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SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF ATORVASTATIN: DESIGN AND PHARMACOKINETICS

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Abstract

Atorvastatin is a highly effective statin whose oral bioavailability is limited by poor aqueous solubility and extensive pre-systemic metabolism. Self-microemulsifying drug delivery systems (SMEDDS), isotropic mixtures of oil, surfactant and cosurfactant that disperse spontaneously in gastrointestinal fluid, have been proposed to overcome these limits. This review draws on published formulation and pharmacokinetic studies and reports no new experimental data. It covers the biopharmaceutics of atorvastatin, excipient selection and design methods, in vitro characterisation, and animal pharmacokinetic findings. Reported systems consistently improve dissolution and exposure in animals, but human data, long-term stability and in vitro to in vivo correlation remain sparse and call for rigorous, standardised evaluation.

1. INTRODUCTION

Statins are among the most widely prescribed drugs in the world, and atorvastatin is one of the most potent members of the class. By competitively inhibiting hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme of hepatic cholesterol synthesis, it lowers low-density lipoprotein cholesterol substantially and reduces cardiovascular events in a wide range of patients [1, 2, 3]. Large meta-analyses of statin trials have shown proportional reductions in major vascular events for each unit of cholesterol lowered, and a trial of atorvastatin 10 mg in hypertensive patients with average or lower cholesterol showed fewer coronary and stroke events than placebo [4, 5]. Doses are taken for years, so small differences in absorption could matter

to many patients. The same logic explains why formulation scientists continue to revisit an old, off-patent drug. If a cheaper or more reliable way of delivering an effective dose exists, the benefit multiplies across a very large population of long-term users.

The difficulty lies in what happens after the tablet is swallowed. Atorvastatin calcium dissolves poorly in the acidic medium of the stomach, and the fraction of an oral dose that reaches the systemic circulation as active drug is low, in the region of one-eighth to one-seventh [2]. The remainder is lost to incomplete dissolution, metabolism in the gut wall and liver, and efflux transport. Because the drug is highly permeable once dissolved, it fits the second class of the biopharmaceutics classification system, where absorption is limited by dissolution rate rather than membrane transport [6, 7]. For such compounds, formulation can have an unusually large influence. Food has a modest effect on absorption, and exposure differs noticeably between individuals, factors that make dissolution-limited absorption a natural target for formulation research rather than a mere academic curiosity [2, 3].

Lipid-based delivery systems are among the most versatile ways of tackling this problem. They present the drug in a solubilised state, take advantage of the digestive handling of dietary lipids, and in some cases reduce the metabolic or transporter-related barriers to absorption [8, 9]. Within this family, self-emulsifying systems are attractive for a pharmacist because they are anhydrous, can be filled into soft or hard capsules and are relatively simple to manufacture. When the mixture contacts gastrointestinal fluid under gentle agitation it forms a fine emulsion spontaneously, and the smallest droplet sizes define the self-microemulsifying class that is the subject of this review [10, 11]. Reviews of oral lipid formulations consistently stress that the approach is not a universal answer, since success depends on the drug being sufficiently soluble in the lipid phase and on the formulation surviving digestion without losing its solubilising capacity [8, 9].

This article reviews the published literature on self-microemulsifying systems for atorvastatin and reports no new experimental data. It first describes the biopharmaceutical features of the drug that justify the approach, then the design of the formulation, in vitro characterisation, and pharmacokinetic results reported in animals. A final section considers limitations and what remains to be shown before such products could be assessed for clinical use. The title of the work refers to design and pharmacokinetics, and these two themes are treated as they appear in the cited papers, with attention to whether the methods used are adequate to support the conclusions drawn. Studies on related statins and on other poorly soluble drugs are cited where they clarify a mechanism or a method, but claims about atorvastatin itself are restricted to papers that actually studied it [6, 7, 12].

2. BIOPHARMACEUTICS OF ATORVASTATIN

Atorvastatin is given as the calcium salt of an open-ring hydroxy acid. In acidic conditions the acid can cyclise into the corresponding lactone, and in the body there is a continuing interconversion between the two forms that influences both disposition and measured concentrations [13]. Solubility is pH dependent and low at gastric pH, rising as the pH approaches neutrality. The drug is lipophilic, and a high partition coefficient favours distribution into lipid phases, a property that makes it well suited to oil-based vehicles. This physical chemistry is the starting point for any formulation, since it determines both the choice of excipients and the risk of precipitation after dilution. Because the lactone is more lipophilic and less soluble in water, analytical methods and in vitro tests must control pH and temperature carefully, otherwise the measured behaviour may reflect conversion during testing and not the properties of the formulation [13, 14].

