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Methods for Making a Nanosuspension of Poorly Soluble Medications

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ABSTRACT

Class II prescriptions are known to dissolve ineffectively in both natural and fluid solvents, making them a significantly more challenging challenge. When it comes to these kinds of high log P synthetic compounds that are insoluble in water, the nanosuspension structure is desired. The overall bioavailability of nanosuspensions is influenced by an increase in surface area and a decrease in molecule size. Sometimes the oral dosage forms of water-soluble drugs that are slowly absorbed and inefficient show insufficient bioavailability. A drug's permeability and solubility have a significant impact on how bioavailable it is. To create sub-micron-sized particles, a suitable emulsifier and a pharmaceutical mixture are fed through a high-pressure homogenization or milling procedure. Both classic milling and precipitation processes are commonly used to create particles larger than one millimetre. In this investigation, the techniques was used to prepare the nanosuspension for improving the solubility of poorly soluble drugs.

Keywords: Nanosuspension, Techniques, Solubility, Poorly soluble drugs

INTRODUCTION

Drugs that are inert in lipids and water can be made into nanosuspensions to improve their solubility. For example, the dynamic material achieves an extreme plasma level considerably faster and floods at a much faster rate. This advantage is significant, not the product of different solvency support strategies. Bad solvency and porousness mixtures, or sometimes both, are desired because they give formulators a difficult task to do. When synthetic chemicals are not adequately fluid in solvents, they can cause serious issues such as: Unfortunate bioavailability, , using harsh excipients, like using co-dissolvables and other excipients excessively, being unable to apply the most effective lead repair, tended to take variations in bioavailability into consideration or not, Absence of proportionality and responsiveness in portions, Not the ideal quantity.

A colloidal dispersion stabilised by surfactants of drug particles smaller than a micron is called a nanosuspension. Pharmaceutical nanosuspension is the term used to describe the administration of solid drug particles orally, parenterally, topically, or through the lungs after their ultrafine dispersion in an aqueous solution.Less than one micrometer makes up the particle size distribution, and the typical range of the solid particle sizes in nanosuspensions is between 200 and 600 nm. Nanosuspension technology helps to keep the medication in the required crystalline form by using minute particles to speed up the drug's dissolution and boost its bioavailability. Particles that have been micronized, or have a particle size that are 10 µm in size, dissolve more quickly when their surface area increases.

Compared to a micronized product, the dissolving velocity increases much more quickly with increased surface area and concentration gradient. When the almost perfect drug microcrystals are broken to form nanoparticles, high energy surfaces are produced, which is another reason for the higher saturation solubility. Dissolution assays can be used to quantify the enhanced saturation

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solubility of a drug that has been transformed into a nanosuspension.[1]

Oral availability limits can be lessened by using the modified Noyes-Whitney equation, which increases the rate of dissolution of even extremely poorly soluble compounds.[2] As to this analysis, the primary tactics for enhancing dissolution are given as: to enhance the quantity of surface area capable of dissolving the solid, decrease the size of its particles, Increase the chemical's ability to moisten the surface, lessen the thickness of the diffusion layer, Ensure that the washbasin is prepared for the dissolution, boost the drug's apparent solubility at conditions that are appropriate for its physiological application.[3]

The Benefits of Nanosuspensions: Stabilisers facilitate the development of large-scale production and ensure long-term physical stability. The advantages of administering nanosuspensions orally include improved absorption, a lowered fed/fasted ratio, and a faster onset. The administration method known as intravenous (IV) can rapidly target and degrade tissue. Medication administered intramuscularly or subcutaneously may reduce tissue irritation. Enhanced bioavailability when administered intravenously and inhaled. To improve their bioavailability, drugs having high log P values can be synthesised as nanosuspensions. Increased biological efficacy due to the medication's rapid rate of solubility and saturation. A rise in saturation solubility that causes the medication to dissolve more quickly. An increase in sticky properties that improves uptake. Increasing the percentage of amorphous particles, which could alter the crystalline structure and enhance solubility. The lack of Ostwald ripening is the cause of the aqueous solution's long-term physical stability. The potential for site-specific delivery through surface modification of the nanosuspensions.[2]

Selection criteria for medications for nanosuspensions: API that is either water- and oil-insoluble or oil-soluble but insoluble in water [high log P]. Drugs with a decreased tendency for the crystal to dissolve in any kind of solvent; extremely high dosages of API.[2]

Nanosuspension Formulation[3]

Table 1: An Examination of Nanosuspensions' Formulation.

