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NANO SUSPENSION BASED DRUG DELIVERY SYSTEM FOR TOPICAL APPLICATION

Shreya Mahendra Pandhare*1, M.R. Deokar*2, Vaishnavi Chopade*3

*1,2,3Late Laxmibai Phadatare College Of Pharmacy, Kalamb, India.

ABSTRACT

Nanosuspension has involved the important Strategy for mitigating the bioavailability challenges of hydrophobic drugs, special who has the poor solubility in both aqueous & organic environment. The solubility Issue of poorly water soluble drug has a largely resolve the need to enhance drug absorption & bioavailability .As mucosal formulation & topical administration progress in future, the nanosuspension drug delivery, direct formulation technique versatile applications will be continued in progress. NanoSuspensions have major importance and demand in preparation for topical application encompassing ocular, pulmonary & dermal usage. There are also various methods used for improving cutaneous application & in nanocrystals. Hence increasing the bioavailability of nanosuspension products mainly designed for oral administration nanocrystals involved increased skin adhesiveness with increase the saturation solubility & dissolution rate thereby augmenting cutaneous distribution.

This article provides a particular overview of nano suspension for topical application. The method involves the well-defined experimental design. The results provides the outcomes in terms & enhanced drug delivery with short discussion of certain Imitations.

Additionally the reference highly focused on recent studies, along with the historical prospective of the subject

Keywords: Nano Suspension, Nanotechnology, Nanocrystals, Topical, Dermal.

I. INTRODUCTION

Over the few decades, there has been significant emergencies of the cutting-edge advancements in the area of Pharmaceutical research & development. The starting of drug discovery process, makes possible by the technologies Such as high throughput screening, combinatorial chemistry & computer aided drug design, has results in the production of important array of highly effective drug candidates. There by the formulation of poorly Water Soluble drugs has been a very challenging problem faced by the scientist and it must be increased because approximately more than 40% new chemical products being generated through drug discovery program are poorly water soluble.

Obviously the poorly water Soluble drugs shows various problems formulating them in conventional dosage form. Hence the predominant challenges faced by Pharmaceutical industry based on development of novel formulation procedures & drug delivery technology changed to effectively address the Solubility limitations associated with therapeutic candidates. These associated with issues related to low oral bioavailability .To attain equilibrium bioavailability. For these medications it is necessary to ensure their rapid absorption post Oral administration. The intravenous route represent an additional viable means of administration.

Furthermore There the various strategies have been produce to address the challenges & problems posed by poorly Soluble medication, hence the effectiveness of these approaches strongly matches on specific chemical characteristics exhibited by molecules ,encompassing factors such as their solubility in different organic solvents their molecular size or configuration.

Micronization is the process which is aimed at augmenting the oral bioavailability of drugs in the Pharmaceutical formulation used for reducing the size of drug powders within the range of 1 to 10 um.These process commonly employed with the objective of bioavailability & enhancing the oral bioavailability of Pharmaceutical compound . The insufficient solubility of commonly used medicine alters the effectiveness of micronization.

The unresolved related to the bioavailability of drugs categorized under the biopharmaceutical classification class 2 which is related to limited solubility.

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Since in 1990 The micronization concept was build up which has emerged as a subsequent development. The field of Nano systems. Has favour for utilisation of nanocrystals rather than the micro crystals to improve oral bioavailability of Pharmaceuticals.

Additionally these non crystals that can be dispersed in water known as the nanosuspension which has the application in the intravenous administration & pulmonary delivery of medications. One of the key advantages of developing drugs with low solubility lies in the technique it employs, which results in creation et nanosuspension. These nanosuspension is mainly a dispersion of drug nanocrystals in liquid medium typically in water. It contains drug nanoparticles ranges from 100 to 1000 nm.

