NANOSUSPENSION: RECENT TRENDS AND TECHNOLOGIES

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ABSTRACT

With the advent of modern technologies, a large number of drugs have been discovered which have a better efficiency but their clinical application is restricted due to poor water solubility. Nearly 40 % of the drugs in the pipeline and around 60 % of compounds coming directly from synthesis have poor solubility. Poor water solubility has become a leading challenge for the formulation of these compounds. Poor solubility is generally associated with poor bioavailability. Nanosuspension has the potential to overcome this issue. Change of materials into the nanodimension dramatically changes its physical properties. Drug nanocrystals are crystals with a size in the nanometer range (mean diameter < 1000 nm). This review article outlines the various pharmaceutical advantages of nanosization industrially relevant production technologies available currently (high pressure homogenization, pearl milling) with advantages and disadvantages of each and the various dosage forms developed using nanocrystals. The nanosuspension products in the market / pipeline will be briefly reviewed and the advantages of these as compared to traditional products would be highlighted.

Keywords: Nanosuspension, high pressure homogenization, pearl milling, drug nanocrystals, dissocubes.

INTRODUCTION

The automation of the drug discovery process by technologies such as high-throughput screening, combinatorial chemistry and computer-aided drug design is leading to a vast number of drug candidates possessing a very good efficacy¹. Unfortunately, many of these drug candidates (about 60 %) are exhibiting poor aqueous and non-aqueous solubility and / or erratic absorption and hence require innovative formulations and drug delivery systems². In addition, poorly water-soluble drugs are specially challenging, as they cannot achieve dissolution and therefore they have a very difficult pass through the dissolving fluid to contact the absorbing mucosa and to be absorbed³. If the dissolution process of the drug molecule is slow, due to the physicochemical properties of the drug molecules or formulation factors, then dissolution may be the rate-limiting step in absorption and will influence drug bioavailability⁴. This is the case of Bio-pharmaceutical Classification System (BCS) Class II and Class IV drugs. For these kind of drugs, micronization⁵⁻⁸, nanonization⁹⁻¹¹, complexation (e.g. cyclodextrins)¹²⁻¹⁷, preparation of liposomes¹⁸⁻²⁰, amorphous solid dispersions²¹⁻²⁵, solubilization using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions, salt formation, precipitation techniques etc. have been proposed to increase the rate of dissolution and especially the drug bioavailability after oral administration for systemic drug absorption²⁶. These techniques have their own limitations and hence have limited utility²⁷. An alternative and promising approach is the production of drug nanosuspensions that improves drug efficacy and pharmacoeconomics²⁸. A nanosuspension consists of drug nanocrystals, stabilizing agents and a liquid dispersion medium. The major advantages of nanosuspension technology are its general applicability to most drugs and its simplicity and are now the universal formulation approach for most drugs²⁹. Nanosuspension technology offers solution not only to solubility of drug but also alters the pharmacokinetic of drug and thus improves drug safety and efficacy³⁰. The poorly soluble and Low-bioavailability drug, so called “brick dust” candidate once abandoned from

formulation development, can be rescued by formulating into nanosuspension³¹. The aim is “maximizing dissolution rate and boosting bioavailability” of drugs.

Nanosuspension: The Formulation Approach For Overcoming Poor Solubility Problems Of Drugs

Definition

A Nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as very finely colloid, Biphasic, dispersed, solid drug particles in an aqueous vehicle, size below 1 µm, without any matrix material, stabilized by surfactants and polymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral, topical, parenteral, ocular and pulmonary routes³².

Properties of nanosuspension

An outstanding feature of nanosuspensions is the increase in saturation solubility and consequently an increase in the dissolution velocity of the compound. The increase in saturation solubility can be explained by the Kelvin–Gibbs and the Ostwald–Freundlich equations. The Kelvin equation describes the vapor pressure over a curved surface of a liquid. It describes droplets in a gas phase. The vapor pressure increases with increasing curvature of the droplets, which means decreasing particle size. It has also been postulated that the surface curvature of the dissolving solid particles will influence solubility in water. The basic theory derives from the classical Gibbs–Kelvin equation, which, when adapted to the solubility of solids, is known as the Ostwald–Freundlich equation:

$$(G) = RT \ln(Sr/S\infty) = (2\gamma V)/r_{(1)} \text{ or it can be simply written as } \ln(Sr/S\infty) = 2\gamma M/pRT_{(2)}$$

where (G) is the difference in the free energy of a solution of small and large particles; Sr and S∞ are the solubility of a spherical particle of radius r and the solubility of a non curved solute surface (r → ∞), respectively; V is the molar volume of the solute; M is molarities of the solute; ρ is density; γ is the solid–liquid interfacial tension; R is the

universal gas constant; T is the absolute temperature; and r is the particle radius. Equation (1) is valid for particles that have a very large surface-to-volume ratio and is of practical importance only for particles smaller than $1.0\ \mu\text{m}$ diameter³³⁻³⁶. This has also been claimed that the surface of finely divided solids may be less regularly crystalline and more amorphous than that of well-grown crystals³⁶. There are thus different reasons behind deviations from the thermodynamically stable solubility. Factors such as impurities, ion effect, particle size and crystal structure are some of the factors that may lead to such deviations. The most important feature of nanocrystals is the increase in saturation solubility and surface area and consequently an increase in the dissolution velocity of the compound. The law of Noyes–Whitney describes the dissolution velocity³⁷:

$$dC/dt = DA(C_s - C_x)/h \quad (3)$$

D is the diffusion coefficient, A is the surface area, C_s is the saturation solubility, C_x is the bulk concentration and h is the so-called “diffusional distance” over which the concentration gradient occurs (note: division of the equation by the volume v leads to dC/dt). It is obvious that an increase in the surface area consequently increases the dissolution velocity, e.g. exploited in micronized or nanosized products. In addition, drug nanoparticles are characterized by an increase in saturation solubility C_s . According to Noyes and Whitney, the increase in C_s —in addition to enlargement surface area—further increases the dissolution velocity. The final saturation solubility achieved is, of course, compound-specific based on the differences in compound-specific dissolution pressures. The dissolution velocity is reversely proportional to the diffusional distance h , which means that reducing h leads to a further increase in dissolution velocity. According to the Prandtl equation³⁸⁻⁴⁰, the diffusional distance h decreases for very small particles. The simultaneous increase in saturation solubility C_s and decrease in h leads to an increased concentration gradient $(C_s - C_x)/h$, thus enhancing the dissolution velocity in addition to the surface effect. 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, leading to an increased dissolution rate and therefore improved bioavailability⁴¹. Drugs encapsulated within nanosuspensions exist in pharmaceutically acceptable crystalline or amorphous state. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption.

Apart from this, nanosuspensions have some following advantages

- Firstly, drugs no longer need to be in the soluble form. It is effective for those molecules insoluble in oils;
- Secondly, the high drug loading can be achieved as a drug exists in the form of pure solids and can significantly reduce the administration volume of high dose;
- Thirdly, nanosuspensions can increase the physical and chemical stability of drugs as they are actually in the solid state;
- Finally, nanosuspensions can provide the passive targeting⁴².

Production of Nanosuspension-Overview of Existing Technologies

There are several production techniques to produce drug nanocrystals. Basically, one can differentiate between top-down and bottom-up technologies. Typically, the drug nanocrystals are generated in a liquid dispersion medium (e.g. by precipitation or a disintegration process). The obtained product from this process is a suspension of drug nanocrystals in a liquid stabilized by a surfactant or polymer (so-called “nanosuspensions”). In contrast to micronized powders, the drug nanocrystals can be administered using very different administration routes⁴³.

Bottom-up Technologies

The term “bottom-up technology” means that one starts from the molecular level and goes via molecular association to the formation of a solid particle. That means that we are discussing classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a non-solvent or changing the temperature or a combination of both. The Latin terminology is via humida paratum (v.h.p.), which means being prepared via a liquid process (solutions are made to obtain a fine powder [precipitate] dispersed in a ‘wet’ environment)⁴⁴.

