Review Article on:- Role of Nanocrystals and Nanosuspensions in Drug Delivery Systems

Sarika Rajaram Patil[1], Mr.Santosh Waghmare[2], Dr Hemant V. Kamble[3]
[1, 2] Dept of Master Of Pharmacy In Chemistry
[1, 2, 3] Loknete Dadapatil Pharate College Of Pharmacy, Mandavgan
Pharata ,Shirur,Pune,Maharashtra,India.

Abstract- *Presently, 70% of compounds in the discovery pipeline are fundamentally insoluble in water, and over 40% of medications entering the market have solvency-related problems.*

According to the literature, nanocrystals are an evident tool to address the problem of poor fluid solubility and aid in increasing the bioavailability of numerous medications.The temperamental nanocrystalline system underwent a particle size reduction, and the ostawald ripening phenomena occurs.

These methods are gearing up for the development of nanoscale objects, which are capable of performing several technological functions.Nanocrystal formulations have a few notable advantages, such as increased oral bioavailability, enhanced dosage proportionality, reduced food effects, suitability for administration via various routes, and potential for sterile filtering. One of the best uses for nanocrystals is their broad range of delivery methods, including ocular, oral, transdermal, pulmonary, intravenous, and targeted distribution, notably for tumour and brain.

Growing interest in using nanocrystal products as a strategy to gain commercial advantages is being drawn to the rise in the commercial worth of nanocrystals as well as the quantity of products containing nanocrystals on the market.

This paper provides a succinct and accurate summary of nanosuspension with a focus on nanosuspension preparation procedures, advantages, and a few key applications.

Keywords- Nanocrystal, Nanosuspension, Bioavailability, Solubility, Media milling, Dissolution rate, Bottom-up approach, High-pressure homogenization

I. INTRODUCTION

Nanomedicine, which incorporates the use of nanotechnology in medication development and improved and offers many more stimulating promises of new diagnostics and remedies, has grown as a result of nanotechnology There has been a lot of interest in a more recent method of medication administration for weakly water-soluble molecules.

When a stabiliser is present on the surface of the nanoparticles, the medication is given as nanometer-sized particles or crystals that can be disseminated in a colloidal solution.The term "nano sizing" refers to the process of reducing an active pharmaceutical ingredient (API) to a submicron size.

A mixture of API and stabilisers, such as a surfactant or polymer, are combined to form nanosuspensions, which are aqueous dispersions in water.These stabilisers aid in preventing nanoparticle clumps. Nanotechnology is defined as science and engineering carried out at the nanoscale (10-9 m2) level.The media milling technique is commonly used to create the nanoparticles.

When milling micron-sized drug crystals, shear forces impinge on them, resulting in nanometer-sized drug particles that can be distributed in water and stabilised by surface ligands familiar with their surface Most significantly, nanomedicine uses molecular-level understanding of the human body to diagnose, treat, prevent disease and traumatic injury, relieve pain, and improve human health .

For medication particles that are delivered orally and fall under the BCS class II and class IV categories of medicines, nanosuspensions have been recommended as an all-inclusive delivery strategy

The Developability Classification System (DCS) was introduced by Butler and Dressman as a mechanism to classify substances in a more biorelevant manner

The intrinsic solubility and the associated intra-luminal drug concentration for compounds falling under classes II and IV are too low, according to the DCS, which contrasts between dissolution rate-limited and solubility-limited compounds, to even consider achieving adequate flux over the epithelial membrane.

Therefore, for chemicals that fall between DCS Classes II b and IV, complexation or formulation procedures rely on solid-state alterations that may be best displayed different,Due to the high throughput screening method, novel chemical entities produced by pharmaceutical industry discovery laboratories now frequently have low water dissolvability .

In order to overcome the low fluid solubility of medicinal substances, numerous formulation strategies have been developed .

Since particle size reduction (i.e., via micronization) is a commonly used technique, it has been used to improve the oral absorption of medications that are least likely to dissolve.

advantages of nanosuspension technique for medicines with limited solubility

1:-Reduced particle size, increased drug dissolving rate, increased rate and extent of absorption, increased bioavailability of the drug, area under the

2:-plasma versus time curve, peak drug level, onset of time, decreased variability, and reduced fed/fasted effects are all positive effects.

3:-Nanosuspension can be used to develop substances that are soluble in oil but insoluble in water. Alternatively, nanosuspension can be used with lipoid systems to formulate substances that are insoluble in both oil and water.

4:-By sticking to the gastrointestinal mucosa, nanoparticles extend the drug's contact duration and hence boost absorption.With its numerous administration options, including parenteral, oral, cutaneous, ophthalmic, and pulmonary, nanosuspension is the most practical.

