized formulations for health care products, consumer products, agricultural products, nutraceutical products, pharmaceutical formulations, veterinary products, foods, research reagents, and industrial products, by simultaneous and sequential processing and assaying of formulations.

Most drug formulations are developed by adaptation of existing formulations to new drugs to achieve the desired delivery characteristics. For example, compounds that are to be delivered orally are usually packaged in a capsule or tablet, optionally including an enteric coating or controlled release formulation. Compounds that are to be delivered topically are formulated in a gel or transdermal patch, again using a carrier that has previously been developed for delivery of other drugs. Even the numerous systems developed for controlled release are typically selected initially based on their general characteristics, then tests conducted using the particular drug to be delivered, with minor changes, to result in an acceptable formulation. Presently, even defining the best dosage is more a matter of selecting a few representative values within a range, testing these dosages, then selecting the best of the few that have been tested.

In most cases, there are only ten to twenty formulation alternatives. It is readily apparent that twenty percent of the top fifty selling drugs would benefit from improved pharmacokinetics (absorption, distribution, metabolism, and/or excretion). Pharmacokinetics mathematically describes the amount of drug present in the bloodstream over time and significantly impacts a drug's efficacy and safety profile. Improved pharmacokinetics could increase compliance and lower healthcare costs.

Optimal formulations can be developed by taking into consideration the solubility and stability of the drug to be delivered, the biological properties of the drug, the release or delivery requirements, the ease of

manufacturing, the avoidance of systemic toxicity due to the components of the formulation, and many other factors, such as cost of manufacture, and even packaging requirements. Some products require only freeze drying for the formulation, but the packaging is critical to keeping the final product dry or to avoid light or other factors negatively impacting stability.

Even formulations for cosmetics or fragrances are a hit or miss affair, with a variety of mixtures being randomly designed and haphazardly tested.

This random process usually results in a formulation that achieves the desired result. It is rarely the best result, however, since it would be too expensive and time consuming to formulate a drug, test the delivery characteristics as well as preservation of the biological characteristics, reformulate the drug, re-test the delivery characteristics and biological properties, and keep repeating the process until the best formulation is achieved, rather than just an acceptable formulation.

It is therefore an object of the present invention to provide a process and system for automatic, systematic processing of materials or formulations to improve one or more properties of the materials used as components of, or in the manufacture or use of, health care products, consumer products, agricultural products, nutraceutical products, veterinary products, products for use in manufacturing or processing industries, military applications, and research reagents.

Summary of the Invention

Methods have been developed which use high throughput combinatorial formulation technologies, preferably in combination with nanotechnology and microarrays, to improve one or more properties of materials used as components of, or in the manufacture or use of, health care products, consumer products, agricultural products, nutraceutical products, veterinary products, products for use in manufacturing or processing industries, military applications, and research reagents. In a preferred application, the bioavailability and pharmacokinetics of drugs, especially small molecule pharmaceuticals, are optimized by making many new formulations and selecting those formulations based on one or more physical

or chemical properties such as solubility in an aqueous solution, without compromising selectivity or potency. Systems employing these technologies have been designed to rapidly, systematically and cheaply identify optimal compositions for a desired purpose.

In a first aspect, the invention provides an array of multiple formulations, wherein: a) the formulations are located at separate sites or in separate wells, b) each formulation comprises a different mixture of at least two materials having known functions, activities or properties, each mixture varying in the concentration or composition of at least one material, c) the array is comprised of more than 1000 different formulations, d) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and e) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, activity, chemical or physical properties.

In a second aspect, the invention provides an automatic multiple processing for preparing an array of multiple formulations, the system comprising:

a) a formulation test array of multiple formulations, wherein:
   1) the formulations are located at separate sites or in separate wells,
   2) each formulation comprises a different mixture of at least two materials having known functions, activities, or properties, each mixture varying in the concentration or composition of at least one material,
   3) the array is comprised of more than 1000 different formulations,
   4) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and
   5) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, activity, chemical or physical properties,
b) a reservoir means for storage of formulation components,
c) a means for inputting formulation components from the reservoir means to the formulation test array, and
d) a processing means for controlling the formulation components inputted into each well or at each site of the formulation test array from the reservoir means so that each formulation comprises at least one material in common but has a different formulation.

In a third aspect, the invention provides a method of determining a formulation comprising two or more materials having one or more desirable characteristics, the method comprising:

a) identifying a compound to be formulated

b) selecting the materials to make the formulation,

c) identifying at least one functional, biological, physical or chemical characteristic to screen the formulation for, and

d) formulating the materials into an array of multiple formulations, wherein:

1) the formulations are located at separate sites or in separate wells,

2) each formulation comprises a different mixture of at least two materials, at least one having a known function, activity, or property, each mixture varying in the concentration or composition of at least one material,

3) the array is comprised of more than 1000 different formulations,

4) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and

5) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, chemical or physical properties.

In one preferred embodiment, new formulations are prepared and tested for bioequivalence to a formulation that is approved or commercially available. In another embodiment, the formulations are initially optimized *in vitro* for their pharmacokinetics, such as absorption through the gut (for an oral preparation), skin (for transdermal application), or mucosa (for nasal, buccal, vaginal or rectal formulation), solubility, degradation or clearance by uptake into the reticuloendothelial system ("RES"), metabolism or elimination, then tested *in vivo*. In another preferred embodiment, the formulation is optimized based on microstructure of the drug, the carrier, or the combination of the two components.

Microstructure includes crystalline or amorphous structures, or combinations thereof, polymorphs, solvates, hydrates, isomorphic desolvates, glasses, solid solutions, and specific unit cells such as hexagonal packing orders, ionic crystals, holes or interstitial spaces, and lattices. Other microstructures can include, or be influenced by the presence of, structures such as enantiomers or racemic forms or mixtures, of the active agents.

Brief Description of the Drawings

Figure 1 is a schematic of the method to optimize formulations.

Figures 2a and 2b is a more detailed schematic of a process to formulate and analyze multiple samples, for parameters such as solubility (UV-Vis HPLC) and oral absorbance, wherein Figure 2a is a schematic of the process wherein solids are deposited in the array, then reconstituted and screened; and Figure 2b is a schematic of the process wherein liquids are deposited into an array, dried, reconstituted and then separated into liquids and solids and screened.

Figure 3a is a graph of the solubility (absorbance) of 3,500 unique formulations containing antibiotic-antifungal with various excipients in

water. Figure 3b is a graph of the data in Figure 3a plotted to show standard deviations for each of the unique formulations.

Figure 4 is a graph comparing solubility (absorbance) of the commercially available drug with five lead formulations (TPI-1 to TPI-5).

Figure 5 is a graph of the ratio of the solubility of various reformulations of one of the lead formulations, TPI-3, reformulated with only one or two of the three excipients shown in relative ratios in the accompanying "pie".

Figure 6 is a graph of the ratio of the solubility of various reformulations of a lead formulation, TPI-1, comparing the effect of reformulating the formulation with one or two of the three excipients in the lead formulation, demonstrating that some excipients actually decrease solubility.

Figure 7 is a graph of the ratio of the solubility of various reformulations of one lead formulation, TPI-2, showing the effect of reformulating the formulation with one or two of the three excipients in the lead formulation, demonstrating that some excipients have a synergistic effect on solubility.

Figure 8 is a graph comparing rates of dissolution and equilibrium solubilities for TPI-2 and the antibiotic-antifungal, showing TPI-2 having a higher rate of dissolution as well as a higher equilibrium solubility compared to the antibiotic-antifungal.

Detailed Description of the Invention

Methods have been developed to optimize formulations to improve one or more properties of materials used as components of, or in the manufacture or use of, pharmaceutical and veterinary products, nutraceutical products, health care products, consumer products, agricultural products, industrial applications, military applications, and research reagents. In a preferred application, the bioavailability and pharmacokinetics of drugs are enhanced by reformulation of the drug with one or more excipients. The method includes the initial step of selecting one or more variables of a drug formulation to be optimized, then formulating the drug using a large number

of combinations of the variable(s) to create a formulation library within an array and screening for the desired bioactivity, physical, chemical or other properties. These methods result in formulations with improved oral bioavailability, expanded therapeutic indices, fewer side effects, or earlier in discovery, and can be used to obtain additional patent protection and achieve regulatory compliance for known compounds using bioequivalent formulations.

In general terms, the methods include the steps of identifying one or more active compounds which are to be formulated (or reformulated); selecting at least one criteria for optimization such as poor bioavailability (due to poor solubility, absorption or metabolism); screening a large number of different combinations of active components (based on different dosages, carriers, packaging, combinations with other actives) and/or excipients preferably using *in vitro* microarray technology to select a small number of the best candidate formulations; then screening these candidates using *in vivo* animal and human models. The screening can be performed at very high inputs – for example, more than 100,000 formulations / day.