Precipitation technique

The particles generated by precipitation, as for example by Sucker, are in most cases crystalline in nature; in contrast to this, the company Knoll (nowadays owned by Abbott, the new name is “Solids”) created amorphous particles by a precipitation technique⁴⁵. The product is Nano Morph TM. The precipitation in the amorphous form is achieved by an aqueous polymer solution. However, for a commercial product, it is necessary to preserve the amorphous character during the shelf life to avoid changes in bioavailability caused by a reduction in the dissolution velocity due to the transfer of the amorphous drug to a crystalline drug⁴⁴. The advantage of the precipitation techniques is that relatively simple equipment can be used. For example, the solvent can be poured into the non-solvent with a constant velocity in the presence of a high-speed stirrer. Very elegant approaches are the use of static mixers or micromixers, which simulates the precipitation conditions in a small volume (i.e. simulating lab scale conditions), but being simultaneously a continuous process. In the case of micromixers, scaling up can be performed in a simple way just by so-called numbering up, which means arranging many micromixers in parallel. The equipment is relatively simple and in the case of large conventional static mixers, of relatively low cost (this is not necessarily valid for the micromixers). However, there are some major general disadvantages of the precipitation techniques. The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and inorganic media).

- The solvent needs to be miscible with at least one non-solvent.
- Solvent residues need to be removed, thus increasing production costs.
- It is a little bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction).

In general, it is recommended that a second consecutive process be performed for particle preservation, that is, spray drying or lyophilization⁴⁴.

Top-Down Technologies

There are basically two top-down techniques, which mean starting from a large-sized powder and performing a size diminution⁴³⁻⁴⁴.

Pearl Milling

Liversidge and co-workers developed the milling process to yield the so-called NanoCrystals^R. The mills used by the Elan Company are basically containers with small pearls, beads, or balls that can have different sizes, a typical size being 1–2 mm. The drug powder is dispersed in a surfactant solution and the obtained suspension is poured into the mill. In the milling process, the pearls are moved, either by using a stirrer or by moving the milling container itself. The drug particles are disintegrated between the moving pearls. This process is accompanied by the erosion of milling material from the pearls, a phenomenon well known for these mills and documented in the literature⁴⁴.

The milling technique clearly has some advantages:

- Simple technology
- Low-cost process regarding the milling itself
- Large-scale production possible to some extent (batch process)
- As disadvantages, we can see:
- Potential erosion from the milling material leading to product contamination
- Duration of the process not being very production friendly
- Potential growth of germs in the water phase when milling for a longtime
- Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.

Homogenization

Homogenization in Water: The second most frequently used disintegration method is milling by high pressure homogenisation. The two existing homogenisation principles (homogeniser types) applied are:

- Microfluidisation (Microfluidics Inc.)
 - Piston-gap homogenisers (e.g. APV Gaulin, Avestin, etc.)
- In microfluidizer, a frontally collision of two fluid streams under pressure up to 1700 bar leads to particle collision, shear forces and cavitation forces. The collision chambers are designed as Y-type or Z-type. A major disadvantage of microfluidizers is the required long production time. In many cases, time-consuming 50–100 passes are necessary for sufficient particle reduction⁴⁶. The company Skye Pharma Canada Inc. applies this technology to produce submicron particles of poorly soluble drugs⁴³⁻⁴⁶. Cavitation was employed as the most important effect to diminish particles in a piston-gap homogenizer. In this homogenizer types, the dispersion (emulsion or suspension) passes a very tiny gap with an extremely high velocity. Prior to entering the gap, the suspension is contained in a cylinder with a relatively large diameter compared to the width of the following gap. In the APV LAB 40, the diameter of the cylinder is about 3 cm, it narrows to about roughly 3–25 μm (varies with applied pressure) when the suspension enters the homogenization gap. The cavitation and shear forces in the gap were sufficiently high to break particles that were distinctly larger than the gap width. Therefore it is possible to disrupt relatively large sized powders (up to 200 μm)^{43,44,47}.

