SOLID DISPERSION TECHNOLOGY

Oral Delivery With Novel Solid Dispersions: Stable Self-Assembled Formulations of Lipophilic Drugs With Improved Bioperformance

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INTRODUCTION

Overcoming solubility limitations remains one of the most challenging aspects of pharmaceutical formulation development. Traditional solutions to this problem, such as pro-drug synthesis, salt formation, and use of co-solvents have been augmented by more recent approaches. These methodologies include: (1) improvement of water miscibility by employing self-emulsification, lipid-based techniques, solubilization into micellar cores, or alternatively complexation with cyclodextrins; (2) reduction of particle size to nano-scale via mechanical milling or high-pressure homogenization accompanied by particle stabilization; and (3) impacting crystal lattice energy using polymorphs or co-crystals, or through the creation of solid dispersions of drug in inert carriers or matrices.[1-10]

Solid dispersions have inherent advantages over other approaches. Presence of an active compound as a molecular or nano-particle dispersion combines the benefits of decreasing crystal lattice energy and surface area maximization, thus facilitating better contact with dissolution media. Advantageously, many of the carriers that can be employed for the production of solid dispersions are already extensively used as excipients, easing the regulatory process.

In spite of these advantages, only very few solid dispersions have reached the market to date. This is due to a number of reasons, including the absence of sufficient in vivo validation, laborious preparation, lack of reproducibility of physico-chemical analytics, cumbersome incorporation into suitable dosage forms, unsuccessful manufacturing scale-up, and instability of the drugs and their vehicles.[11-12] Thus, technologies that can effectively overcome these challenges are highly desirable.

SoluBest has developed a unique solid dispersion technology for significantly improving the bioperformance of poorly soluble drugs. This robust and versatile technological platform, referred to as Solumer™, can be applied toward a wide range of marketed drugs and molecules in development.

TECHNOLOGICAL CONCEPT & METHODOLOGY

Solumerization is based on the self-assembly of selected components, enabling the design of new polymer-drug constructs with well-defined physical-chemical properties. Leveraging the thermodynamic behavior of amphiphilic and hydrophilic polymers in mixed solvents, SoluBest has developed a proprietary platform for the creation of drug-polymer solid dispersions in which the lipophilic drug is homogeneously interwoven within a multi-polymer matrix. Moreover, due to interaction with the amphiphilic polymer, Solumerized drugs exhibit modified physico-chemical properties (eg, decreased enthalpy and temperature of melting) compared to the crystalline lipophilic APIs.

Solubility parameters can be used as a semi-empirical tool for the prediction of component interactions, facilitating their selection.[13] Specific amphiphilic and hydrophilic polymers at optimal ratios yield solid dispersions with a unique built-in hydrophobic-hydrophilic gradient. This gradient enables the rapid disintegration of the powder in aqueous media, generating easily measurable colloidal nano-dispersions.

In the context of the Solumer technology, amphiphilic polymers are defined as soluble both in organic solvents and in water. Examples of

