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Dissocube: The Homogenization Technology to Improve Solubility of Poor Water Soluble Oral Drug Administration

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Tushar Verma*[1], Kavita Maseeh[2], Ashwanee Kumar Sahu[3]

[1]M. Pharmacy, Department of pharmaceutics, Lakshmi Narain Collage of Pharmacy Bhopal (M.P) India.

[2]M. Pharmacy, Department of pharmaceutics, Lakshmi Narain Collage of Pharmacy Bhopal (M.P) India.

[3]M. Pharmacy, Department of Pharmacology, Shri Rawatpura Sarkar Institute of Pharmacy Kumhari Durg (C.G) India.

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ABSTRACT

In list chrono-nanotechnology development a various problem carried out, one of the problem solubility of drug, poor water-soluble drug shows clinically low therapeutic plasma concentration the drug particle size one of reason them, innovation pharmaceutical formulation challenging for development process especially oral drug administration system, its require improvement of solubility of drug and homogenization technique play a major role to enhance solubility. The conventional oral drug delivery lag time is tool duration that why drug dose requires is high. The lag time helps to maintained drug adjustable release pattern and decreasing dosing frequency. Dissocube is a technology for homogenization, preparation for the new form of particle size it's having a high pressure for prepared new insert texture cavitation (Formation of any space within solid) of desired particle size it forms of Nanosuspension. It is consists of the capability of the short duration lag time. The dissolution of the drug also effected therapeutic and there treatment homogenization based Dissocube technology is Enhanceoral drug bioavailability. The main study criteria it is more explore Disssocube technology using aqueous media for better inert texture cavitation solubility of oral administration drug.

INTRODUCTION

The new innovation in pharmaceutical formulation significant complication is drug solubility carried out a hardly soluble drug is more critical achieving the bioavailability of drug and also absorption depended up on drug particle size in specific site absorption. The oral drug administration is the most common and preferable reason achieving the most concentration and is quite successful but with critical particle size is challenging for achieved bioavailability, its effected by long-duration lag time with high dose frequency. They show drug release pattern or absorption pattern after oral drug administration and also show drug bioavailability with sustained release of the drug.[1] In current creative pharmaceutical formulation technology having a homogenization process with high-pressure homogenization for the achieving therapeutic response, it carriedhomogenecity throughout a product by particle size modification is form of nanosuspension. The nanosuspension production explores by Dissocube instrument with homogenization process there operating parameter which affect the efficiency of high-pressure homogenization pressure, temperature, valve, and number of pass[2]. The nanosuspension drug increases the saturation solubility and increases the dissolution velocity of the compound. The ideal particle size defines by the National Technology Initiative (NNI) is 1-1000 nm its leads to Area under the curve (AUC) and bioavailability. Drug encapsulated in nano-suspension having undesired molecule improve the dissolution and good absorption[3], Innovative nanosuspension better contact to intestinal cell grate concentration gradient between blood and gastrointestinal.[4]

Effect of Drug Solubility on Oral Administration[5]

The following parameters are affecting solubility for oral administration:

- ✓ Challenging for micrometer particle size and distribution
- ✓ Low dissolution
- ✓ Undesired absorption, site-specific absorption
- ✓ The low therapeutic effect, Minimum C_{max}
- ✓ Affected pharmacokinetic of drug

Solubility

Solubility defined as using solute and solvent which under the process of dissolution of the solid particle in a liquid system. It is a rate-limiting parameter for oral drug delivery to achieving desired concentration in systemic circulation for pharmacological action.[6]Above the 40% NCES (New chemical entities) developed in the pharmaceutical industry are practically insoluble in water; poor water-soluble drug show low absorption and effected to bioavailability. According to IUPAC system solubility is an analytical composition of a saturated solution. It definedas designated solute proportional to designated solvent. Solubility explain state of unit of concentration, molality, mole fraction, mole ratioSolubility also expressed as solute in gm per kg of solvent and solute per gm in 100ml of solvent.[7]

As per USP and BP solubility criteria is given as:

Table No. 1: Descriptive term of Solubility

Descriptive Term	Part of Solvent Require Per Unit of Solvent
Very soluble	Less than1
Free soluble	1-10
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	10,000 above

Drug dosing system also depended on solubility, the dug particle size has low absorption in plasma concentration it does not give "t" half therapeutic and to maintain its drug dose frequency is high. The technique involves enhance the solubility are pH adjustment, use co-solvent, particle size reduction, Complexation, Micellar Solubilization, etc. is given below.