According to the law of Bernoulli, the flow volume of a liquid in a closed system per cross section is constant. That means the reduction in the diameter leads to a tremendous increase in the dynamic pressure and simultaneously a decrease of the static pressure when the liquid is in the homogenizer gap. A liquid boils when its vapor pressure is equal to the air / static pressure of the environment. In the gap, the static pressure drops below the vapor pressure of the liquid at room temperature. Consequently, the liquid starts boiling, forms gas bubbles that implode after leaving the homogenization gap and being again under normal air pressure conditions^{43,44}. To summarize: homogenization with piston-gap homogenizers has good potential to be used as a production technique because it fulfills the key industrial features such as large-scale production and various regulatory aspects^{43,44}.

Homogenization in water-liquid mixtures and non-aqueous media

The DissoCubes^R patent describes homogenization in pure water as a dispersion medium; the rationale behind is that the cavitation is seen as being responsible for the diminution of the particles. To obtain cavitation in the dispersion medium, one needs to have a high vapor pressure of the dispersion fluid at room temperature. This is fulfilled with water, but not with other liquids such as oils or liquid polyethyleneglycol (PEG) 600. In addition, homogenization at higher temperatures (e.g. 80°C) should be much more efficient than at room temperature because the vapor pressure of water is much higher at 80°C, thus leading to more extensive cavitation⁴⁸. The basic of the Nanopure^R technology is that homogenization was performed against these teachings, leading to a comparable or even improved product. Under the Nanopure^R technology, not only drugs, but also polymers can be processed, leading to a product with a mean diameter in the nanometer range (nanoparticles) or a size of a few micrometers. Nonaqueous dispersion media can be used to produce oral formulations, for example, drug nanocrystals dispersed in liquid PEG 600 or Miglyol (MCT) oil, that can be directly filled into soft gelatin capsules, sealed hard gelatin capsules, or hydroxypropylmethyl cellulose (HPMC) capsules. Nanosuspensions in mixtures of water with water-miscible liquids (e.g. ethanol, isopropanol) can be used in the granulation process for tablet production; the solvent mixture evaporates much better than water. Drugs that are susceptible to hydrolysis in water can be prepared as non-aqueous suspensions, for example ethanol, glycerol, or propylene glycol⁴⁹. Prior to intravenous injection, the glycerol drug nanosuspensions can be diluted with water for injection to yield an isotonic suspension. Alternatively, isotonic water glycerol mixtures can be directly homogenized. Another option of the Nanopure^R technology is the production of aqueous polymer particle dispersions with a diameter of a few micrometers or in the nanometer range. This could be an alternative to polymer dispersions (e.g. surelease, ethyl cellulose) for the coating of tablets that are now produced by using solvents⁴⁴. Table 2 gives a comparison of the three techniques.

Combination technology (NANOEDGE)

In 2001, the Baxter Healthcare Company presented their NANOEDGE^R technology at the annual meeting of the American Association of Pharmaceutical Scientists (AAPS) in Denver. NANOEDGE^R is an aqueous suspension of drug nanoparticles suitable for intravenous injection. The particles

are prepared basically by a high-pressure homogenization process, which means either by microfluidization or homogenization in water using piston-gap homogenizers, or alternatively, by a new production process developed by Baxter⁴⁴. This process is called the “micro-precipitation method,” and is a combination of precipitation followed by a process with high-energy input (e.g., homogenization). The process includes three steps:

- Dissolving the organic compound in a water-miscible first solvent to form a solution;
- Mixing this solution with the second solvent to obtain a “pre-suspension” (= precipitate);
- Adding energy to this “pre-suspension” to form particles having an average effective particle size of 400 nm to 2.0 µm.

The advantages of the Baxter method are that the problem of the precipitation technique—continuing crystal growth after precipitation—have been overcome because the particles are only an intermediate product to undergo subsequent diminution / annealing. In addition, by optimal choice of precipitation conditions, more friable particles (semi-crystalline, amorphous) can be produced which allow more effective diminution in the subsequent high pressure homogenization step. This is of special importance when the available jet milled drug is highly crystalline and simultaneously possesses a very hard crystal structure (high Mohs degree). In such cases, the direct homogenization of the