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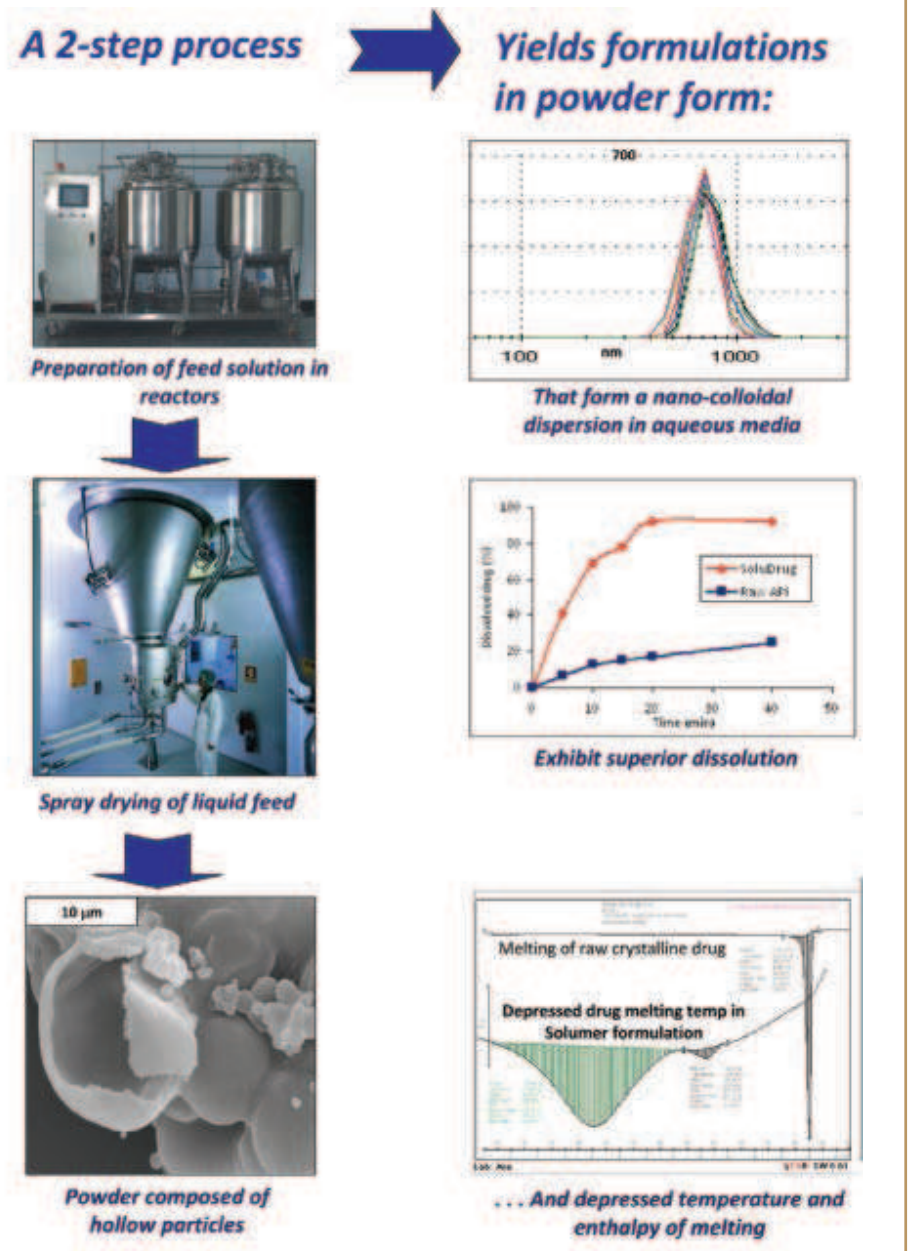
amphiphilic polymers suitable for use with Solumer include but are not limited to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates. Hydrophilic polymers are defined as those soluble in water or in a mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, SoluBest formulations utilize only FDA-approved polymers.

The use of hydrophilic polymers that ionize at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionized at low pH, promotes drug release in the stomach, while sodium carboxymethyl cellulose and sodium alginate, ionized at neutral conditions, facilitate release in the small intestine.

The Solumer process is an easily scalable two-step preparation. The first step involves the preparation of a liquid feed, which is a homogeneous solution of the lipophilic drug and at least two polymers in a mixed solvent (organic/water). The second step involves spray-drying of the solution to obtain a well-characterized powder. In contrast with other technologies, there are no intermediate steps including formation and separation of nano-particles in the liquid media. Thus, drawbacks inherent to other nano-technologies (eg, milling, homogenization), such as the agglomeration of nanoparticles or chemical degradation upon application of shear force, are not relevant to the Solumer platform.[14]

Solumer feed solution amenability to spray-drying results in an attractive industrial process. Spray-drying allows for flexible capacity and continuous and automatic production. The widespread availability of spray-drying equipment enables the process to be easily implemented without an increase in the manufacturing footprint. Furthermore, the Solumer platform is applicable to a wide range of products, including those that are toxic, aseptic and heat sensitive. An illustration of a typical SoluDrug preparation and its physico-chemical characterization is demonstrated in Figure 1.

