AN OVERVIEW OF INTRANASAL NANOSUSPENSION FOR BRAIN TARGETED DRUG DELIVERY

Kinjal Bhatt*, Ankita Patel, Ajay Talele, Dr. Anil G.Jadhav

ARTICLE INFO
Article history
Received 04/02/2015
Available online 28/02/2015

Keywords
Brain Targeting, Nanosuspension, Intranasal Delivery.

ABSTRACT
Problems regarding effective and convenient delivery of drugs to brain are larger as there are large number of barriers to brain and limited vascular access of brain. Many advances are been made in recent years to deliver drugs to brain. Intranasal drug targeting is one of these approaches. It is convenient and easily accessible. Also a desired drug candidate for brain targeting with poor aqueous solubility and high lipophillicity can be formulated into nanosuspension so the intranasal delivery can be convenient and simple. A novel approach to deliver drugs to brain can be in form of nanosuspension. The nanosuspension surpasses the BBB as size range is 1-1000nm. As compared to conventional formulations, nanosuspension serves a promising approach in drug targeting to required organ.

Corresponding author
Kinjal Bhatt
Department of Pharmaceutics,
Smt.B.N.B. Swaminarayan Pharmacy College,
Salvav, NH-8, Vapi - 396 191 Gujarat.
kinjalph@yahoo.com,
+91-9978582618.

Please cite this article in press as Kinjal Bhatt et al. An Overview of Intranasal Nanosuspension For Brain Targeted Drug Delivery. Indo American Journal of Pharm Research. 2015:5(02).

Copy right © 2015 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

www.iajpr.com
INTRODUCTION

Intranasal delivery of a formulation is possible and easily accessible. The segments of nasal cavity include the olfactory epithelium which is a direct pathway for brain targeting. Nanosuspension has a size range from 1-1000nm. So the nanosuspension can be administered intranasal and it crosses the tight cell junctions of the Blood Brain Barrier easily. Thus the nanosuspension is targeted to brain and this therapy is painless and effortless. This has further its own uses and advantages.

Brain Drug Targeting:

The brain is a delicate organ and evolution built very efficient way to protect it. Unfortunately the same mechanisms that protect it against intrusive chemicals also complicate therapeutic interventions. Many existing pharmaceuticals are rendered ineffective in the treatment of cerebral diseases due to inability to effectively deliver and sustain their delivery within brain [1]. Various strategies are been used for manipulating the blood-brain barrier for drug delivery to the brain, which include osmotic and chemical opening of the blood-brain barrier as well as the use of transport systems. Other approaches for drug delivery to the brain involve bypassing the BBB. Various pharmacological agents have been used to open the BBB and direct invasive methods can introduce therapeutic agents into the brain substance. It is important to determine not only the net delivery of the agent to the CNS but also the ability of the agent to access the relevant target site within the CNS [2, 3].

Strategies used for brain targeting:

1. Nanomaterials are found to accelerate the safety and efficacy level of drug delivery devices in brain targeting. Nanoengineered devices are found to be directing the drugs at cellular levels through nano-fluidic channels [4].
2. Different drug delivery systems such as liposomes, microspheres, nanoparticles, nanogels and nanobiocapsules have been used to improve the bioavailability of the drug in the brain but microchips and biodegradable polymeric nanoparticulate careers have been found to be more effective therapeutically in treating brain tumour. The physiological approaches also utilized to improve the transcytosis capacity of specific receptors expressed across the BBB [5].
3. It is found that the low density lipo-proteins related proteing with engineered peptide compound (EpiC) formed the platform incorporating the Angioppep peptide as a new effective therapeutics.
4. The current challenges are to develop the drug delivery careers, which must be able to deliver the drug across the BBB at a non-toxic and effective manner. Nanoparticles are found to be effective careers in delivery of conventional drugs, recombinant proteins, vaccines as well as nucleotides [6].
5. Nanoparticulate drug delivery systems are found to be improving in the pharmacokinetic strategies of the drug molecules such as biodistribution, bioavailability and drug release characteristics in a controlled and effective manner with site specific drug delivery targeting to tissue or cell with reduction in toxic manifestation. Therefore, the use of nanotechnology in the field of pharmaceutical biotechnology helps in improving the drug delivery strategy including the kinetics and therapeutic index to solve the delivery problems of some biotech drugs including the recombinant proteins and oligonucleotides [7].

