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DEVELOPMENT AND EVALUATION OF CYCLIZINE HYDROCHLORIDE NANOCRYSTALS FOR INTRANASAL DRUG DELIVERY

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ABSTRACT

Poorly water-soluble drugs pose a great challenge in drug formation development. The low saturated solubility and dissolution velocity lead to poor bioavailability. For this reason, nanocrystals have attracted a lot of attention. They exhibit advantages like saturation solubility and dissolution velocity. The aim of the study is related to developing and evaluating cyclizine hydrochloride nanocrystals for intranasal drug delivery. Nanocrystals have been prepared by high-pressure homogenization and freeze-drying using lecithin,tween-80, and polyvinyl alcohol. A total of five formulations containing polyvinyl alcohol showed an increase in solubility as compared to other formulations. Studies such as solubility testing, X-ray powder diffractometry, particle size analysis, scanning electron microscopy, drug-polymer interaction, mucoadhesive testing, in-vitro diffusion study, and permeation tests have been done. Nanocrystals increase solubility, thereby increasing bioavailability. An oral dose of cyclizine hydrochloride shows low bio availability due to first-pass metabolism which is also impaired due to gastrointestinal disturbances. The nasal formulation has been prepared in order to pass hepatic metabolism and can be given easily at the of emesis.

Keywords: Nanocrystal, Intranasal drug delivery, Cyclizine hydrochloride, saturation solubility, XRD, SEM.

I. INTRODUCTION

The main drug delivery modalities are oral and injectable, which has slowed down the discovery of new medications. The majority of medications have been designed to work with oral or intravenous delivery systems, which aren't necessarily the best options for a certain therapy. In order to reduce side effects and improve patient compliance, newer delivery systems are needed for new biologic medications such as proteins and nucleic acids. A potential delivery route to obtain a quicker and higher amount of medication absorption has been explored: the nasal mucosa. The vast surface area, permeable endothelium membrane, high total blood flow, avoidance of first-metabolism, and easy accessibility are the causes of this. Recently, there has been a lot of research done on the nasal administration of various chemicals, peptides, and proteins for systemic therapy. Many studies have recently sought to provide medications to the CNS through the nose. The formulations' inadequate contact with the nasal mucosa is the main drawback of nasal route delivery, though. There have been numerous initiatives in recent years to lengthen the duration that medication formulations stay in the nasal cavity, which has increased nasal drug absorption[1].

1.1 Advantages of nasal drug delivery system

1. Easy accessibility and needle-free drug application without the necessity of trained personnel facilitate self-medication, thus improving patient compliance compared to parenteral routes.

2. Good penetration of, especially lipophilic, low molecular weight drugs through the nasal mucosa. For instance, the absolute nasal bioavailability of fentanyl is about 80%[2].

3. Rapid absorption and fast onset of action.

4. Relatively large absorption surface and high vascularization. Thus, Tmax fentanyl after nasal administration was less than or equal to 7 minutes, comparable to intravenous [I.V.]. A nasally administered drug would therefore be effective in emergency therapy as an alternative to parenteral administration routes[3].

5. Avoidance of the harsh environmental conditions in the gastrointestinal tract (chemical and enzymatic degradation of drugs).

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6. Avoidance of hepatic first-pass metabolism and thus potential for dose reduction compared to oral delivery.

7. Potential for direct delivery of drugs to the central nervous system via the olfactory region, thus bypassing the blood-brain barrier.

8. Drug degradation that is observed in the gastrointestinal tract is absent.

9. The bioavailability of larger drug molecules can be improved by means of an absorption enhancer or other approach[4].

10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery[5].

11. Convenient for the patients, especially for those on long-term therapy, when compared with parenteral medication.

12. Drugs possessing poor stability in G.I.T fluids are given by the nasal route.

1.2 Limitations

1. The histological toxicity of absorption enhancers used in nasal drug delivery systems is not yet clearly established.

2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

3. The nasal cavity provides a smaller absorption surface area when compared to the GIT.

4. There is a risk of local side effects and irreversible damage to the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.

5. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high-concentration.

6. There could be a mechanical loss of the dosage form into other parts of the respiratory tract, like the lungs, because of the improper technique of administration[6-7].

1.3 Mechanism of drug absorption

The first step in a drug's absorption from the nasal cavity is its transit through mucus. Small, unmodified particles can easily pass through this layer. However, large or charged particles can find it more difficult to traverse. Mucin, which makes up the majority of mucus, has the capacity to bind to solutes and block diffusion. The first procedure takes advantage of an aqueous transport route, often known as the paracellular pathway. This is a passive, slow route. There is an inverse log-log relationship between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was found for drugs having a molecular weight greater than 1000 Daltons. The second process entails transfer via a lipoidal pathway, also referred to as the transcellular pathway. The second process entails transfer via a lipoidal pathway, also referred to as the transcellular pathway.

1.4 Anatomy and physiology of nasal cavity

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The human nasal cavity has a total volume of about 16 to 19 ml and a total surface area of about 180 cm2 and is divided into two nasal cavities by the septum. The volume of each cavity is approximately 7.5 ml, with a surface area of approximately 75 cm^2. Post-drug administration into the nasal cavity, a solute can be deposited at one or more of the three anatomically distinct regions: the vestibular, respiratory, and olfactory regions.

1.4.1 The vestibular region

This is located at the opening of the nasal passages and is responsible for filtering out airborne particles. It is considered to be the least important of the three regions with regard to drug absorption.

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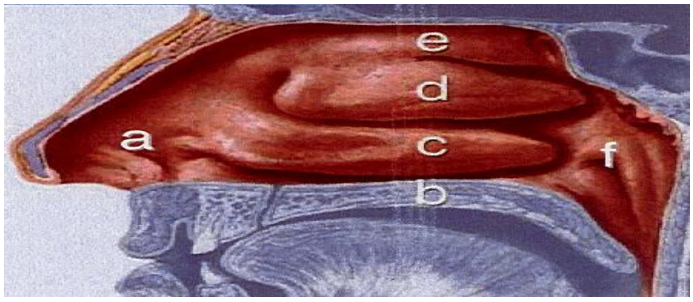

Fig 1: Nasal Cavity

a-nasal vestibule, b-palate, c-inferior turbinate, d-middle turbinate, e-superior turbinate (olfactory mucosa) f- nasopharynx.

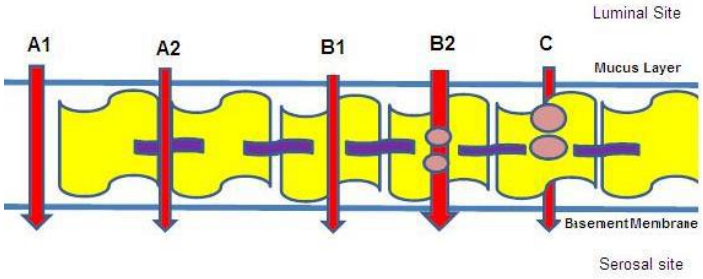

Fig 2: Mechanism of drug absorption

1.4.2 olfactory region

It is about 10 cm2 in surface area and plays a vital role in the transportation of drugs to the brain and the CSF. The olfactory region comprises thick connective tissue, the lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, a bowman bundle, and blood vessels.

