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# DESIGN, DEVELOPMENT AND CHARACTERIZATION OF NANO-PARTICULAR NICARDIPINE CAPSULE 20MG

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## ABSTRACT

Nicardipine belongs to BCS class-II drug having low solubility and orally bioavailability of about 10-40%. The objective of the present study is to develop a nanoparticle based Nicardipine formulation to increase the solubility and dissolution velocity for enhancing the bioavailability while reducing variability in systemic exposure. The obtained ratio of 1:1:1:1 of Drug, chitosan, Hydroxyethyl Beta-Cyclodextrin and cross linking agent sodium tripolyphosphate showing highest solubility of drug in water. The optimized nanoparticles (F3 batch) shown good entrapment efficiency, particle size, poly disparity and zeta potential value. The nanoparticles are filled into a capsule with SSG, Croscarmalose sodium, crospovidone Avicel pH 102 talc and

Mg.sterate. The above results indicated crospovidone containing (f12) shown good dissolution and drug content. The Nicardipine Hydrochloride capsules were shown good stability in the studies. The bioavailability studies of Nicardipine nanoparticle based capsules in the rabbit and compared with the pure drug. Nicardipine Nano capsules were shown $C_{max}$68.33 ng/ml, T max at 6 Hr, AUC(0-∞) at 191 ng.min/ml and t1/2 at 11.53 hr. AUC and maximum plasma concentration of Nicardipine Nano capsule is higher than pure nicardipine drug it indicates Nicardipine Nano capsules produce more bioavailability than nicardipine hydrochloride. Hence there is no significant difference between the pharmacokinetic parameters of Nicardipine hydrochloride obtained with pure drug and optimized formulation. Thus the prepared Nicardipine Nano capsule proved to be a potential technology for enhancing the transfer of poorly water soluble lipophilic compounds to the aqueous phase, thus enhancing the bioavailability.

**Keywords: -Nicardipine; Soy PC, DMPC, Aerosil 200, Propylene Glycol, Tween-80**

## INTRODUCTION

### DRUG DELIVERY SYSTEM [1]

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include capsules, injectable, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in **Figure 1**. To overcome these problems, controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

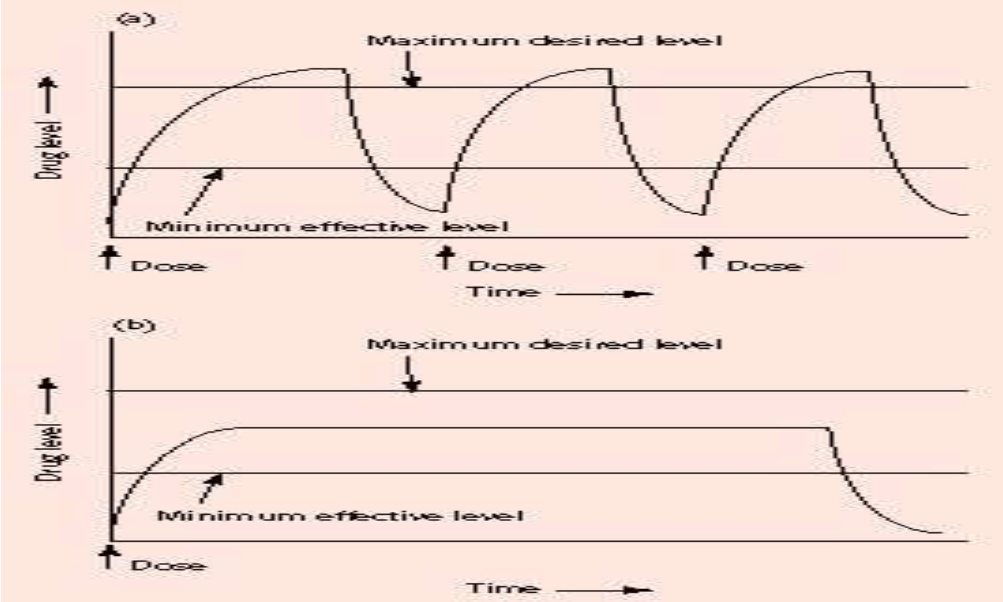



**Figure 1: Drug levels in the blood with**

**a) Conventional drug delivery systems [2]**

**b) Controlled drug delivery systems**

Oral administration is most frequently used route of administration since it is convenient, cost effective, good patient compliance and safe. The pertinent design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in fabricating the product. An essential physical-chemical property of a drug substance is solubility; especially aqueous system solubility **[1, 2]**. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step to absorption of drugs from the gastrointestinal tract. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation to exert a therapeutic effect, it must be in solution. Relatively insoluble compound often exhibit incomplete or erratic absorption. Recent technologies, innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities.