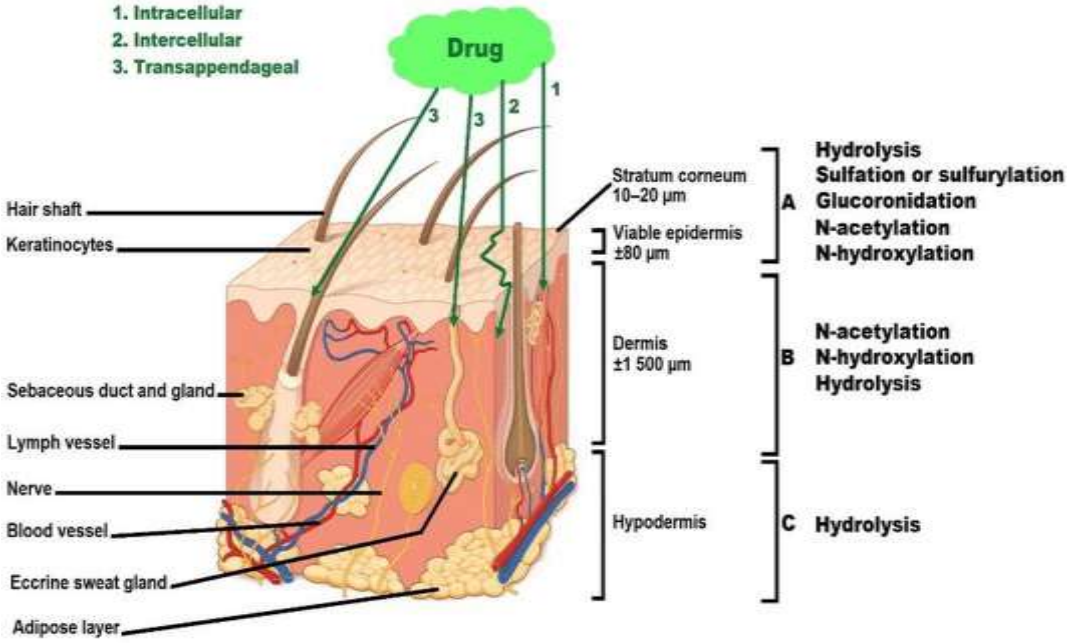
The Pharmaceutical nanosuspension is defined as very finely dispersed Solid drug particles in an aqueous vehicle, stabilized by surfactants for either oral & Topical use or parenteral & pulmonary Administration with reduced particle size, leading to an increased dissolution Rate & Therefore improved bioavailability. As a results of increased solubility the rate of flooding of the active compound. Increase & the maximum plasma level is reached faster.

-The skin is an crucial site for painless & non invasive administration & therapeutic substances which allows for the control their release & avoid the first pass metabolism. The medication can show their effect locally, regionally. Or systematically at various target sites upon dermal absorption. These consideration can lead to an challenging research area to the drug delivery through the skin .Due to the impermiability of Skin, The principle obstacles are overcoming. The skin is an complex tissue That covers the body from invading chemicals, pathogens and physical agent's & regulate essential functions such as temperature regulation.

The various layers of skin consists stratum corneum (sc), the accessible epidermis and the dermis. The primary physical barrier is a situated in the Stratum corneum composed of protein rich cells & lipid rich structures. The nucleated epidermis also contains to barriers through desmosomes, cytoskeletal components, tight junctions & adherence junctions.

Hence the overall structure of skin is determine its efficacy as protective barrier.

The below figure shows the layers of skin.



There are two pathways which access the surface of skin while administration of the drug. They are trans appendageal and trans epidermal routes facilitated by passive diffusion.

The nanosuspension when applied to dermal surface it differs several potential mechanism for improved drug delivery

1. Increased surface area.
2. Improved penetration.

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3. Targeting specific skin layers.
4. Facilitated drug stability
5. Interaction with skin appendages.

