IJPSR (2018), Volume 9, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 October, 2017; received in revised form, 05 March, 2018; accepted, 11 March, 2018; published 01 July, 2018

FORMULATION OF NICERDIPINE HYDROCHLORIDE INCLUSION COMPLEX FOR DISSOLUTION ENHANCEMENT

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Keywords:

Nicardipine hydrochloride, *β*-Cyclodextrin, PVP K 30, Crospovidone, *Ex-vivo* Permeation study, Flux

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ABSTRACT: The purpose of this study was to improve the dissolution rate of poorly soluble Nicardipine hydrochloride with cyclodextrin complexation by using different techniques like physical mixing, solvent evaporation and kneading method. Nicardipine hydrochloride is a calcium channel blocker. It is belonging to BCS class - II having poor solubility and high permeability. It is used to treat Angina having low bioavaibility about 10 - 40% orally is attributed to the hepatic first pass metabolism. The present invention relates to the inclusion complex made by *β*-Cyclodextrins and the methods for enhancing the bioavailability of Nicardipine hydrochloride. Solid inclusion complexes were prepared by conventional methods like physical mixing, solvent evaporation and kneading techniques. Optimized complex was characterized by using powder X-ray diffractometer and FTIR. *Ex-vivo* studies showed that the dissolution rate of Nicardipine hydrochloride was significantly improved by the complexation with *β*-cyclodextrin with respect to the drug alone. Physical mixing method showed highest dissolution rate than the other techniques.

INTRODUCTION: The Bio-pharmaceutics classification system is a system to differentiate the drugs on the basis of their solubility and permeability [1]. This system of classification is helpful in formulation development to know solubility and permeability of drug. BCS class II drug having problem of poor water solubility and high intestinal permeability problem of poor solubility can be overcome by making inclusion complex of drug with different carrier like different grade of cyclodextrin like HP-*β*-CD, *β*-CD or different grade of Poloxamer like Poloxamer 188 [2, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(7).3060-65

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(7).3060-65

Nicardipine hydrochloride is a Ca^{+2} channel blocker [5] used to treat angina [4, 5]. It is belonging to BCS class-II having 10 - 40% bioavaibility on oral administration [6, 7, 8, 9]. Poor solubility of a drug is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work by formulating complex of drug with cyclodextrin mask bitter taste of drug and also leads to improve solubility of drug [3, 4, 10, 11, 12].

Nicardipine hydrochloride is a poorly water soluble drug [9, 11]. The chemical name of the Nicardipine hydrochloride is 2- (Benzylmethylamino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl) -3, 5-pyridinedicarboxylate monohydrochloride [13]. It is a Ca^{+2} channel blocker acting by selective inhibition of calcium influx through cell membranes or on the release and binding of calcium in intracellular pools [11, 14].

Since they are inducers of vascular and other smooth muscle relaxation, they are used in the drug therapy of hypertension and cerebrovascular spasms, as myocardial protective agents, and in the relaxation of uterine spasms [14]. The aqueous solubility of Nicardipine hydrochloride is 2.47 mg/l when determined in vitro at pH 7 and 37 °C. Thus, it is important to enhance the solubility and dissolution rate of Nicardipine hydrochloride to improve its oral bioavailability [9, 15, 16].

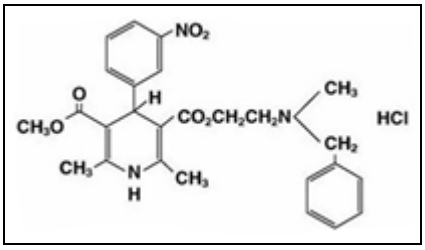

FIG. 1: NICARDIPINE HYDROCHLORIDE [15]

Cyclodextrin is used as the solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents [16]. The permeability through biological membrane is enhanced by the presence of Cyclodextrins [17]. These acts as permeation enhancers by carrying the drug through the aqueous barrier which exists before the lipophilic surface of biological membranes [18, 19, 20, 21]. Cyclodextrins having sweet taste so they are also used for taste masking purpose. Different grade of cyclodextrin molecules have different solubility based on improve in solubility pattern suitable grades are used [20, 21].