Solubility Enhancement Technique

✓ **pH Adjustment:** In this technique using small quantities of material for simple and rapid to formulate.

✓ **Use Co-solvents:** Co-solvent help to enhance the performance of surfactant and decrease interfacial tension between the aqueous and organic phase.

✓ **Particle Size Reduction:** This technique reducing the particle size and maintain the stability and increase bioavailability.

Homogenization

Homogenization technique using two miscible liquid or used uniformity dispersing solid particle and get the emulsion/ suspension like structure and following parameter achieves it product stability, self -life, viscosity, size, shape, uniformity consistency.

Homogenization upgrade with exclusive construction is valve, impact ring, pressure, and flow rate.

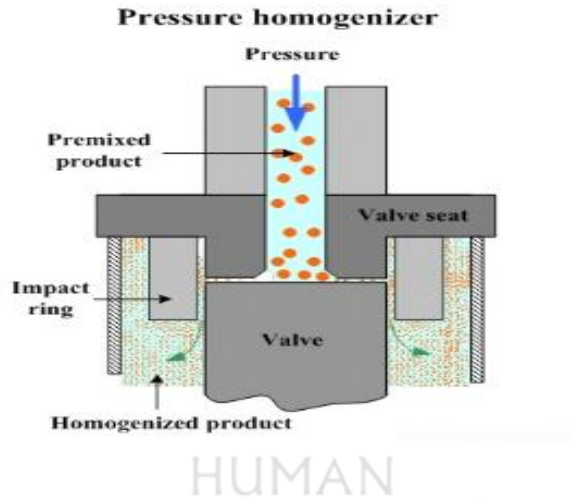

Figure No. 1: Homogenization Technique

Homogenization working criteria are that unhomogenized product inert in a feeding area with the high pressure at 20-4000 bar most commonly used. High pressure builds energy that is relaxed after the dispersion unit and energy can be expressed as the energy density (E^v) that describes the average energy input per emulsion/suspension volume. Homogenization consists of a high pressure plunger pump with a relief valve (Homogenization valve) the plunger pump provides the energy level relief valve consist of two type valve fix and adjustable valve. The liquid flow between valve and seat at high velocity at 3000psi (152.4 m per second) the liquid then impinges on the wearing (impact ring) and is finally discharge as homogenization product.[8]

Types of Homogenization Valve

Homogenization valve is having following types:

Standard flat valve (SV), XFD style, SEO valve

Homogenization valve available in different sizes with the specific manner and they use for homogenization process in the type of condition and preparation, the flow rate would determine which size appropriate.

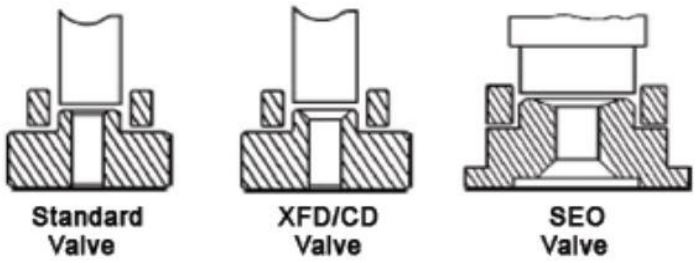

Figure No. 2: Homogenization Valve

In a different chemical application standard flat valve used it is made up of from nonferrous alloy, tungsten carbide or ceramic would be provided for highly abrasive application. When fluid is passed on the standard flat valve it is travel between valve and seat (short land) then getting homogenization product.

XFD style valve also consist of a short land seat and their advantages are that when as the fluid in this valve with the low pressure, the product will be achieved normal self-stability. This type of valve require a second stage valve or back pressure device. XFD type of the valve is available stellite and tungsten.

For the high-pressure homogenization, SEO valve are require (1000psi / 690 bar) for critical emulsion small and uniform type particle size achieved.

