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FORMULATION DEVELOPMENT & *IN VITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF NEVIRAPINE CYCLODEXTRIN COMPLEXES

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ABSTRACT
Nevirapine is an Anti-retro viral agent using in the management of HIV diseases. It is very slightly soluble in water. In the present study attempt has been made to prepare and characterize inclusion complex of Nevirapine with β-Cyclodextrin. The phase solubility analysis indicated he formation of 1:1 molar inclusion complex of Nevirapine with β -CD. Apparent stability constant (Kc) was found o be 164.557 M^{-1}. The inclusion complexes prepared by different methods viz. Physical mixture and Solvent evaporation methods. The prepared complexes were characterized using FT-IR. Further, the inclusion complexes containing Nevirapine: β-Cyclodextrin (1:2) was formulated into immediate release tablets which are stable and enhancing in solubility and faster dissolution. For the development of Nevirapine tablets, the excipients selected were Starlac as diluents, Croscarmellose sodium and Sodium Starch Glycolate as super disintegrants, Microcrystalline cellulose (MCC) as binding agents, Aerosil as glidant, Magnesium Stearate as lubricant. The formulation blend was evaluated for Precompression studies and compressed tablets were evaluated for post compression studies and the results were found to be within the limits. The compatibility studies were performed which resulted in no interactions between drug and excipients.

KEYWORDS: Nevirapine, β-Cyclodextrin, Starlac, Croscarmellose sodium, Sodium starch glycolate

1. INTRODUCTION

Oral drug delivery is the simplest and easiest way of drug administration, because of the greater stability, lesser bulk, accurate dosage, cheaper cost of production and easy process, solid oral dosage forms have advantages over other dosage[1] forms. Infact, all the poorly water soluble drugs after oral administrations are not well absorbed. And thus leads to decreased inherent efficiency of drugs. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility[2] and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work. Solid dispersion, solvent deposition, micronization are some vital approaches routinely employed to enhance the solubility[3] of poorly water soluble drugs. Each approach suffers with some limitations and advantages. Among all, complexation technique has been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs.[4]

2. MATERIALS AND METHODS

2.1 Materials

Nevirapine β-Cyclodextrin, Sodium starch glycolate, Cross povidone, Sodium starch glycolate, Cross povidone, Croscarmellose sodium, MCCPH101, Starlac, Magnesium Stearate, Aerosil were obtained from Richer Pharmaceuticals Pvt Ltd, Hyderabad. All materials used were of analytical grade.

2.2 Method

2.2.1 Preparation of Inclusion Complexes With β-Cyclodextrin

2.2.1.1 Physical mixture: Nevirapine with β-CD in different molar ratios (i.e. 1:1M, 1:2M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccators over fused calcium chloride.

2.2.1.1 Solvent evaporation Method: Drug and cyclodextrin in different molar ratio are dissolved in a common solvent to get a clear solution. Mixed the both solutions than the clear solution was kept for stirring on a

magnetic stirrer till all the solvent got evaporated. The mass obtained was dried at 50°C and further sieved No. 80 or 100 sieve. The different ratios of Nevirapine and β-Cyclodextrin Complexes were mentioned in table.no.1.

2.2.2 Compression of Nevirapine -B-Cyclodextrin Inclusion Complexes into Immediate Release Tablets by Direct Compression Method.

After elucidation of best inclusion complex of drug with β-cyclodextrin which shows that the most satisfactory invitro dissolution criteria and better solubility criteria, the particular complex was formulated as Immediate Release Tablets of Nevirapine β-cyclodextrin Inclusion Complex by mixing it with selected excipients. In this present study, the best superdisintegrant among sodium starch glycolate (SSG), and croscarmellose sodium (CCS) were also screened out. Starlac selected as diluent, MCCPH101 as binder, Aerosil as glidant and Magnesium stearate selected as lubricant. The prepared inclusion complex of drug and excipients were passed through sieve (#60) and mixed thoroughly. The drug and excipients mixture was finally compressed after lubricating with magnesium stearate for 10 min. All batches were mentioned in table.no.2.

