Commentary

Open Access
CrossMark

Lipid nanoparticles – enablers for efficient delivery of drug molecules

Volume 11 Issue 3 - 2022

Jim Huang, Shaukat Ali
Ascendia Pharmaceuticals, Inc., USA

Correspondence: Shaukat Ali, PhD, Sr. Director, Scientific Affairs & Technical Marketing, Ascendia Pharma, Inc., 661 US Highway One, North Brunswick, NJ 08902, USA, Tel 732-640-0058, Cell 732-308-8352, Email shaukat.al@ascendiapharma.com

Received: December 01, 2022 | **Published:** December 07, 2022

Introduction

As the new molecular entities (NMEs) with trends in insolubility continues to rise, reaching over 80%, the drug manufacturers weighing all options to use atypical, innovative formulation technologies with aims to enhance solubility and bioavailability of those molecules.[1] Such trends continue to impede the development and launch of new drug candidates. In fact, in 2021, for example, 50 drugs were approved and over 70% of them were poorly soluble and for different modalities.[2] Thus, as the industry continues to be innovative to create new molecules to fill in the pipelines, the challenges span across the innovators for finding the appropriate technologies in developing and commercializing these molecules. In such cases, the industry is evaluating a range of technologies, with many non-conventional bearing risks for development of optimal formulations with extended stability and shelf life without compromising the efficacy and safety of drug products.[3]

As the interest continues to adapt more efficient, innovative formulation technologies, the industry is highly conservative with respect to accepting the novel excipients and/or new technologies for multiple reasons including the lack of information on safety in a particular dosage and/or the historical use of such technologies in development and commercialization of drug products. The regulatory guidelines are also less evident or unclear when adapting such excipient technologies.[4] Nonetheless, the industry is adapting the novel concept and building partnerships with excipient manufacturers and the agency to evaluate the "new technologies" to ease the bottle neck from innovative drug candidates with high melting, poor solubility, absorption, and bioavailability. Taken together, the industry is also weighing options for outsource to external partners including the contract development manufacturing organizations (CDMOs) offering innovative formulations technologies to expedite the manufacturing and commercialization of new drug products.[5]

Choice of selecting a partner in developing the challenging molecules is not trivial that could significantly impact on the probability of success and the timeline of drug development and clinical manufacturing.[6] The challenges with poor solubility stem from highly crystallinity (MP) and lipophilicity (log P) of the molecules. The higher crystallinity means that the molecules are held together with higher bonding energy within the crystal lattices, and the higher lipophilicity (log P) means that these molecules are preferably partitioned in organic phase with respect to aqueous phase. These two factors are primary causes for insolubility.[7]

Identifying a CDMO partner with the expertise in enabling formulation technologies of poorly soluble molecules and having the capabilities in scale up and cGMP manufacturing could help ensure the success of drug development projects for poorly soluble NMEs. Furthermore, with the technical expertise in analytical R&D, stability and quality assurance programs, CDMO will help expediate the advancement of the drug development process.

Ascendia's enabling formulation technologies offers the solutions to NMEs with poor solubility and bioavailability. Its innovative solubilization platforms such as Emulsol®, Amorsol® and Nanosol®, are fully integrated into the design of new drug formulations, oral and parenteral, leading the way to advancement of molecules in the clinical development.8 Before describing Ascendia's platform technologies, let's examine two commonly applicable non-conventional formulation technologies, namely, solid amorphous dispersions and lipid based liquid dispersions.

Amorphous solid dispersions

Amorphous solid dispersions (ASDs) are applicable to those poorly soluble molecules intended to be primarily delivered by oral route of administration for immediate release dosages. It is equally important as many of the drugs marketed are oral dosage forms. An ASD is prepared by hot melt extrusion, spray drying, co-precipitation, freeze drying, or Kinetisol® among others non-conventional technologies, wherein, the API if fully dispersed in the polymeric matrix in a metastable amorphous state, resulting in higher solubility but higher probability of recrystallization, possibly during storage, as shown in Figure 1.[9]

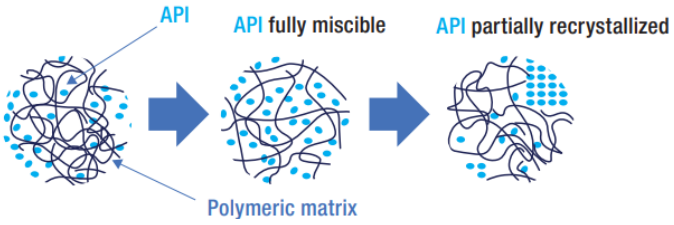

Figure 1 ASD of API showing complete miscibility and partial recrystallization.

