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SWOT ANALYSIS OF NANO-CRYSTALS IN DRUG DELIVERY: REVIEW

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ABSTRACT

The components of poorly soluble drugs is an intractable challenging task in the area of drug layout, improvement and delivery. That is mainly complicated for molecules that present negative solubility in each organic and aqueous media. commonly, this is difficult to remedy using traditional system techniques and has resulted in lots of potential drug applicants not progressing past early stage development. Furthermore, some drug applicants are abandoned because of toxicity or have an unwanted biopharmaceutical profile. Oftentimes drug applicants do not present suitable processing traits to be produced and manufactured at scale. Nanocrystals and co-crystals, are revolutionary processes in crystal engineering which can resolve some of these barriers. Whilst these techniques are distinctly facile, in addition they require optimisation. Combining crystallography with nanoscience can yield Nano co-crystals that characterise the advantages of both fields, resulting in additive or synergistic results to drug discovery and improvement. Nano co-crystals as drug delivery systems can doubtlessly improve drug bioavailability and reduce the aspect-outcomes and tablet burden of many drug applicants that require persistent dosing as a part of treatment regimens. Similarly, Nano co-crystals are carrier-free colloidal drug delivery systems with particle sizes ranging between a hundred and one thousand nm comprising a drug molecule, a co-former and a possible drug delivery strategy for poorly soluble drugs. They're easy to prepare and feature vast applicability. In this newsletter, the strengths, weaknesses, opportunities and threats to the usage of Nano co-crystals are reviewed and a concise incursion into the salient elements of Nano co-crystals is undertaken.

Keywords: Bioavailability, Stability, Solubility, Colloidal Drug Delivery System.

INTRODUCTION

Currently, there were top notch advancements in combinatorial chemistry, high throughput screening and in silico drug candidate discovery ensuing in many potential drug applicants with outstanding target receptor binding. However, many of these applicants have properties together with a large molecular weight and high log[thin space (1/6-em)]P values that restrict their formulation into a final pharmaceutical drug product. Such molecules have inherently low aqueous solubility as a main predicament. Distinctly comparable drug synthesis techniques, i.e. crystal engineering and Nano-

crystallisation have been proposed to bypass the negative aqueous solubility of many drug candidates [1]. Crystal engineering is the use and manipulation of non-covalent interactions between molecular or ionic components for the rational design of solid-state structures that can have exceptional and interesting biological, pharmaceutical, electrical, magnetic, and optical properties in comparison to the determine molecules. It's far obvious that the directionality, specificity and predictability of intermolecular hydrogen bonds may be exploited to bring together supramolecular structures that, at a minimum, can manage or have an effect on dimensionality. It similarly utilises the expertise of intermolecular interactions within the context of crystal packing to design new stable substances with favoured physicochemical properties which includes solubility, permeability, stability, hygroscopicity, wettability, hydration, shade, compaction, tableting and bioavailability. Molecules exist as distinct stable forms which can widely be described as polymorphs, co-crystals, salts, solvates and amorphous solids. active pharmaceutical ingredients (API) are often administered as solid-state polycrystalline substances formulated into the ideal dosage form [2].

Solid dosage forms are a convenient for API garage. API can exist in an expansion of solid-state forms, in which every form might also show specific physicochemical properties along with differences in hygroscopicity, wettability, hydration, coloration, compaction, tableting, permeability, balance, and bioavailability morphology, melting factor and solubility. but, some doubtlessly beneficial compounds with relatively ideal molecular pharmacological properties may never understand their healing capacity due to negative solubility and bioavailability, unwanted processing characteristics and a short shelf-lifestyles stability [3].

Co-crystals are defined as single-section crystalline materials constituting two or more different molecular or ionic compounds blended in molar ratios. Distinct sorts of molecular bonds can be utilised to construct co-crystals and consists of π–π stacking, hydrogen bonds, van der Waal's forces and ionic interactions. Co-crystals have a tendency to be greater thermodynamically stable than the crystalline solids of pristine compounds. For pharmaceutical applications, they're extraordinarily promising to improve the physicochemical properties of an API. Whilst pairing the API with a co-former (i.e. a molecule decided on to co-crystallise with the API), there may be capacity for enhancing the biopharmaceutical and physicochemical properties of the API such as the dissolution kinetics, bioavailability and/or pharmaceutical balance of the API [4].

