IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Brief Introduction to Self-Nano-Emulsifying Drug-Delivery Systems

Swami Prashant[1*], Prashant Patil[1].

1. Ravindra Gambhirrao Sapkal college of pharmacy, Kalyani hills, Anjaneri, Nashik, 422212

Abstract-

Since low-energy emulsification methods like spontaneous or self-nano emulsification were reported, there has been a resurgence of interest in nanoemulsions for diverse medicinal applications. Self-nano emulsifying drug delivery systems (SNEDDS) are anhydrous homogeneous liquid solutions of oil, surfactant, drug, and co-emulsifier or solubilizer that spontaneously produce oil in water nanoemulsions of 200 nm or less in size when diluted with water and gently stirred. The selection of SNEDDS components is heavily influenced by physicochemical features, drug solubilization capability, and physiological destiny. Phase diagrams may be utilized to optimize the composition of SNEDDS, while statistical experimental design can be used to further optimize SNEDDS. Nanotechnology has become a buzzword in the pharmaceutical sciences, and attempts are underway to broaden its uses across the board. Over the last two decades, nanotechnology has had a significant impact on drug delivery research, and numerous nanoscale technologies/carriers have been and are being investigated for increasing medication therapeutic performance. SNEDDS conversion from liquid to solid Researchers have also produced SNEDDS dose forms that may be taken orally or in solid form. SNEDDS has the potential to improve patient compliance while also reducing the difficulties that come with liquid SNEDDS-filled capsules

Kay Words- Nano Technology, SNEDDS, nano-emulsion, self-nano emulsification.

Introduction-

The drug must be dissolved in the gastrointestinal tract before being used. Insufficient drug solubility can lead to inadequate absorption, limited bioavailability, and other problems. After oral administration, there was a great deal of heterogeneity. It's also possible that the oral administration has something to do with it. Precipitation, food-drug interactions, susceptibility to breakdown, and first-pass metabolism are all factors to consider. Low oral bioavailability results. According to the BCS (Biopharmaceutical

Classification System), most of the drugs discovered so far are classified into group II (low solubility, high osmolality) and group IV (solubility). low, low permeability) [1].

Following oral administration, these compounds have low oral bioavailability due to low solubility or membrane permeability. Therefore, there is an urgent need to develop new drug carriers for oral administration. The fact that the oral absorption of poorly water-soluble drugs can be enhanced when administered with lipid-rich foods has led to the use of lipid-based formulations as a means of improving solubility. dissolution and absorption of the drug after oral administration [2].

Lipid-based formulations are considered a promising approach to improving the water solubility and oral absorption of fat burners. The main purpose of these formulations is to keep the drug in solution in the gastrointestinal tract. Among the numerous lipid-based drug delivery systems, the self-nano drug delivery system (SNEDDS) is one of the most studied oral drug delivery systems. SNEDDS has been described as a mixture of oil, surfactant, and co-surfactant or co-solvent [3].

After dispersion in water and slight agitation (as in the gastrointestinal tract), SNEDDS spontaneously forms fine oil-in-water nanoemulsions with droplet sizes less than or equal to 200 nm, as shown in Fig. Figure 1. Emulsification occurs when entropy changes in favor of the dispersion beyond the energy required to increase the surface area of the dispersion [8,9]. SNEDDS has shown great potential to overcome limitations associated with the digestion of certain compounds [4].

These limitations include low solubility in the gastrointestinal tract, inconsistent solubility, enzymatic breakdown, and uneven intestinal absorption. The surfactants and lipid components used in SNEDDS may work together to improve the absorption of drugs from the gastrointestinal tract. In addition, these components can be easily modified as needed to make SNEDDS usable for both hydrophilic and hydrophobic drugs. Recent studies have shown that SNEDDS can be an effective transporter of peptide and protein oral drugs by preventing degradation of the gastrointestinal tract and improving the permeability of their intestinal membranes [5].

Compared with other lipid nanocarriers such as nanostructured lipid carriers (NLCs), solid lipids nanoparticle (SLN), or liposomes or solid dispersion, SNEDDS can be easily miniaturized by mixing components using conventional equipment, then including the mixture in solid dosage form, ie capsules or tablets. In addition, problems with drug delivery systems, such as trends synthesis during storage or for drug release unrelated to SNEDDS, since the fine dispersion is produced directly in the gastrointestinal tract [6].