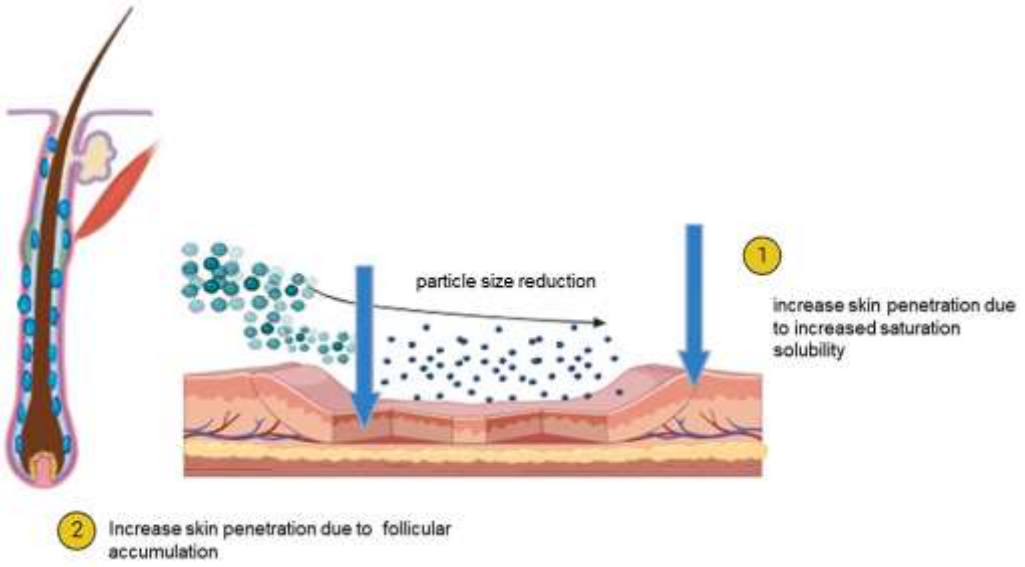
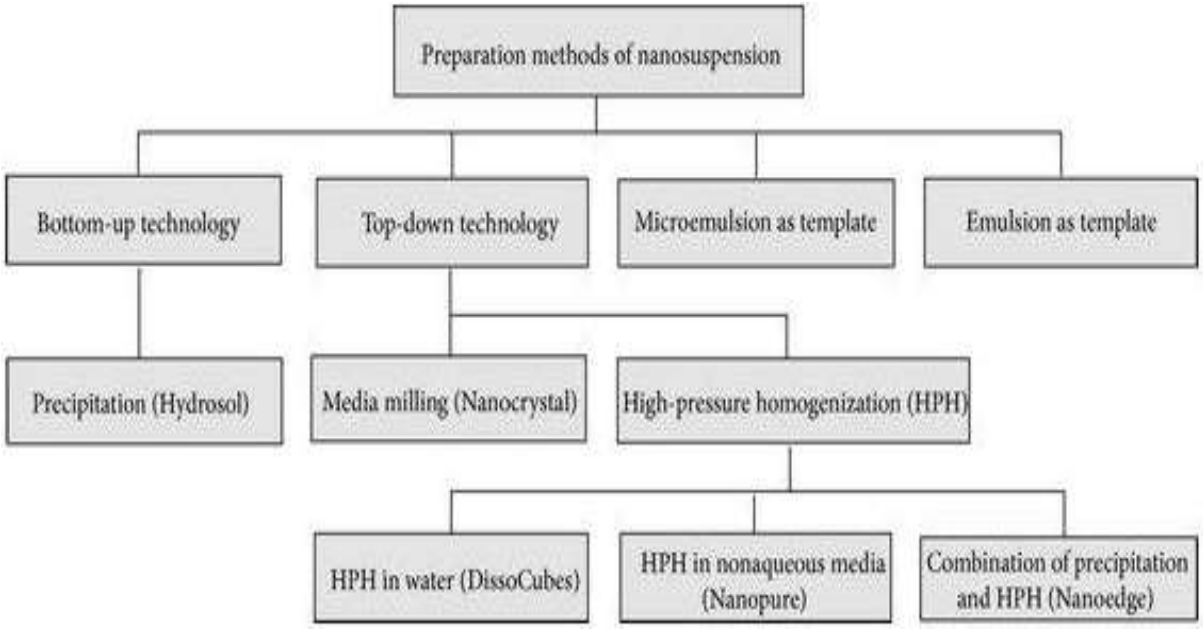


Fig:

From the Figure nanosuspension is a topical drug delivery aim to address challenges associated with drug solubility, penetration, stability and controlled release. Various methods are also employed to achieve Nano sized particles each have their specific advantages depending on the characteristics of the drug and desired application. However the several dermatological conditions such as acne alopecia and various skin tumours are related to sebaceous glands and hair follicles.

The current investigation involved a literature review where articles were gathered through searches on google scholar, PubMed and Scopus utilizing keywords such as nanosuspension, topical application, dermal and drug delivery system. The selection of libraries was based on specific inclusion and exclusion criteria. Inclusion criteria encompassed literature providing insights into the use of nanosuspension based drug delivery system for topical application published between the year 2000 and 2023. Exclusion criteria involve review papers and publication without full text availability.