These issues could lead to a lower exposure (lower C_{max}), due to a failure in maintaining the desired supersaturation in gastrointestinal tract.[10] Thus, finding an appropriate polymeric matrix that promotes

©2022 Huang et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Copyright: ©2022 Huang et al.

the stability of an amorphous API via H-bonding and van der Waal's interactions with polymers and discourages the nucleation of fully dispersed or amorphized drug, remains challenging. In such cases, in order to mitigate the risk of recrystallization, solubilizers play an important role to keep the API in fully dispersed state while maintaining the kinetic stability in aqueous solution via formation of polymeric nanoparticles or nanosuspensions.[11] The polymers like Soluplus® with MW of 118,000 D, an amphiphilic polymer comprised of polycaprolactam, polyvinyl acetate and polyethylene glycol, possesses good solubilizing properties (HLB 16) as well as it forms micelles in aqueous dispersions with APIs and used in several marketed drugs in ASD.[12] Examples of amorphous solid dispersion based on marketed drugs include Kaletra® (Ritonavir/Lopinavir); Norvir® (Ritonavir); Viekira Pak® (Dasabuvir and Ombitasvir and Paritaprevir and Ritonavir); Belsomra® (Suvorexant); Noxafil® (Posaconazole); Sporanox® (Itraconazole); Intelence® (Etravirine); Prograf® (Tacrolimus); Crestor® (Rosuvastatin); Gris-PEG® (Griseofulvin); Cesamet® (Nabilone); Solufen® (Ibuprofen); Zelboraf® (Vemurafenib); Incivek® (Telaprevir) among others.

Self emulsifying/Micro emulsifying drug Delivery Systems (SEDDS/SMEDSS)

A self emulsifying system is composed of an oil, lipid-based surfactant, co-surfactant, and/or a co-solvent. Surfactants and co-surfactants are often used in large amounts to help emulsify the API dissolved in oil/co-solvent.[13] A pre-mix cocktail derived with the appropriate amounts of surfactants and co-surfactants helps create and allows rapid dispersibility of lipid nanoparticles in the aqueous solution. An API sensitive to acidic or alkaline pH are also shielded from outside environment in GI, and therefore, it maintains longer exposure in GI tract, hence, enhancing the absorption and bioavailability. Figure 2 illustrates the design and development of a SEDDS/SMEDDS.[14]

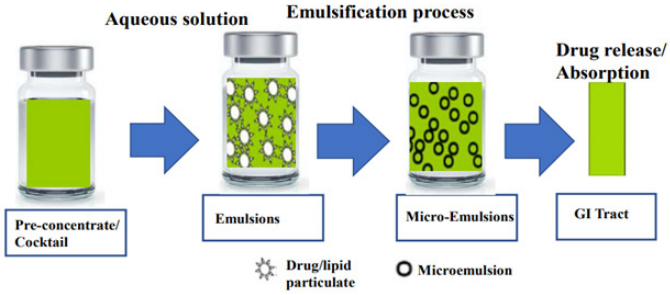

Figure 2 A preconcentrate comprised of lipid/surfactant based excipients for SEDDS/SMEDDS on aqueous dispersion.

As illustrated, the pre-concentrate or cocktail, thermodynamically stable and a clear liquid, is derived from an API and the lipid/surfactant-based excipients. Upon exposure to an aqueous solution, it results in emulsification and formation of oily droplets or emulsion and micro-emulsion particles. Lower amounts of surfactants/co-surfactants create larger particles or emulsions, whereas, higher amounts (> 50%) help create smaller droplets (microemulsions) that expedite faster dispersibility in aqueous media, and rapid absorption in GI tract.[15] Wu et al., for example, evaluated a number a lipid based SEDDS/SMEDDs formulations composed of different oil and lipid/surfactant for a BCS class II molecule, and selected an optimized API formulation comprised of 24.5% castor oil, 40.8% polyethoxylated 35 castor oil (Kolliphor® EL), 28.6% Labrasol® and 2.7% Transcutol® HP.[16] The formulation was stable for over 3 months at 25 °C, and the particle distribution of the aqueous droplet dispersions remained uniform within <30 nm in size with PDI of <0.3 and zeta potential of -2.8 mV. The viscosity of pre-mix cocktail was < 300 cP, ideally suited for capsule filling. On oral exposure in rats, the bioavailability increased by >35-folds as compared to crystalline drug, likely due to lymphatic absorption.[17]