5:-Different advantageous circumstances are provided by nanosuspension of nanoparticles over conventional ocular dosage forms include lower doses, drug release maintenance over a delayed timeframe, decreased systemic toxicity of drug, improved drug absorption due to longer residence time of nanoparticles on corneal surface, higher concentration of drug in infected tissue, suitability for inadequately water-soluble drugs, and smaller particles are preferred endured by patients over bigger particles

6:- In this way, nanoparticles are superior to conventional ocular dosage forms in these respects.

7:-The least amount of excipient-related adverse effects occur with nanosuspension.Nanosuspension has higher physical stability to settle and is resistant to hydrolysis, oxidation, and other processes.

8:-reduction in the amount of medication required for intramuscular, subcutaneous, and ophthalmic usage.

9:-Finally, passive targeting can be aided by nanosuspensions

10:-By preventing the need to dissolve the compounds and by maintaining the medicine in a preferred crystalline state of size sufficiently small for pharmacological acceptability, nanosuspensions alleviate the delivery problems for the compounds.

methods to nanosuspension formulation

The "Bottom-Up" and "Top-Down" technologies are the two production methods for nanosuspensions.

"Base Up Technology" refers to conventional precipitation methods.

The disintegration methods, often known as "Top-Down Technologies," are preferred above the precipitation methods.

This includes high-pressure homogenization in aqueous media, media milling, high-pressure homogenization in nonaqueous media, and ultimately, mixtures of high-pressure homogenization and precipitation.

Two other techniques to the top-down methodology are homogenization and attrition wet media milling.

Wet media attrition milling

The surface of nanocrystals is extremely robust and has a high surface vitality, and it should be stabilised by a single or mixture of stabilisers when an active drug component is distributed with an aqueous solution in which the stabilisers were previously isolated.

Ionic or stearic stabilisers can be used as standalone agents or in conjunction with surfactant and polymeric stabilisers.

Then, while the globules are rapidly pivoting, the solution is injected into the grinding chamber along with sphere-shaped beads and balls.

Particle size reduction is thought to occur as a result of attrition between the surfaces of molecules and globules, with the globules and balls acting as a milling

medium.Globules come in a variety of sizes and are constructed of a variety of substances, although for the most part they are formed of glass, zirconium oxide, or polymeric material.

The globules' construction is important because it affects how well they interact with the dynamic medicinal ingredient.

Although expensive, these Beads are the greatest solution for avoiding contaminants in the previous formulation .

The optimal range of particle size for the creation of nanocrystals is directly related to the size of the beads .

The typical time for conventional milling with overhead stirring is between three and twelve hours.

These conditions might undoubtedly vary from molecule to molecule.

After reaching the specified particle size range, milling should be halted.

The milling media's rotating speed is an extremely important characteristic.

When the speed is too slow, the globules can't pivot effectively, which makes it difficult to execute precision milling, and when the speed is too fast, the equally spinning balls may remain on top of the media, which stops milling.

The formulator chooses the stabilisers and other milling parameters, then optimises them to obtain the desired particle size range and stability by a methodical study of trial and error.

The amount of globules, the amount of active drug substance to the amount of globules, the ratio of active substance concentration to stabiliser, the milling time, temperature, and duration can all affect the final product's features.

This method is straightforward, reasonably priced, and adaptable.

The contamination of the beading material is the only disadvantage of this approach.

Aside from that, a number of products have used this technology to effectively enter the market.

With the use of sodium lauryl sulphate and hydroxyl propyl cellulose SL as stabilisers, Djordje Medarevic et al. created carvedilol nanosuspension via wet media milling, which produced a stabilised formulation with a faster dissolving rate .

Wet medium milling was employed by Ligang Guo et al. to create an and rographolide nanosuspension with ionic and non-ionic stabilisers that had In comparison to nitrofurazone commercial gel, Chengying Shen et alpreparation .'s of nitrofurazone nanosuspension using wet media milling demonstrated higher skin absorption .

Wet milling was utilised by Song Huang et al. to create nanosuspensions of efonidipine hydrochloride, which increased bioavailability .a particle size of about 300 nm and did not degrade chemically .