Principle

The Homogenization principle is explored the uniformity desired particle size given cavitation texture. Under the processing, the viscous fluid passed in the narrow cylinder with high pressure at that point of valve dynamic presser of fluid is increase and static pressure decreases and getting cavitation. The high internal force is sufficient for the break down the microparticles into nanoparticle, High viscosity of fluid also advantages certain cases enhance the power density with the dispersion zone.[9]

Stages of Homogenization

Table No. 2: Homogenization Stages

Single Stages of Homogenization	Second Stages of Homogenization
✓ Applied front pressure ✓ Applied pressure high at 2500psi ✓ Mean size 0.5µm ✓ Particle size range 0.2-2µm	✓ Applied backpressure suppresses ✓ Applied low pressure at 500psi ✓ Particle size range is critical above 0.2-1.0 µm

Merits:

✓ Homogenization technique provides new inert texture nanosuspension in aseptic production scale.

✓ Easy to production and minimum risk factor

✓ Useful for dilute as high concentration nanosuspension

✓ Poor soluble drug treats both aqueous and organic media

Demerits:

✓ Prerequisite of suspension formation using high-speed mixture before subjecting it homogenization

Uses:

✓ Use for dispersion such as benzoyl peroxide in liquid bases.

✓ Homogenization at high pressure is required for perfluorocarbon

✓ For antacid dispersion

✓ Preparation of vitamin suspension

Dissocube

Dissocube is one type of instrument based on homogenization principle it is introduce by R.H. Muller used as piston gap type high-pressure homogenization in 1999. He patient was taken by DDs Gmbh hater and a patent was transferred to skype pharmaceutical.[10]

Dissocube high-pressure homogenization technique based studies are APV Micron Lab 40 capacity 40 liters to 1000 liter, all parameters taken by APV Spax brand guidelines.

Dissocube Illustration

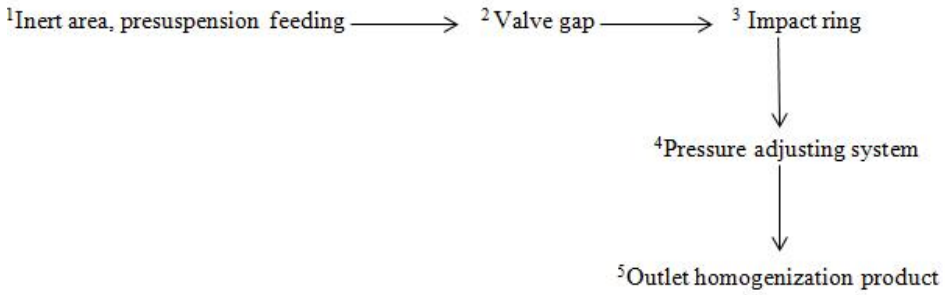

Figure No. 3: Dissocube Illustration

Inert Area:

It is a part of some type of cylinder different capacity they help to force to presuspension in the valve area.

Valve Gap:

The instrument has consisted of fix and adjustable valve they help to reduce the particle size micrometer to the nanometer. They part from an adjustable radical precision gap, the gap conditions the resistance and thus the homogenization pressure varies as a function of the force acting on the valve.

Impact Ring:

It is an external part of the instrument they defined the outline cross-section and prevent the valve casing from being damaged due to the flow.

Pressure Adjusting System:

The instrument can be operated as pressure 100-1500bar some instrument maximum pressure of 2000bar can be reached.

Outlet Homogenization Product:

The outlet section gave the product cavitation from the consisting of the small nanoparticle size with a new inert texture.

Dissocube Elucidation

Dissocube describes homogenization in pure water as a dispersion medium for the cavitation this is fulfilled of water but not with another lipids-like oil and lipid polyethylene glycol (PEG 600). The instrument use of different parameter and various chemical condition they define the continuous and discontinuous version. A continuous version is used most preferably and commonly used in different situations. A discontinuous version is used for the sensible condition if the drug is expensive or limited available. The instrument also uses the different capabilities for the specific types of preparation it's ranging from 40 liters (Laboratory work) 1000liter (Large scale production for micronized drug particle size < 25µm) for production of nanosuspension to prevent blocking of homogenization gap. The final product achieved used the presuspension before they introduction drug to the homogenization process is essential. It is important for achieved micronized drug in surfactant solution.[11]

Presuspension Method of Preparation[5,10]

A presuspension formation using the bottom-up technology[5]

Bottom-up technique is a primary and classical process for presuspension it defines the starting from molecule level and molecular create to a solid particle. In case of the formulation of solid particle pouring the solvent into a non -solvent or charging the temp for reducing the solvent qualities.