A number of lipid-based oral drugs have been approved and those include: Agenerase® (Amprenavir); Norvir® (Ritonavir); Kaletra® (Ritonavir/Lopinavir); Fortovase® (Saquinavir); Aptivus® (Tipranavir); Neoral® (Cyclosporine); Sandimmune® (Cyclosporine); Gengraf® (Cyclosporine) among others.

Figure 3 illustrates the progression toward development of lipid based nanotechnologies over the years.[18] Development of lipid nanoparticles (LNP) with aims to higher drug loading and having ability to deliver drug effectively. It is equally challenging for reasons of API's instability in liquid environment on standing, therefore, an interest in creating solid lipid nanoparticles and nanostructured lipid carriers is phenomenal.[19]

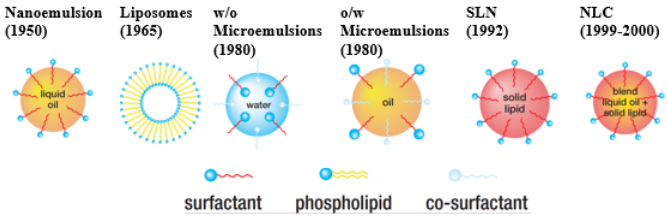

Figure 3 Progression on LNPs over the years.

Huang and Ali recently published an article on LNPs.[6] These LNPs are typically composed of a synthetic lipid that is positively chargeable, a phospholipid, cholesterol, and a PEGylated lipid. The chargeable lipids are cationic in nature comprised of one or more tertiary amines able to ionize under an acidic pH due to amino group and is responsible for complexation with negatively charged phosphate groups of nucleic acids. On the other hand, the phospholipids and cholesterol provide structural stability and promote fusion of LNPs with cell membranes, while the PEGylated lipid at the particle surface, provides steric hindrance preventing aggregation and stealth protection from binding to serum proteins to help prolong the *in vivo* circulation time. The quality attributes for LNP based products are particle size morphology, particle surface properties, PEGylation, charge, mean particle size and size distribution, particle concentration, inherent viscosity, encapsulation and loading efficiency, lipid specifications, *in vitro* release, transition temperature and stability, residual solvents and impurities, sterility, toxicity and efficacy.[20]

Ascendia's formulation capabilities in nanotechnologies

BCS class II and class IV molecules are challenging for their poor solubility and bioavailability. BCS class II drugs have either dissolution (IIa) or solubility (IIb) limited absorption process in GI tract. With class IIb solubility limited APIs, the non-conventional enabling lipid or polymeric based solubilization technologies are primarily used for development of these molecules.[21] Ascendia's platform technologies offer the solutions, by which such molecules can be solubilized and delivered effectively with higher bioavailability. Those technologies include: Amorsol®, Emulsol® and Nanosol®. Illustrated in Figure 4, these technologies can be applied for small and large molecules and/or biologics with higher melting and lipophilicity. For instance, poorly soluble APIs with high melting and relatively lower logP, Nanosol® and Emulsol® offer better choices as compared to those APIs with medium to higher range melting and higher log P. In latter cases, for instance, Amorsol® might be the better option. These approaches are based on empirical assessments, keeping in mind that one size "does

Citation: Huang J, Ali S. Lipid nanoparticles – enablers for efficient delivery of drug molecules. *J Anal Pharm Res.* 2022;11(3):126–129.
DOI: 10.15406/japlr.2022.11.00413

Copyright: ©2022 Huang et al.

not fit all", and therefore, all solubilization technologies, whether polymeric amorphous dispersions or lipid-based dispersions, should be evaluated. As an example, lopinavir (MP 124 °C, logP 4.7) and ritonavir (MP 120 °C, logP 5.6) in a fixed dose combination (e.g. Kaletra®), were first formulated in lipid/surfactant based ingredients comprised of polyoxyl 35 castor oil as surfactant and oleic acid as co-surfactant/solvent in soft gels, and much later both drugs were co-formulated and marketed in amorphous dispersion tablets comprised of copovidone (PVPVA 64) to reduce the pill burden on patients.[22] It is also true for ritonavir (Norvir®) that was first introduced in solution containing polyoxyl 35 castor oil, and much later was launched in solid dispersion tablets containing copovidone (PVPVA 64).