1.4.3 Respiratory region

The respiratory region is the largest, has the highest degree of vascularity and is mainly responsible for systemic drug absorption. The main nasal airway has narrow passages, usually 1-3 mm wide, and These narrow structures are useful for the nose to carry out its main functions. The nasal cavity is covered with a mucous membrane, which can be divided into two areas:

1.4.4 Blood Vessels

Numerous blood vessels can be found in the nasal mucosa's lamina propria. Three things set them apart from the tracheobronchial tree's vasculature. The nose has venous sinusoids as a start. The nose has arteriovenous anastomoses, second. Third, the nasal cycle is caused by periodic variations in congestion in the nasal vasculature. The nasal route of administration is appealing for a number of medications, both peptide and non-peptide pharmaceuticals, due to the nasal mucosa's highly supplied vascular nature and low barrier to drug absorption.

1.4.5 Olfactory epithelium

The olfactory epithelium consists of three different cell types: basal cells, supporting cells, and olfactory receptor cells. Basal cells, which are progenitors of the other cell types, lie on the basement membrane and do not reach the airway lumen. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic fiber extending from the cell body to the free apical surface, where it ends in an olfactory knob carrying non-motile cilia, which extends above the epithelium[8-10].

1.4.6 Sub mucosal glands

The glands in the nose are of two types: anterior serous glands and seromucous glands. There are only 100-150 anterior serous glands on each side. Their long excretory ducts have large openings in the upper part of the internal ostium; droplets of watery secretion can be seen through a magnifying glass, after stimulation of the nasal mucosa. The number of glands per unit surface area is considerably higher in the nose than in the trachea (eight versus one per mm^2).

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1.5 Strategies to improve nasal absorption

Several methods have been used to facilitate the nasal absorption of drugs includes:

1.5.1 Nasal enzyme inhibitors

Enzyme inhibitors can speed up the nasal metabolism of medications. Enzyme inhibitors like peptidases and proteases are primarily used in the synthesis of peptide molecules and proteins. Salts and derivatives of fusidic acid are absorption enhancers that also exhibit enzyme inhibitory action to improve medication absorption and bioavailability. Trypsin, aprotinin, Boro valine, amastatin, bestatin, and boroleucin inhibitors are some of the other enzymes that are frequently used as enzymatic activity inhibitors[10-14].

1.5.2 Prodrug approach

The prodrug approach is mainly meant for optimising favourable physicochemical properties such as solubility, taste, odour, stability, etc. Prodrug is usually referred to as promoiety, it is to cover the undesirable functional groups with another functional group. This prodrug approach is mainly for improving nasal bioavailability, especially for proteins and peptides, to enhance membrane permeability along with increased enzymatic stability. The prodrug undergoes enzymatic transformation to release the active medicament when it crosses the enzymatic and membrane barriers**.**

1.5.3 Particulate drug delivery

Particle design plays an increasingly important role in absorption enhancement. Microspheres, nanoparticles, and liposomes are all systems that can be used as carriers to encapsulate an active drug. The properties of these can be varied to maximize therapeutic efficacy. Overall, this can result in increased absorption efficacy and stability and reduced toxicity of the active ingredient. Systems can be designed to be mucoadhesive to increase retention time and facilitate sustained release.

1.5.3.1 Microspheres

By sticking to the nasal mucosa and lengthening the drug's duration in the nasal cavity, microspheres primarily boost the absorption and bioavailability of medications. Dextran, chitosan, and biodegradable starch were used to make microspheres that successfully increased the bioavailability of a variety of medications. Different material microspheres have been tested in vivo as nasal medication delivery devices. A gel-like layer is formed when albumin, starch, and diethyl aminoethyl (DEAE)-dextran microspheres absorb water to form in the nasal cavity**.**

1.5.3.2 Nanoparticles

The principles and ideas of various nanoparticulate drug delivery systems using various polymers and absorption promoters have been used in attempts to deliver various medicines, particularly peptides and proteins, through the nose route for systemic usage. Since colloidal formulations have been demonstrated to shield medications from the deteriorating environment in the nasal cavity and make it easier for them to overcome mucosal barriers, incorporating drugs into nanoparticles may be a potential strategy. By generating strong immune responses, the use of nanoparticles for vaccine delivery has a positive impact. This might be because the lymphoid tissue in the nasal cavity (NALT), which preferentially transports tiny particles, is the cause.

As direct olfactory transport avoids the blood-brain barrier and nanoparticles are picked up and transported through cell processes of olfactory neurons through the cribriform plate to synaptic connections with neurons of the olfactory bulb, intranasal delivery benefits the brain.

1.5.3.3 Liposomes

Drugs and other compounds may be incorporated in liposomes, which are phospholipid vesicles made of lipid bilayers surrounding one or more water compartments. One benefit of liposomal drug delivery systems is the efficient encapsulation of small and large molecules with a variety of hydrophilicity and PKa values. In fact, they have been discovered to improve membrane penetration, enhancing nasal absorption of peptides like insulin and calcitonin. Due to the amphiphilic nature of these liposomes and their beneficial characteristics for drug absorption through biological membranes, water-soluble medications have been administered orally. Positively charged anionic liposomes are less permeable than cationic liposomes.

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Different methods have been used to distribute liposomes. When compared to distribution in simple solution, liposomes may have an adjuvant effect on tetanus toxoid when administered orally, intravenously, or nasally. This information is relevant to the creation of a non-parenteral immunization method that triggers powerful systemic immunity.

1.5.3.4 Gels

Gels are semisolid systems in which the solvate macromolecules or interlacing three-dimensional networks of particles in the dispersed phase act as barriers to the flow of the dispersion medium. The semisolid state is a result of increased viscosity brought on by interlacing and subsequent internal friction. A gel may also be made up of matted, twisted strands that are frequently bound together by greater Vander Waals forces, resulting in the formation of crystalline and amorphous regions throughout the system. Gels typically have a concentration between 0.5 and 2%, and they remain viscous throughout a wide range of temperatures. Nasal gels are thickened liquids or suspensions with a high viscosity.