Accelerants	Function	Examples
Stabilizers	Completely moisten the drug particles, halt Ostwald's ripening and agglomeration of nanosuspensions, and provide a steric or ionic barrier.	In addition to soy lecithins, poloxamers 188, 407, Polysorbate 80, HPMC E-15, HPMC E-50, PVP K-25, and PVP K-30
Co-surfactants	Influence phase behaviour when making nanosuspensions with microemulsions.	Bile salts, dipotassium glycyrrhizinate, transcutol, ethanol, and isopropanol
Organic solvent	A solvent that is safer and authorised by pharmaceuticals for use in formulation manufacture.	Ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, methanol, ethanol, and chloroform.
Other toppings	Depending on the medication moiety's properties or the delivery route's needs	Buffers, polyols, osmogens, salts, and cryoprotectants, among others.

Readying for Nanosuspension[4]

Bottomup technology: Hydrosols, which are common precipitation mechanisms, are sometimes called Bottom Up technology. The precipitation technique is used to dematerialize drugs in an organic solvent; this solution must be mixed with another miscible antisolvent. Because it is less soluble in solvent-water mixtures, the medicine precipitates in them. There is a relationship between strong shear processing and precipitation. The Nanoedge technique requires friable components in order to work.

Top-down, technically speaking: High pressure homogenization: This technique is mostly used to create pharmaceutical nanosuspensions of different medications that have low water solubility.[5] This procedure entails high pressure straining of the drug and surfactant suspension using a nanosized aperture valve on a high level pressure homogenizer. The fundamental idea depends on cavitation in the aqueous phase. For medication microparticles to become nanoparticles, the cavitation forces of the particles must be powerful enough.

Essential: Particle size is decreased by this piston gap homogenizer by applying cavitational principles. Severe shear pressures and particle collisions also led to a drop in particle counts. The three centimeter-diameter dispersion of the cylinder instantly travels through a 25 µm very tapered gap. A closed system with a rectangular cross section has a constant liquid flow volume, according to Bernoulli's Law. The dynamic pressure increases and the static pressure decreases as the diameter decreases from 3 cm to 25 µm.

Methods of Preparing For Nanosuspensions

1. Methods for Grinding (Nanocrystals or Nanosystem)

In grinding media: Nanosuspensions are made by a process called media milling.[6-9] The patent-protected nanocrystal technology is used to mediate the medication, resulting in drug nanoparticles. The high energy of the milling medium and the shear forces generated when the drug impites with it provide the energy input required to break down the medication into nanosized particles. The milling chamber is filled with the milling medium, water, or the appropriate ratio of buffer, medication, and stabilizer throughout the media milling procedure. Nanosuspensions are made in high-shear media mills and pearl mills.

Distinct co-grinding: High-pressure homo-genization to produce nanosuspensions and media milling in a pearl-ball mill are examples of wet grinding techniques. Dry milling techniques have lately made it possible to make nanosuspensions. It has been demonstrated that after dispersing in a liquid medium, poorly soluble drugs can be dry-ground with soluble polymers and copolymers to create stable nanosuspensions.[10-12]

2. High-pressure standardization

***Dissocubes (aqueous media homogenization)*:** During homogenization, pressure is applied to force the suspension through a valve with a small opening. Muller et al. devised the Dissocube approach, which involves pushing the drug suspension via a tiny hole. As a result, when the static pressure falls below the boiling point of the water, the water boils and releases gas bubbles. When the suspension exits the gap and the air pressure returns to normal, the bubbles shrink, the area that contains the drug particles moves towards the centre, and colloids form, which minimizes the particle size.

***Non-aqueous medium homogenization (nanopure)*:** The nanopure approach is employed to homogenise suspension in media devoid of water or in water combinations.[13] The process is controlled by the cavitation of the Dissocubes technology. Oils and oily fatty acids have a low vapour pressure and a high boiling point in comparison to water. As such, cavitation cannot be caused solely by a static pressure drop. The drug suspensions in non-aqueous media used in nanopure technology were homogenised at zero degrees Celsius or even below, a process known as "deep-freeze" homogenization.

The Precipitation method: The medication is dissolved in an organic solvent using a precipitation technique, and the resulting solution is then combined with a miscible antisolvent. The medication is poorly soluble in mixtures and precipitates, such as water-solvent. The methods for blending are significantly dissimilar. High shear processing has been combined with precipitation. The subsequent fragmentation of friable materials under high shear and/or heat energy is necessary for the nanoedge technology, a registered trademark of Baxter International Inc. and its subsidiaries.[14]

Luminous (Nanoedge): The fundamental ideas of Nanoedge also apply to homogenization and precipitation. When these methods are combined, faster, better outcomes are produced with smaller, more stable particles. Nanoedge technology has the potential to address the two main issues with

the precipitation approach, which are crystal formation and long-term stability. A fast addition of a medication solution to an antisolvent causes the mixed solution to become super-saturated and produces fine crystalline or amorphous particles. When the solubility of the amorphous state is exceeded, precipitation of an amorphous material at high super-saturation may be stimulated.

Using Nanojet technology: This process makes use of a chamber where a suspension stream is divided into two or more halves that collide violently. It is also known as nanojet technology or opposing stream technology. Particle size is reduced during the process due to strong shear stress.