As used herein, compositions refer to combinations of two or more components. The compositions, not the components, are subjected to screening to determine the optimal formulations. This is not a screening technique to identify compounds having a particular activity, but rather screening of novel formulations of known compounds to identify those formulations with the most desirable properties. As used herein, nanoscale refers to formulations or components thereof being present in individual formulations in nanogram quantities; microscale refers to formulations or components thereof being present in individual formulations in microgram quantities. "Microarrays" refer to array plates, reservoirs or other sample retaining means for many very small quantities at separate sites on or in a support means. Sample formulations typically consist of less than one gram (1000 mg). In a preferred embodiment, the samples consist of less than 100 micrograms (either of individual components or the formulation as a whole). In a more preferred embodiment, the samples consist of less than 25

micrograms. "High throughput" refers to the number of samples generated or screened as described herein, typically at least 10, more typically at least 50 to 100, and preferably more than 1000 samples. "Automated" refers to either high throughput in the range of 100 or more samples being generated or generation using software to formulate the samples.

As discussed in more detail below, components can be biologically active molecules such as nucleotide molecules, proteins or peptides, polysaccharides or sugars, or combinations thereof, foods, nutrients, cosmetics or fragrances, dyes. Components can also be carriers for delivery of drugs, reagents for stabilization or excipients altering release, or even packaging or processing reagents or variables. For industrial applications, components can be catalysts, surfactants, optical enhancers, dyes, and other common ingredients of materials such as detergents, coatings, paints, and lubricants. For agricultural applications, the components may be herbicides, pesticides, fertilizers or growth enhancers, as well as oils, stabilizers, and surfactants which are important to application, stability and function of the active ingredients.

As used herein, compositions refer to mixtures of two or more components or to a library in which one or more variable such as concentration of one or more component is varied. In the preferred embodiment, the libraries are constructed using systematic combinations of two or more components, for example, by varying concentrations of drug and selection and concentration of one or more excipients, as demonstrated in the following examples, in a grid or array (i.e., an ordered set of components) such as a 96 well plate, nano- or microarray. Preferably the system is automated to control mixing or blending of the components. Alternatively, the compositions can be prepared prior to insertion into the grid for testing, for example, drug containing microspheres could be prepared by varying drug concentration in an aerosol which is spray dried into each well, yielding microspheres of drug within a carrier matrix, each having a different drug concentration. Once constructed, the libraries are screened using automated screens, for example, testing initially for solubility (for example by optical

absorbance), then testing lead candidates for oral absorption and then bioavailability using additional *in vitro* screening or animal testing. Testing can be done simultaneously or sequentially. Multiple formulations will typically be identified at each step of the testing, then subjected to additional testing. These compositions are further analyzed to determine the optimal formulations or combinations of components in the formulations.

I. Components of the Formulations.

Components can be generally divided into active components, such as drugs, foods, nutrients, cosmetics or fragrances, and other components which may affect stability, solubility or rate of dissolution, release, or pharmacokinetics. Other components can be physical or chemical components that are used to alter the final composition. For example, components may be materials used as drug carriers, hygroscopic compounds to lower water content of materials in the formulation as packaged or packaging which maintains a particular water content, reactants which are inert in the composition when initially formulated but which are intended to alter the composition at its ultimate site of application or use, such as pore forming agents and pH modifying compounds, stabilizers, components which increase adhesion at the site of application, surfactants which enhance solubility, dispersion, or dissolution, etc. As used herein, solubility refers to the equilibrium solubility or steady state (and is usually measured as amount/volume solvent) and dissolution refers to the rate of dissolution (which is usually measured as amount/volume/unit time).

A. Pharmaceutical and Veterinary Formulations

As described herein, the goal is to obtain formulations which are optimized for an intended purpose. Representative purposes include chemical and/or physical stability of the drug and/or formulation during manufacturing, packaging, distribution, storage and administration (as it relates to the active component(s) as well as to the formulation as a whole, and components thereof), drug uptake, drug half-life after administration to a patient, pharmaceutical properties, delivery kinetics, and other factors which determine the efficacy and economics of a drug. In some cases the drug may

have a single property that negatively affects uptake, such as hydrophobicity or low solubility. In other cases, it may be a combination of properties. Accordingly, the screening process will typically vary at least one component of the formulation, and more typically, multiple components of the formulation, and select based on one or more properties of the formulation as a whole.

Therapeutic, Prophylactic and Diagnostic Materials

As used herein, bioactive molecules include therapeutic, prophylactic and diagnostic molecules, which can be proteins or peptides, nucleosides or nucleotide molecules, polysaccharides or sugars, or synthetic chemical entities, or combinations thereof. In a preferred embodiment, the bioactives are drugs. In the most preferred embodiment, the drugs are small molecule drugs. Preferred drugs are those which are already approved for at least one indication. Most preferred drugs are those which can be administered orally, and which exhibit undesirable stability, processing, bioavailability or taste characteristics (due to problems with dissolution, absorption, duration, or other) that can be modified by reformulation. Examples include ZOCAR® or simvastatin, a statin administered orally in tablet form to lower cholesterol, which is characterized by very low solubility in water, and undergoes extensive first pass metabolism in the liver. Another example is LOSEC® or omeprazole, distributed as enteric coated granules in capsules, with poor absorption due to presystemic metabolism. Other drugs of particular interest are PROZAC® or fluoxetine hydrochloride and VASOTEC® or enalapril meleate. Prozac is a well known antidepressant with a slow rate of dissolution, limited solubility, and slow absorption. VASOTEC® is an antihypertensive characterized by degradation during storage, presumably due to hydrolysis, with only about 60% absorption. PRILOSEC® or omeprazole is slowly absorbed and undergoes extensive metabolism in the liver. CLARITIN® or loratidine, an antihistamine, is insoluble in water and therefore formulated as micronized drug, which is rapidly absorbed then undergoes extensive first pass metabolism. PAXIL® or paroxetine hydrochloride is extensively metabolized following oral administration. CIPRO® or ciprofloxacin is practically

insoluble in water, absorption is affected by ingestion of food, and it has a short half-life. PRAVACHOL® or pravastatin is another statin drug characterized by highly variable bioavailability due to extensive first pass metabolism by the liver. Other drugs characterized by extreme variability include VOLTAREN-XR® and ADALAT CC®. Others with poor dissolution properties are NORVASC® and SANDIMMUNE® (cyclosporin). Cyclosporin exhibits extremely variable absorption, regardless of its formulation. Other drugs with poor absorption include ZOVIRAX® and ZESTRIL®. TAXOL® or paclitaxel is another drug in which formulation plays an important role due to its lack of water solubility and highly lipophilic properties. S till other drugs are the complex "natural" formulations such as PREMARIN®, a mixture of conjugated estrogens similar to that in pregnant mare urine.

Other drugs which can be advantageously reformulated are those which exhibit properties such as noxious taste, for example, BIAXIN® or clarithromycin, a crystalline macrolide antibiotic that is practically insoluble in water.

Representative veterinary pharmaceuticals include vaccines, antibiotics, growth enhancing agents, dewormers such as IVERMECTIN® and STRONGID®, and systemic and topical pesticides.

Diagnostic agents include contrast agents for use with ultrasound, x-rays, fluorescence, MRI, CT, and other techniques known to those skilled in the art. Formulation of these materials is typically critical for effective delivery, detection sensitivity, targeting to an intended site, and for improved comfort to the patient.

Research Reagents

Many of the same types of materials which are useful as pharmaceuticals and diagnostics can also be used as research reagents. These materials do not need to include GRAS or FDA approved components, and typically will not have issues relating to pharmacokinetics. Examples include antibodies, labels for proteins or oligonucleotides, buffers, enzymes, and other reagents used in laboratory studies.

Pharmaceutically or Food Grade Acceptable Carriers

Bioactive materials such as drugs, diagnostics, and nutraceuticals can be formulated as tablets, powders, particles, solutions, suspensions, patches, capsules, with coatings, excipients, or packaging which further affects the delivery properties, the biological properties, and stability during storage.

