REVIEW ARTICLE

A Review on Improved Drug Performance of Nanocrystals Formulations

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ABSTRACT

Nano-based technologies are one of the most effective ways to resolve poor aqueous solubility and low absorption of drugs. Nanocrystals are pure drug crystals of particle size below 1000 nm with or without stabilizers adsorbed on it. Nanocrystals are carrier free and can be introduced in any of dosage forms. Reduced particle size and crystallinity offer increased solubility, dissolution velocity, and mucoadhesion. This causes an improvement in pharmacokinetic parameters and drug performance. Top-down approaches like milling, homogenization and bottom-up approach of precipitation are methods of preparation of nanocrystals. Also, combinations of these methods are used for nanocrystals preparation. This review discussed and summarized the improved *in-vitro/in-vivo* performances and pharmacokinetics of drug nanocrystals.

Keywords: Biological, Formulation, Nanocrsytal

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INTRODUCTION

Nanotechnology is considered as one among the most utilized technology in many innovations world-wide. Nowadays nanomaterials can revolutionize various fields like medicine, engineering, agriculture, food industry etc.[1] As per the prefix 'nano', the technology deals with materials on nanometric scale. Nanoscience or nanotechnology has diverse applications in biological systems especially in drug delivery. Nanometric properties can be incorporated into every level of materials, that is from atomic to macroscopic scales. Nano-based drug delivery systems can overcome many formulation limitations like poor solubility, absorption difficulty, intestinal permeation etc.[2] Most naturally occurring compounds like polyphenols has variety of pharmacological actions against many diseases. But these compounds are facing solubility and absorption difficulties which leads to low bioavailability, limits their application for therapeutical use. Therefore, various approaches of nanosizing can improve 15–20 folds the solubility and hence 3–4 folds the bioavailability of naturally occurring drugs.[3] Nano-dimensional approach improves the potential of poorly soluble drugs for their therapeutical properties. Applications of nanomedicine as nanorobots and nano-sensors are the staggering steps in fields of diagnosis, imaging, drug delivery and targeting for various life-threatening diseases like cancer. Various nanostructures like biopolymeric nanoparticles, liposomes, dendrimers, polymeric micelles, nanocrystals, inorganic nanoparticles, metallic nanoparticles, etc., have emerged for diagnosis and drug delivery.[4] Among the nano-based drug delivery systems. Nanocrystals offers carrier-free delivery of drugs with crystalline character. Nanocrystals are pure drug solid particles of mean diameter less than 1-µm. It can be loaded to different dosage forms like tablets, capsules, inhalation, gels, infusions etc., which improves the absorption besides enhancing the modified release of drugs.[5]

Special Properties of Nanocrystals

Drug nanocrystals are available in market from the year 2000, which is nanoscopic crystals of parent drugs that are stabilized with or without surface active agents. The reduced particle size of nanocrystals offers many advantages on bioavailability and therapeutic action.

Enhancement Saturation Solubility

Saturation solubility is drug specific constant that depends on physiochemical characteristics of solvent. As particle size decreases, saturation solubility increases, in case of drugs at least in mm range.[6] *In-situ* saturation solubility study of nanocrystals of dexamethasone, ibuprofen, tacrolimus on dermal application states that, saturation solubility of increases as particle size reduces.[7] Preparation and evaluation study of luliconazole nanocrystals loaded hydrogel for antifungal activity reported as solubility of nanocrystals was enhanced 5-fold than the parent drug.[8]

Enhancement in Diffusion Rate

According to Noyes-Whitney equation, diffusion rate increases with increasing surface area. Particle size reduction causes an increase in surface area.