Procedure:

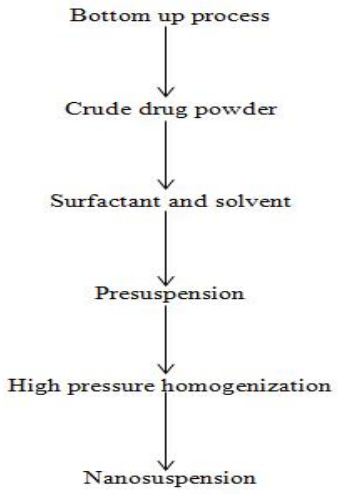

Figure No. 4: Bottom-up Technique

The bottom-up process is consists method which also nanoparticle from a molecule.

- ✓ Supercritical fluid process
- ✓ Emulsification solvent evaporation technique
- ✓ Solvent anti-solvent method
- ✓ Lipid emulsion template

Dissocube Processing[10]

Firstly the drug suspension introduces in an inert cylinder of diameter 3 mm passes then suddenly through a very narrow homogenization gap of 25µm with the high streaming velocity. Water starts boiling at room temperature to the formulation of gas bubbled which improves when the suspension leaves the gap it called cavitation and normal air pressure reach again. In the process create short duration force are sufficient breakdown the drug microparticle to nanoparticle velocity to help improve the efficiency of nanosuspension high viscosity increase density in the dispersion zone.

Principle:[10]

Instrument given homogenized cavitation from the product under the specific flow rate of the liquid with high pressure, they defined under the law of Newton's and Bernoulli equation.

Newton's Second Law

The fluid flow by force and energies involved is known as a fluid dynamic similar to the mechanism of solid, The dynamic of fluid is also governed by Newton's second law of motion. According to the law, the rate of change of momentum of a body directly proportions to the external force and it takes place in the direction of net applied force on it.

$$F=ma$$

Where: F= Net external force

m = Mass of the fluid element on which force act

a = Total acceleration

Bernoulli Equation

Bernoulli can be considered for the conservation of energy. It is the lowering of fluid pressure regions the flow velocity is increasing. In the high-velocity flow through the construction kinetic energy must increase at the pressure energy. Flow of volume a liquid in a closed system per cross-section is constant.

Energy per unit volume before = Energy per unit volume after

$$P_1 + \frac{1}{2}\rho V_1 + \rho g h_1 = P_2 + \frac{1}{2}\rho V_2 + \rho g h_2$$

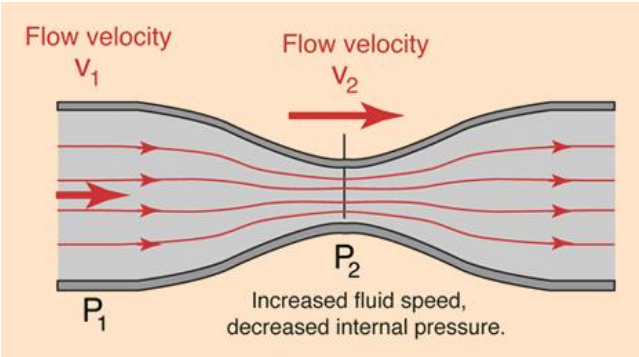

Figure No. 5: Bernoulli Flow of Liquid Velocity

Where:P_1 is pressure energy$\frac{1}{2}\rho V_1$ is a kinetic energy per unit volume,$\rho g h_1$ is potential energy per unit volume.

Dissocube Extended Parameters[2,9]

Mixing:[9]

Mixing is a process a part of the homogenization is applied to start the process. It is applied to reduce minor error during the fluid flow and the drug substance define the distributed in volume, mixing also improves product quality, chemical or biological conversions or heat and mass transfer.

Characterization of Mixing

Macromixing: Used to the largest scale of motion in a fluid it is also rated determining step.

Continuous Mixers: Used in the continuous process can be classified by their residence time, residence time behavior introduce the mixing energy.

