Solubility Enhancement of Poorly Soluble Nicardipine Utilizing Cyclodextrin Inclusion and Solid Dispersion Technique

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ABSTRACT

The drug's solubilization affects the drug's absorption or blood levels. A continuous process known as solubility comprises the solute particle migrating freely in solvent media. The degree of dispersion in fluid, accompanied with blood or plasma mobility, determines the biochemical and pharmacological action of a medicine. Today, the water solubility of 70 to 80 percent of drugs supplied by the healthcare companies is weak. This makes it difficult for the pharmaceutical business to implement new and innovative methodologies that can increase a drug's solubility. There are a few methods for increasing the solubility of medicinal molecules, however solid dispersion and cyclodextrin packed complex (kneading method) have special properties and are simpler to prepare.Therefore, in this research, a sample antihypertensive medication with low solubility (Nicardipine) was chosen, and its solubility was enhanced using the kneading approach with cyclodextrin (CD) and the solid dispersion (SD) approach by HPMC K15M using the solvent evaporation approach.

Key words: Solubility, bioavailability, dissolution, nicardipine, Solid dispersion, cyclodextrin, kneading technique, solvent evaporation technique

DOI: 10.48047/ecb/2023.12.Si9.298

INTRODUCTION:

1.0: Bioavailability and Solubility:

The key factors that regulate the rate and amount of medication uptake in addition to its bioavailability have been explained thoroughly to include solubility, dissolution, and gut penetration.[1] A drug's ability to dissolve in water is a crucial characteristic that affects how well it is absorbed when taken orally. It also controls whether a medicine may be administered parenterally and is helpful for modifying and evaluating drug qualities while a drug is being designed and developed. Solubility of drug is an optimum metric, but when the dissolving time is constrained, it is crucial to consider the rate at which a drug liberates from a pharmaceutical formulation into solution. Low bioavailability is the main issue in the development of oral formulations. Water solubility, drug absorption, dissolving rate, first-pass metabolism, and sensitivity to outflow processes are some of the variables that affect absorption and bioavailability.[2] Poor solubility and inadequate permeability are the two most common factors responsible for poor bioavailability. Inadequate bioavailability is frequently caused by the low solubility and slow dissolution rate of weakly water-soluble medications in aqueous gastric fluid. Increases in the drug's solubility and rate of dissolving in gastric fluid, particularly for class II (poor solubility and high porosity) compounds, may improve bioavailability. Since solubility in the stomach fluid and liberation of drug from the pharmaceutical formulations are the rate-limiting steps for BCS class II medications rather than uptake, boosting solubility also improves the pharmacokinetics of BCS class II pharmaceuticals.

The drug's solubilization affects the drug's absorption or blood levels. A continuous process known as solubility comprises the solute particle migrating freely in solvent media. The degree of dispersion in fluid, accompanied with blood or plasma mobility, determines the biochemical and pharmacological action of a medicine. Today, the water solubility of 70 to 80 percent of drugs supplied by the healthcare companies is weak. This makes it difficult for the pharmaceutical business to implement new and innovative methodologies that can increase a drug's solubility. There are a few methods for increasing the solubility of medicinal molecules, however solid dispersion and cyclodextrin packed complex (kneading method) have special properties and are simpler to prepare.Therefore, in this research, a sample antihypertensive medication with low solubility (Nicardipine) was chosen, and its solubility was enhanced using the kneading approach with cyclodextrin (CD) and the solid dispersion (SD) approach by HPMC K15M using the solvent evaporation approach.

MATERIALS:

Analytical grade drugs and additives were procured for the experimental tests. Nicardipine was a free sample from Cipla Ltd. in Goa. While sodium hydroxide (NaOH), potassium dihydrogen phosphate (KH2PO4), beta-cyclodextrin, and hydroxy propyl methyl cellulose (HPMC K15M) were acquired from Hi-Media in Mumbai, the concentrated hydrochloric acid was procured from SD Fine Chemicals.

METHOD:

1. Solubility determination: Solubility is the greatest concentration of a medicine that can dissolve under typical test conditions. Testing for solubility was done using a conventional orbital shaker for 72 hours (Thomas Scientific). The limit on the amount of medication dissolved in each of three separate solvents' pH levels (1.2, 6.8 and 7.2) was determined spectrophotometrically (UV 1900i, SHIMADZU) [79].