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$$dc/dt = D.A(Cs - Cx)/h$$

dc/dt - Rate of dissolution
D - Diffusion coefficient of the drug in solution in G.I fluid
A - Surface area of the drug particle in contact with G.I fluid
Cs- Saturation solubility of drug in the diffusion layer
Cx- Concentration of drug in solution
h - Thickness of stagnant layer

An increase in saturation solubility also enhances diffusion rate, leading to increasing absorption and improving bioavailabilty of drugs.[9] Reports of study and comparison of properties of aceclofenac nanocrystals with micro suspension and unprocessed aceclofenac show many times enhancement in dissolution rate when compared to unprocessed drug and micro suspension of aceclofenac.[10] *In-vitro* dissolution velocity of rutin nanocrytsals was studied and it found that within 15 minutes rutin nanocrystals rapidly dissolved in gastric and intestinal pH.[11]

Enhancement in Mucoadhesiveness

Nanocrystals has more surface area when compared to unmilled drug particles; therefore contact point towards mucosa is more in case of nanocrystals which increases mucosal adhesion of drug particles and membrane transport.[12] On dermal delivery of nanocrystals, increased solubility raises the concentration gradient and improves diffusion pressure penetration. They also share the possibility of dissolving the drug before entering the uptake pathway due to fast dissolution and adhesion to gut wall in case of oral bioavailabilty.[13]

Advantages of Nanocrystals[6]

- 100% drug without carrier
- Crystalline or amorphous structure with massive surface area
- Enhanced solubility and dissolution
- Increased absorption and bioavailability
- Reduced dose requirement
- Improved performance of drugs
- Can be introduced into different dosage forms

Improved Performance of Drug in Nanocrystals Formulations

Atorvastatin nanocrystals with hypolipidemic activity were prepared, which was stabilized with poloxamer-188 and evaluated its improved bioavailability, safety and hypolipidemic effects. In this study atorvastatin nanocrystals were prepared by high-pressure homogenization. Particle size analysis revealed that size of prepared nanocrystals is nanometric scale. Powder x-ray diffraction results indicated its reduced crystallinity, which enables improved solubility and dissolution. Solubility and dissolution studies reports showed the 40 folds improvement in gastric solubility and dissolution. *In-vivo* studies were carried in wistar rats by inducing hyperlipidaemia using high fat diet. On assessing reports of pharmacokinetic parameter, a lower T_{max} and higher plasma drug concentration can be observed. An increased elimination half-life and improved mean residence time implies a greater absorption of atorvastatin nanocrystals compared to pure drug and ensured ~2.66 folds improvement in relative bioavailability. *In-vivo* efficacy and safety studies showed significant reduction in total cholesterol and triglycerides. Altogether results obtained in the study promises atorvastatin nanocrystals are safer, efficacious, and capable of lipid lowering action even at 50% dose when compared to pure drug of atorvastatin.[14]

Bexotrene nanocrystal with anticancer action bexotrene is a synthetic retinoid and an anticancer agent. But poor solubility limits its application for therapeutical actions. To circumvent this bexotrene nanocrystals formulation for oral and parenteral delivery has been developed and evaluated its pharmacokinetic features. Here combination approach of nanocrystals preparation was done, precipitation followed by micro fluidization aided the particle size reduction. DSC, X-ray diffraction and raman spectroscopic analysis revealed the crystalline nature of obtained bexotrene nanocrystals. Improved solubility and dissolution profile can be observed for bexotrene nanocrystal in saturation solubility and *in-vitro* drug release studies on comparing with bulk drug. Pharmacokinetic behaviors of oral and intravenous administration of bexotrene nanocrystals in wistar rats have improved due to reduced particle size and crystalline nature. Intravenous administration of bexotrene nanocrystals is more effective than oral administration due to rapid onset of action and reduced dosage. Delayed T_{max} and absorbed stabilizers over crystals enable slow release of drug. Overall, the nanocrystal formulation of bexotrene can solves solubility problems and offers targeting chemotherapeutic drug delivery.[15]

