Nat. Volatiles & Essent. Oils, 2021; 8(5): 10036 - 10053

NVEO
Natural Volatiles & Essential Oils

Design, Development and Characterization Of Nano-Crystal Nicardipine HCL Tablet by Spherical Crystallization Technique 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 nano-crystal based Nicardipine Hcl tablet by spherical crystallization technique. The nano crystals were prepared with adding the bridging solvent bad solvent with stabilizing solvents in ration of 1:0.3 of Drug, dichloromethane, PVP K-30 showing highest solubility of drug. The optimized nano-crystals (F8 batch) shown good entrapment efficiency, particle size, poly disparity and zeta potential value. By using the nano-crystal Nicardipine hydrochloride is prepared by using the fast dissolving tablets. The above results indicated crospovidone containing (f20) shown good dissolution and drug content. The Nicardipine Hydrochloride tablets were shown good stability in the studies. The bioavailability studies of Nicardipine nano crystal based tablets in the rabbit and compared with the pure drug. Nicardipine Nano tablets were shown C_{max}57.24 ng/ml, T max at 10 Hr, AUC(0-∞) at 624.4 ng.min/ml and t1/2 at 6.49 hr. AUC and maximum plasma concentration of Nicardipine Hcl Nano crystal tablet is higher than pure nicardipine drug it indicates Nicardipine Nano tablet produce more bioavailability than the 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 tablet proved to be a potential technology for enhancing the transfer of poorly water soluble lipophilic compounds to the aqueous phase, thus enhancing the bioavailability.

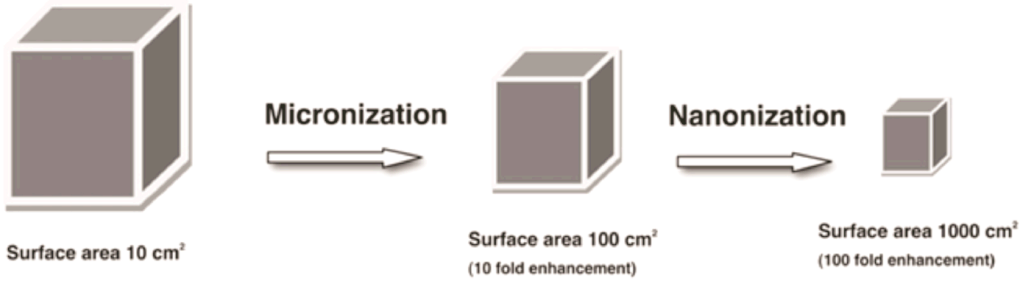
Keywords: -Nicardipine Hcl, Cross Povidone, Mannitol, Mg stearate.

INTRODUCTION

More than half of the new drug molecules face problems of poor bioavailability, instability, adverse effects etc. The prominent cause behind these problems is poor aqueous solubility, as the resulting low bioavailability not only creates an obstacle in formulation development but also delays pharmacological screenings of the drugs [1]. Various approaches to improve solubility viz. salt formation, complexation, solubilization, pH alteration, chemical modification, liposomal delivery have been used. However, wide application of these conventional approaches are restricted by certain limitations like limited ability of solubilizing agents, changed pharmacological activity of drugs on chemical modification, and poor physical & chemical stability of liposomes. In addition, drugs should possess specific properties such as sufficient ionizing ability, solubility in certain organic media, suitable molecular size or conformation [2]. Consequently, these approaches generally result in products with suboptimal and highly erratic performances. To tone down these problems efficiently, exploration of innovative approaches is an earnest need and nanocrystallization for particle size reduction has emerged as a valuable tool.

Micronization of poorly soluble drugs efficiently reduces particle size to micrometer range resulting in an increased surface to volume ratio that ultimately enhances the dissolution velocity and hence bioavailability, but, for highly lipophilic drugs micronization is not much fruitful to attain desired bioavailability due to air entrapment and poor wettability. Hence, 'nanonization' i.e., conversion of micronized particles to nano-sized particles is a logical step forward [1, 3]. Even though, the implementation of nanotechnology still poses certain critical challenges like low ratio of the carried drug to excipients (poor drug loading), toxicity, high production costs etc [4]. Nanocrystals have emerged as an important tool to overcome the aforementioned drug related problems. Drug nano-crystals are carrier-free crystalline clusters of drug without any matrix material with particle size ranging between 10 to 1000 nm. When compared with microcrystals, nano-crystals not only enhance dissolution velocity but improve saturation solubility as well and hence, a higher bioavailability could be logically conceived. The nano-crystals could conveniently be formulated into conventional dosage forms for oral, pulmonary, nasal, ocular and injectable administrations [5]. Manufacturing techniques and process parameters related to this technology have been reviewed in a number of reports. This review mainly focuses on nano-crystal based formulations and applications of drugs used for various disorders. Additionally, it also covers commercialized products based on nano-crystal technology and drugs in the pipelines dealing with solubility problems. Delivery of nano-crystallized drug formulations for improved bioavailability, dosage proportionality and patient safety are reviewed.

Fig. (1). A diagrammatic representation of nanonization mechanism



Advantages of Nanocrystals over Microcrystals [2]

1. Increased bioavailability due to enhanced saturation solubility and dissolution velocity than microcrystals.
2. High adhesiveness compared to microcrystals, which is also an important factor for improved absorption of poorly soluble drugs.
3. High stability compared to micro suspensions due to absence of aggregation and Ostwald ripening (crystal growth).
4. Improved biological performance of drugs in various in various delivery forms irrespective of route of administration.