Pharmaceutical nanocrystals are nanoscale, heterogeneous aqueous dispersions of insoluble drug particles stabilised through surfactants and/or polymers. normally, nanocrystals are considered to be in

the variety of sub-micron dimension. A precis of the properties of nanocrystals and co-crystals is depicted in table 1 [5].

Table 1: Summary of the general functions of natural drug nanocrystals and co-crystals for drug transport

S.No.	Pure Nanocrystals	Co-crystals
1	Particle size < 1 μm	Greater dissolution charge
2	A hundred percent drug (no service)	Greater intrinsic solubility
3	Elevated dissolution charge	Greater melting factor
4	Feasible Nano toxicity and aspect effects	Greater friability
5	Enhanced adhesiveness to floor/cellular membranes	Better compressibility
6	Increased saturation solubility	More suitable hygroscopicity
7	Elevated bioavailability of the drug	Greater bulk density
8	Normally needed to be stabilized by floor active agent	Long-term stability issues

Consequently, merging co-crystallisation with nano-sizing of a drug candidate may be suited as the resultant nano co-crystals (NCCs) can exhibit the mixed advanced physicochemical and biopharmaceutical residences while compared to the determine molecule(s).

On this paper, the strengths and weaknesses of this relatively new combinatorial approach (i.e. NCCs) is assimilated and a concise incursion into the various possibilities and threats is discussed. This SWOT evaluation and future path of NCCs in drug delivery is also provided [6].

STRENGTH

Due to their ability to combine the benefits of nano-sizing and co-crystals, nano co-crystals (NCCs) offer multiple advantages. There are numerous synthesis methods available to enhance the physicochemical characteristics, flexibility of the delivery system, and possibility of subsequent processing to yield better results from novel therapeutic candidates [7].

Critical processing parameters (CPP): In order to guarantee that the synthesis process yields the appropriate API quality, key processing parameters (CPPs) should be tracked or managed. CPPs are procedural restrictions whose variability has an effect on the critical quality attributes (CQAs). The creation of medication candidates that fall within the parameters of the desired quality target product profile (QTPP) is facilitated by further optimisation of the CQAs. Not every CQA is significantly

impacted by a single CPP. Frequently, several One CQA is impacted by CPPs. NCCs can be produced utilising a range of synthesis methods that enable CPPs to be varied to produce a final product with the required QTPPs [8].

Different techniques for creating NCCs: One of the main benefits of NCCs is that, like co-crystals and nanocrystals, they can be made in two ways: either in a bottom-up method that involves nucleating and growing individual monomers that are stopped electrostatically and/or sterically at the nanoscale using stabilisers like surfactants or polymers, or in a top-down method that uses shear forces to reduce the particle size (mm μm−1 to nm). Fig. 1 provides an overview of the general design principle for each technique [9].