1.5.3.5 Cyclodextrins

Several compounds have been investigated for their nasal absorption enhancement potential using cyclodextrins as the optimizers. The two most studied types are natural cyclodextrin and hydroxypropyl cyclodextrin. Only cyclodextrin is a compendia substance and is being considered for GRAS (generally recognised as safe) status[15-19]**.**

1.5.3.6 Permeation enhancers

Permeation enhancers Small and large hydrophilic drugs may be poorly permeable across the nasal epithelium and may show insufficient bioavailability. Their permeation can be improved by being administered in combination with absorption enhancers, which induce reversible modifications in the structure of the epithelial barrier.

1.6 Nanocrystals

Drug nanocrystals are nanoparticles containing 100% drug without any matrix material. Drug nanocrystals are crystals with a size in the nanometer range, which means they are nanoparticles with a crystalline character. Based on the size unit, in the pharmaceutical area, nanoparticles should be defined as having a size between a few nanometers and 1000 nm (=1 µm); microparticles therefore possess a size of 1–1000 µm.

Another feature is that, unlike polymeric nanoparticles, drug nanocrystals are made entirely of the drug; there is no carrier substance. The term "nanosuspensions" (as opposed to "microsuspensions" or "macrosuspensions") refers to the dispersion of drug nanocrystals in liquid media. Generally speaking, it is necessary to stabilise the scattered particles using surfactants or polymeric stabilisers. Water, aqueous solutions, or nonaqueous media (such as oils or liquid polyethylene glycol [PEG]) can all be used as dispersion media. Especially when precipitation is used, the conversion of drug microcrystals into drug nanoparticles might result in either a crystalline or an amorphous output, depending on the production technology. Such amorphous drug nanoparticles shouldn't technically be referred to as nanocrystals. But frequently, one speaks of "nanocrystals in the amorphous state."

1.7 Methods for production of nanocrystals

Two basic approaches are involved in the production of nanocrystals: bottom-up technologies (controlled precipitation or crystallisation) and top-down technologies (nanonizing (large-size drug powder to be reduced in size, e.g., by mechanical attrition). However, combination techniques, combining a pre-treatment with a subsequent size reduction step, are also being employed.

1.7.1 Bottom up precipitation

A drug is dissolved in a solvent and subsequently precipitated by mixing with a non-solvent. It yields crystalline drug nanoparticles. This method requires strict control of the process, the avoidance of crystal growth (to the micrometre range), and drug solubility in at least one solvent. The technology is basically a classical precipitation process known as "via humida paratum" (VHP). This VHP process was already described in the old pharmacopoeia to prepare ointments containing finely dispersed, precipitated drugs. The drug is dissolved in a solvent and subsequently added to a nonsolvent, leading to the precipitation of finely dispersed drug nanocrystals. One needs to bear in mind that these nanocrystals need to be stabilised in order not to grow into

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the micrometre range. In addition, the drug needs to be soluble in at least one solvent, which creates problems for newly developed drugs that are insoluble in both aqueous and organic media. Another precipitation method is the preparation of amorphous drug nanoparticles.

1.7.2 Top down technologies

1.7.2.1 Bead/pearl milling

Shear forces generated by the movement of the milling media lead to particle size reduction. The pearls or balls consist of ceramics (cerium or yttrium-stabilized zirconium dioxide), stainless steel, glass, or highly cross-linked polystyrene resin-coated beads. There are two basic milling principles. Either the milling medium is moved by an agitator, or the complete container is moved in a complex movement leading consequently to a movement of the milling medium.

1.7.2.2 High pressure homogenization

When producing nanocrystals using homogenization methods, there are three important technologies: microfluidizer technology (IDD-P technology), piston gap homogenization in water (Dissocubes technology), and water mixtures or nonaqueous media (Nanopure technology).

1.7.2.2.1 Microfluidizer technology

The microfluidizer technology can generate small particles by a frontal collision of two fluid streams under pressures up to 1700 bar. This leads to particle collisions, shear forces, and cavitation forces. It can be achieved with jet stream homogenizers such as the microfluidizer (Microfluidizer®, Microfluidics Inc.). The collision chamber can be designed in two shapes, either Y-type or Z-type. Surfactants are required to stabilise the desired particle size. Unfortunately, a relatively high number of cycles (50 to 100 passes) is necessary for a sufficient particle size reduction.

1.7.2.2.2 Dissocubes technology

Piston-gap homogenizers are used in the Dissocubes technology. SkyePharma PLC later purchased the technology that Müller and associates had developed. It involves the creation of water-based nanoparticle suspensions at room temperature. An aqueous surfactant solution is used to disperse a drug powder, which is then driven through a small homogenization gap by a piston at pressures of up to 4000 bar, though more often 1500 to 2000 bar. The homogenization gap might be as wide as 5 to 20 m, depending on the suspension's viscosity and the pressure being used. According to Bernoulli's law, the high streaming velocity of the suspension that results in a rise in dynamic pressure is balanced by a decrease in static pressure below the vapour pressure of the aqueous phase. Due to the fact that water begins to boil at room temperature, gas bubbles form. As soon as the liquid exits the homogenization gap and is once again at an atmospheric pressure of 1 bar, these gas bubbles rapidly deflate. Shockwaves are created as a result of the development and implosion of gas bubbles, a phenomenon known as cavitation. Due to the strong shear pressures, turbulent flow, and immense power of these shockwaves, the drug particles shrink in size.
Of course, using water can have drawbacks, such as the hydrolysis of medications that are sensitive to water and issues with later drying operations (such as removing too much water). The drying process could require expensive procedures like lyophilization when used with medications with low melting points. Therefore the technology is most suitable for the formulation of aqueous suspensions of nanocrystals.

1.7.2.2.3 Nanopure technology

PharmaSol GmbH in Berlin owns and develops nanopure technology. The method makes use of a low-vapour pressure dispersion medium and, optionally, low-temperature homogenization. There is very little to no cavitation in the homogenization gap. Without cavitation, the size reduction was still adequate. To produce nanoparticles, enough shear forces, particle collisions, and turbulence must still exist. Drugs that are sensitive to temperature can be processed by homogenising at very low temperatures. To prevent pharmaceuticals from hydrolyzing, the entire procedure can be done in nonaqueous solutions. Gelatin or HPMC capsules can be immediately filled with oils, PEG, or hot-melted polyethylene glycols[19-23].

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II. MATERIALS AND METHODOLOGY

2.1 preparation of nanocrystals

2.1.1 Preparation of nanosuspension

Three different types of surfactants have been used i.e., lecithin, polyvinyl alcohol, and tween-80. Water was used as dispersion medium For the preparation of nanosuspension. Initially particle size was reduced using a mechanical stirrer and high speed homogenizer, by using these types of instruments we got particle size of 40 µm, then proceed on high speed homogenizer. Different type of suspensions was kept for further reducing particle size.

2.1.2 Conversion of nanosuspension into powder form

The obtained nanosuspension was then lyophilized. For the purpose of lyophilization, the samples were kept for three days.