However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility. Improvement of oral bioavailability of poorly water-soluble drugs remains one of most exigent aspects of drug development **[3]**.

**NANOTECHNOLOGY [4, 5]**

Nanoparticles used as drug delivery vehicles are generally < 100 nm in at least

one dimension, and consist of different biodegradable materials such as natural or synthetic polymers, lipids, or metals. Nanoparticles are taken up by cells more efficiently than larger macromolecules and therefore, could be used as effective transport and delivery systems. For therapeutic applications, drugs can either be integrated in the matrix of the particle or attached to the particle surface.

A drug targeting system should be able to control the fate of a drug entering the biological environment. Nanosystems with different compositions and biological properties have been extensively investigated for drug and gene delivery applications. An effective approach for achieving efficient drug delivery would be to rationally develop nanosystems based on the understanding of their interactions with the biological environment, target cell population, target cell-surface receptors, changes in cell receptors that occur with progression of disease, mechanism and site of drug action, drug retention, multiple drug administration, molecular mechanisms, and pathobiology of the disease under consideration.

It is also important to understand the barriers to drug such as stability of therapeutic agents in the living cell environment. Reduced drug efficacy could be due to instability of drug inside the cell, unavailability due to multiple targeting or chemical properties of delivering molecules, alterations in genetic makeup of cell-surface receptors, over-expression of efflux pumps, changes in signaling pathways with the progression of disease, or drug degradation. For instance, excessive DNA methylation with the progression of cancer causes failure of several anti-neoplastic agents like doxorubicin and cisplatin.

Better understanding of the mechanism of uptake, intracellular trafficking, retention, and protection from degradation inside a cell are required for enhancing efficacy of the encapsulated therapeutic agent. In this review we discuss the drug delivery aspects of nanomedicine, the molecular mechanisms underlying the interactions of nanoparticles with cell-surface receptors, biological responses and cell signalling, and the research needed for the widespread application of nano delivery systems in medicine

**HARD GELATIN CAPSULE**

**Composition of Capsule Shell [6, 7]**

Gelatin is the most important constituent of the dipping solutions, but other components are also present to impart desired characteristics.

1. Gelatin

2. Plasticizer: glycerin, sorbitol

3. Water

4. Preservatives: Methyl Paraben, Propyl Paraben

5. Colorants: F.D & C, Certified lakes

6. Opacifier: Titanium dioxide

7. Flavoring agent: Ethyl vanillin

8. Fumaric acid is added to aid solubility and to reduce aldehydes tanning of gelatin

**Advantages of Capsule [3-8]**

- They may be used to mask the unpleasant tastes, aromas, or appearance of a drug
- Products can be encapsulated in various shapes, sizes and colors
- Products with thick slurry type paste medicaments to light oils and powders (with inert media) can be encapsulated in soft capsule
- They offer the pharmacist versatility to prepare any dose desired for a variety of administration routes (e.g. oral, inhalation, rectal, or to be diluted for vaginal, rectal, oral or topical use)
- Lower dose of active ingredients and given as unit dose
- High accuracy in fill weights
- Improved stability
- Longer shelf life
- Improved bioavailability
- They can be colored to protect the content from light and improve the acceptability
- Required less excipient than capsules.

**Disadvantages [3, 5, 7, 8]**

- They are easily tampered
- They are subject to the effects of relative humidity and to microbial contamination.
- More expensive (commercially)
- Bulk dosage cannot be dispensed in capsule
- Additional quality control measures may be required.