2.2.3 Evaluation of Bi-Hcl Inclusion Complexes

a) Physical Appearance: All batches of Nevirapine inclusion complexes were evaluated for the color and appearance.

b) Drug Content Estimation: Inclusion complexes prepared by physical mixture, kneading, and solvent evaporation methods were assayed for Bi-HCL content by dissolving a specific amount of the complexes (Drug Equivalent to 2mg) in methanol and analyzing for the Bi-HCL content spectrophotometrically at 258 nm on a spectrophotometer. The values were mentioned in the table.no.3.

c) *In vitro* dissolution studies for pure drug and its inclusion complexes: *In vitro* drug release studies for the pure Nevirapine and prepared inclusion complexes were conducted in USP II paddle type dissolution apparatus in 500ml of medium at 37 ± 0.5 ^{0}C and at 50 rpm speed. The dissolution studies were carried out in 0.1N HCl. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 258 nm by a UV – visible spectrophotometer. The amount of drug released in the samples were calculated and mentioned in the table.no.4.

d) Drug- Excipients Interaction studies by FTIR Spectroscopy: Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40 ^{0}C/75% RH. Control samples were stored at 4 ^{0}C. The ratio of drug to excipient was 1:1 and samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 4 ^{0}C for 7, 14 and 30days. Chemical stability was confirmed by FTIR spectrophotometry.

2.2.4 Evaluation of Post Compression Characteristics of Tablets

A. Weight variation test: Twenty tablets were selected randomly, weighed individually and average weight was calculated. Not more than two of the individual weights was deviated from the average weight by more than the percentage shown in the table and should deviate by more than twice that percentage.

B. Hardness test: The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto tablet hardness tester. The tablet was held between the edges of the fixed and movable part of the instrument. The scale was adjusted by sliding, so that the zero on the scale coincides with the pointer. The adjustable knob was moved slowly till the tablet breaks. The hardness was measured in kg/cm$^{2.}$

C. Thickness: The thickness of prepared tablets was measured, by placing the tablet between the hands of vernier calipers and the thickness of the tablet is read from the vernier scale.

D. Friability: Friability is the measure of tablet strength. About 10 tablets were carefully dedusted and weighed. The tablets were placed in friability test apparatus and rotated 100 times at 25 rpm for 4mins. The tablets were removed, dedusted and weighed. The percent friability was calculated using the formula.

E. Disintegration Time (DT): The disintegrator as per USP uses 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. The disintegration time was determined by the tablet is placed in each tube, and the basket rack is positioned 0.1N HCl at 37 ± 2 ^{0}C, such that the tablets remain 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A standard motor device is used to move the basket assembly containing the tables up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Then the time was measured, when all the particles passed through the 10-mesh.

F. Drug content uniformity: From each batch 20 randomly selected tablets were weighed accurately and powdered in a clean and dry glass mortar with pestle. Powder equivalent to 2 mg of drug was transferred into 20 mL volumetric flask containing methanol gives 100 µg/ml solution (Stock-1).from the stock-1 4 µg/ml solution was prepared by taking 0.4 ml of stock-1 and make up to 10ml with methanol. The absorbance of 0.4

µg/ml solution was measured at 258 nm, using methanol as a blank.

G. Wetting time: Wetting time of tablet was determined using a simple procedure. A piece of double folded tissue paper was placed in a petri plate containing 6 ml of water and 2 drops of eosin. The tablet was placed on the paper and the time for complete wetting of upper surface of the tablet was measured in seconds.

H. Dissolution studies: *In vitro* drug release studies for the prepared Bi-HCL tablets were conducted in USP II paddle type dissolution apparatus in 500ml of medium at 37 ± 0.5 ^{0}C and at 50 rpm speed. The dissolution studies were carried out in 0.1N HCl. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 258 nm by a UV–visible spectrophotometer. The amount of drug present in the samples was calculated.

3. Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied making a KBr disc. The characteristic absorption peaks of Nevirapine were obtained at different wave numbers in different samples. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

4. DISCUSSION

In the present work inclusion complexes of Nevirapine were prepared with β-cyclodextrin by physical mixture and Solvent evaporation method. The complexes were prepared in different molar ratios of drug and cyclodextrin namely 1:1 and 1:2. The prepared complexes were characterized by Fourier transform infrared spectroscopy (FT -IR). Prepared complexes were evaluated for *In vitro* drug release studies. All the prepared inclusion complexes were white and fine without any stickiness. The drug content of the inclusion complexes was quite uniform. The percent drug content of the complexes was found to be in the range of 98.35% to 102.493%. with low values of standard deviations. *In-vitro* dissolution studies for pure Nevirapine and inclusion complexes prepared were carried out in 500 ml of 0.1N HCL using USP II paddle type dissolution apparatus. The dissolution data of Nevirapine, Nevirapine -β-CD systems are given in Table 7.5.Figure 7.5 shows the dissolution rate profiles of pure Nevirapine and prepared inclusion complexes prepared by physical and Solvent evaporation methods. It is evident that the complex prepared by all methods exhibited a faster dissolution when compared to pure drug dissolution data. The dissolution rate of Nevirapine from various inclusion complexes was found to be 80.02% to 84.46% in 60 minutes, when compared to pure drug which exhibited only 29.09% of drug in 60 minutes. The dissolution data of various complexes prepared by various methods were fitted into mathematical models such as zero order and first order models to assess the kinetics. The dissolution data for inclusion complexes obeyed first order kinetic model. Inclusion complexes of Nevirapine prepared with β-CD exhibited release of 80.02%, 84.62%, 82.02% and 84.46% from NP1, NP2 & NS1 and NS2 respectively in 60 minutes, using 0.1N HCL as dissolution media. A marked improvement in dissolution rates of Nevirapine were observed with NS2 prepared by Solvent evaporation method. The higher dissolution rates observed with inclusion complexes prepared by kneading may be due to better interaction of drug and β-cyclodextrin.