FIGURE 1



Overview of Solumer™ process and product characterization

The resultant spray-dried powder is well-defined and exhibits the following collective unique "fingerprints" of a Solumer solid dispersion:

- Solubilized drug homogeneously interwoven into a polymer matrix,
- Modified thermal behavior demonstrating depressed melting temperature and enthalpy of melting of the drug,
- Spontaneous formation of nano-colloidal dispersions upon contact with aqueous media,

TABLES 1 & 2

TABLE 1

Formulation	Fenofibric Acid		
	C_{max} (µg/ml)	AUC_t (µg·hr/ml)	T_{max} (hrs)
SoluFeno	7.06 ± 1.16	109.20 ± 37.45	3.0 ± 0.8
TriCor 145	8.10 ± 1.63	113.9 ± 38.70	2.0 ± 0.8
Test / Reference	0.87	0.98	-
90 % Confidence Intervals	0.76 – 1.01	0.91 – 1.01	-

Pharmacokinetics of fenofibric acid in the plasma of volunteers (n=12) following oral administration of SoluFenofibrate versus Tricor 145.

TABLE 2

Formulation	Resveratrol			Resveratrol Total Metabolites			
	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hrs)	Mean AUC_{inf} (ng·hr/ml)	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hrs)
SoluResveratrol	504	330	0.50	28410	27600	8820	1.00
Raw Resveratrol	331	111	2.00	23960	22430	4160	1.50
Test/Reference	1.52	2.97	-	1.19	1.23	2.12	-
90% Confidence Intervals	0.90-2.58	1.95-4.54	-	0.95-1.48	0.97-1.56	1.58-2.83	-
Statistical Significance	NS*	<0.00009	<0.0013	NS*	NS*	<0.0009	<0.003
* NS – No statistically significant difference							

Pharmacokinetics of resveratrol and metabolites in the plasma of volunteers (n=12) following oral administration of SoluResveratrol versus raw resveratrol.

- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and

- GI site-targeted release of the drug.

The Solumer platform was validated for a number of marketed compounds. Collectively, these formulations have repeatedly demonstrated the platform's key properties: stability (measured up to 2 years), batch-to-batch consistency, commercial scalability, and clinically proven increased bioavailability compared to API (or bioequivalence to marketed nano-pharmaceuticals). Clinical and preclinical studies on Solumerized molecules demonstrate a direct correlation between their increased solubility and bioperformance (Figures 2 through 4 and Tables 1 and 2).

Lastly, the Solumer platform has distinct advantages in the context of the pharmaceutical development process, due to the rapid screening times possible for determination of candidate suitability (up to 4 weeks) as well as the short time required for product formulation. SoluBest can proceed from feasibility studies to clinical studies in less than 6 months.

ALBENDAZOLE

Albendazole is an anti-helmintic or anti-worm medication that prevents newly hatched insect larvae from growing and multiplying in the body. Albendazole is insoluble in water with MW = 265 Daltons; log P = 3.0; T_{melt} = 215°C, and ΔH_{melt} = 210 J/g. The Solumer formulation of this drug with poloxamer 407 and sodium carboxymethyl cellulose yields a composition with decreased albendazole melting temperature and enthalpy (161°C and 31 J/g, respectively, according to DSC analysis). As evidenced by X-ray analysis, the effective crystallite size of formulated albendazole is 33 nm.[15] Laser Diffraction and Dynamic Light Scattering analysis show that disintegration of formulated powder in water results in colloidal dispersion with a mean particle size of 419 nm. All these properties lead to a high dissolution rate for solubilized albendazole (SoluAlbendazole or SoluABZ) versus raw bulk material in a sodium lauryl sulfate, a surfactant that is a typical medium for dissolution of insoluble drugs (Figure 2A). Supersaturation is shown in physiological media, exemplified by fast state simulating intestinal fluid (FaSSIF) (Figure 2B).