INTANASAL DELIVERY:

Nasal cavity:

The nasal cavity is easily accessible part of nose. It functions to deliver air to the respiratory segment. It has high vascular plexus and larger surface area [8]. It is divided into two segments further olfactory and respiratory segments. The olfactory segment is a direct connection to brain which has been shown in figure 1 as under.

![Figure 1 :- Schematic diagram showing connection of nose to brain.](image)

Olfactory epithelium:

Smell permits humans and animals with olfactory receptors to identify food, mates, predators, and provides both sensual pleasure as well as warnings of danger. The olfactory region of the two nasal passages in humans is an area of about 2.5 cm² containing in total of about 50 million primary sensory receptor cells. The olfactory region consists of cilia projecting down out of the olfactory epithelium into a layer of mucous which is about 60 microns thick. This mucous layer is a lipid-rich secretion that enriches...
the surface of the receptors at the epithelium surface. The mucous layer is produced by the Bowman’s glands which reside in the olfactory epithelium. The mucous lipids assist in transporting the odorant molecules as only volatile materials that are soluble in the mucous can interact with the olfactory receptors and produce the signals that our brain interprets as odour [10]. Olfactory cavity can be seen in figure 2 [11].

Figure 2: Schematic diagram showing olfactory epithelium of nasal cavity.

Factors affecting nasal absorption:
Effect of deposition on absorption: Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability, while posterior portion of the nose is where the drug permeability is generally higher and provides shorter residence time [12].

Nasal mucosal membranes: It is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels [13].

Several enzymes: Those that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino peptidase at the mucosal membrane [14].

Effect of mucociliary clearance: The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.

Effect of pathological condition: Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption [15].

Applications of nasal drug delivery: The applications are shown in table 1 [16].

Table 1: Applications of nasal delivery.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Application</th>
<th>Example</th>
<th>Marketed product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Delivery of vaccines</td>
<td>Human Influenza vaccine</td>
<td>Flumist</td>
<td>MedImmune Inc.</td>
</tr>
<tr>
<td>2.</td>
<td>Delivery of peptide drugs for systemic effects</td>
<td>Buserelin</td>
<td>Profact Nasal</td>
<td>Aventis Pharma.</td>
</tr>
<tr>
<td>3.</td>
<td>Delivery of non-peptide drugs for systemic effects</td>
<td>Zolmitriptan</td>
<td>Asco Top Nasal</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>4.</td>
<td>Delivery of Anti-migraine drugs</td>
<td>Ergotamine</td>
<td>Migranal nasal spray</td>
<td>Novartis</td>
</tr>
<tr>
<td>5.</td>
<td>Delivery for Diabetes therapy</td>
<td>Insulin</td>
<td>Novolin nasal spray</td>
<td>Novo nordisk</td>
</tr>
<tr>
<td>6.</td>
<td>Delivery of Pain relief drug</td>
<td>Morphine</td>
<td>Rylomine nasal spray</td>
<td>Nastech</td>
</tr>
<tr>
<td>7.</td>
<td>Delivery for control of urine output in patients with Diabetes Insipidus</td>
<td>Arginine-Vasopressin</td>
<td>Gel-vac nasal powder</td>
<td>Delsite Inc.</td>
</tr>
<tr>
<td>8.</td>
<td>Delivery for treatment of Erectile Dysfunction</td>
<td>Apomorphine</td>
<td>Otinose nasal spray</td>
<td>Britannia</td>
</tr>
<tr>
<td>9.</td>
<td>Delivery for treatment of menopause</td>
<td>Estradiol</td>
<td>Aerodil Nasal spray</td>
<td>Servier</td>
</tr>
<tr>
<td>10.</td>
<td>Delivery for treatment of Osteoporosis</td>
<td>Calcitonin</td>
<td>Miacalcin nasal spray</td>
<td>Novartis</td>
</tr>
</tbody>
</table>

Nanosuspension: One of the major problems related with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like ropinorole, oxcarbazepine, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system[17]. Formulation of nanosuspension is an attractive
and promising alternative to solve these problems. Nanosuspension consists of the poorly water-soluble drug without any matrix material suspended in dispersion [18].