2.2 Method

About 5g of cyclizine hydrochloride was added in 100ml of water. Different batches were prepared by using different surfactants. Particle size reduction was carried out using the following step

1. Digital displayed mechanical stirrer: stirring of different dispersion was carried out using digital displayed mechanical stirrer. Stirring was carried out for time period of 20 mint. Speed was set depending upon foaming capacity of surfactants. High speed may cause air entrapment.

Table 1. stirring of different dispersion

Name and concentration of surfactant	Speed(rpm)
Tween-80(0.5%)	700rpm
Tween-80(1%)	500rpm
Lecithin (0.5%)	900rpm
Lecithin (1%)	1200rpm
Polyvinyl alcohol (0.5%)	1000rpm

2. High speed homogenizer: Dispersions were kept at speed of 1500rpm for 4mint in order to obtain particle size below 40µm.

3. High pressure homogenizer: Freeze drying: Nanosuspension was converted in to powder form by lyophilization. Dispersions were kept at -110°c for 72hrs.

Table 2. High pressure homogenizer

Number of cycles	Pressure(bars)
2	300
2	500
1	1000
15	1500

4. Composition of batches:

Table 3. Composition of batches

Name of batch	Drug	Tween-80	Lecithin	Polyvinyl alcohol
N1	5%	0.5%	-	-
N2	5%	1%	-	-
N3	5%	-	0.5%	-
N4	5%	-		0.5%
N5	5%	-	1%	

5. Solubility testing: Phosphate buffer (6.4) and water were used. Saturated solution was prepared. Keep the dispersion on sonicator for 24hrs. Calculate concentration from calibration curve

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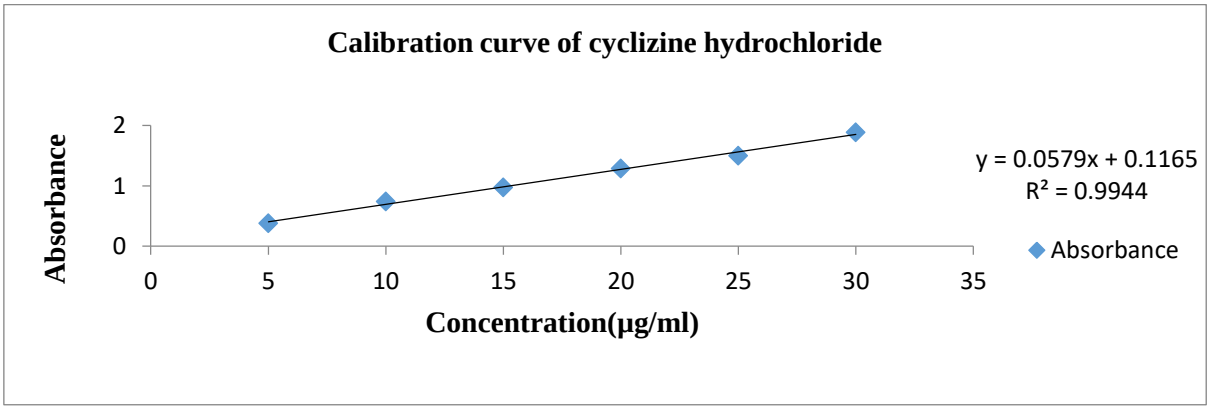

Fig 3: Calibration curve of cyclizine hydrochloride

Table 4. Materials and Equipment

Sr. No	Material	Source
1	Cyclizine Hydrochloride	Gift sample from srikem Mumbai (India)
2	Polyvinyl alcohol	Research lab .fine chem Mumbai (India)
3	Tween 80	Research lab .fine chem Mumbai (India)
4	Lecithin	Research lab .fine chem Mumbai (India)

Table 5. Materials and Equipment

Sr. No	Instrument	Make
1	UV Visible spectrophotometer	JASCO V-630, Japan
2	IR Spectroscopy	JASCO FTIR-4100, Japan
3	Mechanical stirrer	Ambala (Haryana)
4	High speed homogenizer	Omni company Germany
5	High pressure Homogenizer	GEA Nira Saavi
6	Lyophilizer	SCANVAC Germany
7	SEM	UDCT Mumbai
8	XRD	UDCT Mumbai

2.2.1 X- ray powder diffractometry

XRD patterns of the samples were obtained on a Philips X'Pert MPD X-ray diffractomer using Cu Kα (1.54059 Å) radiation with the X-ray generator operating at 45 kV and 40 mA. The samples were prepared by packing about 5 mg of samples in a 9.0 mm cavity mount. The sample was irradiated using a Cu target tube and exposed to all lines. A monochromator was used to select the K_1 line (l = 1.54056). The scanning angle ranged from 51 to 1001 of the diffraction angle (2y), and the counting time used was 1 s/step in steps of 2y = 0.051. The scanning rate used was 31/min. The angle was varied in a range of 1–40 ◦ with a scanning rate of 0.02/step. The (d) basal spacing of the sample layer was determined by using Bragg's equation as n = 2(d) sin ɵ where (d) is the

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inter-planer distance of the diffraction face (A°), ɵ is Bragg angle of the reflection (◦), and n is a whole number, representing the order of diffraction, taken as one in the calculation.

2.2.2 Particle size analysis

The particle size was analysed. Laser diffractometry (LD) was carried out with a LS 230 (Beckmann-Coulter GmbH, Krefeld, Germany), yielding a volume size distribution. Characterization parameters were the diameters D10, D50, and D 90% (i.e., diameter 90% means that 90% of the particles in the volume distribution are below the given size in micrometers).

2.2.3 Scanning electron microscopy

The samples were analyzed using the scanning electron microscope equipped with a field emission, a JEOL JSM 6380, after sputtering the sample with platinum using a coater JEOL JSM 1600.

2.2.4 Angle of repose

Fixed cone height method: A glass funnel with an internal stem diameter of 5mm was placed over a glass slide. Particles are allowed to flow gently through a funnel until a cone is formed, which reaches the funnel orifice. The angle of the cone to the horizontal is recorded.

2.2.5 Drug polymer interaction

Formulation of gel: 1375mg of nanocrystals were dissolved in 2ml warm normal saline solution and the mixture was kept warm at a temperature of about 30°C. To this, 80.8mg of hydroxyl propyl methyl cellulose (HPMC) 4000, which was previously dissolved in 8ml of warm normal saline solution, was gradually added and the mixture was stirred continuously with the aid of a magnetic stirrer for approximately 45 minutes.

Table 6. Drug polymer interaction

Sr. no	Drug(%)	HPMC(%)
1	1.25	0.2
2	1.25	0.4
3	1.25	0.6
4	1.25	0.8
5	1.25	1
6	1.25	1.2

2.2.6 Viscosity measurement

Viscosity of gel was determined by using Brookfield viscometer with spindle no. ranging from 61 to 64.