A variety of materials are known for use in tablets as filler or binders, wet binders, lubricants, disintegrating agents, glidants, stabilizers, wetting agents, and other ingredients. Representative fillers/binders include lactose, micro-crystalline cellulose, calcium phosphate, dibasic and tribasic phosphate, sucrose, pregelatinized starch, mannitol, sorbitol, calcium sulfate, dihydrate, ethyl cellulose, and polyethylene glycols. Representative wet binders include acacia, gelatin, starch, pregelatinized starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose. Lubricants include magnesium stearate, stearic acid, hydrogenated vegetable oils, sodium stearyl fumarate, mineral oil, talc, calcium stearate, polyethylene glycol, and propylene glycol. Disintegrating agents include starch, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, modified starch (EXPLOTAB®, PRIMOGEL®) and cross-linked polyvinylpyrrolidone. Glidants include talc and silicas (silica gel, CABOSIL®). Stabilizers include butylated hydroxyanisole, butylated hydroxytoluene, EDTA, ascorbic acid, sodium bisulfite, sodium metabisulfite, and propyl gallate. Wetting agents include dioctyl sodiumsulfosuccinate, sodium lauryl sulfate, polyoxyethylene sorbitan esters (e.g., polysorbate 80), and lecithin. Other ingredients include enteric coatings, extended release materials, etc., which usually dissolve at specific pH levels or after extended exposure to GA contents. The materials typically consist of natural polymers such as synthetic cellulosic polymer derivatives, waxes, glycerol esters of long chain fatty acids, and synthetic polymers such as polyvinyl acetate.

Materials used in hard gelatin capsules as fillers include lactose and anhydrose lactose, starches such as microcrystalline cellulose, disintigrants such as pregelatinzed starch, sodium starch glycolate, cross-linked sodium

carboxymethyl cellulose, and cross-linked polyvinylpyrrolidone, and wetting agents such as polyoxyethylene sorbitan esters, sodium lauryl sulfate, dioctyl sodium, sulfosuccinate, polyoxyethylene/propylene copolymers (PLURONICS®, BASF), and polyethylene glycols.

Controlled or sustained release formulations typically incorporate a matrix of polymer, polysaccharide or sugar, as described above, or other material which can be used to encapsulate or entrap the drug or other bioactive to be released. The matrix can be in the form of pellets, tablets, slabs, rods, disks, hemispheres, or microparticles, or be of an undefined shape. As used herein, the term microparticle includes microspheres and microcapsules, as well as microparticles, unless otherwise specified.

The matrix can be formed of non-biodegradable or biodegradable matrices, although biodegradable matrices are preferred, particularly for parenteral administration. Non-erodible polymers may be used for oral administration. Matrices may be formed of simple sugars or polysaccharides, as described before, or polymers have defined release characteristics employed. In general, synthetic polymers are preferred due to more reproducible synthesis and degradation, although natural polymers may be used and have equivalent or even better properties, especially some of the natural biopolymers which degrade by hydrolysis, such as polyhydroxybutyrate. The polymer is selected based on the time required for *in vivo* stability, *i.e.* that time required for distribution to the site where delivery is desired, and the time desired for delivery.

Representative synthetic polymers are: poly(hydroxy acids) such as poly(lactic acid), poly(glycolic acid), and poly(lactic acid-co-glycolic acid), poly(lactide), poly(glycolide), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, polyamides, polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol), polyalkylene oxides such as poly(ethylene oxide), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides such as poly(vinyl chloride), polyvinylpyrrolidone, polysiloxanes, poly(vinyl alcohols),

poly(vinyl acetate), polystyrene, polyurethanes and co-polymers thereof, derivativized celluloses such as alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, and cellulose sulphate sodium salt (jointly referred to herein as "synthetic celluloses"), polymers of acrylic acid, methacrylic acid or copolymers or derivatives thereof including esters, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), poly(butyric acid), poly(valeric acid), and poly(lactide-co-caprolactone), copolymers and blends thereof. As used herein, "derivatives" include polymers having substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art.

Examples of preferred biodegradable polymers include polymers of hydroxy acids such as lactic acid and glycolic acid, and copolymers with PEG, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), blends and copolymers thereof.

Examples of preferred natural polymers include proteins such as albumin and prolamines, for example, zein, and polysaccharides such as alginate, cellulose and polyhydroxyalkanoates, for example, polyhydroxybutyrate.

Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, polyamides, copolymers and mixtures thereof.

Bioadhesive polymers of particular interest for use in targeting of mucosal surfaces, as in the gastrointestinal tract, include polyanhydrides, polyacrylic acid, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Solvents

A solvent for the polymer or other carrier, or in some cases for the bioactive component, is selected based on its biocompatibility as well as the solubility of the polymer and where appropriate, interaction with the agent to be delivered. For example, the ease with which the agent is dissolved in the solvent and the lack of detrimental effects of the solvent on the agent to be delivered are factors to consider in selecting the solvent. Aqueous solvents can be used to make matrices formed of water soluble polymers. Organic solvents will typically be used to dissolve hydrophobic and some hydrophilic polymers. Preferred organic solvents are volatile or have a relatively low boiling point or can be removed under vacuum and which are acceptable for administration to humans in trace amounts, such as methylene chloride. Other solvents, such as ethyl acetate, ethanol, methanol, dimethyl formamide (DMF), acetone, acetonitrile, tetrahydrofuran (THF), acetic acid, dimethyl sulfoxide (DMSO) and chloroform, and combinations thereof, also may be utilized. Preferred solvents are those rated as class 3 residual solvents by the Food and Drug Administration, as published in the Federal Register vol. 62, number 85, pp. 24301-24309 (May 1997).

Solvents for drugs that are administered parenterally or as a solution or suspension will more typically be distilled water, buffered saline, Lactated Ringer's or some other pharmaceutically acceptable carrier.

Many other types of formulations can be used, including polymers and other materials such as mineral oil or petrolatum, to form coatings, ointments, salves, "jellies" or even transdermal patches, particularly for

application to skin, mucosal surfaces (vaginal, rectal, nasal, pulmonary) or where controlled release is desired.

Other components include pH modifiers, viscosity modifying agents, solubility enhancers, antioxidants, colorants, and dyes.

B. Nutrients, Nutraceuticals and Food Products

Nutrients and food products which may be formulated include vitamins, herbal remedies, spices, colorings, antioxidants and other preservatives, and materials which modify aggregation, improve storage, enhance flavors, or address processing issues. Nutrients may be vitamin formulations, fertilizers or growth enhancers for plant or tissue culture, or media for cell culture or bacterial fermentation.

Carriers and excipients include many of those useful in pharmaceutical preparations, as well as starches, sugars such as lactose, and emollients, as well as stabilizers, antioxidants, and pH modifying agents.

C. Health Care Products, Cosmetics and Perfumes

Health care products include items such as deodorants, cleansers, cosmetics, feminine products, lotions, shampoos, and hair care items.

Representative components of deodorants include drying agents such as aluminum zirconium and carriers such as sodium bicarbonate, starches and polysaccharides such as corn starch, lubricants such as cyclomethicone, fragrances, propylene carbonate, silica and quaterium complexes. Cleansers include materials such as alcohol, water, glycerin, menthol, sodium borate, dyes such as d&c violet No. 2 or 33, and d&c No. 6. Hair care products include materials such as herbal extracts, surfactants such as cetyl dimethicone, polyglyceryl-4 isostearate, dydrogenated castor oil, cetearyl methicone, and antioxidants.sunscreens such as propylparaben. Shampoos may include materials such as alcohol, surfactants such as cyclopentasiloxane, and dimethicone, protein such as hydrolyzed collagen, fragrances, and chelating agents such as ethylenediaminotetraacetic acid (EDTA).

Cosmetics and perfumes are usually complex mixtures that may be as simple as mixtures of tints or scents, but more commonly include multiple components that affect skin, such as hydroxy acids, absorption, prevent

bacterial growth, and stability of the "active" components such as antioxidants, as well as colors or pigments and compounds altering the viscosity or rheological properties (including compounds which prevent aggregation, increase fluidity or fluid flow).

Many of the same components present in pharmaceutical compositions can be included in cosmetics or perfumes as carriers.

D. Consumer and Industrial Products

Industrial products cover a wide range of materials from household cleaning products such as dishwashing detergents and cleaners to oils and other lubricants for cars and other machinery, to reagents for making and cleaning silicon chips for use in computers and coatings for computer monitors and car windshields to block glare, paints, dyes, adhesives and lubricants, and materials used in the construction industry such as concretes and bulking agents, etc.. Specific applications are in those industries involved in the manufacturing and/or processing of equipment, optical devices, electronic devices, appliances, computers and related hardware, as well as materials used in the operation of these. Further applications include batteries, matches (i.e., combustibles), and light-emitting chemiluminescent materials, as well as any of the multitude of applications of fibers. Other applications include catalysts and enzymes used in industrial processing. New ceramic and polymeric materials can also be formulated.

E. Military Applications

Military applications include materials for biological warfare (biologicals and nerve gases), defenses against biological warfare, coatings that protect or enhance visibility (such as coatings on night vision glasses or gun scopes), and weapons (such as improved munitions formulations, including combustibles, ammunition and explosives).