2. Phase solubility study:

The phase solubility analysis performed using method by Higuchi and Connor [80]. Using a stability constant (Kc), the approach offers details about the stability and applicability of the medicine complexed with CD. The drug was permitted to be shaken closely for 72 hours while the CD mixture's concentration increased. The supernant liquid was gathered and spectrometrically examined (UV Visible Spectrometer; UV 1900i, SHIMADZU). Kc was calculated using the calibration graph and thus from the intrinsic solubility (So) of the pure medication.

3. Preparation of Cyclodextrin inclusion complex

CD and drug inclusion complex was made using method of kneading [81]. The CD was first dissolved in methyl alcohol with the medication added, and it was then mixed with a mortar. In a hot oven (Bionic Scientific) set at 50℃ for 30 minutes, different concentrations of kneaded complexes were also made (1:1, 1:2, 1:3, and 1:5). The compounds that were kneaded were kept in desiccators by Rolex Pvt. Ltd. for future use.

4. Drug content estimation

Estimating drug content reveals whether or not a drug with low solubility was successfully trapped in CD. This approach involves kneading an equal amount of CD into a complex that is then dissolved in 0.1 N HCl to test its solubility. The drug content calculated using the following formula [82].

Drug content (%) = (Practical value/Theoretical value) X 100

5. *In-Vitro* dissolution study

To determine the rate and release from the CD complex, a dissolution estimation is required [83]. In a dissolution 6 test equipment (Veego Tablet Dissolution Test Apparatus) (USP-Type 2), the produced compounds were mixed in appropriate buffer liquids. Occasionally, samples are gathered at specified intervals, absorption is evaluated at the drug's λ maximum, and the standard curve converts the results to the % of overall release profile.

6. Solid Dispersion by Solvent evaporation technique.

The medication and HPMC K15M were both dispersed in methyl alcohol and stored in a rotary vacuum evaporator set at 400°C to allow the solvent to evaporate. For future use, the dehydrated bulk was gathered and stored in a desiccator [84, 85].

RESULTS AND DISCUSSION

Table 1.0 : Solubility values of Nicardipine in different pH ranges

pH	Solubility(mg/ml)
1.2	15.357

6.8	5.252
7.2	4.269

The table 1.0 displayed the solubility (mg/ml) of Nicardipine in different pH (1.2, 6.8, 7.2). Nicardipine is a BCS class 2 drug and it needs improvement of solubility in biological buffer. Hence in further step, the suitability of CD in the project is ascertained by phase solubility study.

1. Phase solubility studies

Table 1.1: Concentration of Nicardipine goes to solution with respect to β-CD.

Sl.No.	Concentration of ß-CD (mM)	Drug concentration (mM)
1	1	0.017
2	3	0.021
3	6	0.028
4	9	0.031
5	12	0.038
6	15	0.046

In present work, complexation of nicardipine with β-CD was tried to enhance its solubility and dissolving rate. To explore the impact of amount of cyclodextrin on drug solubility, phase solubility studies were performed (Fig. No. 8). Solubility of nicardipine in water was improved proportional to the quantity of β-CD [89]. The phase solubility diagram of nicardipine β-CD complex can be classified as A_L type as per Higuchi and Connors. The rise in dissolution was brought about by the creation of a 1:1M complex since the linear model showed a slope that was below 1. The phase solubility slope yielded the expected stability constant (kc), which was discovered to be 149.32. The value of the Kc indicated that the nicardipine β-CD complex is quite stable. This also justifies that, β-CD would be suitable to form the binary kneaded inclusion complex [90, 91].

2. Preparation of drug-cyclodextrin binary mixture

Preparation of drug β-CD inclusion complex (kneading method)

- Four conc^n &drugs: carrier in ratios of 1:1, 1:2, 1:3, and 1:5 were utilized.
- The appropriate amount of cyclodextrin was solubilized in 30 mL of methyl alcohol and nicardipine was added gradually while stirring until a thick paste was formed.
- The paste was thoroughly kneaded and dehydrated.
- The resulting complex was sieved (80#) and preserved in desiccators.

Preparation of drug and β-CD physical mixtures

- A mortar was used to grind up a precise amount of the medication and the carrier according to their corresponding molar ratios.
- This was made using a method called geometric dilution.

3. Drug content estimation (Entrapment efficiency)

Table 1.3: Drug content estimation in Nicardipine loaded kneaded complex (KC) and physical mixture (PM)

DRUG: β-CD RATIO	**NICARDIPINE CONTENT %**	
	β-CD -PREPARATION	
	KC	**PM**
1:1	89.15	83.17
1:2	84.26	79.58
1:3	73.67	65.72
1:5	69.32	59.93

Drug content defines the successful entrapment and provides evidence on solubility enhancement of drugs with low solubility in presence of CD. The successful inclusion mass indicates maximum drug content (entrapment efficiency) [92].

