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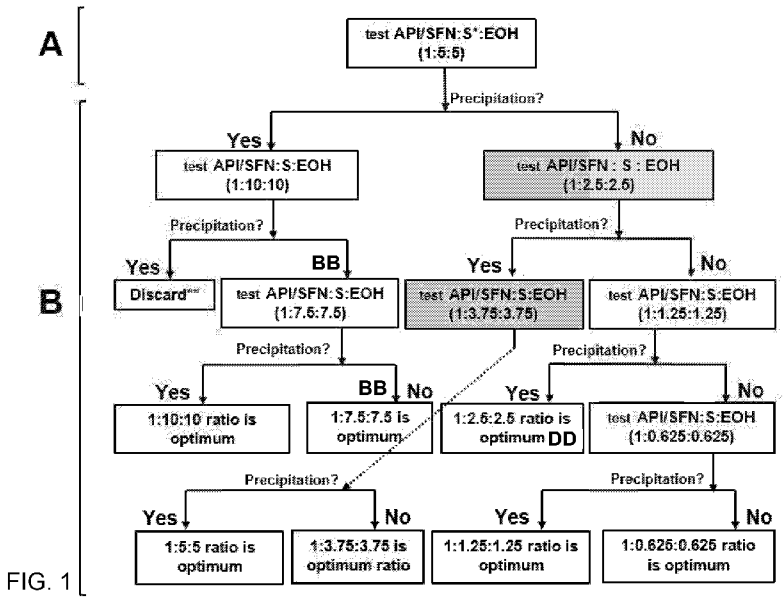

FIG. 1

(57) Abstract: Methods and pharmaceutical compositions for treating a pathology in a mammal comprising an effective amount of a first therapeutic, wherein the first therapeutic is solubilized with a solubilizing liquid including a compound having an isothiocyanate group. Additional embodiments relate to kits and methods for solubizing a lipophilic chemical comprising combining the lipophilic chemical with a compound having an isothiocyanate group. Additional embodiments relate to methods and pharmaceutical compositions for treating a breast cancer in a human comprising an effective amount of a first therapeutic, and a natural oil containing sulforaphane, wherein the first therapeutic is one of paclitaxel and docetaxel, and some combination thereof, the first therapeutic is solubilized with the natural oil, the natural oil is derived from one of broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof, the first therapeutic is contained in one of an emulsion, a microemulsion, and a cream, and the breast cancer is one of MDA-MB-231 and MCF-7.

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[Continued on next page]

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[0001] SULFORAPHANE ENABLED SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

[0002] CROSS REFERENCE TO RELATED APPLICATIONS/PRIORITY

[0003] The present invention claims priority to United States Provisional Patent Application Number 62/567,627 filed October 3, 2017, which is incorporated by reference into the present disclosure as if fully restated herein. Any conflict between the incorporated material and the specific teachings of this disclosure shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this disclosure shall be resolved in favor of the latter.

[0004] BACKGROUND OF INVENTION

[0005] The quest for discovering new pharmaceutical or drug molecules and the ongoing efforts to enhance potency and permeability of drugs often results in highly lipophilic and low water soluble drug candidates. Very often these drugs demonstrate poor bioavailability, thus necessitating large doses of the drugs with subsequent side effects of the large doses. Despite much research performed and many efforts made to address this problem, significant issues remain. There is a pressing, but seemingly irresolvable need for pharmaceutical formulations that improve solubility of insoluble lipophilic drugs.

[0006] SUMMARY OF THE INVENTION

[0007] Wherefore, it is an object of the present invention to overcome the above mentioned shortcomings and drawbacks associated with the current technology. The invention generally relates to formulations for improving solubility of insoluble lipophilic drugs, including the use of a natural product from broccoli, sulforaphane, to develop a self-emulsifying drug delivery system.

[0008] Self-emulsifying drug delivery system ("SEDDS") are physically stable isotropic mixtures of drug solubilized in oils/lipids, surfactants, and co-surfactant/solvent blends. They form fine oil-in-water emulsions under mild agitation by stomach and intestinal motility when they come into contact with the aqueous GI fluid after ingestion. A major challenge in the formulation of SEDDS

is to identify excipients that are capable of solubilizing a significant amount of the lipophilic/water-insoluble drug without compromising the self-emulsification behavior of the formulation and the oral drug absorption.

[0009] The inventors have discovered that sulforaphane ("SFN," 1-Isothiocyanato-4-methylsulfinylbutane), a natural product found in broccoli and other plants such as Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, can act as a super solubilizer for a significant number of drugs, and for other +lipophilic chemicals. The application of this inventive application of this discovery in pharmaceutical food, drug development and the cosmetic industry has tremendous possibilities. As reported in this disclosure, the application of SFN was able to solubilize the lipophilic chemicals paclitaxel, docetaxel, cyclosporine and curcumin, to name a few, to concentrations not achievable with commercially available products, such as Taxol and Neoral. These drugs are not soluble in water and the formulations were generated using much smaller volumes of additives than used in the commercially available products.

[0010] The present disclosure describes the inventors discovery of the solubilizing capacity of sulforaphane (SFN) and its utilization to formulate SEDDS of poorly water soluble drugs. A set of 24 drugs were tested for their solubility in SFN of which compounds such as Cyclosporine A, Celecoxib, Paclitaxel, Docetaxel, and Curcumin were selected for subsequent SEDDS formulation development utilizing SFN as common solubilizer. SFN-SEDDS formulations were developed utilizing a step-wise screening method that enabled the selection of the most efficient surfactants and co-surfactants to yield transparent microemulsions by microscopic analysis and absorbance data. The optimized SEDDS formulation for curcumin was selected for further investigation by DSC and FTIR, and was subjected to a dissolution study where more than 95% of the drug was found to dissolve within ten minutes in both simulated gastric and intestinal fluids. The physical stability of the SEDDS was also confirmed in both media when monitored at three different temperatures (4,

25 and 37 °C) for up to 30 days. This study introduced a new approach to formulating SEDDS by utilizing the solubilizing capacity of SFN and introduced high throughput screening approach to formulation development and stability study.

[0011] Other objects of one or more embodiments of the presently claimed invention is to reduce the bulk or size of commercially available products (e.g., pills that are required to be to large deliver a small amount of drug), increase the concentration of drugs in commercially available products, increase therapeutic activity of drug or reduce toxicity of finished product (a consequence to the side effects of additive), and/or increase the solubility of drug and/or non-drug molecules in water.

[0012] One embodiment of the presently claimed invention relates to a method for creating a therapeutic formulation for medicinal and/or cosmetic purposes comprising solubilizing one of drugs and natural products with a natural product oil. According to other embodiments, the formulation is a self-emulsifying drug delivery system. According to other embodiments, the formulation is one of an emulsion, a microemulsion, and a cream. According to other embodiments, the natural product oil is derived from one of from broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof. According to other embodiments, the solubilized drugs are lipophilic drugs with poor solubility in aqueous solutions, preferably FDA approved drugs, preferably a drug listed in Fig. 3. According to other embodiments, the natural product oil contains a compound with an isothiocyanate group. According to other embodiments, the isothiocyanate group containing compound is sulforaphane, preferably purified sulforaphane. According to other embodiments, the drugs are water insoluble anti-cancer drugs. According to other embodiments, the anti-cancer drugs are one of paclitaxel and docetaxel. According to other embodiments, the drugs are immunosuppressive drugs. According to other embodiments, the

immunosuppressive drugs are one of FK-506 and cyclosporine. According to other embodiments, the natural product is curcumin.

[0013] The invention further relates to kits and methods for using microtiter plates to test combinations of surfactants and co-surfactants with the SFN-API to discover the most soluble combinations. According to other embodiments, the a ratio of SFN:API is preferably between 10:1 and 0.1:1, more preferably between 5:1 and 0.5:1, and most preferably 1:1.

[0014] The invention further relates to methods for solubilizing a chemical, preferably a lipophilic chemical, comprising solubilizing the chemical with a compound having an isothiocyanate group. According to other embodiments, the compound is sulforaphane.

[0015] The invention further relate to therapeutics comprising a liphophilic drug solubilized with a compound having an isothiocyanate group.

[0016] The presently claimed invention relates to methods and pharmaceutical compositions for treating a pathology in a mammal comprising an effective amount of a first therapeutic, wherein the first therapeutic is solubilized with a solubilizing liquid including a compound having an isothiocyanate group. According to a further embodiment, the solubilizing liquid is an oil, the first therapeutic is a lipophilic compound, and the mammal is a human. According to a further embodiment, the oil includes a natural product oil. According to a further embodiment, the natural product oil is derived from one of from broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof. According to a further embodiment, the compound having an isothiocyanate group is sulforaphane. According to a further embodiment, the first therapeutic is one of an anti-cancer drug, an immunosuppressive drug, and a natural product. According to a further embodiment, the anti-cancer drug is one of paclitaxel and docetaxel, and some combination thereofe. According to a further embodiment, the immunosuppressive drug is one of FK-506 and cyclosporine. According to a further embodiment, the natural product is curcumin. According to a further

embodiment, the first therapeutic is one of Docetaxel, Paclitaxel, Cyclosporine A, Curcumin, Celecoxib, Salubrinal, FK-506, and Furesemide. According to a further embodiment, the first therapeutic is contained in one of an emulsion, a microemulsion, and a cream. According to a further embodiment, the pathology is a cancer. According to a further embodiment, the cancer is breast cancer. According to a further embodiment, the breast cancer is one of MDA-MB-231 and MCF-7.

[0017] The invention further relates to kits and methods for solubizing a lipophilic chemical comprising combining the lipophilic chemical with a compound having an isothiocyanate group. According to a further embodiment, the compound having an isothiocyanate group is sulforaphane. According to a further embodiment, the compound having an isothiocyanate group is derived from a natural product oil derived from one of from broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof. According to a further embodiment, the lipophilic chemical is contained in one of an emulsion, a microemulsion, and a cream.

[0018] The invention further relates to methods and pharmaceutical compositions for treating a breast cancer in a human comprising an effective amount of a first therapeutic, and a natural oil containing sulforaphane, wherein the first therapeutic is one of paclitaxel and docetaxel, and some combination thereof, the first therapeutic is solubilized with the natural oil, the natural oil is derived from one of broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof, the first therapeutic is contained in one of an emulsion, a microemulsion, and a cream, and the breast cancer is one of MDA-MB-231 and MCF-7.

[0019] Various objects, features, aspects, and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention, along with the accompanying drawings in which like numerals represent like components. The present invention may

address one or more of the problems and deficiencies of the current technology discussed above. However, it is contemplated that the invention may prove useful in addressing other problems and deficiencies in a number of technical areas. Therefore the claimed invention should not necessarily be construed as limited to addressing any of the particular problems or deficiencies discussed herein.

[0020] DESCRIPTION OF THE DRAWINGS

[0021] The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate various embodiments of the invention and together with the general description of the invention given above and the detailed description of the drawings given below, serve to explain the principles of the invention. It is to be appreciated that the accompanying drawings are not necessarily to scale since the emphasis is instead placed on illustrating the principles of the invention. The invention will now be described, by way of example, with reference to the accompanying drawings in which:

[0022] Figs. 1A and 1B are a flowchart of high-throughput screening (HTS) Step 1: screening and optimization of surfactants, which is subdivided into Step 1A: initial screening of an API/SFN/S/EOH blend at 1:5:5 ratio, and Step 1B subsequent adjustment in ratio between the API/SFN blend to the S/EOH blend. Abbreviations used: API/SFN, Drug-Sulforaphane blend; S, Surfactants; EOH, Ethanol. *Surfactants evaluated: Cremophor EL, Tween 80, Tween 20, Tween 60, Poloxamer 124 and Solutol HS15. **Compositions discarded from formulation scheme due to the requirement of high surfactants amount.

[0023] Fig. 2 is a flowchart of high-throughput screening HTS Step 2: Screening and optimization of co-surfactant and final formulation optimization. Abbreviations used: CoS, Co-Surfactants. #Co-Surfactants evaluated: Labrasol, Transcutol HP, Labrafil 2125CS, Lauroglycol FCC, Acconon CC-6, mPEG350 and Propylene Glycol. ## No further adjustment to composition was done below this ratio. ‡ Starting ratio for CLX and CUR. ¥ Starting ratio for CYL and DTX.

[0024] Fig. 3 is a bar chart of a solubility screening showing the amount of sulforaphane needed to solubilize 1 mg of a given API. *indicates the drug was insoluble at that ratio and no further adjustment to the SFN/API ratio was sought.

[0025] Figs. 4A and 4B are Polarized light microscope images of (A) crystals when the API is insoluble in SFN and (B) absence of precipitates for API when completely dissolved in SFN. The arrows indicate the insoluble crystals.

[0026] Figs. 5A-5D are DSC thermograms of (A) pure CUR (B) CUR-SFN blend at 1: 0.75 Ratio, (C) CUR-SFN Blend at 1: 1.5 Ratio, and (D) CUR-SFN Blend at 1:3 ratio. All samples were heated from 20 °C to 220 °C at a rate of 10 °C /min.

[0027] Figs. 6A-6C are FTIR spectra of (A) CUR, (B) SFN, and (C) CUR/SFN blend.at 1:3 ratio.

[0028] Figs. 7A-7E are absorbance data of the CUR SEDDS during the HTS formulation development process showing the results of surfactant screening during Step 1 at CUR/S:S:EOH ratio of (A) 1:5:5, (B) 1: 2.5: 2.5, and (C) 1: 3.75: 3.75. Also shown are the results of the co-Surfactant screening (Step 2) at CUR/SFN:S:CoS ratio of (D) 1:2.5:2.5 and (E) 1: 1.25: 1.25. Data represent the means ± SD.

[0029] Fig. 8 is a marked up photograph of a representative sample arrangement in 96 well-plates for absorbance data collection during the co-surfactants screening step.

[0030] Fig. 9 is a graph of a dissolution profile of CUR from the optimized SFN-SEDDS formulation in simulated gastric fluid (SGF, pH 1.2) without pepsin, and simulated intestinal fluid (SIF, pH 7.4). Data were collected by UV analysis in real-time using fiber dip probe. Data represent the means ± SD

[0031] Figs. 10A and 10B are photographs of vessels showing the transparent CUR microemulsion after dissolution in (A) simulated intestinal fluid (SIF, pH 7.4) and (B) simulated gastric fluid (SGF, pH 1.2).

[0032] Figs. 11A – 11D are absorbance data showing the stability of the SEDDS formulations in SIF and SGF at three temperature conditions that were

optimized by the HTP process for (A) CYL, (B) CLX, (C) DTX, and (D) CUR SFN-SEDDS. Data represent the means ± SD.

[0033] Figs. 12A and 12B are polarized light microscopy images of (A) Partially soluble DTX in lower DTX to SFN ratio (Arrow directs to the insoluble DTX crystals) (B) Solubilized DTX in SFN.

[0034] Figs. 13A to 13D are bar charts showing percent relative absorbance of the microemulsions during the PTX formulation development process at PTX/SFN:Ethanol ratio of (A) 1:5:5 and (B) 1:10:10. Step (C) shows absorbance data for the PTX/SFN:TPGS:Ethanol microemulsion at a ratio of 1:7.5:7.5. Step (D) shows the absorbance data when ethanol was replaced with transcutol at PTX/SFN:TPGS:Transcutol HP ratio of 1:7.5:7.5.

[0035] Figs. 14A to 14D are bar charts showing the percent relative absorbance of the microemulsions during the DTX formulation development process at DTX/SFN:Ethanol ratio of (A) 1:5:5 and (B) 1:2.5:2.5. Step (C) shows absorbance data for the DTX/SFN:TPGS:Ethanol microemulsion at a ratio of 1:1.25:1.25. Step (D) shows the absorbance data when ethanol was replaced with transcutol at DTX/SFN:TPGS:Transcutol HP ratio of 1:1.25:1.25.

[0036] Figs. 15A and 15B are bar charts showing Physical stability of the (A) PTX microemulsion at PTX/SFN:TPGS:Transcutol HP ratio of 1:7.5:7.5 and (B) DTX microemulsion at DTX/SFN:TPGS:Transcutol HP ratio of 1:1.25:1.25 when diluted when 5% dextrose solution or normal saline and stored at 4, 25, and 37 ^{o}C for 30 days.

[0037] Fig. 16 is a Hemolytic activity of the vehicles used in formulating taxane microemulsion and commercial injection solutions

[0038] Figs. 17A – 17D are line and bar charts showing IncuCyte® cell proliferation assay of the vehicles; TPGS with or without SFN, against (A) MDA-MB-231 and (B) MCF7 cells. Also shown is the in vitro CellTiter-Blue® assay of the same vehicles against the (C) MDA-MB-231 (D) MCF7 cells.

[0039] Fig. 18A – 18D are line charts showing IncuCyte® cell proliferation assay showing the growth inhibition of MDA-MB-231 human breast cancer cells when

treated up to 72 h with (A) PTX/SFN microemulsions, (B) PTX Injection USP, (C) DTX/SFN microemulsion; and (D) DTX Injection USP.