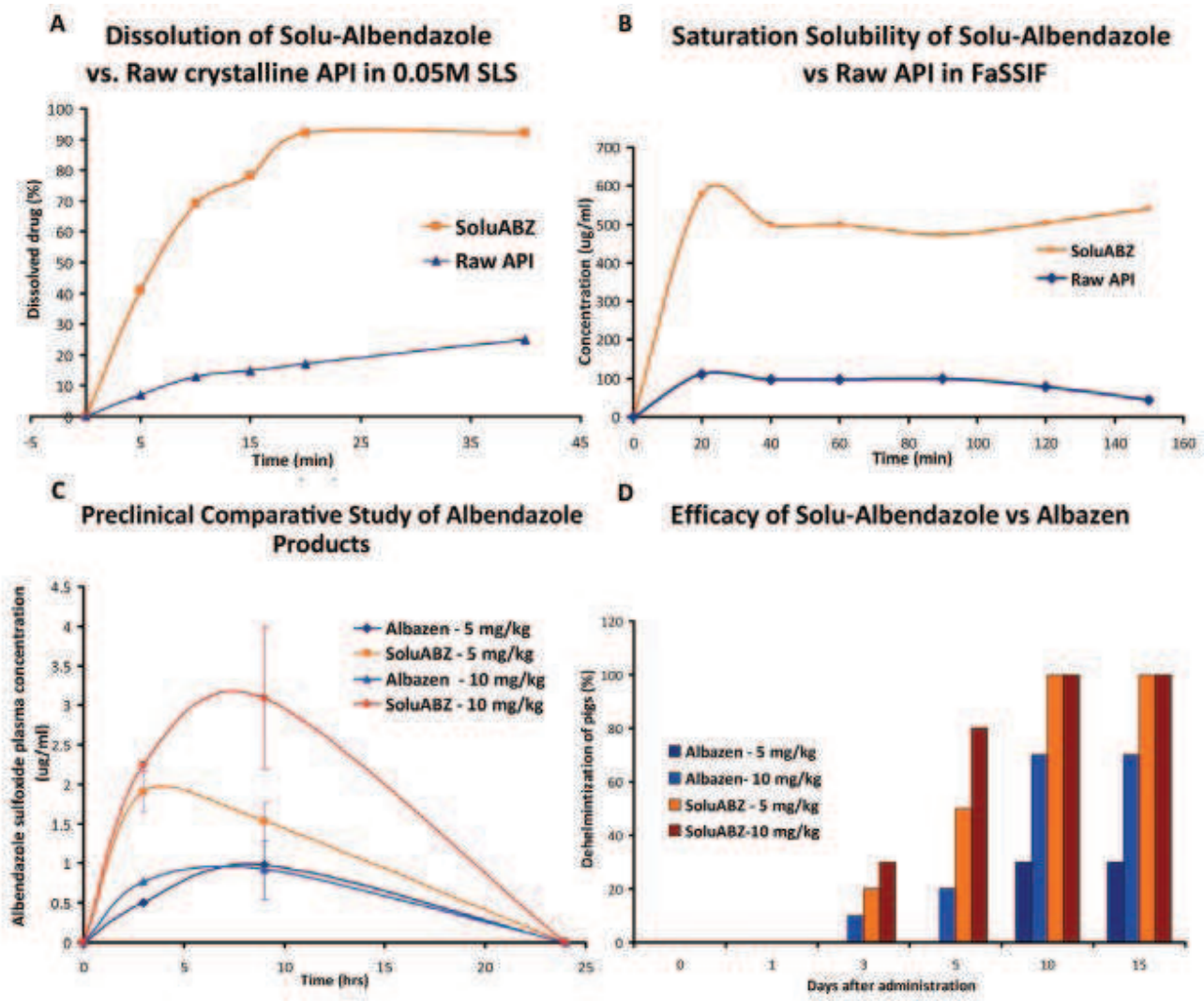
The correlation between physico-chemical properties, demonstrated through in vitro tests, and bioavailability was studied using a pig model. A comparative evaluation of the bioavailability and therapeutic efficacy of an orally administered Solu-Albendazole (test) formulation and a commercial formulation of Albazen (reference) was carried out at Rubikon Ltd. under supervision of its Chief Pharmacologist, Prof. Vasil Piatrou. Albazen, which is manufactured by Rubikon, is the generic version of Pfizer's Valbazen. A total of 40 pigs (aged 75 days) spontaneously infected by nematodes were treated with water suspensions of the test and reference formulations at doses of 5 and 10 mg/kg. Both formulations were administered orally through a pig-dozator under fasted conditions with free access to water.