2.2.7 Mucoadhesive testing

The mucoadhesive strength of the formulations was evaluated using Park and Robinson method. Excised goat nasal mucosa (2.56 cm2) was adhered on lower and upper probe of a modified balance. Nasal gel was placed between the mucosal layers and equilibrated at 37ºC for 15 min. The force of adhesion (N) and bioadhesive strength (S) were determined from the minimum weight required to detach the mucosa from the formulation using Eqs 1 and 2.

$$N = mg \quad \text{..... (1)}$$

Where m = weight required to detach the formulation from the nasal mucosa, and g = acceleration due to gravity (980cm/s^2)

$$S = N/A \quad \text{..... (2)}$$

where A is the mucous surface area exposed to the formulation

2.2.8 In Virto drug diffusion study

The drug diffusion from different formulation was determined using cellophane membrane and diffusion cell. The treated cellophane membrane (pore size 0.2 µm) was fixed between the donor and receptor compartment of the diffusion cell to support the microparticles. 25mg of nanocrystals were placed on the cellophane membrane in the donor compartment, the receptor compartment contained phosphate buffer (pH 6.4). About 1

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ml of sample was withdrawn at different time interval and analyzed spectrophotometrically at 208.5 nm for drug content with sufficient dilution.

2.2.9 Permeation

Goat nasal region was procured from the local slaughterhouse within 1 h of slaughtering the animal. Excised nasal mucosa was separated from the nose bone and tied carefully using a thread over the mouth of the tube. The tube was immersed in a beaker containing 100 ml of phosphate buffer (pH 6.4), which served as the receptor chamber. The temperature was maintained 37 ± 1C° and the solution was stirred continuously using a magnetic starrier. Aliquots (1 ml) were withdrawn at predetermined time intervals from the beaker, diluted, filtered and analyzed spectrophotometrically.

III. RESULTS

3.1 Raw material characterization

3.1.1 Cyclizine hydrochloride

Table 7. Characterization of cyclizine hydrochloride

Sr. no	Characteristics	Observation	Result
1	Description	A White ,crystalline powder,	Compiles
2a	Melting point	282-285ºc	285ºc
2b	Ph	4.5-5.5	4.6
3	Loss on drying	Not more than 1%	0.89% loss in weight
4	Angle of repose	27º48´	
5	Bulk density	0.3703g/cc	0.392g/cc
6	Particle size	58µm	
7	XRD	83% crystallinity	

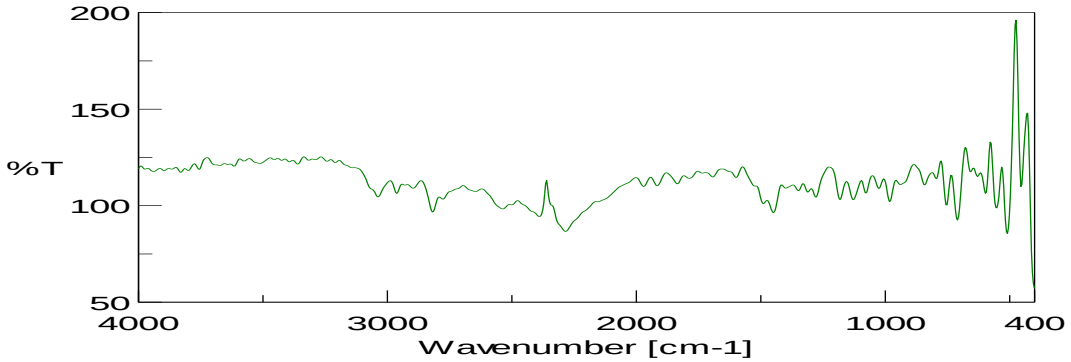

Fig 4: FTIR spectrum of cyclizine hydrochloride

Table 8. wavenumbers

Wave number(cm^{-1})	Functional groups
1600-63	Aromatic C=C stretching
1450 and 1349	C-H bending in CH_3
3072.4	C-H stretching in alkane
1280.5	C-N stretching
794.28	C-H bending in aromatics
840.12	C-H bending in aromatics
752.102	Mono substituted benzene
2353	Nitrile group stretching

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3.1.2 polyvinyl alcohol

Table 9. characterization of polyvinyl alcohol

Sr.no	Characterization	Observation	Results
1	Appearance	white to cream-colored granular powder.	Compiles
2	Solubility	Soluble in water; slightly soluble in ethanol (95%); Insoluble in organic solvents	Compiles
3	Melting point	180–190ºC	182ºC

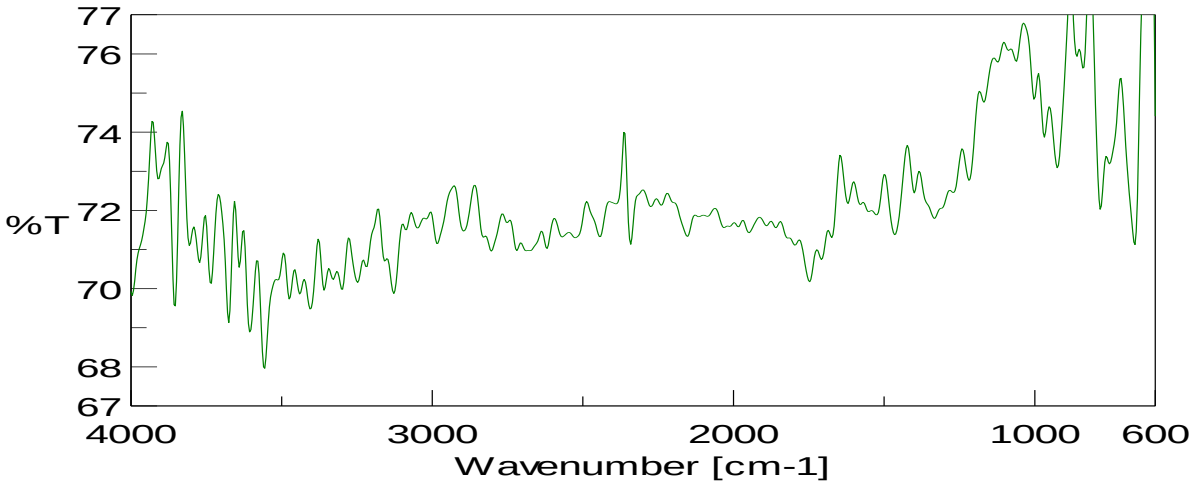

Fig 5: FTIR spectrum of polyvinyl alcohol

Table 10. Wavenumbers

Wavenumber(cm^{-1})	Functional groups
2896.56	Anti-symmetric v_{as} stretching of CH_2 band
2803.99	Symmetric vas stretching of CH band
1334	Wagging vibration of CH
3430	Broad OH absorption stretching vibration
1465.63	Wagging vibration of CH_2