Effect of Homogenization Pressure:

Using of homogenization pressure at the 100 to 150bar for effective particle size. In each case, pressure has changed and different conditions achieving the particle size. It is expected that the higher the high pressure the lower particle size obtained.

Number of Homogenization Cycle[2]

It is a critical phase of homogenization the single cycle of homogenization difficult to achieve the desired particle reason drug and excipients have contained own properties and each mean particle size. Typically multiple cycles are required depending on the hardness of drug the mean particle size and require homogeneity of the product. Homogenization can be carried out in the 3-5 or more cycle.

Merits:

- ✓ Universal applicable
- ✓ Fasted mechanical process

Demerits:

✓ Sometimes possible is contamination occurs from metal ion coming from the wall of the homogenizer.

Nanosuspension

Greater development of pharmaceutical one of the nanosuspension, Is a biphasic system it consists of nanosized drug particles. The particle-stabilized achieved by using surfactant and polymer for the oral administration and another route of administration. Nanosuspension also defines a very fine colloidal, biphasic dispersion pharmaceutical active ingredient in aqueous media. Nanosuspension size below 1µm without any matrix material.[12]

Nanosuspension introduces the newly developed of poorly soluble drugs in both aqueous and organic solvent. Nanosuspension preparation is simple and easy acceptance above all drug insoluble in water.[13]

Stability of nanosuspension is defined as electrostatic forces, steric forces, entropic forces, and van der Waals force among nanoparticle determine overall physical stability of a drug nanosuspension.[14]

Nanosuspension Properties:[3,4]

The magnificent nanosuspension properties are dependent on a various parameter is increasing in saturation solubility and increasing dissolution velocity, it is decreasing the particle size and increasing solubility, they both describe by Noyes Whitney equation and Kelvin Gibbs equation.

Noyes Whitney Equation:[3]

According to the Noyes Whitey equation decreasing particle size causes an increase in particle surface area resulting in drug solubility in aqueous media contributing to improving dissolution rate.

It is based on Fick's first law:

$$\frac{dM}{dt} = \frac{DA}{h}\left(C_{Bulk-}\ C_{Eq}\right)$$

Where $\frac{dM}{dt}$ is a rate of dissolution, D is average diffusion coefficient, A is the surface area of solid, C_{Bulk} is the concentration of drug in bulk solution, C_{Eq} is the concentration of drugs in the dissolution layer surround the drug, h is Diffusion layer thickness.

Kelvin Gibbs Equation[4]

The increase in saturation solubility can be explained by the Kelvin Gibbs and Ostwald Freundlich Equation. The Kelvin equation describes the vapor pressure over a curved surface of a liquid. It describes droplets in a gas phase the vapor pressure increase with increase curvature of the droplets which means decrease particle size resulting in the surface curvature of the dissolving solid particle will be influence solubility in water.

$$C(r) = C(\infty) \exp \frac{2\gamma M}{r\rho RT}$$

Where $C(r)$, $C(\infty)$ are the solubility of the particle of radius r and infinite size, $M$is a molecular weight, $\rho$is the density of the particles, $\gamma$is the inert facial tension, r is the particle radius, $r$is the gas constant, and,$T$is the temperature.

Formulation Consideration of Nanosuspension[15, 16]

Stabilizer:[15]

It helps to improve the physical stability of nanosuspension providing steric or ionic barrier given the high surface energy of nanosized particles can induce agglomeration or aggregation of drug crystal and also prevent Ostwaldripening and agglomeration of nanosuspension. The drug to stabilizer ratio in the formulation 1:20 to 20:1 and should be investigated for a specific case.

Organic Solvent: [15]

For the innovative formulation the pharmaceutical acceptable less hazardous water-miscible solvent.

Co-surfactant:[15]

It provides influence phase behavior and affects the uptake internal phase selected microemulsion composition and drug loading should be investigated.

Surfactant:[15]

Surfactant use to improve the dispersion by reducing the interfacial tension. They act as wetting or foaming agent.

Other Addatives:[15]

It is used according to the requirement of the route of administration or the properties of drug moiety. It is the selective process may be used or some cases maybe not using.