II. METHODS OF PREPARATION OF NANOSUSPENSION



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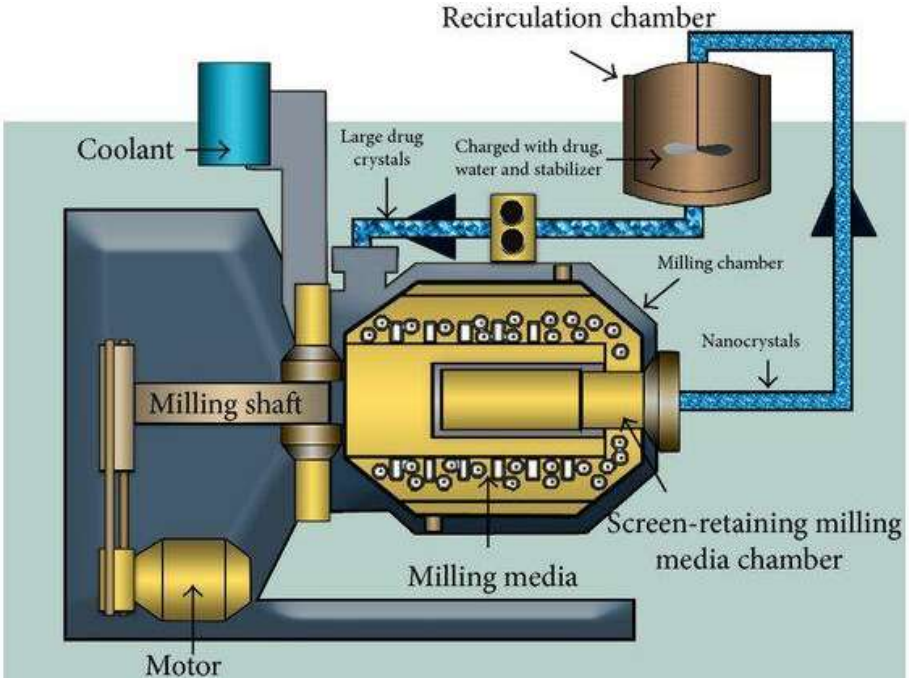
1) Media Milling (Nanocrystals).



This method was discovered by Liversidge et al. in 1992 and first patented by "Nanosystems" group, and now this patent transferred to "Élan drug delivery. "Here, the particle size is reduced by the high shear Rate. And the total process is performed under controlled Temperature. Otherwise, at high shear rate, some temperature Will build up which will degrade some of the ingredients in The dosage form. This equipment is known as high shear media milling or Pearl mills (Figure 3).This mill consists of three major columns:

(a) Milling chamber;
(b) Milling shaft;
(c) Recirculation chamber.

- **Principle**. Here, the main principle involved in the size Reduction is "impaction". By this shear, the microparticles Are braked down into nanoparticles. And it is connected to The recirculating chamber so that continuous production will Be carried out. It is suitable for both batch operation and Continuous operation. By this, we can reduce the particle size Up to <200 nm in 30–60 min only .
- **Advantages**

1. Little batch to batch variations.
2. Ease of handling large quantities of drugs.

- **Disadvantages-**

1. Generation of residue of milling media.
2. Time consuming process.
3. Prolonged milling may induce the formulation.
4. Scale is not easy due to mill size and weight.

2) High-Pressure Homogenization (Disso cubes).

The process Was developed by R. H. Muller, and first patent was taken By DDS Gmbh. Later, patent was transferred to Skype Pharmaceuticals. Commonly used homogenizer is the APV Micron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany). And another Type is piston-gap homogenizers. And it is manufactured by Avestin (Avestin Inc., Ottawa, Canada). And another one is Stansted (Stansted Fluid Power Ltd. Stansted, UK). The main principle is high pressure that is 100–1500 bars. By this pressure we can easily convert the micron size particle, Into Nano size particle. And it initially needs the micron range Particle that is <25 micrometre, so that we have to get the Sample from the jet mill because by using jet mill we can Reduce the particle size up to <25 micrometre (Figure 4).And we can use this equipment for both batch and Continuous operations. Capacity is also 40 mL to thousand Litres. Here, first, we have to convert the particles into form (after jet milling).