F. Packaging and Processing Conditions

Although described herein primarily with reference to formulations containing one or more active components, the high throughput formulating techniques and screening assays can also be used to compare the efficacy of various formulation conditions, for example, the effects of different solvents,

pH, water content, excipients, and means for formulation used to prepare or store the formulation. The assays can also be used to compare packaging. It is well known that these factors can be critical to the usefulness and economics of a drug formulation, but these factors are usually not assessed, or they are assessed using a random sampling process, not a systematic, rapid comparison that allows for determination of the optimal manufacturing process, packaging, or storage conditions. Variables involved in packaging include water permeability, water content, light transfer, oxygen permeability or permeability to solvent. Exemplary variables involved in processing conditions include selection of the formulation process (freeze drying, dialysis, rate of stirring of drug or carrier in solvent, selection of pH or salt concentrations, etc.). Exemplary variables in stability to storage include inclusion of stabilizers such as antioxidants, materials which exclude light from reaching the formulation components, coatings on the interior walls of containers that prevent adhesion or diffusion, and addition of desiccants.

II. Screening of Multiple Variables

A. System Design

Assuming three hundred substances, even with no variations in concentrations and no physical parameter variations, the number of possible combinations is enormous: for two components, there are 44,850 possible combinations, for three components there are 4,455,100 combinations, and for four components, there are 330,791,175 possible combinations. The complexity is increased when the relative abundance of each component is considered and varied. It is well established that combinations of two or more compounds may be extremely beneficial. For example, the combination of cyclosporin A and vitamin E doubles blood levels while cutting oral clearance in half.

As described herein, the goal is not to identify the activity of a known compound, but to make combinations (i.e., formulations) which optimize a desired characteristic of the formulation, such as the bioactivity of a drug under the conditions where it is to be administered. This is normally a tedious process, where each variable is separately assessed, at several points over a

range of conditions or combinations. As described in more detail below, the process includes:

(1) selecting a formulation or active component thereof,

(2) determining which variables (i.e., components and/or their concentrations) can be altered, and then

(3) setting up "a grid" which automatically makes a very large number of combinations which are automatically tested for one or more variables. For example, if the formulation contains a drug characterized by poor oral uptake, the solubility of the drug in a range of salt concentrations; pHs; carriers; and drug concentrations are simultaneous prepared and tested. The key to the process is the use of technologies that can make many combinations at the same time, then automatically feeding each combination into a system for assaying which combinations have the most desirable properties, for example, stability of activity over time during storage, stability during processing (manufacturing, packaging, or during application, and under physiological conditions; solubility; oral absorption (or whatever is appropriate); or function (metabolism, half-life, release characteristics -blood levels). Mechanical properties of drug and food formulations to screen for include taste, size, shape, texture, smell, color, and coatings (such as enteric coatings). Properties for non-medical applications such as household and industrial products include coatings which resist stains, have increased surfactant properties, or better stability.

In a preferred embodiment to select optimal drug formulations for oral delivery, a system assays formulations based on physical parameters, absorption, and metabolism, all using simple, rapid, *in vitro* testing. In a simple embodiment, the various combinations are first screened for solubility, by measuring the rate of dissolution. Those candidates which look promising can then be tested directly in animals or screened for other physical or chemical properties, for example, permeability - passage across the gastrointestinal tract into the blood or lymph systems or into specialized tissues such as the Peyer's patches - using a system such as an Ussing chamber. Metabolism of the

compounds can also be tested. Compounds to be screened initially include both compounds with poor solubility and permeability.

Physical parameters include solubility, dissolution, and microstructure, as well as stability over time, to heat, ultraviolet radiation, oxygen, etc. Microstructures includes crystalline or amorphous structures, or combinations thereof, polymorphs, solvates, hydrates, isomorphic desolvates, glasses, solid solutions, and specific unit cells such as hexagonal packing orders, ionic crystals, holes or interstitial spaces, and lattices. Crystal habits can include rods, needles, spheres, plates, cubes, and combinations thereof. Crystal forms of the active agents, or formulations, can be used to produce pharmaceuticals with superior pharmaceutical properties. Other microstructures can include, or be influenced by the inclusion of, enantiomers or racemic forms or mixtures, of the active agents. Modifying the microstructure can be used to modify uptake, solubility, dissolution, stability including shelf life, bioavailability, metabolism, and formulation manufacturing properties such as compression parameters, bulk powder flow (such as lubrication and dispersion), spatial orientation of crystals in a bulk powder, and purity of the active agent. Crystallinity variants can be produced by changing crystallization, desolvation, solvent vapor, freeze drying, heating, melting, milling, precipitation, quench cooling, slurry conversion, spray drying, solid dispersion, and wet granulation. Unique polymorphs of drug crystal forms with improved pharmaceutical properties can be obtained by chemical variations (i.e., co-solvents) or physical variation (i.e., temperature).

The same issues are also applicable to some non-pharmaceutical materials, such as silicon wafers and photography.

Solubility can be measured using standard technology such as optical density or by colorimetry. Absorption can be measured using an *in vitro* assay such as an Ussing chamber containing HT Caco-2/MS engineered cells (Lennernas, H, J. Pharm. Sci. 87(4), 403-410 (April 1998). As used in this context, permeability generally refers to the permeability of the intestinal wall with respect to the drug, i.e., how much drug gets through. Metabolism can be measured using digestive enzymes and cell lines, such as hepatoma cell lines

which are indicative of the effect of the liver on drug metabolism. Variants of crystallinity can be detected using standard techniques such as solid state spectroscopy, including infrared, Raman, NMR, in a microarray format, or crystallography, x-ray, neutron diffraction, powder x-ray diffraction, light microscopy, electron microscopy, differential scanning calorimetry, thermal gravimetric analysis, and combinations thereof.

In another preferred embodiment to select optimal formulations for oral delivery, high throughput ("HT") dosages are mixed, distributed, and lyophilized, put into different forms (powder versus emulsion) then assayed.

In vitro screening, as used herein, includes testing for any number of physiological or biological activities, whether known or later recognized. In the preferred method, each drug will be subjected to a battery of *in vitro* screening tests for a variety of activities, such as antibacterial activity, antiviral activity, antifungal activity, antiparasitic activity, cytotherapeutic activity especially against one or more types of cancer or tumor cells, alteration of metabolic function of eukaryotic cells, binding to specific receptors, modulation of inflammation and/or immunomodulation, modulation of angiogenesis, anticholinergic activity, and modulation of enzyme levels or activity. Physical and chemical properties to be screened include stability during processing, manufacturing, packaging, distribution, and administration, especially of molecules such as proteins. Metabolic function testing includes sugar metabolism, cholesterol uptake, lipid metabolism, and blood pressure regulation, amino acid metabolism, nucleoside/nucleotide metabolism, amyloid formation, and dopamine regulation.

These screening tests include any that are presently known, and those that are later developed. Typically the initial screening test will be an *in vitro* assay that is routinely used in the field. The preferred assays will yield highly reliable and reproducible results, can be performed quickly, and will give results predictive of *in vivo* results. Numerous *in vitro* screening tests for drug formulations are known. After at least one initial *in vitro* screen, the formulations that have been identified as having one or more optimal characteristics can undergo testing in one or more animal or tissue models and

ultimately, in humans. Safety will be evaluated by LD50 measurements and other toxicologic methods of evaluation (liver function tests, hematocrit, etc.). Efficacy will be evaluated in specific animal models for the type of problem for which treatment is sought.

Screening techniques are well known for specific household and industrial applications. For example, for stain resistant coatings of carpet one applied an aqueous solution of a red dye and measures the absorbance of the resulting stain. For dishwashing detergents, one can measure the amount of grease which is emulsified by the surfactant. For coatings, one can measure the adhesion and resistance to scratching.

B. Microarray and Nanotechnology Systems

Any automatable system for testing can be used to screen the various combinations of drugs. The basic system requirements are that they must have input means that provide for varying at least one factor (component(s) and/or concentration of component(s)), more preferably two or more factors, into test wells or at separate sites that allow for automated screening of each individual formulation for one or more selection criteria.

Figure 1 is a flow chart of the process, beginning with selection of the material sources, i.e., one or more components at one or more concentrations; mixing or deposition of components into sample wells or at separate sites to form a material array, assaying for one or more parameters, then collection of data for subsequent analysis. For example, component drug, and variations thereof (which can be drug in different amounts, different pHs, different chemical forms such as salts or bases, different excipients, etc), are distributed in a liquid, gaseous, or dry phase, or combination thereof, into individual test wells or at separate sites in an array. The different combinations can be screened in the array, and/or further processed, for example, by lypophilization in a lyophilizer, milling in a mill to produce a powder, or emulsified by applying ultrasound to a solvent mixture, then screened in a further test system.