For pharmacokinetic studies, blood samples were collected at 0, 3, 9, and 24 hours after oral administration. Concentrations of the therapeutically active metabolite of Albendazole, Albendazole sulfoxide (ABZSO), in pig plasma were determined using an HPLC method with UV detection.

In order to estimate therapeutic efficacy of the test and reference formulations, feces samples were collected for coproscopy on days 0, 1, 3, 5, 10, and 15 following administration. Hematological and biochemical blood tests were carried out to identify the safety of the formulation. Pharmacokinetic study results are presented in Figure 2C.

As is evident from the PK data, oral absorption of Albendazole from Solu-

FIGURES 2A-2D



Correlation between in-vitro release profiles and bioperformance for SoluAlbendazole vs Albazene

Albendazole is significantly higher (two- to three-fold) than the absorption from a commercial Albazen suspension. Solu-Albendazole exhibits a clear dose dependence, while Albazen does not. Evaluation of hematological and biochemical data demonstrate that increased drug absorption observed subsequent to Solu-Albendazole administration does not cause abnormal changes in blood parameters; the formulation can therefore be considered safe.

A comparison of anti-helminitic activity of the reference and the test formulations (Figure 2D) clearly favors Solu-Albendazole. Solu-Albendazole exhibits higher efficacy at a lower dose. Complete dehelmintization is achieved in ten days after administration of 5 mg/kg of SoluABZ while Albazene does not result in complete dehelmintization even at a higher dose.

Thus, this study demonstrated a good correlation between the in vitro and in vivo behavior of Solumerized Albendazole. Furthermore, the increased bioavailability exhibited by this product resulted in increased efficacy.

FENOFIBRATE

Fenofibrate, a cardiovascular drug used to lower triglycerides and cholesterol, is practically insoluble in water. It is a lipophilic, crystalline substance with MW = 360.8 D; log P = 4.8; T_{melt} = 82°C, and ΔH_{melt} = 74.3 J/g. The Solumerized formulation of this drug with poloxamer 407 and sodium carboxymethyl cellulose yields a composition with decreased temperature and enthalpy of fenofibrate melting (64.4°C and 9.3 J/g, respectively, according to a DSC analysis). As exhibited by X-ray analysis, the effective crystallite size of formulated fenofibrate is about 40 nm. Disintegration of formulated powder in water results in a colloidal dispersion with a mean particle size of 774 nm as measured by Dynamic Light Scattering. These collective properties result in a higher dissolution rate of solubilized fenofibrate as compared to raw API and commercial micronized fenofibrate. The dissolution profile of SoluFenofibrate appears to be similar to that of the leading market nano-formulation TriCor 145, which is manufactured by Abbott using Elan's NanoCrystal milling technology (Figure 3A).

To determine SoluFenofibrate bioavailability in comparison to a reference product (TriCor 145 tablet), a randomized cross-over study was conducted in 12 healthy volunteers. A single oral fenofibrate dose of 145 mg was administered under

fasted conditions. Plasma concentrations of fenofibrate active metabolite, fenofibric acid, were analyzed using HPLC-UV. Monitoring of adverse effects, clinical chemistry, hematology, and urine analysis was performed for all subjects prior to and upon study termination.

The results of these pharmacokinetic studies are presented in Figure 3B and Table 1. As shown in Table 1, the geometric mean test/reference ratios for AUC values fall well within the accepted limits for bioequivalence. The geometric mean test/reference ratio for C_{max} also meets bioequivalence requirements; however, it must be noted that some test/reference C_{max} values for individual volunteers fell outside these requirements. As the pilot study involved a relatively small number of volunteers, it is anticipated that these values would be found within the required limits in a formal bioequivalence study having a greater number of volunteers. Administration of the SoluFenofibrate formulation did not result in any adverse effects or abnormal changes of the blood and urine parameters.