The Nevirapine Tablets prepared by direct compression method containing NS2 inclusion complexes (drug: β-cyclodextrin ratio is 1:2 and the complex was prepared by Solvent evaporation method) were evaluated for their physical characteristics like size, shape, thickness and appearance and from this data all series of Tablets prepared were found to be good. The hardness of the Nevirapine Tablets is 3.22±0.12 to 3.4±0.86kg/cm^2. The disintegration time of Tablets is in between 18 to 34 sec. the friability percentage and weight variation and wetting time of all the Tablets were found within the standard limits. The dissolution of Nevirapine Tablets prepared with NS2 complex and super disintegrants was higher when compared with Nevirapine Tablets prepared without super disintegrants. In this present study I have also evaluated the effect of various super disintegrants on dissolution profile, Disintegration time and wetting time of Nevirapine Tablets and it was found that the presence of SSG shown better results when compared with CCS. The increased concentration of SSG showed improved dissolution criteria along with faster disintegration and wetting time. Formulation F4 containing 7.5% of SSG (when compared with total Tablet weight) showed 99.62% drug release in 60minutes. The dissolution data of Nevirapine Tablets were fitted into mathematical models such as zero order and firs order models to assess the release kinetics. The dissolution data for all 4 formulations (F1 to F4) follows first order release kinetics. To ascertain the mechanism of drug release the data was subjected to first order and zero order equations.

Table 1: Nevirapine, β-Cyclodextrin Complexes.

Method	Drug to Carrier	Drug to Carrier ratio	Formulation Code
Physical Mixture	Nevirapine: β-CD	1:1	NP1
	Nevirapine: β-CD	1:2	NP2
Kneading Method	Nevirapine: β-CD	1:1	NK1
	Nevirapine: β-CD	1:2	NK2
Solvent evaporation method	Nevirapine: β-CD	1:1	NS1
	Nevirapine: β-CD	1:2	NS2

Table 2: Batches prepared for screening of superdisintegrant.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Nevirapine	-	-	-	-	-	-	-	**2**
2	Complexed drug (Nevirapine: β-CD)	5.89	5.89	5.89	5.89	5.89	5.89	5.89	-
3	Starlac	68.51	66.01	66.01	66.01	63.51	61.01	58.51	67.6
4	MCCPH101	20	20	20	20	20	20	20	20
5	SSG	-	2.5						-
6	Crospovidone	-	-	2.5	-	5	7.5	10	-
7	CCS	-	-	-	2.5				4.8
8	Mag. Stearate	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
9	Talc	2	2	2	2	2	2	2	2
	Total Wt	100	100	100	100	100	100	100	100

Table 3: Drug content of complexes is mentioned in the table.

S.No	Complexation method	Drug: cyclodextrin Ratio	Complex Code	Amount of drug present in 2mg Equivalent powder	% Drug content
1	Physical Mixture Method	1:1	NP1	2.02	101
		1:2	NP2	1.967	98.35
2	Kneading Method	1:1	NK1	2.044	102.2
		1:2	NK2	1.988	99.4
3	Solvent Evaporation Method	1:1	NS1	2.002	101.1
		1:2	NS2	2.04	102

Table 4: Comparison of In-vitro dissolution data of all formulations.