## MATERIALS AND EQUIPMENTS

### LIST OF MATERIALS [8]

**Table 1: Materials Used**

| S.No | Name of the material | Category | Supplier |
|---|---|---|---|
| 1 | Nicardipine Hcl | API | Dr.Reddy's Laboratories Ltd. |
| 2 | Sodium TPP | Cross linking agent | SD Fine Chem, Mumbai |
| 3 | Chitosan | Polymer | Merck, Mumbai |
| 4 | HPβCD | Polymer | Fischer scientifics, USA |
| 5 | Sodium sulphate | Cross linking agent | Merck, Mumbai |
| 6 | Sodium citrate | Cross linking agent | Merck, Mumbai |
| 7 | Sodium Starch Glycolate(SSG) | Super disintegrate | SD Fine Chem Mumbai |
| 8 | Croscarmellose sodium | Super disintegrate | SD Fine Chem Mumbai |
| 9 | Crospovidone | Super disintegrate | SD Fine Chem Mumbai |
| 10 | Avicel pH 102 | Diluents | SD Fine Chem Mumbai |
| 11 | Talc | Glidant | SD Fine Chem Mumbai |
| 12 | Capsules | Hard Gelatin capsules | Associated capsules Pvt Ltd.India |

## LIST OF INSTRUMENTS

**Table 2: Details of Instruments Used**

| S.No | Name of the Equipment | Model | Manufacturer |
|---|---|---|---|
| 1 | Semi micro analytical balance | LE 225D | Sartorius, India |
| 2 | Top loading balance | CP 622 | Sartorius, India |
| 3 | Rota shaker | SW 23 | Julabo, North America |
| 4 | Heating mantle | - | Shital scientific industries, Mumbai |
| 5 | pH meter | Orion 420 A+ | Thermo orion, |
| 6 | Overhead Stirrer | RZR 2051control | Heidolph, Germany |
| 7 | Magnetic stirrer | MR-3001,HeiTec | Heidolph, Germany |
| 8 | Sonicator | - | Bandelin sonorex |
| 9 | Disintegration apparatus | ED 2AL | Electrolab, India |
| 10 | Tap density apparatus | ETD 1020 | Electrolab, India |
| 11 | Angle of Repose apparatus | 2T-101-050 | Hansen research |
| 12 | Dissolution apparatus | Disso 2000 | Labindia |
| 13 | Alliance HPLC, PDA detector | 2695, 2996 | Waters, USA |
| 14 | HPLC Column | C4 | Zodiacsil |
| 15 | Differential Scanning Calorimeter | DSC Q-1000 V9.8AA 124 | TA instruments, USA |
| 16 | X-Ray Diffractometer | XPert Pro AA 198 | PANalytical BV, Netherland |
| 17 | Scanning Electron Microscope | S 3000 N | Hitachi |
| 18 | Vacuum Evaporator | HUSGB | Hitachi |
| 19 | Mini Granulator | BMG | LB Bohle |
| 20 | Rota evaporator | | Heidolph |
| 21 | Stability chamber | - | Thermolab |
| 22 | Milli Q Water purifier | - | Millipore (India) Pvt Ltd |
| 23 | Storage bottles | - | Schott Duran, North America |
| 24 | Glass ware | - | Merck, Rankem, Borosil |
| 25 | Pipettes | - | Vensil |
| 26 | Syringe filters (0.45 µ- 47,25,13 mm) | NX047100, ZWGSFN 13045 | Pall Life sciences,India Zodiac Life sciences, India |
| 27 | Syringes | - | Dispo van |

## METHOLODOGY [9-13]

### Preparation of Nicardipine Hcl-Loaded Chitosan-TPP Nanoparticles

Chitosan-TPP nanoparticles were prepared using a modified ionic gelation method **[25]**. Briefly, chitosan was dissolved at 0.2% (w/v) in 0.1 M acetic acid at pH 2.86 **[23, 26]** and HPβCD was dissolved in the same solution. The solution was magnetically stirred for 3 h and then filtered to discard any undissolved chitosan. TPP was dissolved at 0.12% (w/v) in 0.1 M NaOH. Next, the TPP solution was added dropwise to 1 mL chitosan solution **[27]** and the resultant solution was incubated for 60 min. The final suspension was filtered. The reaction was performed at three different ratios to evaluate the effects of the TPP-to-chitosan ratio on nanoparticle size and polydispersity index. Drug-loaded nanoparticles were prepared by solubilizing Nicardipine HCl at 0.5% (w/v) in 2% Tween 20. After the various ratios of Nicardipine Hcl solution were added to the chitosan solution under for 30 min at 25 °C, the TPP solution was mixed with the chitosan solution and Nicardipine HCl under

sonication for 30 min at 40 °C. Finally, nanoparticles were purified by centrifugation for 30 min at 15,000 rpm and then washed twice with distilled water. The resulting particles were lyophilized.