[0040] Fig. 19A – 19D are line charts showing IncuCyte® cell proliferation assay showing the growth inhibition of MCF7 human breast cancer cells when treated up to 72 h with (A) PTX/SFN microemulsions, (B) PTX Injection USP, (C) DTX/SFN microemulsion; and (D) DTX Injection USP.

[0041] Fig. 20A – 20D are bar charts showing In vitro CellTiter-Blue® assay showing the viability of MDA-MB-231 cells treated with (A) PTX microemulsion and Injection USP and (B) DTX microemulsion and Injection USP. Also shown is the viability of the MCF7 cells treated with (A) PTX microemulsion and Injection USP and (B) DTX microemulsion and Injection USP. ****$P<0.05$ considered statistically significant

[0042] **DETAILED DESCRIPTION OF INVENTION**

[0043] The present invention will be understood by reference to the following detailed description, which should be read in conjunction with the appended drawings. It is to be appreciated that the following detailed description of various embodiments is by way of example only and is not meant to limit, in any way, the scope of the present invention. In the summary above, in the following detailed description, in the claims below, and in the accompanying drawings, reference is made to particular features (including method steps) of the present invention. It is to be understood that the disclosure of the invention in this specification includes all possible combinations of such particular features, not just those explicitly described. For example, where a particular feature is disclosed in the context of a particular aspect or embodiment of the invention or a particular claim, that feature can also be used, to the extent possible, in combination with and/or in the context of other particular aspects and embodiments of the invention, and in the invention generally. The term “comprises” and grammatical equivalents thereof are used herein to mean that other components, ingredients, steps, etc. are optionally present. For example, an article “comprising” (or “which comprises”) components A, B, and C can

consist of (i.e., contain only) components A, B, and C, or can contain not only components A, B, and C but also one or more other components. Where reference is made herein to a method comprising two or more defined steps, the defined steps can be carried out in any order or simultaneously (except where the context excludes that possibility), and the method can include one or more other steps which are carried out before any of the defined steps, between two of the defined steps, or after all the defined steps (except where the context excludes that possibility).

[0044] The term "at least" followed by a number is used herein to denote the start of a range beginning with that number (which may be a range having an upper limit or no upper limit, depending on the variable being defined). For example "at least 1" means 1 or more than 1. The term "at most" followed by a number is used herein to denote the end of a range ending with that number (which may be a range having 1 or 0 as its lower limit, or a range having no lower limit, depending upon the variable being defined). For example, "at most 4" means 4 or less than 4, and "at most 40%" means 40% or less than 40%. When, in this specification, a range is given as "(a first number) to (a second number)" or "(a first number)-(a second number)," this means a range whose lower limit is the first number and whose upper limit is the second number. For example, 25 to 100 mm means a range whose lower limit is 25 mm, and whose upper limit is 100 mm. The embodiments set forth the below represent the necessary information to enable those skilled in the art to practice the invention and illustrate the best mode of practicing the invention. In addition, the invention does not require that all the advantageous features and all the advantages need to be incorporated into every embodiment of the invention.

[0045] Turning now to Figs. 1A to 20D, a brief description concerning the various components of the present invention will now be briefly discussed.

[0046] **Curcumin ("CUR") sulforaphane ("SFN") enabled self-emulsifying drug delivery systems ("SEDDS") formulation development by high-throughput screening ("HTS").** CUR SFN-SEDDS formulation was developed using the general two-step HTS procedure described herein. Aside

from CUR, this procedure was also utilized in the formulation of SFN-SEDDS for celecoxib ("CLX"), cyclosporine ("CYL"), docetaxel ("DTX"), and paclitaxel ("PTX"). Before commencing with the formulation development, the liquid active pharmaceutical ingredient ("API")/SFN oil core was first prepared. To avoid supersaturation, an excess amount of SFN (20% above solubilization ratio) was added to the in 2 mL glass vials and thoroughly mixed by stirring and vortexing until complete solubilization was confirmed by visual and polarized light microscopy observations. Aliquots (equivalent to 1 mg of the API) were transferred to the wells of a 24 well-plate for subsequent formulation development process.

[0047] **Table 1**: The composition of the SFN-SEDDS formulations that were optimized for the selected drug molecules at the conclusion of the HTS screening process.

API	Surfactants	Co-surfactants	API/SFN/Surfactant/Co-surfactants
CYL	Cremophor EL	Lauroglycol FCC	1/3.6/5.75/5.75
CLX	Tween 80	mPEG350	1/4.8/14.5/14.5
DTX	Cremophor EL	Transcutol HP	1/2.4/8.5/8.5
CUR	Cremophor EL	Acconon CC6	1/3.6/11.5/11.5

[0048] Step 1: Screening of surfactants and the optimization of the API:surfactant ratio. The first step in formulating the SFN-SEDDS was to identify a suitable emulsion stabilizing surfactant for the API. To do so, a stepwise surfactant screening process (Figs. 1A and 1B) was carried out using a 24 well-plate as the mixing/interaction chamber. Briefly, surfactants (Figs. 1A and 1B and Table 1) were solubilized in ethanol at a 1:1 ratio. This surfactant/ethanol blend was then added, while stirring manually, to the API/SFN blend to attain a final API/SFN:Surfactant:Ethanol ratio of 1:5:5 (Fig 1A). Blends were diluted with deionized water to 0.5 mg/mL API concentration and observed for 24 hours at room temperature. In order to detect precipitation indirectly, samples of the diluted blends (200 µL) were transferred to a 96 well-plate and monitored for

obscurity by measuring their absorbance at 562 nm using a microplate reader (BioTek, VT, USA). Prior to analysis, experiments were carried out to confirm that the selected wavelength would not overlap with the absorbance of the APIs and would only measure the transparency of the emulsion. Microscopic observations were simultaneously carried out to confirm the absorbance data. Surfactants that gave stable emulsions in step 1A (Fig. 1A) were selected for further optimization to determine the least amount of surfactant needed to yield a readily emulsifiable formulation without inducing precipitation. This was accomplished by increasing/decreasing the amount of the surfactant/ethanol blend added to API/SFN (Fig. 1B) while monitoring for precipitation after 24 hours of storage by the absorbance technique as before. The absorbance data were reported as percent (%) relative absorbance (Abs) according to following formula:

[0049] $$\%\ Relative\ Abs = \frac{Abs\ of\ sample - Abs\ of\ dilution\ media}{Abs\ of\ dilution\ media} \times 100$$

[0050] In addition to indirectly detecting crystal growth and precipitation, absorbance was found to vary with the droplet size of the reconstituted emulsions. In order to be able to use the absorbance data in formulation development, preliminary experiments were carried out to identify a threshold % relative absorbance value above which the emulsions were deemed unstable. The threshold value for this study was set at 50% for emulsion with API concentration of 0.5 mg/mL dilution concentration. Any formulation showing % relative absorbance > 50 was found to produce precipitates. It is worth noting that this threshold value was experimentally found for the formulation composition and dilution factors used in this study and may need readjustment when different formulation development protocols are used. Boxes in Figs. 1A and 1B that are shaded show the results that were observed during the development of the CUR/SFN-SEDDS.

[0051] Step 2: Screening of co-surfactants and final formula optimization. In this step, suitable co-surfactants were screened and the optimal excipients ratio in the final SFN-SEDDS formulation was determined. Ethanol from the optimal surfactant/ethanol blend for each API, which was identified in step 1, was replaced with a set of co-surfactants. As in step 1, API/SFN and surfactant/co-surfactant blends were mixed in 24 well-plates. After dilution with deionized water, each well was observed for precipitation for 24 hour during which absorbance data were collected and compared. Also observed was the ease with which the formulations were dispersed upon the addition of the dilution media. To attain the final SFN-SEDDS formulation the API/SFN to surfactants/co-surfactants ratio was optimized by sequential screening as described previously step (Fig. 2). Fig. 2 shows the screening process for API:SFN:S:CoS at a starting ratio of 1:2.5:2.5, which was the optimum ratio observed for CUR in step 1. The results of the screening process for CUR are indicated by the shaded boxes in Fig. 2.

[0052] **Solubility study**: Of the twenty-four drug molecules that were investigated in this study, eight showed complete solubilization within the tested API:SFN ratio limit of 1:10, as follows: Docetaxel, Paclitaxel, Cyclosporine A, Curcumin, Celecoxib, Salubrinal, FK-506, and Furesemide (Fig. 3). Among the soluble molecules, Docetaxel had the lowest API:SFN solubilization ratio of 1:2 whereas Furesemide had the highest ratio of 1:7. Soluble API:SFN blends appeared transparent and were void of any insoluble crystals as confirmed by polarized light microscopy (Figs. 4A and 4B). This is the first reporting of the solubilization potential of SFN and the first utilization of this phenomenon in formulating SEDDS for a range of drug molecules that is known to the inventors. While the exact chemical basis for the solubilization capacity of SFN is not clear, the inventors postulate on its interaction with CUR based on Fourier-transform infrared spectroscopy ("FTIR") analysis presented in subsequent discussion.

[0053] **Analysis of CUR/SFN blends by differential scanning calorimetry ("DSC")**: DSC is a thermos-analytical technique that is used to confirm the

alteration of physical state, phase transition, and decomposition of pharmaceutical materials. DSC thermograms of pure CUR and CUR:SFN blends at three different ratios are shown in Figs. 5A-5D. In case of pure curcumin (Fig. 5A), the endothermic peak at 178.1°C corresponds to its melting point. With addition and successive increase in SFN amount in the blend, a decrease in the endothermic peak was observed from 144.5°C for a 1:0.75 CUR:SFN blend (Fig. 5B) to 94.7°C for a 1:1.5 CUR:SFN (Fig. 5C) indicating a gradual loss in the crystallinity of CUR. Similar trend was observed for the enthalpy changes between pure CUR and CUR/SFN blends. Along with broadening of the peak with respect to pure CUR, enthalpy was significantly reduced from 95.6 J/g for pure CUR to 14.8 J/g for CUR/SFN 1: 0.75 blend and 11.1 J/g for CUR/SFN 1:1.5 blend. This reduction in enthalpy can be attributed to the gradual dissolution of the CUR crystals in SFN. At soluble CUR:SFN ratio of 1 to 3 (Fig. 5D), the endothermic peak disappeared marking complete loss of crystals thereby complete solubilization of CUR in SFN.

[0054] **Interaction between CUR and SFN**: The FTIR spectra of CUR, SFN and transparent CUR/SFN blend (at 1 to 3 ratio) are presented in Fig. 6A to 6C respectively. Spectra for CUR and SFN in Figure 6A and 6B show the unique peaks expected as reported in the literature. For example, the characteristic peak for CUR was observed at 3512.5 cm^{-1} representing the stretching vibration of phenolic O-H group. Peaks at 1629 cm^{-1} and 1602 cm^{-1} can be assigned to the C=C vibration of the aromatic ring whereas the peak at 1509.8 cm^{-1} to the C=O and C-C vibration. Peaks within the 1000-1300 cm^{-1} range represent C-O stretching absorption bands. The peak at 963.5 cm^{-1} represents a plane-bending mode of C-H in aromatic ring. Similarly for SFN, characteristic feature of isothiocyanate functional group N=C=S can be observed at 2106.2 cm^{-1} and 2182 cm^{-1}. Peaks at 1298 cm^{-1} and 1027.1 cm^{-1} represent C-N related vibration and S=O group respectively. When CUR was mixed with SFN to yield a clear solution, as shown in Fig. 6C, several peak shifts and peak broadening were observed. In the CUR/SFN blend, the sharp CUR peak at 3512.5 cm^{-1} was broadened with a peak intensity at 3420 cm^{-1}, which could be due to the

interaction between SFN and CUR. Other aspects that could be taken as evidence of complex formation are peak shifts of aromatic C=C at 1602 cm^{-1} and that of the carbonyl C=O peaks at 1629 cm^{-1}. The CUR peak at 1509.8 cm^{-1}, due to the C-C and C=O, underwent a shift to 1513.5 cm^{-1} when blended with SFN, which may be taken as an evidence of complex formation. In the blend, peaks at 1429.7 cm^{-1} and 963.5 cm^{-1} for C-H shifted to 1426.4 cm^{-1} and 966.5 cm^{-1}, respectively, which might be caused by the formation of hydrogen bonds between CUR and SFN.

[0055] **CUR SFN-SEDDS formulation development**: Another embodiment of the presently claimed invention is described next. One objective of the HTS stepwise formulation development process was to identify the best excipients for SEDDS development and to optimize the amount of the surfactants/co-surfactants in the formulation. In traditional formulation development work, identifying the most suitable excipients requires the screening of a large number of probable ingredients, which results in the usage of large amount of drug molecules. As SFN is an expensive molecule and a goal of the inventors was to develop a process that minimized cost, an efficient HTS process for formulation development was warranted. During this process, the API to SFN ratio was kept constant throughout the study as described before. In each step, some of the surfactants and co-surfactants were excluded as they showed signs of precipitation and/or obscurity within the selected observation period (24 hours) when diluted with water. Surfactants/co-surfactants that withstood dilution were considered for further screening and optimization. This exclusion/carry-on decision was made based on two observations: % relative absorbance of emulsions, another embodiment which marks a novel approach for excipients screening process for SEDDS, and microscopic observation of emulsions for precipitation. When more than one suitable surfactant and/or co-surfactant was identified, decision was made based on the clarity of the emulsion as determined by visual and absorbance data. One embodiment of this process is demonstrated in Figs. 7A – 7E, utilizing CUR as a representative example. A representative example for the arrangement of samples in a 96 well-plate to

collect absorbance data is shown in Fig. 8. In HTS SEDDS formulation development, surfactants were screened first, followed by co-surfactants. For CUR SFN-SEDDS development, the HTS process started with an initial CUR/SFN:Surfactant:Ethanol blend at a ratio of 1:5:5. At this ratio, four surfactants showed good emulsification property without any precipitation (Fig. 7A). When the ratio was adjusted to 1:2.5:2.5 all emulsions showed signs of precipitation (Fig. 7B) indicating the necessity to increase the surfactant amount to attain the optimum surfactants ratio. Therefore, the ratio was adjusted to 1:3.75:3.75 where all emulsions were stable indicating this to be the ideal surfactant ratio. The best surfactant with lowest % relative abs and visual clarity (Cremophor EL) was selected for the second step when screening co-surfactants (Fig. 7C). Addition of co-surfactants improves the emulsification capacity of surfactants by lowering surface tension. In this step, the ethanol in the surfactant/ethanol blend was replaced with co-surfactants at the ratio where first signs of precipitation were observed from the previous step. For CUR that would have been 1:2.5:2.5. By doing so, a formulator can readily identify co-surfactants that have better solubilization and emulsification capacity than ethanol. During this phase of the screening process, two co-surfactants; Acconon CC6 ® and Labrasol ®, produced stable emulsion. Based on % relative abs data, Acconon CC6 ® was selected for final formulation optimization (Fig. 7D). To optimize the amount of co-surfactant, the CUR/SFN:surfactant:co-surfactant ratio was initially adjusted to 1:1.25:1.25, where the emulsion precipitated immediately suggesting a CUR/SFN:cremophor:Acconon ratio of 1:2.5:2.5 as optimum formulation ratio. For different drug molecules, different surfactant and co-surfactants at different ratios were identified as optimal. Due to the expense and limitation in the available quantities of raw materials, fine tuning the surfactant to co-surfactant ratio and the impact of co-solvents was not pursued.

[0056] As an additional embodiment using the disclosed invention, prototype SFN-SEDDS formulations for four drug molecules were developed simultaneously. Paclitaxel (PTX) was excluded from the formulation list due to

high surfactant ratio requirements, which showed emulsion instability even at 1:10:10 ratio of PTX/SFN:surfactant:co-surfactant. The drug to excipient ratios in the final formulations are presented in Table 2.

[0057] **Table 2**: Taxane microemulsifying preconcentrates showing the ratio of each component in the optimized formulations

Taxane	API	SFN	Vitamin E TPGS	Transcutol HP
Paclitaxel (PTX)	1	3.6	34.5	34.5
Docetaxel (DTX)	1	2.4	4.25	4.25

[0058] Unlike conventional SEDDS formulation approach where a large number of test formulations are prepared to obtain the optimum formulations, this invention demonstrated a highly efficient method of formulation development, and optimization by formulating fewer numbers of test formulations, where each step leads towards optimum formula. In addition to enabling the formulation of multiple drug molecules simultaneously, it also permitted the screening of large number of excipients by a high throughput format. Due to the structure of the wells in a 96 well-plate, in some cases minuscule precipitation at the very edge of the well might not be sensible by microplate reader, which was confirmed by microscopic observation.

[0059] **Dissolution study**: The dissolution profiles of the optimized CUR SFN-SEDDS in simulated intestinal fluid ("SIF," pH 7.4) and simulated gastric fluid ("SGF," pH 1.2) are shown in Fig. 9. Approximately 90% of the CUR SFN-SEDDS was dissolved in SIF and SGF media within 2.5 and 3 minutes, respectively. This indicates fast release and efficient self-emulsification property of the formulated SFN-SEDDS. Within 10 minutes of the study, 97% and 96% of CUR was dissolved in SGF and SIF, respectively, forming a transparent yellow solution in both media (Figs. 10A and 10B). This transparency indicates the formation of oil-in-water microemulsion with small particle size, presumably <30 nm, based on the inventors' understanding. As CUR is practically insoluble in water at acidic or neutral pH, and since less than 2% of crude curcumin is

expected to dissolve within 60 minutes, the significant increase in CUR solubility demonstrated the superiority of the SFN-SEDDS formulation as a delivery vehicle. Absorbance detection at 425 nm ensured that the dissolved quantity reflected the amount of CUR dissolved and that no degradation products are present.