**Preparation of nanosuspension:**
There are many techniques for preparing nanosuspension. These can be listed as under:-

1. Bottom up technology
2. Top bottom technology
   a. Media milling
   b. High pressure Homogenisation
3. Micro emulsion as template

**Bottom up technology:**
In this method drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid super-saturation of drug in the solution and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size [19].

**Advantages:**
- Simple process
- Low cost equipments
- Ease of scale up.

**Disadvantages:**
- Drug has to be miscible with one solvent and this solvent should be a good solvent to the co-solvent.
- Surfactant addition is necessary to limit drug crystal growth.[20]

**Example:**
Hydrocortisone nanosuspension was formulated using bottom-up technology. The technique included micro fluidic precipitation process that affect the size of generated drug particles. Altered parameters included flow rates of drug solution and antisolvent, microfluidic channel diameters, microreactors inlet angles and drug concentrations. The experimental results revealed that hydrocortisone nano-sized dispersions in the range of 80-450 nm were obtained and the mean particle size could be changed by modifying the experimental parameters and design of microreactors [21].

**High pressure homogenisation:**
In this method the solvent used may be aqueous or non-aqueous. Following three steps are involved in this technique:-

First, drug powders are dispersed in a stabilizer solution to form pre-suspension; following this, pre-suspension is homogenized by homogenizer at 2800-21,300 psi sometimes for pre-milling; and finally homogenized at a high pressure for 10 to 25 cycles until the nanosuspensions are formed with desired size [22]. The process has been figured out in figure 3 [23].

![Figure 3](image)

**Figure 3:** Figure representing high pressure homogenisation technique for production of nanosuspension.
Advantages:
- Most applicable process.
- Useful for the formulation of very dilute as well as highly concentrated nanosuspension.
- Simple process.
- Aseptic production possible.
- Least risk of contamination.

Disadvantages:
- Lengthy process
- Drug required of micronized size and suspension to be formulated before homogenisation.
- Possible risk of contamination of formulation due to metal ions present on the wall of homogeniser.

Example:
Simvastatin nanosuspension is developed by high pressure homogenization method. Simvastatin powder (1% w/v) was dispersed in aqueous surfactant solution using magnetic stirrer. After drug dispersion first size reduction step is carried out using ultra turax T25 basic homogenizer at 950 rpm for 10 min. Then formulated mixture is homogenized using micron lab 40 homogenizer steps includes first two steps with 10 bar pressure and next two cycles with 50 bar pressure as initial step. Finally, the suspension is homogenized for 15 cycles with 150 bar pressure to obtain nanosuspension [24].

Micro emulsion as template:
Nanosuspensions are also obtained by just diluting the emulsion, formed by using a partially water-miscible solvent as the dispersed phase. The emulsion technique is useful for drugs which are either partially water miscible or soluble in volatile organic solvents. Also, micro emulsion templates can also produce nanosuspensions [25].

Advantages:
- High drug solubilisation.
- Long shelf life.
- Ease of scale up.

Disadvantages:
- Use of hazardous solvent, which can produce toxicity.
- Use of high amounts of solvents and surfactant [26].

Example:
Albendazole, a BCS Class II drug can be formulated into nanosuspension using micro emulsion template method. The stabilizer used includes PVP K30 and emulsifier includes Tween 80 [27].

Media Milling:
In this method drug particles are subjected to media milling for nanoparticle production. Impaction is the main principle of this method. Drug, stabilizer, suitable buffer or water and milling media are subjected to high speed homogenisation on a Milling chamber. The media used can be either glass or zirconium oxide beads [28]. The disintegration of micronized drug occurs following impaction between milling media and drug, leading to nanosized drug particles or zirconium oxide beads. The disintegration of micronized drug occurs following impaction between milling media and drug, leading to nanosized drug particles. The process has been represented diagrammatically in figure 4 [29].
Figure 4: Diagrammatic representation of media milling process for production of nanosuspension.