NANOCRYSTAL BASED FORMULATIONS

2.1. Suspension

The most common approach to formulate a poorly soluble drug is a 'nano-suspension' with the advantage of multiple routes of administration including oral, parenteral, pulmonary etc. It is highly

preferred for intravenous (IV) administration due to omission of toxic chemicals and solvents in formulations hence, shows high safety profile [7]. Hydrosols are colloidal aqueous suspensions containing drug particles with size approximately 200 nm, suitable for IV administration. They are prepared by precipitation method where the drug powder is dispersed in excess of water (about 98%) containing stabilizers. For long-term use, hydrosols are spray-dried and are reconstituted with water before use [8]. Stability is the prime concerns for nano-suspension, as being highly susceptible to crystal growth suitable stabilizers are used. Selection of stabilizers is an essential criterion for formulation development and should meet some important requisites:

(a) High affinity for particle surface (like lecithin, Pluronic F68®)

(b)Sufficiently high diffusion velocity to shield nano-crystal surface instantly and lastly

(c) the indispensable issue is their safety and acceptability to the body [2].

Tablet

Nanocrystals could conveniently be formulated into tablets. Generally, direct compression method is considered as a suitable process for tablet production.

Tablets could be produced by two different ways:

(a) Using Solid PEG as excipient for tabletting. In this case, the drug powder is dispersed in the molten PEG and the suspension is homogenized at high temperature resulting in a hot nano-dispersion, which finally solidifies. Subsequent milling yields a flowable powder, which undergoes direct compression to produce tablets containing nano-crystals [9]

(b) In an aqueous nano-suspension, excipients and polymer(s) required for tablet production are dispersed. This suspension is then spray dried yielding a free flowing powder, which is directly compressed into tablets [3].

Nano-crystal technology could be incorporated into tablets of immediate-release, delayed-release, extended release and fast-melt (waterless) tablets. Based on Nano- Crystal® Technology, Elan has developed an orally disintegrating tablet ingested without water for a more convenient means of taking medication and freeing patients from the problem of swallowing cumbersome dosage forms [5].

2.3. Capsules

Usually, PEGs (liquid, semi-solid and solid) are used for capsule filling. To the hot liquid PEG, drug powder is dispersed and homogenized. After homogenization, the resulting suspension is allowed to cool where PEG recrystallizes entrapping drug nano-crystals within its matrix preventing crystal growth. The liquid PEG nano-suspension is finally filled into capsules. In case of solid PEG, the melted PEG nano-suspension is either directly filled into hard gelatin capsules (where the suspension solidifies within the capsule) or the liquid suspension is first solidified and ground with subsequent filling of the powder into hard gelatin capsules [3].

Filling of solid material is easier than liquid nano-suspension as the latter requires sealing of gelatin capsules [9].

Emulsion

Besides suspensions, emulsions are also preferred as IV formulation when a parenteral product is desired**.** For emulsion fabrication, the drug is first dissolved in an organic solvent containing lecithin

(phospholipid), evaporated, and then the mixture is used for production of emulsion where the drug molecules are incorporated into the interfacial layer of the emulsion.

Powder for inhalation

Nanocrystals are one of the alternatives for preferential pulmonary delivery of drugs for treatment of diseases such as asthma or deep lung delivery for systemic or local effect. Drug particles in nano-sized range could readily be obtained by techniques like milling and high-pressure homogenization, which usually result in nano-suspensions.

Pellets

Like tablets and capsules, nano-crystal pellets are also preferred as oral controlled release dosage forms possessing multiple advantages like free dispersion in the GIT resulting in high drug absorption with minimum side effects, also offering the flexibility of blending different drug substances in a single dosage form.

MATERIALS AND EQUIPMENTS[14-16]

LIST IF MATERIALS

Table No:-9

S.No	Materials	Grade	Manufactures / Suppliers
1.	Nicardipine Hcl	Pharma	Sampler gift
2.	PEG 6000(g)	A.R.	S.D. Fine Chem. Ltd.
3.	PVP K-30 (g)	A.R.	Colorcon Asia Pvt. Ltd.
4	Methanol(ml)	A.R.	C.P. kelco, U.S.A
5.	Dichloromethane(ml)	L.R.	Signet Chemical Corp.
6.	Water (ml)	A.R.	Signet Chemical Corp.
7.	Sodium Starch Glycolate	A.R.	Loba Chemie
8.	Mannitol	A.R.	Loba Chemie
9.	MCC	L.R.	S.D. Fine Chem. Ltd.
10.	Talc	L.R	Nice Chemicals Laboratory
11.	Mg stearate	A.R	S.D. Fine Chem. Ltd.

LIST IF EQUIPMENTS

Table No:-10

S.No	Instruments	Manufactures
1.	Electronic Balance	Afcoset ER-120A
2.	Hardness Tester	Monsanto
3.	Friability test apparatus	Roche Friabilator
4.	Dial Caliper	Mitutoyo, Japan.
5.	USP Dissolution test apparatus type II	Lab India
6.	Tap Density Tester	Electro Lab

7.	UV Spectrophotometer	Shimadzu, UV 1601
8.	IR Spectrophotometer	Thermo Nicolet
9.	Mechanical stirrer	Remi motors, India
10.	Optical microscope	Leica Microsystems
11.	Tablet punching machine	Cadmach sixteen stationary
12.	Bulk density apparatus	Electro Lab
13.	Disintegration test apparatus	Electro lab, Mumbai
14.	HPLC	Lab India

METHOLODOGY[17-20]

Preparation of Nano crystals:

All Nano crystals were obtained by the quasi emulsion solvent diffusion method [2]. Nano crystals were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in Table 1. Nicardipine hydrochloride (1.0 g) was dissolved in good solvent methanol (4.0 mL). The bridging liquid dichloromethane (1.0 mL) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (100 mL) containing different polymers like, PEG-6000 and PVP K-30 with a stirring rate of 500 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through whatmann filter paper no.42.