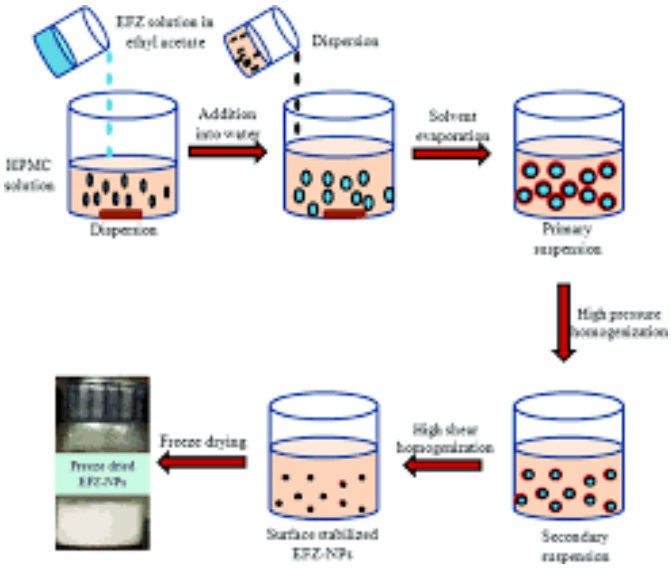

Fig.1: Schematic diagram of preparation methods of nanosuspension

Fig. 2: Top-down and bottom-up approach

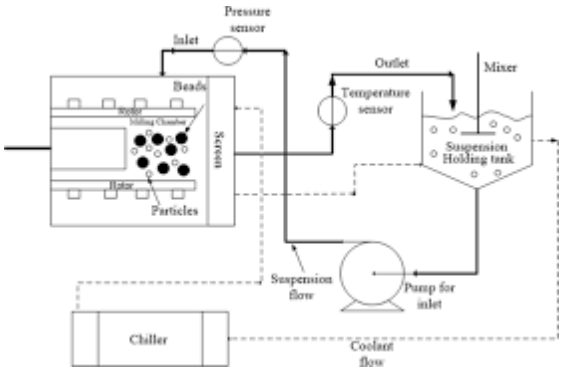

Fig. 3: Schematic representation of attrition wet media milling

Homogenization under high pressure

High pressure between 100 and 1500 bars is the basic standard.

We can unquestionably convert micron-sized particles into nanosized particles using this pressure.Additionally, it requires a particle in the micron range that is 25 micrometres in size at first so that we may use the jet mill as an example. This is because the jet mill allows us to reduce particle size down to 25 micrometres.

Additionally, we are able to do batch and continuous operations using the equipment.

The capacity ranges from 40 cc to 1,000 litres.Here, we must first convert the particles into a pre-suspension state.Particle collisions create strong pressure and severe shear, which reduces the size of the resulting particles.

To increase the viscosity of the nanosuspension in this case, viscosity enhancers must be added.

Pressure and homogenization cycles are two parameters in this approach that require a lot of attention .

In order to increase the solubility and oral bioavailability of daidzein, Hui wang et al. developed a high-pressure homogenization process and used stearic and electrostatic stabilisers .

Ritonavir nanosuspension was created by Alptug Karakucuk et al. utilising a microfluidizer with HPMC 3 cps and sodium dodecyl sulphate as stabilisers, which enhanced oral bioavailability in the fed condition .

Ziprasidone was made into a nanosuspension by Emine Tashan et al. using a microfluidizer, which enhanced the drug's water solubility as compared to a coarse powder and physical drug combinations .

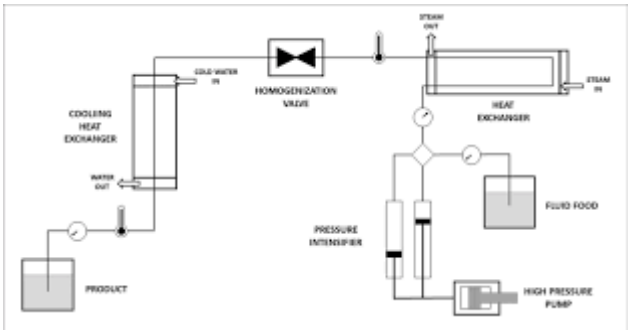

Fig.4: Schematic representation of high pressure homogenization

Bottom up approach

Precipitation method is another name for bottom-up process.

In the past ten years, precipitation has been linked to the formation of submicron particles, particularly for medications that are poorly soluble.The medication is typically first dissolved in a solvent.

Surfactants are then used to combine this solution with a miscible anti-solvent.

Fast addition of a drug solution results in unexpected super-saturation of the drug in the blended solution and the development of ultrafine crystalline or amorphous drug solids.

The anti-solvent is commonly water.The key to creating a stable suspension with the smallest possible particle size is to have a high nucleation rate but a low growth rate.

The difference between the two rates depends largely on temperature, with the ideal temperature for nucleation.
may be below that for crystal formation, allowing for even more temperature optimization .

With the aid of poloxamer, povidone, and phospholipids, Harsha Kathpalia et al. created atovaquone nanosuspension by anti-solvent precipitation and pH based precipitation methods, which led to both stability of suspension and nanosuspension dissolution rate .