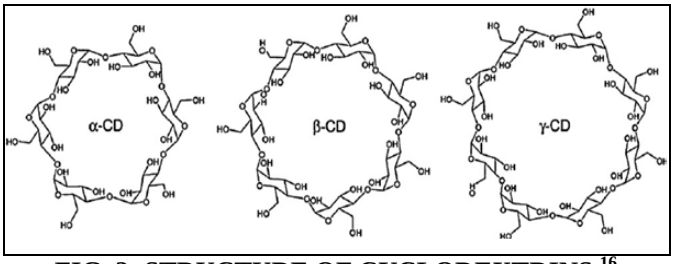

FIG. 2: STRUCTURE OF CYCLODEXTRINS [16]

MATERIALS AND METHODS:

Materials: Nicardipine hydrochloride was obtained as a gift sample from Cadila Pharmaceuticals (Baroda), *β*- Cyclodextrin was obtained as a gift sample from Sunrise Remedies Pvt. Ltd., All other reagents and chemicals were of analytical grade.

Methods:

Preparation of Nicardipine Hydrochloride Inclusion Complex: [22, 23, 24] Solid dispersion were prepared by using different ratio of drug with complexation agent by different method which are mention in **Table 1**.

TABLE 1: NICARDIPINE HYDROCHLORIDE INCLUSION COMPLEX

Drug carrier complex	Carrier	Method
F1(1:0.5)	*β*-cyclodextrin	Physical mixture
F2(1:1)	*β*-cyclodextrin	Physical mixture
F3(1:2)	*β*-cyclodextrin	Physical mixture
F4(1:3)	*β*-cyclodextrin	Physical mixture
F5(1:4)	*β*-cyclodextrin	Physical mixture
F6(1:0.5)	*β*-cyclodextrin	Kneading method
F7(1:1)	*β*-cyclodextrin	Kneading method
F8(1:2)	*β*-cyclodextrin	Kneading method
F9(1:3)	*β*-cyclodextrin	Kneading method
F10(1:4)	*β*-cyclodextrin	Kneading method
F11(1:0.5)	*β*-cyclodextrin	Solvent evaporation
F12(1:1)	*β*-cyclodextrin	Solvent evaporation
F13(1:2)	*β*-cyclodextrin	Solvent evaporation
F13(1:3)	*β*-cyclodextrin	Solvent evaporation
F14(1:4)	*β*-cyclodextrin	Solvent evaporation
F15(1:1)	Poloxamer 188	Physical mixture
F16(1:2)	Poloxamer 188	Physical mixture
F17(1:3)	Poloxamer 188	Physical mixture

Evaluation of Solid Dispersion for Solubility Study:

Phase Solubility Studies: [21, 22, 23, 24, 25] Excess amounts of Nicardipine hydrochloride and Nicardipine hydrochloride – *β*-cyclodextrin complex were suspended in distilled water in tightly closed screw cap vials, equilibrated in a magnetic stirrer at room temperature for 24 h, then filtered using a 0.45 mm Millipore filter and assayed spectrophotometrically (Shimadzu 2450, Japan) at pre-determined λ_{max}. Three determinations were carried out to calculate the saturated solubility of Nicardipine hydrochloride.

Stoichiometry Determination by the Continuous Variation Method (Job's Plot): [26] Stoichiometry of inclusion was determined by the method developed by Job. Equimolar solutions of NCH and *β*-CD were mixed to a standard volume varying the molar ratio but keeping the total concentration of the species constant. The complex formed for each reaction mixture has been allowed to stand for 24 h. The absorbance at 239 nm was measured for all solutions and ΔA = A-Ao, the difference in absorbance in the presence and in the absence of CDs, was plotted against r;

$$r = [Drug] / [Drug] + [CD]$$

[CD] = Conc. of *β*-CD

***Ex-vivo* Permeation Study:** [27, 28] The permeation study of Nicardipine hydrochloride through the goat sublingual mucosa will be performed using Franz diffusion cell at 37 ± 0.5 °C. Fresh goat sublingual mucosa will mount between donor and receptor compartments. The inclusion complex will placed with the core facing the mucosa, and the compartments will clamped together. The donor compartment will be filled with phosphate buffer pH 6.8 containing 1% SLS. The receptor compartment (16 ml capacity) will be filled with phosphate buffer pH 6.8 and hydrodynamics in the compartment will be maintained by stirring with a magnetic bead at uniform slow speed. Five millilitre samples will with-drawn at predetermined time intervals and analysed for drug content by UV spectrophotometer.

