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ADVANCES IN SYNTHESIS AND EVALUATION NANOCRYSTALS: AN OVERVIEW

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ABSTRACT: Nanocrystals show promise to deliver poorly water-soluble drugs to yield systemic exposure. However, our knowledge is regarding the in vivo fate of nanocrystals is in its infancy, as Nano crystallization is simply viewed as an approach to enhance the dissolution of drug crystals. Nanocrystals also offer the advantage of long-term durability in the body for interacting with biological tissues and cells. Nanocrystals are nanosized drug moieties comprising 100% of the drug with insignificant amounts of stabilizer. Their nanoscale dimensions bestow upon them key attributes such as improved dissolution rate due to increase surface area,increased permeability due to increased adhesion, which contributes to improved bioavailability. Significance of nanocrystal drugs is mentioned in this review. They are used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. The method of preparations of nanocrystals is down,top down and bottom up, spray drying and so new techniques. Nanocrystallization is a versatile method for salvaging poorly soluble drugs with the added benefit of a carrier-free delivery system. Additionally, it delves into the integration of nanocrystals in the drug development process, exploring their potential to revolutionize formulation strategies and improve therapeutic efficacy. This review provides insights into the evolving landscape of nanocrystals in pharmaceutical applications, emphasizing their transformative impact on drug development and regulatory compliance. This review articles include method of preparation, properties, advantages of nanocrystals and applications of nanocrystals through all routes of administrations.

KEYWORDS: Nano crystals, Nanoparticles, Nanotechnology, Nanotherapeutics, nanoscience

INTRODUCTION

Over the years,nanoparticles (NPs) made of both organic and inorganic materials have been engineered to circumvent the biological barriers and deliver drugs for a variety of indications.Water insoluble or hydrophobic drugs,pose a challenge in terms of achieving optimal bioavailability and thereby,adequate efficacy. The drug nanocrystals may be defined as pure solid particles with a mean diameter <1micrometer and a crystalline character. The platform offers an exceptional opportunity to deliver hydrophobic drugs that nanocrystals are composed entirely of 100% drug or the payload thereby eliminating the ancillary role of a carrier in addition surfactants or stabilizers are commonly used to stabilize the crystalline dispersions in liquid media. Nanocrystalline drug technology improves the solubility of hydrophobic drugs due to an increased surface area to volume ratio and improve dissolution rates [i.e. dissolution velocity] associated with nanosizing. The drug crystals are singularly well-suited for the rehabilitation of previously unsuccessful biopharmaceutics classification system [BCS] class II and IV drugs.The BCS classification system is an experimental model that measures permeability and solubility under prescribed

conditions. The system divides the drugs into four classes.The system have high solubility and high permeability, class II molecules have low solubility and high permeability, class III identifies with high solubility and low permeability, and drugs in class IV have low solubility and low permeability. Nanocrystals drug formulations have also been to be stable in suspensions and are often refered to as nanocrystal colloidal dispersions [NCDs].The dispersions provide a platform for easy scale up and manufacturing of highly stable and marketable products. Their synthesis and scale up considerations have been described at length elsewhere. Commonly used synthesis. Commonly used synthesis techniquesinclude the use of microfluidic based platforms or the milling method, which among others, is both flexible and tunable.The nanocrystal drug technology has been studied extensively and is well positioned for further exploration in the field of drug delivery. Several hydrophobic drugs have been salvaged via the nanocrystal formulation method. The drugs was successfully developed, and approved by the FDA through treat a variety of indications ranging from dental disorders to cancer in the clinic. Depending on the disease, the approved formulations can be administered via different routes including oral, dermal, and parental. These highlights the versatility of a nanocrystal drug platform.Pharmacokinetics,biodistribution and bioavailability data for organs involved in delivery routes tested using nanocrystal technology. Several articles have been published, discussing the techniquies used to synthesis nanocrystals drugs, the type of stabilizers or surfactants involved,and the methods adapted for physicochemical and biological characterisation. however, a wide translational gap exits between this highly promising platform and its clinical approval. In this review,we discuss the nanocrystals drug technology and its development from a translational perceptive.