Pharmacokinetic studies show rapid absorption, with peak plasma concentrations within one to two hours, followed by a half-life of the parent drug of about 14 hours. Pharmacological activity lasts longer, because the ortho- and para-hydroxylated metabolites are also active and have half-lives up to a day or more [2, 14]. Absolute bioavailability is low and food reduces the rate and extent of absorption modestly, although the effect on lipid lowering is not clinically important.

Because exposure varies between individuals, there is interest in formulation approaches that could reduce the spread, even if the goal in routine practice is usually a standard daily dose. Dose-proportional increases in exposure over the usual range of 10 to 80 mg suggest that absorption is not saturable at clinical doses, which is useful when considering how much improvement a formulation could add [2, 3].

Several mechanisms contribute to low availability. Atorvastatin is a substrate of cytochrome P450 3A4, which metabolises it in the intestinal wall as well as in the liver, and it is also transported by P-glycoprotein at the apical membrane of enterocytes [15]. Hepatic uptake depends on organic anion transporting polypeptides, and inhibition of these transporters has been shown to raise plasma concentrations in volunteers [16]. Each step shaves a fraction from the dose reaching the circulation. A formulation that increases dissolved drug at the absorptive surface, or that modifies interaction with efflux transporters, could in principle raise bioavailability, though the evidence for such effects is largely from animal and cell models. Genetic variation in the transporter gene encoding the hepatic uptake protein is known to change statin exposure in carriers, which illustrates how much of the variability in response has biological rather than formulation-related origins [14, 16].

Variability deserves its own mention. Population studies of statins show wide differences in exposure between individuals, caused by genetic variation in transporter and enzyme activity, concomitant drugs, liver function and age. A formulation cannot remove these biological sources, and it may even amplify some of them, for instance if increased gut-wall permeability makes the dose more dependent on hepatic uptake. Reduced variability is a plausible and valuable aim, but it has to be demonstrated in a study designed to estimate within- and between-subject variance, and published SMEDDS work for atorvastatin has not yet done so [2, 14, 16]. Studies that pair pharmacokinetic sampling with pharmacogenetic information would help to separate the part of the variability that formulation can address from the part that it cannot [14, 16].

The therapeutic site of atorvastatin is the liver, which complicates the interpretation of plasma concentrations. A higher plasma exposure does not automatically mean a better pharmacodynamic effect, since uptake into hepatocytes is efficient and the first-pass extraction is part of how the drug reaches its target [2, 3]. An increase in systemic exposure may be a benefit, a neutral change or a concern, since exposure to the drug outside the liver is linked to muscle toxicity. Dose adjustment and clinical outcome studies would be needed to decide which. Developers therefore need to define in advance what improvement counts as useful. A narrower distribution of exposure, a smaller food effect or a reduced dose with unchanged plasma levels would all be reasonable aims, whereas higher exposure alone might simply increase the burden of adverse effects [1, 4].

The statin class gives some precedent for lipid-based approaches. Simvastatin and lovastatin are lactone prodrugs with low solubility, and several groups have studied self-emulsifying formulations of simvastatin with encouraging improvement in dissolution and in animal absorption [17, 18]. Comparison across statins shows that solubility, metabolism and transport differ in ways that affect how much a given formulation can achieve, so results for one member of the class should not be transferred to another without evidence. Atorvastatin has a higher dose-adjusted exposure than simvastatin but a similar problem of dissolution-limited absorption. Such comparisons also remind us that the conceptual approach is not unique to atorvastatin, which is useful when judging claims of novelty [17, 18].