Curcumin nanocrystals with antioxidant potential were synthesized and validated antioxidant activity against circulatory toxicity in wistar rats. Poor solubility is the problem of naturally occurring drug curcumin with variety of pharmaceutical potential. In this study the superiority of nanocurcumin over bulk curcumin can be observed. Curcumin nanocrystals prepared by the precipitation method and nanocurcumin obtained has good solubility compared to bulk curcumin due high reduction in particle size. X-ray diffraction pattern and high-resolution transmission electron microscopy (HRTEM) results confirms crystallinity of nanocurcumin. In a comparative *in-vivo* study in wistar rats curcumin is equivalent to curcumin nanocrystals for exerting the ameliorative effect on DMH- induced oxidative stress. This may due to reduced particle size, increased surface area and crystalline nature.[16]

Glimipride nanocrystals with antidiabetic effect capsules containing glimepide nanocrystals were prepared and evaluated its pharmacokinetic characters on rats. Nanocrystals are prepared by precipitation-ultrasonication method. Particle size and SEM analysis showed that nanocrystals produced have particle size between 200–400 with irregular shapes. Differential scanning calorimetry (DSC) and X-ray results revealed that crystalline nature diminishes from coarse powder to nanocrystals. Dissolution profile of nanocrystals loaded capsule was dissolved (90%) in first 30 minutes while microcrystals and marketed samples dissolved 40–50% only. Results of *in-vivo* studies in rats showed an improved pharmacokinetic parameters also steady state of therapeutic

effect, therefore eliminate chances of side effects like hypoglycemia.[17]

Glibenclamide a hypoglycaemic agent was engineered into nanocrystals loaded into chitosan patch for assessing the *in-vivo* transdermal drug delivery. Nanocrystals were prepared by combination method of precipitation and homogenization. DSC and X-ray reports revealed crystallinity of the obtained nanocrystals. Drug release studies and permeation studies of glibenclamide nanocrystals loaded transdermal patches showed improvement in drug release (~85%) and permeation (~498 μ/cm^2). *In-vivo studies* on rats pointed out that gliblenclamide nanocrystals transdermal patches show a steady and long-term hypoglycaemic effect on around 3 times more than microcrystals and oral dose. Reduced particle size to nano scale and crystallinity serves in improving hypoglycaemic effects and stability of glibenclamide.[18]

Fenofibrate nanocrystals with hypocholesterolaemia effects were prepared by different bottom-up methods and evaluated its pharmaceutical and pharmacokinetics characters. In this study, three various bottom-up types were used to prepare nanocrystals: antisolvent precipitation augmented by probe sonication (f1), precipitation by stirring with bath sonication, and thermal precipitation (f3). DSC and X-ray results revealed that the nanocrystals obtained by precipitation with sonication retain crystallinity more than the crystals produced by thermal precipitation. Saturation solubility also increased due to particle size reduction 2 times than crude drug. Dissolution rate of crude drug was 20% at first 5 minutes and at same time its 80% for the nanocrystals. *In-vivo* bioavailability studies shows that there was high improvement in pharmacokinetic parameters and relative bioavailability for fenofibrate nanocrystals prepared by antisolvent precipitation than nanocrystals obtained by thermal precipitation. Even though f3 preparation shows high dissolution rate, absorption was slow, this may be due to presence of amorphous state of particles leads aggregation of particles.[19]

Lovastatin, a lipophilic drug used for hypercholesterolemia formulated to nanocrystals to enhancing solubility and dissolution rate. Nanocrystals prepared by anti-solvent precipitation method. In this study lovastatin nanocrystals prepared in different solvents and pure drug were compared. Particle size reduction can be obtained ~579 nm for optimized preparation. Powder X-ray pattern shows that nanocrystals are in crystalline form. This enabled the improvement in solubility more than 20 folds and *in-vitro* drug release above 90% in 3 hours. *In-vivo* studies results show that plasma drug concentration level gradually rises from time of administration up to 8 hours on nanocrytsals administration and increases relative bioavailability when compared to crude drug.[20]