Figures 2A and 2B are more detailed schematics of processes for formulating and testing arrays of unique formulations. Figure 2A depicts a

system where the drug source 10 and excipients 12 are provided in solid form, which is deposited in wells in a 96 well filter plate 14 under the control of formulating software 16. The dry formulations are reconstituted with one or more solvents using an automated liquid pipetting system 18, yield an array 20 of reconstituted formulations. These are separated 22 into liquids and solids (for example, by centrifugation of the filtrate from the wells through the filter into collection reservoirs, as described in the following examples), then the liquids or solids, as appropriate, inputted into one or more devices for analysis, for example, devices for measuring solubility 24 such as UV-Vis spectroscopy, HPLC or LC-MS devices, devices for measuring stability 26 such as UV-Vis spectroscopy, HPLC, or liquid chromatograph-mass spectroscopy (LC-MS) devices, systems for measuring absorption 28 such as a Caco-2 cell line or Ussing Chamber, and systems for measuring metabolism 30 such as P-450, microsomes, lysosomes, (obtainable from companies such as In Vitro Technologies, 1450 South Rolling Road, Baltimore, MD 21227; see also ; Trouet A, Methods Enzymol. Vol. 31, 323-329) and *in vivo* assays. The data 32 from the various assays is then collected and analyzed.

Figure 2B shows essentially the same process but for materials (drug 10 and excipient(s) 12) provided in liquid form which is dispensed using an automated liquid pipetting system 34 to make the formulation array 14. The solvent is then removed 36 using a technique such as lyophilization. The dried formulations 38 are then reconstituted 40 by addition of one or more solvents using an automated liquid pipetting system 42, which are then treated in the same manner as described with regard to the process for making dry formulations.

For analysis the formulations can be pumped by a peristaltic pump through individual optical interrogation windows into a sample valve manifold . From the manifold, sample is processed using an UV-VIS HPLC to access physical parameters and/or through parallel channel Ussing chambers to assess uptake/oral absorbance, then disposed of into waste and/or passed through another manifold for further analysis for example by

HPLC. Other means for analysis include pH sensors, ionic strength sensors, mass spectrometers, optical spectrometers, devices for measuring turbidity, calorimeters, infrared and ultraviolet spectrometers, polarimeters, radioactivity counters, devices measuring conductivity, and heat of dissolution.

A number of companies have developed microarray systems that can be adapted for use in the system described herein, although all are currently used for the sole purpose of screening to identify compounds having a particular defined activity, as opposed to screening of compounds having a known identity to identify the optimal formulations. The most significant modification will be the use of input means that modify one or more variable in each well, rather than inputting different compounds into each well. Examples of companies having microarray systems include Beckman Instruments, Fullerton, CA, MicroFab Technologies, Plano, TX, Robbins Scientific, Sunnyvale, CA; Zymark, Hoplinton, MA, Packard Instruments, Meriden, CT, Tomtec, Hamden, CT, and Cartesian Technologies, Irvine, CA. These devices test samples based on a variety of different systems. All include thousands of microscopic channels that direct sample into test wells, where reactions can occur. These include reactions with receptors, immobilized antibodies or fluorescent labels bound to the surfaces of the wells or immobilized on nanospheres or microparticles, which can be analyzed in situ or pumped into other receptacles for analysis. Luminex Corp. FlowMetrix TM systems pumps reagents into 96 well ELISA plates and then used fluorescence and flow cytometry with latex microspheres for testing. These systems are connected to computers for analysis of the data using appropriate software and data sets. The Beckman Instruments system can deliver nanoliter samples of 96 or 384-arrays, and is particularly well suited for hybridization analysis of nucleotide molecule sequences. The MicroFab Technologies system delivers sample using inkjet printers to aliquot discrete samples into wells. Other systems can also be adapted as required for use herein.

There are basically two types of Infomatics that can be used with these systems with the methods described herein, as depicted in Figures 2a and 2b at the points referring to automated solid or liquid dispensing system and data output, respectively. One is system automation and control software that enables the integrated set of manipulations to occur and track the process flow, including communication and sample tracking through the system, in high throughput. A second is scientific derivatization which collects and stores data to enable further development and design of formulations, including identification of complex interactions between the actives and excipients, and identification of lead formulations. The data can then be processed so as to optimize the ability of scientific personnel to conduct future experiments to optimize the formulations, and to develop future models of new formulations of other active components.

EXAMPLES

The present invention will be further understood by reference to the following non-limiting example of the process disclosed herein for high throughput formulation and screening of drug formulations having desirable properties.

An approximately 350 mw antibiotic having a complex derivatized benzofuran-cyclohexane structure, which is approved for use as an antibiotic and antifungal compound, was selected for reformulation to produce more soluble compositions. This compound is soluble in DMF but only slightly soluble in other organic solvents such as ethanol, methanol, acetone and acetic acid. The low solubility limits applications of the antibiotic-antifungal due to poor bioavailability.

A commercially available preparation consists of ultramicrosized crystals of antibiotic-antifungal partially dissolved in a carrier including polyethylene glycol 8000 and partially dispersed in other inert excipients (corn starch, lactose, magnesium stearate, and sodium lauryl sulfate). A dosage of 3.3 mg/lb body weight is administered per day for children under 50 lbs.. A different dose for adults of 330 mg/day is the typical dosage for

treatment of fungal infections. This product is marketed for oral administration, but is still of limited solubility, and therefore bioavailability.

Formulations containing antibiotic-antifungal have now been developed which have greatly enhanced aqueous solubility. These contain antibiotic-antifungal dispersed with various combinations of the following GRAS ("generally regarded as safe") excipients (all obtainable from Sigma-Aldrich Fine Chemicals or BASF): (1) gum arabic from acacia tree (a branched polymer of galactose, rhamnose, arabinose, and glucuronic acid, mw approximately 25000), (2) beta-cyclodextrin (cycloheptaamylose), (3) sodium dodecyl sulfate (SDS), (4) docusate (sulfobutanedioic acid bis[2-ethyl-hexl ester] or dioctyl sulfosuccinate), (5) sodium benzethonium chloride, (6) benzalkonium chloride (alkyldimethylbenzylammonium chloride), (7) cetrimide (dodecyltrimethylammonium bromide), (8) oleic acid (cis-9-octadecenoic acid), (9) sodium tartrate dihydrate, (10) polyethylene glycol 1000, (11) polyethylene glycol 10,000, (12) polyvinyl alcohol, (13) POLOXAMER® 237 (polyoxyalkylene oxide block copolymer), (14) polyoxyethylene 40 stearate, (15) polyoxyethylene 100 stearate, (16) TWEEN 80® (polyoxyethylenesorbitan), (17) BRIJ 35® (23 lauryl ether), and (18) BRIJ 97® (10 Oleyl ether).

The formulations were developed and analyzed as demonstrated by the following examples.

EXAMPLE 1: Preparation and Identification of Antibiotic-antifungal Formulations with Enhanced Solubility.

Experimental Procedure

Preparation of formulations with improved solubilities

18 GRAS excipients (numbered 1-18, as noted above) were selected. Three of the 18 excipients, 20 microliters each, were added to each well in the microarray (Millipore 96 well filter plates, including one micron pore size polytetrafluoroethylene membranes in the bottom of each well) using the TECAN® liquid handling system. Each excipient was prepared in water at 3 concentrations (0.015 mg/ml, 0.15 mg/ml, and 1.5 mg/ml), allowing for the examination of excipient concentration effects.

The number of possible unique formulations is calculated as:

$$\frac{18!}{3! \times (18-3)!} \times 3^3$$

22,032 unique formulations (a total of 66,096 samples for n=3) were generated, with 32 unique formulations per assay plate and 689 assay plates in total. The samples were generated using the MatLab program. 20 microliters antibiotic-antifungal dissolved in dioxane (0.15 mg antibiotic-antifungal/ml dioxane) was then added to each formulation in each sample well using the TECAN liquid handling system.

Screening of Formulations

All the solvents were removed by lyophilization. 200 microliters of water were added to each dried formulation in each well of the filter plates. The plates were incubated at 37°C for 1 hour, then centrifuged to separate any undissolved solids. The filtrate from each well was collected into UV transparent 96 well plates for measurements on a UV plate reader at 290 nm.

Antibiotic-antifungal alone without any excipient was tested to establish the baseline solubility.

Results

The solubility, measured as absorbance at 290 nm of the filtrates, for 3,500 unique formulations is shown in Figure 3a. Antibiotic-antifungal alone gave a baseline absorbance (solubility) of 0.3. Most formulations showed improved solubility compared to the antibiotic-antifungal. Approximately 1,200 formulations shown in Figure 3a showed significantly higher solubilities than the rest of the formulations.