Advantages:
- Little batch to batch variation
- Ease of scale-up
- High flexibility in handling large quantity of drugs.

Disadvantages:
- Sometimes residues of milling media can be generated [30].

Example:
Phenytoin and nifedipine are formulated into nanosuspension by wet media milling method. The method includes placing the drug in a conical test tube with milling media and stabilizers, which is been held by a holder. The holders are placed in a shaker and oscillated at 2700 rpm for 12hrs. The holder was then cooled at 0°C and the formulation was collected later on [31].

Formulation consideration:

Stabilizer:
Stabilizer plays an important role in the formulation of nanosuspension. In the absence of appropriate stabilizer, the high surface energy of nanosized product can induce agglomeration or aggregation of the drug crystals. The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent Ostwald’s ripening and agglomeration of nanosuspension in order to yield a physically stable formulation by providing steric or ionic barriers [32].

The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases a mixture of stabilizers is required to obtain a stable nanosuspension.

Stabilizers that have been seen so far includes celluloses, poloxamers, polysorbates, lecithins and povidones. Lecithin is of choice as stabilizer if the nanosuspension is autoclavable and parenterally acceptable [33].

Co-surfactant:
The choice of co-surfactant is critical when using micro emulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated [34].

Eg: transcutol, glycofurol, ethanol and isopropanol [35].

Advantages of nanosuspension:
Increase in the dissolution velocity and saturation solubility of the drug:
Actual cause of nanosuspensions being a promising drug delivery strategy behind the increase in the dissolution velocity and saturation solubility of the nanosuspensions can be given as according to the Nernst–Brunner and Levich modification of the Noyes Whitney dissolution model equation, the dissolution velocity of the nanosuspension increases due to an intense increase in the surface area of the drug particles from microns to particles of nanometre size i.e. μm to nm [36].

The equation can be given as under:

\[
\frac{Dx}{dt} = \frac{A.D}{h. (C_s - X_d/ V)}
\]

Where, \(Dx/dt\) = dissolution velocity,
A = surface area of particle,
D = diffusion coefficient,
h = thickness of the diffusion layer,
\( X_d \) = concentration in surrounding liquid,
\( C_s \) = saturation solubility of drug.

**Improved biological performance:**
An increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the in-vivo performance of the drug irrespective of the route used, whether parental or nasal or any other [37].

**Ease of manufacture and scale-up:**
Nanosuspensions are easy to manufacture as compared to nanoparticles. The production processes are easily scaled up for commercial production. Also, the methods are possible to perform on lab scale and require less effort with lower cost and time [38].

**Long-term physical stability:**
One of the special feature of nanosuspension is the absence of Ostwald ripening, the phenomenon in which smallest particles in solution dissolve and deposit on large particles in order to reach a more thermodynamically stable state in which surface to area ratio is minimized. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles [39]. The absence of particles with large differences in their size in nanosuspensions prevents the existence of the different saturation solubility’s and concentration gradients in the vicinity of differently sized particles, which in turn prevents the Ostwald ripening effect.

**Versatility:**
The flexibility offered in the modification of surface properties and particle size, and ease of characterization of formulated nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility [40].

**Evaluation of nanosuspension:**
The evaluation parameters of nanosuspension are as follows:

**Particle size and particle size distribution:**
The particle size was measured using Malvern Zetasizer ZS200 at 25 ± 0.5°C. Each sample was measured at least 3 times and the average values were employed for calculation of response surfaces [41].

**Scanning electron microscopy:**
This technique is used to investigate the shape and surface morphology of the drug nanocrystals and to measure the particle size. Aqueous suspensions of nanoparticles are placed on a sample holder for analysis. Nanocrystals are further observed with a scanning electron microscope [42].

