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REVIEW ARTICLE

NANOSUSPENSION: AN OVERVIEW

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ABSTRACT:

Nanotechnology has emerged as a tremendous field in the medicine. Nano refers to particles size range of 1-1000nm. Nanosuspensions are part of nanotechnology. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Nanosuspension technology is a unique andeconomical approach to overcome poor bioavailability that is related with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous media. Nanosuspensions are important carriers to develop novel drug formulations. Few techniques such as precipitation methods, milling methods and homogenization methods are developed to produce nanosuspension (NS) and have been successfully employed in large-scale production. They are administered by Parenteral, per oral, ocular and pulmonary routes. Now their application also extended to site specific delivery. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspension technology can be used to improve the stability as well as bioavailability of poorly soluble drug.

Nanosuspensions are also use in various dosage forms, including specialized drug delivery system such as mucoadhesive hydrogel. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. Rapid strides have been made in the delivery of nanosuspensions by parenteral, per-oral, ocular and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery.

Keywords: Nanosuspension, Bioavailability, Poorly soluble drugs, Drug Delivery, Nanospheres, High pressure homogenization.

INTRODUCTION:

Nanosuspensions are colloidal dispersions and biphasic system consisting of drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate due to increased surface area and saturation solubility[1].

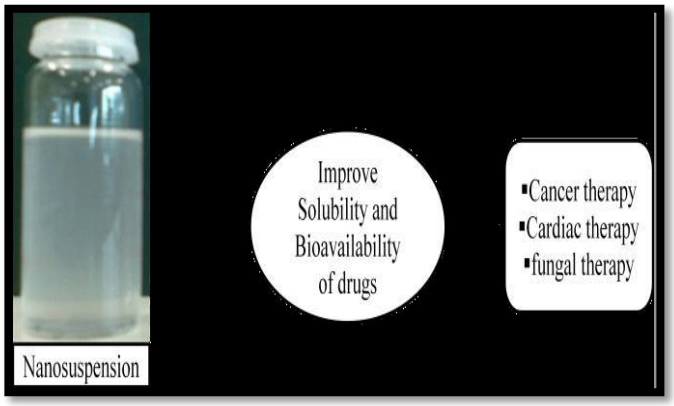

Figure 1: Nanosuspension applications in the field of medicine

Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water-and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies. This review focuses on the various aspects of nanosuspensions and their potentials as promising strategy in drug delivery. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10-9 meters [2].

Nanotechnology is an applicable aspect of a broader area of nano science which is one of the upcoming and highly challenging as well as rewarding key research area in the modern scientific set up. It is the science of small particle having unique properties, which change on altering the size of the particle[3].

Pharmaceutical industries are constantly seeking new approaches in order to obtain an adequate oral bioavailability, as most of biological properties exhibiting NCEs are poorly water - soluble. The increasing frequency of poorly water soluble NCEs exhibiting therapeutic activity is of major concern to the development of new formulations in pharmaceutical industry which leads to low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds. Recently, the formulation of such drugs as nanoscale systems (which have a size below 1µm) has rapidly evolved as a new and novel drug delivery system. The major characteristic of these systems is the rapid

dissolution rate, which enhance bioavailability after oral administration[4].

TECHNIQUE OF PREPARATION OF NANOSUSPENSION

Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols) are called 'Bottom up technology'. In Bottom up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. This technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles[5].The 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege)[6,7].

Improvement of bioavailability

Improvement of bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. By many estimates up to 40% of new chemical entities discovered by the pharmaceutical industry today are poorly water soluble compounds. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved tominimize the limitations to oral availability[8]. The main possibilities for improving dissolution according to thisanalysis are:

• To increase the surface area available for dissolution by decreasing the particle size of the solid compound:

• By optimizing the wetting characteristics of the compound surface,

• To decrease the diffusion layer thickness,

• To ensure sink conditions for dissolution and,

• To improve the apparent solubility of the drug under physiologically relevant conditions[9].

Need of Nanosuspension for bioavailability enhancement

Nevertheless, pharmacokinetic studies of BCS class – II drugs showed that they have a low oral bioavailability, which may be due to poor water solubility of drug. There are many classical pharmaceutical ways to improve drug dissolution rate such as dissolution in aqueous mixtures with an organic solvent[10]; formation of ß-cyclodextrincomplexes[11]; solid dispersions[12]; and drug salt form[13].

ADVANTAGES OF NANOSUSPENSIONS

The major advantages of nanosuspension technology are[14]:

• Provides ease of manufacture and scale-up for large scale production

• Long-term physical stability due to the presence of stabilizers

• Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability

• Rapid dissolution and tissue targeting can be achieved by IV route of administration.