Formulations demonstrating 100% increase in solubility compared to antibiotic-antifungal alone (as measured by absorbance) were identified as lead formulations. Five formulations were identified and boxed in Figure 3a.

Figure 3b gives the standard deviation for each of the 3,500 unique formulations (each tested at n=3). The majority of the formulations tested were reproducible, with standard deviations of less than 10%.

These formulations can be further optimized using the same screening technique described above, by making additional changes to the concentration of each component in the formulations.

EXAMPLE 2: Validation of lead formulations on a larger scale.

Experimental Procedure

The five lead formulations identified from the screen above were validated on a lab scale 10,000x that of the microarray in 96 well plates by weighing each component and mixing them in the solid state in scintillation vials. 30 mg of antibiotic-antifungal was weighed out in the solid state and added to each formulation. Each formulation was formulated three times. These are:

TPI-1: 300 mg PEG 1000, 30 mg beta-cyclodextrin, 30 mg polyoxyethylene 40 stearate

TPI-2: 300 mg PEG 1000, 30 mg SDS, 3 mg polyoxyethylene 40 stearate

TPI-3: 300 mg PEG 1000, 30 mg polyoxyethylene 40 stearate, 3 mg acacia

TPI-4: 300 mg PEG 10000, 30 mg acacia, 30 mg cetrimide

TPI-5: 300 mg polyvinylalcohol, 30 mg benzethonium chloride, 3 mg PEG 1000

15 ml water was added to each vial and the formulations incubated at 37°C for 1 hour before they were filtered through 0.2 micron filters to remove any undissolved solids. The filtrates were measured using a UV spectrometer at 290 nm in a 1 cm pathlength quartz cuvette.

The commercially available drug (165 mg antibiotic-antifungal) in tablet form was ground into powder and an amount containing 30 mg antibiotic-antifungal was tested in the same way as the lead formulations for comparison.

Results

The results from the lab scale dissolution assay are plotted in Figure 4 as absorbance at 290 nm, showing the means and standard deviations from the three measurements. An increase of up to 300% in solubilities (as measured by UV) was achieved compared to the commercial formulation. All five lead formulations identified in the microarray screen were validated

in the solid form in the lab scale (10,000x) dissolution assay to have increased solubility compared to the commercially available drug, proving the results from microarray assay format can now be translated into normal lab scale assays.

EXAMPLE 3: Evaluation of Individual Effect of Each Excipient.

Experimental Procedure

To examine the effect of each excipient on antibiotic-antifungal solubility, the first three lead formulations (TPI-1 to TPI-3) identified above in the microarrays described above were "de-convolved" on the lab scale into antibiotic-antifungal formulations that contain (1) one of the three excipients only, or (2) two of the three excipients in different combinations (example, components one and two, two and three, one and three). Solubilities of each sample were then measured using the same lab procedures described above for lead validation, using absorbance at 290 nm to determine solubility.

The solubilites for the "de-convolved" formulations are shown in Figure 5, 6 and 7 as ratios to their respective lead formulation (It is important to note that some reformulations have greater or less solubilities than the lead formulations identified in Example 1, but that the results are relative to the starting lead formulation; not absolute absorbance).

In Figure 5, excipient 14 (polyoxyethylene 40 stearate) (which is present as a small percentage in TPI-3, as indicated by the area in the pie chart) yields a substantial increase in solubility, which was slightly enhanced by excipient 10 (PEG 1000).

As shown by Figure 5, 14 (polyoxyethylene 40 stearate) was the only important excipient in TPI-3 and addition of 10 (PEG 1000 and 1 (acacia) had no effect on overall solubility. Addition of excipient 2 (cyclodextin B) actually decreased overall solubility of the antibiotic-antifungal in TPI-1, as shown in Figure 6, demonstrating an antagonistic effect among excipients.

In contrast, as shown by Figure 7, excipient 3 (SDS), 10 (PEG 1000), and 14 (polyoxyethylene 40 stearate) show synergy in enhancing solubility of antibiotic-antifungal.

EXAMPLE 4: Dissolution rate comparison under simulated USP conditions

Experimental Procedure

The rates of dissolution of TPI-2 and the commercial product, antibiotic-antifungal (165 mg) were compared at the lab scale using 1000 mL deionized water in 1000 mL Erlenmeyer flasks at 37°C stirred at 300 RPM with a 1.5 inch magnetic stir bar. The rate of dissolution for each formulation was determined separately. Each formulation was added to the stirring deionized water and 1 mL aliquots were removed at 0 seconds, 30 seconds, 1 minute, 3 minutes, 6 minutes, 10 minutes, 15 minutes 25 minutes, 40 minutes, and 50 minutes. Each aliquot was added to a 1.5 mL Eppendorf vial, centrifuged at room temperature at 14,000 RPM for 10 seconds to remove undissolved solids and the ultraviolet absorbance determined at 290 nm in a 1 cm pathlength quartz cuvette.

Results

The rates of dissolution are shown in Figure 8. TPI-2 showed a faster rate of dissolution as well as a higher equilibrium solubility compared to antibiotic-antifungal, further confirming the validity of the lead formulations selected from the microarrays.

These results demonstrate of the efficacy of the high throughput formulation and screening methods, and how it is possible to scale up the results with a high degree of reproducibility.

CLAIMS:

1. An array of multiple formulations, wherein:
   a) the formulations are located at separate sites or in separate wells,
   b) each formulation comprises a different mixture of at least two materials having known functions, activities or properties, each mixture varying in the concentration or composition of at least one material,
   c) the array is comprised of more than 1000 different formulations,
   d) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and
   e) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, activity, chemical or physical properties.

2. The array of claim 1 wherein one of said at least two materials is selected from the group consisting of:
   a) a pharmaceutical product,
   b) a health care product,
   c) a consumer product,
   d) an agricultural product,
   e) a nutraceutical product,
   f) a veterinary product,
   g) a material used in a industrial application,
   h) a material used in a military application, and
   i) a research reagent.

3. The array of claim 2 wherein the formulation comprises a bioactive material selected from the group consisting of:
   a) a therapeutic,
   b) a prophylactic, and
   c) a diagnostic agent.

4. The array of claim 3 wherein the bioactive material selected from the group consisting of:
   a) a nucleoside or nucleotide molecule,
   b) a polysaccharide or saccharide, and

c) a protein or peptide.

5. The array of claim 3 wherein the formulation comprises at least one material selected from the group consisting of:

a) an excipient,

b) an adhesive,

c) a packaging material, and

d) a processing reagent.

6. The array of claim 2 wherein the material enhances stability of one or more of the materials in the formulation, or the formulation, during:

a) processing,

b) manufacturing,

c) packaging,

d) storage,

e) distribution,

f) administration, or

g) *in vivo*.

7. The array of claim 6 wherein the material comprises a bioactive material which is a protein and the material enhancing stability comprises one or more excipients.

8. The array of claim 2 wherein a material in the formulation is selected to enhance solubility or dissolution of the formulation or a component thereof.

9. The array of claim 2 wherein a material in the formulation is selected to increase ease of manufacture or decrease cost of manufacture of the formulation or a component thereof.

10. The array of claim 3 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent, to be administered orally, further comprising one or more materials altering uptake through the gastrointestinal tract of the agent.

11. The array of claim 10 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,

b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

12. The array of claim 10 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

13. The array of claim 3 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent to be administered:
a) topically,
b) transdermally,
c) pulmonary,
d) to a mucosal surface, or
e) ocularly,
further comprising one or more materials altering uptake or transport.

14. The array of claim 13 wherein the material altering uptake is selected from the group consisting of:
a) a compound enhancing solubility of the therapeutic,
b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

15. The array of claim 13 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

16. The array of claim 1 wherein the formulation test array comprises formulations on a microscale.

17. The array of claim 1 wherein the formulation test array comprises formulations on a nanoscale.

18. The array of claim 1 wherein the formulation test array comprises formulations or components in the formulations in the range of 100 micrograms or less in each reservoir or sample site.

19. The array of claim 1 wherein the formulation test array comprises formulations or components in the formulations in the range of 25 micrograms or less in each reservoir or sample site.

20. The array of claim 1 wherein the screening is performed at a rate greater than or equal to 1000 formulations per day.

21. The array of claim 1 wherein the screening means is selected from the group consisting of:

a) a means for chemical analysis,
b) a means for analysis of biological activity, and
c) a means for analysis of physical properties.