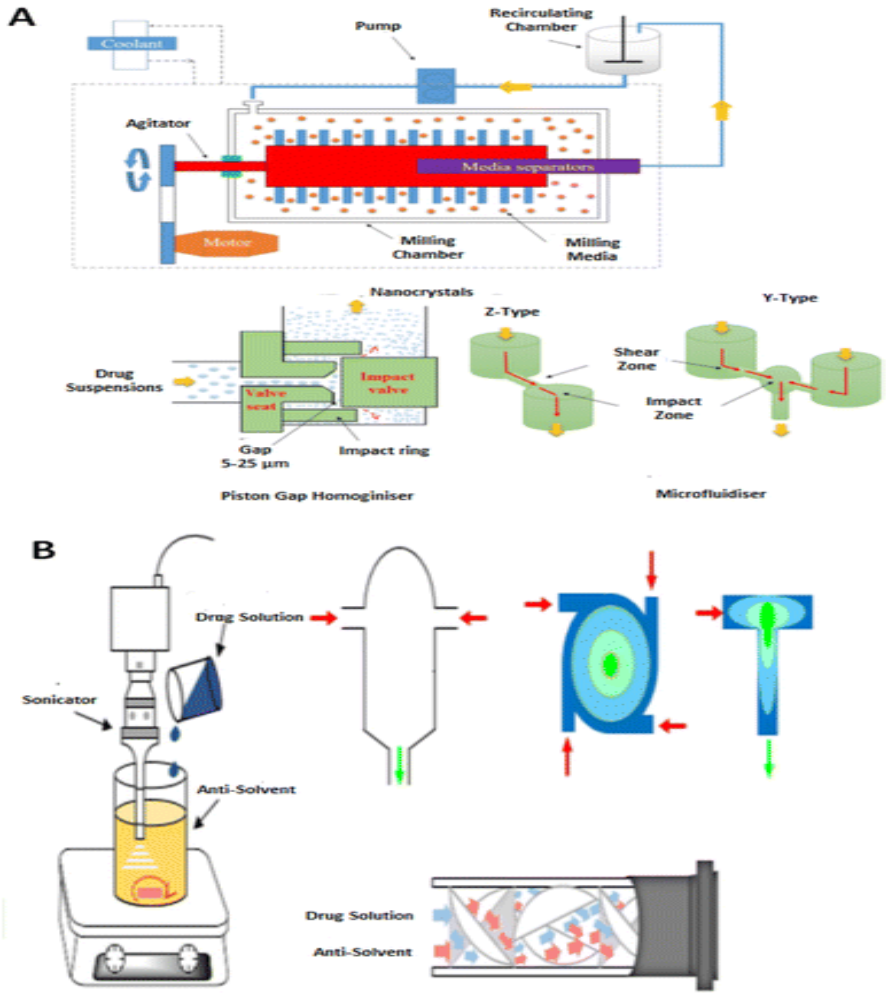

Fig.1 An illustration of the top-down (A) and backside-up (B) techniques for drug nano co-crystal production in the presence of stabilisers. Tailored from ref. one hundred thirty with permission from Elsevier B.V Amsterdam in accordance with innovative Commons

The potential to synthesize NCCs the usage of diverse techniques allow for flexibility in the manufacturing process to produce NCCs of the favoured pharmaceutical attributes.

Top-down strategies: Excessive-energy mechanical forces are required in top-down methods to provide NCCs. Those consist of media milling (MM) viz., NanoCrystals® or HPH, IDD-P®, DissoCubes® and Nanopure® to comminute large crystals to the nano-meter scale. Top-down processes are prevalent for getting ready crystalline nanoparticles and are flexible at manufacturing scale. The manner has been extensively adopted to put together nanocrystals on a industrial scale. For example, the HPH approach has been successfully applied to increase baicalein-nicotinamide (BE-NCT) NCCs. BE-NCT NCCs have been prepared using HPH with poloxamer 188 as a stabiliser in a formulation containing 2% w/w BE-NCT co-crystals and 0.4% w/w poloxamer 188. The gadget was to begin with homogenised at 15[thin space (1/6-em)]000 rpm for 10 min using a lab-scale excessive shear dispersing emulsifier and then HPH using 900 bar changed into carried out for 20 homogenisation cycles to provide a suspension of BE-NCT NCCs [10].

Bottom-up strategies: Bottom-up approaches grow NCCs from solution via important steps viz., nucleation and crystal boom. Nucleation is mainly vital to produce uniform NCCs. the larger the increase in nucleation charge the greater the quantity of nuclei shaped from the supersaturated solution. This then ends in a reduction in super-saturation resulting in much less boom for each nucleus as a end result. If a incredible range of nuclei are generated simultaneously during nucleation, a slim poly-dispersity index is expected [11].

One-pot Synthesis: The of many nanomaterials entails multi step approaches to gain products with appropriate CQAs. some steps contain secondary extrusion or sonication to lessen particle sizes as with vesicular drug delivery systems. NCCs combine the ability to supply nanomaterials with suitable CQAs in a single-step techniques [12].