A volumetric flask was filled with an accurate amount of kneaded complex as well as physical blends equal to 25 mg of nicardipine, which was then solubilized in a small portion of methyl alcohol.

The volume was then increased using 0.1 N HCl, followed by measurement of drug concentration with the help of a UV visible spectrometer at 238 nm.

Using kneading technique, solid β-CD complexes of NIC were generated in various molar ratios (1:1,1:2,1:3,1:5) by kneading method. Likewise physical mixtures were prepared in previous mentioned ratio. The percentages of drug content of all prepared complexes along with the physical mixtures were estimated. Result displayed that 1:1M complex have higher dug content of about 89.15%. This could be full amount of drug entrapped in the hydrophobic cavity of CD [93, 94]. The results were shown in table 6.4. It also can be seen that in both the cases (KC and PM), there is progressive increase in drug content. However, KC complex exhibited more drug as compared to PM [95]. It can be seen that as the amount of CD increased, the % drug content gradually decreased [96]. This can be concluded that, in 1:1 mass maximum amount of drug entrapped and saturated in the hydrophobic cavity of β-CD.

4. ***In-vitro* evaluation of Nicardipine- β-cd preparations**

Table1.4: Percentage cumulative drug release values of Nicardipine fromkneaded complex

Time (Min)	Pure drug dissolution (%)	Cumulative percentage drug release			
		Kneaded complex			
		1:1	1:2	1:3	1:5
0	0	0	0	0	0
15	24.19	84.89	74.39	72.05	73.17
30	36.26	85.78	79.52	78.69	75.17
45	43.12	89.93	82.64	81.42	79.75
60	49.28	92.21	90.59	89.65	83.86
75	57.28	94.65	93.67	91.24	87.26
90	63.18	96.11	94.48	89.72	82.75
105	67.91	100.65	97.92	94.75	86.28
120	70.25		98.49	91.75	87.75

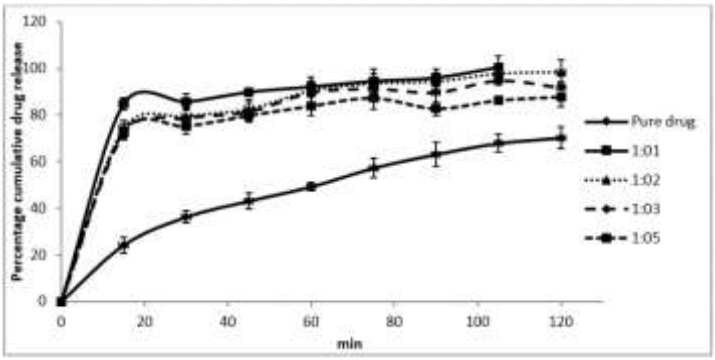

Figure 1.0: Comparative dissolution profile pure drug and kneaded complexes

Table 1.5: Percentage cumulative drug release values of Nicardipine from physical mixture

Time (Min)	Pure drug	Cumulative percentage drug release			
		Physical mixture			
		1:1	1:2	1:3	1:5
0	0	0	0	0	0
15	24.19	79.35	71.67	69.65	59.35
30	36.26	82.14	73.24	70.12	63.75
45	43.12	84.67	75.34	73.19	65.15
60	49.28	89.12	79.34	75.98	69.46
75	57.28	91.78	83.85	78.34	72.24

90	63.18	93.56	87.23	80.45	77.53
105	67.91	95.86	88.35	83.87	79.34
120	70.25	97.34	90.12	85.27	80.13
135	72.15	100.12			

