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NANO SUSPENSION: A NOVEL APPROCH FOR DRUG DELIVERY SYSTEM

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ABSTRACT

The poor water solubility of drugs is major problem for drug formulation. To date, nanoscale systems for drug delivery have gained much interest as a way to improve the solubility problems. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. Nanosuspensions are promising candidates that can be used for enhancing the dissolution of poorly water soluble drugs. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Production of drugs as nanosuspensions has been developed for drug delivery systems as an oral formulation and non-oral administration. This review describes the methods of nanosuspension production, formulation, evaluation and applications in pharmaceutical drug delivery as well as the marketed products.

Keywords: Poor water soluble drugs, Bioavailability, Drug delivery, Nanosuspension

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INTRODUCTION

Nanotechnology is likely to revolutionize our lives, in general, and health scenario,in particular. It is emerging descipline that emcompasses an increasingly sophisticated ability to manipulate matter at the nanoscale (0.1 nm to 1000 nm) resulting in new material, product and device that demonstrate new and unusual behaviour. It is one of the most important research and development area in modern science. Apart from this nanomaterial, nanoparticle, and nanocomposite used for the biomedical purpose constitute a burgeoning new field called nanomedicine, which implies the medical application of nanotechnology and related research leading to the designing, testing and optimizing of the pharmaceutical formulations. Nanotechnology is an applicable aspect of a broader area of nano science which is one of the upcoming and highly challenging as well as

rewarding key research area in the modern scientific set up. It is the science of small particle having unique properties, which change on altering the size of the particle[1].

More than 40 % of the drugs coming from high-throughoutput screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and erratic absorption. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability include micronization, solublization using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions, salt formation and precipitation techniques. These techniques for solubility enhancement have some limitations and hence have limited utility in solubility enhancement. Hence there is need of some different and simple approach to tackle the formulation problems to improve their efficacy and to optimize the therapy with respect to pharmacoeconomics. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like bottom up technology (precipitation) and top down technology or disintegration methods[2].

A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size (i.e increase in the surface area) leading to an increased dissolution rate and therefore improved bioavailability. Nano sized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient result to a much more pronounced increase in the dissolution velocity as compared to a micronized product. The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Ostwald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles[3].

PREPARATION OF NANOSUSPENSIONS

Bottom Up Technology

The conventional methods of precipitation (Hydrosols) are called Bottom Up technology. Using a precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible antisolvent. In the water-solvent mixture the solubility is low and the drug precipitates. Precipitation has also been coupled with high shear processing. The Nanoedge process (is a registered trademark of Baxter International Inc. and its subsidiaries) relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy[3]. This is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid addition of a drug solution to an antisolvent leads to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favoured at high supersaturation when the solubility of the amorphous state is exceeded.

Top Down Technology

High pressure homogenization: High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs[4]. In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required. Dissocubes

technology is an example of this technology developed by R.H. Müller using a piston-gap-type high pressure homogenizer, which was recently released as a patent owned by SkyePharm[5]. Other technologies and patents which are based on the homogenization processes are shown in Table 1 [6].

Table 1: Overview of the technologies and patents/patent applications on which the various homogenization processes are based

Nanocrystal	Company	Patent/patent application examples
Hydrosol	Novatis (Prev. Sandoz)	GB 22 69 536 GB 22 00 048
Nanomorph™	Soligs/Abbott	D 1963 7517
Nanocrystal™	Élan Nanosystems	US 5,145,684
Dissocubes®	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
NANOEDGE™	Baxter	US 6,884,436

Lipid emulsion/microemulsion template: Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants. Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension[5]. An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate[7].

Media milling: Nanocrystal is a patent protected technology developed by Liversidge et al. In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The major concern with this method is the residues of milling media remaining in the finished product could be problematic for administration[5,8,9].

Dry co-grinding: 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 co-polymers after dispersing in a liquid media has been reported. Itoh et al reported the colloidal particles formation of many poorly water soluble drugs; griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS). Many soluble polymers and co-polymers 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 co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug[10].

Here below the summary of the nanosuspension formation technologies and compounds produced in nanosuspension given in Table 2.