2. PREPARATION METHODS OF NANOCRYSTALS:

Nanocrystal preparation methods can be divided into top-down and bottom-up techniques. The size reduction of relatively large particles into smaller particles are known as top-down technique, whereas bottom-up techniques consist of the growth of small particles from individual molecule . The driving force for the growth of a crystal from individual molecules is supersaturation. Bottom up technique is usually a precipitation or crystallization technique and considered as the oldest technique to prepare nanocrystals . In this Review, we first briefly discuss the methods to produce nanosized particles, which include direct crystallization using high supersaturation (bottom up technique), particle breakage (top-down technique) and crystallization in a constrained environments (bottom up technique). Next, we summarize the merits and demerits of these methods, scale up issues and application in drug delivery of nanocrystals prepared by different methods. We highlight advantages of the Bottom up technique and top-down technique.

2.1 Top Down Approach:

The top down approach is the most important technique for the production of nanocrystals. Milling and high-pressure homogenization are the two basic top-down techniques for size reduction. Wet milling produces the most nanocrystal products that have reached the market . Wet milling involves mechanical attrition, where particles are wetted by an aqueous solution of surfactants and sheared and grinded by milling balls in a milling container. The particle size is reduced and may reach a few hundred micro-meter, but the conventional milling with modifications can be used for generating nanosized crystals . The preparation process can be carried out in a reproducible manner. The contamination from erosion of metal milling balls or pearls, high energy input, prolonged operation time and decreased crystallinity are the major drawbacks of the technique . The use of polymeric beads may be helpful in minimizing the erosion and contamination. A new process known as Jet milling to prepare micro-particles without the use of organic solvent was described by Nykamp et al. The important advantages of solvent free jet milling are the prevention from toxicity due to the absence of organic solvents and very short preparation time . High-pressure homogenization is the process in which two fluid streams of particle suspensions collide under high pressure in a chamber, leading to particle collision and subsequent particle rupture. Nanosized solid particles are produced in Piston-gap homogenizers by forcing a suspension of drug particles with a piston through a thin gap under high pressure. The high shear forces, and turbulent flow fractures the particles and the particle outcome was decided by the power of homogenization, particle hardness, and number of the piston-moving cycles . High-pressure homogenization required high process

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temperature, high-energy input, required complex equipment and might have possible degradation of the components and may yield less when compared with wet milling and these are the major drawbacks of the technique. The nonexistence of a large-scale production method yielding a product of a quality that is acceptable by the regulatory authorities hampers the introduction of solid nanoparticles to the market . Wet Milling and High-pressure homogenizers are widely used in many industries including the pharmaceutical industry for the production of micro and nano-particles. Hence, Wet milling and High-pressure homogenizer are considered as being industrially the most feasible one for nanocrystal production with no regulatory problem.

2.2 Bottom-Up Techniques:

CFC creates the optimum process condition for nanocrystal production after controlling the size, location, density, and intensity of implosion of bubbles in the cavitation zone. The controlled energy released by the implosion of micro bubbles and the ability to control the energy of cavitation, the particles can be brought to desired particle size distributions.CFC converts destructive force into constructive with high intensity energy force to produce nano and micro structured materials CFC technology has been exploited in many industries with multiple CFC chamber designs customized for hydrodynamic, chemical, biomedical and cleaning applications .The CFC is highly scalable and efficient process with excellent process control and outstanding reproducibility

2.3 Spray drying:

Spray Drying is a single-step process for converting solutions, emulsions, suspensions, slurries, and pastes into powders in a continuous manner. It also allows the production of particles with controlled size and morphological aspects. Due to the limited collection efficiency related to cyclone separators, the traditional spray drying process is limited for producing particles of 2–5 μm sizes. A spray dryer with a piezoelectric driven vibrating mesh atomizer and a high-efficiency electrostatic powder collector seems to correct these limitations. A new Nano spray dryer technology B-90, has been developed by Büchi(Switzerland) and has been applied to perform nano crystallization and drying . The other new technology includes the dissolution of drug and a polymeric dispersant system in a suitable solvent. After spray drying the resulting solution the powder containing the drug are produced as either the molecularly dispersant system in the polymer matrix to form a solid solution or dispersed as submicron particles to form solid suspension . The spray drying process is very rapid; can be designed to any capacity, adaptable to a fully automated control system that allows continuous preparation, and also wide ranges of spray dryer designs are available in the market. The spray dryer can be used for heat resistant and heat sensitive products and the feedstock can be as a solution, slurry, gel, suspension or melt form. The current advantage of nanotechnology has increased the stress on existing spray dryer systems to produce nanoparticles with high yield and controlled size distribution.