[0060] **Stability of the emulsions**: The physical stability of the four SFN-SEDDS formulations that were developed by the HTS process for CYL, CLX, DTX, and CUR, was monitored in different media and temperatures (Figs. 11A-11D). In acidic media, CUR SFN-SEDDS dispersion was stable for the total test period of 30 days except at 37°C, where it was stable for only 12 days (4 days in SIF, Fig. 11D). Although absorbance values above the 50% threshold were recorded for CUR dispersions in SIF (pH 7.4) at 4° C and 25° C, no precipitation was observed. This could be due to the hydrolytic degradation of the CUR in basic pH producing different molecules with higher absorbance intensity. This result also indicates that measurement of absorbance during the HTS screening process may not only be useful in detecting drug precipitation or phase separation, but potentially chemical degradation of susceptible drug molecules such as CUR.

[0061] For CYL emulsion (Fig. 11A), no precipitation was observed for the total observation period of 30 days. The percent relative absorbance value was below threshold limit (50%) at all time points. Absence of precipitation and/or crystal growth was also confirmed by polarized light microscopically. For CLX (Fig. 11B) and DTX (Fig. 11C), SEDDS dispersions in water showed variable stability based on media and temperature conditions, which was confirmed both by change in absorbance and microscopic observation. As mentioned previously, due to the limitation of the microplate reader, DTX dispersions at 4° C and 25°C in SGF media did not show meaningful change in absorbance although minuscule precipitation was observed by microscopy. Despite this limitation, the disclosed HTS method bears huge potential in SEDDS development and warrants further optimization in parallel with other techniques,

such as particle size and turbidity measurements that have been adopted to test the physical stability of formulations.

[0062] **Additional Embodiments**

[0063] **Solubility study and development of taxanes-SFN microemulsions**: During the solubility study of compounds other than curcumin, a gradual loss of taxane crystals was observed with an increase in the amount of SFN in the blend. PTX and DTX dissolved completely and almost instantaneously in SFN at a taxane to SFN w/w ratio of 1:3 and 1:2, respectively. Absence of crystals in the blend when completely dissolved was confirmed by polarized light microscopy (Figs. 12A and 12B).

[0064] For the formulation development work, 1 mg of PTX or DTX was dissolved in 3.6 mg and 2.4 mg of SFN, respectively. 20% more SFN was used in the blend than needed to avoid any possible supersaturation of taxanes in subsequent formulation development steps. To solubilize the taxane-SFN oily blend in water, three surfactants; D-α-Tocopherol polyethylene glycol 1000 succinate ("Vitamin E TPGS" or "TPGS"), Macrogol-15-Hydroxystearate ("Solutol® HS 15"), and Polyoxyethylene-Polyoxypropylene Block Copolymer ("Poloxamer 124"), were evaluated. These surfactants were selected as they have a history of being extensively used as excipients in drug delivery including injectable dispersions. TPGS has been approved for use in several specialty products in the US and Europe. Most notable is its use in the formulation of the Tocosol® injectable emulsions. Similarly, due to its solubilizing capacity and favorable safety profile, Solutol® HS15 was officially published as polyoxyl 15 hydroxystearate *NF* monograph in *USP* 33–*NF* 28 and was suggested for the use in the formulation of intravenous rolapitant. Poloxamer 124, a liquid triblock copolymer of polypropylene glycol and polyethylene glycol, is another surfactant that was found to be safe and effective for use in drug delivery systems.

[0065] TPGS, Solutol® HS15, and Poloxamer 124 were screened as described earlier by measuring the percent relative absorbance of the microemulsion formed after the taxane/SFN blend in the surfactant/ethanol mixture was gently dispersed in water (Figs. 13A-13D for PTX and Figs. 14A-14D for DTX). A

relative absorbance reading greater than 50% indicated that the drug was precipitating out of the solution, which was confirmed by microscopic and visual analysis. Within few hours of preparation, PTX was found to precipitate from microemulsions that were prepared at an initial PTX/SFN:S:EOH ratio of 1:5:5 when stored at normal room conditions (Fig. 13A). When the ratio was adjusted to 1:10:10, only formulations made with TPGS were stable for up to 72 hours, which was the duration of the monitoring period (Fig. 13B). PTX microemulsions with TPGS remained stable even after the composition was adjusted to 1:7.5:7.5 (Fig. 4C) or when ethanol was replaced with Transcutol HP (Fig. 13D). Transcutol is a highly purified diethylene glycol monoethyl ether, which has a similar consistency and viscosity as ethanol. It was recognized as a powerful solvent in microemulsions and was found to be well tolerated across animal species and gender with toxicity occurring only at levels well above those intended for human use.

[0066] At a 1:7.5:7.5 ratio, a PTX microemulsion pre-concentrate was found to readily disperse in water into a transparent solution under mild agitation. A significantly lesser amount of surfactant, however, was needed to solubilize an equal weight of DTX in water. When formulated at a DTX/SFN:S:EOH ratio of 1:5:5 using either TPGS or Solutol, DTX microemulsions readily dispersed into transparent solution (Fig. 14A). Both surfactants remained equality effective when the ratio was adjusted to 1:2.5:2.5 (Fig. 13B) and 1:1.25:1.25 (Fig. 14C), even when ethanol was replaced as a co-solvent with Transcutol to make an alcohol-free formulation (Fig. 14D). At a 1:1.25.1.25 ratio, DTX a microemulsion pre-concentrate was found to yield a transparent solution when diluted with water under mild agitation. Although both TPGS and Solutol were found to be suitable for formulating DTX, TPGS was selected for subsequent testing based on visual observation of the formulations. The use of TPGS in the formulation may also offer a potential for high cellular adhesion and adsorption.

[0067] The compositions of the optimized PTX and DTX formulations as predicted by the screening study are given in the Table 1. This study marks the first report on utilizing the solubilization capacity of SFN to prepare taxane

microemulsifying formulations that the inventors are aware of. When compared to the commercial taxanes injection solutions, SFN-enabled formulations had significantly lower amount of added excipients. The PTX SFN microemulsifying formulation contained 72.6 mg of excipients per 1 mg of PTX whereas PTX Injection Solution USP contains approximately 153.8 mg of excipients per 1 mg of PTX, or 527 mg of Cremophor EL and 396 mg of Ethanol per 6 mg of PTX. Similarly, DTX Injection Solution USP uses approximately 46.7 mg of excipients per 1 mg of DTX or 540 mg of Tween 80 and 395 mg of alcohol per 20 mg of DTX. The amount of excipients in the DTX formulation was reduced by more than 4 folds in the reformulated DTX-SFN microemulsifying formulation in which only 10.9 mg of excipients was used for each 1 mg of DTX.

[0068] **Droplet size and PDI measurement**: Droplet size of emulsions impacts the rate and extent of drug release as well as intestinal absorptions and bioavailability of active ingredients. Both PTX and DTX SFN microemulsion pre-concentrates gave a transparent microemulsion when deionized water was added. The droplet size of the resultant microemulsions was 16.1 nm ± 1.9 nm and 13.6 nm ± 0.2 nm, respectively. The small droplet size confirms the formation of thermodynamically stable, transparent microemulsions. The polydispersity index ("PDI") for both microemulsions was also low; 0.37 ± 0.04 for the PTX microemulsion and 0.22 ± 0.05 for the DTX microemulsion, which indicates a uniform size distribution of the microemulsion droplets.

[0069] **Physical stability of microemulsions**: The physical stability of the PTX and DTX microemulsions in 5% dextrose solution and normal saline (0.9% sodium chloride solution) when stored at 4 ^{o}C, 25 ^{o}C, and 37 ^{o}C was monitored over a period of 30 days by microscopic analysis and absorbance measurements (Figs. 15A and 15B). The stability of the PTX microemulsions in both media was found to be temperature dependent (Fig. 15A). PTX readily precipitated when the microemulsions were stored in an oven at 37 ^{o}C. Even when stored at room temperature, signs of precipitation were observed after approximately two weeks. Microemulsions were nonetheless stable, up to 30 days, when refrigerated. These results indicated that special considerations should be taken when handling PTX reconstituted microemulsions. On the other hand, DTX microemulsions were found to be stable in all tested media at all

storage conditions throughout the study period of 30 days as indicated by the low absorbance values, which was also confirmed by microscopic analysis (Fig. 15B).

[0070] **Hemolysis testing**: A hemolysis study was carried out to investigate the toxicity of the SFN formulations and their ability to induce hemolysis by compromising the integrity of the erythrocytes cell membrane. The hemolytic effect of TTR and SFN-TTR was investigated and compared to the vehicle used in formulating PTX and DTX in commercial injection solutions within a broad concentration range from 0.001 to 1.0 mg of vehicle/mL (Fig. 16). All vehicles were found to be safe where no hemolysis was detected even when the red blood cells (RBCs) were treated with vehicle concentration of up to 1.0 mg/mL. Of note is the observation that the vehicle in commercial DTX solution induced approximately 4% hemolysis at a concentration of 1.0 mg/mL. These findings suggest that using SFN to develop vehicles to solubilize PTX and DTX may be suitable for *in vivo* delivery of these drugs.

[0071] ***In vitro* anticancer activity against human breast cancer cells**: The *in vitro* anticancer activity study was carried out against two human breast cancer cell lines; MDA-MB-231 and MCF-7. This study was intended to examine the activity of the newly developed SFN based self-microemulsifying taxane formulations and to compare their activity to the marketed PTX and DTX injection solutions. The vehicle used in the SFN enabled formulations was also evaluated as a control against the two cell lines.

[0072] The growth inhibitory activity of the formulations was evaluated by IncuCyte® live cell analysis and further confirmed by the CellTiter-Blue® assay. The IncuCyte® system allows for real time monitoring of cell growth inhibition by determining the confluence of the cells under treatment. To determine whether the observed changes in the confluence is due to the reduction in cancer cell viability, a traditional cell viability assay was also performed in parallel. This combination of real time confluency monitoring via the IncuCyte® assay and end-point cell viability assay approach ensured effective and reproducible readout for the anticancer activity of the formulations.

[0073] Initially the *in vitro* cytotoxicity of the drug-free vehicles; TPGS blend with Transcutol, with or without SFN were evaluated against both cell lines (Figs. 17A to 17D). In case of MDA-MB-231 cells, no growth inhibition of cells was observed compared to control at 72 hour time point when cells were treated with up to 10 μM of TPGS (Figure 17A). Although TPGS was toxic at concentrations > 25 μM (data not shown), a treatment concentration of 10 μM is the upper extreme as it represents the amount of TPGS in the 500 nM PTX microemulsion formulation. The amount of TPGS in the 500 nM DTX was only about 1.1 μM. A similar trend of growth inhibition was observed when SFN was added to the vehicle. Although some reduction in confluence was observed when cells were monitored by the IncuCyte® systems, no significant differences were found between the vehicles with or without SFN when cell viability was quantified by the CellTiter-Blue® assay. In the inventors' experiments, SFN was shown to suppress confluence and induce cell death, but at concentrations > 15 μM (data not shown). These concentrations, however, were too high to have a meaningful impact on the activity of the PTX or DTX microemulsions. A treatment of 500 nM PTX microemulsion contained approximately 8.7 μM SFN and only 5.5 μM in the 500 nM DTX treatment. Therefore, the vehicle, with or without SFN was not expected to have an impact on MDA-MB-231 cell viability when treated with PTX or DTX as shown later. TPGS, however, was found to be toxic against MCF7 cells at 10 μM concertation. Therefore, the toxicity of the 500 nM PTX microemulsion against the MC7 cells could be discarded as the artifact of TPGS toxicity. This however could not be said about the 500 nM DTX or the 100 nM PTX treatments that contained about 1.1 and 2 μM TPGS, respectively. At 2 μM, TPGS had significantly lower toxicity against the MCF7 cells as observed by the IncuCyte® analysis and CellTiter-Blue® assay. As observed with the MDA-MB-231 cells, SFN had a marginal effect on MCF7 viability at 2 and 10 μM concentrations.

[0074] Since MDA-MB-231 cells are sensitive to both PTX and DTX in nM range, the activity of the drug loaded formulations was tested from 5 to 500 nM range. For PTX formulations (Figs. 18A and 18B), a notable growth inhibition was observed at 50 nM concentration when cells were monitored by live IncuCyte® analysis, with a significant

reduction in confluence when cells were treated with either the PTX-SFN microemulsion or the injection solution at 100 and 500 nM PTX concentrations. Similar results were observed when cell viability was quantified by the CellTiter-Blue® assay (Figure 20A). Both the PTX-SFN microemulsion and the injection solution had similar cytotoxic effect on cells. However, when treated with 500 nM PTX, approximately 71% of cells remained viable when treated with the commercial injection solution, which was reduced to 50% when cells were treated with the PTX-SFN microemulsion, marking a statistically highly significant difference ($p=0.0001$) between the two formulations. The significant effect of the PTX-SFN microemulsion could be attributed to the presence of SFN in the formulation. As the concentration of PTX increased to 500 nM, the concentration of the associated SFN also increased simultaneously to 8.67 μM; which showed some cytotoxic effect when tested by the IncuCyte® assay. For lower concentrations of PTX, the amount of associated SFN was too low to show a noticeable enhancement in effect, and therefore no significant differences between the injection solution and the PTX-SFN microemulsion was observed ($P>0.05$). Similar observations could be made on the effect of DTX on the viability of the MDA-MB-231 cells. Both DTX-SFN microemulsion and the commercial injection solution significantly reduced cell confluence at concentrations as low as 10 nM when monitored by the IncuCyte® assay (Figs. 18C and 18D). Both formulations also showed dose dependent reduction in cell viability when quantified by the CellTiter-Blue® assay (Fig. 20B). No significant differences, however, were observed between the two formulations. Unlike the PTX-SFN microemulsions, the amount of SFN present in the DTX microemulsion at 500 nM DTX concentration was only 5.47 μM, which was shown to have an insignificant effect on cell viability. Therefore, due to the comparatively small amount of SFN present in the formulations the difference between the DTX formulations was not significant.

[0075] As with MDA-MB-231, IncuCyte® data for the MCF7 cell line showed dose dependent reduction in confluency when treated with either the reformulated or commercial PTX or DTX products (Figs. 19A to 19D). For all PTX and DTX formulations almost complete inhibition of confluency was observed from 10 nM treatment. Viability data when quantified by the CellTiter-Blue® assay for PTX-SFN microemulsions showed significant decrease in all concentration when compared to the injection solution (Fig. 20C). At 50 nM treatment, for example, PTX-SFN microemulsion reduced cell viability to 48.8% whereas cells treated with the commercial PTX injection

solution showed 61.8% viability. Reformulated PTX-SFN microemulsions showed statistically significant ($P<0.05$) reduction in cell viability when compared to the injection solution at 50, 100 and 500 nM PTX treatment, which might be attributed to the presence SFN. No significant differences in cell viability, however, were observed between the two DTX formulations (Fig. 20D).

[0076] The invention illustratively disclosed herein suitably may explicitly be practiced in the absence of any element which is not specifically disclosed herein. While various embodiments of the present invention have been described in detail, it is apparent that various modifications and alterations of those embodiments will occur to and be readily apparent those skilled in the art. However, it is to be expressly understood that such modifications and alterations are within the scope and spirit of the present invention, as set forth in the appended claims. Further, the invention(s) described herein is capable of other embodiments and of being practiced or of being carried out in various other related ways. In addition, it is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items while only the terms “consisting of” and “consisting only of” are to be construed in the limitative sense.

Wherefore, I/we claim

1. A pharmaceutical composition for treating a pathology in a mammal comprising:

an effective amount of a first therapeutic;

wherein the first therapeutic is solubilized with a solubilizing liquid including a compound having an isothiocyanate group.

2. The pharmaceutical composition of claim 1 wherein the solubilizing liquid is an oil, the first therapeutic is a lipophilic compound, and the mammal is a human.

3. The pharmaceutical composition of claim 2 wherein the oil includes a natural product oil.

4. The pharmaceutical composition of claim 3 wherein the natural product oil is derived from one of from broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof.

5. The pharmaceutical composition of claim 2 wherein the compound having an isothiocyanate group is sulforaphane.

6. The pharmaceutical composition of claim 5 wherein the first therapeutic is one of an anti-cancer drug, an immunosuppressive drug, and a natural product.

7. The pharmaceutical composition of claim 6 wherein the anti-cancer drug is one of paclitaxel and docetaxel, and some combination thereofe.

8. The pharmaceutical composition of claim 6 wherein the immunosuppressive drug is one of FK-506 and cyclosporine.

9. The pharmaceutical composition of claim 6 wherein the natural product is curcumin.

10. The pharmaceutical composition of claim 5 wherein the first therapeutic is one of Docetaxel, Paclitaxel, Cyclosporine A, Curcumin, Celecoxib, Salubrinal, FK-506, and Furesemide.