Therefore, SNEDDS exhibits better medicinal properties for improved solubility and oral bioavailability. Recently, however, the development of SEDDS formulations are marketed, such as Norvir (ritonavir), Sandimmunefi (cyclosporin), Fortavasefi (saquinavir), and Neoral (cyclosporine), which have stimulated growing interest in the use of SNEDDS to improve the solubility and oral bioavailability of drugs [7].

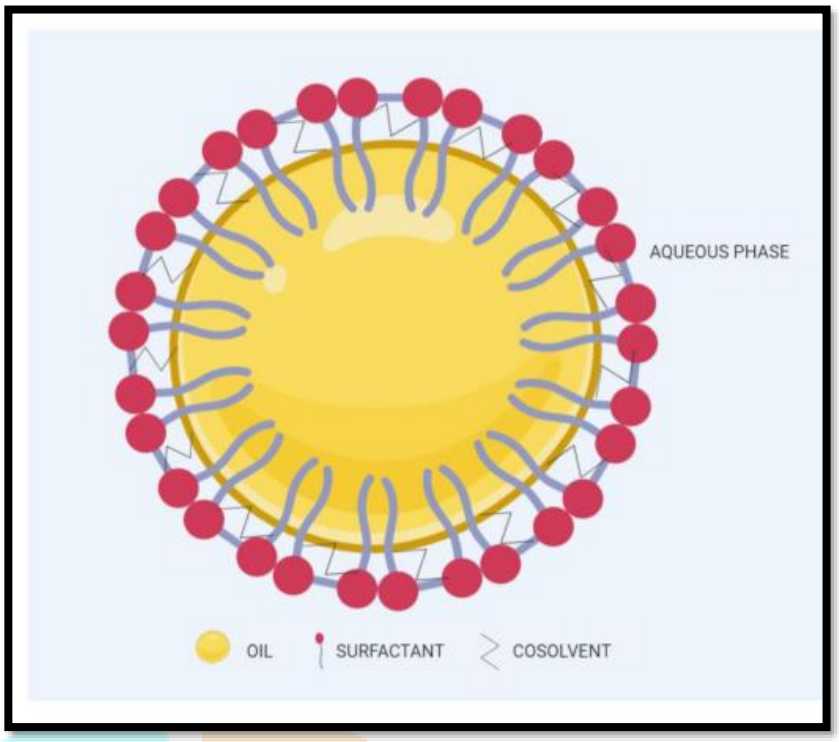

Fig no 1- Typical structure of SNEDDSs after aqueous dispersion.

General Components of SNEDDS

Oil Phase-

In general, oils contain medium-chain and long-chain triglycerides (TG) to varying degrees saturation is used to construct SNEDDS. Oil with maximum solubility is a drug often chosen for its primary effect on both formulation and drug-carrying capacity absorption. However, an exception to this general rule was reported by Larsen et al., who demonstrated that SNEDDS contained the oil with the lowest solubility demonstrating the highest drug absorption, indicating that high oil solubility is not always the best indicator of better performance in vivo [8].

Natural food-grade oils (i.e., castor oil, soybean oil, coconut oil, etc.) are still reasonable and desirable oils. components, but they exhibit relatively low drug loading and low emulsifying efficiency. Modified medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) are mainly used to improve the solubility of the drug in the formulation [9, 10].

Surfactants-

The second required ingredient of SNEDDS is a surfactant. Due to their hermaphroditic nature properties, surfactants are found at the oil-water interface and help stabilize nanoemulsion by reducing surface tension. In general, surfactants are classified according to charge and the hydrophilic-lipophilic equilibrium (HLB) [11].

For their charge, the surfactant is classified into ionic (anionic, cationic, and zwitterionic) and non-ionic surfactants. Compare to ionic surfactants, non-ionic surfactants are commonly used due to their low

toxicity and ability to stabilize emulsions over a wider pH range and the ionic strength of nanoemulsion. About the HLB value, a surfactant can be classified as a lipophilic surfactant (HLB <10> 10). Nonionic surfactants with HLB >12 are most recommended because they allow forming of nano-emulsions with particle size below 200 nm after dispersing in water [12].