Emulsions as models: Emulsions are not only a vehicle for delivering drugs, but they can also serve as models for the production of nanosuspensions. Emulsions are useful as models for drugs that dissolve in a volatile organic solvent or a somewhat water-soluble solvent. These solvents can be used to create the dispersed phase of the emulsion. Using the emulsification approach, drug nanosuspensions can be made in two different ways. The first approach involves dispersing a drug-loaded organic solvent or solvent mixture into an aqueous phase that also contains the appropriate surfactants to create an emulsion. The drug's particles precipitate instantaneously to create a surfactant-stabilized nanosuspension, while the organic phase evaporates at room pressure. Since each emulsion droplet contains a single particle, the size of the emulsion can be adjusted to regulate the size of the particles in the nanosuspension. The organic phase is employed more when the surfactant's composition is enhanced, which eventually enhances the medication loading in the emulsion. Organic solvents like methylene chloride and chloroform were initially employed.[15]

Using microemulsions in models: Microemulsions are dispersions of two immiscible liquids, such as oil and water that are isotropically transparent and thermodynamically stable due to an interfacial coating of co-surfactant and surfactant.

They are an excellent drug delivery strategy due to their various benefits, which include high drug solubility, long shelf life, and ease of production. Solid lipid nanoparticles and polymeric nanoparticles have recently been comprehensively described using microemulsions as templates.[16-17]

3. The method of supercritical fluid: Supercritical fluid technology can be applied to the production of nanoparticles from drug solutions. Several strategies have been tested for precipitation, including a compressed antisolvent process, a supercritical antisolvent process, and a rapid expansion of supercritical solution. The solution becomes supersaturated and precipitates as tiny crystals when the solvent is withdrawn. A drug that is not well soluble in a supercritical fluid is mixed with a drug solvent that is also miscible in the supercritical fluid in order to create the supercritical antisolvent technology.

Post-production adjustments/ Adjustments performed following manufacturing: Nanosuspensions require post-production processing if the drug candidate is extremely amenable to hydrolytic or chemical degradation. Processing might also be necessary if there are limitations on acceptable pathways or if the nanosuspension cannot be kept stable over an extended period of time with the best stabiliser in place. These variables may lead to the employment of techniques such as spray drying or lyophilization to produce a dry powder of nanoscale sized medicinal particles.

Nanosuspension Characterisation

Particle size distribution and mean particle size: The mean and distribution of particle sizes are important characterisation characteristics for nanosuspensions because they affect their physical stability, rate of dissolution, and biological performance. Research has indicated that when medicine particle size is changed, there is a notable change in both saturation solubility and dissolving rate.[18-20]

Particle shape and crystallisation state: Understanding the polymorphism or morphological changes that a medicine may undergo when it is subjected to nano-sizing is made easier when crystalline state and particle morphology are assessed together. Additionally, amorphous drug particles could arise during the

production of nanosuspensions. Investigating the amount of amorphous drug nanoparticle generated during the production of nanosuspensions is therefore essential.

Particle charge [zeta potential]: An essential component of the stability study of suspensions is the particle charge. It is often accepted that for the dispersions to remain stable, their zeta potential needs to be higher than ±40 mV. A minimum zeta potential of ±20 mV is needed for combined steric and electrostatic stabilisation, while a minimum zeta potential of ± 30 mV is needed for electrostatically stabilised nanosuspension.

A study of soluble: The ability of a substance to combine with another to create a solution is another definition of solubility. The solute, or material that has to dissolve, and the solvent, or liquid that allows it to dissolve, combine to form a solution.

Research on drug release in vitro: The amount of drug substance that enters the solution per unit of time under typical conditions, which include temperature, solvent composition, and liquid/solid interface, is known as the drug release rate. It can be interpreted as a particular kind of heterogeneous process where mass transfer occurs as a result of solute molecule escape and solid surface deposition.[21]

Nanosuspension stability: The stability of suspensions is impacted by particle size. The particles' surface energy increases and they start to clump together as they approach the nanoscale. In order to enhance suspension stability and reduce the likelihood of the Ostwald ripening effect, stabilisers are employed. These stabilisers produce steric or ionic barriers. Poloxamer, lecithin, polyoleate, polysorbates, cellulosic acid, and povidones are a few of the stabilisers that are commonly utilised in nanosuspension applications. [22]

Clinginess: Compared to coarse particles, ultra-fine powders have a substantially increased adhesiveness. The capacity of tiny drug nanoparticles to bind together may be exploited to improve oral medication delivery. The finding that danazol's bioavailability increased from 5 to 82% is the most notable.