Methotrexate nanosuspension was created using the nanoprecipitation process by Aline Martins dos Santos et al., which increased the drug's rate of solubility .

Furosemide's relative bioavailability was enhanced by around 2.3 fold when prepared as a nanosuspension by Mohammad H. Shariare et al. using the anti-solvent precipitation approach .

PVP was utilised as a stabiliser by Suna et al. to prepare teniposide nanosuspension utilising an anti-solvent sonication-precipitation process. produced a suspension that was physically and chemically stable for at least 10 days at 4°C .

In order to generate nanosuspensions of naproxen, Bibaswan Mishra et al. used the controlled precipitation ultrasonication approach . This has helped to address the issue of bioavailability.

Valsartan nanosuspension was created by Manishaanjane et al. using the nanoprecipitation process, which demonstrated improved stability and increased solubility .

Curcumin nanosuspension was created by Dekate S et al. using precipitation procedures, and it had a higher in vitro dissolution rate than ordinary curcumin when taken orally .

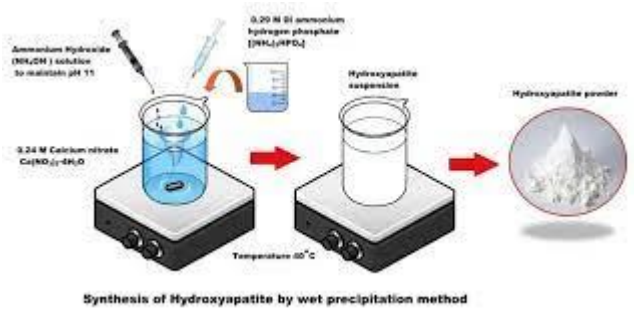

Fig. 5: Schematic representation of the precipitation method

Method of emulsion diffusion

The emulsion can be used to make nanosuspension in addition to drug delivery vehicles.

The emulsions can be used as a model for drugs that are soluble in either or partially water-miscible solvent or volatile organic solvent.

These solvents can be used as the emulsion's dispersed phase.

An emulsion is created by dispersing a mixture of organic solvents and medication in an aqueous phase that also contains the right surfactants while stirring.

High-pressure homogenization was also used to further homogenise the created emulsion.

Water was added to the emulsion after homogenization cycles, which diffused the organic solvent and turned the droplets into solid particles.

Since each emulsion droplet contains a single particle, it is possible to regulate their number.

the size of the emulsion while optimising the composition of the surfactant, which improves the uptake of the organic phase and ultimately results in the loading of the medication in the emulsion.

Fundamentally, organic solvents including methanol, ethanol, ethyl acetate, and chloroform are used.

Template for a microemulsion

This method aims to create an emulsion by dispersing a drug-loaded mixed solvent or organic solvent in an appropriate surfactant-containing aqueous phase.

Further, under lower pressure, the organic phase was evaporated to cause the drug particles to precipitate fast, resulting in the nanosuspension, which is then stabilised by surfactants.

Another approach substitutes the dispersed phase with somewhat water-miscible solvents like butyl lactate, benzyl alcohol, and triacetin.

combination strategy

- To overcome the drawbacks of the top down and bottom up approaches, the combination strategy was developed.
- This approach combines top-down and bottom-up approaches.
- The two-stage procedure is used in this technology.
- Pre-treatment is the first phase (bottom up), and particle size reduction is the second.High pressure homogenization is used in the second stage.
- The process is also referred to as annealing.The process of turning unstable matter into stable form through a single or repeated energy consumption, followed by thermal relaxation, is known as annealing.

- The nanocrystals created by combining technologies have particles smaller than 200 nm.

The uses of nanosuspension

Applications for nanosuspensions have a storied past.

Below are a handful of these applications.

oral medication administration

The significant problem with oral drug administration is insufficient solubility, insufficient breakdown, and insufficient efficacy.

Oral nanosuspensions are significantly employed to increase the rate of absorption and bioavailability of least dissolvable medicines due to the smallest particle size and increased surface to volume ratio.

If azithromycin nanosuspensions were to occur, it was shown that more than 65% of the medication would dissolve in 5 hours as opposed to 20% of micronized medications .

The nanosuspensions have a significant role in better dosage proportionality, oral absorption, and inter-subject variability.