2.4 Supercritical Fluid:

Supercritical antisolvent (SAS) processes are lately proposed for the production of micro- and nanosized particles. The solute, solvent, and the supercritical antisolvent are the three important components of SAS.A very high level of supersaturation was generated due to the high power of supercritical fluids to dissolve the organic solvents as well as by the low solubility of the solute in the SAS. A very fast diffusion and high supersaturation creates precipitation of nanoparticles that are not possible to obtain with antisolvent precipitation or any other techniques. The main advantage is the complete removal of obtained by varying pressure and temperature and their diffusivities can be about two orders of magnitude greater than those of liquids . More recently Caputo et al. proposed the use of SAS for the precipitation of sulfathiazole from acetone solution by the use of urea as habit modifier and in the recent past poly (sebacic unhydride) was used by Jarmer et al. as growth inhibitor for griseofulvin using a SAS .

2.5 Impinging Jet Crystallization:

Current advancement to directly produce small particles include impinging jet crystallization in which jets are used to create impinging fluid jet streams and thereby achieve high intensity micro mixing of the fluids prior to nucleation . Two or more jets and two fluids with different solvent composition can be used to micro mix the solvent and antisolvent for initiating the precipitation of solute from solution. Woo et al. studied the control distribution by combining controlled seeding by impinging jet crystallization with a batch crystallizer operating

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at a controlled constant growth rate. The goal of their study was to propose control strategies to produce crystals with a target crystal size distribution (CSD), that are combinations of optimal control and an impinging jet crystallizer. The barium sulphate nanocrystal precipitations are studied experimentally by Schwarzer and Peukert et al. and the mean particle size of the nanoparticles are also predicted accurately by CFD model. The impinging jet crystallization offers very high-energy dissipation rate, efficient micro mixing and tightly controlled conditions to high product quality.

2.6 Emulsion Method:

The method of preparation of nanocrystals by microemulsion is gaining a significant interest in both basic research and in different industrial fields . The organic nanocrystal fabrication using the emulsion method is a three-step process . The first step is the preparation of emulsion by the quick addition of solution of compound in the organic phase to the aqueous phase at high temperatures . High stirring speed and irradiating ultrasound was used to produce the stable emulsion . In the second step the solutes are crystallized by gradually cooling the dispersion to low temperatures. In the third step an antifoaming agent was added to break the emulsion and separate the organic solvent. A nanocrystals were obtained as a stable dispersion in an aqueous phase . Ujiiye-Ishii and co-workers described how to prepare perylene nanocrystals using emulsion and Reprecipitation method. Schulman et al. first described the method in 1959 and prepared macroemulsion and microemulsion of hydrocarbons. A significant feature of this method is its ultralow interfacial tension, large interfacial area, and thermodynamic stability of the resulting nanocrystal dispersions in aqueous media .