RESVERATROL

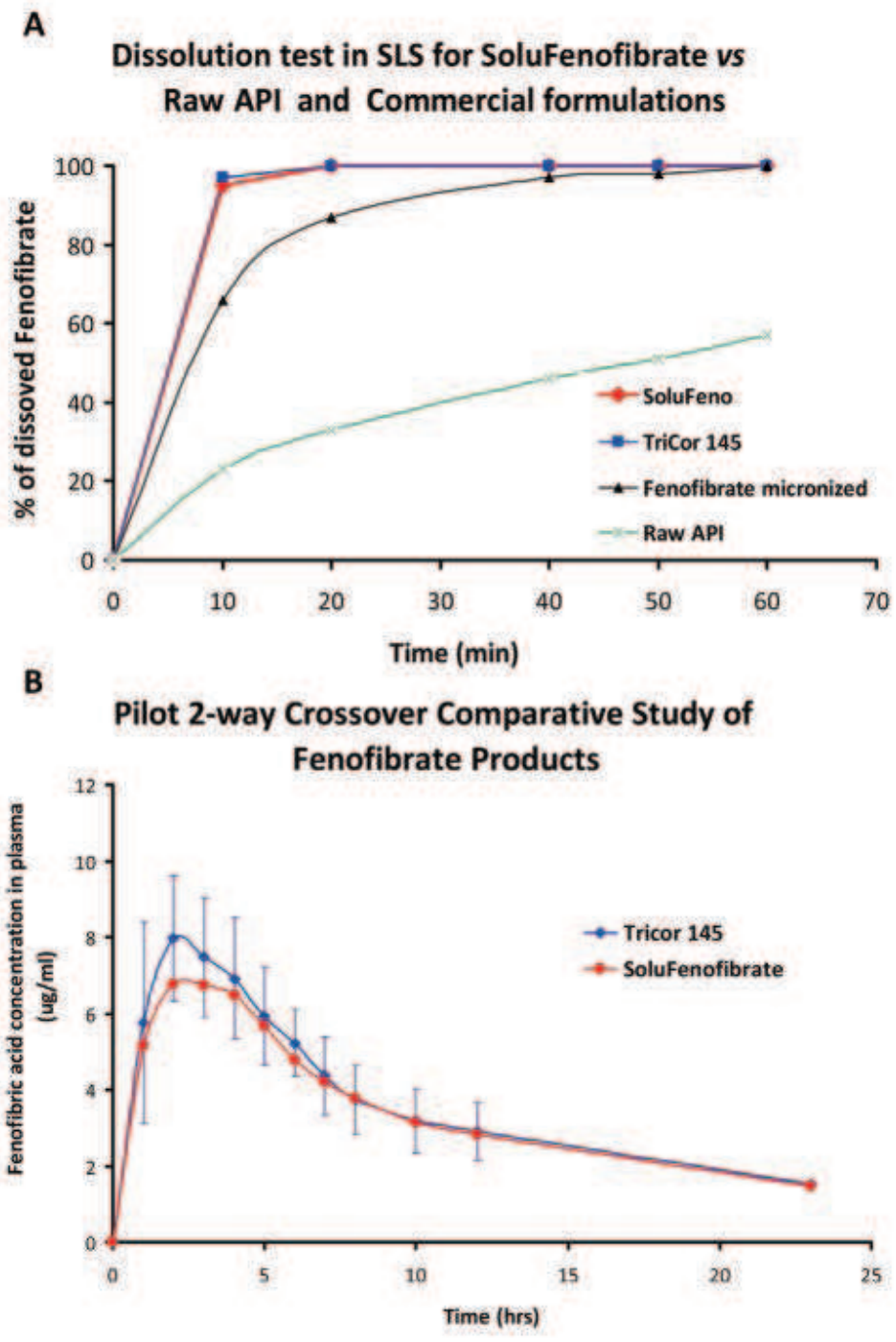
Resveratrol is a small molecule activator of sirtuin enzymes, which may control age-related disorders in various organisms and in humans. These disorders include the aging process, obesity, metabolic syndrome, type II diabetes mellitus, etc.[16] Resveratrol was also found to be an effective agent in reversing arterial damage, in increasing nitric oxide concentration, in neurodegenerative protection and as an anti-cancer drug.[17-20]

Resveratrol exists as two geometric isomers: cis-resveratol and trans-resveratrol; however; only the trans-resveratrol was found to be biologically active. Trans-resveratrol is degraded or converted to the inactive cis-isomer when exposed to light, heat, or oxygen.[21] Resveratrol is practically insoluble in aqueous media, demonstrates very low bioavailability, and rapid, extensive metabolism resulting in only trace amounts of unchanged resveratrol in the systemic circulation.[22]

Resveratrol is currently marketed as an oral nutritional supplement. However, its therapeutic effects are being extensively tested in the clinic. If successful, these trials may potentially elevate resveratrol to drug status in a number of therapeutic fields.