Drug nanosuspensions can essentially be combined into various dosage forms, such as rapid melts, capsules, and tablets, by employing regular manufacturing techniques.
Ketoprofen's nanosuspension was properly consolidated

Parental drug delivery

- The current methods for parental delivery include salt creation, solubilization using co-solvents, cyclodextrin complexation, loaded micellar solutions, solubilization using co-solvents, and more recently, vesicular frameworks like liposomes and niosomes.
- In any case, there are limitations to these tactics, including solubilization limits, parental acceptance, and high manufacturing costs. Nanosuspension technology is employed to address the aforementioned issues.
- Different parenteral routes, such as intra-articular, intraperitoneal, intravenous, and others, are used to provide nanosuspensions. They also increase the survivability of parenterally administered medications.
- According to reports, paclitaxel nanosuspension has a dominant role in reducing the median tumour burden .
- In female mice with Mycobacterium avium infections, clofazimine nanosuspension showed improvements in stability and efficacy over liposomal clofazimine .
- It was demonstrated by Rainbow et al. that intravenous itraconazole

Pulmonary drug delivery

- Nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for pulmonary delivery.
- All aerosol droplets contain medicinal nanoparticles, which are visible as fine particles.
- For distribution via the pulmonary route, budesonide corticosteroid has been successfully created as a nanosuspension .
- Due to their very small particle sizes, aqueous solutions of the drug can be efficiently nebulized and administered via the pulmonary route.
- For the administration of liquid formulations, various nebulizer types are available.
- Ibuprofen, ketotifen, indomethacin, budesonide, doxorubicin, nifedipine, interleukin-2, itraconazole, p53 gene, leuprolide, and other few deugs have been successfully tried with the pulmonary route .

Ocular drug delivery

- The lachrymal gland's produced tear fluid has a low drug-dissolving capacity.
- Its bioavailability and solvability will increase if it is designed as nanoparticles .
- Drugs are delivered using nanosuspension via the ocular pathway in order to achieve prolonged release.
- With the use of eudragit, Liang and colleagues created a cloricromene nanosuspension for ocular administration.
- Examination revealed that the medication was more readily available in the rabbit eye's aqueous humour.
- As a result, nanosuspension presents a viable method for enhancing the drug's bioavailability and shelf life following ophthalmic administration .

Targeted drug delivery

- In light of their surface characteristics, nanosuspensions are suitable for targeting particular organs.
- In light of this, modifying the stabiliser is a simple way to modify in vivo behaviour.
- The mononuclear phagocytic system will take up the medicine and distribute it to the desired area.

- If the pathogens are suffering intracellularly, this can be exploited to concentrate anti-fungal, anti-mycobacterial, or anti-leishmanial medications to macrophages .
- Kayser created an aphidicolin nanosuspension that enhanced the drug's targeting of leishmania-infected macrophages.He claimed that the drug's ec50 in nanosuspension was 0.003 g/ml, compared to 0.16 g/ml in the traditional form .
- In their treatment plan for toxoplasmic encephalitis, Scholer et al. showed increased medication targeting to the brain.

Transdermal drug delivery

- In light of their surface characteristics, nanosuspensions are suitable for targeting particular organs.
- In light of this, modifying the stabiliser is a simple way to modify in vivo behaviour.
- The mononuclear phagocytic system will take up the medicine and distribute it to the desired area.
- If the pathogens are suffering intracellularly, this can be exploited to concentrate anti-fungal, anti-mycobacterial, or anti-leishmanial medications to macrophages .
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Mucoadhesion of the nanoparticles

A nanoparticle can cling to the mucosal surface because of its ability to contain extremely small nanoscale particles.

Particle attachment occurs early on, followed by its absorption.Hydrogels manufactured from a range of mucoadhesive polymers are used in the formulation of nanosuspension to increase significantly higher contact times.

The nanosuspension's adhesiveness optimises targeting of the parasites still present in the GIT and increases bioavailability.

It has been reported that bupravaquone Mucoadhesive Nanosuspensions display a good position in TRC Alpha Deficient animals contaminated with Cryptosporidium Parvum Oocytes .

Future perspectives

Although the design of nanoparticulate formulations has become increasingly advanced, essentially simple nanocrystals offer a unique advantage in the development of commercial products.

With simple production and component technologies, nanocrystals can significantly improve the saturation dissolvability and dissolving rate of the least dissolvable pharmaceuticals.

The large surface area of nanocrystals allows for improved medication absorption by allowing for a more significant interaction with tissue or cell surfaces.

There are a few oral nanocrystal products on the market, and dermal and IV products are being researched successfully.

Nevertheless, the potential of nanocrystals for a variety of applications, such as local or targeted medication delivery, has not been fully investigated.

However, the current techniques for creating and modifying nanocrystals do not adequately address the issues that are emerging with such products, and it is clear that new approaches to dealing with engineer nanocrystals are anticipated.

II. CONCLUSION

All poorly soluble medications can use nanocrystals to overcome their solubility and bioavailability problems.