Interesting special features of nanosuspensions

• Increase in saturation solubility and consequently an increase in the dissolution rate of the drug.

• Increase in adhesive nature, thus resulting in enhanced bioavailability[15].

Criteria for selection of drug for nanosuspensions

Nanosuspension can be prepared for the API that is having either of the following characteristics[16]. Water insoluble but which are soluble in oil (high log P) or API are insoluble in both water and oils Drugs with reduced tendency of the crystal to dissolve, regardless of the solvent API with very large dose.

CHARACTERIZATION TECHNIQUES:

Nanosuspensions are characterized for appearance, color, ordor, assay, related impurities, particle size, zeta potential, crystalline status, dissolution studies and in vivo studies. Among this, the most important characterization techniques were discussed.

1. Mean particle size and particle size distribution

The mean particle size and the span of particle size distribution (polydispersity index, PI) are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability, even in-vivo behavior of nanosuspensions[17].

2. Surface charge (zeta potential)

Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself[18].

3. Crystalline state and particle morphology

The assessment of the crystalline state and particle morphology togather helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing[17]. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressurehomogenization[19].

4. Saturation solubility and dissolution velocity

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturationsolubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature.

FORMULATION OF NANOSUSPENSION

1. Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing stericor ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable Nanosuspension.

2. Organic solvents

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical area, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating a nano suspensions using emulsions or microemulsions as templates.

3. Co-surfactants

The choice of co-surfactant is critical when using microemulsions formulate nanosuspensions. Since co-surfactant scan greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsions composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassiumglycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions[20,21].

4. Other additives

Formulation considerations Nanosuspensions may contain additives such as buffers, salts, polyols, osmogentand cryoprotectant, depending on either the route of administration or the properties of the drug moiety[22].

4.1. *In-vitro* evaluations

4.1.1. Particle size and size distribution

4.1.2. Particle charge (Zeta Potential)

4.1.3. Crystalline state and morphology

4.1.4. Saturation solubility and dissolution velocity[23].

4.2. *In-vivo* evaluation

4.3. Evaluation for surface-modifirdnanosuspension

4.3.1. Surface hydrophilicity

4.3.2. Adhesion properties

4.3.3. Interaction with body proteins.

4.1. *In-vitro* evaluation:

4.1.1. Mean particle size and size distribution

The mean particle size and the width of particle size distribution (called Polydidpersity Index) are determined by Photon Correlation Spectroscopy (PCS). Particle size and polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3 nm- 3 μm only. PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD).

4.1.2. Particle charge (zeta potential)

The determination of the zeta potential of a nanosuspension is essential as it gives an idea about the potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspensions exhibiting good stability, for an electrostatically stabilized nanosuspensions minimum zeta potential of 30mV is required whereas in the case of a combined electrostatic and 20 mV is desirable.

4.1.3. Crystalline state and particle morphology

The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug. Differential Scanning Calorimetry (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. **See table 1.**

Table 1: **Current Marketed Pharmaceutical Products Utilizing Nano crystalline Formulation:**

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

4.1.4. Solubility and Dissolution velocity

The main advantage associated with then a nosuspensions is improved saturation Solubility as well as dissolution velocity. These are studied in different physiological solution sat different pH. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. Determination of these parameters is useful to assess in vivo performance of theformulation.

4.2. In-*vivo* evaluation

The in vivo evaluation of the nanosuspensions is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometry.

Applications

Applications of nanosuspensions had land marking history and the applications given are few.

1. Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. .Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability[24].

2. Parenteral drug delivery

One of the important applications of nanosuspension technology is the formulationof intravenously administered products. IV administration results in several advantages,such as administration of poorly soluble drugs without using a higher concentration of toxicco-solvents, improving the therapeutic effect of the drug available as conventional oralformulations and targeting the drug to macrophages nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as use of surfactants, cyclodextrins, etc., to improve bioavailability[25].

3. Pulmonary drug delivery

Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibitpoor solubility in pulmonary secretions. Aqueous nanosuspensions can benebulized using mechanical or ultrasonic nebulizers for lung delivery. Because oftheir small size, it is likely that in each aerosol droplet at least one drug particle iscontained, leading to a more uniform distribution of the drug in lungs[26]**.** The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action.

4. Ocular drug delivery

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility inlachrymal fluids. Nanosuspensions, by their inherent ability to improve the saturationsolubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs and Nanoparticulate nature of the drug allows its prolonged residence in the culdesac, giving sustained release of the drug[24].

