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Formulation and Evaluation of Nimodipine Nano Crystal for Ophthalmic Drug Delivery System

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ABSTRACT
Due to their low solubility and low-slung bioavailability, weakly feasible trivial pieces usuallyface translational challenges in addition to creating tasks encounters. With the additional helpof a carrier-permitted transmitting system, nano crystallization is a multifunctional strategy forsaving sickle cell drugs. We provide an extensive examination of nanocrystals togetherprominently arranged detached translation transformation in this review assessment. Furthermore, the review provides insights into both clinically authorised and in-development nanocrystal medicinal formulations. By hydrolysing biomass in acid, nanocrystals can be produced. The main problem with their applied use is linked to the standardised spreading of these nanoparticles within a polymeric environment. Sea water is the favourite handling intermediate. An innovative and stimulating way for the managing of polyose nanocrystals- grounded nanocomposites is their conversion into a co-unceasing substance finished extendedgroup plane compound conversion. In addition to having an extended computerising tail and an attaching manager's behaviour, it involves the surface biological alteration of the nanoparticles. One significant characteristic of nanocrystal particles is that they displayproperties different from the component nanoparticles due to coupling.

KEY WORDS*: Bioavailability, Solubility, Diffusion, Emulsion, Nanocrystals.*

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I. INTRODUCTION

Nanocrystals

Nanocrystals are minuscule crystalline structures that measure between 1 and 100 nanometers. At this scale, the characteristics of the material can vary greatly from those of its bulk counterpart. These nanocrystals possess distinctive electronic, optical, magnetic, and catalytic properties, making them highly valuable for a range of applications in sectors such as electronics, optoelectronics, energy conversion, and healthcare. The process of synthesizing nanocrystals requires precise control over their size, shape, and crystalline structure. Various methods, including chemical synthesis, sol-gel techniques, vapor deposition, and solid-state reactions, can be employed to create nanocrystals. The selection of a synthesis technique is influenced by the specific properties and intended applications of the nanocrystals. A notable characteristic of nanocrystals is their elevated surface-to-volume ratio. Due to their diminutive size, the surface area is significantly larger in relation to the volume, which enhances their reactivity and charge properties[1,2,3]. Nonetheless, the incorporation of these agents or residualorganic solvents may result in heightened adverse effects or toxic responses within theorganism. This imperative has led to various chemical and physical modifications, such as theformation of salts from ionizable substances. Pharmaceuticals by increasing the surface-to- volume ratio, thus enhancing dissolution rates. Micronization, which can be accomplished through methods like jet milling or wet milling, serves as a straightforward approach to decrease the particle size of these drugs. However, due to the limited solubility of many contemporary pharmaceuticals, micronization alone may not adequately improve bioavailability; as a result, this process frequently leads to the generation of drug nanocrystals (4,5,6).

II. EXPERIMENTAL SECTION

Materials :

Nimodipine was provided as a free sample by A.R .Life science in Hyderabad.Scientific Laboratories in Hyderabad supplied Soya lecithin , PVPK30,HPMC K5,and Ethanol all other chemical reagents utilized were of analytical laboratory grade.According to IP,distilled waterwas used to make a buffer with a pH of 6.8.

PREFORMULATION STUDIES:

Preformulation studies:

Investigations of solubility:

The solubility of Nimodipine was assessed in a range of solvents. A specific amount of the drug was dissolved in 10 ml of each solvent examined at room temperature. (25 ^{0}C) in tightlyand kept for equilibrium 24 hrs.

Determination of λmax of nimodipine:

Nimodipine, at a concentration of 100 mg, was initially dissolved in a few milliliters of ethanoland then adjusted to a final volume of 100 ml using a phosphate buffer with a pH of 6.8, yielding a 1000 µg/ml. A 10 ml aliquot of this stock was then placed into a 100 ml volumetric flask with the phosphate buffer (primary solution). The solution was analyzed over a wavelength spectrum of 200-400 nm, where it exhibited a peak absorbance at 238.5 nm.