The increased particle surface, curvature, saturation solubility, dissolution velocity, and additional tolerable bioavailability are all benefits of the reduction in particle size to the nanometer range.

Nanosuspensions are a targeted and financially viable solution to address the problems associated with hydrophobic drugs, such as poor solubility and poor bioavailability.
High pressure homogenization and media milling technology have been successfully applied to the fabrication of excessively large-scale nanosuspensions.

The applications of nanosuspensions for various administration routes have been expanded thanks to standout properties including increased saturation solubility, improved bioadhesivity, adaptability in surface modification, and burden-free postproduction processing.

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AUTHORS CONTRIBUTIONS

Equal contributions have been made by each author.

CONFLICT OF INTERESTS

The authors say they have no competing interests.

REFERENCES

[1] Chan VS. Nanomedicine: an unresolved regulatory issue. Regul Toxicol Pharmacol 2006;46:218-24.
[2] Liversidge ME, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poor-water soluble compounds. Eur J Pharm Sci 2003;18:113-20.
[3] Freitas RA. What is nanomedicine? Nanomedicine 2005;1:2-9.
[4] Keck CM, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high-pressure homogenisation. Eur J Pharm Biopharm 2006;62:3-16.
[5] Shegokar R, Muller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm 2010;399:129-39.
[6] Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics concepts to formulation development. J Pharm Sci 2010;99:4940-54.
[7] Moschwitzer JP. Drug nanocrystals in the commercial pharmaceutical development process. Int J Pharm 2013;453:142-56.
[8] Lipinski CA. Drug-like properties and the causes of poor solubility. J Pharmacol Toxicol Methods 2000;44:235-49.
[9] Bevernage J, Brouwers J, Brewster ME, Augustijns P. Evaluation of gastrointestinal drug supersaturation and precipitation: strategies and issues. Int J Pharm 2013;453:25-35.
[10] Dave RH, Shah DA, Patel PG. Development and evaluation of high loading oral dissolving film of aspirin and acetaminophen. J Pharm Sci Pharmacol 2014;1:112-22.
[11] Cooper ER. Nanoparticles: a personal experience for formulating poorly water soluble drugs. J Controlled Release 2010;141:300-2.
[12] Sigfridsson K, Lundqvist AJ, Strimfors M. Size reduction for improvement of oral absorption of the poorly soluble drug UG558 in rats during early development. Drug Dev Ind Pharm 2009;35:1479-86.
[13] Liversidge GG, Conzentino P. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm 1995;125:309-13.
[14] Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystallinedanazol in beagle dogs. Int J Pharm 1995;125:91-7.
[15] Kesisoglou F, Panmai S, Wu Y. Nanosizing–oral formulation development and biopharmaceutical evaluation. Adv Drug Delivery Rev 2007;59:631-44.
[16] Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: I. A thermodynamic analysis. J Pharm Sci 2010;99:1254-64.
[17] Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: II. Application of quantitative thermodynamic relationships for prediction of solubility enhancement in structurally diverse insoluble pharmaceuticals. Pharm Res 2010;27:2704-14.
[18] Liu G, Zhang D, Jiao Y, Guo H, Zheng D, Jia L, et al.In vitro and in vivo evaluation of riccardin D nanosuspensions with different particle size. Colloids Surf B 2013;102:620-6.
[19] Detroja C, Chavhan S, Sawant K. Enhanced antihypertensive activity of candesartan cilexetil nanosuspension: formulation, characterization and pharmacodynamic study. Sci Pharm 2011;79:635-51.
[20] Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm 2005;299:167-77.
[21] Schmelzer JW, Schmelzer J. Kinetics of nucleation at increasing supersaturation. J Colloid Interface Sci 1999;215:345-55.
[22] Shah KB, Patel PG, Khairuzzaman A, Bellantone RA. An improved method for the characterization of supersaturation and precipitation of poorly soluble drugs using pulsatile microdialysis (PMD). Int J Pharm 2014;468:64-74.
[23] Cheow WS, Hadinoto K. Self-assembled amorphous drug–polyelectrolyte nanoparticle complex with enhanced dissolution rate and saturation solubility. J Colloid Interface Sci 2012;367:518-26.
[24] Eerdenbrugh VB, Vermant J, Martens JA, Froyen L, Humbeeck JV, Mooter VDG, et al. Solubility increases associated with crystalline drug nanoparticles: methodologies and significance. Mol Pharm 2010;7:1858-70.
[25] Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address