5. Targeted drug delivery

Nanosuspensions can be used for targeted delivery as their surface properties and in-vivobehavior can easily be altered by changing either the stabilizer or the milieu. The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems[27].

6. Mucoadhesion of the nanoprticles

Nanoparticles orally administered in the form of a suspension diffuse into the liquidmedia and rapidly encounter the mucosal surface. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption[28]. **See table 2.**

Table 2: The New Drug Application Based on Nanosuspensions Technique Reported and Marketed by Now:

Drugs	Indication	Author or Company	Route	Status
Paclitaxel	Anticancer	American Bioscience	Intravenous	Marketed
Danazol	Hormone	Rogers T.L.	Oral	Reported
Naproxen	Anti-inflammatory	AnchaleeAin-Ai	Oral/parenteral	Reported
Probucol	Lipid lowering	JyutaroShudo	Oral	Reported
Rapamune	Immunosuppressant	ElanNanosystems	Oral	Marketed
Emend	Anti-emetic	ElanNanosystems	Oral	Marketed
Cytokine inhibitor	Crohn's disease	ElanNanosystems	Oral	Phase II
Fenofibrate	Lipid lowering	SkyePharma	Oral	Marketed
Megestrol acetate	Steroid hormone	Par Pharmaceuticals	Oral	Marketed
Paliperidone pal-mitate	Anti-schizophrenia	Johnson and Johnson	Oral	Phase III
Loviride	Antivirotic	B. Van Eerdenbrugh	Intravenous	Reported
Busulfan	Anticancer	Skye Pharma	Intrathecal	Undisclosed
Budesonide	Asthma	Jerry Z. Yang	Pulmonary	Reported
Fluticasone	Asthma	Jerry Z. Yang	Pulmonary	Reported
Insulin	Diabetes	BioSante	Oral	Undisclosed
Clofazimine	Antimycobacterials	K. Peters	Intravenous	Reported

Buparvaquone	Antibiotic	Müller R. H.	Oral	Reported
Oridonin	Anticancer	Lei Gao	Intravenous	Reported
AZ68	Anticancer	Kalle S.	Oral/I.V.	Reported
Ascorbylpalmitate	Ascorbylpalmitate	Veerawat T.	Intravenous	Reported
Hydrocortisone	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Prednisolone	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Hexadecadrol	Glucocorticoid	M.A. Kassem	Ophthalmic	Reported
Aphidicolin	Antileishmanial	O. Kayser	Oral	Reported
Dihydroartemisinin	Antimalarial	Jiraporn C.	Intravenous	Reported
Cilostazol	Antiplatelet agent	Jun-ichiJinno	Oral	Reported
Carbamazepine	Psychotolytic	D. Douroumis	Oral	Reported
Omeprazol	Proton pump inhibitor	Jan Möschwitzer	Intravenous	Reported
Thymectacin	Anticancer	Elan Nanosystems	Intravenous	Undisclosed
Silver	Eczema	NUCRYST	Topical	Phase III
Mitotane	Adrenal Cortex Hormones	Michele Trotta	Oral	Reported
Griseofulvin	Antifungal	Boris Y. Shekunov	Oral	Reported
Tarazepide	Selective CCKa-antagonist	C. Jacobs	Oral	Reported
Albendazole	Anthelmintic drug	Mittapalli P. K.	Oral	Reported
Azithromycin	Antimicrobial	Dianrui Zhang	Oral	Reported
Ketoprofen	Analgesic	Remon J.P.	Oral	Reported

CONCLUSION

Nanosuspensions are administering poorly water soluble drugs have been largely solved the dissolution problems to improve drug absorption and bioavailability. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, and can be used for parenteral products.Drugs with poor solubility and low bioavailability are called ‘brick dust’ candidates once abandoned from formulation development work can be rescued with nanosuspensions technology. A nanosuspension not only solve the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.To take advantage of nanosuspension drug delivery, simple formation technologies and variety applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future. Production techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The advances in production methodologies using emulsions or microemulsions as templates have provided still simpler approaches for production but with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various routes. Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form.

REFERENCES:

[1] Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs**.** *Int J Pharm* 2006; **312**: 179-186.

[2] Kostas K, The emergence of Nanomedicine 2006; **1**: 1-3.

[3] Dubey R. Impact of Nanosuspension technology on drug discovery and development. *Drug Deliv Technol* 2006; **6**: 65–67.

[4] Dhiman SD and Thakur GS “Nanosuspension: A recent approach for nano drug delivery system”, *Int J Curr Pharm Res*; **34**: 96-101.