2.7 Patterned Micro Well and Patterned Gold Islands:

The patterned micro wells are well-defined two-dimensional or confined three dimensional structures that are mainly used as templates to guide the crystal nucleation and growth . The templates can be self-assembled organic monolayers , polymeric matrix , silica , highly ordered graphite or carbon nanotubes .Recently, significant attention has been directed to design protein nanocrystals with uniform shapes for improving bioavailability and providing alternative release route Wang et al. demonstrated that patterned micro wells provide a platform for controlling the crystallization of protein nanocrystals using industry-standard crystallization conditions . Previously, patterned Self assembled Monolayers (SAM) were used to crystallize organic molecules such as Stirring and irradiating ultrasound Hot water Hot organic solvent At high temperature At room temperature Nucleation and crystal growth Cooling Breaking of emulsion. Schematic model of the organic nanocrystal fabrication using the emulsion method .16 Methods for Nano-Crystals Preparation 281 glycine. The bifunctional SAMs pattern contains hydrophilic islands surround by hydrophobic regions on which small hemispherical droplets are formed when wetted with polar solvents . The nanocrystals of glycine are formed either by slow cooling, slow evaporation or slow diffusion of an antisolvent . Lee et al. showed that the polymorphic outcome of glycine is primarily influenced by the solvent evaporation rate. The slow evaporation results into α-glycine while fast evaporation favours β-glycine due to creation of high supersaturation . The control of the supersaturation during vapour diffusion experiments results into the crystallization of metastable β-glycine polymorphs. The study shows that the organic vapour diffusion was used to obtain the metastable β-glycine, while slow cooling and slow evaporation are used to prepare the α-glycine and γ-glycine polymorphs.By controlling the initial glycine concentration and the rate of diffusion the nanocrystals with a size between 200 nm to 1.2 μm were prepared based on the island size. Kim et al. also calculated the solubility of glycine crystals in methanol using Ostwald-Freundlich equation and 100 nm crystals displayed two times more solubility then the equilibrium solubility of glycine. The solubility results calculated from the Ostwald-Freundlich equation for α-glycine and β-glycine polymorphs indicates that β-glycine is more stable than α-glycine due to the effect of surface molecules when the crystal size is under 97 nm. The patterned SAMs technique is very simple, with a large variability of molecules and highest density of SAMs and many functional thiols are commercially available. A major limitation is the removal of crystals from the surface while scraping or ultrasound can be used to remove the crystals from the surface.

2.8 Microfluidics Devices:

A microfluidic system can be used for the continuous production of nanocrystals mainly due to the improved reaction control and performance of mixing, the particle size distribution becomes sharper and the particle size decreases.

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The microfluidic devices fall into broad categories: capillary- and chip based systems. In capillary reactors the simple fluidic components can be joined by appropriate lengths of tubing. Chips are precisely tailored and typically fabricated from a plastic, glass or silicon substrate, wet etching or micromachining techniques. Both types of reactor play an important role in nanocrystal synthesis . Single phase or two-phase reactors are two important microfluidic reactors. The singlephase reactors are commonly used reactors, in which miscible streams of reagents are injected into a channel or capillary where they mix and react, making it easy to conduct multistep reactions and produce more complex structures. The undesirable velocity dispersion and fouling on the reactor wall are the two important limitations and can limit the performance of a single phase reactor. In case of two-phase reactors an additional immiscible fluid was injected (which can be a gas or a liquid) into the channel divides and creates a split plug that passes through the reactor at a common speed, eliminating velocity dispersion . The size of the split plugs was proportional to the relative flow rates in the two outlet channels and can be controlled by varying the relative hydrostatic pressures at the two outlets . The microfluidic reactor is still a long way from displacing the conventional reactor for nanocrystal synthesis, which cannot satisfy industrial demand .

2.9 Nanocrystal Preparation Using Nanoporous Materials:

A novel process to generate nanocrystals of active pharmaceutical ingredients within the nanopores of nanoporous materials is the simplest approach for nanocrystal preparation . Many studies have been performed investigating the potential of carrier materials including metal organic frameworks, mesoporous silica, controlled pore glass, porous polycyclohexyl ethylene and polystyrene and nanostructured lipid carriers . O'Mahony et al. developed a process with the aim of generating nanocrystalline products within the controlled pore glass (GPG), filling the pores of CPG with API solution . The inhibition time was estimated by the Washburn equation in order to facilitate complete filling of the pores of CPG during the process. The Washburn equation usually predicts the capillary flow of liquids in porous material to describe the migration of this liquid air interface with time t within a channel .

$$L^2 = \frac{\gamma D t}{4\eta}$$

Where t is the time for a liquid of viscosity η and surface tension γ to penetrate a distance L into a fully wettable, porous material whose average pore diameter is D