Calibration procedure for standard curve:

From the initial primary solution, 10 ml diluted to a final volume of 100 ml using 6.8 PBS buffer, forming a secondary solution. Aliquots of 2, 4, 6, 8, and 10 ml were then pipetted into 10 ml volumetric flasks adjusted the mark 6.8 pH buffer, yielding concentrations of 2, 4, 6, 8,and 10 µg/ml. The absorbance of each concentration was measured at 238.5 nm..

Compatibility studies using FTIR spectroscopy

FT-IR spectroscopy serves as a valuable tool for examining and forecasting the physico- chemical interactions or potential incompatibilities among various components within a formulation.

Getting ready for nimodipine nanocrystals

Formulation of Nimodipine Nanocrystals(Anti-solvent method)

The NMD nanoparticles were synthesized using a solvent-antisolvent precipitation technique, commonly referred to as nanoprecipitation. In this process, 30 mg of NMD was eliminated in 3 ml of ethanol (the solvent) and then introduced dropwise via a syringe pump at rates of 30 and 60 ml/hr into a beaker containing 27 ml of distilled water (the antisolvent). Various stabilizers, including lecithin, Tween 80, PVPK 30, and HPMC K5, were incorporated at different ratios while the mixture was stirred magnetically at 300 rpm. The solid nanoparticles precipitated immediately. The resulting nanosuspension was stirred for an additional hour to facilitate the evaporation of the organic solvent. Subsequently, the nanosuspension with the smallest particle size was lyophilized using a Labconco freeze dryer, with the addition of mannitol as a cryoprotectant, to yield the nanoparticle powder [7,8].

Formulation code for nimodipine nanocrystals

Table 1: Formulation code for nanocrystals preparation

Formulation	**Function**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Nimodipine (mg)	Calcium channel blocker	60	60	60	60	60	60	60	60	60
Polymers (mg)	Particles forming agent	2	4	6	8	4	4	4	6	6
Solvent (ml)	Penetrationenhancer	2	2	2	2	3	4	5	2	2
Ant solvent	Vehicle	qs	qs	qs	qs	qs	qs	qs	qs	qs

Description of nanocrystals:

Nanocrystals morphology:

The morphology of nimodipine nanocrystals can be observed using the process of negative staining the formulation with an aqueous solution of substances such as phosphotungstic acid is known as scanning electron microscopy (SEM).

Nanocrystals size analysis:

The vesicle size was assessed using sing the Malvern Zetasizer for dynamic light scattering (DLS) instrument.

Zeta potential:

The Zeta Potential, a parameter that reflects variations in the electric charge on the surfaces ofvesicles and the physical stability of colloidal systems, was assessed through the measurement of electrophoretic mobility utilizing the Malvern Zetasizer**.**

Entrapment Efficiency: The ultracentrifugation technique was used to determine the efficiency of nanocrystals entrapment.60mg of drug - loaded nimodipine nanocrystals was placed in tubes and centrifuged for 30 min at 400 rpm. The supermatant layer was separated and diluted with buffer ;the free drug concentration was measured at 238.5 nm.
Entrapment Efficiency = (T – C) / T × 100

In this context, 'T' signifies the overall quantity of the drug identified in both the supernatant and the resident layer, while 'C' indicates the quantity of the drug present exclusively in the supernatant..

III. Results And Discussion

Preformulation studies:
Solubility:

Table 2: solubility Nimodipine

S. NO.	Solvents	Solubility
1	Water	-
2	Ethanol	++
3	Phosphate buffer	+++
4	Chloroform	+++

+++ Soluble (1 g drug in less than 10-30 ml solvent), ++ Sparingly soluble (1 g drug in 30-100 ml solvent), - Practically insoluble (1 g drug in more than 10,000 ml solvent).

Determination of λmax of Nimodipine :
The standard solution of nimodipine concentration of 10 ug/ml was scanned in the range of wavelength 200-400 nm using phosphate buffer pH 6.8 as a blank. The absorption spectrum was found to be sharp and maximum at wavelength of 238nm, therefore, it was selected as thewavelength.