3. DESIGN OF SELF-MICROEMULSIFYING SYSTEMS

A SMEDDS contains oil, a surfactant of relatively high hydrophilic-lipophilic balance, and usually a cosurfactant or cosolvent, with the drug dissolved in the mixture. The lipid formulation classification system divides these formulations according to composition

and dispersion behaviour, with the self-microemulsifying class (type IIIB) containing little or no oil and a high content of water-soluble components [19, 20]. Such systems form clear or slightly opalescent dispersions with droplet diameters usually below 100 nm, and they are thermodynamically stable once formed. The classification is useful for communication because it links composition to the expected behaviour during digestion and dilution. Droplet size matters because a larger interfacial area speeds drug release and absorption, although the relationship between very small droplets and measurable pharmacokinetic benefit is less direct than often assumed [10, 11].

Excipient screening is the first practical step in design. Solubility of atorvastatin is measured in a range of oils, surfactants and cosolvents, and components that dissolve the highest dose in the smallest volume are shortlisted, since the capsule volume sets a limit on the total mass of formulation [12, 21]. Medium-chain triglycerides and mixed glycerides, polyoxyl castor oil derivatives, polysorbates and short-chain alcohols or glycols are the usual candidates. The choice is constrained by capsule compatibility, regulatory acceptance and, for chronic use, tolerability, since some surfactants cause gastrointestinal irritation when taken daily for long periods. Drug loading also decides the practical value of the system. If the dose of atorvastatin requires most of the capsule volume, the surfactant and oil content must be kept low enough for the capsule to remain a reasonable size, which forces compromises between solubilisation and tolerability [8, 20].

Pseudo-ternary phase diagrams are then constructed by titrating mixtures of oil and surfactant with water and noting where clear microemulsions form. The region of efficient self-emulsification is mapped, and compositions within it are selected for further work [18, 22]. In the published atorvastatin work, the usual finding is that a surfactant-to-cosurfactant ratio between about one and three to one gives a broad microemulsion region, and that increasing the proportion of surfactant reduces droplet size. Phase diagrams are simple and informative, though they describe equilibrium behaviour in water, not the dynamic environment of the stomach and intestine. Experimental points are usually prepared in triplicate with simple visual grading of the resulting dispersion, so the phase diagram is a semi-quantitative tool. It does not predict what happens when the mixture meets bile salts and phospholipids in the small intestine [19, 23].

Characterisation follows a standard pattern. Droplet size and polydispersity are measured by dynamic light scattering, zeta potential indicates surface charge, and transmission electron microscopy confirms the shape of droplets. Self-emulsification time is assessed visually or by turbidimetry, and dispersion in media of different pH checks robustness against gastric acidity [21, 24]. Thermodynamic stress tests such as heating-cooling cycles, centrifugation and freeze-thaw cycles screen out compositions prone to phase separation or drug precipitation. Results are typically reported for a handful of optimised formulations, and the reproducibility of manufacture is rarely examined in detail. Reported droplet sizes for atorvastatin systems are typically in the tens of nanometres, with low polydispersity, and the zeta potential is usually mildly negative, but numbers differ with composition and with the instrument and dilution used for measurement [12, 22].

Choice of capsule and dose deserves some thought. Soft gelatin capsules are the usual container for liquid systems, and fill volumes of around one millilitre are practical, whereas hard capsules need sealing to prevent leakage. A once-daily dose of atorvastatin ranges from 10 to 80 mg, which means a formulation that works at a low strength may not scale to a high one without compromising drug loading. Developers sometimes report a single dose level, usually a low one, so it is unclear whether the benefits claimed would hold across the licensed range [12, 20, 21]. Another practical point is that an optimum found for a model drug may not carry over, since the phase behaviour depends on the drug as well as the excipients [10, 24].

Statistical experimental design is increasingly applied. Mixture designs and response-surface methods link the proportions

of oil, surfactant and cosurfactant to droplet size, emulsification time and drug loading, so that an optimum can be located with fewer experiments. This is in line with the quality-by-design philosophy, in which a design space is defined and critical quality attributes are identified [25, 26]. For SMEDDS, relevant attributes include drug content, droplet size after dilution, resistance to precipitation, and compatibility with the capsule shell. Applied properly, the approach produces robust formulations and a documented rationale. The methodology behind this thinking is described in the design-of-experiments literature, which also assumes knowledge of the process and its control strategy, matters that academic formulation papers seldom address in full [25, 26]. Exposure of the formulation to digestion products, and the wide range of gastric emptying times between patients, are two further reasons why simple designs of experiment need confirmation in biorelevant systems [23, 27].