The surface area to volume ratio can affect the thermotropic properties of very small crystals, which results in substantial melting point depression due to the limitations on crystal size imposed by the pores. The Gibbs-Thomson equation can be used to describe the melting point depression seen in nanocrystals. The Gibbs-Thomson equation for nanocrystals confined to pores is defined as

$$\Delta T_m = T_m(d) = \frac{4\gamma_{solid-liquid} M T_m}{d\Delta H_{fus}\rho_{solid}} \cos(\theta)$$

where Tm is the bulk melting temperature, Tm (d) is the melting temperature of a confined crystal with diameter d assumed equal to the pore diameter, M is the molecular mass, ρsolid is the density of the solid, γsolidliquid is the surface free energy of the solid-liquid interface, ΔHfus is the molar enthalpy of fusion, and θ is the contact angle between the wall and crystal. The melting point depression for nanosized crystalline material has been reported for particles confined within nanosized pores for a number of compounds .The important advantage is the sizes of the nanocrystals are limited by the channel diameter, which in turn limits growth of the crystals along the channel length and the melting behaviour is influenced by the matrix material .CPGs have the advantage of being available in a number of different pore diameters, shapes and of nanosuspension size.

3. EVALUATION PARAMETERS:

3.1 Particle size analysis: The particle sizes of the nanoparticles were evaluated by scanning electron microscope were ranging from 350 nm to 600 nm, particle size varies depending on the polymer load.

3.2 Scanning Electron Microscopy (SEM) studies: The particle shape and surface morphology of nanoparticles were examined by scanning electron microscopy. Lyophilised and completely moisture free samples were consigned on aluminium stubs using adhesive tapes and coated with gold using sputter coater and observed for morphology at an acceleration voltage of 20 kV.

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3.3 Determination of percentage of drug entrapment efficiency: Prepared nanoparticle suspensions were centrifuged at 2000 rpm for 30 min. The supernatant was collected and the particles were washed with water and then subjected to another cycle of centrifugation. The amount of free drug in the supernatant was determined by the UV-Visible Spectrophotometer.

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$$\text{Drug Entrapment (\%)} = \frac{\text{Amount of drug aded} - \text{Amount of free drug}}{\text{Amount of drug added}} \text{X } 100$$

3.6 Determination of zeta potential: The zeta potential of the drug-loaded chitosan nanoparticles was measured on a zetasizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate.

3.7 Fourier Transforms Infrared (FTIR) spectroscopy analysis: The chemical integrity and possible chemical interaction between the drug and polymer can be determined by FTIR analysis. Samples were mixed separately with potassium bromide (200–400 mg) and compressed by applying pressure of 200 kg/cm2 for 2 min in hydraulic press to prepare the pellets. The pellets of the native drug, polymer and the drug loaded nanoparticles were analysed by placing it on the light path. All samples were scanned by aver-aging 32 interfero grams with resolution of 2 cm−1 in the range of 4000–400 cm−1.

3.8 Accelerated stability study: The nanoparticles were packed in borosilicate glass vials and these samples were stored in environmental simulation chambers for constant climatic conditions. The storage conditions used in the stability study, as well as the times when the samples were tested according to the protocol of International Conference on Harmonization (ICH) guidelines. Physicochemical characterization of the drug loaded EudragitRS100 nanoparticles was carried out over 6 months at regular intervals by dispersing 1 mg of drug loadedEudragitRS100 nanoparticles in 10 ml of distilled water to observe any degradation. The studies were carried out in triplicates from time to time. Particle size and zeta potential was measured using Zeta sizer, based on quasi-elastic light scattering, at a given wavelength at 25°C.

4. APPLICATIONS OF NANOCRYSTALS:

4.1 Oral drug delivery:

Inadequate solubility, lacking disintegration, and deficient efficacy are the serious issue of oral route of drug administration. Because least size of particles and higher surface to volume ratio, oral nanosuspensions are remarkably used to build the rate of absorption and bioavailability of least dissolvable drugs. If there should be an occurrence of azithromycin nanosuspensions, over 65% of medication was seen to be dissolved in 5 h as appeared differently in relation to 20% of micronized drugs. The nanosuspensions have major involvement in improved oral absorption, dose proportionality, and low inter subjected variability. By using standard manufacturing strategies, drug nanosuspensions can be basically joined into different dosage forms like fast melts, capsules and tablets. The nanosuspension of ketoprofen was adequately consolidated into pellets for the sustained release of the drug over the time of 24hours.