An increase in the saturation solubility and rate of dissolution of the drug: The increase in drug-resistant surface area particles size-wise ranging from mm to nm has improved drug dissolution. As stated by the Noyes-Whitney equation, the dissolving velocity rises as surface area particles get bigger—from micron to nm. This formula considers the particle surface area, the diffusion coefficient, the dissolving velocity, the volume of the dissolution medium, and the concentration of the surrounding liquid.[23]

Nanosuspensions: Application in Medication Delivery

Intravenous administration : Nanosuspensions are practically perfect drug delivery vehicles for the parenteral route from a formulation standpoint. Because the drug particles are directly nanosized, nearly all medications can be manufactured for parenteral administration, making this process relatively simple. Because of this, nanosuspensions can significantly raise the parenterally tolerated dose of the drug, lowering therapy costs and improving therapeutic efficacy. The highest amount of paclitaxel nanosuspension that was shown to be safe was three times more than the amount of Taxol that is already on the market, which solubilizes the medication with ethanol and Cremophore EL.[24]

Taking oral medication: Owing to its many well-established benefits, administering medication orally is recommended. A medicine taken orally is usually evaluated based on how well it dissolves and absorbs in the gastrointestinal system. Therefore, it is assumed that a drug candidate would have delayed and/or highly variable oral bioavailability if they have poor water solubility and/or a dissolving rate that limits absorption.

Supply of ocular drugs: Drugs that do not dissolve well in lachrymal fluids could be good candidates for nanosuspensions. Among the many advantages of suspensions is their prolonged duration of action in treating the majority of ocular issues without producing the excessive tonicity that certain water-soluble drugs may. The lachrymal fluid solubility of the medicine determines its true efficacy. As a result, the drug's inherent rate of breakdown in lachrymal fluids

regulates both its release and bioavailability to the eye.

Administration of medication via the lungs and pulmonary regulation: The most efficient way to take medication that are poorly soluble in pulmonary secretions might be via nanosuspensions. These days, these medications are administered by dry powder inhalers or suspension aerosols. Micron-sized drug particles are frequently jet milled and used in dry powder inhalers and suspension aerosols.

The drug moiety found in dry powder inhalers and suspension aerosols has some disadvantages due to its micro-particulate nature and wide particle size distribution. These include limited drug diffusion and dissolution at the site of action, rapid lung clearance, short drug residence times, and undesired drug particle deposition in the mouth and pharynx.[25-26]

An increased degree of bioavailability: Inadequate gastrointestinal permeability or solubility is the reason of a medication's inadequate oral bioavailability. Nanosuspension solves the issues of low solubility and poor permeability across membranes to improve poor bioavailability.

Delivery of medications: Because the stabiliser or the milieu can easily be changed to affect the surface properties and in-vivo behaviour of nanosuspensions, they can also be employed for targeted distribution. Because of their adaptability, simplicity in scaling up, and commercial product, it is possible to create nanosuspensions for targeted distribution that are commercially viable.

Topical groupings: Drug nanoparticles are found in creams and waterless ointments. The drug's increased saturation solubility in the topical dose form of the nanocrystalline form improves medication diffusion into the skin.[27-30]

The adherence of nanoparticles to mucosal membranes is known as mucoadhesion: Orally administered drug nanoparticles from a nanosuspension quickly diffuse into a liquid media and touch the mucosal surface. The "bioadhesion" adhesion mechanism causes the particles at the gut surface to become stationary.

Eye care procedures: It is better to use suspension and ointment for poorly soluble drugs in cul-de-sac systems. Suspensions have two advantages: they have a longer half-life and can stop medications that dissolve in water from becoming more tonic. The bioavailability of ophthalmic solutions can be determined by measuring the pace at which the medicine dissolves in lachrymal fluid.

Candesartan Cilexetil: The Biopharmaceutical Classification System [BSC] has classified candesartan cilexetil as class II due to its low solubility (0.0595 mg/L), and weak acid behavior (pka1: 3.50 and pka2: 5.85) and low bioavailability (when taken as a solution, candesartan has an approximate 40% absolute bioavailability; when given as pills, it is 14%.).[31-34]

Telmisartan: The range of absolute oral bioavailability after a 40-mg dosage is dose-dependent, spanning from 42% to 58%. Telmisartan is easily absorbed through the gastrointestinal tract] and it is essentially insoluble at physiological pH 3–7 [0.09 µg/mL in water], telmisartan is classified as a class II medication by the Biopharmaceutics Classification System.[35-38]

Ziprasidone Hydrochloride: According to the BCS, ziprasidone hydrochloride is classified as a Class II medication due to its limited water solubility. Which include poor solubility, weak organic base, high lipophilicity, high permeability, and due to its slow absorption in the gastrointestinal tract and intrinsic solubility of 0.3µg/mL [pH. 6.5], ziprasidone has a poor 60% bioavailability.[39-40]