11. The pharmaceutical composition of claim 5 wherein the first therapeutic is contained in one of an emulsion, a microemulsion, and a cream.

12. The pharmaceutical composition of claim 5 wherein the pathology is a cancer.

13. The pharmaceutical composition of claim 12 wherein the cancer is breast cancer.

14. The pharmaceutical composition of claim 13, wherein the breast cancer is one of MDA-MB-231 and MCF-7.

15. A method for solubizing a lipophilic chemical comprising:

combining the lipophilic chemical with a compound having an isothiocyanate group.

16. The method of claim 15 wherein the compound having an isothiocyanate group is sulforaphane.

17. The method of claim 16 wherein the compound having an isothiocyanate group is derived from a natural product oil derived from one of from broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof.

18. The method of claim 16 wherein the lipophilic chemical is contained in one of an emulsion, a microemulsion, and a cream.

19. A pharmaceutical composition for treating a breast cancer in a human comprising:

an effective amount of a first therapeutic; and

a natural oil containing sulforaphane;

wherein the first therapeutic is one of paclitaxel and docetaxel, and some combination thereof,

the first therapeutic is solubilized with the natural oil;

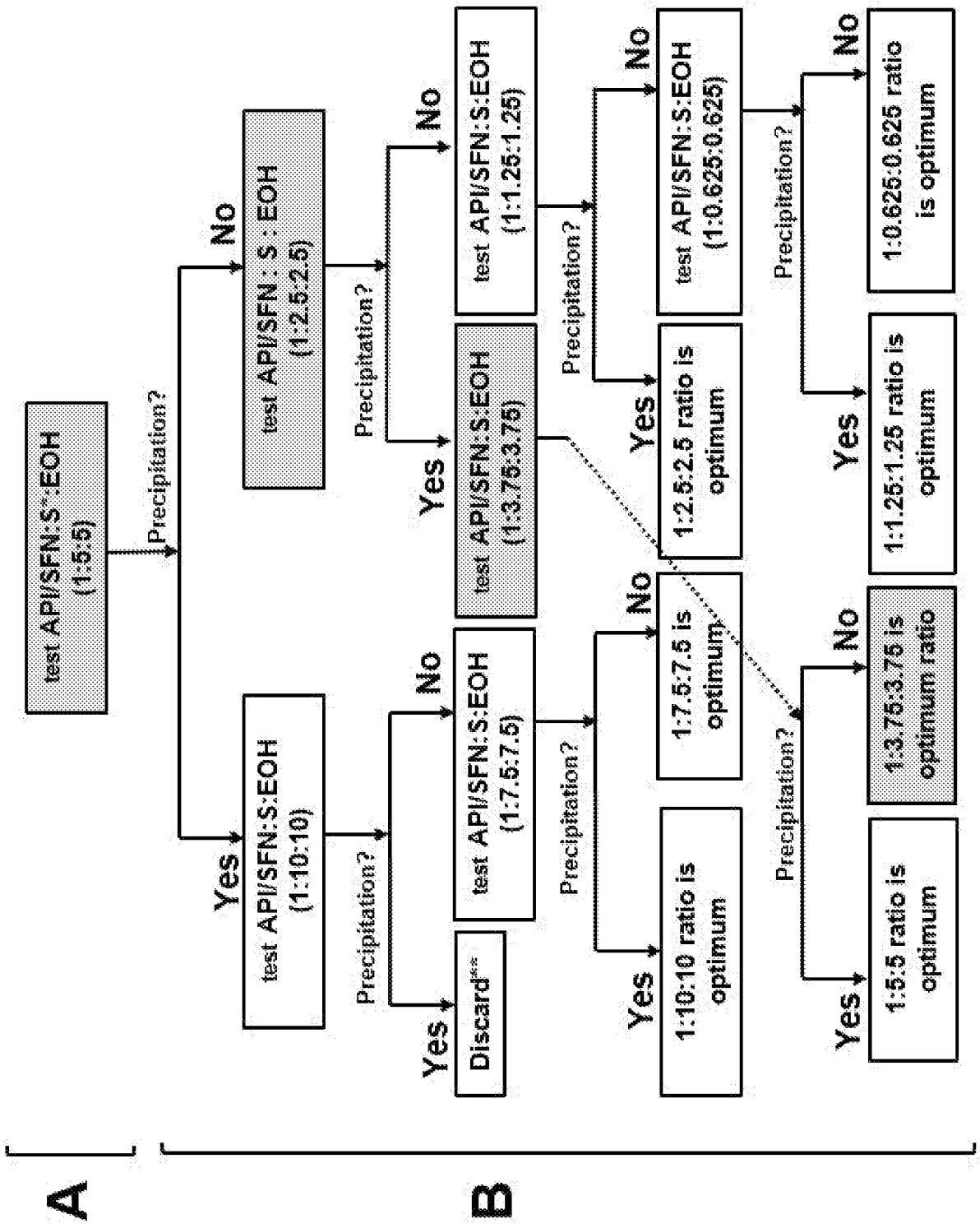
the natural oil is derived from one of broccoli, Brussels sprout, cabbage, cauliflower, bok choy, kale, collards, Chinese broccoli, broccoli raab, kohlrabi, mustard, turnip, radish, arugula, and watercress, and some combination thereof;

the first therapeutic is contained in one of an emulsion, a microemulsion, and a cream;

the breast cancer is one of MDA-MB-231 and MCF-7; and

the composition is a self-emulsifying drug delivery system.

FIG. 1


A
B
test API/SFN:S*:EOH (1:5:5)
Precipitation?
Yes
No
test API/SFN:S:EOH (1:10:10)
test API/SFN:S:EOH (1:2.5:2.5)
Precipitation?
Yes
No
Discard**
test API/SFN:S:EOH (1:7.5:7.5)
test API/SFN:S:EOH (1:3.75:3.75)
Precipitation?
Yes
No
1:10:10 ratio is optimum
1:7.5:7.5 is optimum
test API/SFN:S:EOH (1:1.25:1.25)
test API/SFN:S:EOH (1:0.625:0.625)
Precipitation?
Yes
No
1:5:5 ratio is optimum
1:3.75:3.75 is optimum ratio
1:2.5:2.5 ratio is optimum
1:1.25:1.25 ratio is optimum
1:0.625:0.625 ratio is optimum

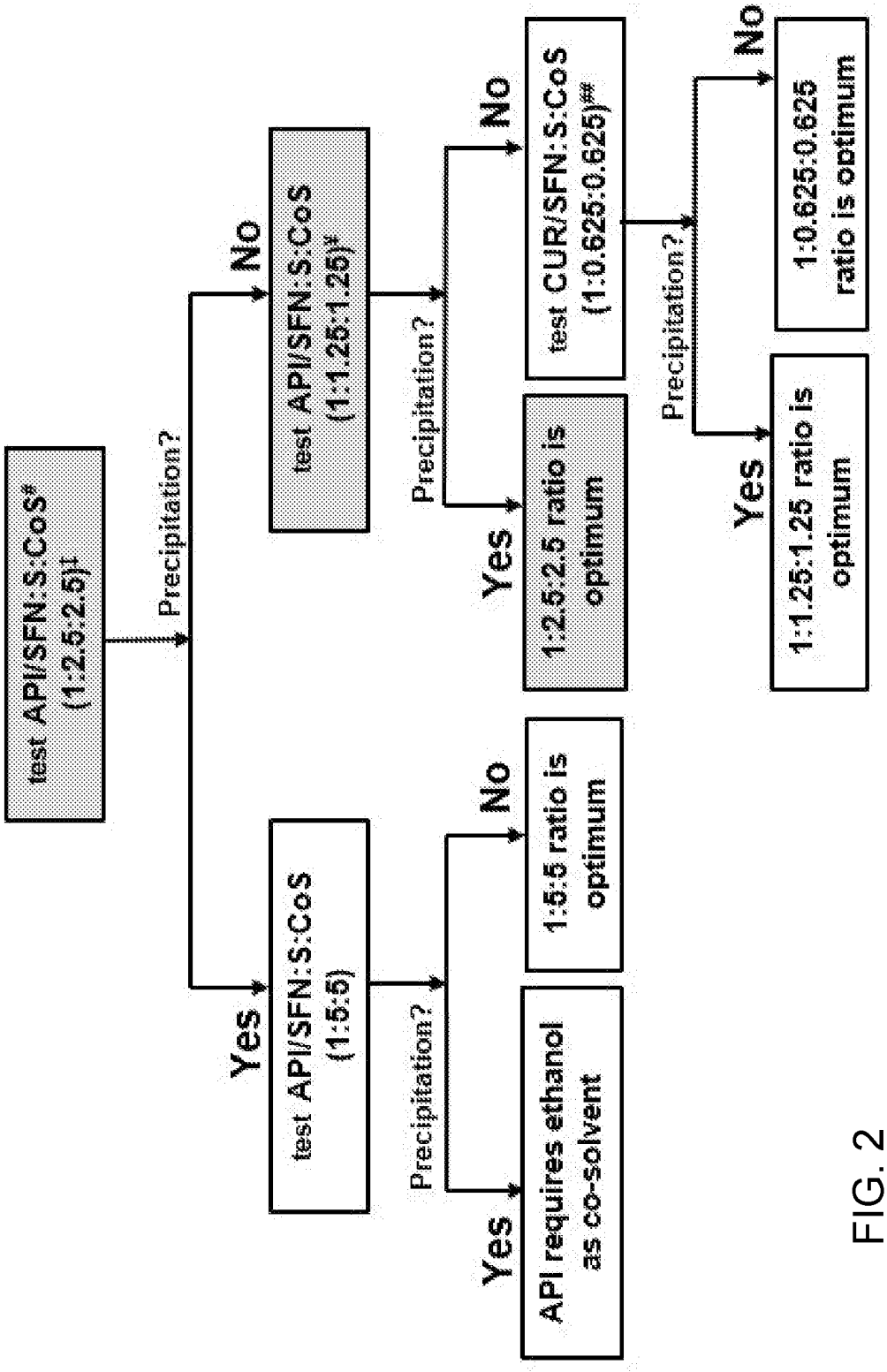
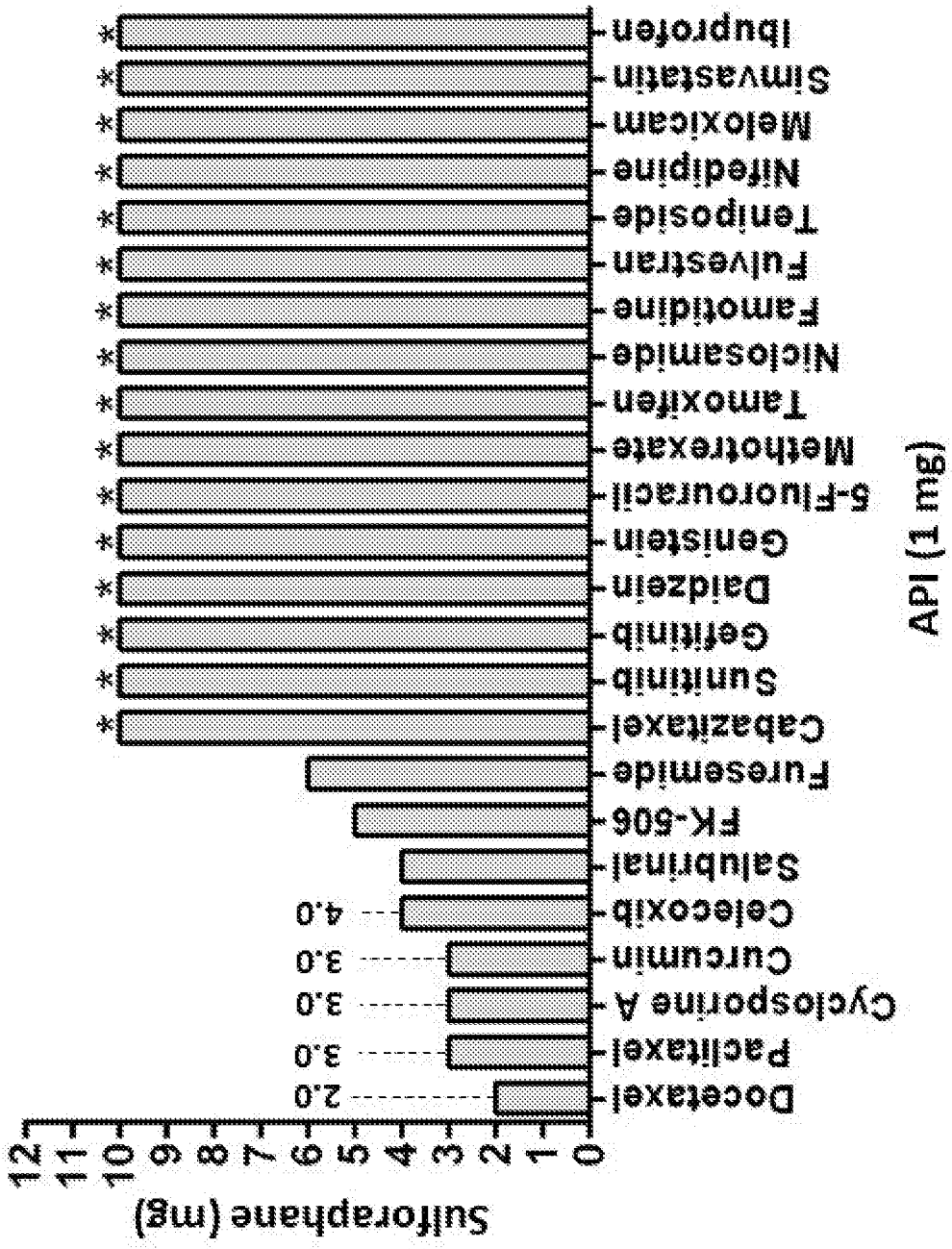

test API/SFN:S:CoS# (1:2.5:2.5)‡
Precipitation?
No
test API/SFN:S:CoS (1:1.25:1.25)#
Precipitation?
No
test CUR/SFN:S:CoS (1:0.625:0.625)##
Precipitation?
No
1:0.625:0.625 ratio is optimum
Yes
1:1.25:1.25 ratio is optimum
Yes
1:2.5:2.5 ratio is optimum
Yes
test API/SFN:S:CoS (1:5:5)
Precipitation?
No
1:5:5 ratio is optimum
Yes
API requires ethanol as co-solvent

FIG. 2

FIG. 3


Sulforaphane (mg)
0
1
2
3
4
5
6
7
8
9
10
11
12
API (1 mg)
Docetaxel
Paclitaxel
Cyclosporine A
Curcumin
Celecoxib
Salubrinal
FK-506
Furosemide
Cabazitaxel
Sunitinib
Gefitinib
Daidzein
Genistein
5-Fluorouracil
Methotrexate
Tamoxifen
Niclosamide
Famotidine
Fulvestran
Tenipside
Nifedipine
Meloxicam
Simvastatin
Ibuprofen
2.0
3.0
3.0
3.0
4.0
*