**X-ray Diffraction:**
X-ray diffraction studies are used in order to characterise the crystalline nature of the formulated nanosuspension. The molecules with random arrangement in noncrystalline substances makes them poor and coherent scatters of x-ray, which gives broad, diffuse maxima in diffraction patterns. The crystalline patterns thus, become easy to distinguish from non-crystalline particles as they show sharply defined diffraction peaks. The X-ray diffraction is now a common technique for the study of crystal structures and atomic spacing [43].

**Surface charge (zeta potential):**
Surface charge properties of the nanosuspensions are studied through zeta potential. The value of zeta potential indicates the stability of nanosuspensions at the macroscopic level. A maximum zeta potential of ±30 mV is required for electrostatically stabilized nanosuspensions and a minimum of ±20 mV for steric stabilization. The zeta potential values are commonly calculated by determining the particle’s electrophoretic mobility and then converting the electrophoretic mobility to the zeta potential. Electroacoustic technique is also used for the determination of the zeta potential in the areas of material sciences [44].

**In-vitro drug release study of nanosuspension:**
Dialysis bag diffusion technique was used to study in-vitro release of drug from the prepared nanosuspension. The formulation (2ml) has to be placed in the dialysis bag, hermetically sealed and immersed into a 100 ml beaker containing 50 ml of the release media maintained at 37±0.5°C and stirred at 50 rpm. Aliquots of 5 ml are to be withdrawn at pre-determined time intervals and immediately restored with the same volume of fresh media maintained at the same temperature. The study has to be carried out in phosphate buffer 6.5, 1% v/v Tween 80 can be used to maintain the sink condition.
Dissolution:-
The dissolution of a nanosuspension can be performed using Dissolution Apparatus USP Type II Paddle at 37±0.5°C, 50 rpm and specific buffer solution. Aliquots of 5 ml are to be withdrawn at pre-determined time intervals and immediately restored with the same volume of fresh media maintained at the same temperature. The study has to be carried out in phosphate buffer 6.5, 1% v/v Tween 80 can be used to maintain the sink condition [46].

In-vitro permeability study of nanosuspension:-
In-vitro permeability studies for nanosuspensions are performed using semi permeable artificial membranes such as cellophane membrane or biological membrane. Diffusion cell is used for performing study and phosphate buffer 6.5.

In-vivo study:-
The animals are to be divided into four groups of five rats each. Group I, Normal control and receives standard pellet diet, water and orally administered with 5% CMC. Group II, Negative control and receives a single dose of triton administered at a dose of 400mg/kg, p.o. After 72 hours of triton injection, this group receives a daily dose of 5% CMC (p.o) for 7 days. The Group III receives a daily dose of nanosuspension nasally, for 7 days, after inducing specified disease. Group IV will receive standard drug (10mg/kg nasally).

On the 8th day blood has to be collected by retro orbital sinus puncture, under mild ether anaesthesia. The collected samples are to be centrifuged for 10 minutes and serum samples are used for various biochemical experiments. Then animals are to be sacrificed by using 5ml Diethyl ether and collected the liver, brain, heart and spleen. The liver, heart, brain and spleen were homogenized in cold 0.15M KCl and extracted with CHCl₃:CH₃OH (2%v/v). The extracts are to be assayed after dilution using HPLC. The AUC for each extract has to be calculated and compared. The broader the AUC, the higher the amount of drug in that organ. So here, the brain extract should have the broadest peak of all, as the nanosuspension is for brain targeting [47, 48].

Stability studies:-
The formulated nanosuspension was divided in to 3 samples and stored at different temperatures for a period of 3, 6 months.
- 4°C, refrigerated temperature
- 27°C ± 2°C at 65% RH, room temperature
- 40°C ± 2°C at 65% RH, accelerated temperature.
After 3, 6 months formulation is evaluated for remaining drug content in by specific methods [49].

Toxicity studies:-
A general range of compounds formulated as nanosuspension are of BCS Class II/IV with higher log P values. Formulation in nanosuspension increases solubility so it can be said that a dose reduction is required for drugs. A nanosuspension can result in highest exposure of drug, so a higher plasma concentration of drug is achieved. So a specific toxicity study has to be performed in different animal species such as Sprague-Dawley rats, Rhesus Monkeys, Beagle Dogs and Yukatan Minipigs in fed as well as fasted state. Parameter to be studied includes Tmax, Cmax and AUC. After assessing safety of nanosuspension in these animals, human volunteer studies have to be performed [50].