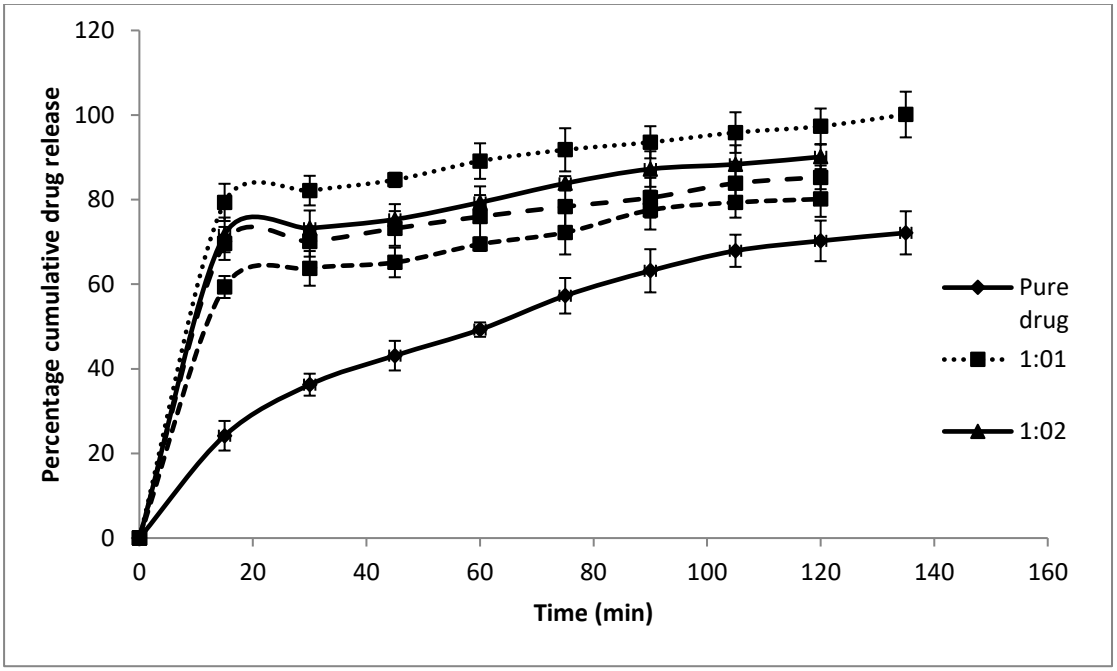

Figure 1.1: Comparative dissolution profile pure drug and physical mixtures.

5. Preparation of Solid dispersion

Preparation of drug-HPMC-K15M solid dispersions by Solvent evaporation method

- Four different drugs: carrier in ratios of 1:1, 1:2, 1:3, and 1:5 were utilized.
- The appropriate amount of HPMC-K15M was solubilized in methanol (30 ml) and nicardipine was added gradually while stirring.
- Solvent was removed by evaporation at 40 degree Celsius.
- The resulting solid dispersion was grinded, sieved (80#) and preserved in desiccators.

Preparation of drug - HPMC-K15M physical mixtures

The physical mixtures of nicardipine with HPMC-K15M were made by combining precisely measured amounts of the medication and carrier in the recommended ratios in a mortar and sifting using mesh no (80#).

6. Drug content estimation SD (Entrapment efficiency)

Drug content defines the successful entrapment and provides evidence on solubility enhancement of drugs with low solubility in presence of HPMC. The successful SD mass indicate maximum drug content (entrapment efficiency) [101].

A volumetric flask was filled with an accurate amount of kneaded complex as well as physical blends equal to 50 mg of nicardipine, which was then solubilized in a small portion of methyl alcohol. The volume was then increased using 0.1 N HCl, followed by measurement of the drug concentration with the help of a UV visible spectrometer at 269 nm.

Table 1.6: Drug content estimation in Nicardipine loaded in HPMC solid dispersion (KC) and physical mixture (PM)

DRUG: HPMC RATIO	NICARDIPINE CONTENT %	
	SD with HPMC	PM with HPMC
1:1	82.38	78.89

1:2	79.18	72.87
1:3	75.96	68.84
1:5	66.91	61.39

7. *In-vitro* evaluation of Nicardipine- SD

Table 1.7: Percentage cumulative drug release values of Nicardipine fromkneaded complex

Time (Min)	Pure drug dissolution (%)	Cumulative percentage drug release			
		Solid dispersion			
		1:1	1:2	1:3	1:5
0	0	0	0	0	0
15	24.19	81.98	71.73	69.24	65.76
30	36.26	82.96	73.36	71.64	67.64
45	43.12	86.84	77.65	73.85	69.76
60	49.28	88.36	81.65	77.26	73.18
75	57.28	91.24	85.67	80.25	76.96
90	63.18	94.75	88.14	83.19	80.29
105	67.91	97.14	91.86	88.57	81.18
120	70.25	101.75	92.87	89.14	84.28