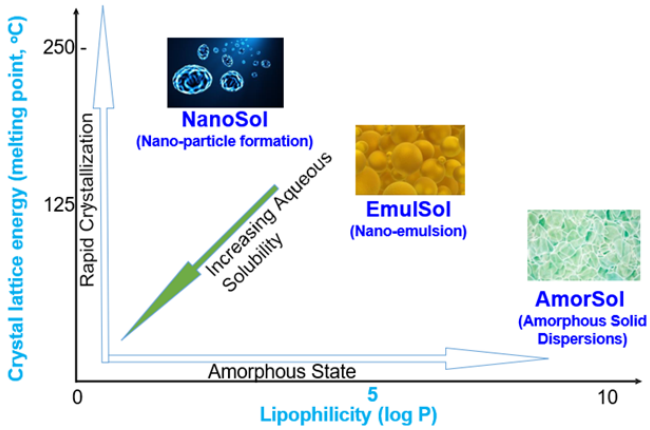

Figure 4 Ascendia's enabling formulation technologies: Amorsol®, Emulsol® and Nanosol®.

A few examples of Ascendia's nanotechnologies applicable to poorly water-soluble drugs are cited below.

An oil/water (o/w) nano-emulsion comprised of 0.2% cyclosporine, 20% soy oil, 7.2% each of egg lecithin and polysorbate 80 in aqueous buffer, pH 6.8, was prepared at 60°C by mixing and heating and applying high pressure homogenization to achieve the desired particle size (*ca.* < 50 nm (d50) and passed through 0.22 micron sterile filter. On stability at 40 °C, the average particle size unchanged and the API stability was maintained over 5 months period.[23]

Ascendia's platform technologies are also applied to poorly soluble drugs like clopidogrel (pKa 4.5), an anti-coagulant drug that prevents platelet aggregation. It is commercially available in tablets as an (S) enantiomer in bi-sulfate salt (Plavix®) and is prescribed for prevention of atherothrombotic symptoms like myocardial infraction, stroke and cardio-vascular health conditions. Clopidogrel free base was formulated for oral and parenteral in nanoemulsions comprised of soybean oil, egg lecithin, oleic acid and glycerol and was compared with bi-sulfate salt formulation as described.[24,25] These formulations were subjected to evaluation for particle size distribution and chemical stability of API following autoclaving for enantiomeric impurity, as shown in Figure 5.

The data following autoclaving at 121 °C for 20 min or freeze thaw cycle showed that the mean particle size distribution of nanoemulsions of free base were within 200-250 nm range, whereas, for salt formulations, it changed significantly, suggesting that clopidogrel as a free drug in nanoemulsions was stable within the inner core, therefore, its conversion from (S) enantiomer to (R) enantiomer was minimized. In comparing with two formulations in b-cyclodextrins, the conversion of (S) to (R) enantiomer of free drug was also minimal (< 2%) in nanoemulsions (data not shown).

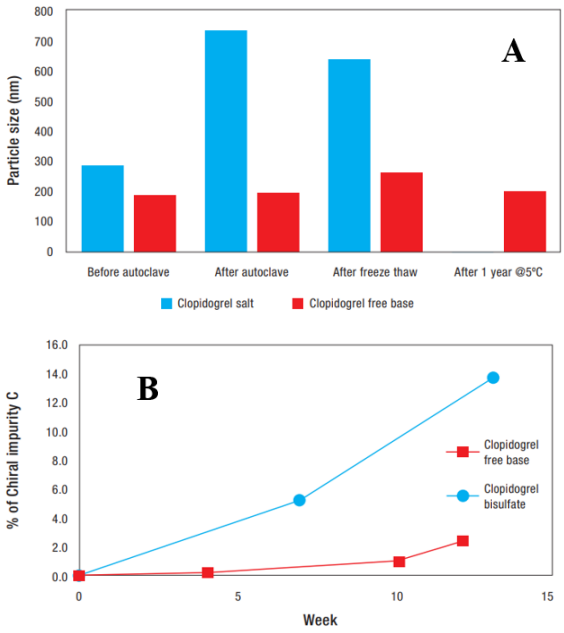

Figure 5 Particle size distribution of droplets and stability of API derived from free base and bi-sulfate salt of clopidogrel.