Supersaturation is a related strategy. Adding a polymer such as hydroxypropyl methylcellulose that delays crystallisation can maintain the drug above its equilibrium solubility for long enough to be absorbed, creating a supersaturable SMEDDS with a lower surfactant load and therefore improved tolerability [28]. For a drug such as atorvastatin that crystallises readily from aqueous media, the idea is attractive, though published work specific to this statin is still limited. Evaluating the effect of precipitation inhibitors in a realistic dynamic setting would be the logical next step. At present the supersaturation concept is better supported by studies of other drugs than by direct work on atorvastatin [23, 28]. Research groups sometimes combine a precipitation inhibitor with a lower surfactant load, which may make daily dosing more comfortable.

4. IN VITRO PERFORMANCE AND PHARMACOKINETICS

Dissolution testing offers the first indication that the system improves release. In published work, atorvastatin SMEDDS capsules released the drug rapidly and almost completely into aqueous media, whereas the reference tablet or the pure drug dissolved slowly and incompletely, particularly in acidic medium [12, 21]. Paddle apparatus at 50 or 75 rpm with surfactant-containing media is a common set-up. A caution is that sink conditions and surfactant concentrations in these tests can mask differences, and a conventional compendial method may not discriminate between formulations in a way that predicts performance in the intestine. Some papers add an acid-stage test followed by a change to neutral medium, which gives a rough impression of how the formulation behaves on transit from the stomach to the small intestine. Reports of this kind, where available, support the view that SMEDDS keep atorvastatin in solution across the pH range [12, 21].

A more physiologically relevant approach is the lipolysis model, in which pancreatic enzymes digest the lipid components in the presence of bile salts and the partitioning of the drug between aqueous and lipid phases is followed. Such models show that surfactant digestion and loss of solubilising capacity can lead to precipitation, even if the formulation disperses well, and they have been shown to correlate better with animal exposure than simple dissolution for some lipophilic drugs [23, 27, 29]. For atorvastatin, few lipolysis studies have been published, which leaves a gap in the evidence for formulation robustness during digestion. The practical lesson for atorvastatin is that screening should include digestion, since a formulation that looks optimal in a simple dispersion test may precipitate drug once surfactant is digested. Studies on danazol and fenofibrate support the principle but do not prove it for this statin [23, 27].

Animal pharmacokinetic studies are the main in vivo evidence. In an early study by Shen and Zhong, a SMEDDS of atorvastatin was compared with a conventional tablet in beagle dogs, and the microemulsion gave higher plasma exposure than the reference [12]. Subsequent work with self-emulsifying systems in rats reported improved bioavailability and higher peak concentrations relative to a suspension of the drug [22]. Studies of other statins show the same direction of effect, with a self-microemulsifying system of simvastatin

raising relative bioavailability in dogs [18]. The direction of effect is consistent, though study designs differ. Rats and dogs differ from humans in gastric pH, bile salt composition and metabolic enzymes, and the dog in particular has a higher gastric pH under fasting conditions, which can flatter formulations that perform best at near-neutral pH. Species choice therefore influences how far the reported gain can be believed [12, 18].

Typical pharmacokinetic readouts are maximum concentration, time to maximum concentration, area under the concentration-time curve, and relative bioavailability against a reference. Studies often report a higher maximum concentration and a larger area under the curve for the SMEDDS, with time to peak either unchanged or shortened [12, 22]. Interpretation depends on the analytical method. Because atorvastatin interconverts with its lactone and has active metabolites, assays that measure only the parent acid may under- or overestimate the active drug exposure, and sample handling must prevent conversion between forms [13, 14]. Sampling schedules are sometimes too sparse to capture the peak or to estimate the elimination phase, and the number of animals per group is often small, so confidence intervals are wide and are rarely presented. A reader should treat reported fold increases as estimates with considerable uncertainty [12, 22].

The main findings are collected in table 1, which brings together formulation studies on atorvastatin, comparable statin systems, mechanistic work and stability and bioequivalence methodology. Most entries concern dissolution and bioavailability in small animals, and the number of entries per category is shown in fig. 1. The pattern is that the formulation literature is large for lipid-based systems in general, moderate for statins as a group, and small for atorvastatin specifically. The table is also a reminder of how few human data exist, and of how often conclusions rely on a single species and a single reference product [12, 18, 22]. Regulators evaluating lipid products ask for evidence of in vitro to in vivo relationships, and many entries in the table lack them. The table therefore highlights research gaps as much as findings, which is a legitimate function of a synthesis [21, 30].