jet-milled powder can require a higher number of homogenization cycles, which means longer production times. In the case of very hard crystals, the maximum homogenization pressure applicable during production (e.g. 2000 bar) might potentially lead to a maximum dispersivity being rather close to 1 µm and not in the preferred nanometer range⁴³⁻⁴⁴. Another combination technology has been developed by Petersen using ball milling and subsequent high-pressure homogenization (CT)⁵⁰. With the CT technology, the performance (e.g. physical stability) of nanocrystals could be distinctly improved, as for example for dermal application. Nanocrystals can increase the penetration of poorly soluble cosmetic and pharmaceutical actives into the skin. The increased saturation solubility leads to an increased concentration ingredient, thus promoting passive penetration. Molecules penetrated into the skin are very fast replaced by new molecules dissolving from the nanocrystal depot in the cream. The first four cosmetic nanocrystal products with rutin were launched by Juvena. Compared to the water-soluble rutin glucoside, the original rutin molecule as smart Crystal formulation possesses a 500 times higher bioactivity (as measured by sun protection factor [SPF]^{50,51}. Of course the same principle can be applied to poorly soluble pharmaceutical drugs of interest for dermal application. Dermal application of nanocrystals is protected by a US and Patent Cooperation Treaty (PCT) patent application^{50,51}.

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

Nanocrystal	Company	Patent / patent application examples
Hydrosol	Novartis (prev. Sandoz)	GB 22 69 536 GB 22 00 048
Nanomorph™	Soligs/ Abbott	D 19637517
Nanocrystal™	elan Nanosystems	US 5,145,684
Dissocubes®	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
NANOEDGE™	Baxter	US 6,884,436

Table 2: Advantages and disadvantages of different methods for the production of Nanocrystals

Technology	Advantages	Disadvantages
Precipitation	<ul style="list-style-type: none"> • Finely dispersed drug • Good control of desired size 	<ul style="list-style-type: none"> • Needs to be Stabilized • Organic solvent residue • Not universally applicable, only drugs with certain properties are possible (e.g., soluble in at least one solvent)
Milling	<ul style="list-style-type: none"> • Low-energy technique • Proven by 4 FDA approved drugs 	<ul style="list-style-type: none"> • Residue from milling media • Can be a slow process • Needs to be stabilized • Large batches difficult to produce due to size of milling chamber
Homogenization	<ul style="list-style-type: none"> • Universally applicable • No problem with large batches • Fast method (several minutes possibly) • Water free production possible 	<ul style="list-style-type: none"> • High-energy technique • Great experience needed

Final Formulations of Drug Nanosuspensions

Aqueous or non-aqueous drug nanosuspensions exhibit a physical long-term stability, which in theory should be sufficient to place them on the market as liquid products. This might be suitable for certain groups of patients, e.g. children or elderly patients, but not for the “normal” patient. In general, a dry oral dosage form is preferred, that means a tablet or a capsule. In case of drug nanosuspensions in pure water (Disso-Cubes) or in water containing mixtures (Nanopure) they can be used as granulation fluid in the granulation process for the production of tablets or alternatively as wetting agent for the extrusion mass to produce pellets. Spray-drying is also possible whereas water-ethanol mixtures will evaporate faster than pure water. The

produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules. The new feature of Nanopure is that drug nanocrystals can be produced in non-aqueous media such as oils or liquid / solid PEG which can directly be used for the filling of capsules. The dispersion of the crystals in oil promotes drug absorption exploiting the absorption enhancing effect of lipids. 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 powder in the capsules. To summaries, there are manifold

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; the shelf life of up to 3 years was shown for selected nanosuspensions. Alternatively, lyophilised products can be offered to be reconstituted prior to administration⁵².

Applications of Drug Nanosuspension

Oral administration of the nanosuspension

First choice of application is oral administration. When a drug is given orally, the bioavailability and finally its efficacy depends on the solubility and absorption in the gastrointestinal tract. A way to improve bioavailability of atovaquone or buparvaquone would be to increase the absorption rate by formulating them as a nanosuspension. Oral administration of nanosuspensions can overcome this problem because of the high adhesiveness of drug particles on biological surfaces—here the epithelial gut wall—and prolonging the absorption time. In comparison to Wellvone-treated mice, containing a micronized drug, nanosuspensions of atovaquone at equivalent doses reduced infectivity from 40 % to 15 % at a reduced drug concentration of only 7.5 mg/kg after oral administration⁵³. These results reflect the potency of the nanosuspension technique, reducing drug load from 22.5 to 7.5 mg/kg (Wellvone^R), but increasing activity 2.5-fold at the same time^{53,54}. It is also worth mentioning that a prepatant is classified as a BCS Class II and IV compound, emphasizing that nanonizing is not only confined to high-permeability compounds but may also be applicable to low-permeability drugs, provided dissolution is the slower step in the absorption process^{55,56}.