Carvedilol is marketed as Coreg® tablet. We formulated carvedilol @6.8% in lipid-based liposomes comprised of about 52% DMPC, 21% Cholesterol and 22% DSPE and prepared by phase inversion method using ethanol as a solvent.[26] The particle size ranged 75-150 nm with PDI 0.12-19 and drug encapsulation efficiency of 80-90%. For comparison, carvedilol both in aq. solution and in liposomes encapsulated @7.6% comprised of 65% egg phospholipids and 27% cholesterol were also used to evaluate *in vitro* drug release and study the pharmacokinetic profiles in rats. The carvedilol was single dosed at 2.5 mg/kg. *In vitro* and pharmacokinetic (PK) data from 3 animal groups (Liposomes #1/Group 1 with DMPC, Liposomes # 2/Group 2 from egg PC and aq. solution Group # 3, are shown in Figure 6.

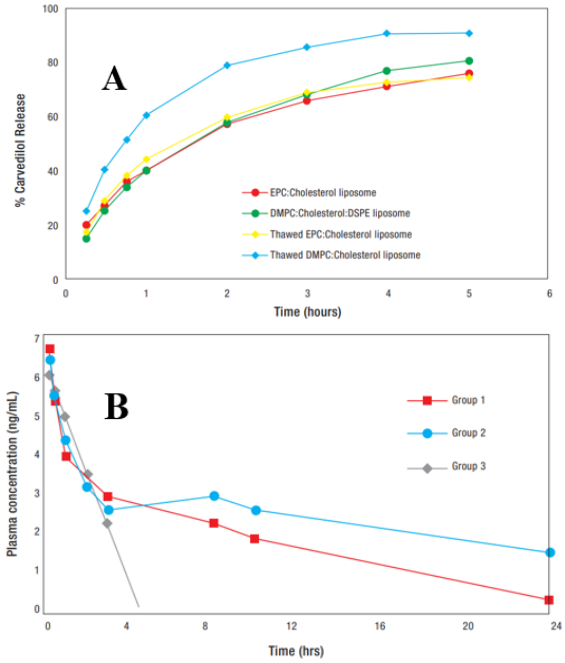

Figure 6 *In vitro* dissolution of carvedilol in liposome formulations (A) and PK profile of drug encapsulated in DMPC/Chol/DSPE (liposomes 1) and egg PC/Chol (liposomes 2) and aq. Solution.

Citation: Huang J, Ali S. Lipid nanoparticles – enablers for efficient delivery of drug molecules. *J Anal Pharm Res.* 2022;11(3):126–129. DOI: 10.15406/japlr.2022.11.00413

Copyright: ©2022 Huang et al.

In vitro dissolution data in Figure 6A shows that drug is released over 6 hours regardless of liposome compositions either with DMPC or egg PC, prepared fresh or subjected to freeze thaw cycles. *In vivo* data in Figure 6B shows that the drug is maintained in plasma over 24 hours as compared to drug in aq. solution which is cleared out within 3 hours following iv administration.

Conclusion

As the pharma industry continues to generate new drug entities, small, large and/or biologics, the needs for enabling technologies will also grow for improving the solubility and performance of these molecules. As the reliance of pharma industry on the CDMOs continues to grow due, in part, to lack of their technical capabilities or lack of developing capacities for cGMP manufacturing of oral and sterile products, the CDMOs like Ascendia can leverage its technologies and cGMP capability with those interested in developing the difficult NMEs from discovery to clinic. With its enabling technologies, Amorsol®, Emulsol® and Nanosol®, and having equipped with the state-of-the art non-GMP and GMP facilities for non-sterile and sterile capabilities, Ascendia can lead the way for developing and manufacturing the innovative molecules coming out of discovery to clinical development as potential new drug candidates.