**Measurement of Particle Size and Polydispersity Index**

The particle size distribution and polydispersity index of nanoparticles were determined using a light-scattering spectrophotometer (Zetasizer Nano S90, Malvern Instruments Ltd., Malvern, UK). The zeta potential of nanoparticles was measured using a light-scattering spectrophotometer (ELS-Z, Otsuka, Japan). The samples were diluted with deionized water and then transferred in a quartz cuvette in the light scattering instrument to measure particle size and zeta potential, respectively. The stability of chitosan-TPP nanoparticles containing Nicardipine HCl was investigated for 4 weeks by measuring particle size and the Polydispersity index.

**Table 3: Formulation of Nicardipine hydrochloride nanoparticles prepared with chitosan and by using different cross linking agents**

| Cross linking agents | | | | | |
|---|---|---|---|---|---|
| Sodium TPP | | Sodium sulphate | | Sodium citrate | |
| Formulation Code | Drug : Chitosan:HPβCD: Cross linking agent | Formulation Code | Drug : Chitosan:HPβCD: Cross linking agent | Formulation Code | Drug : Chitosan:HPβ CD: Cross linking agent |
| F-1 | 1:1:1:0.5 | F-4 | 1:1:1:0.5 | F-7 | 1:1:1:0.5 |
| F-2 | 1:1:1:0.75 | F-5 | 1:1:1:0.75 | F-8 | 1:1:1:0.75 |
| F-3 | 1:1:1:1 | F-6 | 1:1:1:1 | F-9 | 1:1:1:1 |

**Evaluation of Nicardipine Nano particles:**

**a) Particle size determination:** The surface morphology of the particles can be well investigated using the Scanning electron microscopy. These SEM studies of pure Nicardipine revealed its crystalline structures. Considering the Placebo lipid formulation the surface of the particles was adsorbed with the adsorbent and the particles were spherical in shape. In the Granulated lipid formulation the structures of the crystalline drug particles in the granulated formulation were observed indicating the complete entrapment of the drug particles within the lipid vesicles.

**c) Total Drug Content (TDC)** The amount of drug present in formulations were determined by dissolving 1g of Nicardipine NCP in pH was adjusted to 3.0 using dilute o-phosphoric acid. 1280 ml of this buffer was added to 720 ml of Acetonitrile. The above solution is degassed by sonication for 30 minutes and then filtered. Nicardipine NCP was analyzed individually with a photodiode

array detector and the was observed at **287 nm** and was selected as its absorption wavelength. Each experiment was performed in triplicate. Placebo formulation treated similar to that of the sample was used as blank. The total drug content was calculated by using the equation given below.

**TDC= concentration X dilution factor X volume of formulation**

**d) Entrapment Efficiency** The EE was determined by analyzing the free drug content in the supernatant obtained after centrifuging the CNC in high speed centrifuge at 16000 rpm for 30 min at 0 °C using Remi cooling centrifuge (Mumbai, India). The EE was calculated as follows

$$EE\% = \frac{\text{actual drug loading}}{\text{theoretical drug loading}} \times 100\%$$

**e) Dissolution studies of Nicardipine Nano particles:**

*In-vitro* dissolution studies of pure drug and Nicardipine Nano particles were carried out for 60min using dialysis bag method using dialysis membrane having molecular weight of 12000—14000 Da at 100 rpm. Nicardipine Nano particles equivalent to 60 mg of pure drug (Nicardipine) used for dissolution study at $37\pm0.5^0$ C in 0.001 N HCl as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were analyzed by using HPLC at 287 nm. $DE_{30}$%, $T_{50}$, $T_{90}$ and $k^{-1}$ values were calculated from dissolution data.

**f) Zeta Potential Measurement**

The analysis was performed by using the Malvern Zetasizer ver. 6.12 (Malvern instrument, UK) the electrophoretic mobility was converted to the zeta potential. To determine the zeta potential, nanoparticle samples were diluted with KCl (0.1 mM) and placed in electrophoretic cell where an electrical field of 15.2 V/cm was applied. All measurement was performed in triplicate The system was maintained at 25 °C.