Table 1: Published evidence on lipid-based systems for atorvastatin and related statins

System or study	Reported finding	Ref.
Atorvastatin SMEDDS Beagle dogs	Higher plasma exposure than a conventional tablet after oral dosing.	[12]
Atorvastatin SEDDS Rats	Improved dissolution and oral bioavailability relative to a drug suspension.	[22]
Atorvastatin SMEDDS In vitro	Rapid, near-complete release in aqueous media, especially at acidic pH.	[12, 21]
Atorvastatin SMEDDS Hyperlipidaemic rats	Greater lipid lowering than plain drug suspension in small animal models.	[12, 22]
Simvastatin SMEDDS Beagle dogs	Higher relative bioavailability than a conventional tablet.	[18]
Simvastatin self-emulsifying system	Improved dissolution and in vivo performance relative to a reference.	[17]
Coenzyme Q10 SEDDS	Bioavailability assessment showing enhancement of a very lipophilic compound.	[31]
Lipolysis model Danazol and fenofibrate	Digestion of surfactant can limit solubilisation and affect exposure.	[27, 29]
Polyoxyl castor oil and glycerides Cell models	Excipients can reduce P-glycoprotein efflux.	[32]
Stability and BE methods	Accelerated ageing predicts chemical stability; crossover designs are standard for bioequivalence.	[26, 30, 33]
Lipid-based vehicle Lymphatic transport	A lipid vehicle improved bioavailability and lymphatic transport of a poorly soluble compound.	[34]

Mechanistic explanations offered for the improvement include faster dissolution, maintenance of solubilised drug in digestion products, increased intestinal permeability from surfactant action, inhibition of P-glycoprotein by excipients such as polyoxyl castor oil, and lymphatic transport of lipophilic drugs [15, 32, 35]. Lymphatic uptake would bypass the liver and hence first-pass metabolism, but for a drug with a modest lipophilicity and a hepatic site of

action the relevance is unclear. Most of these claims are supported by cell studies or by inference. Few papers test which mechanism is responsible in the formulation under study. Cell-based experiments typically use concentrations of excipients that may exceed what the gut wall would see, which limits their direct relevance [32, 35].

5. LIMITATIONS AND FUTURE DIRECTIONS

Stability is a recurring concern. Liquid SMEDDS in soft gelatin capsules can interact with the shell, causing migration of components, brittleness or softening, and drug may precipitate or degrade on storage. Stability work conventionally uses defined temperature and humidity conditions, with accelerated ageing used to predict chemical stability, and many academic papers report only short periods at accelerated conditions or none at all [26, 33]. For a drug that is prone to lactone formation and oxidation, long-term chemical stability in a lipid vehicle deserves particular attention, and packaging may need to include protection from light and moisture. The risks are well known to industry, and capsule fill compatibility studies are an established part of development, but they rarely appear in research publications. Absence from the paper should not be taken as evidence that the problem does not exist [26, 33].

Converting liquid systems to solid dosage forms is one way forward. Adsorption onto porous carriers, spray drying, melt granulation and extrusion have all been used to produce solid self-emulsifying powders or pellets that can be compressed into tablets or filled into hard capsules [28, 36]. These approaches improve handling and stability but may lower drug loading and can change the dispersion behaviour, so that droplet size and release need to be re-established after solidification. The published atorvastatin work is mostly on liquid systems, and the solid versions would have to be assessed with the same care. Pellet and bead technologies offer a further option, since lipid mixtures can be layered or granulated with excipients that maintain flow and compressibility. The published literature suggests that adding solid carriers lowers the fraction of drug released in the first minutes, so that optimisation is needed [28, 36].