Parenteral Nanosuspension –Intravenous administration

Administration of drugs via the parenteral route is critical. Formulation of atovaquone as a nanosuspension for intravenous (I.V.) use to treat murine toxoplasmosis showed a significant reduction of *Toxoplasma gondii* at a dose of 0.3 mg/kg in comparison to 30 mg/kg when given orally⁵³. The nanoparticle-based product Abraxane^R was approved by the Food and Drug Administration (FDA) in 2006 for intravenous administration. Abraxane^R is a novel formulation consisting of lyophilized particles with 10 % (w/w) paclitaxel and 90 % (w/w) albumin. The particle size of the suspension is about 130 nm. In a Phase I trial, 39 patients with advanced non-hematologic malignancies were treated at dose levels from 80 to 200 mg/mL in multiple cycles of weekly 30 min intravenous infusions. In contrast to Taxol treatment, no premedication was used in this study. The maximum tolerated dose observed from this study was higher than the commercial Taxol^R formulation⁵⁷. Other investigators reported that particle size played an important role in pharmacokinetics and tissue distribution of oridonin nanosuspension⁵⁸.

Pulmonary Drug Delivery

Many water-insoluble drugs were delivered to the respiratory tract for local or systemic treatment of diseases. The nebulized nanosuspensions produce aerosol droplets loaded with a large number of drugs nanocrystals. The respirable fraction is distinctly increased using nebulized nanosuspensions compared to nebulized microcrystals (conventional MDIs). The smaller particle the size of the drugs nanocrystals, the more droplets are loaded with drug. In addition, the muco-adhesive property of nanoparticles leads to a prolonged residence time at mucosal surface of the

lung⁴⁶. Yang *et al.* reported that nanosuspensions of fluticasone exhibited good physical / chemical properties for pulmonary delivery. The pharmacokinetic studies after the intra tracheal administration of nanosuspensions showed deep lung deposition and fast lung absorption, with solubility playing an important role in lung retention and duration of action⁵⁹. Superiority of the drug nanosuspension was also shown by Hernandez-Kirstein using buparvaquone nanosuspensions for pulmonary delivery system⁶⁰.

Transdermal Delivery of Nanosuspension

It has been reported to use diclofenac sodium nanosuspension for transdermal delivery. The basic transdermal characteristics of the nanosuspension were evaluated using a Yucatan micropig (YMP) skin model. Diclofenac sodium nanosuspension was successfully dispersed into isopropylmyristate as a nanosized suspension via complex formation with sucroseerucate. The resultant nanosuspension increased the permeability flux of diclofenac sodium across the skin by up to 3.8-fold compared to the control. The optimal weight ratio for the highest diclofenac sodium permeation was 8.8, at which point the mean diameter of the nanosuspension was 14.4 nm⁶¹.

Ocular Delivery of Nanosuspension

Drug nanosuspension for ocular drug delivery system has been developed by Pignatello *et al.*⁶²⁻⁶⁵. The codispersion of cloricromene- hydrochloride (AD6) in Eudragit RS or RL polymers resulted in nanosuspensions that showed good mean sizes for ophthalmic applications and a positive surface charge. The suspensions allowed for improved corneal adhesion and stability upon storage, particularly at low temperatures. When preparation was performed in an isotonic saline solution, the dispersion of AD6 in the polymer network protected the ester drug from the hydrolytic cleavage into the inactive and insoluble acid form. According to preliminary biological evaluation of the nanosuspensions that showed higher drug availability in the rabbit aqueous humor after the drug's administration in Eudragit RL nanosuspensions, AD6-loaded Eudragit Retard nanosuspensions appear to offer a promising means of improving the shelf life and bioavailability of this drug after ophthalmic application⁶².

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