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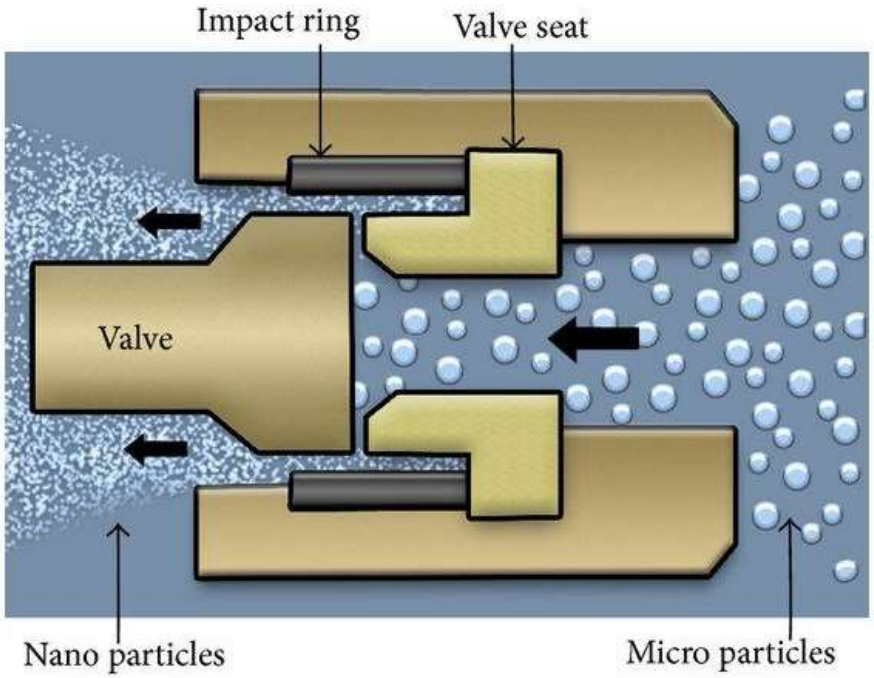

- **Principle**. High shear and high pressure are due to Particle collisions; the particle size will be reduced. Here, we Have to add viscosity enhancers to increase the viscosity of Nanosuspension. In this methods we have to mainly concentrate on two parameter called pressure and homogenization Cycles (depending on particle hardness analysed by particle Size and polydispersibility index) .
- **Advantages-**

1. General applicability to most drugs.
2. For dilute and high concentrated Nanosuspension preparation.
3. Simple technique.
4. Sterile products preparation.
5. Drugs which belongs to BCS class 2 a4.
6. Ease of scale up and little batch to batch variations.

- **Disadvantages-**

1. High number of homogenization cycles.
2. Prerequisites micronized drug particles.
3. Possible contamination of products could occur from metal ions coming off from the walls of homogenizers.
4. Pre suspension is required.

3). Emulsion as Template These emulsions are also Media Milling (Nanocrystals). This method was discovered by Liversidge et al. in 1992 and first patented by "Nanosystems" group, and now this patent transferred to"Elan drug delivery." Here, the particle size is reduced by the high shear rate. And the total process is performed under controlled temperature. Otherwise, at high shear rate, some temperature will build up which will degrade some of the ingredients in the dosage form. This equipment is known as high shear media milling or pearl mills .This mill consists of three major columns:

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- **Principle**. Here, the main principle involved in the size reduction is "impaction". By this shear, the microparticles are braked down into nanoparticles. And it is connected to the recirculating chamber so that continuous production will be carried out. It is suitable for both batch operation and continuous operation. By this, we can reduce the particle size up to <200 nm in 30–60 min only .
- **Advantages-**

1. High drugs Solublization

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2. Long shelf life.
3. Large scale preparation.
4. Low cost.
5. Simple manufacturing method.
6. Some organic solvents like ethyl acetate and ethyl format can used.

- **Disadvantages-**

1. Used organic solvents are much unsuitable as human health cost.
2. Use of high amount of surfactant and stabilizers.

3) The emulsion as Template -. These emulsions are also useful for the preparation of nanosuspensions. The drugs which were insoluble in volatile organic solvents or partially soluble in water are prepared by this method. This method is done by two types.

5) Microemulsion as Template-. Microemulsions are thermodynamically stable and isotropically clear dispersion of the two immiscible liquids such as oil and water, and they were stabilized by an interfacial film of surfactant and co surfactant. In this, firstly, the micro emulsion was prepared the dug solution was mixed to that prepared emulsion and drug loading efficiency was tested .

6) Precipitation Method Precipitation has been applied for years to prepare submicron particles within the last decade, especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in the solvent. Then solution is mixed With a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually Water) leads to sudden super saturation of drug in the mixed Solution and generation of ultrafine crystalline or amorphous Drug solids . This process involves two phases: Nuclei formation and crystal growth. When preparing a Stable suspension with the minimum particle size, a high Nucleation rate but low growth rate is necessary. Both rates Are dependent on temperature: the optimum temperature for Nucleation might lie below that for crystal growth, which Permits temperature optimization

- **Advantages**

1. Simple process.
2. Economical production.
3. Ease of scale up.

- **Disadvantages**

1. Drug has to be soluble at least one solvent and that this solvent is need to be miscible with non solvent.
2. Growing of crystals need to be limited by surfactant addition.