22. The screening means of claim 21 selected from the group of means of chemical or physical analysis consisting of:

a) HPLC,
b) a pH sensor,
c) an ionic strength sensor,
d) diffractometry,
e) mass spectroscopy,
f) optical spectroscopy,
g) a means for measuring turbidity,
h) a polarimeter,
i) a calorimeter, and
j) a fluorimeter.

23. The screening means of claim 21 selected from the group of means for analysis of biological activity consisting of:

a) an *in vitro* assay,
b) a cell culture assay, and
c) a tissue assay.

24. An automatic multiple processing for preparing an array of multiple formulations, the system comprising:

a) a formulation test array of multiple formulations, wherein:

1) the formulations are located at separate sites or in separate wells,

2) each formulation comprises a different mixture of at least two materials having known functions, activities, or properties, each mixture varying in the concentration or composition of at least one material,

3) the array is comprised of more than 1000 different formulations,

4) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and

5) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, activity, chemical or physical properties,

b) a reservoir means for storage of formulation components,

c) a means for inputting formulation components from the reservoir means to the formulation test array, and

d) a processing means for controlling the formulation components inputted into each well or at each site of the formulation test array from the reservoir means so that each formulation comprises at least one material in common but has a different formulation.

25. The array of the system of claim 24 wherein one of said at least two materials is selected from the group consisting of:

a) a pharmaceutical product,

b) a health care product,

c) a consumer product,

d) an agricultural product,

e) a nutraceutical product,

f) a veterinary product,

g) a material used in an industrial application,

h) a material used in a military application, and

i) a research reagent.

26. The array of claim 25 wherein the formulation comprises a bioactive material selected from the group consisting of:

a) a therapeutic,

b) a prophylactic, and

c) a diagnostic agent.

27. The array of claim 26 wherein the bioactive material selected from the group consisting of:

a) a nucleoside or nucleotide molecule,

b) a polysaccharide or saccharide, and

c) a protein or peptide.

28. The array of claim 26 wherein the formulation comprises at least one material selected from the group consisting of:

a) an excipient,

b) an adhesive,

c) a packaging material, and

d) a processing reagent.

29. The array of claim 25 wherein the material enhances stability of one or more of the materials in the formulation, or the formulation, during:

a) processing,

b) manufacturing,

c) packaging,

d) storage,

e) distribution,

f) administration, or

g) *in vivo*.

30. The array of claim 29 wherein the material comprises a bioactive material which is a protein and the material enhancing stability comprises one or more excipients.

31. The array of claim 25 wherein a material in the formulation is selected to enhance solubility or dissolution of the formulation or a component thereof.

32. The array of claim 25 wherein a material in the formulation is selected to increase ease of manufacture or decrease cost of manufacture of the formulation or a component thereof.

33. The array of claim 26 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent, to be administered orally, further comprising one or more materials altering uptake through the gastrointestinal tract of the agent.

34. The array of claim 33 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,
b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

35. The array of claim 33 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

36. The array of claim 26 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent to be administered:

a) topically,
b) transdermally,
c) pulmonary,
d) to a mucosal surface, or
e) ocularly,

further comprising one or more materials altering uptake or transport.

37. The array of claim 36 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,
b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

38. The array of claim 36 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

39. The array of the system of claim 24 wherein the formulation test array comprises formulations on a microscale.

40. The array of the system of claim 24 wherein the formulation test array comprises formulations on a nanoscale.

41. The array of the system of claim 24 wherein the formulation test array comprises formulations or components in the formulations in the range of 100 micrograms or less in each reservoir or sample site.

42. The array of the system of claim 24 wherein the formulation test array comprises formulations or components in the formulations in the range of 25 micrograms or less in each reservoir or sample site.

43. The array of the system of claim 24 wherein the screening is performed at a rate greater than or equal to 1000 formulations per day.

44. The array of the system of claim 24 wherein the screening means is selected from the group consisting of:

a) a means for chemical analysis,
b) a means for analysis of biological activity, and
c) a means for analysis of physical properties.

45. The screening means of claim 44 selected from the group of means of chemical or physical analysis consisting of:

a) HPLC,
b) a pH sensor,
c) an ionic strength sensor,
d) diffractometry,
e) mass spectroscopy,
f) optical spectroscopy,
g) a means for measuring turbidity,
h) a polarimeter,
i) a calorimeter, and
j) a fluorimeter.

46. The screening means of claim 44 selected from the group of means for analysis of biological activity consisting of:

a) an *in vitro* assay,

b) a cell culture assay, and

c) a tissue assay.

47. The system of claim 24 further comprising means for screening one or more properties of each formulation.

48. The array of the system of claim 47 wherein one of said at least two materials is selected from the group consisting of:

a) a pharmaceutical product,

b) a health care product,

c) a consumer product,

d) an agricultural product,

e) a nutraceutical product,

f) a veterinary product,

g) a material used in an industrial application,

h) a material used in a military application, and

i) a research reagent.

49. The array of claim 48 wherein the formulation comprises a bioactive material selected from the group consisting of:

a) a therapeutic,

b) a prophylactic, and

c) a diagnostic agent.

50. The array of claim 49 wherein the bioactive material selected from the group consisting of:

a) a nucleoside or nucleotide molecule,

b) a polysaccharide or saccharide, and

c) a protein or peptide.

51. The array of claim 49 wherein the formulation comprises at least one material selected from the group consisting of:

a) an excipient,

b) an adhesive,
c) a packaging material, and
d) a processing reagent.

52. The array of claim 48 wherein the material enhances stability of one or more of the materials in the formulation, or the formulation, during:
a) processing,
b) manufacturing,
c) packaging,
d) storage,
e) distribution,
f) administration, or
g) *in vivo*.

53. The array of claim 52 wherein the material comprises a bioactive material which is a protein and the material enhancing stability comprises one or more excipients.

54. The array of claim 48 wherein a material in the formulation is selected to enhance solubility or dissolution of the formulation or a component thereof.

55. The array of claim 48 wherein a material in the formulation is selected to increase ease of manufacture or decrease cost of manufacture of the formulation or a component thereof.

56. The array of claim 49 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent, to be administered orally, further comprising one or more materials altering uptake through the gastrointestinal tract of the agent.

57. The array of claim 56 wherein the material altering uptake is selected from the group consisting of:
a) a compound enhancing solubility of the therapeutic,
b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

58. The array of claim 56 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

59. The array of claim 49 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent to be administered:

a) topically,

b) transdermally,

c) pulmonary,

d) to a mucosal surface, or

e) ocularly,

further comprising one or more materials altering uptake or transport.

60. The array of claim 59 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,

b) an encapsulating agent,

c) a diagnostic or prophylactic agent, and

d) an enteric coating.

61. The array of claim 59 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

62. The array of the system of claim 47 wherein the formulation test array comprises formulations on a microscale.

63. The array of the system of claim 47 wherein the formulation test array comprises formulations on a nanoscale.

64. The array of the system of claim 47 wherein the formulation test array comprises formulations or components in the formulations in the range of 100 micrograms or less in each reservoir or sample site.

65. The array of the system of claim 47 wherein the formulation test array comprises formulations or components in the formulations in the range of 25 micrograms or less in each reservoir or sample site.

66. The array of the system of claim 47 wherein the screening is performed at a rate greater than or equal to 1000 formulations per day.

67. The array of the system of claim 47 wherein the screening means is selected from the group consisting of:

a) a means for chemical analysis,
b) a means for analysis of biological activity, and
c) a means for analysis of physical properties.

68. The screening means of claim 67 selected from the group of means of chemical or physical analysis consisting of:

a) HPLC,
b) a pH sensor,
c) an ionic strength sensor,
d) diffractometry,
e) mass spectroscopy,
f) optical spectroscopy,
g) a means for measuring turbidity,
h) a polarimeter,
i) a calorimeter, and
j) a fluorimeter.

69. The screening means of claim 67 selected from the group of means for analysis of biological activity consisting of:

a) an *in vitro* assay,
b) a cell culture assay, and
c) a tissue assay.

70. The system of claim 24 further comprising processing means directing each formulation separately from the array to the screening means.

71. The array of the system of claim 70 wherein one of said at least two materials is selected from the group consisting of:

a) a pharmaceutical product,

b) a health care product,

c) a consumer product,

d) an agricultural product,

e) a nutraceutical product,

f) a veterinary product,

g) a material used in an industrial application,

h) a material used in a military application, and

i) a research reagent.

72. The array of claim 71 wherein the formulation comprises a bioactive material selected from the group consisting of:

a) a therapeutic,

b) a prophylactic, and

c) a diagnostic agent.

73. The array of claim 72 wherein the bioactive material selected from the group consisting of:

a) a nucleoside or nucleotide molecule,

b) a polysaccharide or saccharide, and

c) a protein or peptide.