low drug solubility in discovery and development. Pharmacol Rev 2013;65:315-499.
[26] Sun B, Yeo Y. Nanocrystals for the parenteral delivery of poorly water-soluble drugs. Curr Opin Solid State Mater Sci 2012;16:295-301.
[27] Barret ER. Nanosuspensions in drug delivery. Nat Rev Drug Discovery 2004;3:785-96.
[28] Nanosuspension Systems. Hamamatsu Nano technology. Available from: http://www.hamanano.com/e/products/ C3/C3_1/. [Last accessed on 10 Jul 2019]
[29] Raval JA, Patel JK, Patel MM. Nanosuspensions as particulate drug delivery systems. Pharm Rev 2006;4:5.
[30] Prabhakar C, Krishna BK. A review on nanosuspensions in drug delivery. Int J Pharma Bio Sci 2011;2:549-58.
[31] Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discovery 2004;3:785-96.
[32] Liu P, Rong X, Laru J. Nanosuspensions of poorly soluble drugs: preparation and development by wet milling. Int J Pharm 2011;411:215-22.
[33] Ibrahim HM, Ismail HR, Lila AEA. Formulation and optimization of ocular poly-D, L-lactic acid nano-drug delivery system of amphotericin-B using box behnken design. Int J Pharm Pharm Sci 2012;4:342-9.
[34] Sutradhar KB, Khatun S, Luna IP. Increasing possibilities of nanosuspension. J Nanotechnol 2013. http://dx.doi.org/ 10.1155/2013/346581.
[35] Arole VM, Munde SV. Fabrication of nanomaterials by top-down and bottom-up approaches–an overview. J Adv Appl Sci Technol 2014;1:89-93.
[36] Salazar J, Muller RH, Moschwitzer JP. Combinative particle size reduction € technologies for the production of drug nanocrystals. J Pharm 2014;14. http://dx.doi.org/10.1155/ 2014/265754.
[37] Weber U. The effect of grinding media performance on milling a water-based color pigment. Chem Eng Technol 2010;33:1456-63.
[38] Singh SK, Srinivasan KK, Gowthamarajan K, Singare DS, Prakash D, Gaikwad NB. Investigation of preparation parameters of nanosuspension by top-down media milling to improve the dissolution of poorly water-soluble glyburide. Eur J Pharm Biopharm 2011;78:441-6.
[39] Tashan E, Karakucuk A, Celebi N. Optimization and in vitro evaluation of ziprasidone nanosuspensions produced by a top-down approach. J Drug Delivery Sci Technol 2019;52:37-45.
[40] Guo L, Kang L, Liu X, Lin X, Di D, Wu Y, et al. A novel nanosuspension of Andrographolide: preparation, characterization and passive liver target evaluation in rats. Eur J Pharm Sci 2017;104:13-22.
[41] Shen C, Shen B, Liu X, Yuan H. Nanosuspensions based gel as the delivery system of nitrofurazone for enhanced dermal bioavailability. J Drug Delivery Sci Technol 2018;43:1-11.
[42] Huang S, Zhang Q, Li H, Sun Y, Cheng G, Zou M, et al. Increased bioavailability of efonidipine hydrochloride nanosuspensions by the wet-milling method. Eur J Pharm Biopharm 2018;130:108-14.
[43] Malamatari M, Taylor KMG, Malamataris S, Douroumis D, Kachrimanis K. Pharmaceutical nanocrystals: production by wet milling and applications. Drug Discovery Today 2018;23:534-47.
[44] Reddy GA, Anilchowdary Y. Nanosuspension technology: a review. J Pharm Cosmetol 2012;2:47-52.
[45] Wang H, Xiao Y, Wang H, Sang Z, Han X, Ren S, et al. Development of daidzein nanosuspensions: preparation, characterization, in vitro evaluation, and pharmacokinetic analysis. Int J Pharm 2019;566:67-76.
[46] Karakucuk A, Teksin ZS, Eroglu H, Celebi N. Evaluation of improved oral bioavailability of ritonavir nanosuspension. Eur J Pharm Sci 2019;131:153-8.
[47] Nagaraju P, Krishnachaithanya K, Srinivas VDN, Padma SVN. Nanosuspensions: promising drug delivery systems. Int J Pharm Sci Nanotechnol 2010;2:679-84.
[48] Sumathi R, Tamizharasi S, Sivakumar T. Formulation and evaluation of polymeric nanosuspension of naringenin. Int J Appl Pharm 2017;9:60-70.
[49] https://www.researchgate.net/figure/Schematic-diagram-of-the-process-of-high-pressure-homogenization-21_fig.2_ 280444393. [Last accessed on 10 Jul 2019].
[50] Kathpalia H, Juvekar S, Shidhaye S. Design and in vitro evaluation of atovaquone nanosuspension prepared by ph based and anti-solvent based precipitation method. J Colloid Interface Sci 2019;29:26-32.
[51] Santos DAM, Carvalho FC, Teixeira DA, Azevedo DL, Barros WMD, Gremiao MPD. Computational and experimental approaches for the development of methotrexate nanosuspensions by bottom-up nanoprecipitation. Int J Pharm 2017;524:330-8.
[52] Shariare MH, Altamimi MA, Marzan AL, Tabassum R, Jahan B, Reza HM, et al.In vitro dissolution and bioavailability study of furosemide nanosuspension prepared using a design of experiment (DoE). Saudi Pharm J 2018;27:96-105.
[53] He S, Yang H, Zhang R, Li Y, Duan L. Preparation and in vitro-in vivo evaluation of teniposide nanosuspensions. Int J Pharm 2014;478:131-7.
[54] Mishra B, Sahoo J, Dixit PK. Formulation and process optimization of naproxen nanosuspensions stabilized by hydroxyl propyl methylcellulose. Carbohydr Polym 2015;127:300-8.
[55] Manishaanjane, Agrawal S, Khan A. Formulation and evaluation of nanosuspension of valsartan. Int J Curr Pharm Res 2018;10:68-74.