Construction of Calibration Curve:

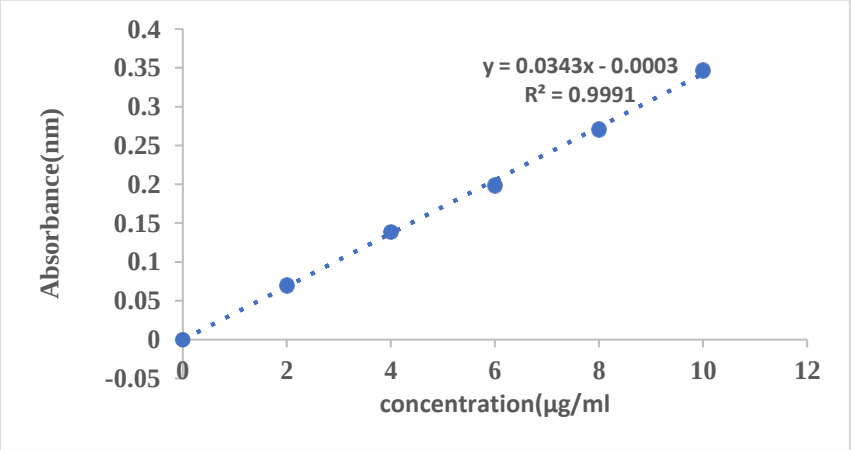

FIG NO: 1 Standard Graph of Nimodipine at 238nm

The standard graph of Tolnaftate demonstrated good linearity with an R2 0.991, indicatingthat it obeys the "Beer- Lamberts" law.

FTIR spectra of Nimodipine pure drug

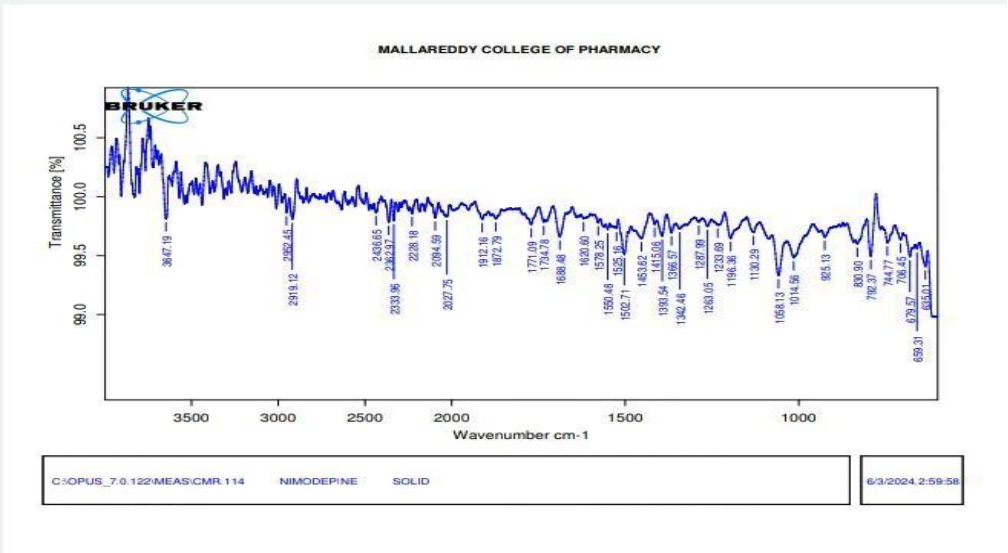

FIG NO 2 : FTIR Spectrum of Nimodipine (Pure drug)

Table No 3: Interpretations of IR Spectrum (pure drug)

Functional group	Wavelength Range	Types of vibration
C-H	3860 cm^{-1}	Stretching
C-H	3825 cm^{-1}	Stretching
C-H	3747 cm-1	Stretching
N-H	3341cm^{-1}	Stretching