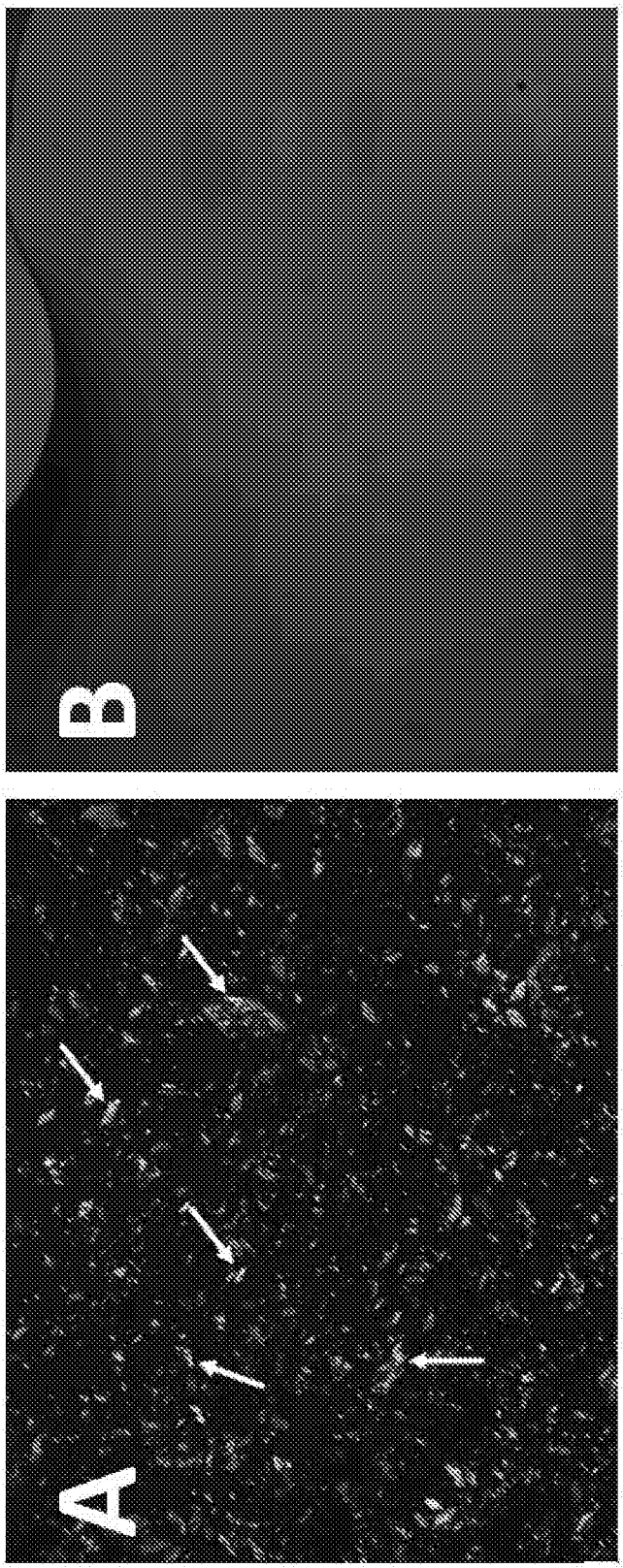
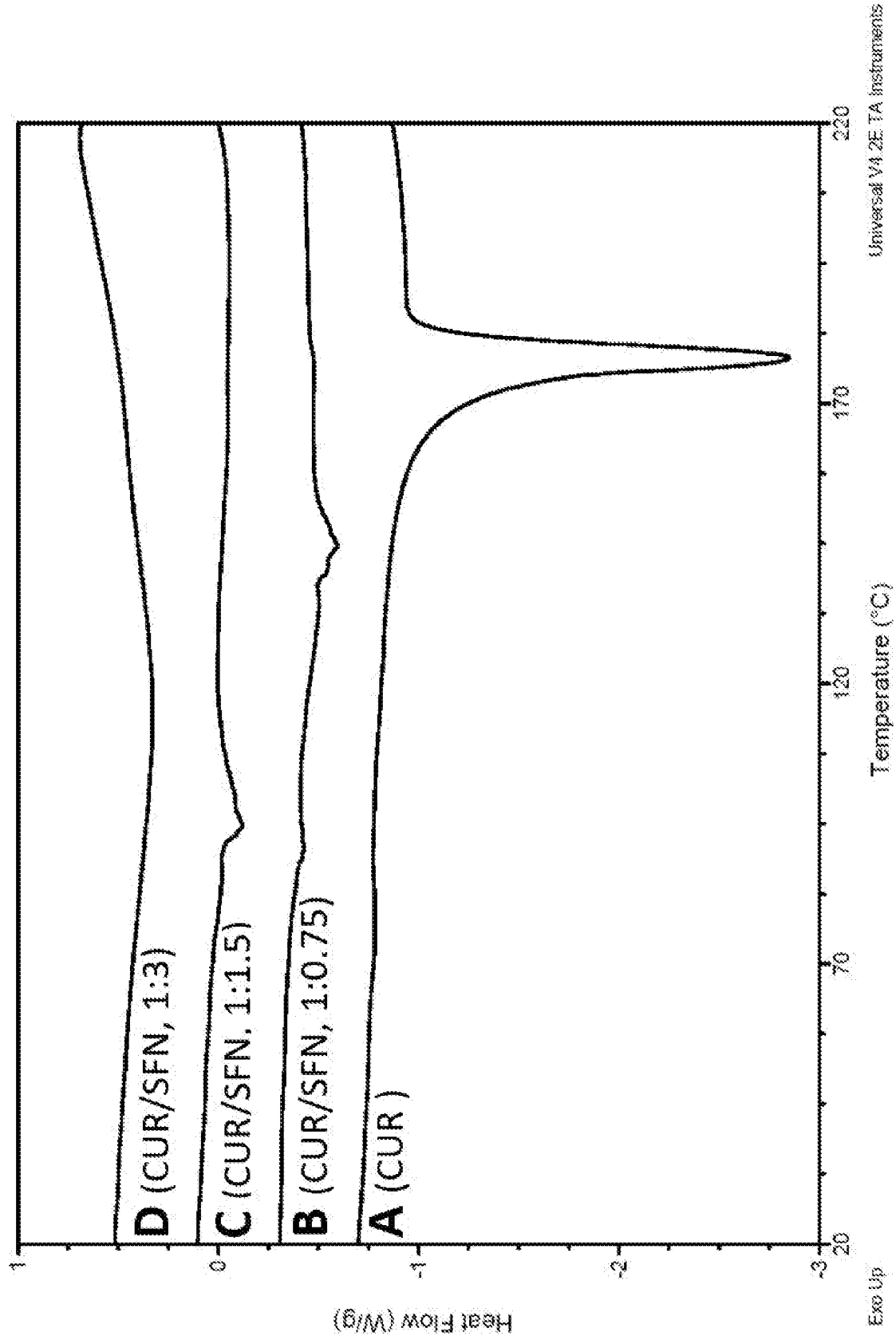


FIG. 4

FIG. 5


D (CUR/SFN, 1:3)
C (CUR/SFN, 1:1.5)
B (CUR/SFN, 1:0.75)
A (CUR)
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.2E TA Instruments

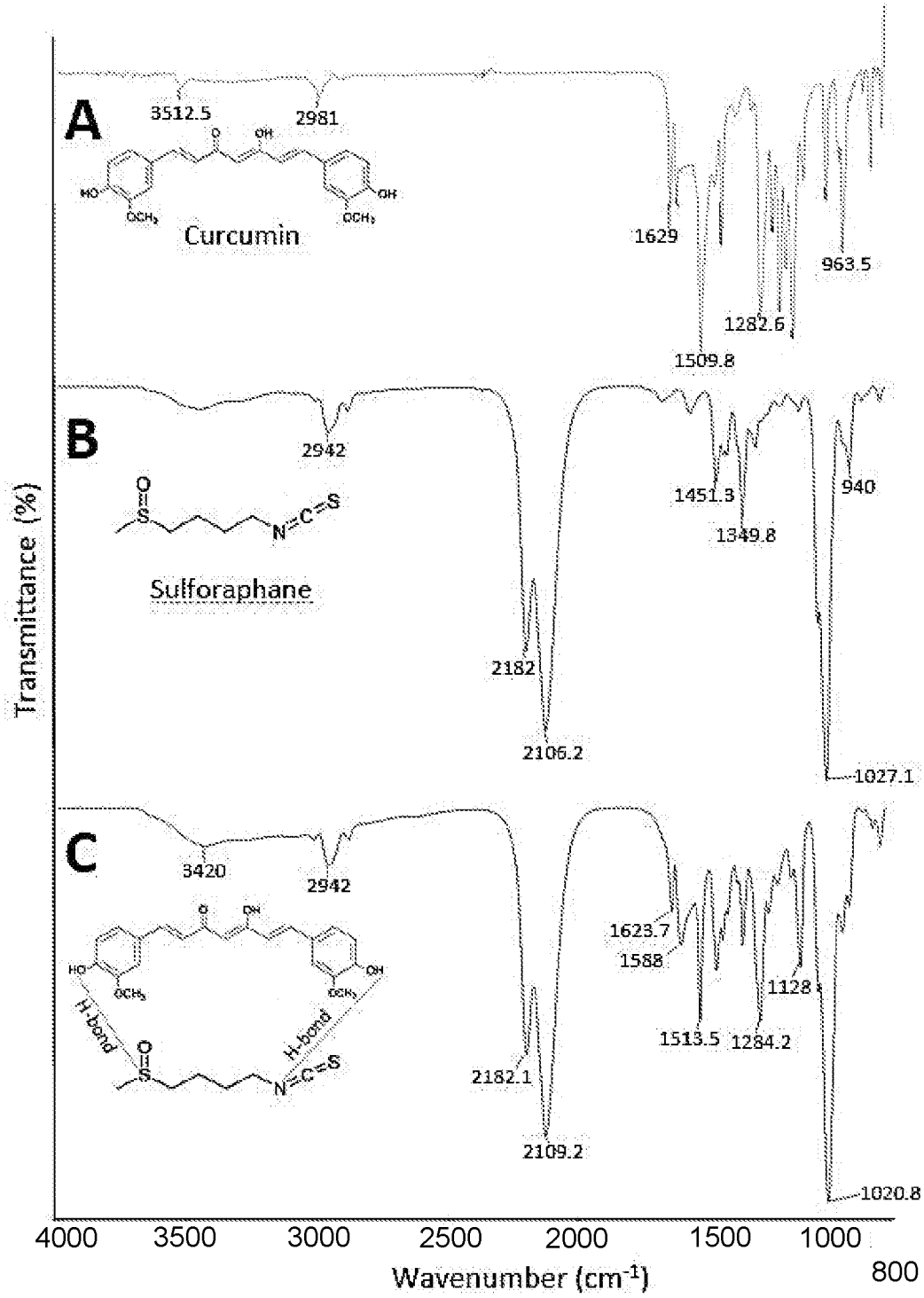

A
3512.5
2981
Curcumin
1629
1509.8
1282.6
963.5
B
2942
Sulforaphane
1451.3
1349.8
940
2182
2106.2
1027.1
C
3420
2942
H-bond
H-bond
1623.7
1588
1513.5
1284.2
1128
2182.1
2109.2
1020.8
Transmittance (%)
4000
3500
3000
2500
2000
1500
1000
800
Wavenumber (cm-1)

FIG. 6

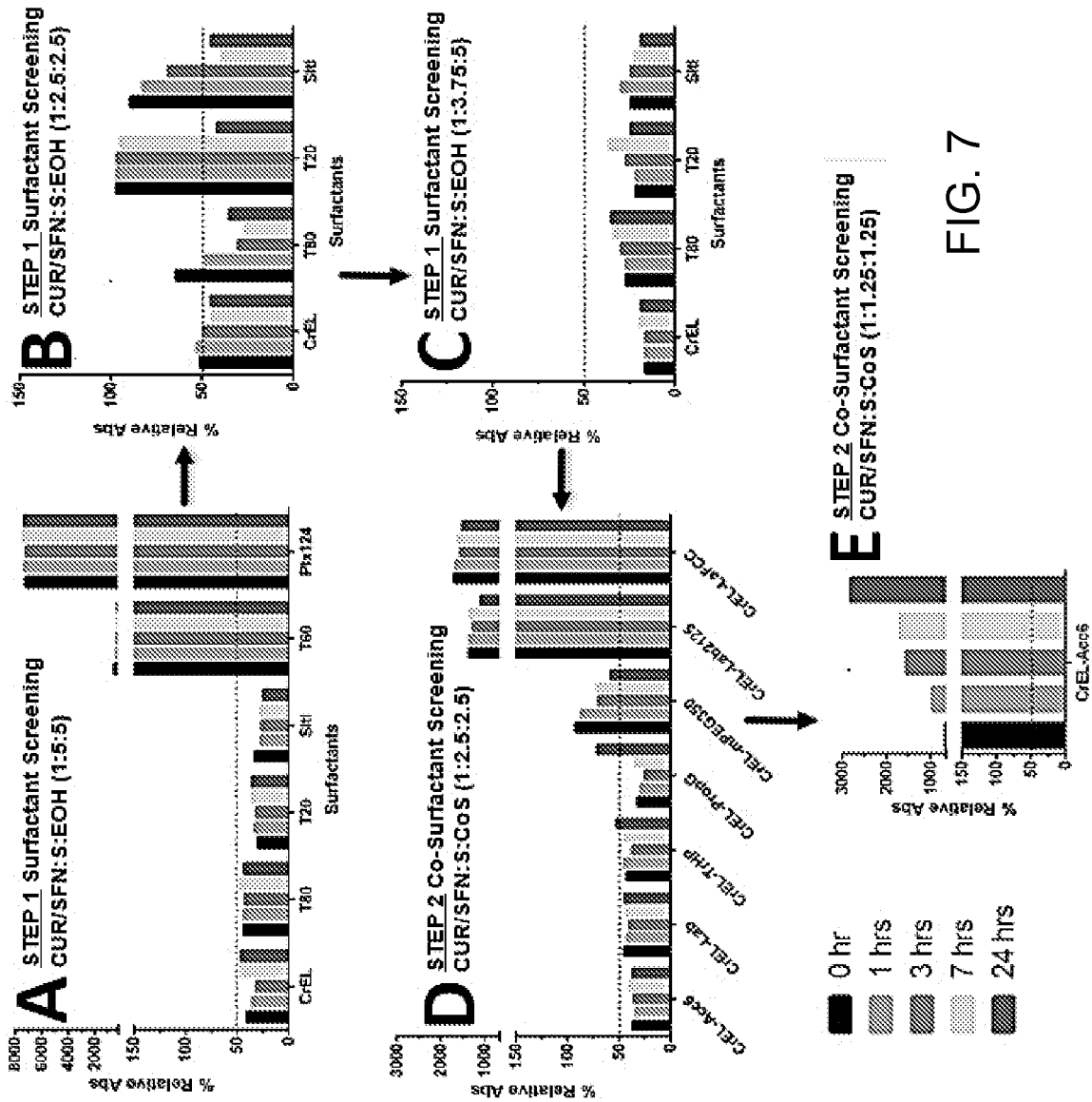

A STEP 1 Surfactant Screening
CUR/SFN:S:EOH (1:5:5)
% Relative Abs
Surfactants
CrEL
T80
T20
Slkl
T60
Pls124
B STEP 1 Surfactant Screening
CUR/SFN:S:EOH (1:2.5:2.5)
C STEP 1 Surfactant Screening
CUR/SFN:S:EOH (1:3.75:5)
D STEP 2 Co-Surfactant Screening
CUR/SFN:S:CoS (1:2.5:2.5)
CrEL-Ace6
CrEL-Lab
CrEL-THP
CrEL-Prop6
CrEL-apEG350
CrEL-Lab2125
CrEL-LaFCC
E STEP 2 Co-Surfactant Screening
CUR/SFN:S:CoS (1:1.25:1.25)
CrEL-Ace6
0 hr
1 hrs
3 hrs
7 hrs
24 hrs