[56] Dekate S, Bhairy S, Hirlekar R. Preparation and characterization of oral nanosuspension loaded with curcumin. Int J Pharm Pharm Sci 2018;10:90-5.
[57] Paun JS. Nanosuspension: an emerging trend for bioavailability enhancement of poorly soluble drugs. Asian J Pharm Tech 2012;2:157-68.
[58] Vaghela A. Nanosuspension technology. Int J Universal Pharm Life Sci 2012;2:306-17.
[59] Bhargavi R. Technical review of nanosuspensions. Int J Pharm Technol 2011;3:1503-11.
[60] 60:-Verma KAK. Nanosuspensions: advantages and disadvantages. Indian J Novel Drug Delivery 2012;4:179-88.
[61] Rao SK, Prasad T, Mohanta GP, Manna PK. An overview of statins as hypolipidemic drugs. Int J Pharm Sci Drug Res 2011;3:178-83.
[62] Boedeker BH, Lojeski EW, Kline MD, Haynes DH. Ultra-long duration local anesthesia produced by injection of lecithin-coated tetracaine microcrystals. J Clin Pharmacol 1994;34:699-702.
[63] Jia L, Wong H, Cerna C, Weitman SD. Effect of nanonization on absorption of 301029:Ex vivo and in vivo pharmacokinetic correlations determined by liquid chromatography/mass spectrometry. Pharm Res 2002;19:1091-6.
[64] Liversidge ME. Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. Pharm Res 1996;13:272-8.
[65] Peters K, Leitzke S, Diederichs JE, Borner K, Hahn H, Muller RH, et al. Preparation of a clofazamine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in murine Mycobacterium avium infection. J Antimicrob Chemother 2000;45:77-83.
[66] Rainbow B, Kipp J, Papadopoulos P, Wong J, Glosson J, Gass J, et al. Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat. Int J Pharm 2007;339:251-60.
[67] Trejo HN, Kayser O, Steckel H, Muller RH. Characterization of nebulized bupravaquone nanosuspensions-effect of nebulization technology. J Drug Target 2005;13:499-507.
[68] Mansour HM, Rhee YS, Wu X. Nanomedicine in pulmonary delivery. Int J Nanomed 2009;4:299-319.
[69] Aher SS, Malsane ST, Saudagar RB. Nanosuspension: an overview. Int J Curr Pharm Res 2017;9:19-23.
[70] Liang Y, Binner J. Effect of triblock copolymer non-ionic surfactants on the rheology of 3 mol% yttria-stabilized zirconia nanosuspensions. Ceram Int 2008;34:293-7.
[71] Kayser O, Lemke A, Trejo HN. The impact of nanobiotechnology on the development of new drug delivery systems. Curr Pharm Biotechnol 2005;6:3-5.
[72] Kayser O. Nanosuspensions for the formulation of aphidicolin to improve drug targeting effects against leishmania infected macrophages. Int J Pharm 2000;196:253-6.
[73] Scholer N, Krause K, Kayser O, Moller RH, Borner K, Hahn H, et al. Atovaquone nanosuspensions show excellent therapeutic effect in a new murine model of reactivated toxoplasmosis. Antimicrob Agents Chemother 2001;45:1771-9.
[74] Du J, Li X, Zhao H, Zhou Y, Wang L, Tian S, et al. Nanosuspensions of poorly water-soluble drugs prepared by bottom-up technologies. Int J Pharm 2015;495:738-49.
[75] Lakshmi P, Kumar GA. Nano-suspension technology: a review. Int J Pharm Pharm Sci 2010;2:35-40.