74. The array of claim 72 wherein the formulation comprises at least one material selected from the group consisting of:

a) an excipient,

b) an adhesive,

c) a packaging material, and

d) a processing reagent.

75. The array of claim 71 wherein the material enhances stability of one or more of the materials in the formulation, or the formulation, during:

a) processing,

b) manufacturing,

c) packaging,

d) storage,
e) distribution,
f) administration, or
g) *in vivo*.

76. The array of claim 75 wherein the material comprises a bioactive material which is a protein and the material enhancing stability comprises one or more excipients.

77. The array of claim 71 wherein a material in the formulation is selected to enhance solubility or dissolution of the formulation or a component thereof.

78. The array of claim 71 wherein a material in the formulation is selected to increase ease of manufacture or decrease cost of manufacture of the formulation or a component thereof.

79. The array of claim 72 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent, to be administered orally, further comprising one or more materials altering uptake through the gastrointestinal tract of the agent.

80. The array of claim 79 wherein the material altering uptake is selected from the group consisting of:
a) a compound enhancing solubility of the therapeutic,
b) an encapsulating agent,
c) a diagnostic or prophylactic agent, and
d) an enteric coating.

81. The array of claim 79 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

82. The array of claim 72 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent to be administered:
a) topically,
b) transdermally,
c) pulmonary,
d) to a mucosal surface, or

e) ocularly,

further comprising one or more materials altering uptake or transport.

83. The array of claim 82 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,

b) an encapsulating agent,

c) a diagnostic or prophylactic agent, and

d) an enteric coating.

84. The array of claim 82 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

85. The array of the system of claim 70 wherein the formulation test array comprises formulations on a microscale.

86. The array of the system of claim 70 wherein the formulation test array comprises formulations on a nanoscale.

87. The array of the system of claim 70 wherein the formulation test array comprises formulations or components in the formulations in the range of 100 micrograms or less in each reservoir or sample site.

88. The array of the system of claim 70 wherein the formulation test array comprises formulations or components in the formulations in the range of 25 micrograms or less in each reservoir or sample site.

89. The array of the system of claim 70 wherein the screening is performed at a rate greater than or equal to 1000 formulations per day.

90. The array of the system of claim 70 wherein the screening means is selected from the group consisting of:

a) a means for chemical analysis,

b) a means for analysis of biological activity, and

c) a means for analysis of physical properties.

91. The screening means of claim 90 selected from the group of means of chemical or physical analysis consisting of:

a) HPLC,

b) a pH sensor,

c) an ionic strength sensor,

d) diffractometry,

e) mass spectroscopy,

f) optical spectroscopy,

g) a means for measuring turbidity,

h) a polarimeter,

i) a calorimeter, and

j) a fluorimeter.

92. The screening means of claim 90 selected from the group of means for analysis of biological activity consisting of:

a) an *in vitro* assay,

b) a cell culture assay, and

c) a tissue assay.

93. A method of determining a formulation comprising two or more materials having one or more desirable characteristics, the method comprising:

a) identifying a compound to be formulated

b) selecting the materials to make the formulation,

c) identifying at least one functional, biological, physical or chemical characteristic to screen the formulation for, and

d) formulating the materials into an array of multiple formulations, wherein:

1) the formulations are located at separate sites or in separate wells,

2) each formulation comprises a different mixture of at least two materials, at least one having a known function, activity, or property, each mixture varying in the concentration or composition of at least one material,

3) the array is comprised of more than 1000 different formulations,

4) the array is formed by input of the materials at separate sites from multiple sources under the control of an automatic processor, and

5) wherein the array can be connected to or accessed by means for screening each formulation for at least one variable relating to intended function, chemical or physical properties.

94. The array of the method of claim 93 wherein one of said at least two materials is selected from the group consisting of:

a) a pharmaceutical product,
b) a health care product,
c) a consumer product,
d) an agricultural product,
e) a nutraceutical product,
f) a veterinary product,
g) a material used in an industrial application,
h) a material used in a military application, and
i) a research reagent.

95. The array of claim 94 wherein the formulation comprises a bioactive material selected from the group consisting of:

a) a therapeutic,
b) a prophylactic, and
c) a diagnostic agent.

96. The array of claim 95 wherein the bioactive material selected from the group consisting of:

a) a nucleoside or nucleotide molecule,
b) a polysaccharide or saccharide, and
c) a protein or peptide.

97. The array of claim 95 wherein the formulation comprises at least one material selected from the group consisting of:

a) an excipient,
b) an adhesive,
c) a packaging material, and
d) a processing reagent.

98. The array of claim 94 wherein the material enhances stability of one or more of the materials in the formulation, or the formulation, during:

a) processing,

b) manufacturing,

c) packaging,

d) storage,

e) distribution,

f) administration, or

g) *in vivo*.

99. The array of claim 98 wherein the material comprises a bioactive material which is a protein and the material enhancing stability comprises one or more excipients.

100. The array of claim 94 wherein a material in the formulation is selected to enhance solubility or dissolution of the formulation or a component thereof.

101. The array of claim 94 wherein a material in the formulation is selected to increase ease of manufacture or decrease cost of manufacture of the formulation or a component thereof.

102. The array of claim 95 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent, to be administered orally, further comprising one or more materials altering uptake through the gastrointestinal tract of the agent.

103. The array of claim 102 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,

b) an encapsulating agent,

c) a diagnostic or prophylactic agent, and

d) an enteric coating.

104. The array of claim 102 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

105. The array of claim 95 wherein the formulation comprises a therapeutic, diagnostic or prophylactic agent to be administered:

a) topically,

b) transdermally,

c) pulmonary,

d) to a mucosal surface, or

e) ocularly,

further comprising one or more materials altering uptake or transport.

106. The array of claim 105 wherein the material altering uptake is selected from the group consisting of:

a) a compound enhancing solubility of the therapeutic,

b) an encapsulating agent,

c) a diagnostic or prophylactic agent, and

d) an enteric coating.

107. The array of claim 105 wherein the formulation comprises a material improving absorption, distribution, metabolism, excretion, toxicity, or pharmacokinetics of the formulation in the body.

108. The array of the method of claim 93 wherein the formulation test array comprises formulations on a microscale.

109. The array of the method of claim 93 wherein the formulation test array comprises formulations on a nanoscale.

110. The array of the method of claim 93 wherein the formulation test array comprises formulations or components in the formulations in the range of 100 micrograms or less in each reservoir or sample site.

111. The array of the method of claim 93 wherein the formulation test array comprises formulations or components in the formulations in the range of 25 micrograms or less in each reservoir or sample site.

112. The array of the method of claim 93 wherein the screening is performed at a rate greater than or equal to 1000 formulations per day.

113. The array of the method of claim 93 wherein the screening means is selected from the group consisting of:

a) a means for chemical analysis,

b) a means for analysis of biological activity, and

c) a means for analysis of physical properties.

114. The screening means of claim 113 selected from the group of means of chemical or physical analysis consisting of:

a) HPLC,

b) a pH sensor,

c) an ionic strength sensor,

d) diffractometry,

e) mass spectroscopy,

f) optical spectroscopy,

g) a means for measuring turbidity,

h) a polarimeter,

i) a calorimeter, and

j) a fluorimeter.

115. The screening means of claim 113 selected from the group of means for analysis of biological activity consisting of:

a) an *in vitro* assay,

b) a cell culture assay, and

c) a tissue assay.

116. The method of claim 93 further comprising processing means directing each formulation separately from the array to the screening means.

117. The method of claim 93 further comprising screening each formulation in the array to measure the intended function, activity, chemical or physical property.

118. The method of claim 117 further comprising selecting those formulations having the most desirable measurements of the intended function, chemical or physical property.

119. The method of claim 118 wherein the formulations comprise a bioactive material further comprising testing the formulations having the most desirable measurements in vivo.

120. The array of claims 1, 24, 47, 70, 93, 116, 117, 118, or 119 wherein the formulation comprises a material selected from the group consisting of:

a) deodorants,
b) cleansers,
c) cosmetics,
d) feminine products,
e) lotions,
f) shampoos,
g) hair care items,
h) fragrances,
i) herbicides,
j) pesticides,
k) fertilizers or growth enhancers,
l) oils,
m) stabilizers,
n) foods,
o) nutrients,
p) vitamins,
q) herbal remedies,
r) spices,
s) colorings,
t) antioxidants,
u) preservatives,
v) catalysts,
w) surfactants,
x) optical enhancers,
y) detergents,
z) coatings,
aa) paints,
bb) dyes,
cc) adhesives,
dd) lubricants,

ee) biologicals,

ff) nerve gasses,

gg) coatings that protect or enhance visibility, and

hh) munitions formulation

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