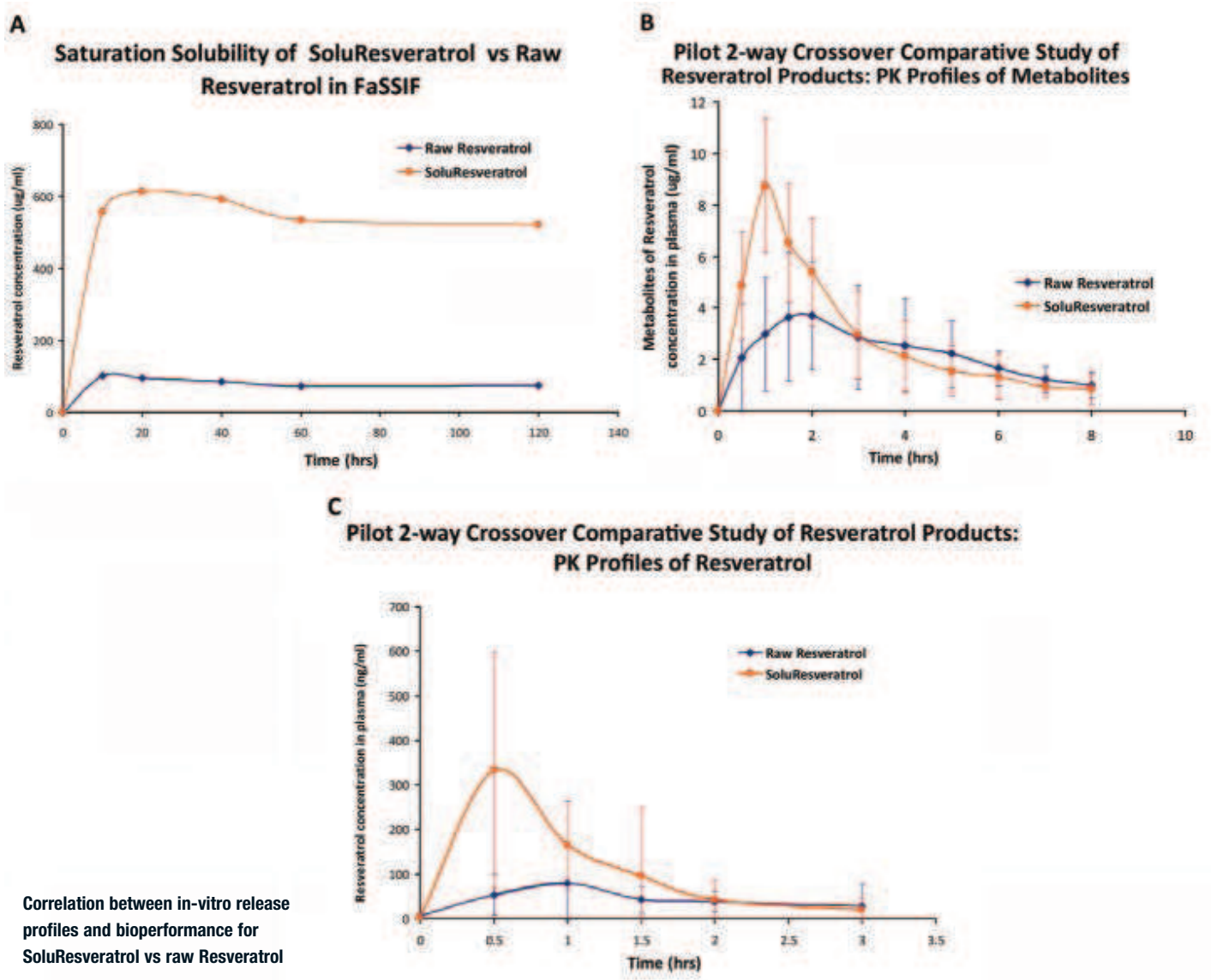
The physico-chemical characteristics of resveratrol are similar to other lipophilic small molecules, which are typical candidates for Solumerization. Its molecular weight is 228 D; log P = 3.1; T_{melt} = 267.4°C, and ΔH_{melt} = 253.6 J/g. The Solumer formulation of this compound with poloxamer 407 and sodium alginate comprises only the active trans-resveratrol isomer. This formulation possesses decreased temperature and enthalpy of resveratrol melting (199.1°C and 14 J/g, respectively, according to DSC analysis). As exhibited by X-ray analysis, the effective crystallite size of formulated resveratrol is 45 nm, and it shows a 55% decrease in the amount of crystallinity compared to the raw material.