Table 1: Composition of Nicardipine hydrochloride Nano crystals

Ingredients	F1	F2	F3	F4	F5	F6	F7	**F8**
Nicardipine hydrochloride(g)	1	1		1	1	1	1	**1**
PEG 6000(g)	0.25	0.5	0.75	1	--	--	--	**--**
PVP K-30 (g)	--	---	--	--	0.25	0.5	0.75	**1**
Methanol(ml)	25	25	25	25	25	25	25	**25**
Dichloromethane(ml)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	**12.5**
Water (ml)	100	100	100	100	100	100	100	**100**

CHARACTERIZATION OF NANO CRYSTALS

1. Particle size analysis: Size and size distribution of the crystals in dried form was determined following redispersion in water containing 0.1% polyvinyl alcohol (PVA&403) by dynamic light scattering through particle size analyser Nanotrac 150 (Japan) with a wet sampling system and the diameters reported were calculated using mean particle size distribution.

2. Determination of drug content: The drug content of freeze dried samples was checked by UV & spectrophotometer to confirm the purity of the prepared samples. For quantitative determination of drug content in formulations aqueous dispersions of formulations (25mg/10ml distilled water) were passed through 0.8 <m filter. The filtrates containing fine particles smaller than 0.8 <m were dissolved in 4% sodium lauryl sulphate solution and the concentration of drug was determined

spectrophotometrically. The amount of drug in filtrate relative to the total amount of drug in the dispersion was calculated and expressed as nanocrystal yield.

3. Scanning electron microscopy: The surface morphology of the commercial drug powder and the freeze-dried formulation samples was examined by SEM. samples were mounted on top of double sided sticky carbon tape on metal discs and coated with 80 nm Gold/palladium in Blazers 120B sputtering device.

4. Powder X-ray diffraction (PXRD): The PXRD was carried out using Philips Analytical XRD B.V. at the scanning rate of 40 /min 2θ range of 10&70 0.

5. Solubility: Saturation solubility measurements were assayed through ultraviolet absorbance determination at 291 nm using an UV spectrophotometer. An excess amount of griseofulvin powder and formulations were added to 150 ml of 4% SLS solution the mixture were stirred in mechanical shaker for 24 hours at a temperature of 37+ .05 0 C using GLF 1086 shaker. Visual inspection was carefully made to ensure there was excess sample in solid state indicating that saturation had been reached. The mixtures were filtered using 0.2<m filter and filtrates were diluted suitable to determine the solubility of griseofulvin from each formulation.

6. Dissolution test: A dissolution test for commercially available griseofulvin and formulations was carried out by filling them in hard gelatin capsules (Zydus Cadilla, Goa, India). The prepared samples and the drug powder were filled in capsules (125mg) and subjected to dissolution studies with 900 ml 4% SLS solution as dissolution medium preheated and Maintained at 37 + 0.5 0 C. The baskets were rotated at a speed of 75 rpm/min. 10ml samples were withdrawn at specified time intervals, filtered through 0.2<m filter, and the concentration of was determined by UV& spectrophotometer.

7. Stability studies: All the formulations were subjected to stability study as per ICH guidelines the formulations were divided into two parts and stored at 30 o ± 2 o C and 65% ± 5% RH and 40 o ± 2 o C and 70% ± 5% RH. The drug release and the drug content were estimated after specified intervals of time.

RESULTS

Table 2: Particle size and % of Drug content of Nicardipine hydrochloride spherical agglomerates

Formulation	Particle size (µm)	% of Drug content	Poly dispersity Index (X±SD)	Zeta Potential (mV±SD)
FI	555±0.13	98.18±0.08	0.385±0.12	-33.6±1.4
F2	542±0.11	98.63±0.10	0.376±0.14	-35.6±1.2
F3	534±0.08	99.23±0.07	0.363±0.11	-38.5±1.6
F4	529±0.10	98.44±0.12	0.3541±0.07	-40.6±1.2
F5	543±0.05	98.88±0.09	0.381±0.08	-46.8±1.4
F6	532±0.07	99.27±0.08	0.363±0.06	-46.6±1.3
F7	526±0.04	98.88±0.07	0.351±0.07	-45.7±1.4
F8	**517±0.08**	**99.27±0.05**	**0.342±0.11**	**-48.3±1.6**

Figure 1: Histogram of size- frequency data for F8 formulation

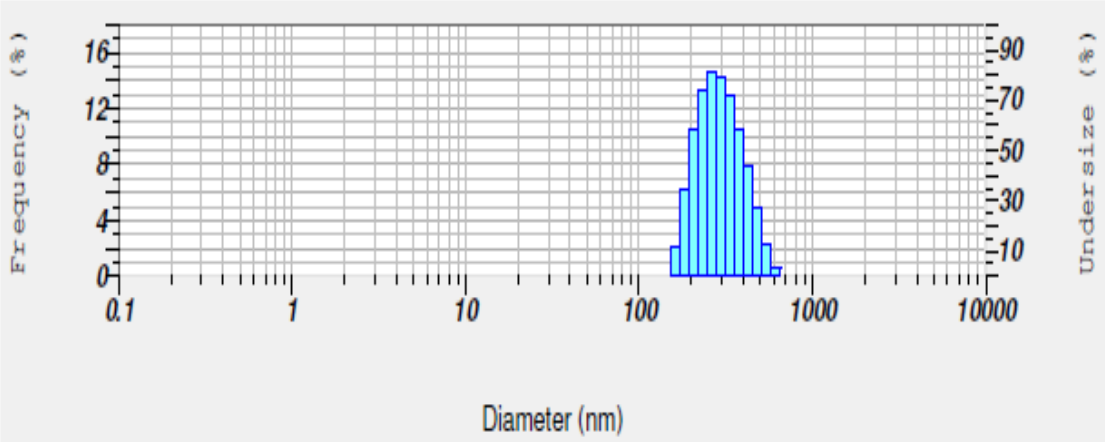


Table 3: *In-vitro* dissolution data of Nicardipine hydrochloride Nano crystals prepared with different concentrations of PEG6000