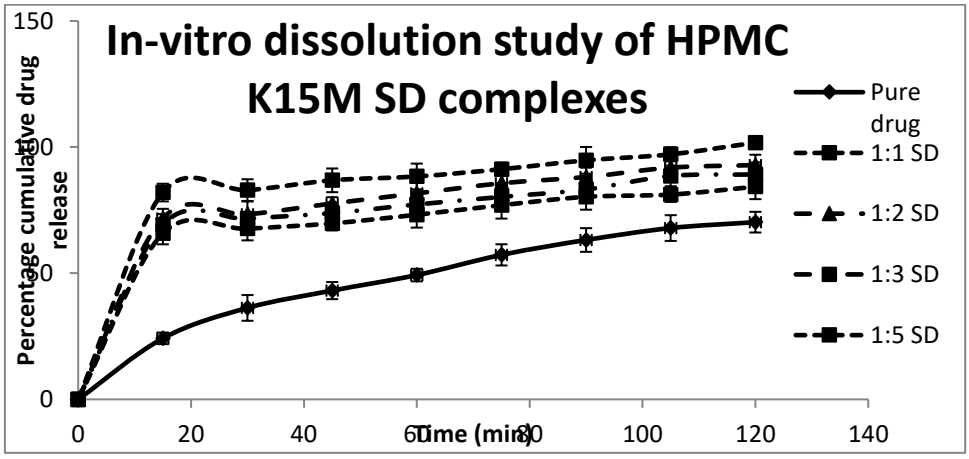

Figure 1.2: Comparative dissolution profile pure drug and SD complexes

Table 1.8: Percentage cumulative drug release values of Nicardipine from physical mixture

Time (Min)	Pure drug	Cumulative percentage drug release			
		Physical mixture with HPMC			
		1:1	1:2	1:3	1:5
0	0	0	0	0	0
15	24.19	78.28	69.38	65.17	56.45
30	36.26	81.97	71.67	67.64	59.34
45	43.12	83.19	73.27	71.75	63.56
60	49.28	85.73	77.18	73.23	68.46
75	57.28	87.19	81.49	77.43	72.97
90	63.18	89.45	85.38	81.34	76.34

105	67.91	93.17	88.13	85.23	76.97
120	70.25	95.46	90.12	86.12	77.23
135	72.15	99.28	93.75	87.45	79.92
150	73.13	100.86	97.12	90.98	81.41

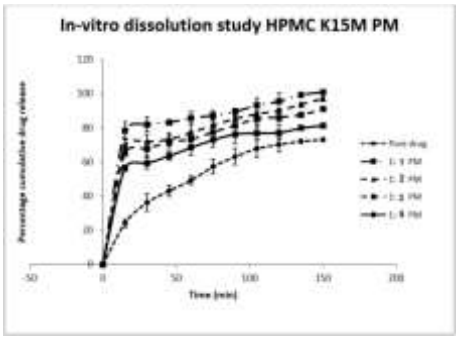

Figure 1.3: Comparative dissolution profile pure drug and physical mixtures in study of SD.