**g) Scanning Electron Microscopy (SEM)**

The surface morphology of the particles can be well investigated using the Scanning electron microscopy. These SEM studies of pure Nicardipine revealed its crystalline structures. Considering the Placebo lipid formulation the surface of the particles was adsorbed with the adsorbent and the particles were spherical in shape. In the Granulated lipid formulation the structures of the crystalline drug particles in the granulated formulation were observed indicating the complete entrapment of the drug particles within the lipid vesicles.

**Table 4: Mean particle size, Poly disparity Index and zeta potential of the Nicardipine Hydrochloride Nanoparticles**

| S.No | Batch Code | Entrapment Efficency (%) | Average Particle size (nm±S.D) | Poly dispersity Index (X±SD) | Zeta Potential (mV±SD) |
|---|---|---|---|---|---|
| 1 | F1 | 91.40 ± 1.1 | 376.1±2.23 | 0.374±0.11 | -31.8±1.9 |
| 2 | F2 | 94.56 ± 0.9 | 363.4±1.28 | 0.368±0.17 | -34.7±1.3 |
| 3 | F3 | 99.67 ± 1.2 | 351.5±2.12 | 0.351±0.13 | -37.3±1.8 |
| 4 | F4 | 77.34 ± 0.7 | 399.3±2.85 | 0.362±0.09 | -40.8±1.3 |
| 5 | F5 | 80.44 ± 0.6 | 387.2±2.65 | 0.350±0.05 | -44.4±1.6 |
| 6 | F6 | 84.34 ± 0.6 | 375.3±1.2 | 0.337±0.08 | -45.3±1.5 |
| 7 | F7 | 85.37 ± 1.6 | 366.2±2.13 | 0.349±0.09 | -42.9±1.7 |
| 8 | F8 | 88.43 ± 1.4 | 345.5±2.16 | 0.329±0.15 | -47.1±1.9 |
| 9 | F9 | 91.57 ± 0.9 | 334.0±1.47 | 0.319±0.07 | -48.3±2.4 |

**Table 5: *In-vitro* dissolution data of Nicardipine hydrochloride nanoparticles prepared with Sodium TPP as cross linking agent in different Ratios**

| S.No | Time (min) | Cumulative % of Drug Dissolved ( $\bar{x} \pm$ s.d., n = 3 ) | | | |
|---|---|---|---|---|---|
| | | PURE DRUG | F1 | F2 | F3 |
| 1 | 0 | 0 | 0 | 0 | 0 |
| 2 | 10 | 2.69 ± 0.02 | 29.93 ± 0.04 | 34.37 ± 0.01 | 37.16 ± 0.01 |
| 3 | 20 | 4.8 ± 0.01 | 36.28 ± 0.02 | 40.14 ± 0.03 | 44.69 ± 0.04 |
| 4 | 30 | 6.93 ± 0.03 | 51.14 ± 0.01 | 56.07 ± 0.02 | 60.3 ± 0.02 |
| 5 | 40 | 9.76 ± 0.04 | 69.22 ± 0.03 | 74.18 ± 0.04 | 78.09 ± 0.03 |
| 6 | 50 | 11.6 ± 0.02 | 80.07 ± 0.03 | 84.01 ± 0.02 | 88.2 ± 0.02 |
| 7 | 60 | 13.1 ± 0.03 | 87.15 ± 0.04 | 91.11 ± 0.03 | 94.71± 0.04 |

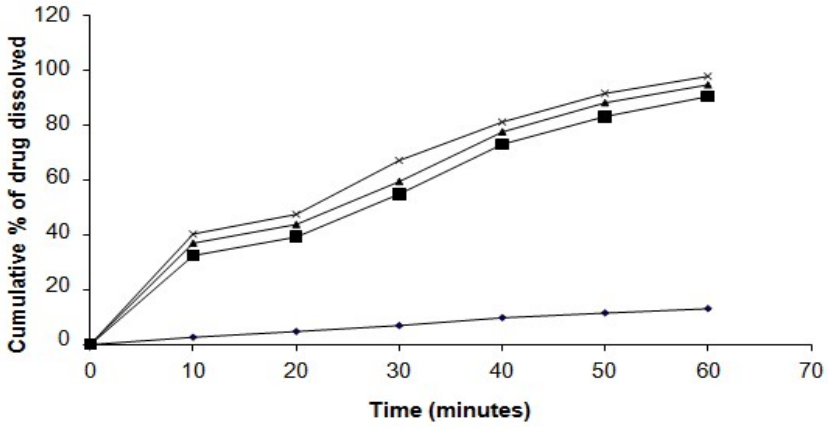



**Figure 2: Dissolution Profiles of Nicardipine Hydrochloride Pure Drug and nanoparticles prepared with Sodium TPP as cross linking agent in different Ratios**