MATERIAL AND METHODS

Candesartan cilexetil was obtained as kind gift Sample from Sun Pharma LTD. Mumbai (Manufacturer: Dr. Reddy's Laboratories). Telmisartan was obtained as kind gift Sample from Macleods pharmaceutical Ltd. Sikkim. Ziprasidone HCL Monohydrate was obtained as kind gift Sample from Sun pharma LTD. Mumbai (Manufacturer: Dr. Reddy's Laboratories). Poloxamer 188 and Poloxamer 407 were obtained as kind Gift Sample from Astron Research Centre, Ahmedabad. Polyvinyl alcohol was provided by Loba Chemie Pvt. Ltd., Mumbai. PVP K30 was provided by S. D. Fine Chemicals, Mumbai. Sodium Lauryl Sulphate was provided by Himedia

Laboratories Pvt. Ltd., Mumbai. All the materials were used as an analytical grade.

RESULT AND DISCUSION

Case 1. Candesartan Cilexetil nanosuspension

During preparation, the candesartan cilexetil nanosuspension was stabilized using PVP K-30. PVP K-30 had the highest saturation solubility and the smallest mean particle size, 50 mg of it was selected. The stirring speed of 1200 RPM was chosen since it showed the lowest mean particle size and greatest saturation solubility. After the drug particles precipitated in suspension, a probe sonicator was employed to transform them into uniformly nanosized particles. The time of 30 minutes was selected for sonication since this resulted in samples that had the lowest average particle size and the highest solubility at saturation.[41] The pure drug solubility and batch optimization values for candesartan cilexetil nanosuspension were determined to be 1.191 µg/ml and 109.7 µg/ml, respectively. Fig 1 displays the dissolution profiles of the commercial formulation [Atacand® Tablet], unmilled [pure drug] suspension, and nanosuspension. More than 97.14% of the medication was released from the nanosuspension after 2 minutes, compared to 34.64% and 75.98% at 60 minutes for the cumulative percentage release of the marketed formulation and unmilled suspension, respectively. Candesartan cilexetil's rate of dissolution was greatly accelerated by nanosuspension.

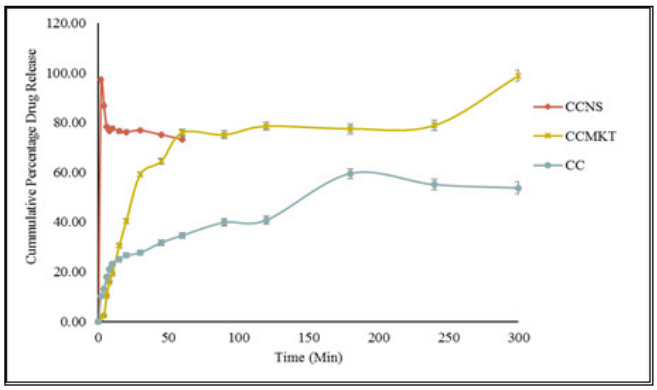

Fig. 1: Comparison of in-vitro dissolution of Candesartan Cilexetil nanosuspension with Marketed formulation and Un-milled suspension

Case 2. Telmisartan nanosuspension

Poloxamer 407 was used as a stabiliser to create telmisartan nanosuspension. 50 mg of poloxamer 407 was chosen since it had the smallest mean particle size and highest saturation solubility. The 1:8 solvent: antisolvent volume ratio was chosen because it had the shortest mean particle size and the highest saturation solubility of the prepared nanosuspensions when tested using multiple evaluation parameters like mean particle size and saturation solubility. Once the drug particle precipitation had taken place in suspension, a probe sonicator was utilised to transform it into uniform nanosized particles. Sonication period of 30 minutes was chosen since it produced the smallest mean particle size and highest saturation solubility.[42] The saturation solubility of telmisartan nanosuspension from an improved batch and pure medication were 100.18 µg/ml and 3.53 µg/ml, respectively. The dissolving profiles for the commercial formulation [Inditel 40 Tablet], unmilled [pure drug] suspension, and nanosuspension are displayed in Fig 2. In nanosuspension, more than 102.61% of the medication was released in less than two minutes, despite the fact that the cumulative percentage of drug release from un-milled suspension and commercially manufactured suspension revealed 16.42% and 77.09% at 60 minutes, respectively.[42-43]

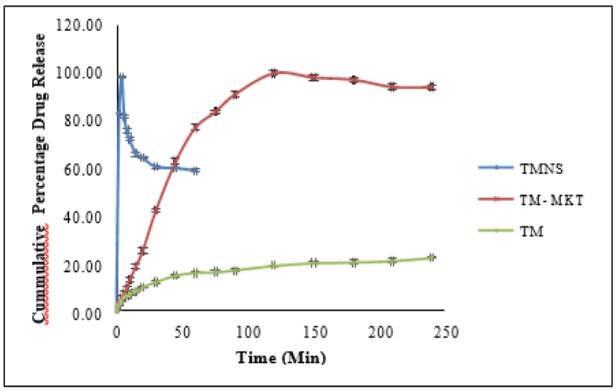

Fig. 2: Comparison of in-vitro dissolution of telmisartan nanosuspension with marketed formulation and un-milled suspension.