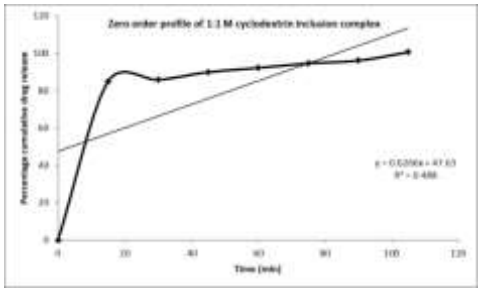

Figure 1.4: Zero order profile of 1:1 M cyclodextrin inclusion complex

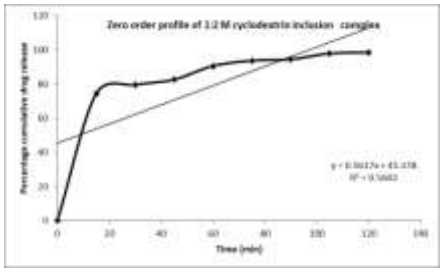

Figure 1.5: Zero order profile of 1:2 M cyclodextrin inclusion complex

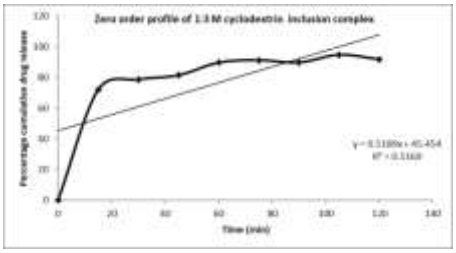

Figure 1.6: Zero order profile of 1:3 M cyclodextrin inclusion complex

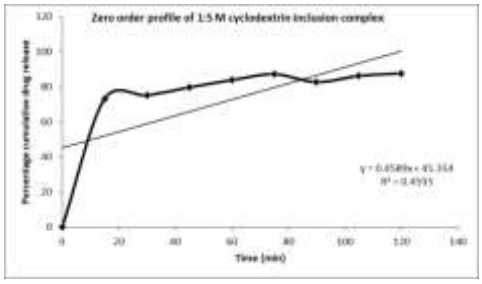

Figure 1.7: Zero order profile of 1:5 M cyclodextrin inclusion complex

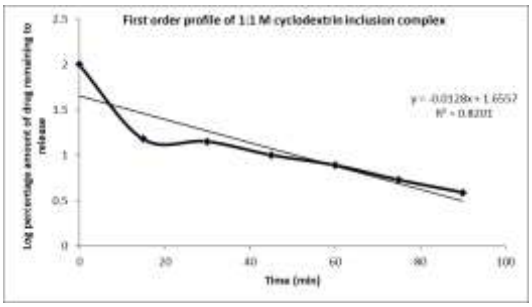

Figure 1.8: First order profile of 1:1 M cyclodextrin inclusion complex

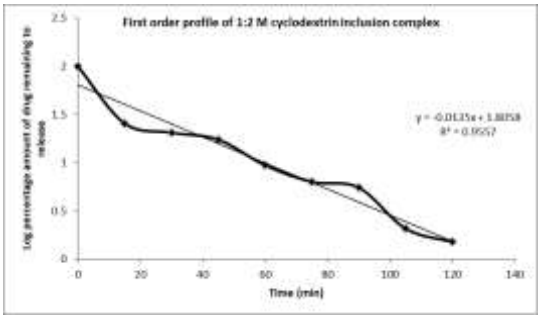

Figure 1.9:First order profile of 1:2 M cyclodextrin inclusion complex

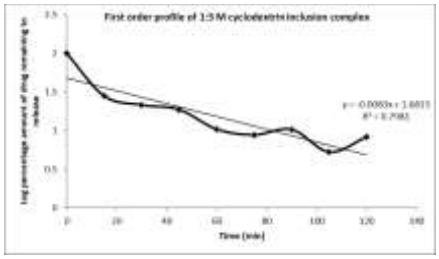

Figure 2.0: First order profile of 1:3 M cyclodextrin inclusion complex

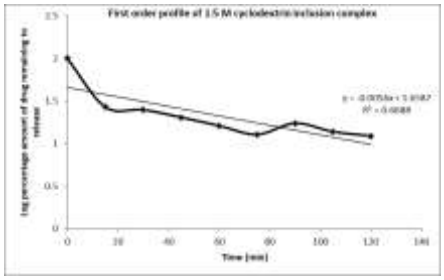

Figure 2.1: First order profile of 1:5 M cyclodextrin inclusion complex

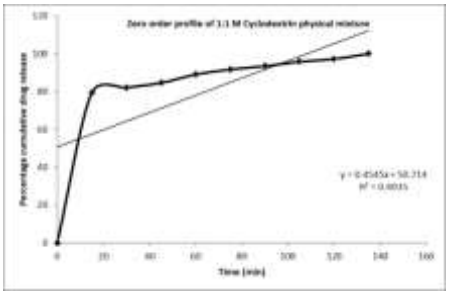

Figure 2.2: Zero order profile of 1:1 M Cyclodextrin physical mixture

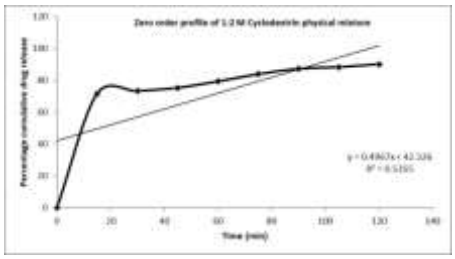

Figure 2.3: Zero order profile of 1:2 M Cyclodextrin physical mixture

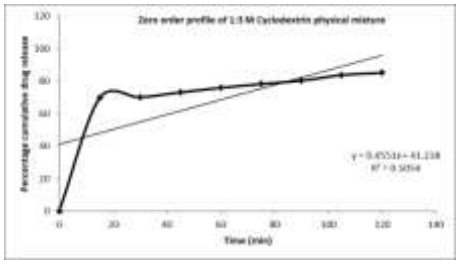

Figure 2.4: Zero order profile of 1:3 M Cyclodextrin physical mixture

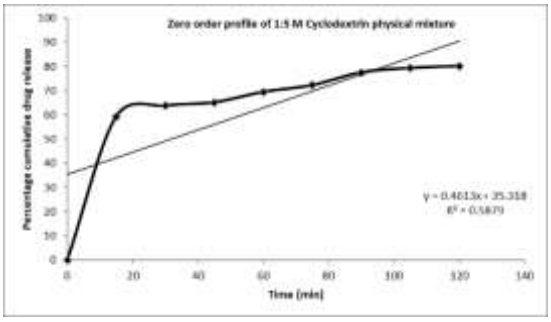

Figure 2.5:Zero order profile of 1:5 M Cyclodextrin physical mixture

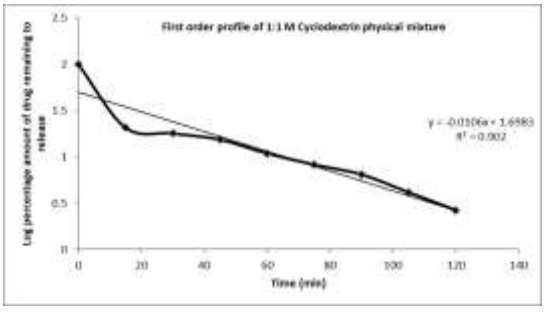

Figure 2.6:First order profile of 1:1 M Cyclodextrin physical mixture

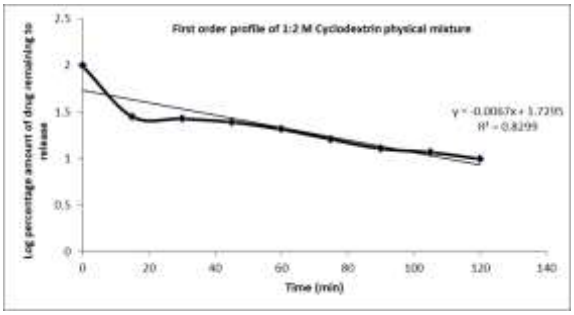

Figure 2.7:First order profile of 1:2 M Cyclodextrin physical mixture