Time (min)	% CDR						
	PURE DRUG	NP1	NP2	NK1	NK2	NS1	NS2
0	0	0	0	0	0	0	0
5	6.52322	36.5778	39.6516	42.0423	53.6543	38.9685	47.8483
10	20.5479	55.3620	58.4357	58.4357	74.1461	56.3866	56.0450
15	25	59.8019	63.5587	76.1953	82.3429	72.4385	77.2199
30	26.0274	62.1926	78.2445	82.0013	85.4166	76.5368	79.2691
45	27.7397	74.1461	81.3183	83.3674	90.8811	80.2937	82.6844
60	28.0821	79.6106	83.3674	86.0997	93.9549	82.0013	87.4658

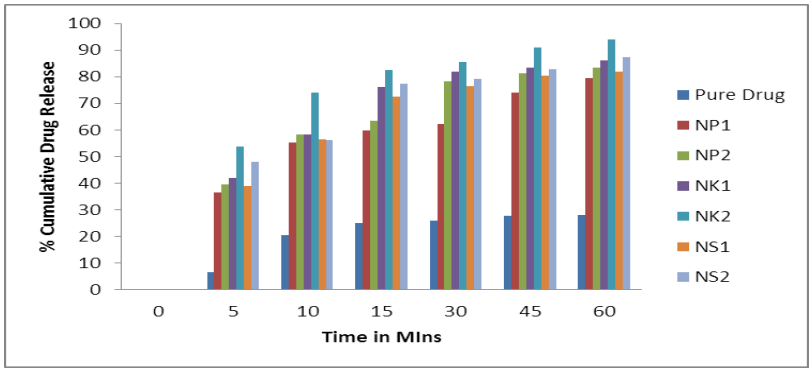

Fig 1: Dissolution Rate Data Profile graph of Nevirapine and its complexes.

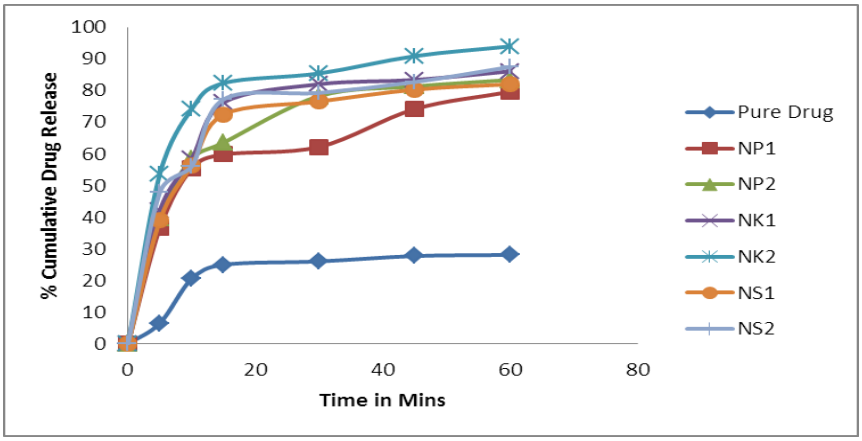

Figure 2: Zero Order plots of Nevirapine and Its Complexes in 0.1 N HCL.

Table 4: Results of pre-compression parameters of tablet blend

Formulation code	F1	F2	F3	F4	F5	F6	F7
Angle of repose(Degree) (Avg±S.D)	33.61± 0.923	32.28± 0.395	32.55± 0.596	33.21± 0.602	33.45± 0.4	31.08± 0.78	32.48± 0.39
BulkDensity(gm/cm$^{3)}$ (Avg±S.D)	0.563± 0.0097	0.553± 0.0069	0.565 ±0.004	0.572± 0.0034	0.574 ± 0.006	0.572 ± 0.007	0.563± 0.0069
Tapped density (gm/cm$^{3)}$ (Avg±S.D)	0.627 ± 0.004	0.635 ± 0.0046	0.646 ± 0.0046	0.651 ± 0.0046	0.660± 0.005	0.663± 0.007	0.625± 0.0046
Compressibility index	13.20	12.91	12.53	11.82	12.63	12.20	13.19
Hausner's ratio	.113	1.148	1.143	1.134	1.14	1.15	1.158

* Values are mean ± SD, n=3.