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\bar{X}$ ± S.D.)			
		F_1	F 2	F3	F_4
1	0	0.000	0.000	0.000	0.000
2	15	22.492±0.07	24.844±0.08	27.083±0.08	31.339±0.02
3	30	37.622±0.03	41.779±0.06	50.525±0.05	55.028±0.06
4	45	40.854±0.06	47.273±0.02	53.269±0.07	70.878±0.02
5	60	45.222±0.08	53.132±0.06	59.161±0.08	74.984±0.08
6	75	48.382±0.04	55.784±0.02	61.837±0.06	78.196±0.04
7	90	53.573±0.05	57.990±0.08	64.191±0.06	80.303±0.06
8	105	55.463±0.06	59.341±0.02	66.456±0.06	81.708±0.02
9	120	57.343±0.03	62.564±0.06	67.364±0.05	82.931±0.02

Figure 4: *In-vitro* dissolution profile of Nicardipine hydrochloride Nano crystals prepared with different concentrations of PEG6000

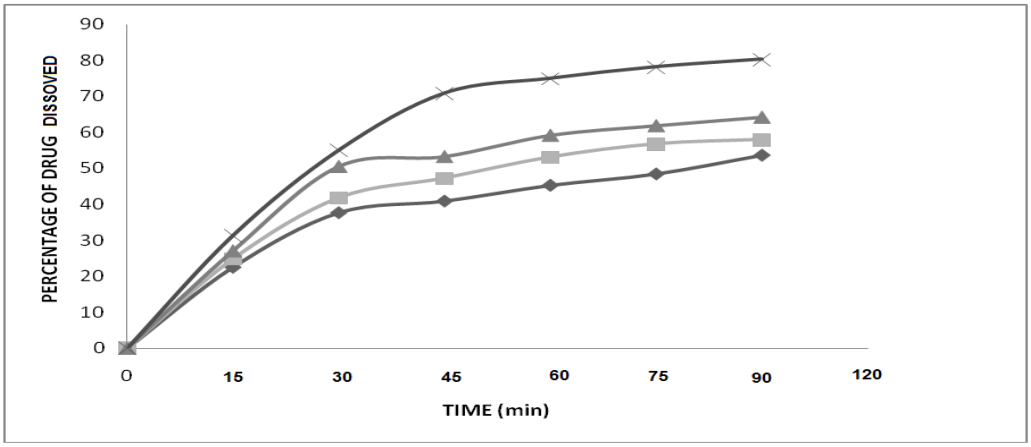


Table 6: *In-vitro* dissolution data of Nicardipine hydrochloride Nano crystals prepared with different concentrations of PVP K-30

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		F_1	F 2	F3	F_4
1	0	0.000	0.000	0.000	0.000
2	15	5.031±0.08	5.702±0.02	12.634±0.08	33.43±0.02
3	30	16.910±0.06	24.740±0.04	32.045±0.05	53.29±0.06
4	45	22.706±0.02	48.467±0.08	57.155±0.07	72.37±0.02
5	60	40.607±0.06	53.096±0.02	61.496±0.08	83.17±0.08
6	75	44.186±0.02	58.866±0.04	68.319±0.06	89.55±0.04
7	90	57.733±0.08	64.891±0.08	73.501±0.06	95.52±0.06
8	105	60.733±0.04	70.053±0.02	76.809±0.05	98.61±0.02
9	120	63.301±0.07	70.994±0.05	79.015±0.02	100.26±0.06

Figure 6: *In-vitro* dissolution profile of Nicardipine hydrochloride Nano crystals prepared with different concentrations of PVP K-30

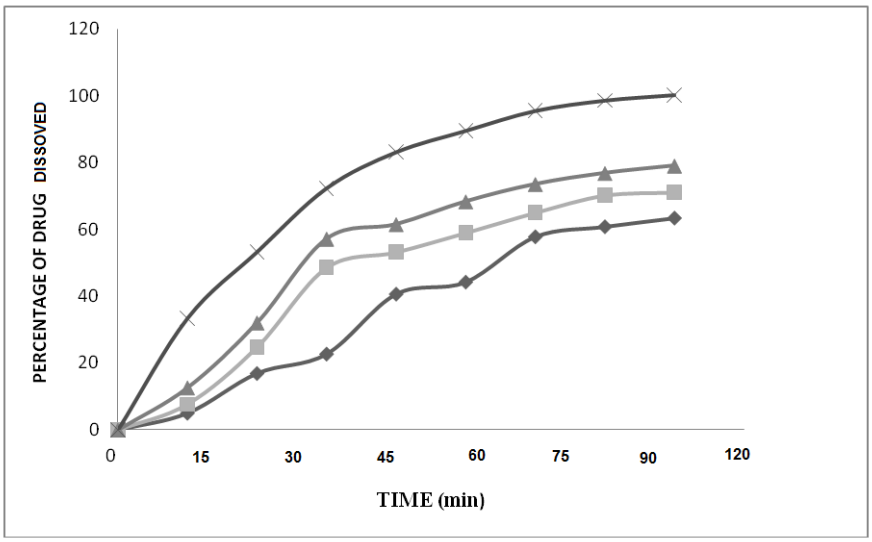


Table 9: Composition of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

S.No.	Ingredients	F9	F10	F11	F12
1	Nicardipine hydrochloride nano-crystals	40	40	40	40
2	Sodium Starch Glycolate	4	6	8	10
3	Mannitol	52.5	50.5	48.5	46.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 10: Physical parameters of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