Table 2: Summary of nanosuspension formation technologies and compounds produced in nanosuspension.[1]

Technology	Advantage	Disadvantage	Drug
Precipitation	-Simple process -Low cost equipment -Ease of scale up	-Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent. -Growing of drug crystals needs to be limit by surfactant addition	Carbamazepine Cyclosporine Griseofulvin Retinoic acid
High pressure Homogeniza-tion	-General applicability to most drugs -Useful for formation of very dilute as well as highly concen-trate nanosuspension -Simple technique -Aseptic production possible -Low risk of product contamination	-High number of homogenization cycles -Prerequisite for drug to be in micronized state and suspension formation before homogenization -Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer	Albendazole Amphotericin B Aphidicolin Atovaquone Azithromycin Budesonide Bupravaquone Clofazamine Fenofibrate Glucocorticoid drugs
Emulsion/ Microemulsion template	-High drug solubilization -Long shelf life -Ease of manufacture	-Use of hazardous solvent -Use of high amount of surfactant and stabilizers	Breviscapine Griseofulvin Ibuprofen Mitotane
Media milling	-Ease of scale up -Little batch to batch variation -High flexibility in handling large quantities of drugs	-Generation of residue of milling media -Require milling process for hours to days -Prolonged milling may induce the formation of amorphous lead to instability	Cilostazol Danazol Naproxen
Dry Co-grinding	-Easy process -No organic solvent -Require short grinding time	-Generation of residue of milling media	Clarithromycin Glibenclamide Glisentide Griseofulvin Naproxen Nifedipine Phenytoin Pranlukast

PROPERTIES OF NANOSUSPENSIONS

Physical Long-term Stability: Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles because of that Ostwald ripening is totally bsent in nanosuspension which is also responsible for long-term physical stability of nanosuspensions[11-13].

Increase in Saturation Solubility and Dissolution Velocity of drug: Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation (Equation no.1) dissolution velocity increase due to increase in the surface area from micron size to particles of nanometer size.

$$Dx/dt = [(D \times A)/ h] [Cs-X/V] \text{ -----(1)}$$

Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

Internal Structure of Nanosuspensions: The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to

high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenisation cycles chemical nature of drug and power density applied by homogeniser.[11-13]

FORMULATIONS OF DRUG NANOSUSPENSIONS

Aqueous or non-aqueous drug nanosuspensions exhibiting a physical long-term stability should be sufficient to place them on the market as liquid products. In general, a dry oral dosage form as tablet or capsule is preferred. In the case of drug nanosuspensions in pure water or in water containing mixtures, they can be used as granulation fluid in the granulation process for the production of tablets or alternatively as wetting agents for the extrusion mass to produce pellets. Spray-drying of the nanosuspension is also possible. The produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules. The drug nanocrystals produced in non-aqueous media such as oils or liquid/solid PEG can be used directly for filling in capsules. Production of drug nanosuspensions in melted PEG which is solid at room temperature opens further perspectives. Direct filling of capsules with the hot nanosuspension is possible. Alternatively after solidification of the PEG, the drug nanocrystal containing mass can be ground and filled as a powder into the capsules[14]. To summarize, there are different ways to transfer the drug nanocrystals to a final dry oral dosage form for the patient. With regard to parenteral products, the drug nanosuspensions can be used as they are; a shelf life of up to three years was shown for selected nanosuspensions. Alternatively, lyophilized products can be offered to be reconstituted prior to administration. The current marketed pharmaceutical products and new drug application utilizing nanosuspensions is presented in Table 3 and Table 4 respectively [15,16].

Table 3: Current Marketed Pharmaceutical Products Utilizing Nanocrystalline Formulation.

Product	Drug Compound	Indication	Company	Nanoparticle technology
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Elan Drug DeliveryNa-nocrystals
EMEND®	Aprepitant	Antiemetic	Merck	Elan Drug Delivery Nanocrystals®
TriCor®	Fenofibrate	Hypocholesteremic	Abbott	Elan Drug Delivery Nanocrystals®
MEGACE® ES	Megestrol Acetate	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals®
Triglide™	Fenofibrate	Hypocholesteremic	First Horizon Pharmaceutical	SkyePharma IDD®-P technology

Table 4: The New Drug Application Based on Nanosuspensions Technique Reported and Marketed by Now

