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Formulation and Evaluation of Nitrendipine Nanospheres in Order to Improved Bioavailability and Therapeutic Effectiveness

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ABSTRACT

The present study focuses on the development and evaluation of sustained-release nanospheres of Nitrendipine to enhance its solubility and bioavailability. Given Nitrendipine s poor aqueous solubility, polymeric nanospheres were formulated using the solvent evaporation technique, employing various polymers such as HPMC K4M, HPMC K100M, and ethyl cellulose. A total of nine formulations (F1–F9) were prepared and characterized for particle size, percentage yield, drug content, entrapment efficiency, and in vitro drug release. Preformulation studies including solubility analysis, FTIR spectroscopy, and DSC confirmed compatibility between Nitrendipine and selected excipients. The optimized formulation F9 exhibited a particle size of 245.3 nm, 98.9% drug release over 24 hours, and followed zero-order kinetics with non-Fickian diffusion. FTIR and DSC analyses indicated no significant drug-polymer interaction. Stability studies over three months confirmed the formulation's physical and chemical stability. Overall, formulation F9 demonstrated promising potential as a sustained-release nanoparticle system for effective Nitrendipine delivery, warranting further in vivo studies.

Keywords: Nitrendipine, Nanospheres, Sustained Release, Solvent Evaporation, Drug Release Kinetics, Polymeric Nanoparticles, In Vitro Dissolution

INTRODUCTION

Solubility plays a crucial role in achieving the required drug concentration in systemic circulation for effective therapeutic action. However, only about 8% of new drug candidates exhibit good solubility and permeability. Poor water solubility remains a major challenge in developing optimal dosage forms, as it limits bioavailability and consistent pharmacological effects. This issue is increasingly common among newly developed drugs, complicating formulation efforts and therapeutic success. (1) Nanoparticles are particulate dispersions ranging from 10 to 1000 nm, used to dissolve, trap, encapsulate, or attach drugs. Based on preparation, they form nanosphereswhere the drug is uniformly dispersedor nanocapsuleswhere the drug is enclosed within a polymer membrane. Biodegradable polymeric nanoparticles, especially those coated with hydrophilic polymers like PEG, offer prolonged circulation and targeted delivery, making them promising drug delivery systems. (2)

Nanoparticles have emerged as promising drug delivery systems due to their ability to enhance drug stability, control release, and enable targeted delivery. Compared to liposomes—which suffer from issues like poor storage stability, low encapsulation efficiency, and rapid drug leakage—polymeric nanoparticles offer distinct advantages, including controlled release, improved drug and protein stability, and modifiable degradation profiles through matrix selection. Their surface properties can be engineered for passive or active targeting, enhancing therapeutic efficacy and minimizing side effects. Additionally, they are suitable for multiple administration routes and can effectively reach target organs such as the liver, spleen, lungs, and lymphatic system. However, limitations such as aggregation, handling difficulties, and restricted drug loading remain challenges. This study discusses recent advances in nanoparticle-based drug delivery, focusing on surface modification, drug loading strategies, release control, and future applications. (3)

Method of preparation of nanospheres:[42]
There are various types of method by which Nanospheres are prepared.

1. Polymerization (Emulsification polymerization).
2. Solvent Evaporation.
3. Solvent displacement technique.
4. Phase inversion temperature methods.

1. Polymerization (Emulsification polymerization): Polymerization methods like emulsification and interfacial polymerization use monomers (e.g., polymethylmethacrylate, polyethylcyanoacrylate) to form nanospheres in aqueous media. The drug is incorporated either during polymerization or adsorbed afterward. Purification involves centrifugation or resuspension to remove stabilizers. Finally, nanospheres are dispersed in an isotonic, surfactant-free medium.(4)

2. Solvent Evaporation: This method forms nanospheres by dissolving macromolecules in an organic solvent, followed by solvent removal via evaporation or diffusion, leading to polymer precipitation. Unlike polymerization, it uses both synthetic and natural polymers like chitosan or alginate, enhancing biocompatibility.(5)

3. Solvent displacement technique: The solvent displacement method, a low-energy technique, forms nanospheres by dissolving polymers (e.g., polyesters, PEG) in a water-miscible organic solvent, then adding it to an aqueous phase to induce polymer precipitation. This spontaneous nano-emulsification creates uniform nanospheres without high energy input. Widely studied by Fessi and Leroux, it supports various polymers and solvents for enhanced versatility.(6)

4. Phase inversion temperature method: In this method, nanospheres are formed via polymer desolubilization within nano-emulsion droplets, using volatile solvents evaporated below the phase inversion temperature (PIT). However, using harmful organic solvents negates PIT's key advantage of avoiding such solvents, limiting its further modification.(7)

Nanospheres As Targeted Drug Delivery :
There are various ways to using of nanospheres as targeted drug delivery system.

1. Targeting on Tumor
2. Long Circulation of nanospheres
3. Nanospheres for drug delivery
4. Nanospheres for drug delivery in brain

There are also other drug delivery systems present for this purpose.
Nanospheres for gene delivery & Nanospheres targeting to epithelial cells etc (8)

MATERIALS AND METHODS

Materials Used:
The following materials were used in the present study: Nitrendipine was procured from Hetero, while Hydroxypropyl methyl cellulose (HPMC) grades K4M and K100M were obtained from Aurobindo Pharma Ltd. Ethyl cellulose was sourced from Sd. Fine Chemicals Ltd., and dichloromethane was purchased from Molychem. Methanol was procured from Yarrow, and sodium lauryl sulphate was obtained from Merck. All reagents and solvents used were of analytical grade and used as received.

Preformulation Research:
The process of understanding a drug's properties and how they interact with excipients prior to creating a dosage form is referred to as "preformulation."

Preformulation testing is the first phase in the scientific creation of a drug's dosage forms. The physical and chemical properties of the drug ingredient are examined, both on their own and in combination with excipients. The primary objective of preformulation testing is to generate information that the formulator can use to develop stable and bioavailable dosage forms.(9)

Investigation of solubility:
Preformulation solubility analysis was done to determine the best solvent system to dissolve the drug as well as the various excipients used in formulation and to assess the medication's solubility in the planned dissolution medium.

Infra-Red Spectroscopy:
The IR absorption spectrum of Nitrendipine was determined by FTIR spectrophotometer using KBr dispersion method. The IR spectrum of the obtained sample of fabricated nanoparticles was compared with the standard IR spectra of the pure drug.

FTIR spectra help to confirm the identity of the drug and detect the interaction of the drug with polymers was carried out to check compatibility between drug and polymer.