7) Dry Cogrinding.- Recently, nanosuspensions can be Obtained by dry milling techniques. Successful work in Preparing stable nanosuspensions using dry grinding of Poorly soluble drugs with soluble polymers and copolymers After dispersing in a liquid media has been reported. Colloidal particle formation of many poorly water soluble Drugs like like griseofulvin, glibenclamide and nifedipine Obtained by grinding with polyvinylpyrrolidone (PVP) and impact ring Valve seat Valve Nano particles Micro particles

Figure 4: Schematic representation of the high-pressure homogenization process .Sodium dodecylsulfate (SDS) [16]. Many soluble polymers And copolymers such as PVP, polyethylene glycol (PEG), Hydroxypropyl methylcellulose (HPMC), and cyclodextrin Derivatives have been used. Physicochemical properties and Dissolution of poorly water-soluble drugs were improved by Cogrinding because of an improvement in the surface polarity And transformation from a crystalline to an amorphous drug. Dry cogrinding can be carried out easily and economically And can be conducted without organic solvents. The cogrindIng technique can reduce particles to the submicron level and A stable amorphous solid can be obtained.

- **Advantages-**

1) Easy process.
2) No organic solvents.
3) Requiring short grinding time generation of residue of milling media.

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Preparation Method	Advantages	Limitations
Bottom-up technology	• Simple in principle and operation • No device requirement • Rapid preparation	• Poor reproducibility • Non-homogeneous particle size • Risk of toxic effects of the solvent • Difficult to scale up
Top-down technologies		
High-pressure homogenization method	• Easy to scale up • Easy to reproduce • Obtaining homogeneous particle size • Obtaining the desired particle size with process modifications • Decreasing for recrystallization	• Expensive equipment • Risk of heating in the device because of high pressure • Risk of clogging the chamber
Wet media milling method	• Easy to scale up • Easy to reproduce • Obtaining homogeneous particle size • Obtaining the desired particle size with process modifications	• Expensive equipment • Risk of corrosion of beads and milling chamber

III. TOPICAL APPLICATION OF NANO SUSPENSION

Various routes of drug delivery of nanosuspension.

Nanosuspensions are used in topical drug delivery to address challenges with drug solubility, stability, penetration, and controlled release. Here are some ways nanosuspensions are used topically:

Ocular medication delivery- Nanosuspensions are used to treat external and internal eye conditions. The approach depends on whether the drug needs to stay at the cornea or conjunctiva, or if it needs to reach the internal eye tissues.

Skin conditions - Nanosuspensions can help with skin conditions like eczema, psoriasis, and fungal infections. Nanocrystals can enhance skin penetration by adhering to the skin, creating a diffusional corona, and targeting hair follicles.

Hair follicles - Nanosuspensions can be used to target hair follicles. Gels with different properties can be loaded with nanosuspensions to efficiently deliver them into hair follicles.

Nanosuspensions can be prepared using top-down methods like wet milling, dry milling, high-pressure homogenization, and co-grinding. Bottom-up methods include anti-solvent precipitation, liquid emulsion, and sono-precipitation.

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IV. CHALLENGES AND LIMITATIONS

Nanosuspension-based drug delivery systems have several challenges and limitations, including:

1. **Stability**: Physical stability, sedimentation, and compaction can cause problems. The type and amount of stabilizer used can also affect the stability of the nanosuspension.
2. **Toxicity**: Long-term use of large quantities of stabilizers can be toxic. For example, Tween 80, a common surfactant used in nanosuspension preparation, can cause neuro- and nephrotoxicity.
3. **Dose**: It can be difficult to achieve a uniform and accurate dose.
4. **Handling and transport**: Nanosuspensions are bulky, so care is needed when handling and transporting them.
5. **Preparation**: Designing an appropriate nanosuspension preparation approach with low energy input and erosion contamination can be challenging.
6. **Milling**: The milling chamber or the impact of the beads can cause wear.
7. **Nanocarriers**, such as nanoparticles, liposomes, micelles, niosomes, and dendrimers, can help overcome the limitations of conventional drug delivery systems.

V. CONCLUSION

According to a review on nanosuspension technology, the conclusion is that nanosuspensions can play a crucial role in drug delivery by:

1. **Improving bioavailability**

Nanosuspensions can improve the bioavailability of drugs that are poorly soluble in water or are unstable due to environmental factors.

2. **Targeting organs**

Nanosuspensions can target specific organs due to their surface properties.

3. **Solving issues with poorly soluble drugs**

Nanosuspensions can help solve issues related to poor bioavailability, dosing frequency, and site-specific drug delivery.