The emulsifying capacity of the surfactant, its HLB value, and the maximum solubility of the drug are three important factors to keep in mind when selecting surfactants in SNEDDS. If not, Surfactant concentration has been shown to affect emulsion particle size. Get a raise The amount of surfactant can reduce the size of the emulsion particles due to its surface tension-reducing properties Surfactants at the oil-water interface reduce the free energy for emulsification. However, in some cases, an increase in the amount of surfactant leads to larger particle size, due to Excessive penetration of water into lipid droplets causing large oil-water breaks surface and relaxation of highly dispersed nanoemulsion droplets [14].

Different from the fine sphere training, many non-ionic surfactants, such as Tweenfi 80 and Cremophorfi EL, are capable of increasing membrane fluidity and inhibition of flow transporters, which are contributing factors in improving drug bioavailability [15].

Cosurfactants/Cosolvents-

A surfactant can rarely produce low surface tension; so another surfactant (surfactant) or co-solvent is usually required. They can cooperate in synergy with surfactants to improve drug solubility and surfactant dispersibility in oil, thus promoting the stability and homogeneity of nanoemulsions[16].

The use of co-surfactant or co-solvent can reduce surfactant irritant potential and dose variation of formulation by improving surface fluidity. It has also been reported that the surfactant/co-surfactant ratio or co-solvent weight ratio has a significant influence affects the size distribution and extent of the nanoemulsion region. Co-solvent is commonly used including propylene glycol, ethanol, poly(ethylene glycol) (PEG), and newer cosolvents, such as Transcutolfi HP. However, although co-solvents can improve drug solubility in formulations, the amount should be kept to a minimum due to their polarization [17].

Co-solvent readily converts to the water phase followed by dispersion in water, leading to the precipitation of the drug. In addition, alcohol and Other volatile solvents may evaporate in the capsule shell, leading to drug precipitation. In the SNEDDS formula, in addition to the previously presented ingredients, other ingredients such as Antioxidants, viscosity enhancers, and modified drug release ingredients can be used [18].

Method of preparation-

Solvent displacement method-

The solvent displacement technique for spontaneous fabrication of nanoemulsion has been followed by the nanoprecipitation technique used for polymeric nanoparticles. In this technique, the oily segment is dissolved in water-miscible natural solvents, which include acetone, ethanol, and ethyl methyl ketone [19].

The natural segment is poured into an aqueous segment containing surfactant to yield spontaneous nanoemulsion with the aid of using rapid diffusion of natural solvent. The natural solvent is eliminated from the nanoemulsion with the aid of using a suitable means, which includes vacuum evaporation. Bouchemal et al. have studied different factors that influence the fabrication of nanoemulsions with the aid of using the solvent displacement technique [20].

Interestingly, spontaneous nano emulsification has additionally been reported whilst the answer of natural solvents containing a small percent of oil is poured into the aqueous segment with no surfactant. This phenomenon is called the `Ouzo effect. This phenomenon has particularly been used for fabricating polymeric nanoparticles or nanocapsules using nanoemulsion as a template [21].

Solvent displacement strategies can yield nanoemulsions at room temperature and require easy stirring for fabrication. Hence, researchers in pharmaceutical sciences are using this technique for fabricating nanoemulsions, particularly for parenteral use. However, the foremost disadvantage of this technique is using natural solvents, such as acetone, which require extra inputs for their elimination from nanoemulsion. Furthermore, an excessive ratio of solvent to grease is needed to obtain a nanoemulsion with acceptable droplet size [22].

Phase inversion composition method-

This method has attracted the attention of scientists from various fields (including pharmaceutical science) because it produces nanoemulsions at room temperature without the use of any organic solvents. or heat. Forging et al. observed that the kinetically stable nanoemulsion with a small droplet size (~50 nm) could be produced by gradually adding water to the oil-surfactant solution with gentle stirring. and constant temperature. Although the ingredients used in the aforementioned investigation were not pharmaceutical grade, the investigation paved the way for the design of pharmaceutical nanoemulsions using a similar approach [23].

Spontaneous nano emulsification is associated with phase transition in emulsification and involves laminar liquid crystal phases or two-dimensional D-type microemulsions in the process. Sadurni et al. investigated spontaneous nanoemulsion of a mixture of Cremophor® EL and Miglyl® 812 and confirmed the presence of liquid crystals during small-angle X-ray scattering. It is important to study or know the phase behavior of the system to determine the suitable conditions to form nanoemulsions by this process [24].