S.No.	Parameters	F_9	F_{10}	F_{11}	F_{12}
1	Average weight (mg)	201 ± 0.17	200 ± 0.31	201 ± 0.26	200 ± 0.36
2	Drug content (%)	96.3 ± 0.23	99 ± 0.16	99.4 ±0.36	99.3 ±0.13
3	Disintegration time (min)	1.6 ± 0.36	1.2 ± 0.21	1 ± 0.17	0.7± 0.25
4	Friability (%)	0.78 ± 0.27	0.88 ± 0.31	0.79 ±0.19	0.77 ±0.22
5	Hardness (kg/sqcm)	2.83 ± 0.26	3.2 ± 0.21	2.95 ±0.38	2.8 ± 0.21

Table 11: *In-vitro* dissolution data of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		F_9	F 10	F11	F 12
1	0	0.000	0.000	0.000	0.000
2	15	15.988±0.08	15.988±0.02	22.696±0.08	26.832±0.02
3	30	26.139±0.06	29.157±0.04	36.909±0.05	43.640±0.06
4	45	27.401±0.02	31.443±0.08	40.132±0.08	44.776±0.02
5	60	37.838±0.06	38.436±0.02	46.614±0.06	51.507±0.08
6	75	39.499±0.02	51.504±0.08	60.398±0.02	66.100±0.06
7	90	45.641±0.08	58.271±0.02	66.207±0.08	70.487±0.02
8	105	50.029±0.04	61.385±0.06	68.245±0.03	73.219±0.07
9	120	53.094±0.05	63.061±0.08	71.299±0.05	76.076±0.03

Table 12: *In-vitro* dissolution kinetics of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{25} (%)	K (min^{-1})	Correlation coefficient values		
						Zero Order	First Order	Hixson-Crowell cube root
1	F_9	35.82	62.98	28.28	0.064	0.975	0.991	0.974
2	F_{10}	24.13	43.87	32.69	0.064	0.975	0.987	0.963
3	F_{11}	22.89	40.56	39.98	0.077	0.960	0.986	0.977
4	F_{12}	19.17	38.27	44.30	0.088	0.946	0.986	0.981

Table 13: Statistical treatment for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

Trial	Dissolution efficiencies (%) ($D.E_{25}$)				ANOVA Parameters		
	F_9	F_{10}	F_{11}	F_{12}	Calculated value (F)	Degree of freedom	Significance
1	28.29	32.69	39.98	44.30	9884	3,8	P<0.05

2	28.32	32.54	39.96	44.10			
3	28.00	32.72	39.84	44.34			

Figure 8: *In-vitro* dissolution profile of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

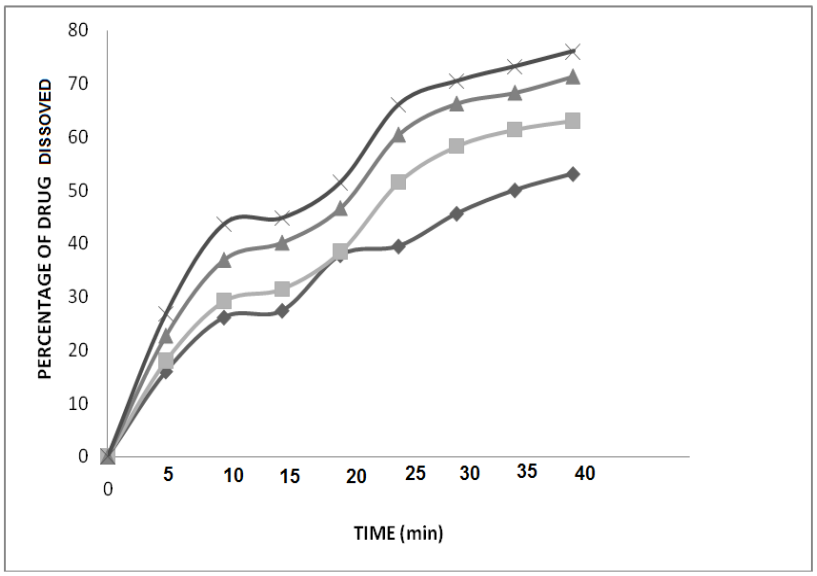


Figure 10: Comparison for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Sodium Starch Glycolate

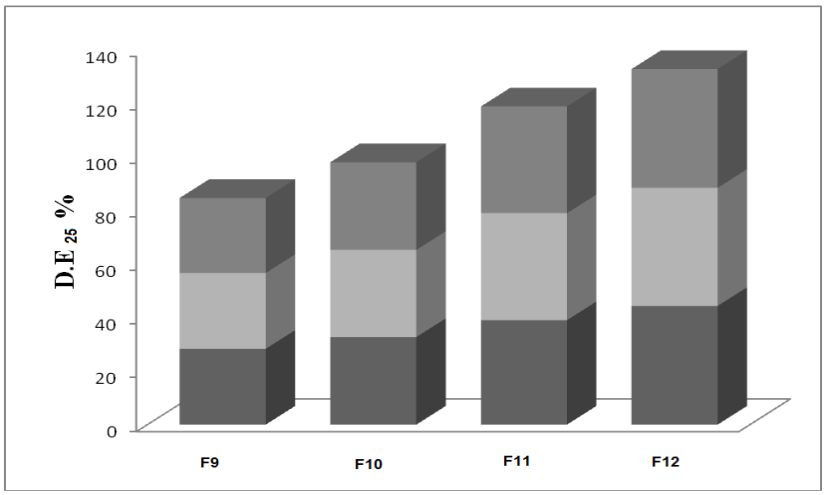


Table 14: Composition of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Croscarmellose sodium

S.No.	Ingredients	F_{13}	F_{14}	F_{15}	F_{16}
1	Nicardipine hydrochloride nano-crystals	40	40	40	40
2	Croscarmellose sodium	4	6	8	10