Nitrendipine, a calcium channel blocker, nanocrystals are formulated and evaluated its *in-vitro* and *in-vivo* characteristics. Precipitation-homogenization method were used in the preparation of nanocrystals, followed by spray drying and solid form nanocrystals were obtained. Homogenization pressure and cycle influenced on particle size and crystals growth. DSC and X-ray observations confirmed that nitrendipine still remains in crystalline state. There was found a high dissolution rate of nanocrystals, that is 100% within minutes in *in-vitro* studies where only 50% of commercial tablet get released. *In-vivo* studies revealed that nanocrystals formulation offers an improved bioavailability of nitrendipine, since its plasma concentration and absorption were highly greater than commercial tablet. Hence the nanocrystals approach of nitrendipine showed overall improvement in drug performance.[21]

Olmesartan medoxomil nanocrystals with selective angiotensin II antagonist action olmesartan has low bioavailabilty due to poor solubility. As a resolution for this olmesartan medoxomil nanocrystals and microcrystals were prepared and compared its pharmacokinetic effects in beagle dogs. Nanocrystals prepared using wet milling process and obtained nanocrystals particles of size range 100–300 nm. Crystalline character was confirmed using DSC and X-ray characterization. Dissolution rate improved to 65%, which is double the rate of microcrystals and crude drug. *In-vivo* studies reported that plasma concentration and absorption of nanocrytals are two fold more than microcrystals which confirmed an improvement in bioavailability.[22]

Trans resverastrol, a polyphenolic compound with anticancer potential were fabricated into nanocrystals and evaluated *in-vitro/in-vivo* characters. Nanocrystals produced by probe sonication. Rod-shaped trans-resverstrol nanocrystals of ~110 nm particle size were obtained. This resulted in increased saturation solubility and dissolution. The dissolution profile of nanocrystals showed ~94% drug release in 5 hours in same time crude drug has ~39% drug release. DSC and X-ray pattern pointed out that crystallinity was retained. *In-vitro* cell cytoxicity study against MDA-MB-231 breast cancer cell line using MTT assay was carried out and reports showed that nanocrystals were more effective than plain drug for cancer cell cycle arrest and apoptosis. Pharmacokinetic study evidenced that the bioavailability of trans resveratrol has been improved due to increased plasma concentration and AUC. This may be achieved by size reduction, thereby increased solubility, dissolution, and diffusion across cell membranes.[23]

Paclitaxel nanocrytals with anticancer action were fabricated to improve oral bioavailability and evaluated its *in-vitro* and *in-vivo* performances. Even paclitaxel is anticancer drug it faces problems of insolubility and rapid metabolism. Here nanocrystals formulation is prepared by high pressure homogenization using microfluidizer. The particle size was reduced to 200–400 nm and obtained nanocrystals show irregular shape. pH stability studies carried out on simulated gastric and intestinal pH confirmed less changes for instability. Three times increase in dissolution rate can be observed on nanocrystals compared to plain oral drug solution. MCF-7 and MDA-MB cell lines were used for *in-vitro* cell line studies and reports revealed that paclitaxel nanocrystals stabilized tween 80 have higher cancer cell cycle arrest. *In-vitro* oral pharmacokinetic studies reported that significant increase

in C_{max} and AUC for nanocrystals promises improved bioavailability.[24]

CONCLUSION

Nanocrystals technology has been proved to circumvent the major problem of poor solubility on drug development. Studies on poorly water soluble drugs by formulation of nanocrystals show improvement in saturation solubility, dissolution velocity and pharmacokinetic parameters. From this we can assume that bioavailability and increased therapeutic effects can be able to achieve by formulating drug into nanocrystals. Many drugs nanocrytsals formulations are marketed and prove the increased efficacy of drugs. Nanocrystals are a promising tool for improving solubility and absorption hence the bioavailability of poorly soluble drugs.

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