It was also determined that the physicochemical properties of the components and proportions of the 4044 surfactants of the oil were the main determinants of the properties of the 4044 nanoemulsions obtained by this method. . Detailed mechanistic aspects of the self-nano process can be found in various journals. It should be noted that nanoemulsions are obtained from spontaneous nanoemulsions? 4044s are thermodynamically stable, although they may have high colloidal kinetics, 4044s are long-term stable. Recently, Anton and Vandamme in an interesting investigation showed that nanoemulsion was generated

by spontaneous nanoemulsion and the PIT method. Method The actual value may depend on the surfactant level in the oil in the system [25].

Table No 1- The general methods and models used to evaluate SNEDDSs

sSr No	Characterization	Method	Information	Reference
1	**Physico-chemical characterization**	Electrophoretic velocimetry	Zeta potential	[26]
		Spectrophotometry	Transmittance percentage, cloud point,	[27]
		TEM, SEM	Morphology	[28]
2	**Preclinical in vitro and ex vivo evaluation**	pH-stat unit	Formulation digestion, drug distribution across	[29]
		PAMPA	Permeation across the intestinal barrier	[30]
3	**Preclinical In vivo evaluation**	Animals Pharmacokinetic, toxicity, pharmacodynamic	Pharmacokinetic, toxicity, pharmacodynamic	[31]
	Clinical trials	Humans	Pharmacokinetic, bioequivalence toxicity,	[32]

Factors that restrict medication bioavailability in the mouth and the possibility of SNEDDS for oral drug delivery-

Dissolution rate-limited absorption-

As previously stated, around 40% of currently available therapeutic medicines have low solubility in physiological environments. BCS class II and IV treatment drugs include cyclosporine, celecoxib, and artemether, among others. The limited absorption from the GI tract is due to these chemicals' slow dissolving rate. The materials utilized to make SNEDDS have a strong solubilization potential for a variety of hydrophobic medicines. When compared to medication, the substance solubilized in SNEDDS has a significantly high dissolution velocity. Additionally, SNEDDS presents the medication as very small nanodroplets with a large surface area for absorption. This aids in the drug's rapid absorption and boosts oral bioavailability [33].

Poor permeability-

Poor permeability is likewise one of the fundamental factors that limit the oral bioavailability of numerous capsules, which include atenolol and acyclovir (BCS elegance III). Owing to terrible permeability, such capsules have to be administered at substantially better doses. Interestingly, numerous SNEDDS components have the cap potential to beautify the membrane permeation of the healing agents [34].

For example, oily phases (e.g., oleic acid, monoglycerides of caprylic acid, and propylene glycol esters of caprylic acid), surfactants (e.g., Labrasol®, diet E tocopheryl polyethylene glycol 1000 succinate [TPGS] and polysorbate 80) and cosurfactants (e.g., PEG 400, Transcutol and alcohol) are acknowledged to have permeation enhancing properties. Bruesewitz et al. have evaluated the impact of poloxamer-primarily based nanoemulsion on Caco-2 permeability of various capsules, which include danazol (BCS elegance II), atenolol (BCS elegance III), and metoprolol (BCS elegance I) [35].

Interestingly, they found that nanoemulsion may want to substantially enhance the Caco-2 permeability of a majority of these capsules without inflicting any considerable damage/toxicity to Caco-2 cells. This in reality suggests the capacity of SNEDDS in oral delivery [36].

P-glycoprotein efflux-

P-glycoprotein (Pgp) is a flow pump found in many places in the body, including the gastrointestinal. Pgp prevents the penetration of the drug into the systemic circulation, thereby reducing the oral bioavailability of the drug. A significant number of molecules, such as amphotericin B, paclitaxel, digoxin, and doxorubicin are known substrates of Pgp, and bioavailability is impaired by Pgp-mediated efflux [37].

Many surfactants, e.g. vitamin E TPGS, Solutol® HS 15, Labrasol, Cremophor EL, Gelucire 44/14 (lauroyl macrogol glycerides) and Polysorbate 80, and oil phases, including Imwitor® 742 and Akoline MCM® (caprylic mono and diglycerides) acid) and Peceol® (glyceryl monooleate), with the ability to inhibit Pgp efflux. Therefore, SNEDDS can also inhibit the Pgp spillover process and improve the oral bioavailability of drugs [38, 39].