PREPARATION OF STANDARD GRAPH OF NITRENDIPINE

Preparation of 1%Sodium lauryl sulphate solution:
To make 1% sodium lauryl sulphate solution, 10 gm of sodium lauryl sulphate were accurately measured and added to 1000 ml of distilled water.

Preparation of standard graph in 1%SLS Solution:
10 mg of Nitrendipine was consumed and dissolved in 10 g of sodium lauryl solution in 1000 ml of volumetric flask water. To make 5, 10, 15, 20, 25 and 30 g/ml, 5, 10, 15, 20, 25 and 30 ml of the stock were taken separately and built up to 10 ml with 1%SLS solution. When this solution was scanned in the UV range, from 200 nm to 800 nm, a UV-Visible Spectrophotometer revealed that the maximum wavelength was discovered to be 275 nm for Nitrendipine in 1%SLS as a blank (Libra- Biochrome). These solutions' 223 nm absorbance was measured, and a concentration versus absorbance graph was created. (10)

FT-IR Spectroscopy:
To identify any potential interactions between medications and the polymers or excipients, IR spectral matching experiments are used. FT-IR was used to assess the medicine Nitrendipine compatibility with various polymers in the present (PERKIN ELMER FT-I Insf. USA). The samples were scanned using an FT-IR spectrophotometer with a range of 4000 to 400 cm-1. Similar to that, all of the individual drugs and created nanocrystals had their IR spectra recorded. To look for any potential physical and chemical interactions, the samples' outward appearance as well as the presence or removal of peaks in the spectra were observed. (11)

Differential scanning calorimetry (DSC) measurement:
Using a DSC-41 instrument, the thermal characteristics of the lyophilized powder samples were studied (Shimadzu, Japan). Each lyophilized powder sample had its scanning temperature adjusted between 25 and 200 °C with a heating rate of 10 °C/min. In an open aluminium pan, 10 mg of each sample were examined, and magnesium served as the standard. Thermal analysis was done on Nitrendipine and the excipients to assess the internal structure changes following the nanosizing process.(12)

Formulation of Nitrendipine nanospheres:
Utilizing a variety of polymers, emulsion followed by solvent evaporation was employed to create Nitrendipine drug nanospheres.

Making the polymer and medication solution:

1. Placed the necessary amount of polymer in a dry beaker after weighing it.
2. Methanol, the required solvent, was measured out into a cylinder.
3. Methanol was now gradually added to the beaker containing the polymer.
4. To create the polymer solution, it was continually agitated with a glass rod.
5. Add precisely measured amounts of Nitrendipine 3 mg, and carefully combine.

Making an aqueous solution:
One gramme of SLS was added to one thousand millilitres of water as needed, and the mixture was then set aside to remove air bubbles.

Simple Mixing:
As a successful method for creating nanodrugs, emulsion followed by solvent evaporation was used to create Nitrendipine nanospheres.

Polymers were first dissolved in chloroform, followed by the addition of 10 mg of the drug Nitrendipine, which was thoroughly mixed into the polymer solution.

Next, 1% SLS solution was added to the mixture, which was then stirred continuously for 20 minutes at 400-500 rpm. Finally, the beaker was placed in a probe sonicator for 15 minutes. Nanoparticles formed right away after mixing.

FORMULATION

Table 3: Formulation Table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nitrendipine (mg)	3	3	3	3	3	3	3	3	3
HPMC K4M (mg)	75	150	95	92	140	94	75	150	95
HPMC K100 (mg)	120	130	94	75	150	95	150	75	130
Ethyl cellulose (mg)	150	75	130	150	75	130	120	110	73
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10	10	10
2% SLS (ml)	50	50	50	50	50	50	50	50	50

POST FORMULATION STUDIES

Assay:
3 mg of Nitrendipine (manufactured nano crystals) should be precisely weighed. It should then be dissolved in 40 mL of methanol and titrated with 0.1 mol/L sodium hydroxide VS (potentiometric titration, Endpoint Detection Method in Titrimetry).

Each mL of sodium hydroxide at 0.1 mol/L VS equals 35.419 milligrammes of C16H13Cl2NO4.

When dried, Nitrendipine has a concentration of 99.0% to 101.0% .

Modified Dissolution Test:
The open cut boiling tube containing 25mL of the nanoparticle solution and the beaker containing 100mL of the 1% sodium lauryl sulphate (SLS) solution in distilled water were used for the in vitro dissolution investigations. The studies lasted for 24 hours. The temperature of the water bath in which the dissolving medium was kept was thermostatically controlled at 37 0.05 °C. 50 rpm was chosen as the basket rotation speed. 3 ml samples were taken out at regular intervals and examined spectrophotometrically at 275 nm for the drug release. To keep the sink condition, 3 ml of new matching media were added to the dissolution flask each time a sample was withdrawn.

Scanning Electron Microscopy (SEM):
The particle morphology of the unprocessed drug as well as the manufactured drug nanoparticles was studied using scanning electron microscopy. A small portion of each drug powder sample was glued to a double-sided carbon conductive tape and sputtered with a Pt-Pd alloy coating measuring 5 nm. On a Zeiss DSM 982 Field Emission Gun Scanning Electron Microscope, micrographs were taken (Carl Zeiss AG, Germany).

Particle Size Distribution:
Immediately following precipitation, the size of drug nanoparticles was determined using dynamic laser light scattering (Nanoparticle size analyzer, Malvern). Purified water was used to dilute the drug suspension to 0.2 mg/ml prior to analysis. The outcomes of the particle size study were interpreted using the graphic mean size (Mz) and computed surface area (Cs).

Zeta potential:
Zeta sizer was used to assess the nanoparticles' size, size distribution, and zeta potential (ZS 90 Malvern). The lyophilized materials were diluted with PBS to a pH of 6.0 on mg/ml and 67 mm before being tested. These samples were stored in another clean cubet during the size analysis process before being placed on the zeta size analysis chamber to obtain distinct peaks and then determine its average zeta size. Surface charge potential or zeta potential samples were kept in the zeta sizer analysis chamber on for analysis and watched for its peak to obtain zeta potential data. When analysing these data, monodisperse rather than polydisperse character is always taken into account.

Percentage Yield: the yield of nanoparticles was determined by comparing the whole weight of nanoparticles formed against the combined weight of the copolymer and drug.

$$\%yield = \frac{amount\,of\,nanoparticle}{amount\,of\,drug + polymer} \times 100$$

Drug Content / Surface entrapment / Drug entrapment: after centrifugation amount of drug present in supernatant [w] determined by UV spectrophotometry.