Case 3. Ziprasidone hydrochloride nanosuspension

Ziprasidone hydrochloride nanosuspension was produced with Poloxamer 407 acting as a stabilizer. A range of assessment criteria, such as saturation solubility and mean particle size, were used to test the prepared nanosuspensions. Since poloxamer 407 had the highest saturation solubility and the smallest mean particle size, 50 mg of it was selected. When testing using numerous evaluation metrics, such as mean particle size and saturation solubility, the 1:8 solvent:antisolvent volume ratio was found to have the smallest mean particle size and the maximum saturation solubility of the generated nanosuspensions.[44] The drug particle precipitation was transformed into uniform nanosized particles using a probe sonicator after it had occurred in suspension. A variety of assessment parameters, including saturation solubility and mean particle size, were used to evaluate the produced nanosuspensions in order to find the ideal sonication time for further formulation work. The sonication time of 30 minutes was selected because it resulted in the maximum saturation solubility and the smallest mean particle size. The saturation solubility of the pure drug and an improved batch were determined to be 7.20 µg/ml and 76.27 µg/ml, respectively, for the ziprasidone hydrochloride nanosuspension. The solubility profiles of the commercial formulation [Zipsydon® 20 Capsule], unmilled [pure drug] suspension, and nanosuspension are displayed in Fig. 3.

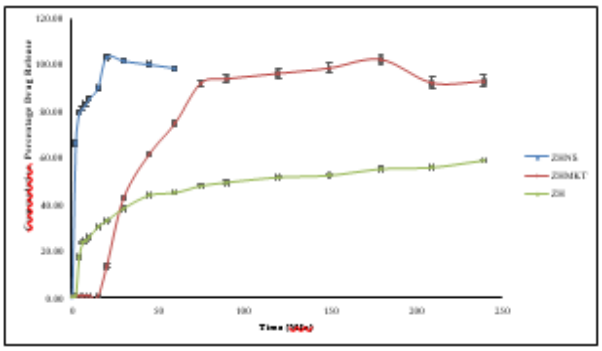

Fig 3. Comparison of in-vitro dissolution of Ziprasidone HCl nanosuspension with marketed formulation and unmilled suspension

Compared to un-milled suspension and marketed formulation, which had cumulative percentages of 44.94% and 74.81% at 60 minutes, respectively, more than 96.62% of the drug was released in nanosuspension in 15 minutes. Thus, nanosuspension significantly sped up the rate of dissolution of ziprasidone hydrochloride.

CONCLUSION

Techniques for grinding, top-down technique, high-pressure standardization, and bottom-up technique are employed in the creation of nanosuspension. Case 1, Case 2, and Case 3 illustrate the preparation of Candesartan Cilexetil nanosuspension, Telmisartan nanosuspension, and Ziprasidone hydrochloride nanosuspension, respectively. Saturation solubility was found to be better than that of the pure medication, and in vitro dissolution was shown to be better than that of the marketed formulation and unmilled suspension.

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REFERENCES

1. Müller RH, Peters K. Nanosuspensions for the formulation of poorly soluble drugs: I. Preparation by a size-reduction technique. International Journal of Pharmaceutics. 1998;160(2):229–37.
2. Nagaraju., Krishnachaithanya., Srinivas., Padma. Nanosuspensions: A promising drug delivery systems. PCI- Approved-IJPSN [Internet]. 2010;2(4):679–84. Available from: http://dx.doi.org/10.37285/ijpsn.2009.2.4.1
3. Patravale VB, Date AA, Kulkarni RM. Nanosuspension: A promising drug delivery strategy. Journal of Pharmacy and Pharmacology. 2004;56(7):827–40.
4. Geetha G, Poojitha U, Khan A. Various techniques for preparation of nanosuspension - a review. International Journal of Pharma Research & Review. 2014;3(9):30–7.
5. Keck CM, Müller RH, Liversidge GG, Conzentino P, Müller RH, Peters K, et al.

Formation of fine drug particles by co-grinding with cyclodextrin. I. the use of beta-cyclodextrin anhydrate and hydrate. International Journal of Pharmaceutics. 1995;62(1):171–4.