3	Mannitol	52.5	50.5	48.5	46.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 15: Physical parameters of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Croscarmellose sodium

S.No.	Parameters	F_{13}	F_{14}	F_{15}	F_{16}
1	Average weight (mg)	198 ± 0.54	199+0.19	201+0.16	200+0.23
2	Drug content (%)	97.6 ± 0.16	99± 0.31	98.5± 0.42	99± 0.41
3	Disintegration time(min)	1.8 ± 0.10	1.1± 0.19	0.9± 0.23	0.65 ± 0.24
4	Friability (%)	0.64 ± 0.02	0.6± 0.08	0.68± 0.12	0.53± 0.08
5	Hardness (kg/sqcm)	2.9 ± 0.13	3.3± 0.15	3.2± 0.11	3± 0.15

Table 16: *In-vitro* dissolution data of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Carmalose Sodium

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		F_{13}	F_{14}	F_{15}	F_{16}
1	0	0.000	0.000	0.000	0.000
2	5	7.826±0.08	14.422±0.02	23.814±0.08	44.273±0.02
3	10	15.696±0.06	24.565±0.04	45.300±0.05	56.209±0.06
4	15	35.236±0.02	42.030±0.08	50.358±0.08	71.159±0.02
5	20	41.692±0.06	48.411±0.02	56.002±0.06	77.029±0.08
6	25	54.555±0.02	61.423±0.08	64.061±0.06	90.980±0.03
7	30	57.762±0.08	64.667±0.02	68.768±0.09	93.135±0.08
8	35	60.538±0.02	67.480±0.07	71.379±0.03	96.341±0.07
9	40	61.874±0.04	72.543±0.04	74.561±0.07	98.942±0.02

Table 18: Statistical treatment for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Carmalose Sodium

Trial	Dissolution efficiencies (%) ($D.E_{25}$)				ANOVA Parameters		
	F_{13}	F_{14}	F_{15}	F_{16}	Calculated value (F)	Degree of freedom	Significance
1	30.65	37.20	46.65	49.08	20650	3,8	P<0.05
2	30.62	37.32	46.54	49.00			
3	30.54	37.00	46.72	49.14			

Figure 5.11: *In-vitro* dissolution profile of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Croscarmellose sodium

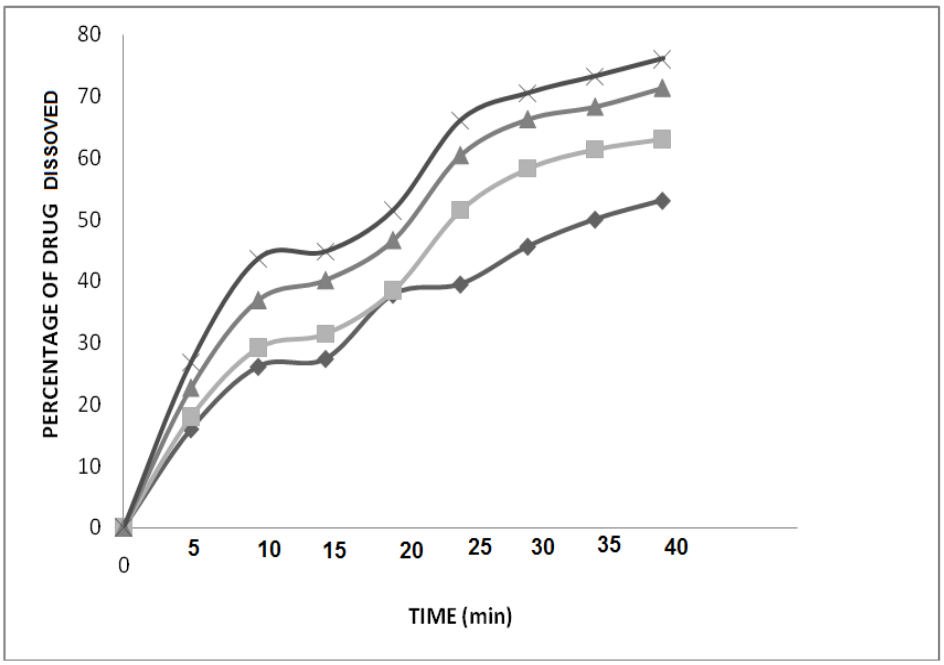


Figure 5.13: Comparison for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Croscarmellose sodium

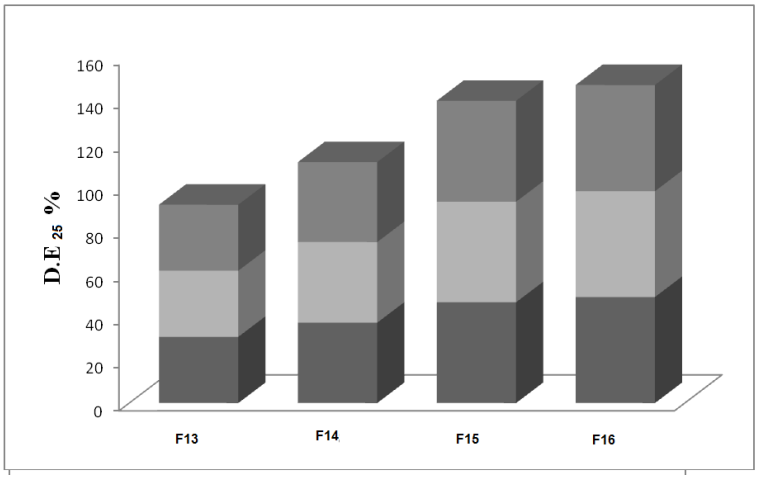


Table 19: Composition of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

S.No.	Ingredients	F_{17}	F_{18}	F_{19}	F_{20}
1	Nicardipine hydrochloride nanocrystals	40	40	40	40
2	Cross Povidone	4	6	8	10
3	Mannitol	52.5	50.5	48.5	46.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 20: Physical parameters of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