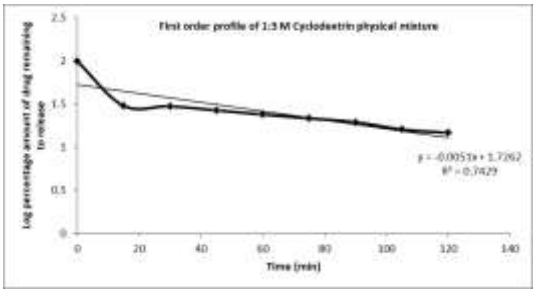

Figure 2.8:First order profile of 1:3 M Cyclodextrin physical mixture

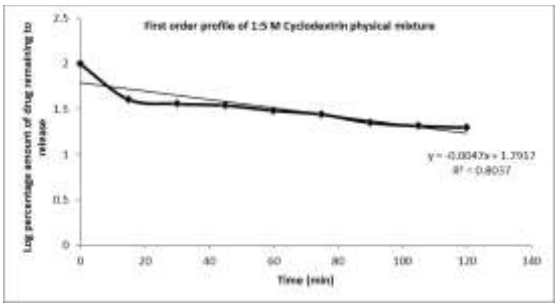

Figure 2.9: First order profile of 1:5 M Cyclodextrin physical mixture

Table 1.10: R^2 values of zero order and first order kinetics of Cyclodextrin treated

Cyclodextrin Inclusion	**Zero order**	**First Order**
1:1 M	0.488	0.82
1:2 M	0.56	0.955
1:3 M	0.516	0.798
1:5 M	0.459	0.668
Cyclodextrin physical mixture		
1:1 M	0.493	0.902
1:2 M	0.535	0.829
1:3 M	0.505	0.742
1:5 M	0.587	0.803

Table1.11: R^2 values of 0 order and 1st order kinetics of Cyclodextrin treated drug

HPMC K15M treated solid dispersion	Zero order	First Order
1:1 M	0.503	0.859
1:2 M	0.559	0.885
1:3 M	0.551	0.832
1:5 M	0.542	0.779
HPMC K15M treated physical mixture		
1:1 M	0.496	0.807
1:2 M	0.588	0.904
1:3 M	0.577	0.882
1:5 M	0.593	0.821

Discussion:

Pure nicardipine SD as well as a physical mixture were the subjects of dissolution tests utilizing USP paddle type equipment at 37 ± 0.5℃& 50rpm. The dissolution solvent employed was 0.1 N HCl in a volume of 900 ml. In order to deliver the equal amount of 30 mg of pure nicardipine at different time periods, the drug, SD, as well as physical mixture were deposited inside hard gelatin capsule casings. Five milliliters of the sample were then removed from a stable point of the container and substituted with new dissolution medium. The filtered sample's absorbance was measured at 238 nm. Calculations were made for the medication released at periodic times