**(-♦-) Nicardipine Hydrochloride pure drug**

**(-■-) Nanoparticles prepared with Drug: Chitosan: HPβCD: Cross linking agent in 1: 0.5 ratio**

**(-▲-)Nanoparticles prepared with Drug: Chitosan: HPβCD: Cross linking agent in 1: 0.75 ratio**

**(-×-)Nanoparticles prepared with Drug : Chitosan: HPβCD: Cross linking agent in 1: 1 ratio**

**Table 6: Composition of Nicardipine hydrochloride capsules filled with Superdisintegrants**

| S. No. | Ingredients ( mg) | F10 | F11 | F12 |
|---|---|---|---|---|
| 1 | Nicardipine hydrochloride nanoparticles | 80 | 80 | 80 |
| 2 | Sodium Starch Glycolate (SSG) | 10 | -- | -- |
| 3 | Croscarmellose sodium | -- | 10 | -- |
| 4 | Crospovidone | -- | -- | 10 |
| 5 | Avicel pH 102 | 106 | 106 | 106 |
| 6 | Talc | 2 | 2 | 2 |
| 7 | Magnesium stearate | 2 | 2 | 2 |
| | Total weight | 200 | 200 | 200 |

**Table 7: Evaluation Parameters of Nicardipine hydrochloride capsules prepared with Superdisintegrants**

| S.No. | Parameters | F10 | F11 | F12 |
|---|---|---|---|---|
| 1 | Average weight (mg) | 198±0.2 | 199±0.1 | 200±0.2 |
| 2 | Drug content (%) | 98.3 | 99.8 | 97.9 |
| 3 | Disintegration time (sec) | 154 | 141 | 121 |

**Table 8: *In-vitro* Dissolution Data of Nicardipine hydrochloride capsules prepared with Superdisintegrants**

| S.No. | Sampling time (min) | Cumulative % of drug Dissolved ( $\bar{x} \pm$ s.d., n = 3 ) | | |
|---|---|---|---|---|
| | | F10 | F11 | F12 |
| 1 | 0 | 0 | 0 | 0 |
| 2 | 5 | 43.44 ± 0.05 | 51.82 ± 0.02 | 63.64 ± 0.02 |
| 3 | 10 | 64.28 ± 0.02 | 75.14 ± 0.04 | 88.12 ± 0.01 |
| 4 | 15 | 77.2 ± 0.01 | 84.29 ± 0.01 | 94.2 ± 0.05 |
| 5 | 20 | 85.65 ± 0.04 | 92.78 ± 0.03 | 99.25 ± 0.03 |
| 6 | 25 | 93.11 ± 0.06 | 98.82 ± 0.02 | -- |
| 7 | 30 | 98.15 ± 0.03 | -- | -- |