4. **Administering drugs through various routes**

Nanosuspensions can be used to administer drugs through a variety of routes, including oral, transdermal, ocular, parenteral, and pulmonary. Other characteristics of nanosuspensions include: high loading of drugs, protection against degrading agents, rapid dissolution, high particle stability, and lower toxicity compared to other nanocarriers.

Abbreviations-

API, active pharmaceutical ingredient;

DoE, Design of Experiments;

GmbH, company with limited liability;

HEC, Hydroxyethyl cellulose;

HPH, high-pressure homogenization;

HPMC, Hydroxypropyl Methylcellulose;

IV, intravenous;

LD, laser diffraction;

MPa, megapascal;

NSAIDs, Nonsteroidal Anti-Inflammatory Drugs;

NSs, nanosuspensions;

PCS, Photon correlation spectroscopy;

PS, particle size;

PVA, polyvinyl alcohol;

PVP, Polyvinylpyrrolidone;

SC, stratum Corneum;

TPGS, tocopherol polyethylene glycol succinate;

TRA, to assess the photostability of tretinoin;

VI. REFERENCES

[1] Guan W, Ma Y, Ding S, et al. The technology for improving stability of nanosuspensions in drug delivery. J Nanopart Res. 2022;24(1):14.Huang S, Wu H, Jiang Z, Huang H. Water-based nanosuspensions: formulation, tribological property, lubrication mechanism, and applications

[2] Nabavi M, Nazarpour V, Alibak AH, Bagherzadeh A, Alizadeh SM. Smart tracking of the influence of alumina nanoparticles on the thermal Coefficient of nanosuspensions: application of LS-SVM methodology. Appl Nanosci. 2021;11(7):2113–2128. Doi:10.1007/s13204-021-01949-7

[3] Ma Y, Cong Z, Gao P, Wang Y. Nanosuspensions technology as a master key for nature products drug delivery and in vivo fate. Eur J Pharm Sci. 2023;185:106425. Doi:10.1016/j.ejps.2023.106425

[4] Guner G, Seetharaman N, Elashri S, Mehaj M, Bilgili E. Analysis of heat generation during the production of drug nanosuspensions in a wet Stirred media mill. Int J Pharm. 2022;624:122020. Doi:10.1016/j.ijpharm.2022.122020

[5] Karakucuk A, Celebi N. Investigation of formulation and process parameters of wet media milling to develop etodolac nanosuspensions. Pharm Res. 2020;37(6):1–18. Doi:10.1007/s11095-020-02815-x

[6] Bilgili E, Guner G. Mechanistic modeling of wet stirred media milling for production of drug nanosuspensions. AAPS Pharm Sci Tech. 2021;22 (1):1–23. Doi:10.1208/s12249-020-01876-w

[7] Liu T, Müller RH, Möschwitzer JP. Production of drug nanosuspensions: effect of drug physical properties on nanosizing efficiency. Drug Dev Ind Pharm. 2018;44(2):233–242. Doi:10.1080/03639045.2017.1386207

[8] Du Y, Yuan X. Coupled hybrid nanoparticles for improved dispersion stability of nanosuspensions: a review. J Nanopart Res. 2020;22(9):261. Doi:10.1007/s11051-020-04991-8

[9] Perrin L, Pajor-Swierzy A, Magdassi S, Kamyshny A, Ortega F, Rubio RG. Evaporation of nanosuspensions on substrates with different Hydrophobicity. ACS Appl Mater Interfaces. 2018; 10(3): 3082–3093. Doi:10.1021/acsami.7b15743

[10] Azimullah S, Sudhakar CK, Kumar P, et al. Nanosuspensions as a promising approach to enhance bioavailability of poorly soluble drugs: an Update. J Drug Delivery Ther. 2019;9(2):574–582. Doi:10.22270/jddt.v9i2.2436

[11] Wang N, Qi F, He X, et al. Preparation and Pharmacokinetic Characterization of an Anti-Virulence Compound Nanosuspensions. Pharmaceutics. 2021;13(10):1586. Doi:10.3390/pharmaceutics13101586

[12] Khandbahale SV. A review-Nanosuspension technology in drug delivery system. Asian J Pharm Res. 2019;9(2):130–138. Doi:10.5958/22315691.2019.00021.2

[13] Dewangan HK. The emerging role of nanosuspensions for drug delivery and stability. Curr Nanomedicine. 2021;11(4):213–223.