Formulation Acceptance using Excipients in Nanosuspension[16]

Table No. 3: Formulation Acceptance using Excipients in Nanosuspension

Excipients	**Example**
Stabilizer	Polysorbates, Lecithins, Provides
Organic solvent	Menthol, Chloroform, Isopropanol
Co-surfactant	Ethanol, Glycofurol, Bile salt
Surfactant	Tween 80 or Span 80
Other additives	Osmogent, Polyols, Buffer, salt

Merits:

- ✓ Water-free production possible
- ✓ Quick method
- ✓ High drug loading capacity
- ✓ Dose frequency is less
- ✓ Drug lag time is short
- ✓ No problem with large batches
- ✓ Provide passive targeting
- ✓ Increase physical and chemical stability

Difference Between Conventional and Nanosuspension Oral Drug administration[17]

Table No. 4: Difference between Conventional and Nanosuspension Oral Drug Administration

Conventional Oral Administration	Nanosuspension Oral Administration
✓ Slow on rapid action	✓ Rapid onset action
✓ The dosing frequency is high	✓ Dosing frequency low
✓ Limited amount of drug use	✓ High drug loading capacity
✓ Particle size in nanometer	✓ Particle size in micrometer

Nanosuspension Efficiency Measurement[3, 18]

Viscosity Increase and Decrease:[3]

During the preparation of nanosuspension maintain viscosity increase and decrease time to time it helps to determine friction between molecule and fluid in different concentration. It is easy to select the desired viscosity of nanosuspension.

Viscosity is the measurement by Brookfield type rotatory viscometer. The instrumentation room for sample measurement must be maintained at 37°C by using a thermo bath.

Average Particle Size:[3]

Average particle size determines by particle counting in a Coulter counter (Multisizer 3), It provides the number, volume, mass, and surface area size distribution in one measurement. Microscopically another technique to determine the particle size.

Rate of Separation:[3]

It is a quality control tool to optimize the process condition such as a method of agitation, time of screening, feed rate, etc. Itis determine by Cyclone separator and Air separator they consisting centrifugal force principle used to separate the solids from the liquid.

Physical and Chemical Appearance:[18]

✓ **Color, Taste, Odor:** This is very important for oral formulation it is also dependent on the dissolution rate.

✓ **Crystal Morphology**: Using the X-ray diffraction analysis technique with differential thermal analysis and differential scanning calorimeter for determining a change in the crystalline nature of a nanosuspension from amorphous to other polymeric from can occur due to high-pressure homogenization.

✓ **pH Value**: Prepared nanosuspension was taken in a beaker and measured by using a pH meter.

✓ **Osmolarity**: Measure by osmometer

✓ **Density**: A drop in density indicates the entrapped air present within the formulation, precision hydrometer facilitates the measurement of density.

Evaluation Process: Collect the sample from Dissocube homogenizer at different pressure settings and analysis evaluate parameter versus homogenized process.

Application:[19,20]

Schematic of the nanosuspension drug delivery system for oral administration:

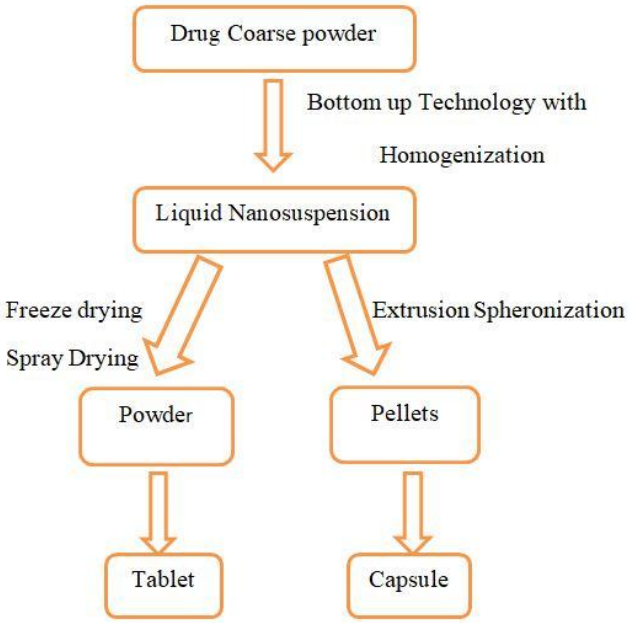

Figure No. 6: Schematic of the Nanosuspension Drug Delivery System for Oral Administration

Powder Dosage Form for Oral Administration

Powder represents one of the oldest dosage forms, powder consists a several advantages the dry powder had high dissolution rate and easy to be wetted and redispersed to nanosuspension, the in vivo pharmacokinetic study showed that the redispersed nanosuspension have good oral bioavailability. The Scutellarin (S.G) drug is a poorly insoluble drug for the treatment of cerebrovascular diseases prepared a liquid nanosuspension of aglycone scutellarin as a precursor and then transformed in to dry powder using freeze-drying.