6. Liversidge GG, Conzentino P. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm [Internet]. 1995;125(2):309–13. Available from: http://dx.doi.org/10.1016/0378-5173(95)00148-c
7. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov [Internet]. 2004;3(9):785–96. Available from: http://dx.doi.org/10.1038/nrd1494
8. Wongmekiat A, Tozuka Y, Oguchi T, Yamamoto K. Formation of fine drug particles by co-grinding with cyclodextrin. I. the use of beta-cyclodextrin anhydrate and hydrate. Pharmaceutical Research. 2002;19(12):1867–72.
9. Itoh K, Pongpeerapat A, Tozuka Y, Oguchi T, Yamamoto K. Nanoparticle formation of poorly water-soluble drugs from ternary ground mixtures with PVP and SDS. Chem Pharm Bull (Tokyo) [Internet]. 2003;51(2):171–4. Available from: http://dx.doi.org/10.1248/cpb.51.171
10. Mura P, Cirri M, Faucci MT, Ginès-Dorado JM, Bettinetti GP. Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide. J Pharm Biomed Anal [Internet]. 2002;30(2):227–37. Available from: http://dx.doi.org/10.1016/s0731-7085(02)00252-2
11. Venkatesh T, Reddy AK, Maheswari JU, Dalith MD, Ck AK. Nanosuspensions: Ideal approach for the drug delivery of poorly water-soluble drugs. Der Pharmacia Lettre. 2011;3(2):203–13.
12. Kipp JE, Wong JCT, Doty MJ, Rebbeck CL. Microprecipitation method for preparing submicron suspensions. United States Patent, US 7037528B2; 2006.
13. Bodmeier R, Mcginity JM. Solvent selection in the preparation of poly (DL- lactide) microspheres prepared by a solvent evaporation method. International Journal of Pharmaceutics. 1998;43(1–2):179–86.
14. Corrias F, Lai F. New methods for lipid nanoparticles preparation. Recent Pat Drug Deliv Formul [Internet]. 2011;5(3):201–13. Available from: http://dx.doi.org/10.2174/187221111797200597
15. Watnasirichaikul S, Rades T, Tucker IG, Davies NM. Effects of formulation variables on characteristics of poly (ethyl cyanoacrylates) nanocapsules prepared from w/o micro-emulsions. International Journal of Pharmaceutics. 2002;235(1–2):237–46.
16. R Dabhi M, K Ghodasara U, D Mori D, A Patel K, Manek R, Sheth. Formulation, optimization and characterization of candesartan cilexetil nanosuspension for in vitro dissolution enhancement. Afr J Pharm Pharmacol [Internet]. 2015;9(5):102–13. Available from: http://dx.doi.org/10.5897/ajpp2013.3887
17. Detroja C, Chavhan S, Sawant K. Enhanced antihypertensive activity of candesartan cilexetil nanosuspension: formulation, characterization and pharmacodynamic study. Sci Pharm [Internet]. 2011;79(3):635–51. Available from: http://dx.doi.org/10.3797/scipharm.1103-17
18. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. J Pharm Bioallied Sci [Internet]. 2011;3(3):426–34. Available from: http://dx.doi.org/10.4103/0975-7406.84459
19. Liu D, Xu H, Tian B, Yuan K, Pan H, Ma S, et al. Fabrication of Carvedilol Nanosuspensions through the antisolvent precipitation-ultrasonication method for the improvement of dissolution rate and oral bioavailability. AAPS PharmSciTech. 2012;13(1):295–304.
20. Gurunath S, Nanjwade BK, Patila PA. Enhanced solubility and intestinal absorption of candesartan cilexetil solid dispersions using everted rat intestinal sacs. Saudi Pharm J

[Internet]. 2014;22(3):246–57. Available from: http://dx.doi.org/10.1016/j.jsps.2013.03.006