FTIR Studies of best formulation

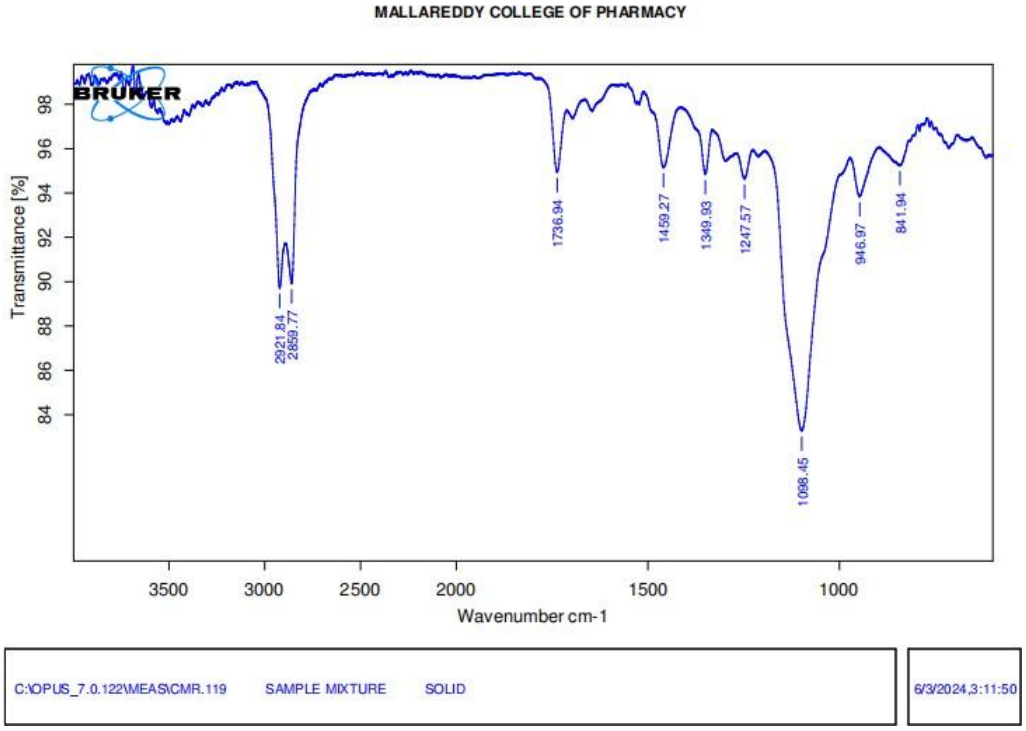

FIG NO:3 FTIR Spectrum of optimized formulation (F5)

Table No 4: Interpretations of IR Spectrum (pure drug)

Functional Group	Wavelength Range	Types of vibration
C-H	3853cm^{-1}	Stretching
C-H	3822cm^{-1}	Stretching
C-H	3750cm^{-1}	Stretching
N-H	3332cm^{-1}	Stretching

The FTIR spectra of crystals revealed peaks for C-H stretching, N=C=N stretching, C=O stretching, and C-O stretching, which are similar to the FTIR spectra of pure drugs. The presence of drug and other compounds was confirmed by the appearance of the above peaks . It has been established that there is no significant shifting or loss of functional peaks between the spectra of drug and drug-loaded nimodipine crystals.

FORMULATION OF NIMODIPINE NANOCRYSTALS

FIG NO 4 :F1 to F5 Nanocrystal formulation

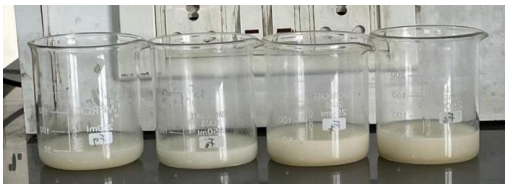

FIG NO 5:F6 to F9 Nanocrystalformulation

Nimodipine nanocrystals formulation was prepared using anti-solventmethod. Nine formulations was prepared by varying lecithin and surfactants ratio.