FIG. 7

FIG. 8

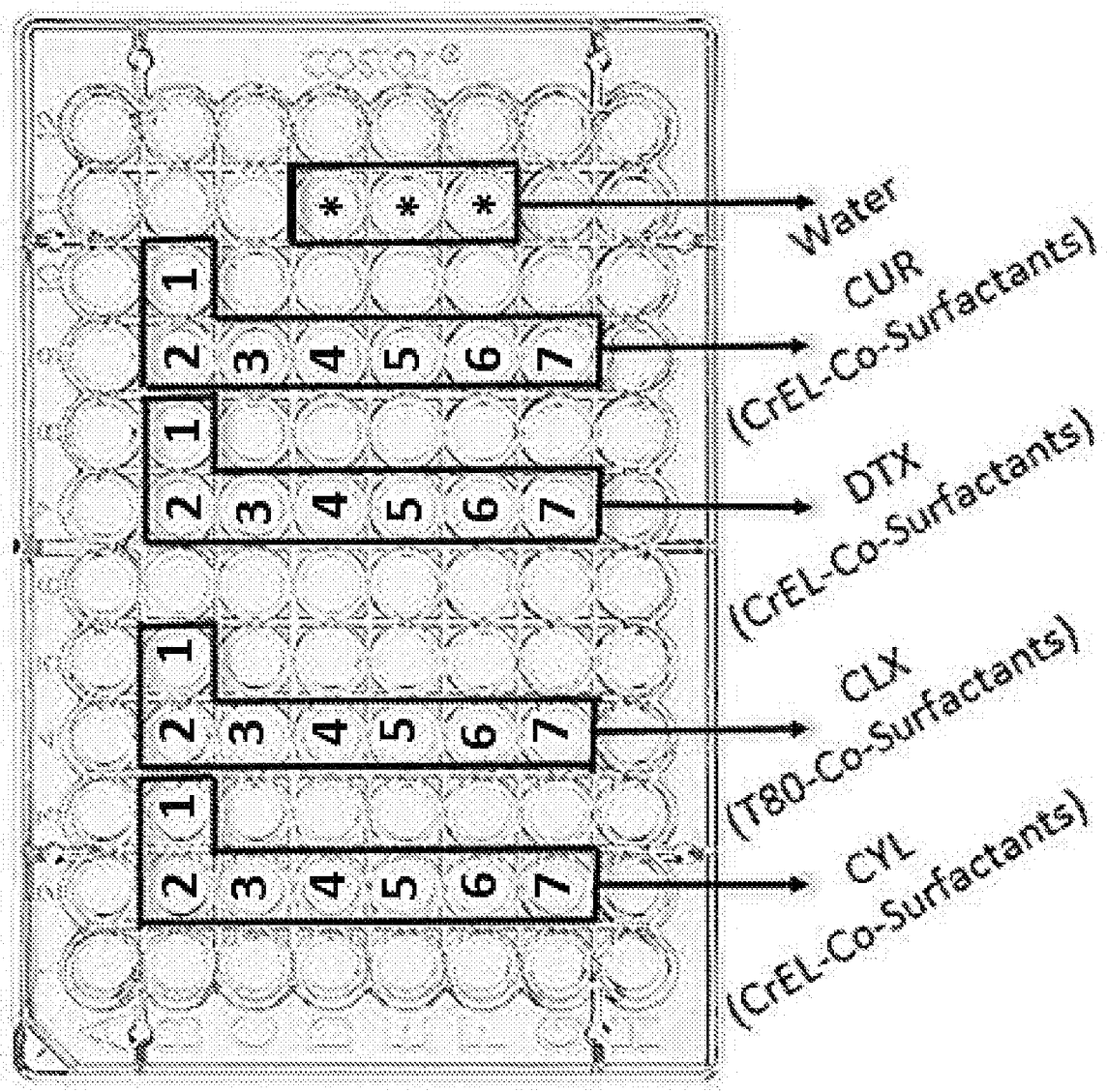
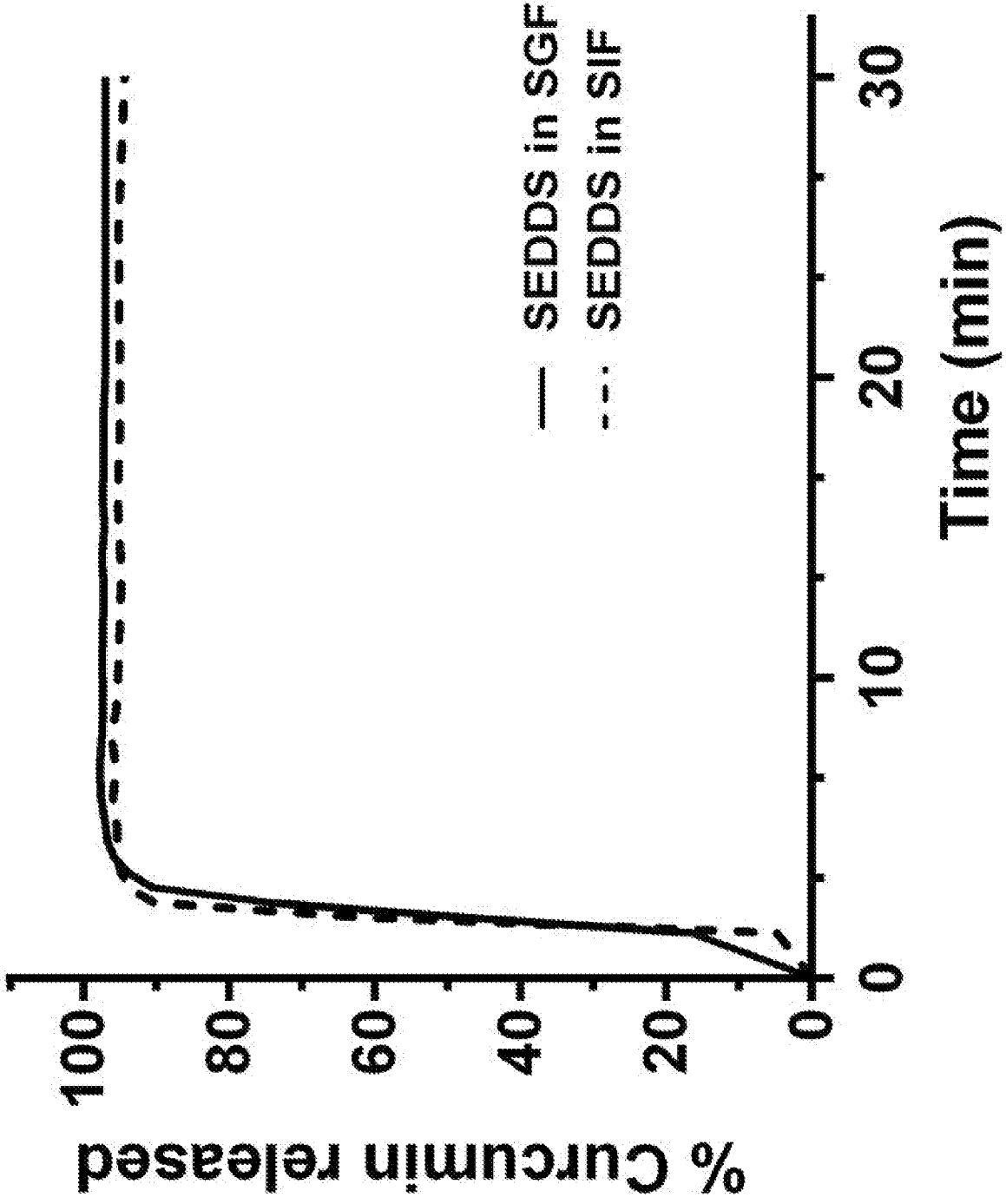

* * *
Water
1
2 3 4 5 6 7
CUR
(CrEL-Co-Surfactants)
1
2 3 4 5 6 7
DTX
(CrEL-Co-Surfactants)
1
2 3 4 5 6 7
CLX
(T80-Co-Surfactants)
1
2 3 4 5 6 7
CYL
(CrEL-Co-Surfactants)

FIG. 9


% Curcumin released
100
80
60
40
20
0
0
10
20
30
Time (min)
SEDDS in SGF
SEDDS in SIF

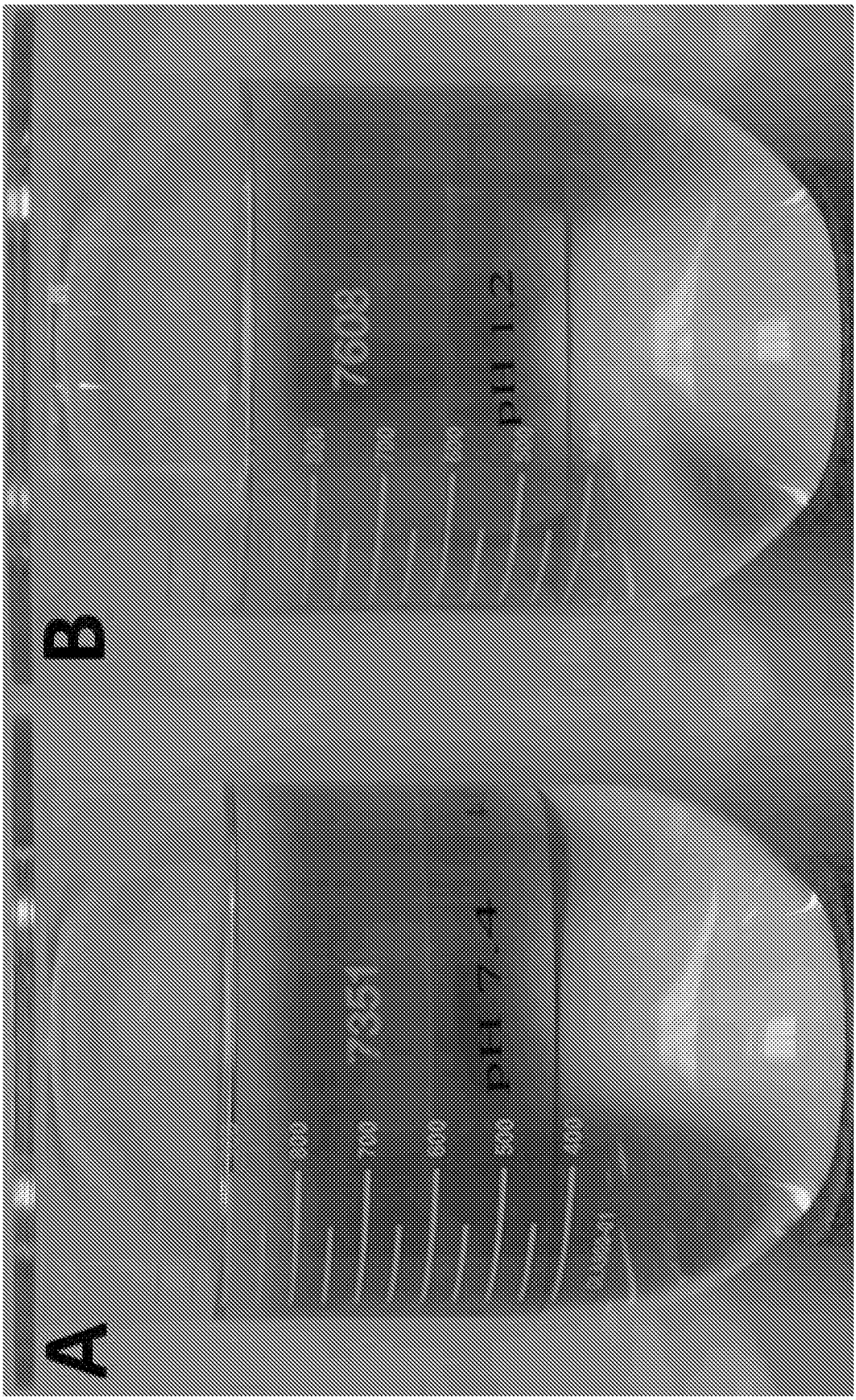
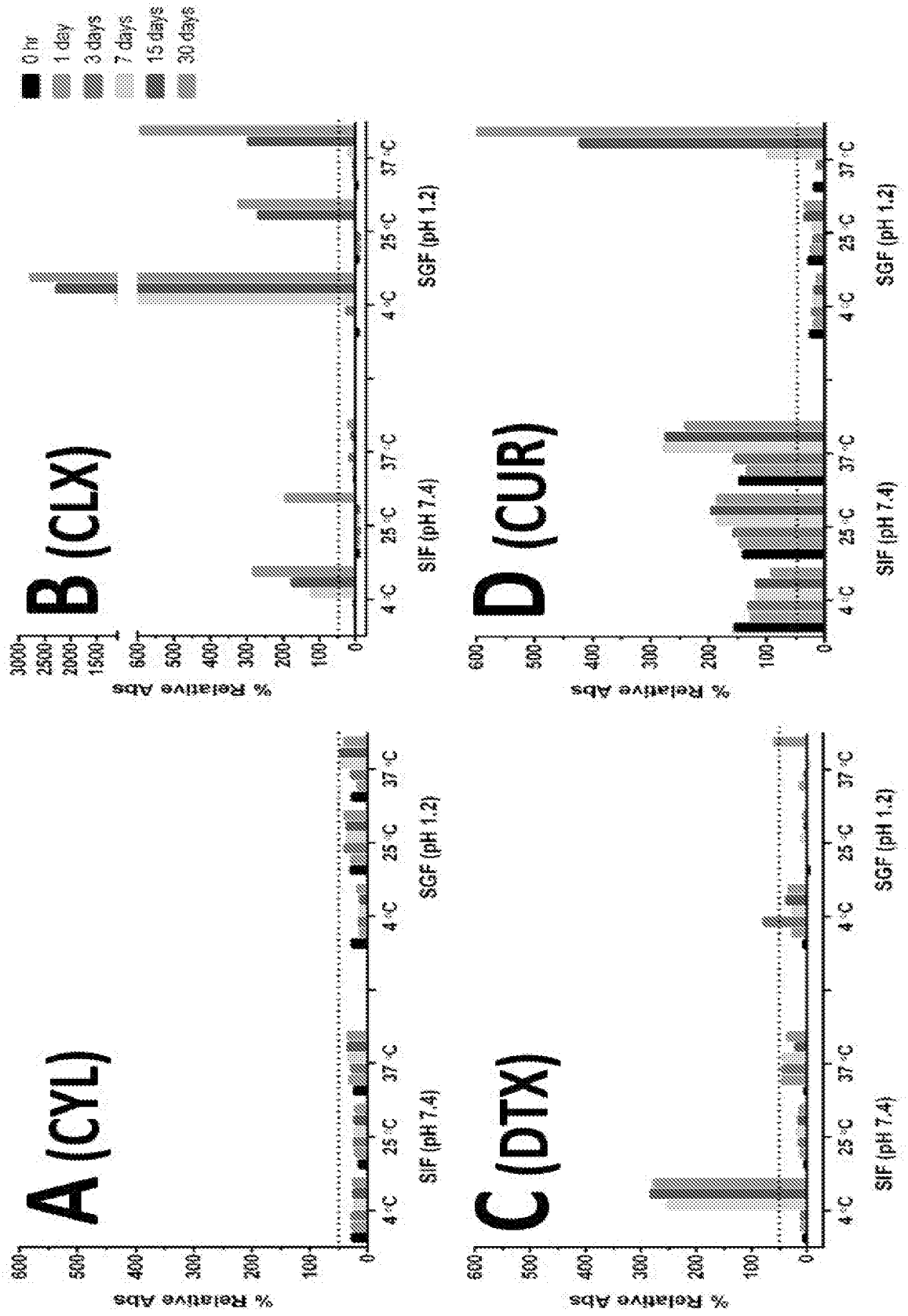


FIG. 10

FIG. 11


A (CYL)
B (CLX)
C (DTX)
D (CUR)
0 hr
1 day
3 days
7 days
15 days
30 days
% Relative Abs
SIF (pH 7.4)
SGF (pH 1.2)
4 °C
25 °C
37 °C