After that standard calibration curve plotted. Then amount of drug present in supernatant subtracted from the total amount used in the preparation of nanoparticles [W]. [W-w]is the amount of drug entrapped. % drug entrapment calculated by % $drugentrapment=W-wW\times100$

In-Vitro Release Study: in vitro drug release studies were performed in USP Type II dissolution apparatus at rotation speed of 50 rpm. The prepared immersed in 900 ml of phosphate buffer solution in a vessel, and temperature was maintained at 37±0.20ºC. required quantity 5mi of the medium was withdrawn at specific timeperiods and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn samples were analyzed using UV spectrophotometer.

Surface Morphology: surface morphology study carried out by Scanning Electron Microscopy [SEM] of prepared nanoparticle.

Stability Studies: stability studies of prepared nanoparticles determined by storing optimized formulation at 4ºC ±1ºC and 30ºC±2ºC in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2 and 3 months for their drug content, drug release rate [t50%] as well as any changes in their physical appearance.

Drug Release Kinetics:
The cumulative drug release from the formulated tablets at different time Intervals were fitted to zero order kinetics, first order kinetics, Higuchi model and Korsmeyer – Peppas model to characterize mechanism of drug release.

RESULTS AND DISCUSSION

Preformulation studies:
Characterization of Pharmaceutical Active Ingredients was carried out:
Characterization of API (appearance, identification test by FTIR, assay) was carried out in preformulation investigations, and it was discovered that all fall within the parameters set forth in the pharmacopoeia.

Table 4: Defining the active medicinal component Description	**Specifications**	**Observations**
Appearance	White Crystalline powder	White
Identification	FTIR	Complies
Assay	Not less than 99.0% w/wand not more than 101.0% w/w of Carvedilol	99.97%w/w

Standard curve for Nitrendipine in 0.1% SLS solution:
Nitrendipine standard graph was created using 0.1% SLS. Concentrations ranging from 2 to 10 g/ml were made. At 301 nm, the absorbance of the produced concentrations was measured after being calibrated with a blank sample. Concentration and absorbance were shown on a graph, and the best fit line, regression value, and equation were constructed to describe the data.

Table 5: Standard curve table for Nitrendipine Concentration (µg/ml)	absorbance
0	0
4	0.2
8	0.39
12	0.55
16	0.72
20	0.89

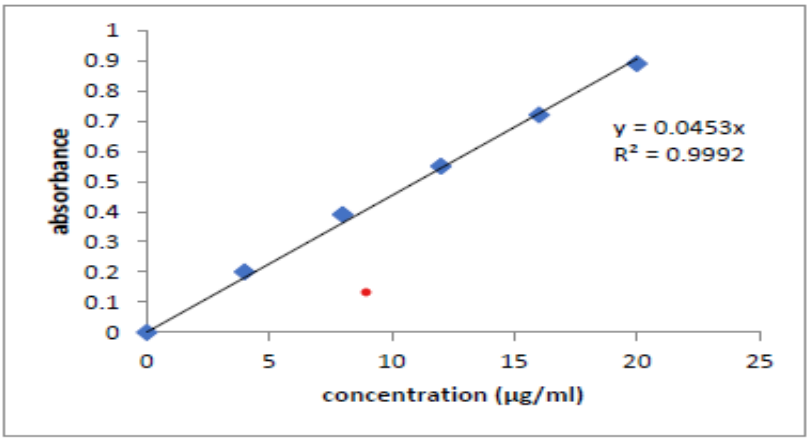


Fig 1: Standard Absorbance Graph

EVALUATION OF NANO PARTICLES

Percentage of Yield:

Table 6: Particle size and % yield Formulation code	Particle size (nm)	**% yield**	**Entrapment** efficiency	**Drug content**
F1	200.5	98.5	77.8	298.5
F2	210.2	80.7	87.5	297.8
F3	246.7	79.5	97.6	298.2
F4	198.2	96.2	75.2	298
F5	205.3	87.5	80.2	298.2
F6	226.7	79.8	91.8	297.4
F7	197.2	98.8	77.4	298.4
F8	220.2	84.2	83.4	296.3
F9	245.3	75.8	95.2	295.5

Particle Size:

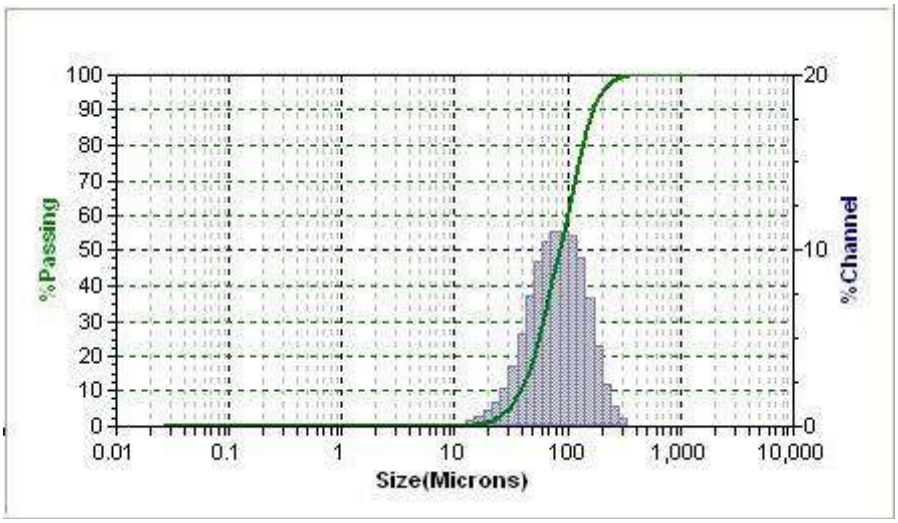


Fig 2: Particle Size

Zeta Potential:

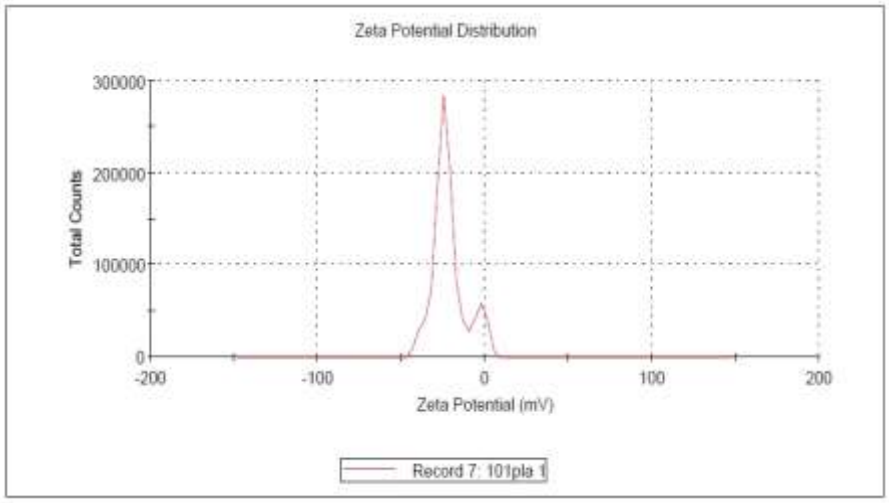


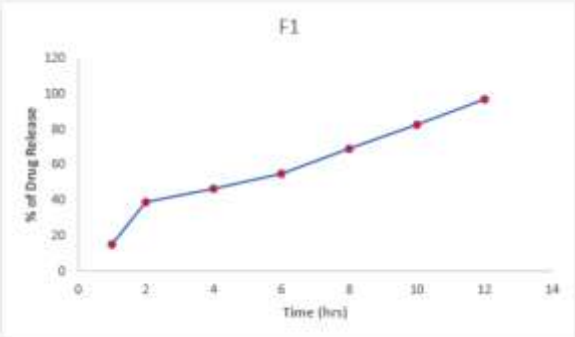
Fig 3: Zeta Potential

In vitro dissolution study:

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15	13	11	21	18	15	25	23	9.5
2	39	26	22	29	26	22	39	30	18
4	46	35	31	35	32	30	46	43	28
6	55	46	43	49	44	41	55	52	39
8	69	59	56	56	51	49	62	60	48
10	83	68	64	70	60	57	77	72	55
12	97	85	82	85	77	71	90	85	68
14	92	95	91	97	88	84	98	95	80
16	91	90	96	95	96	94	97	98	87
20	90	86	93	94	97	93	86	98	99

The in vitro dissolution profiles of formulations F1 to F9 were evaluated by sampling at specific time intervals and analyzing the cumulative percentage of drug release using a UV spectrophotometer. The obtained drug release values were used to construct the respective dissolution graphs.

Formulation F1 showed gradual release with values ranging from 15.2% to 96.7%, while F2 and F3 exhibited slightly slower release patterns. F4 to F6 demonstrated moderate release, with F4 reaching up to 96.8%. Formulations F7 and F8 showed faster drug release, exceeding 97%, whereas F9 exhibited the slowest release initially but reached up to 98.9% at the final time point. The dissolution profiles are presented in Figures 4 to 12.



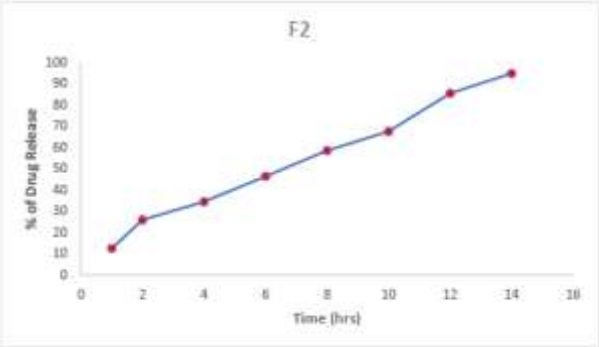
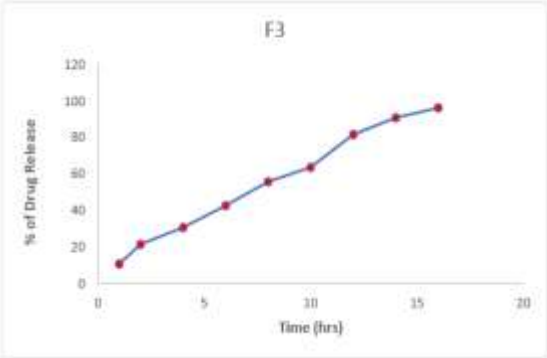


Fig 4: In vitro dissolution profile of F1 **Fig 5: In vitro dissolution profile of F2**



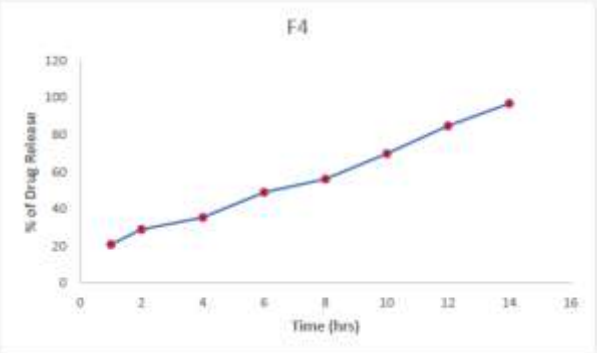
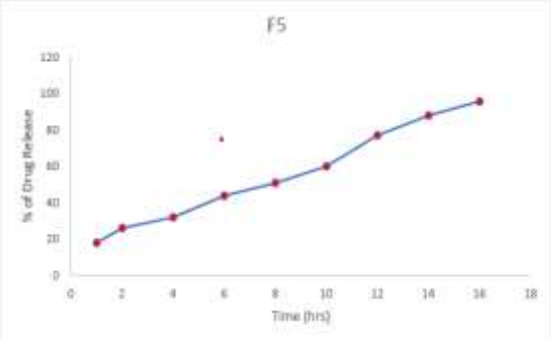


Fig 6: In vitro dissolution profile of F3 **Fig 7: In vitro dissolution profile of F4**



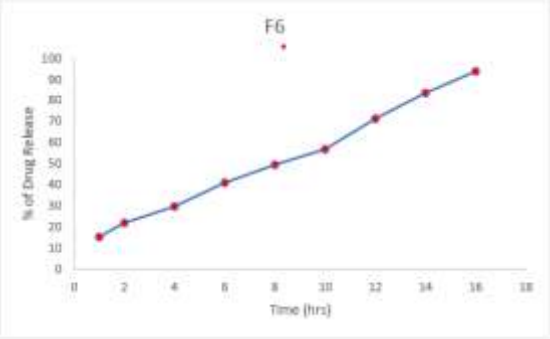
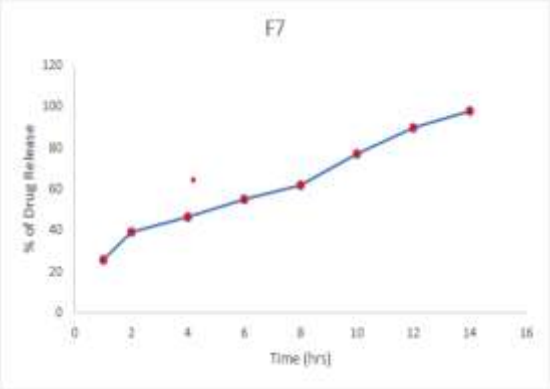