3.1.3 Lecithin

Table 11. Characterization of lecithin

Sr.no	Characterization	Observation	Results
1	Appearance	Brown colour	Compiles
2	Solubility	Lecithin are practically insoluble in cold vegetable and animal oils, polar solvents	Compiles
3	Density	0.97g/cm^3	0.97g/cm^3

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3.2 Evaluation of nanocrystals

Table 12. Evaluation of preliminary batches

Name of batch	Angle of repose	Bulk density (g/cc)	Solubility (mg/ml)		XRD	Particle size	SEM
			Water	PB 6.4			
N1	29º 22´	0.360	18.39	19.56	Sharp peaks with some broadening	D (10%)-1.475µm D (50%)-80.29µm D (90%)-124.64µm	Spherical seprated
N2	31º 22´	0.347	29.54	29.33	Sharp peaks with some broadening	-	Spherical aggregates
N3	32º 38´	0.338	31.06	31.26	Sharp peaks with some broadening	D (10%)0.601µm D (50%)-81.057µm D (90%)-152.74µm	Cuboidal and needle
N4	32º 47´	0.314	32.45	32.87	Sharp peaks	D (10%)-0.144µm D (50%)-0.973µm D (90%)-6.488 µm	Spherical aggregates and some sepration

3.2.1 XRD of nanocrystal

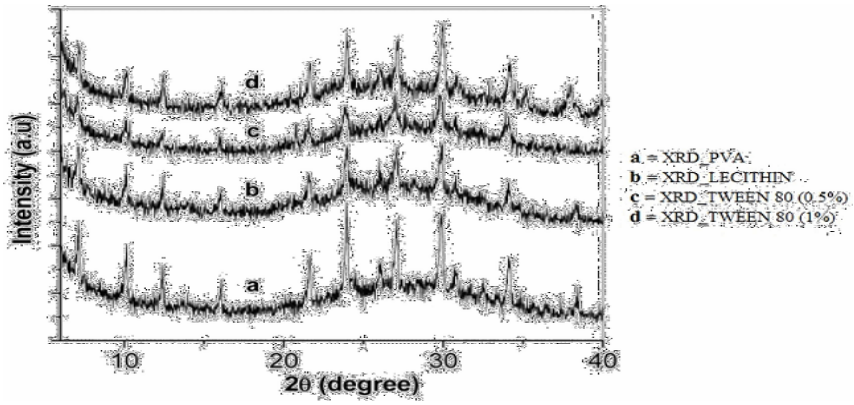

Fig 6: XRD of nanocrystal

Table 13. Interpretation of XRD data of N1

Sr. No.	Angel 2θ	d-value	Intensity	Intensity %
1	5.602	15.784	1872	37.5
2	10.21	8.694	823.68	16.5
3	12.51	7.1126	1737.21	34.8
4	16.57	5.405	1812	36.3
5	22.66	4.001	4288.128	85.9
6	24.32	3.739	1992	100
7	26.28	3.4854	54.912	1.1
8	27.62	3.323	4422.91	88.6
9	29.87	3.0933	4882.1	97.6
10	39.42	2.426	3334.656	66.8

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Table 14. Interpretation of XRD data of N2

Sr No.	ANGLE (2ɵ)	d value (A°)	Intensity (Count)	Intensity (%)
1	5.402	16.34623	4778	68.3
2	10.117	8.73643	2733	39.1
3	12.577	6.07195	1253	17.9
4	16.567	5.34681	2436	34.8
5	22.748	4.99342	6010	85.9
6	24.485	4.13259	6994	100
7	26.268	3.81988	80.9	1.2
8	27.542	3.48461	6324	90.4
9	30.145	2.86933	6917	98.9
10	34.124	2.62537	4933	70.5

Table 15. Interpretation of XRD data of N3

Sr. No.	ANGLE (2ɵ)	d value (A°)	Intensity (Count)	Intensity (%)
1	5.76	15.329	3569.6	67.2
2	10.32	8.6018	1992	37.5
3	12.87	6.9395	876.48	16.5
4	16.64	5.3866	1848.5	34.8
5	22.92	3.9563	4547	85.6
6	24.87	3.668	5312	100
7	26.43	3.462	111.552	2.1
8	27.54	3.346	4440.8	83.6
9	29.92	3.0892	5173.88	97.4
10	38.42	2.479	3658.98	68.8

Table 16. Interpretation of XRD data of N4

Sr. No.	ANGLE (2ɵ)	d value (A°)	Intensity (Count)	Intensity (%)
1	5.32	16.61	4955.67	69.7
2	10.02	8.859	2929.32	41.2
3	12.42	7.1655	1301.1	18.3
4	15.56	5.34681	2460	34.6
5	22.12	4.0973	6086	85.6
6	24.583	3.7028	7110	100
7	26.268	3.81988	207.93	2.9
8	27.66	3.318	6512	91.6
9	30.12	3.07	7046.01	94.1
10	38.62	2.4686	5083.6	71.5