Safety and tolerability are rarely discussed. High surfactant content raises the risk of gastrointestinal irritation and may alter membrane integrity, and some excipients inhibit transporters and enzymes that handle other drugs, raising the possibility of interactions in patients taking several medicines. Statin users are often elderly and on multiple therapies, so a formulation that changes the exposure to co-administered drugs would be undesirable. Toxicity testing of the final composition, cell viability studies and exposure data are needed alongside efficacy [15, 35, 37]. Practical safety work would include long-term repeat-dose studies in animals with the final excipient mix and consideration of interaction with commonly co-prescribed drugs such as calcium channel blockers, macrolides and fibrates, which already complicate statin therapy [14, 15]. Such a screen should record not only gastrointestinal complaints but also biochemical markers of liver and muscle injury, which are the established safety concerns with statins [1, 3].

Reporting standards are another weakness. Many papers on SMEDDS give a composition and a list of results without enough detail to reproduce the formulation, such as the grade or supplier of excipients, the mixing temperature, the equilibration time or the exact dissolution conditions. Animal studies often lack information on randomisation, blinding and sample size justification, items that have been recommended for decades in guidance on reporting preclinical work. Better reporting would make it easier to compare studies and to see which differences are real [12, 18, 22]. The weakest part of the argument for clinical use is therefore the missing link between formulation performance and measurable benefit for the patient [4, 5].

The translational gap is the largest. Human bioavailability studies of atorvastatin SMEDDS are not available in the literature reviewed, and standard designs for bioavailability and bioequivalence studies call for crossover studies in volunteers with validated assays, including measurement of

metabolites where relevant [14, 30]. Pharmacokinetic results from dogs or rats do not translate directly, since gut physiology, bile composition and metabolism differ. Establishing an in vitro to in vivo correlation, ideally with digestion models, would help to select formulations for human work and to support regulatory submissions. Bioequivalence between a new formulation and a marketed tablet would be judged on peak concentration and area under the curve within accepted limits, but a formulation designed to raise exposure would by definition not be bioequivalent, and would need a different regulatory pathway and clinical justification [26, 30].

Cost and manufacturing should not be overlooked. Atorvastatin is available as generic tablets at a very low price, so a lipid-based product will need clear advantages to compete. Possible advantages include lower dose, reduced food effect, better performance in patients with impaired absorption, or fixed-dose combinations in which solubility is a problem. Whether any of these is worth the extra complexity is a decision for development teams, regulators and payers, and it will depend on convincing clinical data rather than on laboratory enhancement alone [36, 37]. Pricing is therefore as much a part of the evidence as pharmacokinetics [36, 37].

Education and communication matter too. Pharmacists meet patients who ask whether a newer formulation of a familiar drug is better, and the honest answer for atorvastatin SMEDDS is that the idea is sound but the proof is incomplete. Explaining the difference between a laboratory improvement in dissolution and a demonstrated clinical benefit helps patients and prescribers to treat claims with proportion and supports sensible decisions about switching between products. Such conversations are easier when the published evidence is summarised honestly [4, 5, 12]. Reliable information is the best protection against both hype and unwarranted scepticism.

6. CONCLUSION

Published studies suggest that self-microemulsifying systems can improve the dissolution and oral exposure of atorvastatin in animals, and the rationale is well grounded in the drug's low solubility, extensive first-pass metabolism and transporter interactions [2, 12, 22]. Design relies on solubility screening, phase diagrams and characterisation of droplet size, and the most robust work uses statistical optimisation and digestion-aware testing. These findings are encouraging but they come mostly from small animal studies with a single reference product. Differences between species and the lack of digestion-based testing add to the uncertainty [23, 27].

The gap to clinical use remains wide. Human pharmacokinetic data, long-term stability, safety of high-surfactant compositions, and proof that the extra exposure offers a clinical benefit are all missing. Future work should adopt biorelevant testing, validated assays that account for metabolites, and quality-by-design principles, with comparisons against marketed tablets in humans [30, 33, 37]. Until then, atorvastatin SMEDDS should be regarded as a promising formulation concept rather than a proven product. Cost relative to generic tablets will also shape any realistic path to use [37].

7. ABBREVIATIONS

BCS-Biopharmaceutics classification system, CYP3A4-Cytochrome P450 3A4, HMG-CoA-Hydroxymethylglutaryl coenzyme A, LDL-Low-density lipoprotein, P-gp-P-glycoprotein, SEDDS-Self-emulsifying drug delivery system, SMEDDS-Self-microemulsifying drug delivery system

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9. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

10. CONFLICT OF INTERESTS

Declared none

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