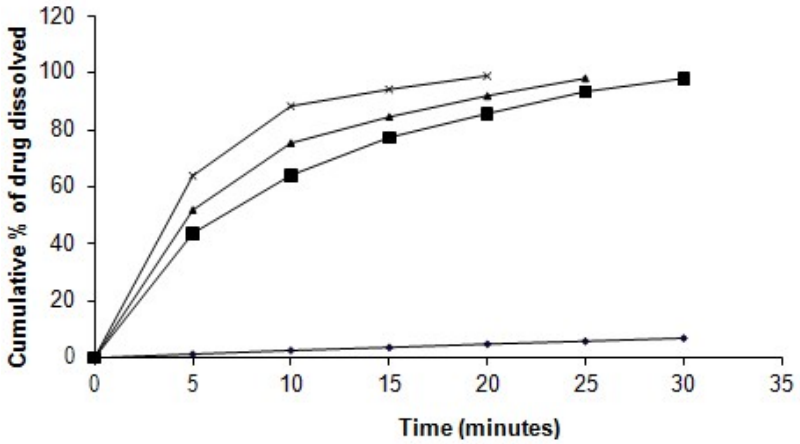



**Figure 3: Dissolution Profiles of Nicardipine hydrochloride capsules prepared with various Superdisintegrants**
**(-♦-) Nicardipine hydrochloride pure drug**
**(-■-) Nicardipine hydrochloride capsules prepared with Sodium Starch Glycolate**
**(-▲-) Nicardipine hydrochloride capsules prepared with Croscarmellose sodium**
**(-×-) Nicardipine hydrochloride capsules prepared with Crospovidone**

**Table 9: *In-vitro* Dissolution Data of Nicardipine hydrochloride capsule stored at 25±2$^0$ C/60±5% RH and 40±2$^0$ C/75±5% RH**

| S.No | Time (min) | Initial | Percentage of Nicardipine hydrochloride dissolved ($x \pm$ sd) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 25±2$^0$ C/60±5% RH | | | 40±2$^0$ C/75±5% RH | | |
| | | | 1st month | 2nd month | 3rd month | 1st month | 2nd month | 3rd month |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 5 | 63.95 ± 0.01 | 63.91 ± 0.02 | 63.87 ± 0.01 | 63.82 ± 0.02 | 63.84 ± 0.03 | 63.78 ± 0.02 | 63.67 ± 0.02 |
| 3 | 10 | 88.39 ± 0.03 | 88.27 ± 0.03 | 88.24 ± 0.04 | 88.19 ± 0.01 | 88.22 ± 0.02 | 88.17 ± 0.01 | 88.13 ± 0.01 |
| 4 | 15 | 94.29 ± 0.01 | 94.23 ± 0.01 | 94.28 ± 0.02 | 94.24 ± 0.03 | 94.25 ± 0.01 | 94.21 ± 0.01 | 94.17 ± 0.03 |
| 5 | 20 | 99 ± 0.03 | 98.72 ± 0.02 | 98.67 ± 0.03 | 98.61 ± 0.01 | 98.64 ± 0.03 | 98.59 ± 0.03 | 98.54 ± 0.04 |

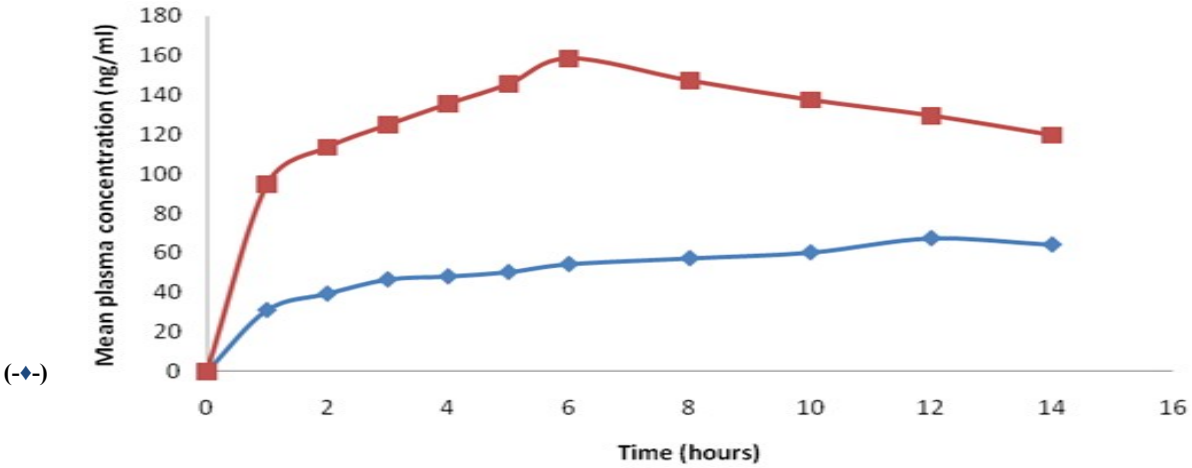
Table 10: Dissolution Kinetics of Nicardipine hydrochloride capsule stored at 25±2$^0$ C/60±5% RH and 40±2$^0$ C/75±5%RH