[14] Goel S, Sachdeva M, Agarwal V. Nanosuspension technology: recent patents on drug delivery and their characterizations. Recent Pat Drug Deliv Formul. 2019;13(2):91–104. Doi:10.2174/1872211313666190614151615

[15] Lynnerup JT, Eriksen JB, Bauer-Brandl A, Holsæter AM, Brandl M. Insight into the mechanism behind oral bioavailability-enhancement by Nanosuspensions through combined dissolution/permeation studies. Eur J Pharm Sci. 2023;184:106417. Doi:10.1016/j.ejps.2023.106417

[16] Alexandra S, Schönenberger M, Niederquell A, Kuentz M. Temperature-induced surface effects on drug nanosuspensions. Pharm Res. 2018;35 (3):1–11. Doi:10.1007/s11095-017-2300-6

[17] Kovalchuk NM, Johnson D, Sobolev V, Hilal N, Starov V. Interactions between nanoparticles in nanosuspension. Adv Colloid Interface Sci. 2019;272:102020. Doi:10.1016/j.cis.2019.102020

[18] Kirichenko MN, Chaikov LL, V SA, et al. General features of size distributions and internal structure of particles in aqueous nanosuspensions. Phys Wave Phenom. 2020;28(2):140–144. Doi:10.3103/S1541308X20020077

[19] Minakov AV, Pryazhnikov MI, Zhigarev VA, Rudyak VY, Filimonov SA. Numerical study of the mechanisms of enhanced oil recovery using Nanosuspensions. Theor Comput Fluid Dyn. 2021;35(4):477–493. Doi:10.1007/s00162-021-00569-9

[20] Han WX, Liu Y, ying SC, na ZR, long YH, Yuan H-L. Effect of particle size on in vitro and in vivo behavior of astilbin nanosuspensions. J Drug Deliv Sci Technol. 2019;52:778–783. Doi:10.1016/j.jddst.2019.05.005

[21] Xiang Y, Liang G, Alvaro P, et al. Resonant optical nonlinearity and fluorescence enhancement in electrically tuned plasmonic nanosuspensions. Adv Photonics Res. 2021;2(5):2000060. Doi:10.1002/adpr.202000060

[22] Gaur PK. Nanosuspension of flavonoid-rich fraction from Psidium guajava Linn for improved type 2-diabetes potential. J Drug Deliv Sci Technol. 2021;62:102358. Doi:10.1016/j.jddst.2021.102358

[23] Galinovskiy AL, Htet KM, Provatorov AS. Ultra-Jet as a Tool for Dispersing Nanosuspensions. Polym Sci Ser D. 2020;13(2):209–213. Doi:10.1134/S1995421220020070

[24] Dos Santos AM, Meneguin AB, Fonseca-Santos B, et al. The role of stabilizers and mechanical processes on physico-chemical and Anti-inflammatory properties of methotrexate nanosuspensions. J Drug Deliv Sci Technol. 2020;57:101638. Doi:10.1016/j.jddst.2020.101638

[25] Ali AMA, Warsi MH, Abourehab MAS, Ali AA. Preparation and transformation of solid glass solutions of clotrimazole to nanosuspensions With improved physicochemical and antifungal properties. J Pharm Innov. 2022;17(4):1420–1433. Doi:10.1007/s12247-021-09595-w

[26] Tian Y, Wang S, Yu Y, et al. Review of nanosuspension formulation and process analysis in wet media milling using microhydrodynamic modelAnd emerging characterization methods. Int J Pharm. 2022;623:121862. Doi:10.1016/j.ijpharm.2022.121862

[27] Pandey NK, Singh SK, Gulati M, et al. Overcoming the dissolution rate, gastrointestinal permeability and oral bioavailability of glimepiride and Simvastatin co-delivered in the form of nanosuspension and solid self-nanoemulsifying drug delivery system: a comparative study. J Drug Deliv Sci Technol. 2020; 60: 102083.Doi:10.1016/j.jddst.2020.102083

[28] Guner G, Yilmaz D, Bilgili E. Kinetic and microhydrodynamic modeling of fenofibrate nanosuspension production in a wet stirred media mill. Pharmaceutics. 2021; 13(7): 1055. Doi:10.3390/pharmaceutics13071055

[29] Kathpalia H, Juvekar S, Shidhaye S. Design and in vitro evaluation of atovaquone nanosuspension prepared by pH based and anti-solvent based Precipitation method. Colloid Interface Sci Commun. 2019; 29:26–32. Doi:10.1016/j.colcom.2019.01.002

[30] Flach F, Breitung-Faes S, Kwade A. Model based process optimization of nanosuspension preparation via wet stirred media milling. Powder Technol. 2018;331:146–154. Doi:10.1016/j.powtec.