TABLE 2: INTERPRETATION OF DRUG AND DRUG+ *β*-CD COMPLEX FTIR SPECTRA

Functional Group	Wave number Pure drug (cm^{-1})	Wave number Drug + Excipients (cm^{-1})
C-N stretching	1342.46	1346.81
N-H stretching	3129.89	3365.33
C-0 stretching	1273.	1149.57
C=O stretching	1759.08	1764.88
Aromatic C-C	1674.80	1676.64
C-H stretching	2970.38	2928.45
N=O stretching	1527.62 & 1489.06	1525.04 & 1488.09

RESULT AND DISCUSSION:

Nicardipine Hydrochloride *β*-CD Interaction Study: [29, 30]

FTIR:

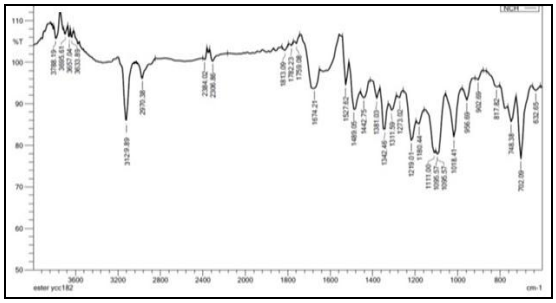

FIG. 3: FTIR SPECTRA OF NICARDIPINE HYDROCHLORIDE

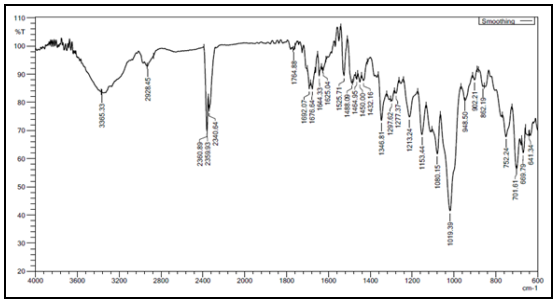

FIG. 4: NICARDIPINE HYDROCHLORIDE + *β*-CD

DSC of Nicardipine Hydrochloride: [31, 32]

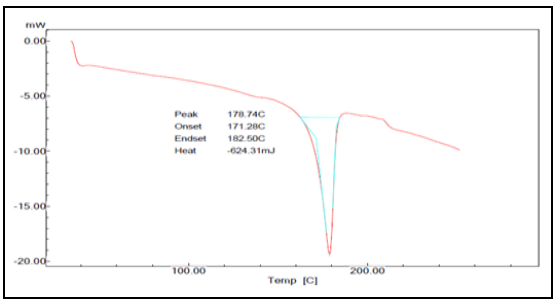

FIG. 5: DSC OF NICARDIPINE HYDROCHLORIDE

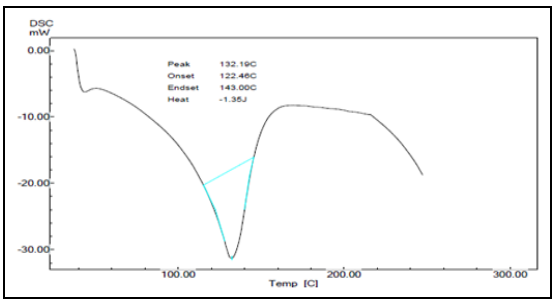

FIG. 6: DSC OF DRUG + *β*-CD

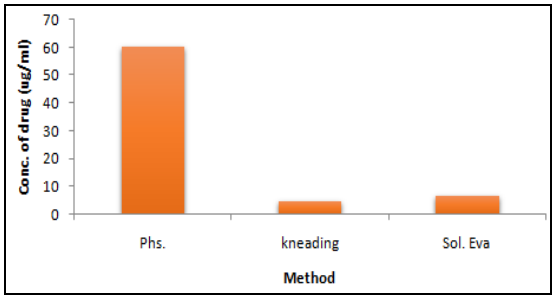

FIG. 7 SELECTION OF METHOD OF PREPARATION OF INCLUSION COMPLEX

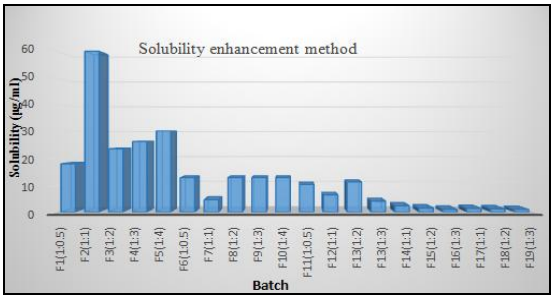

FIG. 8: SELECTION OF METHOD OF PREPARATION OF INCLUSION COMPLEX

For quick dissolution of dosage form high solubility of drug is necessary and this can achieve by enhancing the solubility of drug at its higher level. Here F12 (1:6) batch was selected because, there was higher solubility observed in this batch.