21. Patel B, Parikh RH, Swarnkar D. Enhancement of dissolution of Telmisartan through use of solid dispersion technique - surface solid dispersion. J Pharm Bioallied Sci [Internet]. 2012;4(Suppl 1):S64-8. Available from: http://dx.doi.org/10.4103/0975-7406.94142
22. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. Journal of Pharmacy and Bioallied Sciences. 2011;3(3):426–34.
23. Kumar S, Naved T, Alam S, Chauhan R. Design and Optimization of Telmisartan Nanosuspension for Improved Drug Delivery, Eur. Eur Chem Bull. 2023;12(6):947–56.
24. Bhargav E, Chaithanya Barghav G, Padmanabha Reddy Y, Pavan kumar C, Ramalingam P, Haranath C. A Design of Experiment (DoE) based approach for development and optimization of nanosuspensions of telmisartan, a BCS class II antihypertensive drug. Futur J Pharm Sci [Internet]. 2020;6(1). Available from: http://dx.doi.org/10.1186/s43094-020-00032-2
25. Latha M, Latha MM, Sundar Devendiran S, Kumar MD. Design and Evaluation of Sustained Release Tablets containing Solid dispersion of Ziprasidone hydrochlorid". International Journal of PharmTech Research. 2014;6(3):959–68.
26. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc [Internet]. 1897;19(12):930–4. Available from: http://dx.doi.org/10.1021/ja02086a003
27. Galia E, Nicolaides E, Hörter D, Löbenberg R, Reppas C, Dressman JB. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res [Internet]. 1998;15(5):698–705. Available from: http://dx.doi.org/10.1023/a:1011910801212
28. Lakshmi P, Kumar GA. Nanosuspension technology: A review. International Journal of Pharmacy and Pharmaceutical Sciences. 2010;2(4):35–40.
29. Blunk T, Hochstrasser DF, Sanchez J-C, Müller BW, Müller RH. Colloidal carriers for intravenous drug targeting: Plasma protein adsorption patterns on surface-modified latex particles evaluated by two-dimensional polyacrylamide gel electrophoresis. Electrophoresis [Internet]. 1993;14(1):1382–7.
30. Tao T, Zhao Y, Wu J, Zhou B. Preparation and evaluation of itraconazole dihydrochloride for the solubility and dissolution rate enhancement. Int J Pharm [Internet]. 2009;367(1–2):109–14. Available from: http://dx.doi.org/10.1016/j.ijpharm.2008.09.034
31. Merisko-Liversidge E, Sarpotdar P, Bruno J, Hajj S, Wei L, Peltier N, et al. Formulation and anti- tumor activity evaluation of nanocrystalline suspensions of poorly soluble anti-cancer drugs. Pharmaceutical Research. 1996;13(2):272–8.
32. Jacobs C, Müller RH. Production and characterization of a budesonide nanosuspension for pulmonary administration. Pharm Res. 2002;19(2):189–94.
33. Ponchel G, Montisci M, Dembri J, Durrer A, Duchene C. Mucoadhesion of colloidal particulate systems in the gastrointestinal tract. European Journal of Pharmaceutics and Biopharmaceutics. 1997;44(1):25–31.
34. Shim J, Kang HS, Park WS, Han S, Kim J, Chang I. Transdermal delivery of minoxidil with block copolymer nanoparticles. Journal of Controlled Release. 2004;97(3):477–84.
35. Kohli AK, Alpar HO. Potential use of nanoparticles for transcutaneous vaccine delivery: effect of particle size and charge. Int J Pharm [Internet]. 2004;275(1–2):13–7. Available from: http://dx.doi.org/10.1016/j.ijpharm.2003.10.038
36. Yamaguchi Y, Nagasawa T, Nakamura N, Takenaga M, Mizoguchi M, Kawai S, et al.

Successful treatment of photo-damaged skin of nano-scale at RA particles using a novel transdermal delivery. Journal of ControlledRelease. 2005;104(1):29–40.

37.Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. Eur J Pharm Sci [Internet]. 2014;57:152–63. Available from: http://dx.doi.org/10.1016/j.ejps.2014.01.009

38.Figueroa-Campos A, Sánchez-Dengra B, Merino V, Dahan A, González-Álvarez I, García-Arieta A, et al. Candesartan cilexetil in vitro-in vivo correlation: Predictive dissolution as a development tool. Pharmaceutics [Internet]. 2020;12(7):633. Available from: http://dx.doi.org/10.3390/pharmaceutics12070633

39.Bhagwat G, Arkate RAH, Shaikh SIP, Vishwakarma SR. Improvement in solubility of BCS class II drug: Telmisartan. World Journal of Biology Pharmacy and Health Sciences. 2023;14(01):222–30.

40.Park J, Cho W, Cha K-H, Ahn J, Han K, Hwang S-J. Solubilization of the poorly water soluble drug, telmisartan, using supercritical anti-solvent (SAS) process. Int J Pharm [Internet]. 2013;441(1–2):50–5. Available from: http://dx.doi.org/10.1016/j.ijpharm.2012.12.020

41.Kundu S, Kumari N, Soni SR, Ranjan S, Kumar R, Sharon A, et al. Enhanced solubility of telmisartan phthalic acid cocrystals within the pH range of a systemic absorption site. ACS Omega [Internet]. 2018;3(11):15380–8. Available from: http://dx.doi.org/10.1021/acsomega.8b02144

42.Thombre AG, Shamblin SL, Malhotra BK, Connor AL, Wilding IR, Caldwell WB. Pharmacoscintigraphy studies to assess the feasibility of a controlled release formulation of ziprasidone. J Control Release [Internet]. 2015;213:10–7. Available from: http://dx.doi.org/10.1016/j.jconrel.2015.06.032

43.Pawar SR, Kale RN, Chitlange SS. Solubility Enhancement and Formulation Development of Ziprasidone Immediate Release Oral Drug Delivery. Pharmaceutical Resonance. 2018;1(1):26–9.

44.Zakowiecki D, Cal K, Kaminski K, Adrjanowicz K, Swinder L, Kaminska E, et al. The improvement of the dissolution rate of ziprasidone free base from solid oral formulations. AAPS PharmSciTech [Internet]. 2015;16(4):922–33. Available from: http://dx.doi.org/10.1208/s12249-015-0285-1