Critical Material Attributes (CMAs): Important fabric attribute (CMAs) are defined as a material with variability having an impact at the CQAs and consequently need to be monitored or controlled to make certain that the preferred QTPPs are attained. Often, NCCs, similar to nanocrystals, are clean to synthesise, however their balance and the choice of stabiliser(s) is the maximum hard and vital step. NCCs are stabilised by way of using either polymers or surfactants. The polymers and/or surfactants used impart steric and/or electric powered stabilisation there via preventing agglomeration of molecules arresting the development growth on the nanoscale [12].

Enhancement Of Critical Quality Attributes (CQA): Vital best attributes are defined as physical, chemical, biological or microbiological properties or traits that need to be within the suitable restriction, variety, or distribution to ensure the product is of preferred excellent. Pharmaceutical nanocrystals and co-crystals present a promising and rising technique to modulate the overall performance of prescribed drugs viz., physical balance, chemical stability, mechanical properties, optical properties, launch profiles, bioavailability and healing impact.

Solubility Enhancement and Improvement Of Dissolution Price: It's been substantially studied and proven that the atomic packing in the unit cell and crystal lattice have a right away effect on the physicochemical properties of crystalline materials. many of the properties affected is the solubility and solubility fee and these form, in part, the premise for co-crystal solubility enhancement. Nanonisation of substances is another technique widely recognized to increase the solubility of crystalline substances. NCC integrate these two techniques and will likely have more impact at the solubility of materials than either generation [13].

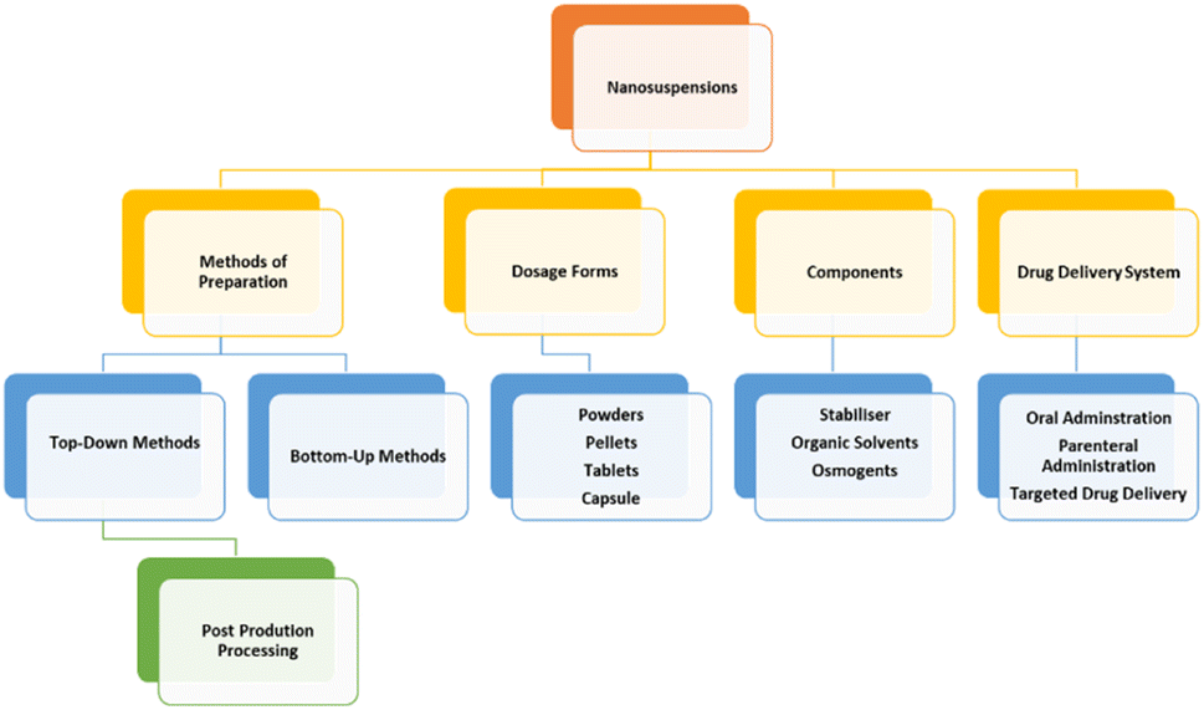

Fig. 2: Precise strengths of NCC. Reproduced with change from ref. 1 with permission from Springer Nature and in accordance to creative Commons agreement

Weaknesses

Critical Material Attributes: Regardless of the numerous homes that make NCC one of these applicable

era, there continue to be some components that remain cardinal and may delay their capacity for successful development and translation into marketable products.