Pellet Dosage Form for Oral Administration

Pellets are multiparticulate dosage form which formed by the agglomeration of fine powder excipient and drugs together, the formation of small free-flowing spherical or semispherical particles. It's giving less sensitivity effect of stomach emptying minimal gastrointestinal tract irritation. It is directly converted liquid nanosuspension from to pellet dosage for oral administration using fluid bed coating technology, prepare liquid indomethacin nano-suspension by precipitation ultrasonication method.

Tablet Dosage Form Oral Administration

Clinically it has been proved the oral tablet dosage form is easily administered and more consisting of concentration of the drug, it is several advantages to deliver an accurate drug dosage and uniform content to a specific site. After a solidification process of liquid nanosuspension, the resultant drug nanoparticle powder can be mixed with excipients and then be converted in to tablet dosage form using press machine, tablet prepares using gelatin or croscarmellose as excipients showed a higher dissolution rate, Also particle size reduction and protective agent for solidification also play important role in the properties of poorly soluble drugs loaded tablets.

Capsule Dosage Form for Oral Administration

The capsule dosage form in which the drug substance is enclosed in a water-soluble shell. A shell is made from gelatin and its available both as hard capsule and soft capsule, it also provides the sustained release with containing high concentration drug, Drug is filled in the hollow hard capsule or sealed in an elastic soft capsule it has several advantages include

odorless and good stability, Drug nanoparticle loaded capsule dosage can be prepared by filling dry drug nanoparticle powder into a capsule. A nanosuspension using a wet-milling method and then converted in to powder using a fluid bed spray granulation method.

Types of Drug Enhanced the Dissolution Rate and Bioavailability with Nanosuspension

Table No. 5: Types of Drug Enhance the Dissolution Rate and Bioavailability with Nanosuspension

Active Drugs	Treatment Description	Enhanced Dissolution rate/Enhanced Effectivity
Oleanolic acid	It's much application such as Lepatoprotective antitumor, antibacterial, anti-inflammatory.	Applying oleanolic acid nanosuspension dissolution rate about 90% in the first 20min.
Atovaquone and Bupravaquone	For treatment Leishmanial	Atovaquone in the form of micronized particle and nanosuspension show that the letter decrease infectivity from 40% to 15%, nanosuspension reduce infection from 2.0 to1.02 and micronized particle only1.47
Danazol	Gonadotropin inhibitor	Increase bioavailability, Danazol nanosuspension lead to bioavailability 82.3% whereas the marketed Danazol suspension was 5.2% bioavailability
Amphotericin B	Highly effective polyene antibiotic used for systemic mycoses and Leishmaniosis.	Amphotericin B nanosuspension produces a substantial improvement in its oral absorption to orally administration conventional formulation.

CONCLUSION

The Dissocube is an advanced technology for treating poorly water-soluble, they provide the unique particle size for enhanced drug dissolution rate and bioavailability, Nanosuspension the work has been successful to evaluate Dissocube efficacy and properties of nanosuspension to enhanced bioavailability of an oral drug. Oral drug administration show more frequency other route administration (Ex. Drug elimination time is increase and elimination amount decreases) for critical treatment of diseases with sustained release of a drug. The advance work nanosuspension formulation with help of homogenization in laboratory-scale which has show potency of clinical significant.