Characterization of Nanocrystals:

Surface Morphology: The prepared crystals was observed under microscope

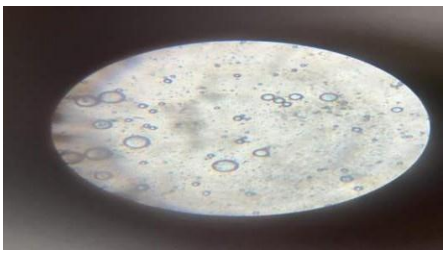

FIG NO 6: Microscopic view of drug loaded nanocrystals

Scanning Electron Microscope:

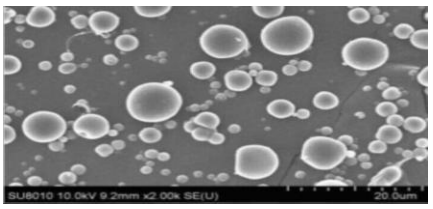

FIG NO 7: SEM image for the F5 formulation

Particle Size:

Particle size plays a major role. Particle size reduction on a nanoscale range enhances the delivery. Smaller the vesicles greater bioavailability of encapsulated compounds. The preparednimodipine loaded nanocrystals average vesicle size was measured. The optimizeformulation mean particle size was 152.6nm.

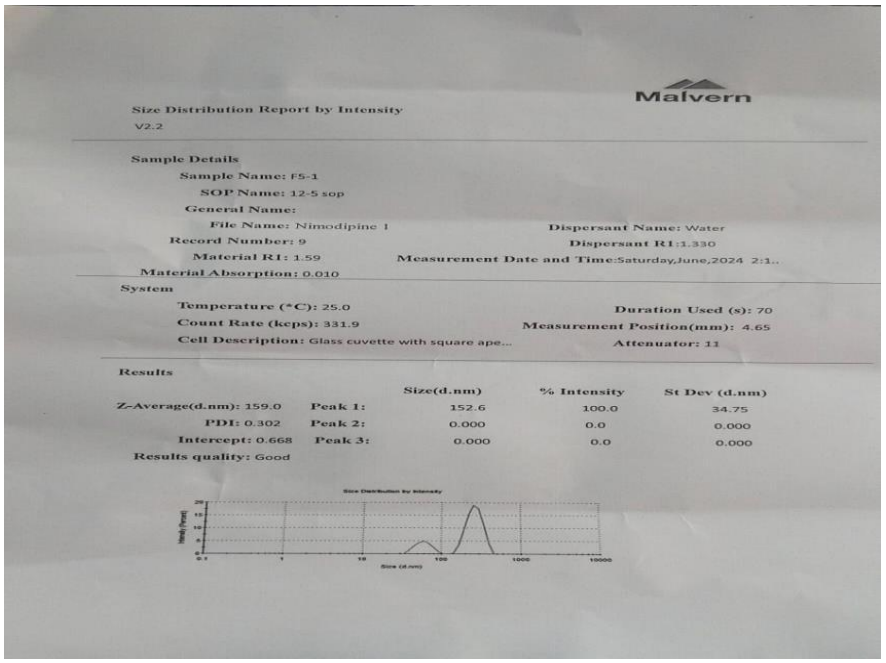

FIG NO 8 :Size analysis of nanoceystals

Zeta Potential:

The Zeta potential (Surface Charge) indicates the stability of the nanocrystals. The prepared nimodipine nanocrystals zeta potential was determined using a zetasizer. The average Zeta potential values of the nanovesicles in the range of -30 to -60 mV. Nano dispersions are generally stabilized with a combination of electrostatic and steric forces, with an accepted value of -30 mV as a minimal negative charge for prolonged stability. Crystals prepared using lecithinF5 formulation-42 nmValue