Co-former Selection: As a result of the hybrid nature between co-crystals and nanocrystals, NCC nonetheless have the ability to be unsuccessful if a suitable co-former isn't recognized. The process of co-former selection is same to that of co-crystal manufacture and largely determines how effective the technology may be. The primary technique considered tactless and entails the screening of the co-formers from a library of materials which are GRAS. A unique and possibly greater useable approach is to utilise a supramolecular synthon approach which uses Cambridge Structural Database (CSD) for statistical evaluation of records. This approach requires a detailed appreciation of supramolecular chemistry and the functional groups found in API of choice. the use of the Hansen Solubility Parameter (HSP) technique is likewise used to are expecting the miscibility and co-crystal formation via the usage of group contribution approach and to calculate partial solubility parameters and Van Krevelen–Hoftyzer, Bagley and Greenhalgh strategies to expect miscibility. regularly this approach is handiest capable of in predicting miscibility. however, all co-formers which might be expected won't be miscible making this simplest a theoretical basics primarily beneficial for short list potential co-formers previous to exhaustive laboratory screening experiments. This can result in more efficiency in co-crystal screening applications [14].

Stabiliser Selection: Much like in the case of co-former selection, the selection of appropriate stabiliser stays one of the weaknesses of this technology. Huang et al., confirmed that in some cases with no trouble to be had polymers may not yield the NCC as predicted. The have a look at validated that polyvinylpyrrolidone (PVP) and hydroxypropyl methyl cellulose (HPMC) had been now not capable of shape Nano suspensions and best hydroxypropyl cellulose (HPC), Tween® 80 and poloxamer 407 had been capable of providing stability to the NCC suspensions. The effects proven the flexibility of parting stability to the NCC suspensions. The study did not provide a particular motive for the failure of the stabilisers to stabilise the technology [15].

Quality Target Product Profile of The NCC Final Product: It remains distinctly proper to provide NCCs with the potential to satisfy end consumer requirements. Those consist of but are not limited to long term stability, high efficacy, convenient dosing time table and clean administration. NCC may be laid low with among the capacity weakness of either co-crystals or nanocrystals.

Stability: The stability of final product is a primary fine searched for in a system. almost about NCC, there are many capability sources of instability that could exist in arise before the final components gets

to the quit consumer. It is, therefore, very critical to take these potential concerns when thinking about formulating NCC [16].

Final Dosage Form Balance: The unique traits of drug nanocrystals have enabled their vast application in numerous dosage forms inclusive of oral, parenteral, ocular, pulmonary, dermal and other specialised delivery structures. As successors to nanocrystals, NCC have the identical benefits and could probably be implemented as in similar occasions [17].

Agglomeration of NCCs: Due to their small length, it is expected that the massive floor location of NCC would create excessive total surface energy, which is thermodynamically unfavourable. therefore, the NCC will have a tendency to agglomerate to minimise the floor power. Agglomeration can bring about a variety of troubles for NCC which include rapid settling/creaming, crystal growth and inconsistent dosing. Consequently, using a suitable stabiliser is required to wet the NCC surfaces and prevent agglomeration. Even though distinct dosage forms may share a few commonality concerning stability concerns which include sedimentation, particle agglomeration or crystal growth, their effects on drug products are not standard [18].

Sedimentation: In suspension, NCC can both settle down or cream up inside the method medium depending on their density relative to the dispersion medium. in line with Stoke's regulation, the sedimentation rate of particles in suspension is closely associated with particle length, medium viscosity and density difference between medium and dispersed phase. inside the manufacture of NCC, a reduction of particle size forms an essential issue in manufacture and forms the most usually utilised method to lessen particle settling. similarly, the use of use of thickening retailers to increase the viscosity of the dispersing media as well as matching NCC drug particle density to that of the dispersion media have additionally been utilised [19].