Fig 8: In vitro dissolution profile of F5 **Fig 9: In vitro dissolution profile of F6**



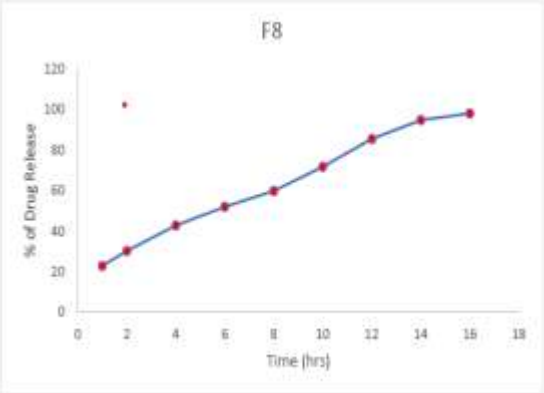


Fig 10: In vitro dissolution profile of F7 **Fig 11: In vitro dissolution profile of F8**

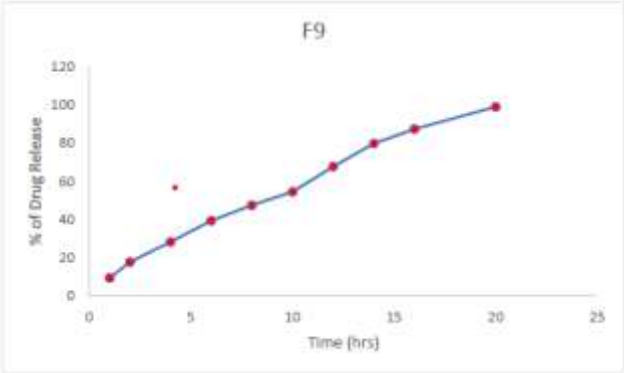


Fig 12: In vitro dissolution profile of F9

FT IR spectra of Nitrendipine:

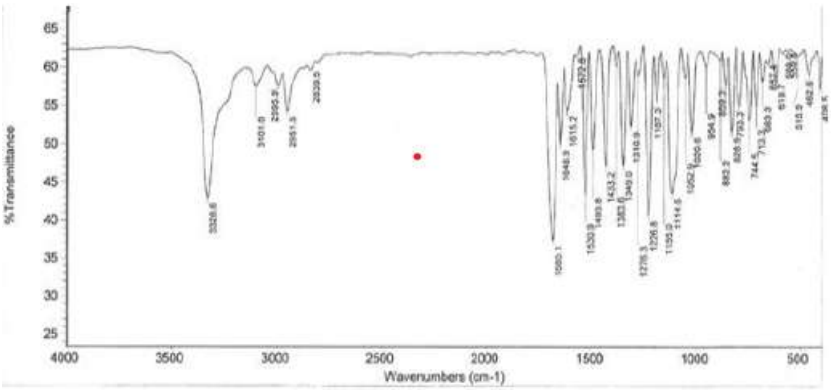


Fig 13: FT IR spectra of Nitrendipine

Table 8: Interpretation of Nitrendipine FTIR

S.No	Type of bond	Type of vibration	Actual frequency (cm-1)	Observed frequency (cm-1)	Confirmation
1	N-H	Stretching	3300-3500	3328.14	Amine
2	C-H	Stretching	2850-3000	2995.54	Alkane
3	C=C	Stretching	1400-1600	1589.26	Aromatic
4	C-N	Stretching	1080-1360	1114.21	Amine
5	C-H	Bending	685-770	756.33	Aromatic

FT IR spectra of Nitrendipine + Polymer:

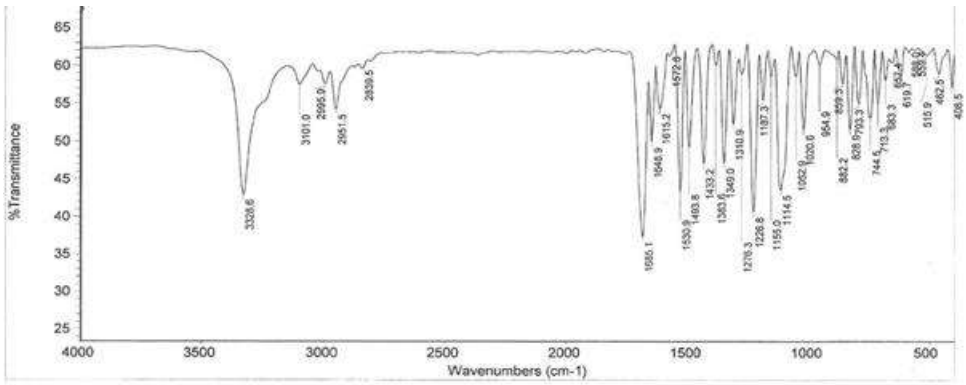


Fig 14: FT IR spectra of Nitrendipine + Polymer

Table 9: Interpretation of Nitrendipine FTIR+ Polymer

S.No	Type of bond	Type of vibration	Actual frequency (cm-1)	Observed frequency (cm-1)	Confirmation
1	N-H	Stretching	3300-3500	3427.53	Amine
2	C-H	Stretching	2850-3000	2937.11	Alkane
3	C=C	Stretching	1400-1600	1589.26	Aromatic
4	C-N	Stretching	1080-1360	1312.55	Amine
5	C-H	Bending	685-770	756.33	Aromatic

FT IR spectra of complete formulation:

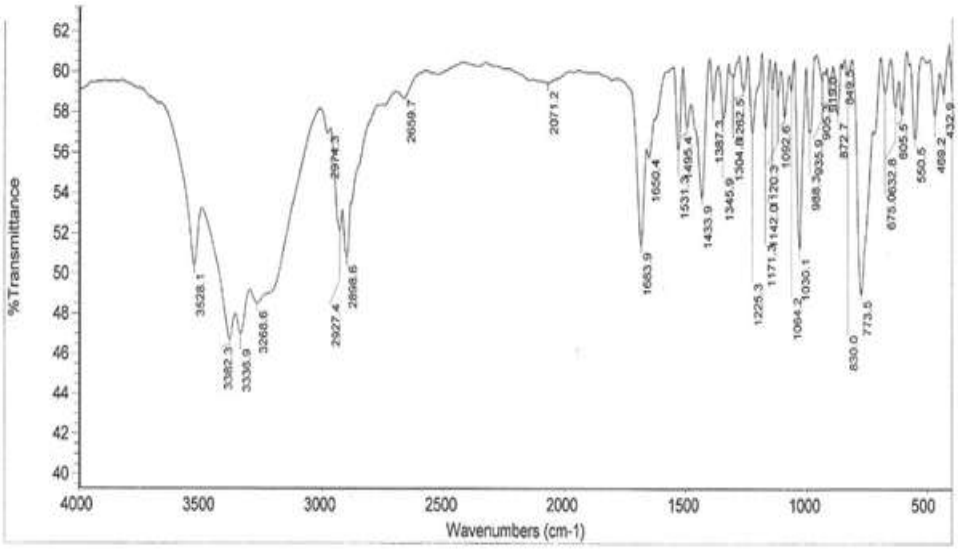


Fig 15: FT IR Spectra of Complete Formulation

Table 10: Interpretation of Complete Formulation

S.No	Type of bond	Type of vibration	Actual frequency (cm-1)	Observed frequency (cm-1)	Confirmation
1	N-H	Stretching	3300-3500	3528.53	Amine
2	C-H	Stretching	2850-3000	2927.21	Alkane
3	C=C	Stretching	1400-1600	1650.32	Aromatic
4	C-N	Stretching	1080-1360	1225.51	Amine
5	C-H	Bending	685-770	756.33	Aromatic

Kinetic Analysis of Dissolution Data:

The in-vitro release data was fitted into different release equations and kinetic models, including zero order, first order, Higuchi and Korsmeyer Peppasmodel, to analyse the drug release mechanism. The release kinetics of the optimised formulation is displayed in TABLE.

Table 11: *In-Vitro* drug release kinetics of all formulations

Formulation Code	Zero Order R^2	Slope	Higuchi R^2	Slope	First Order R^2	Slope	Korsmeyer-Peppas R^2	n Value	Drug Release Mechanism
F1	0.9649	6.603	0.9639	29.76	0.8227	-0.105	0.9417	0.6597	Non-Fickian
F2	0.9921	6.095	0.9720	29.005	0.8664	-0.082	0.9862	0.7265	Non-Fickian
F3	0.9921	5.778	0.9774	29.196	0.8947	-0.083	0.9930	0.7775	Non-Fickian
F4	0.9919	5.727	0.9490	26.936	0.7981	-0.088	0.9631	0.5697	Non-Fickian
F5	0.9912	5.197	0.9497	25.897	0.8547	-0.073	0.9666	0.6016	Non-Fickian
F6	0.9949	5.159	0.9546	25.726	0.8567	-0.064	0.9781	0.6518	Non-Fickian
F7	0.9863	5.301	0.9625	25.184	0.8243	-0.096	0.9690	0.4806	Fickian
F8	0.9913	5.142	0.9794	26.022	0.8759	-0.077	0.9856	0.5396	Non-Fickian
F9	0.9906	4.791	0.9808	26.280	0.7982	-0.082	0.9967	0.7798	Non-Fickian

Stability Studies:
After three months, there was no discernible change in the physical or chemical characteristics of the tablets of formulation F-9. The parameters that were quantified at different times were displayed.

Table 12: Results of stability studies of optimized formulation F-9

S.NO	Parameters	Initial	1 month	2 month	3 month	Limits as per specification
1	**400C/75% RH % Release**	98.9	98.52	97.79	96.56	**Not less than 85%**
2	**400C/75% RH Assay Value**	98.9	97.96	96.22	96	**Not less than 90% Not more than110%**

DISCUSSION

The goal of the current work was to create Nitrendipine-solid lipid nanoparticles.

Solid lipid nanoparticles:
GMS, Chitosan, PEG6000 SLN, and other additives were made using a variety of polymers. The preparation of the nanoparticles was done using the solvent evaporation method. Nine formulations in total were created and assessed.

Particle Size Analysis:
The presence of stabiliser has an effect on particle size, according to the particle size study for the Nitrendipine fabricated nanoparticles utilising different polymers. The results of the particle size study were interpreted using the graphic mean (Mz) and computed surface area (Cs). While it includes the median value, Graphic Mean provides a different and potentially better control value since both small particles and large particles are included in the calculation.

This results in amean particle size that is less coarse-particle weighted than the mean diameter of the volume distribution. When GMS (F3) was utilised at 10%, smaller graphic mean (Mz) values suggesting smaller particles were discovered. The greatest Mz value for formulation F7 (275 nm) was discovered, indicating larger particles. The polymer concentration was shown to affect particle size. The particle size was reduced when the concentration of the majority of the investigated polymers was raised from 6 to 10%.

In vitro dissolution:
Using a modified dissolving method apparatus and a solvent solution containing 0.1% SLS, in vitro dissolution investigations are carried out on prepared nanoparticles. It was discovered that the dissolving rate increased linearly with polymer concentration. The best formulations are (F9), and in 24 hours, the formulation recorded 98.9% of the medication.

Drug Release Kinetics:
To determine the mechanism of drug release, in vitro drug release data from all formulations was subjected to a goodness of fit test by linear regression analysis in accordance with zero order and first order kinetic equations, Higuchi's and Korsmeyer models. As observed from the above data, all of the formulations showed first order release kinetics. According to the Higuchi and Peppas study, the medication is delivered through a non-fickian diffusion process (n0.5). It is clear from the factorial formulations' kinetic data that the F9 formulation exhibits zero order kinetic drug release. The r values for Higuchi's formulation equation. This information demonstrates that the Higuchi model of non-Fickian diffusion governs drug release.

CONCLUSION

Success of the in vitro drug release experiments suggests the product be used in future in vivo research, which might increase patient compliance. According to the findings, formulation F9, which uses a combination of polymers and contains Nitrendipine nanoparticles, evolved as the best formulation and releases more than 98.9% of the drug in 24 hours.

There are no drug-excipient interactions in the improved formulation, according to IR spectroscopic measurements. The improved formulation F9 is a potential Sustained Release Nitrendipine nanoparticles are a medication delivery method that offers almost zero order drug release over the course of 24 hours.