Comparative studies of intranasal delivery to delivery via other routes:-
Intranasal vs. Buccal route:-
Anderson et al. (Jan 2012) compared buccal lorazepam to nasal midazolam using a crossover design volunteer study they found that buccal drug does not absorb as rapidly as nasal drug and so is not as clinically effective for disease states that require rapid onset of action (seizure, breakthrough pain, opiate reversal for examples). Nasal lorazepam achieves therapeutic levels in the blood and CSF more rapidly and therefore its clinical onset of action is earlier. The figure 5 shows resulting serum levels in the first 10 minutes.

![Figure 5](image-url)
intranasal vs. oral route:
in case of diabetes, metoclopramide oral tablet is ineffective in symptoms of gastro paresis so it has to be given in form of
nasal spray. as studied by parkman hp et al. 88.9% of subjects who received oral 10 mg, 91.2% who received nasal 10 mg, and
97.1% who received nasal 20 metoclopramide were classified as responders. the side-effect profile of the metoclopramide nasal
spray was favourable. more side effects, especially nausea, occurred with the oral tablets [51].

equipments required for formulation and evaluation of nanosuspension:
the equipments are listed in table 2 [51]

Table 2:- Equipments required for formulation and evaluation of nanosuspension.

<table>
<thead>
<tr>
<th>Sr no.</th>
<th>Equipments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>High speed magnetic stirrer</td>
</tr>
<tr>
<td>2.</td>
<td>Fourier Transform Infrared Spectrophotometer</td>
</tr>
<tr>
<td>3.</td>
<td>X-ray Diffraction</td>
</tr>
<tr>
<td>4.</td>
<td>Scanning Electron Microscopy</td>
</tr>
<tr>
<td>5.</td>
<td>Zeta analyser</td>
</tr>
<tr>
<td>6.</td>
<td>Franz Diffusion Apparatus</td>
</tr>
<tr>
<td>7.</td>
<td>UV-Vis Spectrometer</td>
</tr>
<tr>
<td>8.</td>
<td>Dissolution Apparatus</td>
</tr>
</tbody>
</table>

conclusion
from the present review, the use of nanosuspensions for brain targeting has been highlighted. nanosuspension serves the
criteria for nasal administration and is very beneficial over other nasal formulations. a further research on formulation of any drug for
CNS disorder into nanosuspension can be performed to serve the basic criteria for brain targeting and obtaining the required efficacy
in treatment of the specific CNS disorder (eg: Epilepsy).

acknowledgement
the first author sincerely acknowledges the managing trust of SMT BNB Swaminarayan pharmacy college, salvav and
principal dr anil jadhav for providing basic requirements to conduct research. a sincere thanks to HOD, pharmaceutics Mr Ajay
talele and guide miss ankita patel for providing an expertise in conducting the review. a sincere thanks to Mr. Harsh upadhyay and
pranshu for all the help provided.

Conflict of interests:
the author declares none conflict of interests.

abbreviations and symbols
BBB: blood brain barrier
Nm: nanometre
CNS: central nervous system
BCS: biopharmaceutical classification system
Psi: pounds per square inch
PVP: polyvinyl pyrrolidone
Rpm: rounds per minute
KCl: potassium chloride
CHCl3: chloroform
CH3OH: methanol
HPLC: high performance liquid chromatography
CSF: cerebro-spinal fluid
SLN: solid lipid nanoparticles
AUC: area under curve
Cmax: maximum plasma concentration
Tmax: maximum time required
SEM: scanning electron microscopy
FTIR: Fourier transform infrared spectroscopy
CMC: carboxy methyl cellulose
RH: relative humidity
p.o: orally
REFERENCES


Werling et al. Nanosuspensions of anti-retroviral agents for increased central nervous system delivery, United States Patent Application, 60540718. [USPTO]