Drugs	Indication	Author or Company	Route	Status
Paclitaxel	Anticancer	American Bioscience	Intravenous	Marketed
Danazol	Hormone	Rogers T.L.	Oral	Reported
Naproxen	Anti-inflammatory	Anchalee Ain-Ai	Oral/parenteral	Reported
Probucol	Lipid lowering	Jyutaro Shudo	Oral	Reported
Rapamune	Immunosuppressant	Elan Nanosystems	Oral	Marketed
Emend	Anti-emetic	Elan Nanosystems	Oral	Marketed
Cytokine inhibitor	Crohn's disease	Elan Nanosystems	Oral	Phase II
Fenofibrate	Lipid lowering	SkyePharma	Oral	Marketed
Megestrol acetate	Steroid hormone	Par Pharmaceuticals	Oral	Marketed
Paliperidone pal-mitate	Anti-schizophrenia	Johnson and Johnson	Oral	Phase III
Loviride	Antivirotic	B. Van Eerdenbrugh	Intravenous	Reported
Busulfan	Anticancer	SkyePharma	Intrathecal	Undisclosed
Budesonide	Asthma	Jerry Z. Yang	Pulmonary	Reported
Fluticasone	Asthma	Jerry Z. Yang	Pulmonary	Reported
Insulin	Diabetes	BioSante	Oral	Undisclosed
Clofazimine	Antimycobacterials	K. Peters	Intravenous	Reported
Buparvaquone	Antibiotic	Müller R. H.	Oral	Reported
Oridonin	Anticancer	Lei Gao	Intravenous	Reported
AZ68	Anticancer	Kalle S.	Oral/I.V.	Reported
Ascorbyl palmitate	Ascorbyl palmitate	Veerawat T.	Intravenous	Reported
Hydrocortisone	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Prednisolone	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Hexadecadrol	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Aphidicolin	Antileishmanial	O. Kayser	Oral	Reported
Dihydroartemisinin	Antimalarial	Jiraporn C.	Intravenous	Reported
Cilostazol	Antiplatelet agent	Jun-ichi Jinno	Oral	Reported
Carbamazepine	Psychotolytic	D. Douroumis	Oral	Reported
Omeprazol	Proton pump inhibitor	Jan Möschwitzer	Intravenous	Reported
Thymectacin	Anticancer	Elan Nanosystems	Intravenous	Undisclosed
Silver	Eczema	NUCRYST	Topical	Phase III
Mitotane	Adrenal Cortex Hormones	Michele Trotta	Oral	Reported
Griseofulvin	Antifungal	Boris Y. Shekunov	Oral	Reported
Tarazepide	Selective CCKa-antagonist	C. Jacobs	Oral	Reported
Albendazole	Anthelmintic drug	Mittapalli P. K.	Oral	Reported
Azithromycin	Antimicrobial	Dianrui Zhang	Oral	Reported
Ketoprofen	Analgesic	Remon J.P.	Oral	Reported

POST-PRODUCTION PROCESSING

Solidification Techniques: The nanosuspensions usually have the stability issues involved in the physical (e.g. Ostwald ripening and agglomeration) and chemical (e.g. hydrolysis) processes. In this case, solid dosage forms are considered more attractive, due to their patient convenience (marketing aspects) and good stability. Therefore, transformation of nanosuspensions into the solid dosage form is desirable. Solidification methods of the nanosuspensions include some unit-operations such as pelletization, granulation, spray drying or lyophilization [17]. As the primary objective of the nanoparticulate system is rapid dissolution, disintegration of the solid form and redispersion of the individual nanoparticles should be rather rapid, so that it does not impose a barrier on the integrated dissolution process. Drying of nanoparticles can create stress on the particles that can cause aggregation. For example, drying may lead to crystallization of the polymers such as poloxamers, thereby compromising their ability to prevent aggregation. Drying can also create additional thermal stresses that may destabilize the particles. Due to the above considerations, adding matrix-formers to the suspension prior to solidification is necessary. Van Eerdenbrugh *et al.* had successfully used microcrystalline cellulose to displace sucrose as a matrix former during freeze-drying of itraconazole nanosuspensions[18] and had again evaluated four alternative matrix formers [Avicel®PH101, Fujicalin® (CaHPO4), Aerosil®200 SiO2) and Inutec®SP1] for their capability in preserving rapid dissolution after spray-drying of nanosuspensions[19]. In addition, the effect of surface hydrophobicity on drug dissolution behaviour upon redispersion had been investigated, indicating the more intense hydrophobicity, the more aggregation of the nanoparticles and the slower the drug's dissolution after solidification[20].