[5] Muller RH, Bohm BHL, Grau J. Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. *In D. Wise* (Ed.) Handbook of pharmaceutical controlled release technology 2000; **17**: 345-57.

[6] Chowdary KPR, Madhavi BLR. Novel drug delivery technologies for insoluble drugs. *Ind. Drugs* 2005; **42**(9): 557-563.

[7] Lipinski CA. Avoiding investment in doomed drugs, is poor solubility an industry wide problem? *Curr Drug Discov*. 2001; 17-19.

[8] Cornelia MK, Rainer H, Muller. Drug nanocrystals of poorly soluble drugs produced high pressure homogenizations. *Eur. J. Pharm. Biopharm* 2006; **62**: 3–16.

[9] Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. *J Am Chem Soc*. 1897; **19**: 930–934.

[10] Galia E *et al*. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm Res*. 1998; **15**: 698-705.

[11] Stovall DM et al. Solubility of crystalline nonelectrolyte solutes in organic solvents: mathematical correlation of 4-chloro-3-itrobenzoic acid and 2-chloro-5-nitrobenzoic acid solubilities with

the Abraham solvation parameter model. *Phys Chem Liq.* 2005; **43**: 351–360.
[12] Makhlof A et al. Cyclodextrins as stabilizers for the preparation of drug nanocrystals by the emulsion solvent diffusion method. *Int J Pharm*. 2008; **357**: 280–285.
[13] Park YJ, Hyun CK. Revaprazan-containing solid dispersion and process for the preparation thereof. *WO Patent* 078922. 2008.
[14] Nagaraju P *et al*. Nanosuspensions: Promising Drug Delivery Systems. *International Journal of Pharmaceutical Sciences and Nanotechnology*. 2010; **2**(4): 679-684.
[15] Dhiman S, Thakur GSD. Nanosuspension: A recent approach for nano drug delivery system. *International Journal of Current Pharmaceutical Research*. 2011; **3**(4): 96-101.
[16] Patil SA, Rane BR, Bakliwal SR, Pawar SP. Nano Suspension:At a glance. *Int J Ph Sci*. 2011; **3**(1): 947-960.
[17] Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. *Int J Pharm*. 1995; **125**(1): 91–97.
[18] Chen Y, Liu J, Yang X, Zhao X, Xu H. Oleanolic acid nanosuspensions: preparation, in-*vitro* characterization and enhanced hepatoprotective effect. *J Pharm. Pharmacol.* 2005; **57**: 259-264.
[19] Kumar NA, Deecaraman M, Rani C. Nanosuspension technology and its applications in drug delivery, *Asian journal of pharmaceutics* 2009; **3**(3): 168-173.
[20] Kawakami K, Yoshikawa T. Microemulsion's formulation for enhanced absorption of poorly soluble drugs prescription design. *J. Control. Release* 2000; **81**: 65–74.
[21] Kayser O. Nanosuspensions for the formulation of aphidicolinto improve drug targeting effects against Leishmania infected macrophages. Int. *J. Pharm*. 2000; **196**: 253–256.
[22] Kayser O. A new approach for targeting to Cryptosporidium parvum using mucoadhesive nanosuspensions research and applications. Int. *J. Pharm*. 2001; **214**: 83–85.
[23] Muller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy Rationale for development and what we can expect for the future. *Ad. Drug Del. Rev*. 2001; **47**: 3-19.
[24] Kreuter J, Petrov VE, Kharkevich DA, AlyautdinRN. Influence of the type of surfactant on the analgesic effects induced by the peptide dalargin after 1st delivery across the blood–brain barrier using surfactant coated nanoparticles. *J Control Release*. 1997; **49**: 81–87.
[25] Chen Y. Liu J, Yang X, Zhao X, Xu H. Oleanolic acid nanosuspensions: preparation, in-*vitro* characterization and enhanced hepatoprotective effect. *J.Pharm. Pharmacol*. 2005: **57:** 259-264.
[26] Pignatello R, Ricupero N, Bucolo C, Maugeri F, Maltese A, Puglisi G. Preparation and characterization of Eudragit retard nanosuspensions for the ocular delivery of cloricromene. *AAPS Pharmscitech* 2006;**7**: E27.
[27] N Arunkumar, M Deecaraman and C Rani, Nanosuspension technology and its applications in drug delivery, *Asian journal of pharmaceutics* 2009; 3(3): 168-173.
[28] Ponchel G, Montisci MJ, Dembri A, Durrer C, Duchкne. D. Mucoadhesion of colloidal particulate systems in the gastrointestinal tract. *Eur J Pharm Biopharm* 1997; **44**: 25-31.

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