| S. No. | Storage conditions | Time interval | K (min$^{-1}$) | T 50 (min) | T 90 (min) | DE 15 (%) |
|---|---|---|---|---|---|---|
| 1 | 25±2$^0$ C/ 60±5% RH | 1$^{st}$ month | 0.22 | 3.1 | 10.3 | 66.31 |
| | | 2$^{nd}$ month | 0.22 | 3.1 | 10.3 | 66.31 |
| | | 3$^{rd}$ month | 0.22 | 3.1 | 10.3 | 66.31 |
| 2 | 40±2$^0$ C/ 75±5% RH | 1$^{st}$ month | 0.22 | 3.1 | 10.3 | 66.31 |
| | | 2$^{nd}$ month | 0.22 | 3.1 | 10.3 | 66.31 |
| | | 3$^{rd}$ month | 0.22 | 3.1 | 10.3 | 66.31 |

Table 11: Plasma Concentration of Nicardipine hydrochloride following Pure Drug Administration and Nicardipine hydrochloride optimized formulation

| S. No. | Time (h) | Plasma concentration (ng/ml) (Mean ± s.d) | |
|---|---|---|---|
| | | Pure drug | Optimized formulation |
| 1 | 0 | 0 | 0 |
| 2 | 0.5 | 08.51±1.86 | 28.23±1.36 |
| 3 | 1 | 11.35±1.74 | 36.44±1.78 |
| 4 | 1.5 | 12.51±1.52 | 42.20±1.56 |
| 5 | 2 | 14.61±1.14 | 45.24±1.24 |
| 6 | 3 | 16.75±1.64 | 49.62±1.12 |
| 7 | 4 | 18.81±1.35 | 54.12±1.65 |
| 8 | 5 | 19.62±1.43 | 61.18±1.67 |
| 9 | 6 | 21.93±1.24 | 68.33±1.85 |
| 10 | 8 | 22.76±1.43 | 62.15±1.72 |
| 11 | 10 | 24.90±1.24 | 57.42±1.22 |
| 12 | 12 | 27.72±1.27 | 49.23±1.36 |
| 13 | 14 | 24.64±1.36 | 42.20±1.43 |
| 14 | 16 | 21.96±1.53 | 35.24±1.64 |
| 15 | 18 | 18.84±1.32 | 28.53±1.18 |
| 16 | 20 | 15.92±1.21 | 23.12±1.62 |
| 17 | 24 | 12.28±1.39 | 17.18±1.47 |

Figure 4: Comparative Plasma Concentration -Time Curve of Nicardipine hydrochloride following Pure drug and optimized formulation




(-♦-) plasma Concentration -Time Curve of Nicardipine hydrochloride following pure drug administration

(-■-) plasma Concentration -Time Curve of Nicardipine hydrochloride following optimized formulation

**Table No. 12: Statistical Treatment of Pharmacokinetic Parameter (mean ± s.d.) of Nicardipine hydrochloride obtained with pure drug and optimized formulation**

| Pharmacokinetic parameter | Pure Drug | Optimized formulation | Calculated value of 't' |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 27.72± 0.31 | 68.33± 0.42 | 26.70*** |
| $t_{1/2}$ (h) | 11.53± 0.011 | 6.09± 0.072 | 40. 75*** |
| $K_{el}$ ($h^{-1}$) | 0.58± 0.012 | 0.53± 0.014 | 6.87*** |
| $K_a$ ($h^{-1}$) | 1.68± 0.01 | 5.53± 0.02 | 19.67*** |
| $AUC_{0-\alpha}$ (ng h/ml) | 191± 1.43 | 686.1.±2.07 | 256.60*** |
| Null hypothesis ($H_0$): There is no significant difference between the pharmacokinetic parameters of Nicardipine hydrochloride obtained with pure drug and optimized formulation. Table value of't' with 10 DF at the 0.001 level is 4.587. | | | |
| Result: $H_0$ is not accepted as the calculated't' value more than the table Value of 't' with 10 DF at 0.001 levels of significance. It was therefore concluded that there was significant difference between the pharmacokinetic parameters of obtained with pure drug and optimized formulation. | | | |

**CONCLUSION:-** Thus the prepared nanoparticle based formulation proved to be a potential technology for enhancing the transfer of poorly water soluble lipophilic compounds to the aqueous phase, thus enhancing the bioavailability.

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