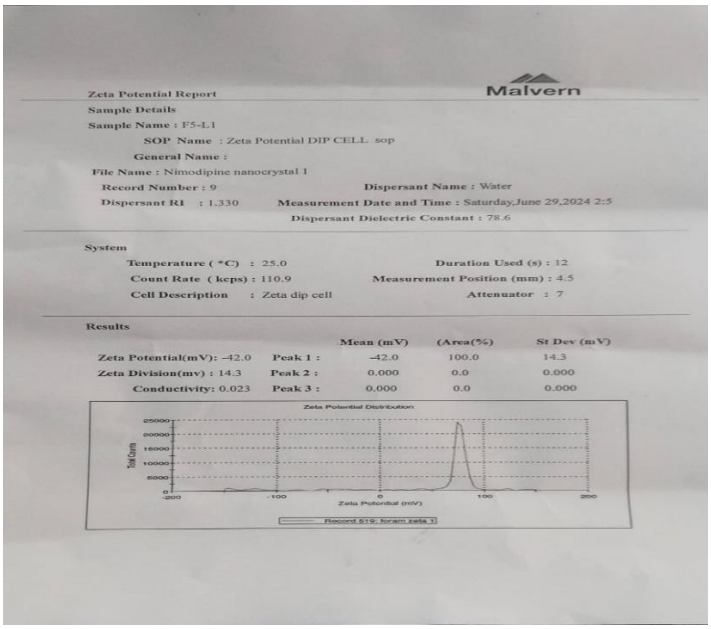

FIG NO : 9 Zeta potential of nanocrystal

Entrapment Efficiency:

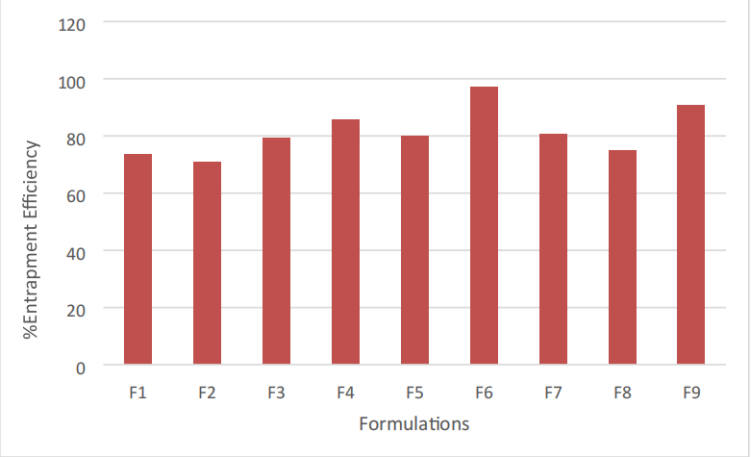

FIG NO :10 Entapment Efficiency

The formulations entrapment efficiency was found to be between 73% and 96%. The entrapment efficiency of crystals prepared by Lecithin was higher than that of Tween 80 and HPMC K5 . This could be due to a variety of factors such as HLB value and hydration temperature. The F6, 2:1 ratio had the highest entrapment efficiency. As a result, F5 was chosenas the best formulation.
The order of entrapment efficiency: F5>F9>F4>F7>F3>F6>F8>F1>F2.

CRYSTALS EVALUATION PARAMETERS:

Table No : 5 Crystals evaluation parameters

F.NO	Homogenity	Drug content(%)	pH	Drug release
F1	Excellent	97.65±0.12	5.2±0.12	89.14± 0.12
F2	Satisfactory	95.98±0.15	5.9±0.15	90.12± 0.65
F3	and White,opaque	96.12±0.25	6.8±0.08	95.23± 0.12

Table No 6 : *Invitro* dissolution studies

Time in min	%Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	20.2±0.02	18.2±0.14	13.5±0.14	11.2±0.24	37.3±0.17	5.6±0.58	11.6±0.11	79.3±0.24	50.3±0.14
30	35.2±0.4	27.3±0.12	22.7±0.08	18.4±0.26	45.7±0.28	9.3±0.45	17.0±0.54	81.0±0.64	55.9±0.18
45	44.3±0.05	32.6±0.02	36.3±0.17	25.1±0.78	52.4±0.45	39.8±0.48	20.8±0.53	66.3±0.47	67.8±0.17
60	56.3±0.12	47.4±0.047	47.9±0.45	32.4±0.28	64.8±0.41	37.9±0.24	53.1±0.87	88.5±0.17	77.5±0.47
75	68.4±0.14	52.7±0.52	54.8±0.28	45.7±039	79.3±0.24	45.07±0.58	59.4±0.74	76.6±0.36	87.2±0.70
105	75.5±0.13	62.3±0.04	63.3±0.25	54.5±0.46	80.2±0.21	52.4±0.45	64.8±0.25	78.1±0.41	85.1±0.24
120	87.7±0.11	73.6±0.61	71.4±0.64	62.3±012	90.9±0.28	67.9±0.34	72.8±0.11	88.0±0.84	90.00±0.24
135	95.1±0.13	82.2±0.37	78.3±0.85	71.4±0.31	95.6±0.24	73.0±0.27	78.3±0.47	90.9±0.54	91.4±0.21