S.No	Parameters	F_{17}	F_{18}	F_{19}	F_{20}
1	Average weight (mg)	198 ± 0.54	199+0.19	202+0.16	199+0.28
2	Drug content (%)	97.6 ± 0.16	99± 0.31	98.5± 0.42	99.3± 0.21
3	Disintegration time (min)	1.6 ± 0.10	1.4± 0.19	1± 0.23	0.49± 0.43
4	Friability (%)	0.74 ± 0.02	0.6± 0.08	0.64± 0.12	0.59± 0.32
5	Hardness (kg/sqcm)	3 ± 0.13	2.9± 0.15	2.7± 0.11	2.8± 0.32

Table 21: *In-vitro* dissolution data of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		F_{13}	F_{14}	F_{15}	F_{16}
1	0	0.000	0.000	0.000	0.000
2	5	5.702±0.08	6.596±0.02	11.739±0.08	32.53±0.02
3	10	16.690±0.06	23.403±0.04	29.245±0.05	54.62±0.06
4	15	29.528±0.02	37.396±0.08	45.842±0.08	67.44±0.02
5	20	46.461±0.06	49.901±0.02	56.605±0.06	78.21±0.08
6	25	48.619±0.02	55.431±0.08	62.842±0.06	84.34±0.06
7	30	55.085±0.08	62.531±0.02	64.976±0.03	86.37±0.04
8	35	61.038±0.05	69.216±0.05	76.287±0.04	98.24±0.02
9	40	63.383±0.04	79.830±0.07	80.280±0.08	101.68±0.05

Table 22: *In-vitro* dissolution kinetics of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

S. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{25} (%)	K (min^{-1})	Correlation coefficient values		
						Zero Order	First Order	Hixson-Crowell cube root
1	F_{17}	27.59	50.57	29.09	0.0806	0.973	0.984	0.973
2	F_{18}	23.48	42.18	33.19	0.0817	0.978	0.982	0.967
3	F_{19}	18.86	32.80	40.17	0.101	0.973	0.990	0.977
4	F_{20}	7.72	12.38	43.01	0.186	0.939	0.990	0.987

Figure 14: *In-vitro* dissolution profile of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

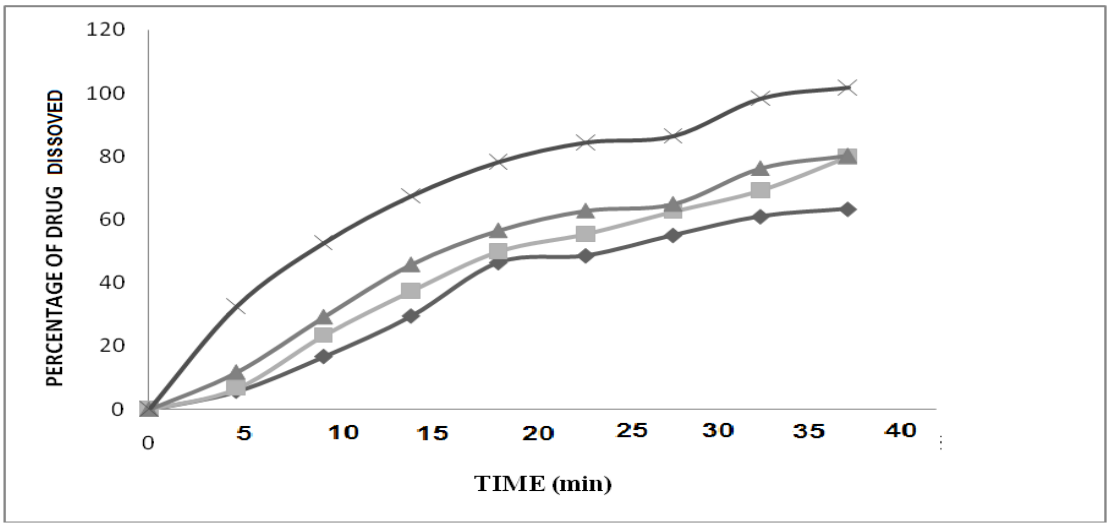
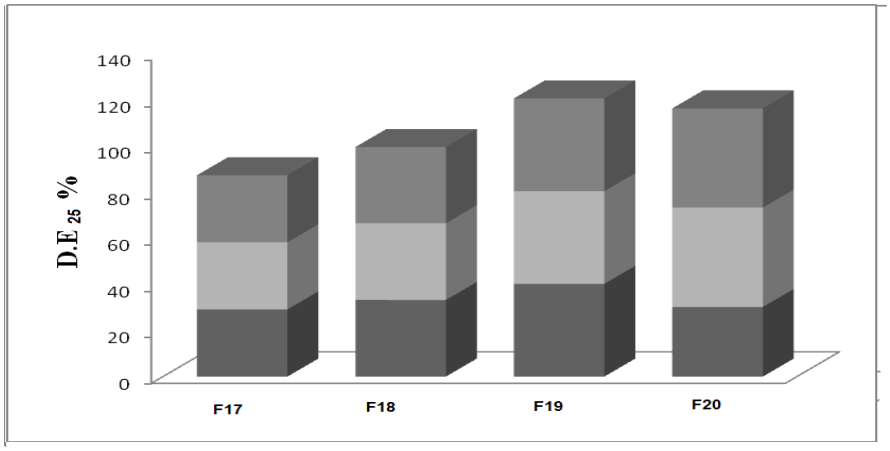


Table 23: Statistical treatment for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone

Trial	Dissolution efficiencies (%) ($D.E_{25}$)				ANOVA Parameters		
	F_{17}	F_{18}	F_{19}	F_{20}	Calculated value (F)	Degree of freedom	Significance
1	29.09	33.19	40.17	30.14	26120	3,8	P<0.05
2	29.10	33.22	40.14	43.05			
3	29.00	33.00	40.16	42.98			

Figure 16: Comparison for dissolution efficiency of Nicardipine hydrochloride Fast dissolving tablets prepared with different concentrations of Cross Povidone



STABILITY STUDIES [21]

Table No.24: *In-vitro* Dissolution Data of Nicardipine hydrochloride Fast dissolving tablets 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 ± 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	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	5	32.53±0.02	32.47±0.03	32.43±0.05	32.41±0.02	32.51±0.03	32.48±0.04	32.43±0.01
3	10	54.62±0.06	54.60±0.04	54.57±0.03	54.53±0.01	54.61±0.04	54.58±0.05	54.52±0.02
4	15	67.44±0.02	67.41±0.01	67.38±0.04	67.36±0.02	67.40±0.05	67.38±0.02	67.34±0.03
5	20	78.21±0.08	78.20±0.04	78.18±0.06	78.16±0.03	78.19±0.07	78.16±0.04	78.14±0.03
6	25	84.34±0.06	84.32±0.04	84.30±0.03	84.28±0.02	84.31±0.01	84.27±0.03	84.24±0.05
7	30	86.37±0.04	86.35±0.01	86.31±0.02	86.27±0.04	86.33±0.02	86.30±0.01	86.26±0.03
8	35	98.24±0.02	98.21±0.04	98.17±0.03	98.14±0.02	98.20±0.01	98.16±0.02	98.12±0.03
9	40	101.68±0.05	101.24±0.02	100.98±0.03	100.78±0.04	101.168±0.02	100.88±0.03	100.69±0.01

Table No. 25: Dissolution Kinetics of Nicardipine hydrochloride Fast dissolving tablets 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 25 (%)
1	25±2^0 C/ 60±5% RH	1st month	0.186	7.72	12.38	43.01
		2nd month	0.186	7.72	12.38	43.01
		3rd month	0.186	7.72	12.38	43.01
		1st month	0.186	7.72	12.38	43.01

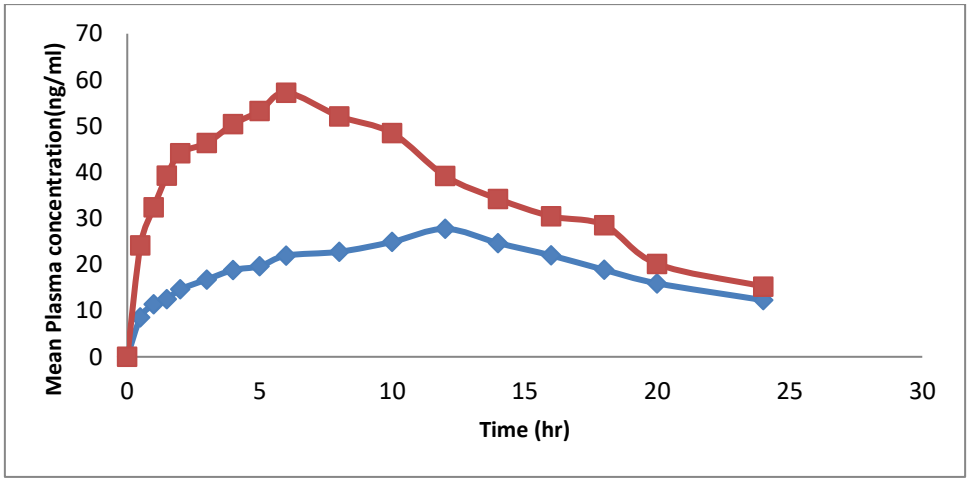
2	**40±2^0 C/ 75±5% RH**	**2nd month**	0.186	7.72	12.38	43.01
		3rd month	0.186	7.72	12.38	43.01

INVIVO STUDIES[22]

Table No. 26: 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	24.15±1.216
3	1	11.35±1.74	32.36±1.12
4	1.5	12.51±1.52	39.26±1.23
5	2	14.61±1.14	44.14±1.28
6	3	16.75±1.64	46.32±1.26
7	4	18.81±1.35	50.42±1.43
8	5	19.62±1.43	53.24±1.46
9	6	21.93±1.24	57.24±1.36
10	8	22.76±1.43	52.11±1.23
11	10	24.90±1.24	48.45±1.44
12	12	27.72±1.27	39.16±1.26
13	14	24.64±1.36	34.20±1.13
14	16	21.96±1.53	30.44±1.34
15	18	18.84±1.32	28.53±1.18
16	20	15.92±1.21	20.12±1.92
17	24	12.28±1.39	15.23±1.33

Figure 17: 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. 27: Statistical Treatment of Pharmacokinetic Parameter (mean ± s.d.) of Nicardipine hydrochloride obtained with pure drug and optimized formulation

rmacokinetic parameter	**Pure Drug**	**Optimized formulation**	**Calculated value of 't'**
Cmax (ng/ml)	27.72± 0.31	57.24± 0.41	23.40***
$t_{1/2}$ (h)	11.53± 0.011	6.49± 0.072	38. 34***
K_{el} (h^{-1})	0.58± 0.012	0.52± 0.014	6.75***
K_a (h^{-1})	1.68± 0.01	5.32± 0.01	20.08***
$AUC_{0-\alpha}$ (ng h/ml)	191± 1.43	624.4.±1.87	217.36***
Null hypothesis (H_O): 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_O 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:

The present study was concluded that nano crystals were prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compatibility, wettability, flowability and bioavailability. These Nicardipine hydrochloride nano crystals also showed excellent physico-chemical characters as compared with pure drug which indicates that the Nicardipine hydrochloride nano crystals can suitable for directly compressible tablet process.

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