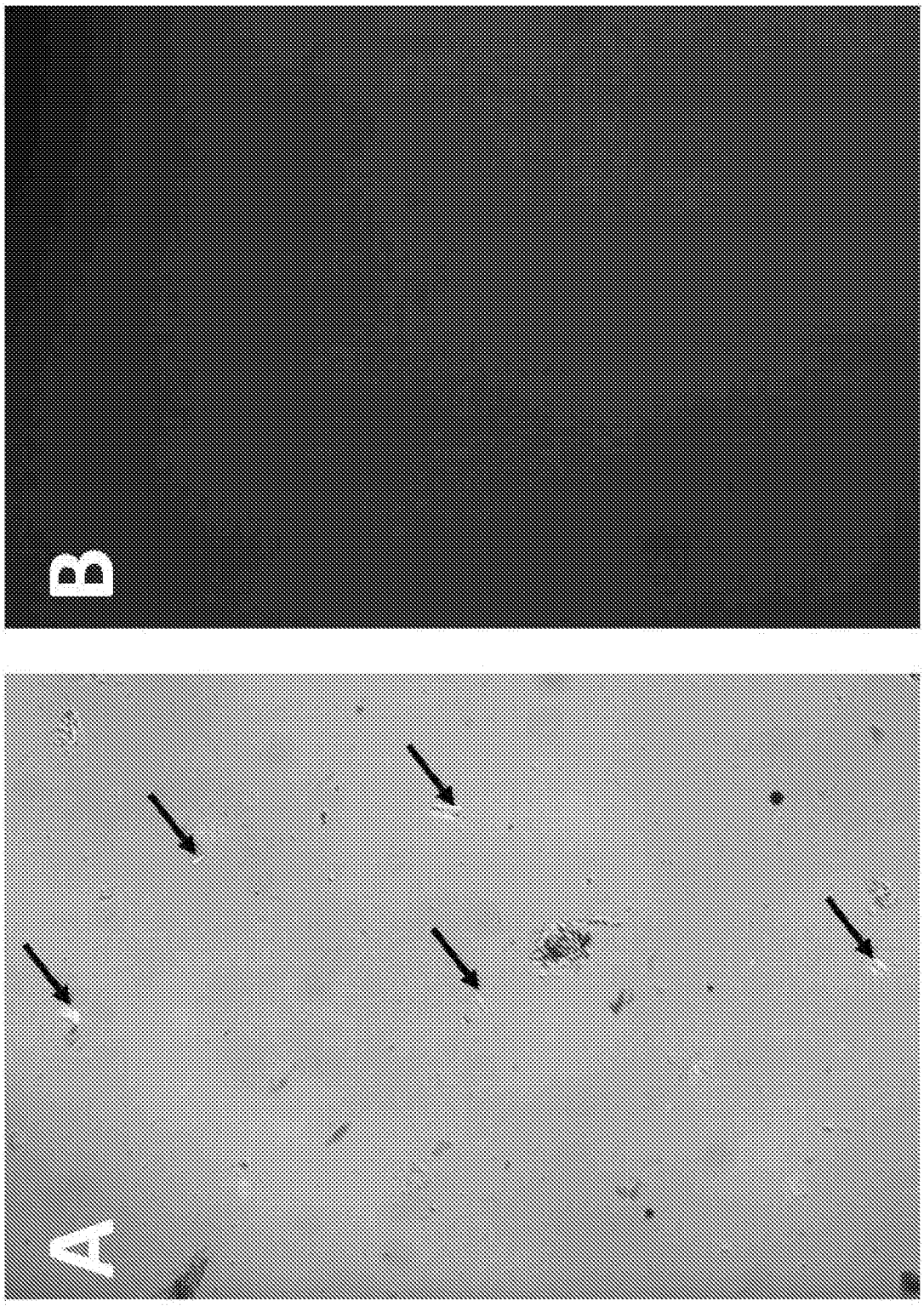


FIG. 12

FIG. 13

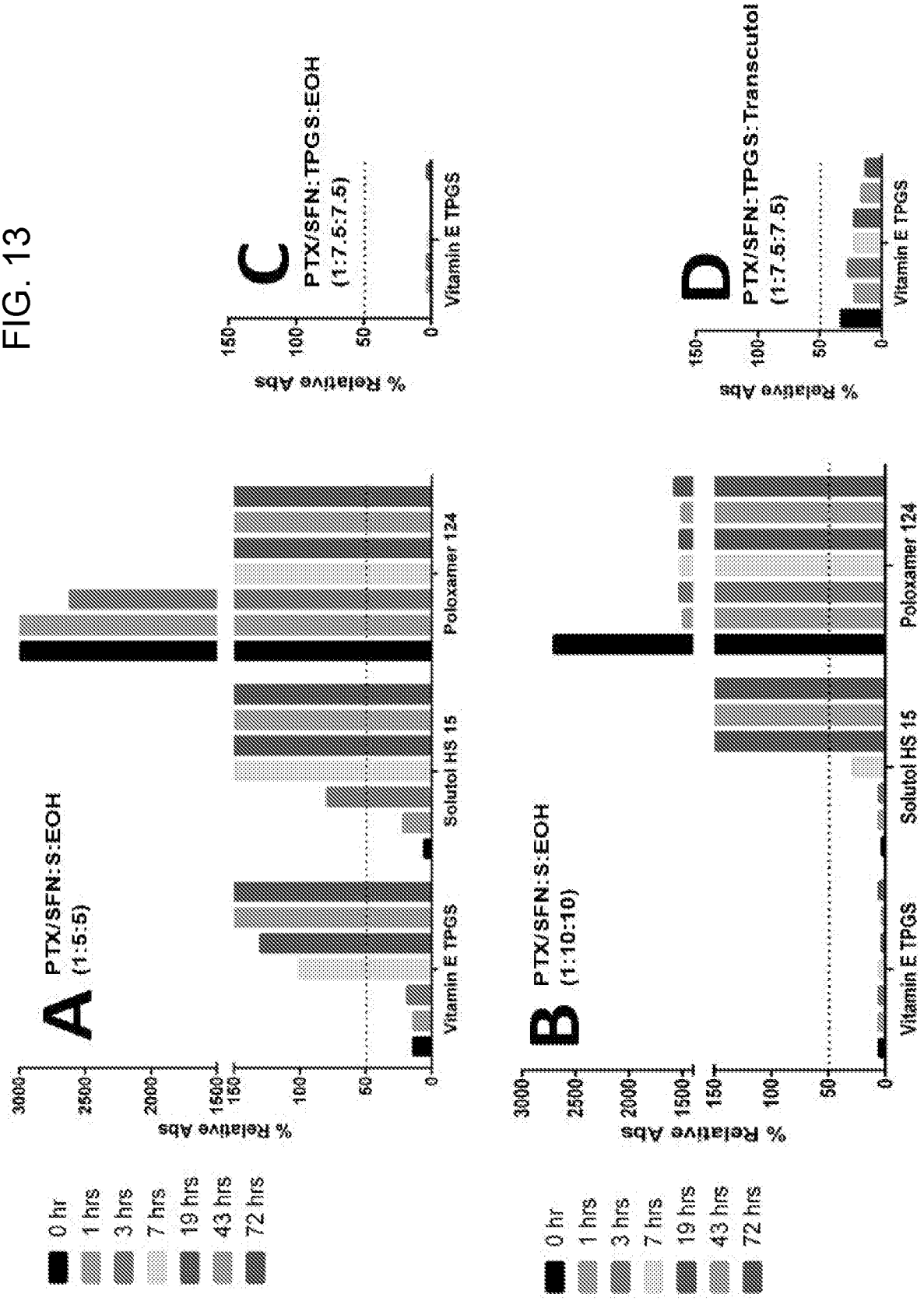
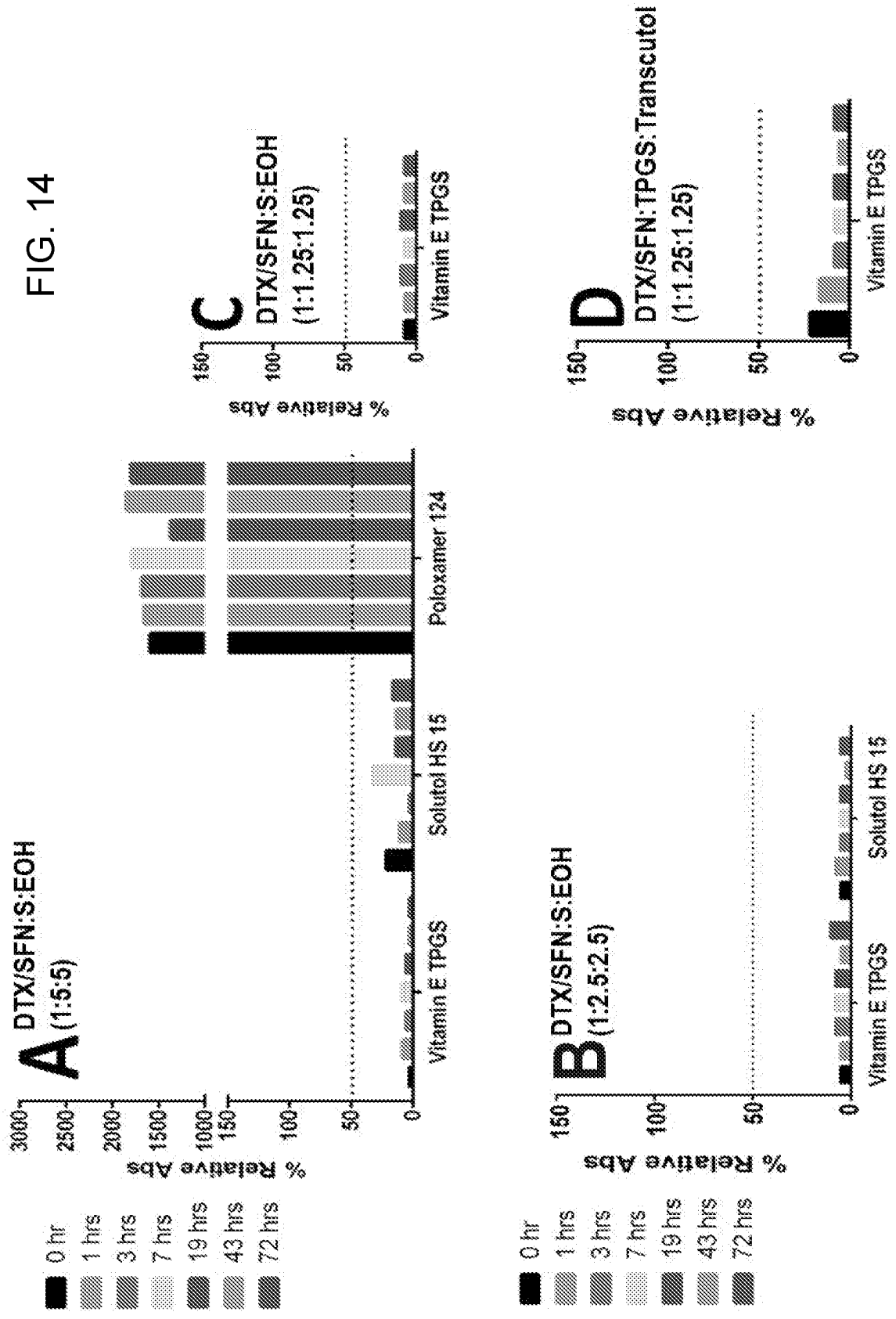

A
PTX/SFN:S:EOH
(1:5:5)
B
PTX/SFN:S:EOH
(1:10:10)
C
PTX/SFN:TPGS:EOH
(1:7.5:7.5)
D
PTX/SFN:TPGS:Transcutol
(1:7.5:7.5)
% Relative Abs
0 hr
1 hrs
3 hrs
7 hrs
19 hrs
43 hrs
72 hrs
Vitamin E TPGS
Solutol HS 15
Poloxamer 124

FIG. 14


A
DTX/SFN:S:EOH
(1:5:5)
B
DTX/SFN:S:EOH
(1:2.5:2.5)
C
DTX/SFN:S:EOH
(1:1.25:1.25)
D
DTX/SFN:TPGS:Transcutol
(1:1.25:1.25)
% Relative Abs
0 hr
1 hrs
3 hrs
7 hrs
19 hrs
43 hrs
72 hrs
Vitamin E TPGS
Solutol HS 15
Poloxamer 124

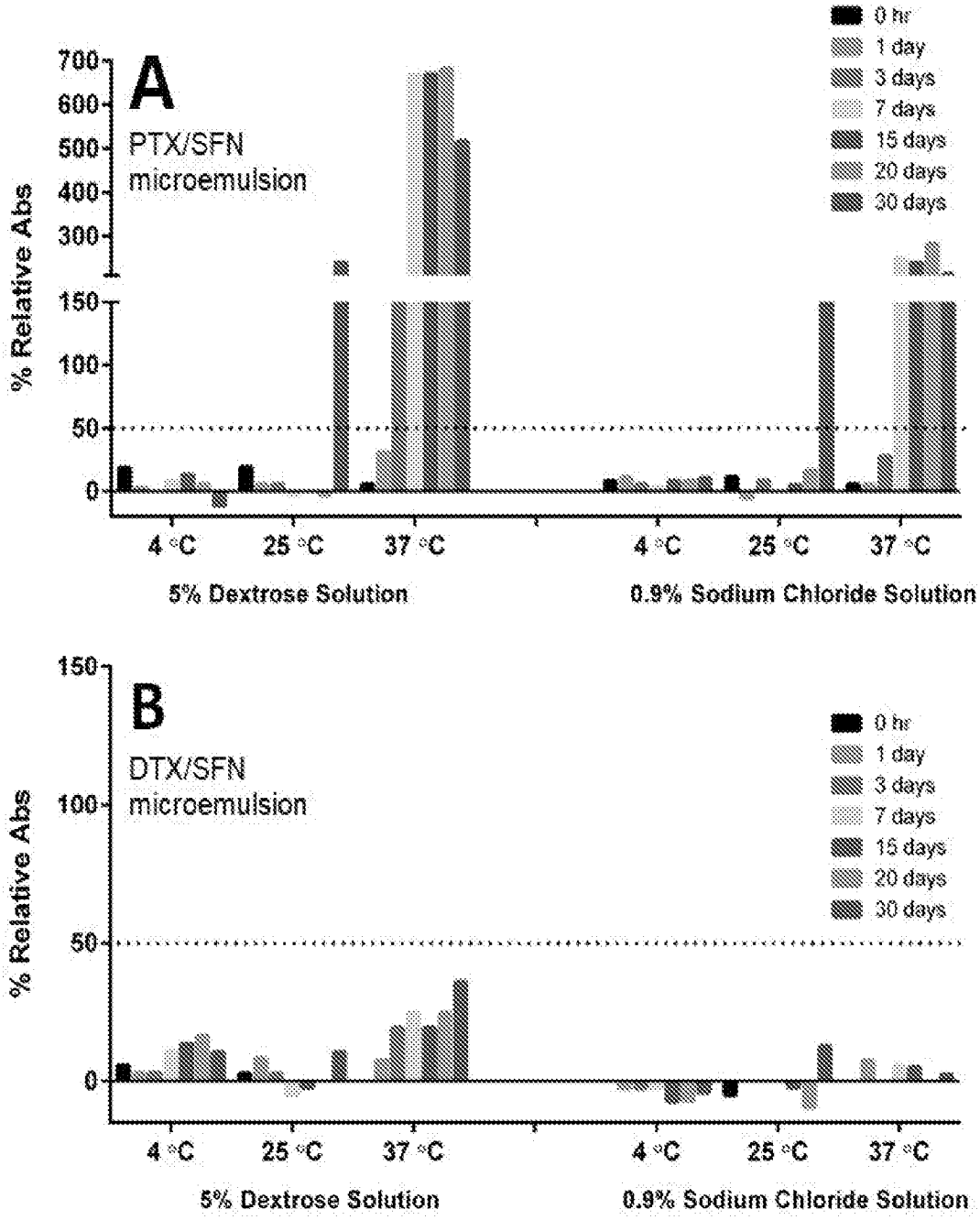

A
PTX/SFN
microemulsion
% Relative Abs
700
600
500
400
300
150
100
50
0
0 hr
1 day
3 days
7 days
15 days
20 days
30 days
4 °C
25 °C
37 °C
4 °C
25 °C
37 °C
5% Dextrose Solution
0.9% Sodium Chloride Solution
B
DTX/SFN
microemulsion
% Relative Abs
150
100
50
0
0 hr
1 day
3 days
7 days
15 days
20 days
30 days
4 °C
25 °C
37 °C
4 °C
25 °C
37 °C
5% Dextrose Solution
0.9% Sodium Chloride Solution

FIG. 15

FIG. 16

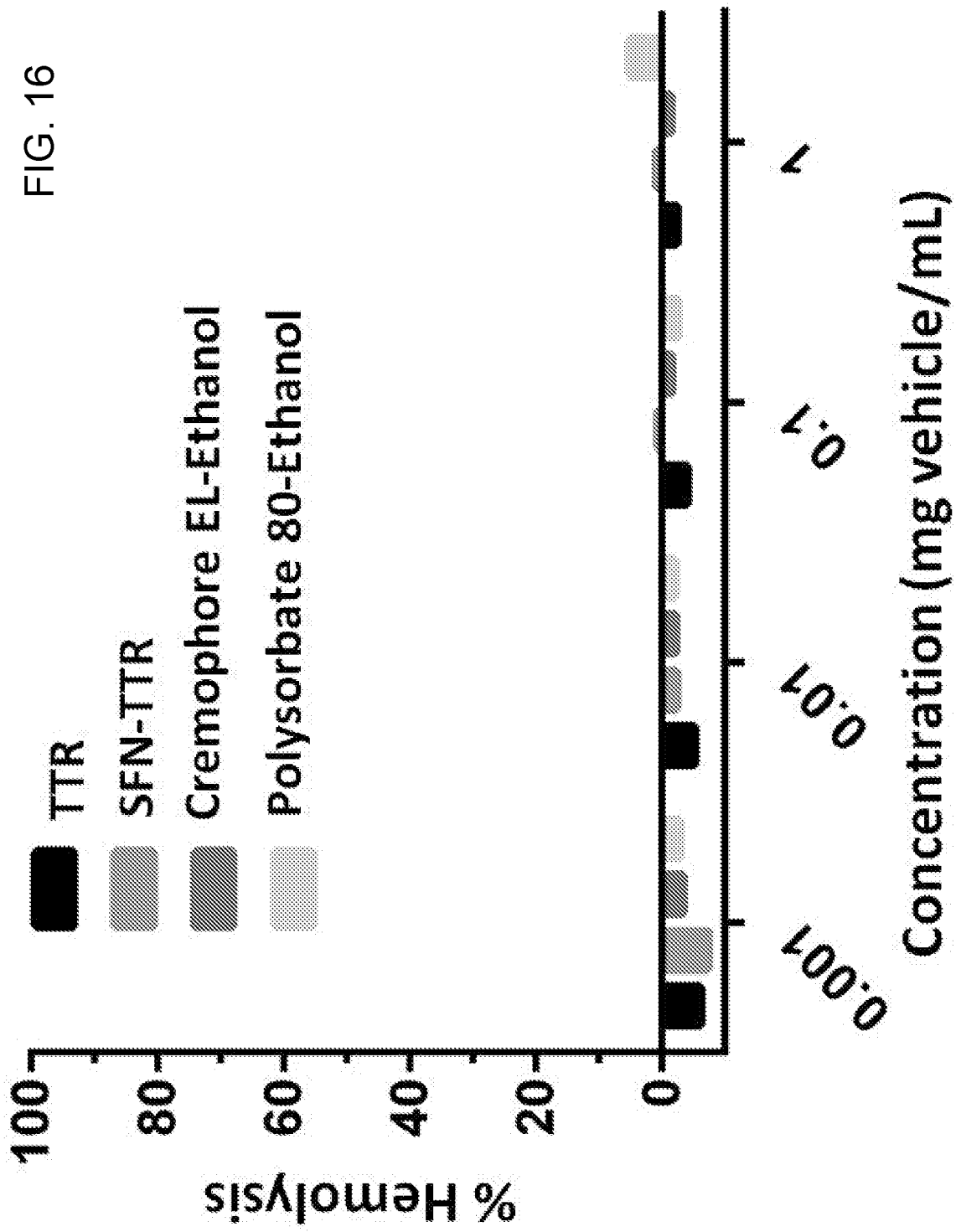

TTR
SFN-TTR
Cremophore EL-Ethanol
Polysorbate 80-Ethanol
% Hemolysis
100
80
60
40
20
0
0.007
0.07
0.7
7
Concentration (mg vehicle/mL)