N=3 Standard deviation

***Invitro* dissolution studies**

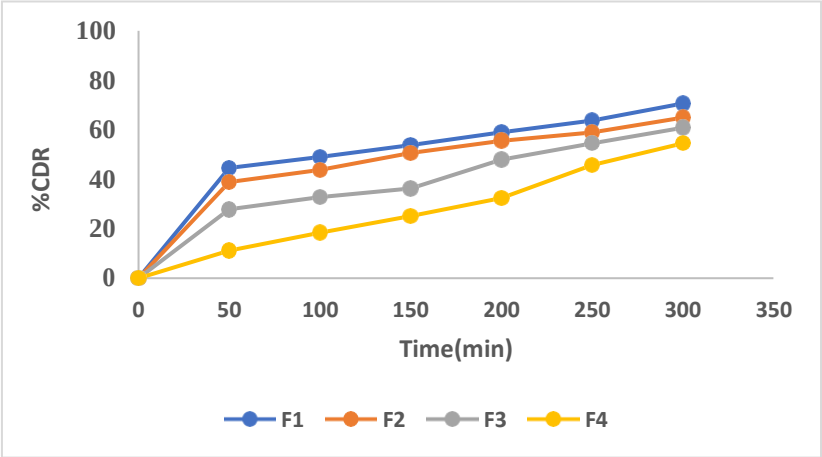

FIG NO 11 : F1 to F4 *invitro* dissolution studies

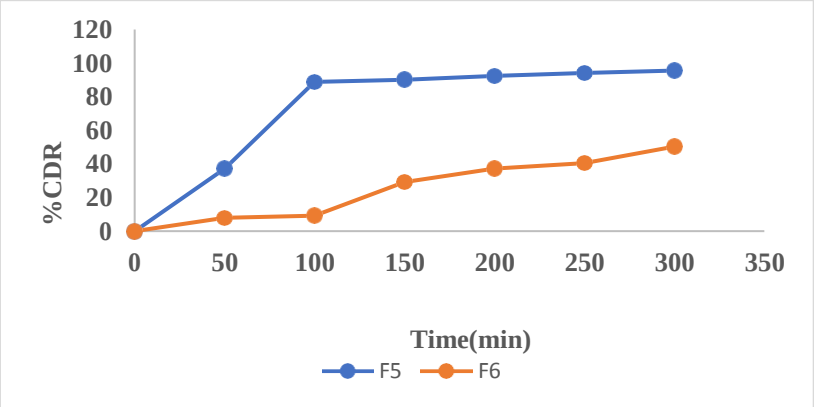

FIG NO 12 : F1 to F4 *invitro* dissolution studies

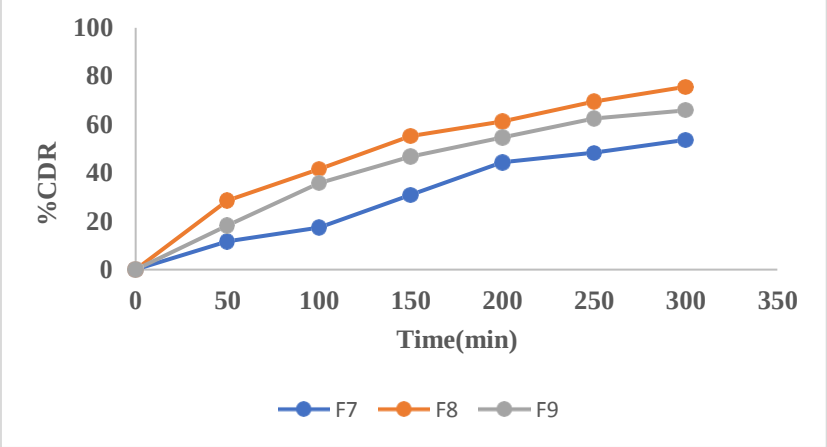

FIG NO 13 : F1 to F4 *invitro* dissolution studies

Dissolution studies were conducted for the batches (F1, F2, F3, F4,F5,F6,F7,F8,F9) from the results it was found that F5formulation has the best drug release rate (95.6%) compared to otherbatches. When compared to marketed tablets the dissolution rate of F5 is more and less affectedby the P^H deviation on drug release.