Surface Modification Techniques: Nanosuspensions have the particular characteristics to increase the saturation solubility and dissolution rate for the poorly soluble drugs. But in some cases, the rapid or burst release of nanosuspensions may result in the side effect and toxicity. As a colloid nanoparticle system, nanosuspensions usually can target the monocyte phagocytic system (MPS), which can aid in the treatment of lymphatic-mediated diseases [21], like *Mycobacterium tuberculosis, Listeria monogyna, Leishmania* sp. The action is called as 'passive targeting'. However, the passive targeting process could pose an obstacle when either macrophages are not the desired targets or accumulated drug is toxic to MPS cells. Hence, in order to bypass the phagocytic [22,23] uptake of the drug, its surface properties need to be tuned, just like stealth liposomes and nanoparticles [24,25]. Faced with the above problems, the surface modification of nanosuspensions will be very necessary. In the case of burst release and passive targeting, the controlled release and long residence at site of action may be effective. For example, Tan *et al*. had prepared layer-by-layer self-assembly coated procaine hydrochloride.

EVALUATION OF NANOSUSPENSIONS

In vitro Evaluations

Mean particle size and size distribution: The mean particle size and the width of particle size distribution (called Polydidpersity Index) are determined by Photon Correlation Spectroscopy (PCS)[26]. Particle size and polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3nm-3µm only. PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability. PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD). LD measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force microscopy[27] is used for visualization of particle shape.

Particle charge (Zeta Potential): Particle charge determines the stability of nanosuspension. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ± 20mV[28].

Crystalline state and particle morphology: Differential Scanning colorimeter[29] (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction[30] (XRD) is also used for determining change in physical state and extent of amorphous drug.

Saturation solubility and dissolution velocity: The nanosuspension increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility[28].

pH: Prepared nanosuspension was taken in 10ml beaker and pH was measured using pH meter (Digital Instrument Corporation, India).

Osmolarity: Practically Osmolarity was measured using Osmometer[28].

Drug content: Drug content of nanosuspension formulation was carried out by taking lyophilized powder (weigh equivalent to 5mg of drug) in Methanol:THF (1:1) mixture, shaken well, Mannitol is slightly soluble in Methanol:THF (1:1) mixture so it was then centrifuged at 8000rpm for 10min. The supernatants were taken and diluted with Methanol:THF (1:1) mixture and the absorbance was measured at 210nm. The drug content was calculated using the calibration curve[31].

Stability Study: Stability of optimized nanosuspension formulation was evaluated by determining change in particle size during storage at 2-8°C. Any change in particle size of nanosuspension formulation was observed using Malvern Master sizer 2000 at periodic time intervals[32].

Evaluation for surface-modified Nanosuspensions-can be done by Surface hydrophilicity, Adhesion properties and Interaction with body proteins[28].

PHARMACEUTICAL APPLICATIONS OF NANOSUSPENSIONS IN DRUG DELIVERY

Parenteral Administration: Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 µm to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumour burden[33]. Similarly, Aphidicolin, a poorly water soluble new anti-parasitic lead molecule, when administered as a nanosuspension resulted in an improvement in EC_{50} in comparison to DMSO-dissolved drug[34].

Ophthalmic Drug Delivery: Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids as it governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. One example of a nanosuspension intended for ophathamic controlled delivery was developed as a polymeric nanosuspension of Ibuprofen[35]. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the duration of drug action [36].

Pulmonary Drug Delivery: Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Basically the nanosuspensions can be used in all nebulizers. The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery[37].

Target Drug Delivery: Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing the stabilizer. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of *Cryptosporidium parvum*, the organism responsible for cryptosporidiosis was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone[38].

Topical Formulations: Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the

topical dosage form, thus enhancing the diffusion of the drug into the skin[39] .

CONCLUSION

Drugs with poor solubility and low bioavailability are called 'brick dust' candidates once abandoned from formulation development work can be rescued with nanosuspensions technology. A nanosuspension not only solve the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Nanosuspension technology can be combined with traditional dosage forms such as tablets, capsules, pellets, and can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formation technologies and variety applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future.

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