Table 2. Potential of self-nano emulsifying drug delivery systems in oral drug delivery.

Sr no	Drug	Therapeutic Use	Observation	Reference
1	b-lactamase	A model protein	2–3-fold BA increment compared	[40,41]
2	Biphenyl dimethyl dicarboxylate	Hepatoprotective	1.7–6-fold improvement in BA	[42]
3	Matrine	Natural alkaloid	Greater BA compared with matrine powder and matrine phospholipid complex	[43, 44]
4	Lutein	Carotenoid	Greater in vitro dissolution rate	[45, 46]
5	Retinol acetate	Antioxidant	Improvement in dissolution rate4	[47]
6	Danazol	Antiandrogen	Greater in vitro dissolution and no effect	[48, 49]
7	Genistein	Natural antioxidant	100% in vitro drug release in 5 min	[50]

Conclusion-

Drug discovery applications generate a huge percentage of the latest lipophilic chemical entities that are poorly soluble. Homemade nanoemulsion formulations have proven first-rate capacity in enhancing the bioavailability of such water-limit remedy agents. The nanoscale dimensions of those formulations are liable for facilitating stronger drug dissolution and absorption, because of their huge floor area. The lipid nature of those structures permits drug shipping to the lymphatic gadget. However, sure problems, which include drug-excipient interactions, oxidation of vegetable oils, toxicity, and Safety merit interest all through the improvement of SNEDDS. Ability to transform SNEDDS right into a nano self-producing stable The gadget permits to development of a stable dosage form. Therefore, stable nanoemulsion structures can function as a technological platform for the shipping of poorly soluble drugs

Conflicts of interest-

There are no conflicts of interest and disclosures regarding the manuscript.

Acknowledgment-

The authors express their sincere gratitude to Ravindra Gambhirrao Sapkal college of pharmacy, University Libraries, and all other sources for their cooperation and advice in writing this review

Reference-

1. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. Vol. 12, Pharmaceutics. MDPI AG; 2020. p. 1–52.
2. Nukolova N v., Oberoi HS, Zhao Y, Chekhonin VP, Kabanov A v., Bronich TK. LHRH-targeted nanogels as a delivery system for cisplatin to ovarian cancer. Molecular Pharmaceutics. 2013 Oct 7;10(10):3913–21.
3. Yin Y, Hu B, Yuan X, Cai L, Gao H, Yang Q. Nanogel: A versatile nano-delivery system for biomedical applications. Vol. 12, Pharmaceutics. MDPI AG; 2020.
4. Syukri Y, Martien R, Lukitaningsih E, Nugroho AE. Novel Self-Nano Emulsifying Drug Delivery System (SNEDDS) of andrographolide isolated from Andrographis paniculata Nees: Characterization, in-vitro and in-vivo assessment. Journal of Drug Delivery Science and Technology. 2018 Oct 1;47:514–20.
5. Syukri Y, Martien R, Lukitaningsih E, Nugroho AE. Novel Self-Nano Emulsifying Drug Delivery System (SNEDDS) of andrographolide isolated from Andrographis paniculata Nees: Characterization, in-vitro and in-vivo assessment. Journal of Drug Delivery Science and Technology. 2018 Oct 1;47:514–20.
6. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. Vol. 12, Pharmaceutics. MDPI AG; 2020. p. 1–52.
7. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. Vol. 12, Pharmaceutics. MDPI AG; 2020. p. 1–52.
8. Kazi M, Al-Swairi M, Ahmad A, Raish M, Alanazi FK, Badran MM, et al. Evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for poorly water-soluble talinolol: Preparation, in vitroand in vivoAssessment. Frontiers in Pharmacology. 2019;10(MAY).
9. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007 May;66(2):220–6.

10. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. International Journal of Pharmaceutics. 2006 Jun 6;315(1–2):110–21.

11. Desale SS, Raja SM, Kim JO, Mohapatra B, Soni KS, Luan H, et al. Polypeptide-based nanogels co-encapsulating a synergistic combination of doxorubicin with 17-AAG show potent anti-tumor activity in ErbB2-driven breast cancer models. Journal of Controlled Release. 2015 Jun 28;208:59–66.