Crystal growth: Particle size and poly-dispersity indices in colloidal suspensions increase as a result of Ostwald ripening, usually known as crystal increase. Solubility dependency on particle size is the important thing concept of Oswald ripening. consistent with the Ostwald–Freundlich equation,8 smaller debris have a better saturation solubility than larger ones, which leads to a gradient in drug concentration among small and huge particles. As a result, molecules flow from regions of smaller particles with higher drug awareness to regions of larger particles with lower drug attention. As a result, a supersaturated answer forms around the massive fragments, causing the medicine to crystallize on top of them.

Stability on solidification: ln lots of cases the selection of the NCC in the final product is in stable nation as many stability issues are eliminated inside the strong. The most utilised process to attain stable dry

powders are freeze drying and spray drying these dry powders are intended for reconstitution into nano-suspensions previous to management and as such there is a requirement to prevent the of increase or agglomeration of NCC throughout the drying. ln this manner, the capabilities related to nano-sizing which include rapid dissolution following the reconstitution are maintained and avoidance of arterial or venous blockage inside the occasion of IV administration. To prevent this instability in the solidification process, the addition matrix formers, inclusive of mannitol, sucrose and cellulose previous to drying is usually utilised [20].

THREATS

Translation into marketable products: For each product this is developed there may be an apparent need to translate the usage of the product to the health center. The NCC generation is one this is commonly implemented to compounds that have a low developability. NCC technology can normally be considered delayed to marketplace for comparable reasons as nanocrystals were initially delayed. These worries to start with had been targeted around organization and companies lacking experience and abilties to cover the complete scale-up and clinical production technique that's quite sophisticated for nanocrystal arrangements and might ideally be extra complex for NCC. This would entail the era will ought to compete with other permitting strategies to formulate drug applicants of low developability, that could greater easily be carried out in-house [21].