FIG. 17

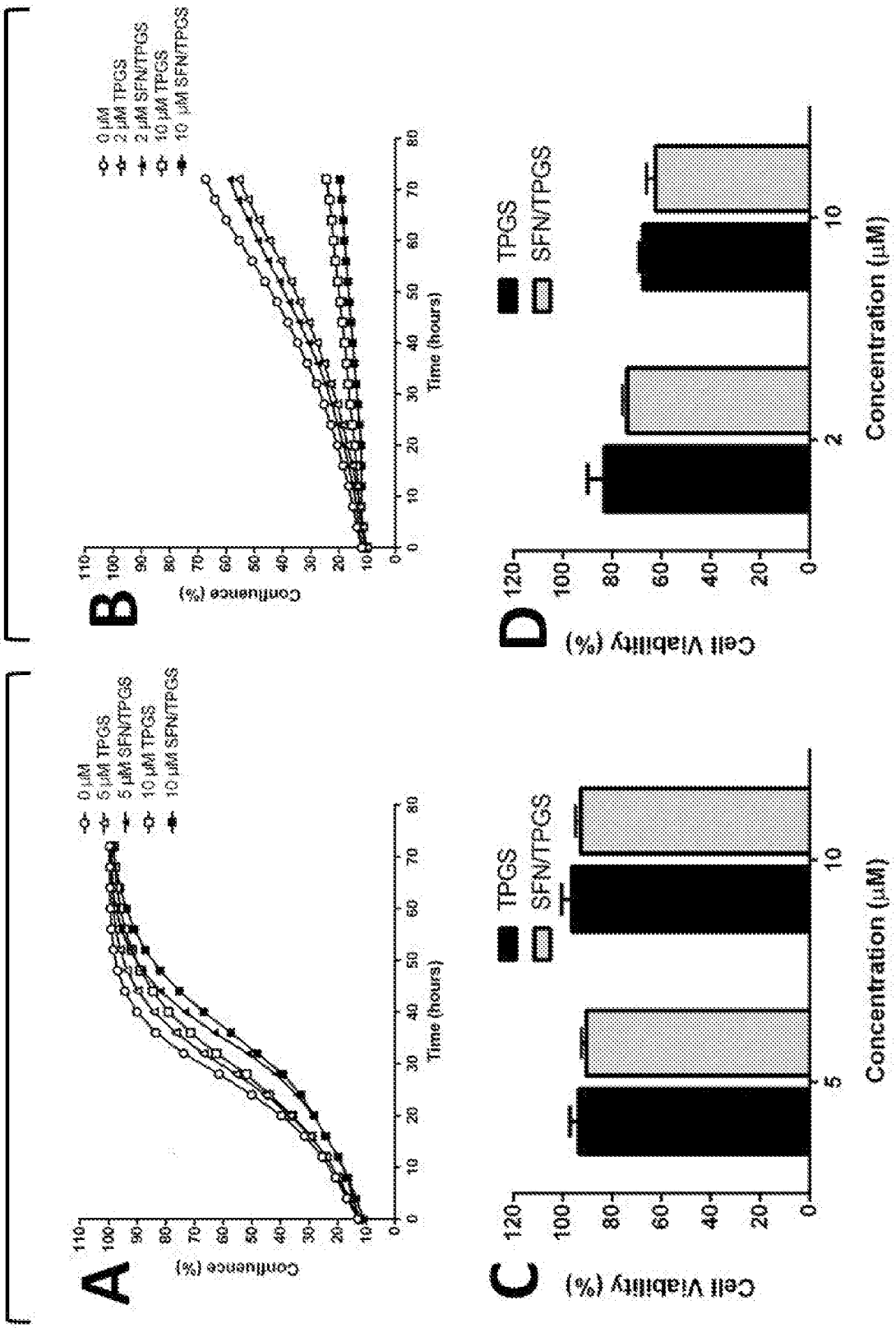

MDA-MB-231
MCF7
A
B
C
D
Confluence (%)
Time (hours)
0 µM
5 µM TPGS
5 µM SFN/TPGS
10 µM TPGS
10 µM SFN/TPGS
2 µM TPGS
2 µM SFN/TPGS
Cell Viability (%)
TPGS
SFN/TPGS
Concentration (µM)

FIG. 18

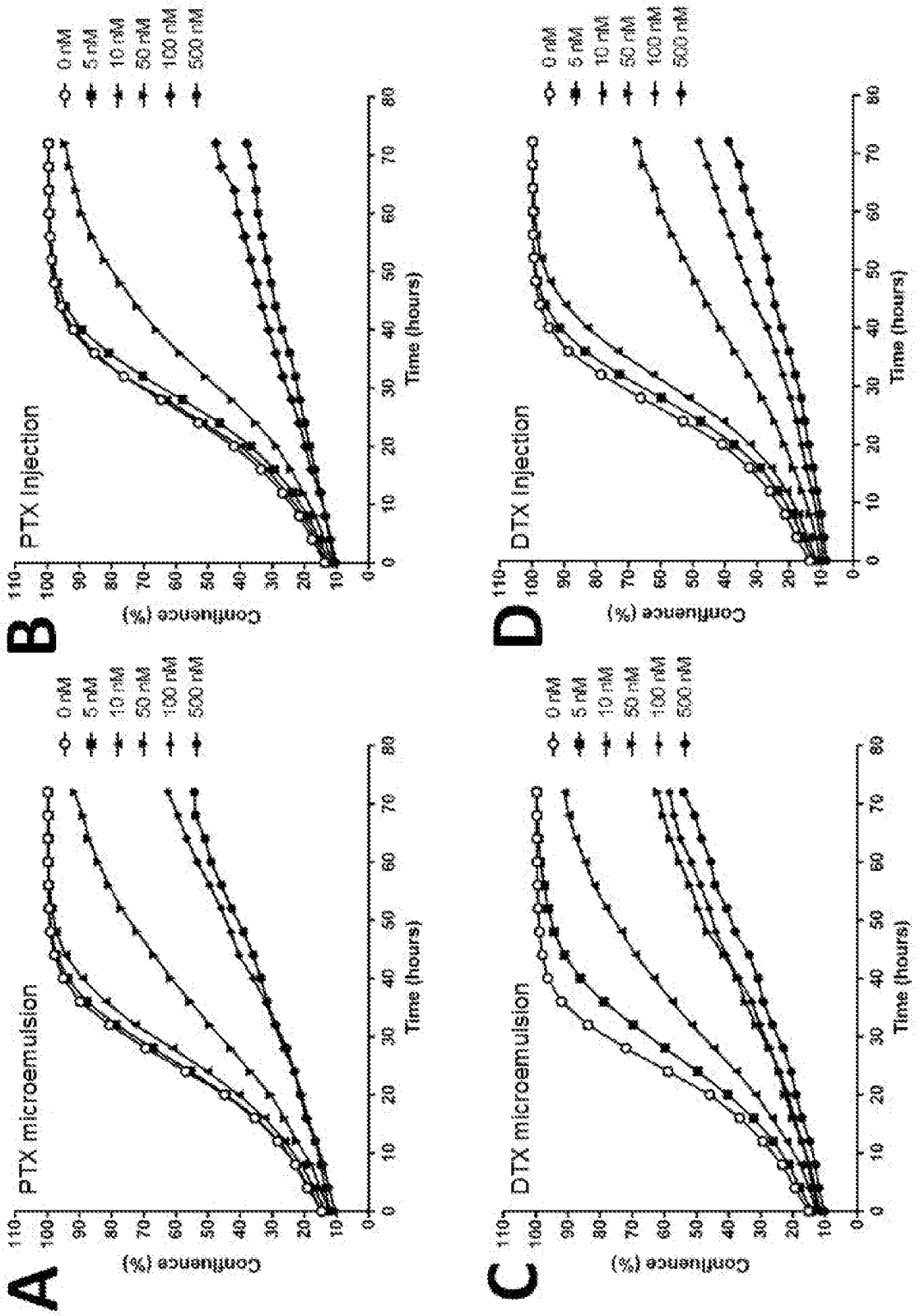

A
PTX microemulsion
B
PTX Injection
C
DTX microemulsion
D
DTX Injection
Confluence (%)
Time (hours)
0 nM
5 nM
10 nM
50 nM
100 nM
500 nM

FIG. 19

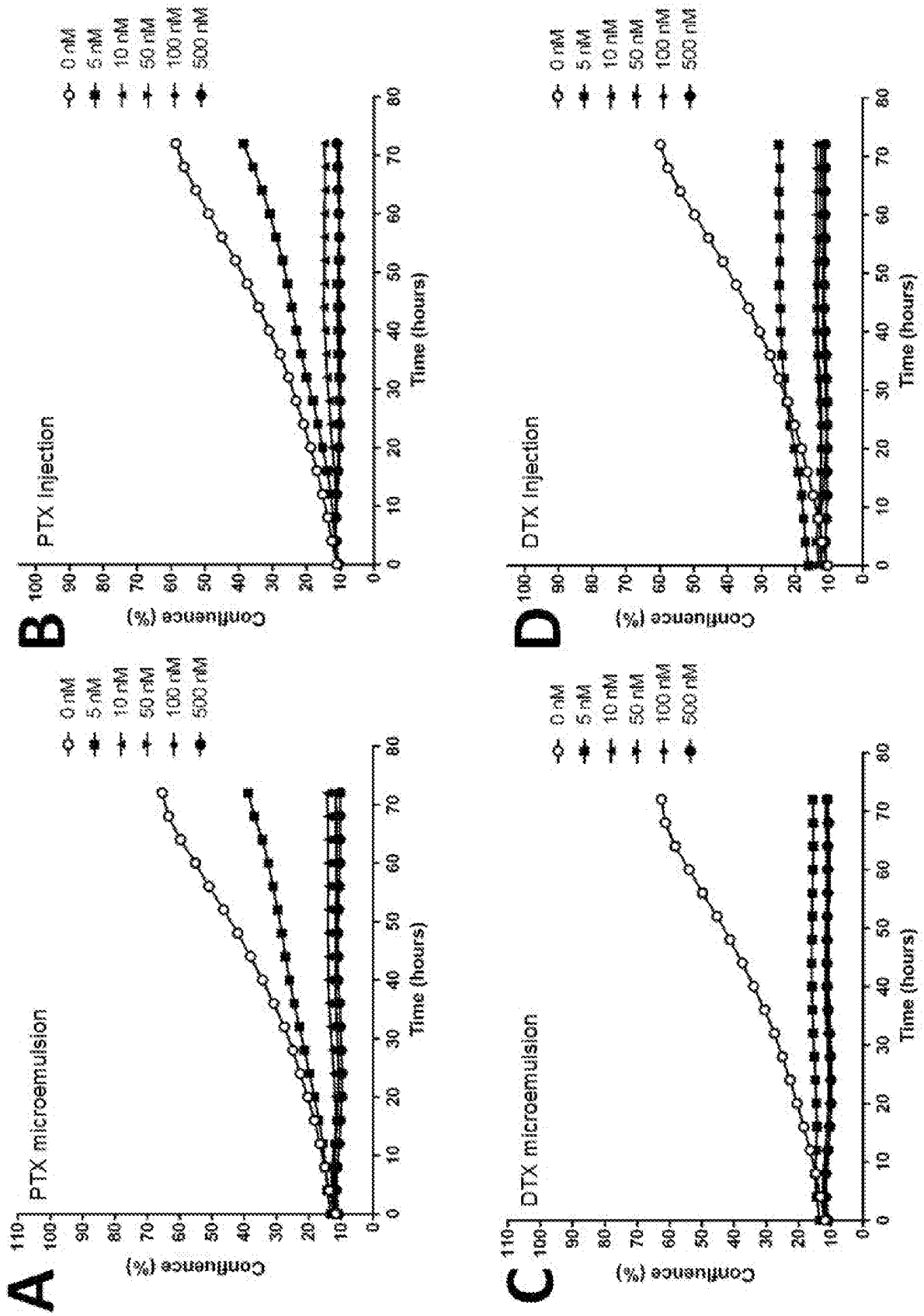
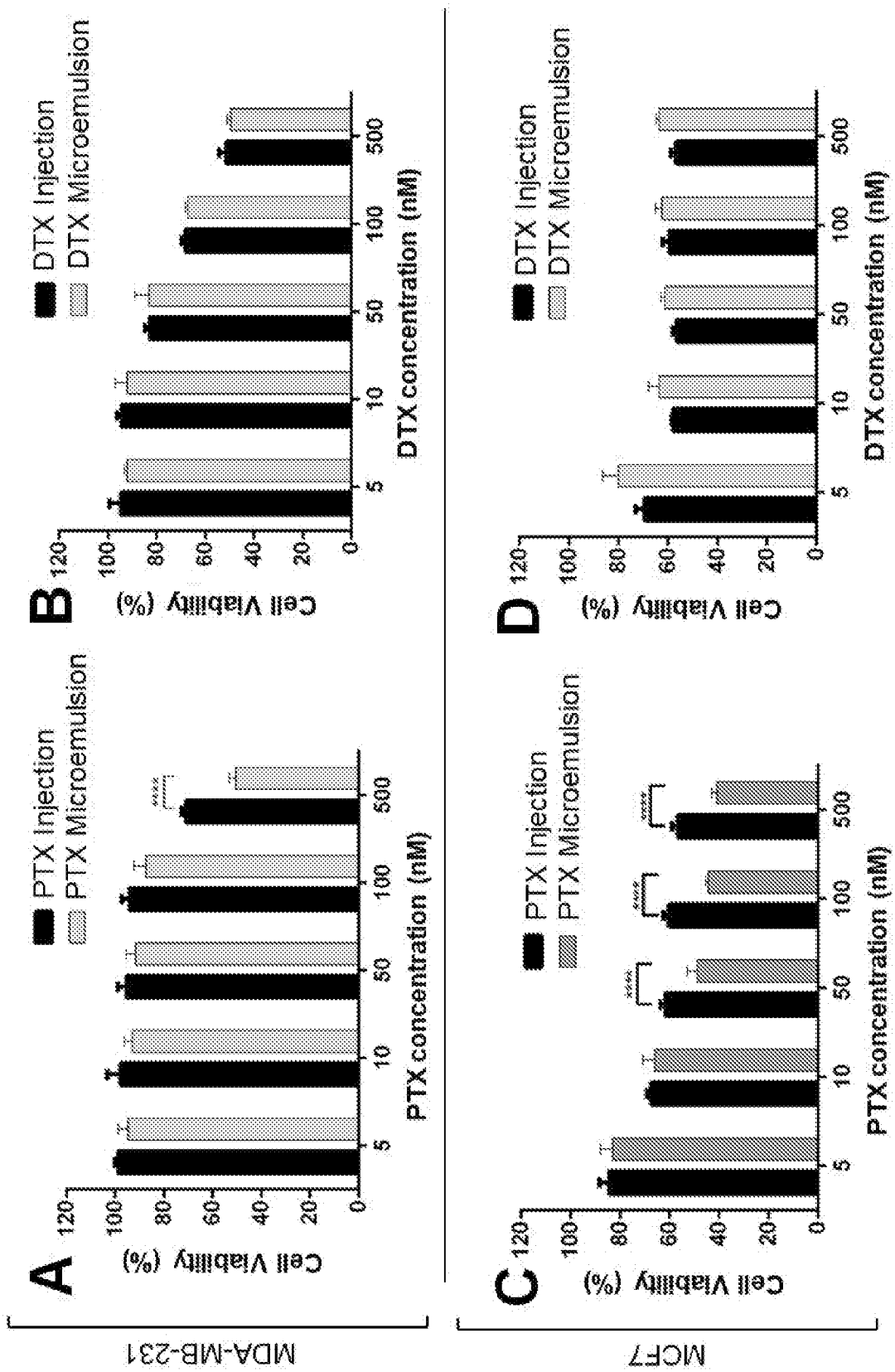

A
PTX microemulsion
B
PTX injection
C
DTX microemulsion
D
DTX injection
Confluence (%)
Time (hours)
0 nM
5 nM
10 nM
50 nM
100 nM
500 nM

FIG. 20


MDA-MB-231
MCF7
A
B
C
D
PTX Injection
PTX Microemulsion
DTX Injection
DTX Microemulsion
Cell Viability (%)
PTX concentration (nM)
DTX concentration (nM)
0
20
40
60
80
100
120
5
10
50
100
500
****

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/54179

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 49/18, A61K 9/10, A61K 9/107 (2018.01)
CPC - A61K 47/62, A61K 47/6909, A61K 49/1809

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	WO 2012/142511 A2 (Md Matrix Health Llc Dba Md Matrix Health Inc) 18 October 2012 (18.10.2012); entire document, especially abstract calim 1, claim 8, [0014], [0045], [0054], [00124]	1-4, 6-7, 10-14 ---------- 8-9, 15 ----- 20
X --- A	CN 103877066 A (Second Military Medical University) 25 June 2014 (25.06.2014); entire document, especially abstract, [0009], [0020]-[0022]	16-19 --------- 20
Y	US 2016/0051634 A1 (Academia Sinica) 25 February 2016 (25.02.2016); entire document, especially abstract, [0004], [0008], [0063], [0066], [0068], [0070]	8-9, 15
A	Wikipedia , "Sulforaphane", 13 June 2017 (13.06.2017) retrieved on 27 November 2018 from https://en.wikipedia.org/w/index.php?title=Sulforaphane&oldid=785384467; entire document, especially pg 1 para 1	1-4, 6-20
P/X	Kamal et al., "Novel sulforaphane-enabled self-microemulsifying delivery systems (SFNSMEDDS) of taxanes: Formulation development and in vitro cytotoxicity against breast cancer cells", 28 November 2017 (28.11.2017), International Journal of Pharmaceutics 536 (2018) 187-198 https://doi.org/10.1016/j.ijpharm.2017.11.063; entire document	1-4, 6-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2018	27 DEC 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774