Selection of Solubility Enhancing Agent and Method: [33] Phase solubility study of Nicardipine hydrochloride was conducted and the result of phase solubility study is given in **Table 3**. Here *β*-cyclodextrin was selected as solubility enhancing agent and physical mixture as solid dispersion method, because drug:*β*-cyclodextrin (1:1) complex gave higher solubility of Nicardipine hydrochloride.

TABLE 3: RESULT OF PHASE SOLUBILITY

Drug carrier complex	Carrier	Method	Solubility (µg/ml)
F1(1:0.5)	*β*-cyclodextrin	Physical mixture	18
F2(1:1)	*β*-cyclodextrin	Physical mixture	60
F3(1:2)	*β*-cyclodextrin	Physical mixture	23.6
F4(1:3)	*β*-cyclodextrin	Physical mixture	26.3
F5(1:4)	*β*-cyclodextrin	Physical mixture	30.25
F6(1:0.5)	*β*-cyclodextrin	Kneading method	12.8
F7(1:1)	*β*-cyclodextrin	Kneading method	4.6
F8(1:2)	*β*-cyclodextrin	Kneading method	12.8
F9(1:3)	*β*-cyclodextrin	Kneading method	12.8
F10(1:4)	*β*-cyclodextrin	Kneading method	12.8
F11(1:0.5)	*β*-cyclodextrin	Solvent evaporation	10.29
F12(1:1)	*β*-cyclodextrin	Solvent evaporation	6.36
F13(1:2)	*β*-cyclodextrin	Solvent evaporation	11.2
F13(1:3)	*β*-cyclodextrin	Solvent evaporation	4.07
F14(1:1)	Poloxamer 188	Physical mixture	2.3
F15(1:2)	Poloxamer 188	Physical mixture	1.5
F16(1:3)	Poloxamer 188	Physical mixture	1.02
F17(1:1)	Poloxamer 407	Physical mixture	1.36
F18(1:2)	Poloxamer 407	Physical mixture	1.2
F19(1:3)	Poloxamer 407	Physical mixture	0.95

Phase Solubility:

TABLE 4: PHASE SOLUBILITY

Molar conc. of *β*-CD	Molar conc. of drug
0	0.1
0.02	0.0374
0.04	0.066
0.06	0.092
0.08	0.102
0.1	0.116

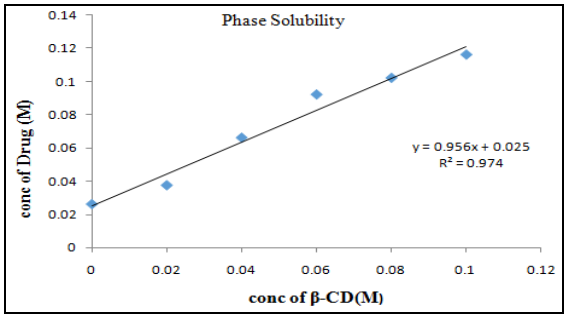

FIG. 9: RESULT OF PHASE SOLUBILITY

Inference: As shown in **Fig. 9** Phase solubility diagrams revealed a linear increase in drug solubility with an increase in the concentration of *β*-CD. Nicardipine hydrochloride solubility increased linearly with cyclodextrin concentration and the slope was smaller than unity, over the entire concentration range studying indicating an A_L type diagram with the formation of a complex with 1:1 Stoichiometry according to Highuchi and Connors. A_L slope of Diagram was < 1.0; it was possible to assess a 1:1 Stoichiometry.