FIGURES 3A & 3B



Correlation between in-vitro release profiles and bioperformance for SoluFenofibrate vs Tricor 145

FIGURES 4A-4C



Correlation between in-vitro release profiles and bioperformance for SoluResveratrol vs raw Resveratrol

Disintegration of the formulated powder in water results in a colloidal dispersion with a mean particle size of 1244 nm as shown by Laser Diffraction Analysis. These collective properties impact a significantly increased saturation solubility for Solumerized resveratrol versus raw API in a fast state simulated intestinal fluid (Figure 4A).

The in vitro data correlates well with the enhanced bioavailability of Solu-Resveratrol compared to raw resveratrol as was shown in an exploratory clinical study. In a two-way crossover randomized trial in 12 healthy volunteers with a single oral administration of 500 mg of resveratrol, under fasting conditions, test and reference formulations were administered as a powder dispersed in water. The plasma concentrations of resveratrol and its metabolites were analyzed by HPLC-UV with complementary LC-MS analysis. The results of these pharmacokinetic studies are presented in Figures 4B and 4C and Table 2.

As can be clearly seen from the data presented, a significantly higher bioavailability was demonstrated not only for the total resveratrol metabolites but also for resveratrol itself subsequent to oral administration of Solu-Resveratrol.

SUMMARY

Solumer is a novel technology improving the solubility of lipophilic drugs, hence enhancing their bioavailabilities. The technology is based on vastly improved solid dispersions possessing a unique collection of "fingerprint" features, exemplified by modified thermal behavior, nano-colloidal dispersions formation upon contact with aqueous media, and GI site-specific release. Investigations involving the insoluble drugs, albendazole, fenofibrate, and reseveratrol have shown that an excellent correlation was obtained between physico-chemical characteristics, dissolution profiles, and oral bioavailability. Furthermore, Solumer lends itself easily to industrial scale-up, employing spray-drying processing. The Solumer platform allows for rapid candidate screening as well as formulation development.

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BIOGRAPHIES

Dr. Galia Temstin Krayz, directs SoluBest Formulation R&D, analytical method development, process optimization and scale-up. She earned her PhD in Organic and Material Chemistry from Ben Gurion University in Beer Sheva, Israel. She has both academic and industrial experience in organic synthesis and process development of APIs.

Dr. Maryana Averbuch, SoluBest's Chief Technology Officer is responsible for development and implementaion of polymer enhanced drug solubilization concepts. She has extensive expertise in the physico-chemical properties of polymers and colloidal systems. She brings valuable experience in instituting and evaluating correlation between physico-chemical properties and biological activity of drug delivery systems.

Anna Berman earned her MSc from the Institute of Civil Engineering, St. Petersburg, Russia. She has brought to SoluBest essential experience in the bioanalytical field after having worked previously for two of Israel's leading commercial analytical laboratories.

Dr. Amir Zalcenstein is involved in business development and planning at SoluBest. He earned his PhD in Cancer Genetics, completed his post-doc in Nanotechnology from the Weizmann Institute of Science, and received his MBA from the Technion, Israel Institute of Technology. His experience entails business development and public relations in the life science sector.

Dr. Irene Jaffe has been involved in technological management and evaluation in the biomedical sector, and at SoluBest directs R&D and IP strategy. She earned her PhD in Chemistry from the Weizmann Institute of Science in Israel and completed post doctoral research at MIT's Dept. of Chemistry. Her scientific experience spans organic, organo-metallic, and polymer chemistry as well as materials research.