Dissolution profiles of pure nicardipine, nicardipine HPMC K15M surface solid dispersions and physical mixtures were assessed. The overall percentage of drug release verses time are tabulated in table 6.8 and 6.9. A comparative dissolution profile of all produced solid dispersions as well as physical mixtures were established, displayed in fig no. (11,12). It has been demonstrated that barely 28% of the drug content dissolves within fifteen min, but 49.28% of the drug dissolves by 1 hour, as opposed to nicardipine HPMC K15M prepared by solvent evaporation technique in a 1:1 ratio. At 15 minutes, 81.98 % of drug was liberated and approximately 88.36 % was released seen after 60 minutes. As indicated in table 6.8, the dissolution rate of nicardipine was highly correlated with its relative concentration to the HPMC K15M proportion. Nicardipine's dissolving rate from solid dispersions rose when the amount of HPMC K15M was raised upto drug: carrier [103,104]. Dissolution rate lowered as HPMC K15M concentration was further increased. The leaking from the carrier while dissolving may generate a dense zone of solution surrounding the drug particles, restricting the diffusion of the liberated drug particles towards the bulk solution and decreasing the dissolving rate of solid dispersions with greater polymer percentages [105].

The release kinetics study was ascertained to findout the release mechanism of improvised soluble drug from Cyclodextrin inclusion and binary physical mixture complex. Zero order and first order kinetics plotted in 0.1 N HCl for specified duration of time (figure 6.7-6.22). The higher the R^2 value indicated the predominant mechanism of drug release from the prepared masses. In Table 6.10, in both inclusion and physical mixture it found higher value of R^2 (ranged from 0.79 to 0.95) in first order kinetic study, whereas comparatively less value found in zero order study. This confirms that, the solubilized drug released from both inclusion and physical mixture followed first order release study and ascertained amount of Cyclodextrin dependent proportionate drug (Nicardipine) release [108, 109].

The release kinetics study was ascertained to findout the release mechanism of improvised soluble drug from HPMC K15 loaded solid dispersion and binary physical mixture complex. Zero order and first order kinetics plotted in 0.1 N HCl for specified duration of time (figure 6.23-6.38). The higher the R^2 value indicated the predominant mechanism of drug release from the prepared masses. In Table 6.11, in both solid dispersion and physical mixture it found higher value of R^2 (ranged from 0.779 to 0.885) in first order kinetic study, where as comparatively less value found in zero order study. The same pattern also observed in HPMC K15M loaded physical mixture of R^2 ranged from 0.807 to 0.904. This confirms that, the solubilized drug released from both SD and physical mixture followed first order release study [110-112]. This provides evidence that Nicardipine release depends on concentration based HPMC K15M.

Summary and conclusion

The present work discussed about increasing the dissolution of an anti-hypertensive medication (Nicardipine), which has low solubility. The two most prevalent techniques, solid dispersion method using HPMC K15M and cyclodextrin (CD) complexation, were chosen. Previously, the stability constant was determined using the phase solubility technique described by Higuchi and Connor. The method supports the decision to use β-CD in the aforementioned complexation approach and justified the rise in dissolved drug content (mM) in comparison to β-CD. Complex made of CD with drug: β-CD ratio of 1:1, 1:2, 1:3 and 1:5. Result showed increased in drug content; maximum of 89.15% of solubilized drug. To demonstrate the effect of β-CD in solubility improvement technique, a physical mixture also prepared. It found still an increase in drug concentration of 83.17%; comparatively lesser than kneading method. Moreover, it showed 1:1 M only exhibited higher amount of drug as compared to remaining ratio of drug: β-CD. Those inclusion complexes subjected to *in-vitro* dissolution study in 0.1 N HCl and compared with pure drug. Result clearly exhibited higher quantity of dissolved drug in all complexes in comparison with pure drug and dependent on concentration of β-CD.

Likewise, solid dispersion of Nicardipine was created using the solvent evaporation method using HPMC K15M as a hydrophilic carrier. In comparison to pure drug, the weights of solid dispersion also exhibited higher dissolved drug (embedded weight). Additionally, solid dispersion as well as a physical mixture packed with HPMC K15M released drugs in a dose-dependent manner. It carefully observed that, at maximum amount of HPMC K15M the drug released comparatively less. This could be the formation of thick layer of polymer which hindered release of solubilized drug.

Future Work

The remaining approaches may be used in the future to improve the dissolution of the specified medicine with poor solubility, and comparisons could be done to determine which approach is optimal for use in prospective product design. It is possible to construct another few polymeric materials and dosage forms loaded with drugs, and to research the release pattern. The experiment solely uses in-vitro procedures; however, an animal model may also be used if the appropriate ethics approval for animals was obtained.

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