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REFERENCES

1. Savjani Ketan T, Gajjar Anuradha K, Savjani Jignasa K. Review on Drug solubility Important and Enhancement Techniques, *International Scholarly Research Network*, 2012; 01; 1-10.
2. Dhnakar Poonam, Homogenization Fundamental, *Journal of Engineering* 2014; 04; 1-8.
3. Alwhat Priyanka, Diwan Anupama, Singh Robin, Review on Nanosuspension Recent Trends And technology, *International Research Journal of Pharmacy* 2014; 5-11.
4. Yadollahi Roya, Vasilev Kasimir, Simovic Spomenka, Review on Nanosuspension Technologies for Delivery of Soluble Drugs, *Hindawi Publishing Corporation Journal of Nanomaterials,* 2015; 1-13.
5. Patel Mitesh, Shah Arpit, Patel N.M, Patel M.R, Patel K.R, Review on Nanosuspension A Novel Approach on Drug Delivery System, *Journal of pharmaceutics science and Bio scientific Research*, 1; 2011;1-10.
6. Almidia Pereira de, Birto P, Sausa.A, Portugal A, Figueiredo M, Modelling dissolution of sparingly soluble powders, Research Gate; 1997; 243-246.
7. Nayak Shankar Bhabani, Mohanty Biswaranjan, Roy HareKrishna, Patnaik Arvind, Nanosuspension Bioavailability Enhancing Novel Approach, *International Journal of Pharmacy and Biological Sciences;* 08; 2018; 540-554.
8. Ah Pis Yong, Md Aminul Islam, Nurul Hasan, Research on Effect of Pressure on Homogenization, *Sigma Journal of Engineering and Natural Sciences Sigma Mühendislik ve Fen Bilimleri Dergisi*, 01;2017;1-22.
9. Gall Vanessa, Runde Marc, P. Schuchmann Heike, Extending Applications of High-Pressure Homogenization by Using Simultaneous Emulsification and Mixing (SEM)—An Overview, *Multidisciplinary Digital Publishing Institute*, 2016; 1-15.
10. Vedanga S. B., Gondkar S.B., Saudagar R.B., Nanosuspension: An emerging trend to improve solubility of poorly water soluble drugs, *Journal of Drug Delivery and Therapeutics*,2019; 9(3):549-553.
11. Patravale V. B., Date Abhijit A., Kulkarni R. M., Nanosuspensions: a promising drug delivery strategy, *Journal of Pharmacy and Pharmacology*,2004, 56: 827–840.
12. Garasiya Sneha B, Nanosuspension: An Attempt to Enhance Bioavailability of Poorly Soluble Drugs, *International Journal of Advance in Pharmacy, Biology, and Chemistry*, 2012; 01; 91-99.
13. Afifi Samar A, Hassan Maha A, Abdelhameed Ali S, Elkhodairy Kadri A, Nanosuspension: An Emerging Trend for BioavailabilityEnhancement of Etodolac, *International Journal of Polymer Science*,2015; 1-16.
14. Bhowmik Debjit, Harish G, Duraive S, Pragathi Kumar B, Raghuvanshi Vinod, Kumar Sampath K. P.Nanosuspension -A Novel Approaches In Drug Delivery System, *The Pharma Innovation Journal*,2013; 01; 50-63.
15. Kayser O., "Nanosuspension for the formulation of aphidicolin to improve drug Targeting effect against leishmania infected Macrophage", *International journal of pharmacy*, 2000, 196, 253-56.
16. Mayuri Y, Sgashikanth Dhole, Prajkta Chavan," Nanosuspension: A Novel Techniques in Drug Delivery system", *World journal of pharmacy and pharmaceutical science*, 2014, vol 3,410-33.
17. Sutradhar Bishwajit Kumar, Khatun Sabera, Luna Parven Irin, Increasing Possibilities of Nanosuspension, *Hindawi Publishing Corporation Journal of Nanotechnology*.2013;1-12.
18. Bhakay Anagha, Rahman Mahbubur, Dave Rajesh N., Bilgili Ecevit, Review Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites: Formulation–Processing Aspects and Challenges, *Multidisciplinary Digital Publishing Institute*,2018; 3-62.
19. Patil Hasmukhlal Payal, Belgamwar Sailendra Veena, Patil Ramratan Pratibha, Surana Sanjay, Enhancement of solubility and dissolution rate of poorly water-soluble raloxifene using microwave-induced fusion method, *Brazilian Journal of Pharmaceutical Sciences*2013; 04; 571-578.

20. Chen Ang, Shi Ye, Yan Zhiqiang, Hao Hongxun, Zhang Yong, Zhong Jian, Hou Huiming, Dosage Form Developments of Nanosuspension Drug Delivery System for Oral Administration Route, *Current Pharmaceutical Design*,2015;1-11.