Acknowledgements

None.

Conflicts of interest

Authors declared no conflicts of interest.

References

1. Elder DP. Effective formulation development strategies for poorly soluble active pharmaceutical ingredients (APIs). *Am Pharm Rev*. 2010.
2. Ebied M, Elmariah H, Cooper-DeHoff RM, et al. New drugs approved in 2021. *Am J Med*. 2022;135(7):836–839.
3. Lehmkemper K, Kyerematen SO, Bartels M, et al. Physical stability of API/polymer-blend amorphous solid dispersions. *Eur J Pharm Biopharm*. 2018;124:147–157.
4. FDA guidelines on novel excipients. *Pilot program for the review of innovation and modernization of excipients (PRIME);* 2022.
5. Huang, Ali S. A CDMO perspective on developing biological modalities from discovery to commercialization. *Am Pharm Rev*; 2022.
6. Huang J, Ali S. Lipid nanoparticles: Tackling solubility challenges with lipid-based technologies for oral & injectable formulations. *Drug Dev & Deliv*. 2022;22.
7. Yalkowsky SH. *Solubility and Solubilization in aqueous media*. Published by American Chemical Society. 1999: ISBN 10: 0841235767.
8. Ascendia pharma.
9. Huang Y, Daib W. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharma Sin*. 2014;4(1):18–25.
10. Tsinman O, Tsinman K, Ali S. Excipient update - soluplus®: An understanding of supersaturation from amorphous solid dispersions. *Drug Deliv Dev.* 2015.
11. Wilson VR, Lou X, Osterling DJ, et al. Amorphous solid dispersions of enzalutamide and novel polysaccharide derivatives: investigation of relationships between polymer structure and performance. *Nature Research, Scientific Report*. 2020;10:18535.
12. Ali S, Langley N, Djuric D, et al. Soluplus®, tablets & capsules – Eye on excipients. 2010;8(7):48.
13. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs. *Drug Deliv*. 2022;29(1)1811–1823.
14. Ali S, Kolter K. Tackling the challenges with poorly soluble drugs. *J Anal Pharm Res* 2015;1(1):1–3.
15. Mullertz, A. Ogbonna, S. Ren, et al. New perspectives on lipid and surfactants-based delivery systems for poorly soluble drugs. *J Pharm Pharmacol.* 2010;62:1622-1633.
16. Wu L, Qiao Y, Wang L, et al. A self micro-emulsifying drug delivery system (SMEDDS) for a novel medicative compound against depression: a preparation and bioavailability study in rats. *AAPS PharmSci Tech.* 2015;16:1051–1058.
17. Yadez JA, Wang SWJ, Knemeyer IW, et al. Intestinal lymphatic transport for drug delivery. *Adv Drug Deliv Rev.* 2011;63: 923–942.
18. Wen Z, Liu B, Zheng Z, et al. Preparation of liposomes entrapment essential oil from Atractylodes macrocephala Koidz by modified RESS technique. *Chem Eng Res Des*. 2010;88:1102-1107.
19. Duan Y, Dhar A, Patel C, et al. Brief review on solid lipid nanoparticles: part and parcels of complementary drug delivery systems. *RSC Adv.* 2020;10:26777-26791.
20. Fan Y, Yen C, Shi Z, et al. Chen, Am Pharm. Rev. 2022 October 1.
21. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? *J Pharm Sci.* 2009;98:2549-2572.
22. Breitenbach J. Melt extrusion can bring new benefits to HIV therapy-The example of Kaletra® tablets. Am J Drug Deliv. 2006;4:61–64.
23. Huang J. Composition of nanoemulsion delivery systems, US Patent 10,251,837 (April 9, 2019).
24. Huang J. Stable pharmaceuticals composition of clopidogrel free base for oral and parenteral delivery, US Patent 9,480,680 (November 1, 2016).
25. Huang J. Stable pharmaceutical composition of clopidogrel free base for oral and parenteral delivery, US Patent 9,884,016 (February 6, 2018).
26. Ivanova V, Maeda K, Wang W, et al. Parenteral sustained release delivery of carvedilol disperse system, US Patent 10,792,244 (October 6, 2020).