Jobs Plot: [34]

TABLE 5: JOB's PLOT

Nicardipine hydrochloride	*β*-Cyclodextrin	R = NCH/ (NCH+*β*-CD)	ΔA *r
0.01	0	0.1	0
0.02	0.08	0.2	0.0048
0.04	0.06	0.4	0.0168
0.05	0.05	0.5	0.027
0.06	0.04	0.6	0.0246
0.08	0.02	0.8	0.0032

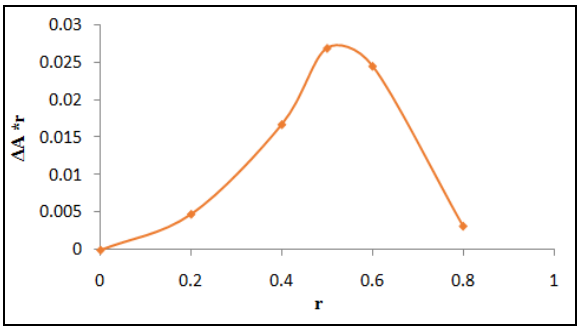

FIG. 10: JOB's PLOT

Inference: According to the continuous variation method, if a physical parameter directly related to the concentration of the complex can be measured for a set of samples with continuously varying molar fraction of its components. The maximum concentration of the complex was present in the sample where the molar ratio r corresponds to the complexation stoichiometry.

Ex-vivo Permeation Study:

TABLE 6: FLUX

Time (Min)	% CPR	% CPR/A
0	0	0
5	41.02	10.80
10	53.46	14.07
15	61.71	16.24
20	74.57	19.63
25	89.91	23.67
30	97.80	25.74

As shown in **Fig. 10** the maximum absorbance variation for Nicardipine hydrochloride in CDs was Observed for r = 0.5 which might indicate the main stoichiometry is 1:1, in agreement with the stoichiometry suggested from the Phase solubility study.

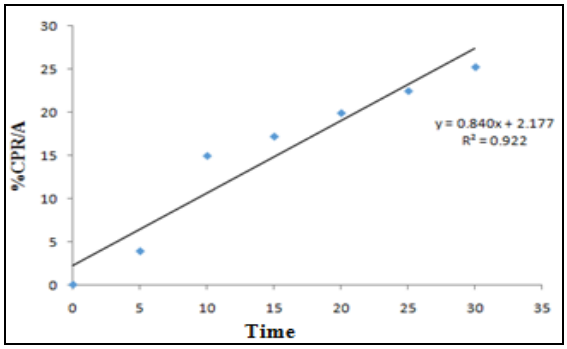

FIG. 11: FLUX

Inference: For determination of flux ex-vivo permeation study of drug *β*-CD Complex using goat buccal mucosa was carried out and the flux value found was 40 sec which is described in following calculation:

$$\text{Slope} = 0.8404 \text{ mg/cm}^2\text{/min}$$

Which indicates, from 1 cm^2 area 0.8404 mg drug permeated in 1 min. So, from total sublingual mucosal area (26.5 cm^2) 22.27 mg drug permeated in 1 min. Here, dose of formulation was 10 mg so time required to permeate drug was found 40 sec.

Pre-formulation Study:

Physical Properties of Solid Dispersion: [32, 33]

TABLE 7: PHYSICAL PROPERTIES OF SOLID DISPERSION

Description	Amorphous
Colour	Yellowish white
Odor	Odorless
Taste	Slightly bitter
Bulk density (gm/ml)	0.37
Tapped density (gm/ml)	0.5
Angle of repose (°)	33.53
Carr's index	26
Hausner's ratio	1.35

Angle of repose was within the range of [30, 31, 32, 33, 34]; moreover, Hausner ratio was less than 1.25 which indicates passable flow property of the solid dispersion. While in terms of Carr's index, it showed good compressibility. Flow property can be improved by adding glidant.

CONCLUSION: Nicardipine hydrochloride is a BCS class II drug having poor solubility, the solubility of drug can be enhanced by preparing inclusion complex using various complexation agent like *β*-cyclodextrin, Poloxamer 188 and Poloxamer 407. Amongst this solubility of drug was improved by using (1:1) molar ratio of Drug: *β*- cyclodextrin. The result of FTIR and DSC showed that there was no interaction between drug and selected excipients used. Bioavaibility of drug may be enhanced by avoiding hepatic first pass metabolism. Bitter taste of Nicardipine hydrochloride was also be masked by using *β*-cyclodextrin. By *ex-vivo* permeation study Flux was set disintegration time of complex was 40 sec.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Makwana S, Kharadi R and Samova S: Formulation of nicerdipine hydrochloride inclusion complex for dissolution enhancement. Int J Pharm Sci & Res 2018; 9(7): 3060-65. doi: 10.13040/IJPSR.0975-8232.9(7).3060-65.