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3.3 Particle size analysis

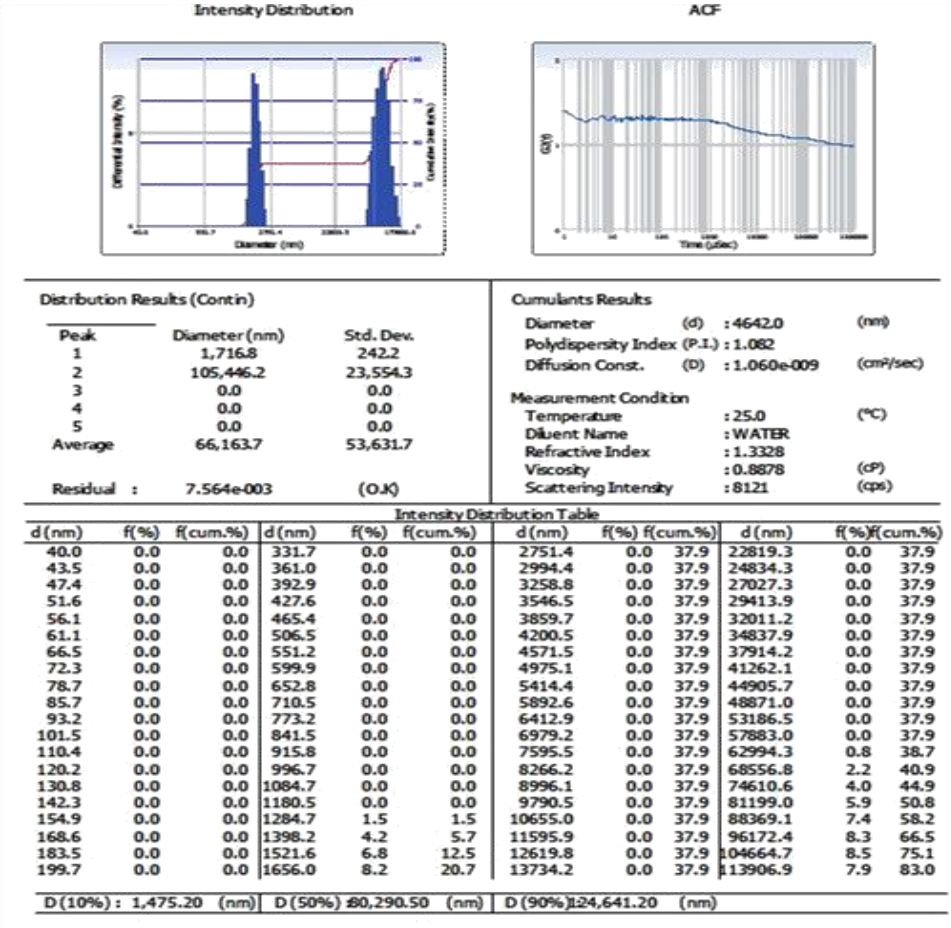

Fig 7: Particle size analysis of N1

3.4 SEM

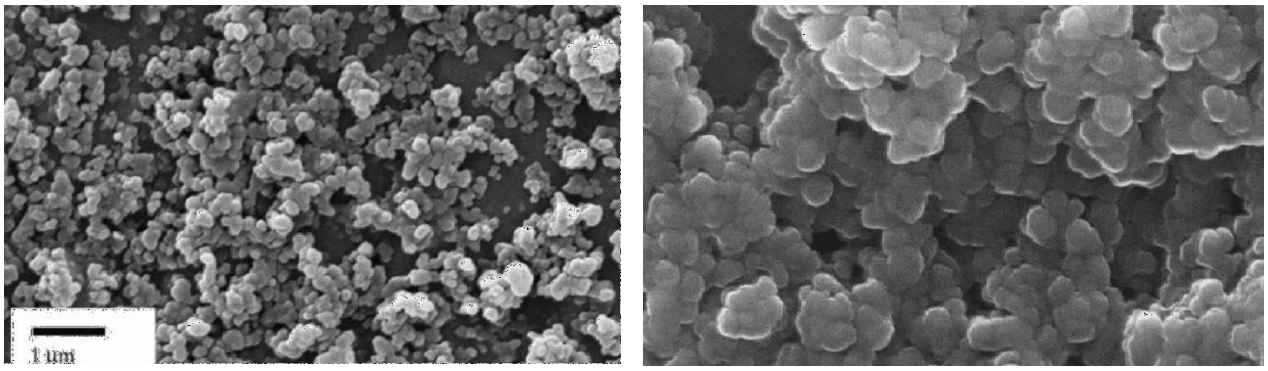

Fig 8: SEM of N1 and N2

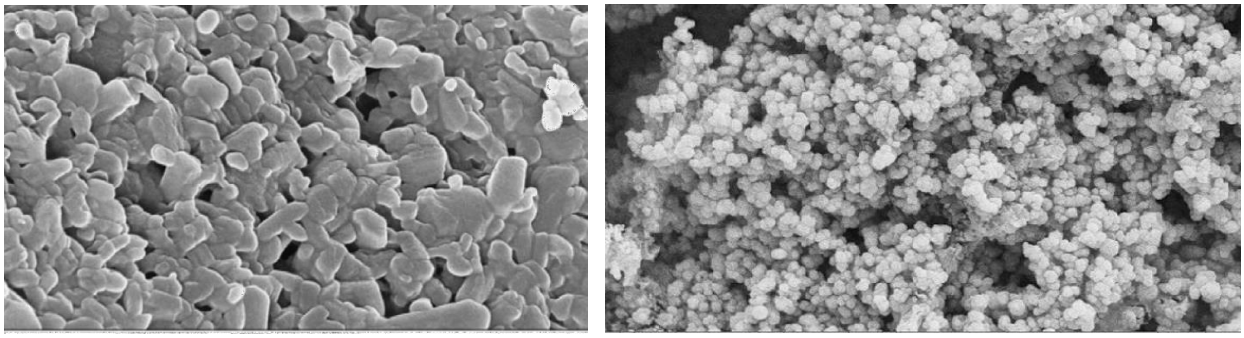

Fig 9: SEM of N3 and N4

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3.4 Mucoadhesive strength testing

Table 17. Mucoadhesive strength testing

Sr. No	Name of the batch	Mucoadhesive strength(Dyne/cm^2)
1	NH1	1148.4±0.93
2	NH2	1513.25±1.2
3	NH3	1914±0.53
4	NH4	2296±0.52
5	NH5	2871±0.36

3.5 In–vitro drug diffusion study

Table 18. In –vitro drug diffusion study

Sr. No	Time(min.)	% Cumulative drug diffused for different batches		
		NH3	NH4	NH5
1	5	17.28±0.17	13.78±0.60	10.94±0.16
2	10	28±0.55	21.96±0.36	18.78±0.45
3	15	38.68±0.45	28.40±0.26	24.57±0.26
4	20	49.86±0.20	35.33±0.54	31.21±0.56
5	25	57.33±0.65	48.37±0.38	41.79±0.18
6	30	64.56±0.30	54.54±0.26	48.98±0.33
7	40	69.25±0.89	61.87±0.41	53.34±0.40
8	50	75.68±0.58	72.53±0.30	57.8±0.21
9	60		77.93±0.03	65.96±0.73
10	70		83.72±1.06	69.22±0.20
11	80			70.88±0.53

IV. DISCUSSION

For the formation of nanocrystals, homogenization techniques were used. The different surfactants were selected in order to see their effect on particle size. The compositions of surfactants were different with regards to the kind of stabilisation mechanism. Lecithin stabilises nanosuspension by electrostatic repulsion because it is an amphoteric surfactant. Polyvinyl alcohol and Tween-80 stabilise nanosuspension through steric mechanisms. Polyvinyl alcohol also acts as a cryoprotectant during the freeze-drying process. Water was used as a dispersion medium. The obtained nanosuspensions were lyophilized. The polymer selected to prepare gel was hydroxypropyl methylcellulose due to its ciliofriendliness, mucoadhesive, and bioadhesive properties. It increased the retention time of the dosage form within the nasal passages through bond formation with the nasal mucosa, thereby increasing the contact time between the absorbing mucosa and the dosage form. This interaction between the mucoadhesive substance and the nasal mucosa may have resulted in the modification of tissue permeability (possibly a transient opening of the tight junctions) and an eventual increase in drug penetration or absorption.