4.2 Parental drug delivery:

The present methodologies for parental delivery loaded micellar solutions, salt formation, solubilisation using co-solvents, cyclodextrin complexation, and all the more as of late vesicular frameworks for instance, liposomes and niosomes. In any case, these strategies have constrainments like solubilisation limit, parental acceptability, high manufacturing cost, to solve the above problems, the nanosuspension technology is used. nanosuspensions are administered through different parental routes, for example, intra-articular, intraperitoneal, intravenous, and so on also, nanosuspensions increment the viability of parenterally administered drugs.

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Paclitaxel nanosuspension was reported to have their predominance in diminishing the median tumour burden. Clofazimine nanosuspension exhibited advancement in stability and also efficacy above the liposomal clofazimine in mycobacterium avium-infected female mice. Rainbow et al. showed that intravenous nanosuspension of itraconazole enhanced the adequacy of antifungal action in rats relative to the solution formulation.

4.3 Pulmonary drug delivery:

For delivering via pulmonary, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Inside seeing fine particles, all aerosol droplets contain medicated nanoparticles. Budesonide Corticosteroid has been viably formulated as nanosuspension for delivery via pulmonary route. Aqueous suspensions of the medication can be effectively nebulized and directed by pulmonary route as the particle size is practically low. Different sorts of nebulizers are accessible for the administration of liquid formulations. There are few deugs that have been effectively attempted with pulmonary route are ibuprofen, ketotifen, indomethacin, budesonide, doxorubicin, nifedipine, interleukin-2, itraconazole, p53 gene, leuprolide, etc.

4.4 Ocular drug delivery:

The tear fluid secreted from lachrymal gland has least drug dissolving capabilities. On the off chance that it is planned as nanoparticles its dissolvability and bioavailability will elevate. Nanosuspension is used to deliver drugs via ocular route for the purpose of sustained release. Liang and co-workers formulated cloricromene nanosuspension for ocular delivery with help of eudragit. Examination indicated higher availability of drug in aqueous humor of rabbit eye. As such, nanosuspension offers a promising strategy for improving the bioavailability and shelf-life of the drug after the ophthalmic application.

4.5 Targeted drug delivery:

Nanosuspensions are suitable for targeting specific organs in perspective on their surface properties. Close by this, it is anything but difficult to adjust in vivo conduct by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery of the drug. This can be used for concentrating on anti-fungal, anti-mycobacterial, or anti-leishmanial drugs to macrophages if the pathogens suffer intracellularly. Kayser prepared an aphidicolin nanosuspension that improved the targeting of drug to macrophages which were infected by leishmania. He expressed that the drug as nanosuspension had ec50 of 0.003µg/ml, while the conventional form had 0.16µg/ml . Scholer et al. depicted an increased targeting of drug to the brain in the treatment of toxoplasmic encephalitis by utilizing an atovaquone nanosuspension.

4.6 Transdermal drug delivery:

Nanocrystals are evolved greatly in the field of transdermal delivery of the drug to overcome the solubility issues of drugs, in this manner expanding the concentration gradient in between the formulation and the skin, subsequently, transdermal permeation of the drug. Due to its nano size in nature it exhibits better permeability than micro-sized particles. A transient stability test demonstrated that all nanosuspension remained sensibly stable at various temperatures. The Lutein nanocrystals had the option to penetrate through cellulose nitrate layers, utilized as an in vitro model of a penetration barrier, 14 times superior to coarse powder. In any case, no permeation through pig ear skin was watched, which shows that the Lutein entering the skin stayed there because of the lipophilicity.

4.7 Mucoadhesion of the nanoparticles:

A nanoparticle has got capabilities to adhere on the mucosal surface because of tiny nano sized particles. During initial stages adhesion of particle occur followed by its absorption. To elevate much higher contact period nanosuspension is formulated along hydrogels made from variety of mucoadhesive polymers. The adhesiveness of the nanosuspension enhances the bioavailability as well as improves targeting of the parasites continuing in the GIT. Bupravaquone Mucoadhesive Nanosuspensions have been accounted for to exhibit a favorable position in TRC Alpha Deficient mice tainted with Cryptosporidium Parvum Oocytes.

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