12. Vinogradov S v., Batrakova E v., Kabanov A v. Nanogels for Oligonucleotide Delivery to the Brain. Bioconjugate Chemistry. 2004;15(1):50–60.

13. AboulFotouh K, A. Allam A, El-Badry M. Self-Emulsifying Drug Delivery Systems: Easy to Prepare Multifunctional Vectors for Efficient Oral Delivery. In: Current and Future Aspects of Nanomedicine. IntechOpen; 2020.

14. Torchilin VP. Multifunctional nanocarriers. Vol. 58, Advanced Drug Delivery Reviews. 2006. p. 1532–55.

15. Kim JO, Oberoi HS, Desale S, Kabanov A v., Bronich TK. Polypeptide nanogels with hydrophobic moieties in the cross-linked ionic cores: Synthesis, characterization and implications for anticancer drug delivery. Journal of Drug Targeting. 2013 Dec;21(10):981–93.

16. Nukolova N v., Oberoi HS, Cohen SM, Kabanov A v., Bronich TK. Folate-decorated nanogels for targeted therapy of ovarian cancer. Biomaterials. 2011 Aug;32(23):5417–26.

17. Qureshi MA, Khatoon F. Different types of smart nanogel for targeted delivery. Vol. 4, Journal of Science: Advanced Materials and Devices. Elsevier B.V.; 2019. p. 201–12.

18. Wang Y, Xu H, Wang J, Ge L, Zhu J. Development of a thermally responsive nanogel based on chitosan-Poly(N- Isopropylacrylamide-co-Acrylamide) for paclitaxel delivery. Journal of Pharmaceutical Sciences. 2014;103(7):2012–21.

19. Smitha KT, Nisha N, Maya S, Biswas R, Jayakumar R. Delivery of rifampicin-chitin nanoparticles into the intracellular compartment of polymorphonuclear leukocytes. International Journal of Biological Macromolecules. 2015 Mar 1;74:36–43.

20. Tan JPK, Tan MBH, Tam MKC. Application of nanogel systems in the administration of local anesthetics. Vol. 3, Local and Regional Anesthesia. 2010. p. 93–100.

21. Gratton SEA, Pohlhaus PD, Lee J, Guo J, Cho MJ, DeSimone JM. Nanofabricated particles for engineered drug therapies: A preliminary biodistribution study of PRINT™ nanoparticles. Journal of Controlled Release. 2007 Aug 16;121(1–2):10–8.

22. Xie J, Chen K, Huang J, Lee S, Wang J, Gao J, et al. PET/NIRF/MRI triple functional iron oxide nanoparticles. Biomaterials. 2010 Apr;31(11):3016–22.

23. Sun B, Yeo Y. Nanocrystals for the parenteral delivery of poorly water-soluble drugs. Vol. 16, Current Opinion in Solid State and Materials Science. Elsevier Ltd; 2012. p. 295–301.

24. Tiwari AD, Mishra AK, Mishra SB, Kuvarega AT, Mamba BB. Stabilisation of silver and copper nanoparticles in a chemically modified chitosan matrix. Carbohydrate Polymers. 2013 Feb 15;92(2):1402–7.

25. Yadi M, Mostafavi E, Saleh B, Davaran S, Aliyeva I, Khalilov R, et al. Current developments in green synthesis of metallic nanoparticles using plant extracts: a review. Vol. 46, Artificial Cells, Nanomedicine and Biotechnology. Taylor and Francis Ltd.; 2018. p. S336–43.

26. Vodnik V v., Šaponjić Z, Džunuzović J v., Bogdanović U, Mitrić M, Nedeljković J. Anisotropic silver nanoparticles as filler for the formation of hybrid nanocomposites. Materials Research Bulletin. 2013 Jan;48(1):52–7.

27. Zhao Y, Yang X, Tian J, Wang F, Zhan L. Methanol electro-oxidation on Ni@Pd core-shell nanoparticles supported on multi-walled carbon nanotubes in alkaline media. International Journal of Hydrogen Energy. 2010 Apr;35(8):3249–57.