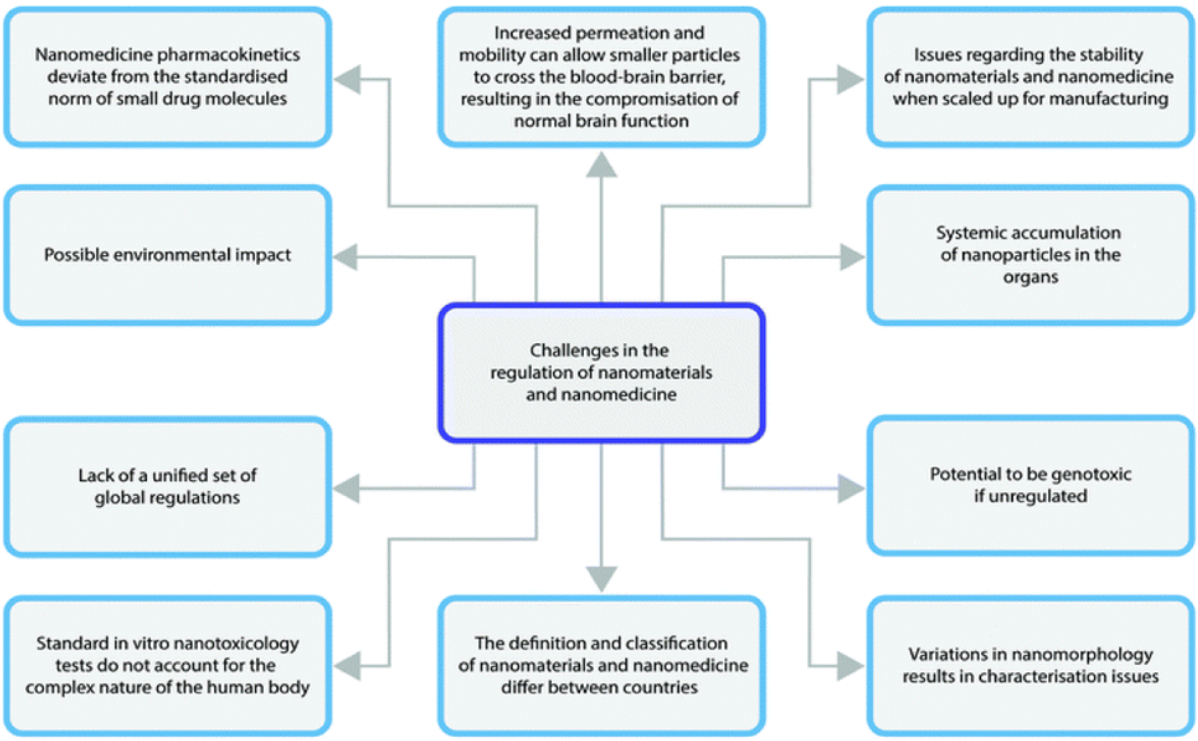

Fig. 4 Schematic illustration highlighting the principal challenges in nanomaterials law. Reproduced without amendment from ref. with permission from the Royal Society of Chemistry according with the creative Commons agreement[22].

Contamination: The improvement of NCC may be by using either top-down or bottom-up strategies. Even as these strategies are exceptionally straightforward, they present with the possibility of contamination from the milling media in top-down strategies within the top-down technique and the possibility of the concentration of residual solvents exceeding desirable limits in bottom-up techniques. This could be a chance to the development of the technology because the purity of the NCC formulation might be compromised [23].

Other established nano drug delivery structures: The development of NCC is also under hazard from other more established and translated nano drug delivery structures like liposomes, micelles or solid lipid nanoparticles that have already entered the marketplace and maximum groups have the ability to utilise already current infrastructure and employees. This was specially obvious within the rapidity with which lipid primarily based nanoparticles were utilised within the current coronavirus disease 2019 vaccine improvement and may offer an insight to future nano medicines and vaccines improvement. In addition, many of the benefits related to NCCs consisting of more suitable solubility and advanced stability also can be carried out by using the aforementioned established drug delivery systems [24].

Future Perspectives

The potentialities of nano-suspensions in the form of NCC are promising as they are able to contribute as an alternative device for drug improvement scientists to avoid many components and drug transport challenges especially with tough API. The sector on NCC continues to be in its infancy and can only develop primarily at the successes of the numerous published. One clearly exciting region for this generation, which may be extrapolated from nanocrystal technology, is within the advancement in biotechnology and useful resource of amendment tools together with antibody–drug conjugate and Nano-bodies with the ability to create simultaneous administration of API and high concentration monoclonal (mAb) and biosimilar products [25]. These would be predicted to have properties more desirable biopharmaceutical and safety traits. It was recently verified that a biologically energetic, nanocluster dispersion of antibodies in answer the use of carbohydrate stabilisers may be synthetic with the capacity enable patient self-management via subcutaneous injection of antibody therapeutics. Future

improvement of permitting technologies like NCC can provide technical solutions to many system challenges presently confronted through protein and peptide-primarily based API [26].

Conclusions

Nano-crystallisation and co-crystallisation are styles of crystal engineering typically used for development of physicochemical residences of many APIs usually within the BCS elegance II and IV. They may be considered as one of the pinnacle alternatives for components of intractable hydrophobic payloads limited via high molecular weights, noticeably fine log [thin space (1/6-em)]P values, excessive melting factors and high dose. Orthodox size discount techniques which include moist media milling and HPH for pinnacle-down and cold sono-precipitation, emulsion-solvent evaporation, solvent diffusion and micro-emulsion strategies for backside-up methods may be effectively used to combine nano-crystallisation with co-crystallisation and advantage from a synergy between the techniques. The strategies of manufacture are effortlessly scalable to supply nano-suspensions with multiple payload. The NCC technology can be utilised to enhance the bioavailability of API due to expanded saturation and intrinsic solubility. Moreover, NCC can be used to impart appreciable muco-adhesivity through adaptability for surface modification on the co-crystal floor. The surface of the co-crystal can similarly be changed for on-target drug delivery, lowering damaging results. It is also cardinal to word the ability of NCC with regards to routes of administration and ability to acquire drug delivery in methods Nano-suspensions or co-crystals had been incapable. It does remain, but, to be visible how nice this novel era can be explored to conquer the shortcomings of its predecessors.

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