REFERENCES

[1]. Tiwari R., Pathak K. Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: comparative analysis of characteristics, pharmacokinetics and tissue uptake. *International Journal of Pharmaceutics.* 2021;415(1-2):232–243. doi: 10.1016/j.ijpharm.2021.05.044.
[2]. Elsaesser A., Howard C. V. Toxicology of nanoparticles. *Advanced Drug Delivery Reviews.* 2021;64(2):129–137. doi: 10.1016/j.addr.2021.09.001.
[3]. Müller R. H., Radtke M., Wissing S. A. Nanostructured lipid matrices for improved microencapsulation of drugs. *International Journal of Pharmaceutics.* 2020;242(1-2):121–128. doi: 10.1016/S0378-5173(02)00180-1.
[4]. Park J., Choi J., Lee S., Lee H., Lee B., Kang C. Physical properties of Gelucire-based solid dispersions containing lacidipine and release profile. *Journal of Korean Pharmaceutical Sciences.* 2020;40(1):9–14. doi: 10.4333/kps.2020.40.1.009.
[5]. Micheli D., Collodel A., Semeraro C., Gaviraghi G., Carpi C. Lacidipine: a calcium antagonist with potent and long-lasting antihypertensive effects in animal studies. *Journal of Cardiovascular Pharmacology.(2020)*
[6]. McCormack P. L., Wagstaff A. J. Lacidipine: a review of its use in the management of hypertension. *Drugs.* 2018;63(21):2327–2356. doi: 10.2165/00003495-200363210-00008.
[7]. Sweetman S. C.,editor. *Martindale—The Complete Drug Reference.* 36th. London, UK: Pharmaceutical Press; 2018.
[8]. Zhuang C.-Y., Li N., Wang M., et al. Preparation and characterization of vinpocetine loaded nanostructured lipid carriers (NLC) for improved oral bioavailability. *International Journal of Pharmaceutics.* 2016;394(1-2):179–185. doi: 10.1016/j.ijpharm.2016.05.005.
[9]. Okeahialam B. N., Thacher T. D., Ibrahim T. M., Anjorin F. I. Lacidipine in the treatment of hypertension in black African people: antihypertensive, biochemical andhaematological effects. *Current Medical Research and Opinion.* 2016;16(3):184–189. doi: 10.1185/030079900750120287.
[10]. Ukpo G. E., Owolabi M. A., Adewole T. A., Awa N. O. Biochemical evaluation and toxicological effects of lacidipine on normotensive rats. *Nigerian Quarterly Journal of Hospital Medicine.* 2016;15(3):131–137. doi: 10.4314/nqjhm.v15i3.12773.
[11]. Pathak P., Nagarsenker M. Formulation and evaluation of lidocaine lipid nanosystems for dermal delivery. *AAPS PharmSciTech.* 200;10(3):985–992. doi: 10.1208/s12249-009-9287-1.
[12]. OECD. OECD guidelines for the testing of chemicals—repeated dose 28-day oral toxicity study in Rodents. No. 407, October 2014.
[13]. Chandiran I. S., Jayaveera K. N., Karimulla S. Preliminary phytochemical and preclinical toxicity studies of Grewia serrulata DC. *Drug Invention Today.* 2013;5(3):267–274. doi: 10.1016/j.dit.2013.06.010.

[14]. Koontongkaew S., Poachanukoon O., Sireeratawong S., et al. Safety evaluation of *Zingiber cassumunar* Roxb. rhizome extract: acute and chronic toxicity studies in rats. *International Scholarly Research Notices.* 2013;2013:14. doi: 10.1155/2014/632608.632608
[15]. Akhand M. M., Bari M. A., Islam M. A., Khondkar P. Sub- acute toxicity study of an antimicrobial metabolite from *Streptomyces lalonnenis* sp. nov., on long evan's rats. *Middle-East Journal of Scientific Research.* 2013;5:34–38.
[16]. Yavasoglu A., Karaaslan M. A., Uyanikgil Y., Sayim F., Ates U., Yavasoglu N. U. K. Toxic effects of anatoxin-a on testes and sperm counts of male mice. *Experimental and Toxicologic Pathology.* 2013;60(4-5):391–396. doi: 10.1016/j.etp.2013.04.001.
[17]. Amresh G., Singh P. N., Rao C. V. Toxicological screening of traditional medicine Laghupatha (*Cissampelos pareira*) in experimental animals. *Journal of Ethnopharmacology.* 2012;116(3):454–460. doi: 10.1016/j.jep.2012.12.008. [PubMed] [CrossRef] [Google Scholar]
[18]. Teo S., Stirling D., Thomas S., Hoberman A., Kiorpes A., Khetani V. A 90-day oral gavage toxicity study of D-methylphenidate and D,L-methylphenidate in Sprague-Dawley rats. *Toxicology.* 2012;179(3):183–196. doi: 10.1016/S0300-483X(02)00338-4. [PubMed] [CrossRef] [Google Scholar]
[19]. Sharma P., Singh R., Jan M. Dose-dependent effect of deltamethrin in testis, liver, and Kidney of wistar rats. *Toxicology International.* 2012;21(2):131–139. doi: 10.4103/0971-6580.139789. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[20]. Diallo A., Eklu-Gadegkeku K., Agbonon A., Aklikokou K., Creppy E. E., Gbeassor M. Acute and sub-chronic (28-day) oral toxicity studies of hydroalcohol leaf extract of *Ageratum conyzoides* L (Asteraceae) *Tropical Journal of Pharmaceutical Research.* 2010;9(5):463–467. [Google Scholar]
[21]. Adeneye A. A., Ajagbonna O. P., Adeleke T. I., Bello S. O. Preliminary toxicity and phytochemical studies of the stem bark aqueous extract of *Musanga cecropioides* in rats. *Journal of Ethnopharmacology.* 2010;105(3):374–379. doi: 10.1016/j.jep.2010.11.027. [PubMed] [CrossRef] [Google Scholar]
[22]. Thanabhorn S., Jaijoy K., Thamaree S., Ingkaninan K., Panthong A. Acute and subacute toxicity study of the ethanol extract from *Lonicera japonica* Thunb. *Journal of Ethnopharmacology.* 2010;107(3):370–373. doi: 10.1016/j.jep.2006.03.023. [PubMed] [CrossRef] [Google Scholar]
[23]. Patrick-Iwuanyanwu K. C., Amadi U., Charles I. A., Ayalogu E. O. Evaluation of acute and sub—chronic oral toxicity study of baker cleansers bitters—a polyherbal drug on experimental rats. *EXCLI Journal.* 2010;11:632–640. [PMC free article] [PubMed] [Google Scholar]
[24]. Ramaiah S. K. Preclinical safety assessment: current gaps, challenges and approaches in identifying translatable biomarkers of drug induced liver. *Clinics in Laboratory Medicine.* 2010;31(1):161–172.doi: 10.1016/j.cll.2010.10.004. [PubMed] [CrossRef] [Google Scholar]
[25]. Wasan K. M., Najafi S., Wong J., Kwong M., Pritchard P. H. Assessing plasma lipid levels, body weight, and hepatic and renal toxicity following chronic oral administration of a water soluble phytostanol compound, FM-VP4, to gerbils. *Journal of Pharmacy and Pharmaceutical Sciences.* 2010;4(3):228–234. [PubMed] [Google Scholar]
[26]. Mythilypriya R., Shanthi P., Sachdanandam P. Oral acute and subacute toxicity studies with kalpaamruthaa, a modified indigenous preparation, on rats. *Journal of Health Science.* 2010;53(4):351–358. doi: 10.1248/jhs.53.351.
[27]. Crook M. A. *Clinical Chemistry and Metabolic Medicine.* 7th. London, UK: Hodder Arnold; 2009.
[28]. Tilkian S. M., Conover B. M., Tilkian A. G. *Clinical Implications of Laboratory Tests.* 2nd. St. Louis, Mo, USA: Mosby; 2009.
[29]. Hamid Reza Pouretedal, Vida Vosoughi, and Mansour Mansouri. Ibuprofen Nanoparticle Preparation by Solvent/Antisolvent Precipitation Technique, International J. J Pharmacy Science Research 331 (2009) 93–98
[30]. Zhouhua Wang, Lingui Dian, Feng Li, Zhouwen Yang, and Xin Pan. Developed Cubic phase nanoparticles for ibuprofen's prolonged release, International J of Nanomedicine, 8, 845-854 (2009).
[31]. Clarithromycin Nanoparticles Prepared by Solvent/Antisolvent Precipitation Technique, International Journal of Nanomedicine, Mansour Mansouri, Hamid Reza Pouretedal, and Vida Vosoughi J. Pharm. Sci. Res. 5, 472-474 (2008).
[32]. Dianrui Zhang, Qingyan Xu, Leilei Hao, and Xiaoyong Wang. Amoitone bnanocrystal preparation, characterization, and pharmacokinetics International JS Pharmacy 433 (2008), 157- 164.
[33]. Dandan Zheng, Yang Jiao, Dianrui Zhang, and Guangpu Liu. Stable Riccardin D nanocrystal synthesis, J. Adv Pharm Tech & Res ., 45 (2008), 8723-8727.
[34]. Nanocrystal preparation: low-energy precipitation method revisited. Shahzeb Khan, Marcel de Matas, Jiwen Zhang, and Jamshed Anwar. Cryst. 2008 Growth Des., 2766-2777
[35]. Hongze Piao, Hongyu Piao, Na Liang, Kai Shi, and Peng Quan. Nitrendipine nanocrystals with an unique surface modification that improves absorption and stability International (2008) J. Pharm. 430: 366–371.
[36]. Kazuko Sagawa, Jaymin C. Shah, Avinash G. Thombre, and W. Brett Caldwell. Characterization of amorphous, nanocrystalline, and crystalline ziprasidone formulations in vitro and in vivo. Int. JS Pharmacy 428 (2008) 8- 17.