28. Zeng W, Miao B, Li T, Zhang H, Hussain S, Li Y, et al. Hydrothermal synthesis, characterization of h-WO3 nanowires and gas sensing of thin film sensor based on this powder. In: Thin Solid Films. Elsevier B.V.; 2015. p. 294–9.

29. Yoon KY, Hoon Byeon J, Park JH, Hwang J. Susceptibility constants of Escherichia coli and Bacillus subtilis to silver and copper nanoparticles. Science of the Total Environment. 2007 Feb 15;373(2–3):572–5.

30. Yang H, Shi R, Zhang K, Hu Y, Tang A, Li X. Synthesis of WO3/TiO2 nanocomposites via sol-gel method. Journal of Alloys and Compounds. 2005 Aug 2;398(1–2):200–2.

31. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007 May;66(2):220–6.

32. Wasylaschuk WR, Harmon PA, Wagner G, Harman AB, Templeton AC, Xu H, et al. Evaluation of hydroperoxides in common pharmaceutical excipients. Journal of Pharmaceutical Sciences. 2007;96(1):106–16.

33. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007 May;66(2):220–6.

34. Chambin O, Jannin V, Champion D, Chevalier C, Rochat-Gonthier MH, Pourcelot Y. Influence of cryogenic grinding on properties of a self-emulsifying formulation. International Journal of Pharmaceutics. 2004 Jun 18;278(1):79–89.

35. Bhandari V, Avachat A. Formulation and characterization of self emulsifing pellets of carvedilol. Brazilian Journal of Pharmaceutical Sciences. 2015 Jul 1;51(3):663–72.

36. Date AA, Desai N, Dixit R, Nagarsenker M. Self-nanoemulsifying drug delivery systems: Formulation insights, applications and advances. Vol. 5, Nanomedicine. 2010. p. 1595–616.

37. Bhandari V, Avachat A. Formulation and characterization of self emulsifing pellets of carvedilol. Brazilian Journal of Pharmaceutical Sciences. 2015 Jul 1;51(3):663–72.

38. Cole ET, Cadé D, Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Vol. 60, Advanced Drug Delivery Reviews. 2008. p. 747–56.

39. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007 May;66(2):220–6.

40. Chambin O, Jannin V, Champion D, Chevalier C, Rochat-Gonthier MH, Pourcelot Y. Influence of cryogenic grinding on properties of a self-emulsifying formulation. International Journal of Pharmaceutics. 2004 Jun 18;278(1):79–89.

41. Bhandari V, Avachat A. Formulation and characterization of self emulsifing pellets of carvedilol. Brazilian Journal of Pharmaceutical Sciences. 2015 Jul 1;51(3):663–72.

42. Chambin O, Jannin V, Champion D, Chevalier C, Rochat-Gonthier MH, Pourcelot Y. Influence of cryogenic grinding on properties of a self-emulsifying formulation. International Journal of Pharmaceutics. 2004 Jun 18;278(1):79–89.

43. Wasylaschuk WR, Harmon PA, Wagner G, Harman AB, Templeton AC, Xu H, et al. Evaluation of hydroperoxides in common pharmaceutical excipients. Journal of Pharmaceutical Sciences. 2007;96(1):106–16.

44. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. International Journal of Pharmaceutics. 2006 Jun 6;315(1–2):110–21.

45. Chambin O, Jannin V, Champion D, Chevalier C, Rochat-Gonthier MH, Pourcelot Y. Influence of cryogenic grinding on properties of a self-emulsifying formulation. International Journal of Pharmaceutics. 2004 Jun 18;278(1):79–89.

46. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. International Journal of Pharmaceutics. 2006 Jun 6;315(1–2):110–21.

47. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. Vol. 12, Pharmaceutics. MDPI AG; 2020. p. 1–52.

48. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. European Journal of Pharmaceutics and Biopharmaceutics. 2007 May;66(2):220–6.

49. Parmar K, Patel J, Sheth N. Self nano-emulsifying drug delivery system for Embelin: Design, characterization and in-vitro studies. Asian Journal of Pharmaceutical Sciences. 2015 Oct 1;10(5):396–404.

50. Thorat S, Kamble AA. A Technical Review on Cryogenic Grinding. Journal of Thermal and Fluid Science [Internet]. 2021 Mar 30;2(1). Available from: https://www.rame.org.in/pdf/jtfs/paper2/v2i1paper3.html