The preliminary study was done to determine the choice and concentration of surfactants and the speed of the mechanical stirrer, high-speed homogenizer, and high-pressure homogenizer. The surfactant can prevent the aggregation of the produced nanocrystals. Less concentration of surfactant caused the aggregation; high concentration of surfactant caused problems during the freezing process. From the regularity aspect, the number and concentration of ingredients accompanying the therapeutic compound should be kept low to minimize hurdles. Therefore, 0.5% and 1% of surfactants were used. The critical factors were the speed of the

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mechanical stirrer, the high-speed homogenizer, and the high-pressure homogenizer. The speed was varied from 700 to 1200 rpm depending upon the foaming capacity of the surfactant, as foams cause a problem during homogenization. Particle size should be less than 40 m, which is a prerequisite for high pressure homogenization and is achieved by high speed homogenizations. The particle size confirmation was done using an electron microscope. A speed of 1500 rpm for 4 minutes was required for high-speed homogenization. The pressure was varied from 300 to 1500 bar in high-pressure homogenization for particle size reduction. For this study, four formulations. The composition of the preliminary batches prepared is given in Table. The effect of variation in concentration of surfactant on particle size, crystallinity, morphology, and solubility was studied. The large number of repose for the nanoparticles was probably the result of strong adhesion forces between nanocrystals. Solubility studies were performed in water and phosphate buffer 6.4. The solubility of N4 was comparatively higher because of the smaller size of the crystals. It was found to be increased by 15.2, 14.5, 13.8, and 8.6 folds for N4, N3, N2, and N1, respectively, with respect to the original drug.

Beckman-coulter was employed to determine particle size of nanocrystals which yields the mean particle size and polydispersity index(PDI). d (10 %), d (50 %) and d (90 %) were also determined. For N1 d (10%)-1.475µm, d (50%)-80.29µm, d (90%)-124.64µm were obtained. For N3 d (10%)-0.601µm, d (50%)-81.057µm, d (90%)-152.74µm were obtained. For N4 d (10%)-0.144µm, d (50%)-0.973µm,d (90%)-6.488 µm were obtained. The mean particle size was found to be smallest in N4 (1.59 µm) with a polydispersity index of 0.589. The achievable particle size reduction depends on the hardness of the drug and the applied homogenization parameters as pressure and number of applied cycles. The XRD patterns revealed the nanocrystalline nature of the as-prepared samples due to the broadening of the diffraction peaks. X-ray patterns of nanocrystals displayed the presence of numerous distinct peaks at 2ɵ of 5.402, 22.748, 24.485, 27.542, and 30.145, which suggests that nanocrystals were of crystalline form. There was some slight shifting of fix to the higher side as compared to pure drug. The nanocrystals showed diffraction peaks with low intensity in some amorphous forms. An amorphous or metastable form dissolves at a faster rate because of its higher internal energy and greater molecular mobility compared to crystalline material. The intensities were found to be higher in N4 as compared to N1, N2, and N3.

The morphology of nanocrystals was observed using a scanning electron microscope equipped with a field emission. SEM of N2 showed more aggregation of nanocrystals due to high surface adherence. The presence of spherical to slightly cuboidal shapes was observed in N1 and N4, but they were not in such aggregate form, suggesting that there was transformation to some amorphous state. There was a presence of needles and some cuboidal crystals in N3. The angular surfaces of the crystals were found to be smoother in the cases of N1, N2, and N3. From the above characterization, N4 was selected because of its smaller particle size and higher solubility. The different batches of gel were prepared by using N4 at variable concentrations.

The musoadhesive strength and viscosity were found to be higher in NH3, NH4, and NH5, so these batches were selected for further studies. In vitro drug diffusion studies of NH3, NH4, and NH5 were done. The percentage of drug diffusion was found to be 75.68 in NH3 and 83.72 in NH5. It was found to be higher in NH4 and less in NH5 as compared to NH3 and NH4. In this study, time (i.e., 80 min) was required in NH5, but percent drug diffusion was comparatively low. The residence times for NH3, NH4, and NH5 were 50 and 70, respectively. NH4 showed good results in viscosity, mucoadhesive strength (22960.52 dyne/cm2), and percent drug diffusion (82.72). This might be due to the fact that smaller particles offer more surface area to release the drug. From the above results, NH4 was selected for permeation studies. Permeation of pure drug as well as NH4 was done. In the study, it was found that the permeation of NH4 was faster than that of a pure drug. 81.39±0.837% of NH4 permeated through the nasal mucosa in 70 min. 39.83±0.164% of NH5 permeated through the nasal mucosa in 80 min.

V. CONCLUSION

In the present study, cyclizine hydrochloride nanocrystals were prepared by the homogenization technique. The first step was the production of nanosuspension. The different surfactants Tween-80, lecithin, and polyvinyl alcohol are widely used in pharmaceutical dosage forms. The obtained nanosuspension was formulated into a gel by using HPMC as a polymer. This polymer was selected because of its good mucoadhesive and bio-adhesive properties. Cyclizine hydrochloride is an antiemetic drug that controls emesis

by inhibiting the CTZ center. The concentration of surfactant (0.5% PVA) and speed up to 1500 bar are appropriate to obtain the mean particle size of 1.5 m, d (10%) -0.144 m, d (50%) -0.973 m, and d (90%) -6.488 m. A batch of nanocrystals containing cyclizine hydrochloride (5%) and PVA (0.5%) showed good results in solubility. There was an increase of 15.2 fold. The obtained solubility for this batch was 32.45 mg/ml, whereas that for cyclizine hydrochloride was 2.132 mg/ml.

XRD patterns revealed the nanocrystalline nature of the as-prepared samples due to the broadening of the diffraction peaks and slight variation in 2 values. The highest intensity was observed in nanocrystals containing drugs and PVA. The diffraction peaks for the sample showed some sharp peaks of higher intensity, which are due to the crystal's nature. SEM analysis showed variable results for cuboidal and needle-shaped crystals in nanocrystals containing lecithin. whereas spherical in nanocrystals containing PVA. Nanocrystals containing drug and PVA (0.5%) were selected and formulated into gels from different batches. For this, polymer HPMC was selected. The concentration varied from 0.2 to 1%. Mucoadhesive strength and viscosity were found to be higher in 0.6, 0.8, and 1% of HPMC. An in vitro diffusion study was done for batches containing nanocrystals and a variable amount of HPMC (0.6, 0.8, and 1%). The highest percentage of drug diffusion was observed at a concentration of 0.8%, i.e., 83.72% for 70 minutes. Drug permeation was found to be higher in formulations containing nanocrystals N4 and HPMC (0.8%) as compared to gels containing unprocessed drugs. Drug permeation was found to be 81.39% for 70 minutes. FTIR spectra and DSC thermograms of individual compounds and their formulations indicate that no chemical interaction takes place; only a physical interaction takes place. Finally, we can conclude that nanocrystals containing drug (5%) and PVA (5%) and further formulating into gel by using HPMC (0.8%) show potential for consideration as nasal drug delivery for cyclizine hydrochloride.

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