[37]. Peter York, Nicholas Blagden, and Hany S.M. Ali. employing microfluidic reactors and the bottom-up nanoprecipitation method to create hydrocortisone nanosuspensions. 2008, 107–113, International Journal of Pharmaceutics, vol.
[38]. Jeong-Soo Kim, Hee Jun Park, Min-Soo Kim, Shun-Ji Jin, and Ha-Seung Song. Amorphous atorvastatin calcium nanoparticles were created, characterised, and tested in vivo utilising the supercritical antisolvent (SAS) method. Eur. 454–465 in J Pharm and Biopharm 69 (2008).
[39]. Mohan raj VJ, Chen Y. Nanoparticles - A review, Tropical Journal of Pharmaceutical Research, 5, 2006, 561-573.
[40]. Langer R. Biomaterials in drug delivery and tissue engineering: one laboratory's experience, Accounts of Chemical Research, 33, 2006, 94-101
[41]. Bhadra D, Bhadra S Jain, Jain NK. Pegnology: a review of PEG-ylated systems, Pharmazie, 57, 2006,
[42]. Singh A., Garg G., Sharma P.K., Nanospheres: A Novel Approach for Targeted Drug Delivery System International Journal of Pharmaceutical Sciences Review and Research Volume 5,3, 2006, 34-38.
[43]. Ramteke K.H., Joshi S.A., Dhole S.N., Solid Lipid Nanoparticle: A Review IOSR Journal of PharmacyVolume 2,6 2006, 34-44.
[44]. Dangi A.A., Ganur e A.L., Jain D., Formulation and Evaluation of Colon Targeted Drug Delivery System of Levetiracetam Using Pectin as Polymeric CarrierJournal of Applied Pharmaceutical Science Vol-3 (1) 2006, 78-87.
[45]. Prasanth V.V., Jayaprakash R., MathewS.,T.Colon Specific Drug Delivery Systems: AReview on Various Pharmaceutical Approaches Journal of Applied Pharmaceutical Science, Vol-2 (1) 2004, 163-169.
[46]. Colson P., Henrist C., ClootsR.,Nanosphere Lithography: A Powerful Method for the Controlled Manufacturing of Nanomaterials Journal of Nanomaterials 2004, 1-19.
[47]. Jun Li geboren am 03. November 2002 ,Development, Characterization and In Vivo Evaluation of Biodegradable Nanospheres and Nanocapsules.
[48]. Allen, T.M., Cullis, P.R., 2002. Drug Delivery Systems: Entering the Mainstream Science 303, 1818-1822.
[49]. Smitha K. Nair, an overview on nanosphere drug delivery, european journal of pharmaceutical and medical research 2002: 192-198.
[50]. Wang Z, Ruan J, Cui D. Advances and prospect of nanotechnology in stem cells, Nanoscale Research letters, 2002; 4: 593-605..
[51]. Bianco, A., Kostarelos, K., Prato, M., 2005. Applications of carbon nanotubes in drug delivery. Current Opinion in Chemical Biology 9, 674-679
[52]. Ghosh, P., Han, G., De, M., Kim, C.K., Rotello, V.M., 2001. Gold nanoparticles in delivery applications. Advanced Drug Delivery Reviews 60, 1307-1315.
[53]. Jin-ming LI1, 3, #, Wei CHEN2, Preparation of albumin nanospheres loaded with gemcitabine and their cytotoxicity against BXPC-3 cells in vitro, Acta Pharmacologica Sinica (2001) 30: 1337– 1343.
[54]. Rao Jp Gekeler KF, polymer nanoparticles, preparation techniques and size control parameters, prog polym Sci 2001:6(7);887-913.
[55]. Tejas Pachpute *Formulation and Evaluation of Mesalamine Nanosphere Tablet, Journal of Drug Delivery & Therapeutics. 2001; 9(4-s):1045-1053 [10] Amit Singh., Nanospheres: A Novel Approach For Targeted Drug Delivery System, Volume 5, Issue 3, November – December 2001, aticle-15, 84-88.