MARKETED FORMULATION

Comparison of Nimodipine pure drug , marketed nimodipine formulation and F5formulation

Characteristics of the chosen formulation (F5) was first compared with conventional marketed formulation of nimodipine . Results it was discovered that tablet composition exhibitedsuperior dissolution profile maximum medication release close to marketed tablet. From the result of comparison study, the F5 batch had a better dissolution rate 95.6%. Hence F5 formulation may be attributed due to the adopted nimodipine nanocrystals.

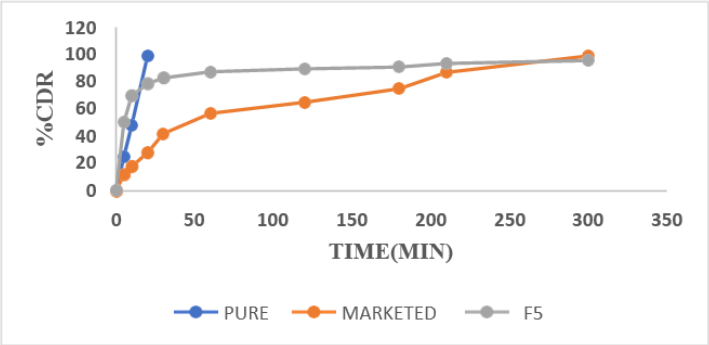

FIG NO 14: *invitro* dissolution studies between pure drug,marketed formulation andbest formulation

DRUG RELEASE KINETICS:

Table no 6: Kinetic Data of F1 Formulation

Batch	Zero order	First order	Higuchi's plot	Korsmeyer-Peppas plot	
	R^2	R^2	R^2	R^2	n
Optimized formulationF5	0.998	0.980	0.930	0.972	0.898

For the optimised formulation, the kinetics of drug release were investigated. According to thefindings, the r2 values of the optimised formulations for zero order kinetics demonstrated linearity, indicating that drug release is independent of concentration and directly proportionalto time. However, the n value of the Korsmeyer-Peppas model strongly indicates that the mechanism of drug release is case-II transport.

Stability Studies:

There was no change in any formulation after storage at 25°C ±2°C for 30,60 days. The colour,drug content, and pH were all identical to the initial preparation. However, after 90 days of storage at 25°C ±2°C, the percentage of drug content in the formulation was less than 97%.

FIG NO 15: Optimized crystals of F5 formulation

IV. DISCUSSION:

The concentration of soya lecithin and the HLB value of surfactants are the main factors influencing the size and shape of the vesicle. An increase in soya lecithin concentration improves the entrapment efficiency of vesicles, preventing drug leakage. That the entrapmentefficiency of nanocrystals prepared by Tween 80 was higher than that of HPMC K5 and PVPK30. This could be due to a variety of factors such as the hydration temperature used to create crystals, the phase transition temperature of the surfactant, the alkyl chain length of thesurfactant, the HLB value of the surfactant, and the saturation and unsaturation of the alkylchain length. The hydration temperature should be higher than the crystal to liquid phase is lessleaky and with high entrapment efficiency.

V. CONCLUSION

It has been undertaken to increase the bioavailability of nimodipine by formulating it as the nanocrystals that increases the drug release rate, reduce side effects, large doses and increases the therapeutic efficiency of drug. Nanocrystals of nimodipine was prepared by using anti method by taking different concentration of ethanol and lecithin. In all the formulations F5 (3% lecithin, 30% ethanol) showed highest entrapment efficiency (95.99%), Zeta potential (-42.5 mV) and it is formulated into three different percentages of crystals (1%,1.5%,2%). And all the three crystals formulations showed good evaluation parameters. Out of all the three gel formulations F5 showed highest permeation rate (95.45%) and found to be stable. So, it is considered as the optimized formulation. Hence confirmed that crystals are very efficient for opthalamic of drug delivery.

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