Table 6: Results of Post-compression parameters.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Hardness(kg/force/m m$^{2)}$(avg ±S.D)	3.46± 0.0577	3.23± 0.0577	3.26± 0.057	3.3± 0.057	3.33± 0.057	3.23±0.11 5	3.23± 0.0577	3.26± 0.057
Thickness (mm) (avg ±S.D)	2.513± 0.0057	2.503± 0.0057	2.513± 0.0057	2.513± 0.0057	2.513± 0.0057	2.513±0.0 057	2.503± 0.0057	2.513± 0.0057
Friability % (avg ±S.D)	0.497± 0.0995	0.231± 0.0571	0.264± 0.0577	0.069± 0.00579	0.231± 0.151	0.296± 0.25	0.231± 0.0571	0.264± 0.0577
Weight variation (gm)(avg ±S.D)	100.55 ± 2.459	100.15 ± 1.773	99.95 ±1.848	99.8 ± 1.794	100.3 ± 1.719	99.8 ± 1.609	100.15 ± 1.77	99.95 ± 1.848
Wetting Time (Sec) (avg ±S.D)	38± 1.123432	24± 0.3245	28± 0.674302	29± 0.126242	18± 0.428645	10± 0.224322	22± 0.3245	28± 0.674302
Disintegration time(Sec) (avg ±S.D)	43± 0.965445	27± 0.624536	32± 0.524238	33± 0.864042	19± 0.964246	16± 0.452678	15± 0.624536	20± 0.524238
% Drug content (avg ±S.D)	101.35± 008425	99.78± 0.065428	99.89± 0.041286	101.54± 0.126422	100.62± 0.102264	100.62± 0.102264	99.97± 0.065428	99.8± 0.081286

Table 7: Dissolution profile for all formulations.

Time (Min)	Cumulative % Drug Release of Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	**0**	0	0
5	53.9959	55.36202	54.33743	54.33743	56.38661	56.04508	56.72814	7.206284
10	70.7308	73.80464	72.43852	71.0724	74.82923	76.19536	75.5123	23.9726
15	82.6844	86.09973	84.05055	83.36749	87.46585	87.80738	88.83197	27.39726
30	84.7331	89.1735	86.09973	85.07514	94.29645	94.97951	95.32104	39.0411
45	87.8073	92.24727	88.83197	89.1735	95.66257	96.68716	96.0041	42.12329
60	92.9303	95.32104	94.29645	93.61339	96.34563	98.73634	97.02869	46.23288

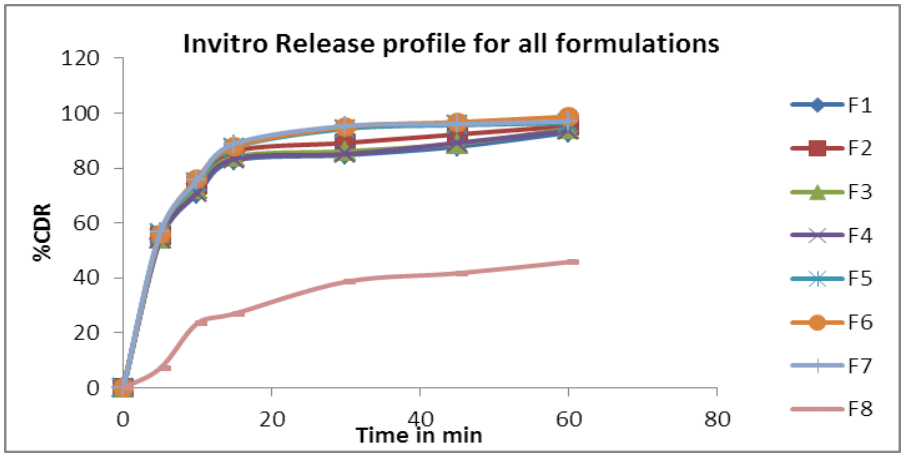

Fig 3: Zero order release Plots for all formulations.

SUMMARY AND CONCLUSION

In the present work, studies were carried out on design, formulation development and evaluation of immediate release tablets of Nevirapine inclusion complex with a view to improve its aqueous solubility, dissolution rate and oral bioavailability. The inclusion complexes of Nevirapine were prepared with β-cyclodextrin by physical mixture and solvent evaporation method. The complexes were prepared in different molar ratios of drug and β-cyclodextrin namely 1:1M, 1:2M with β-cyclodextrin.

The phase solubility diagram for the complex formation between Nevirapine and β-cyclodextrin in water are AL type. Phase solubility diagram of Nevirapine with β-cyclodextrin illustrate the solubility enhancement capacity of cyclodextrin. The aqueous solubility of Nevirapine increased linearly (R2=0.989) as the function of β-cyclodextrin concentration. The stability constant "Kc" was found to be 164.557M-1. In vitro dissolution studies for pure drug and inclusion complexes and prepared tablets were carried out in 500 ml of 0.1N HCL using USP II paddle type dissolution apparatus. It is evident that the complex and tablets prepared were exhibited a faster dissolution when compared to pure drug dissolution data. A marked improvement in the dissolution rates observed with BS2 prepared by Solvent evaporation method. The higher dissolution rates observed with inclusion complexes and tablets prepared by Kneading may be due to better interaction of drug β-cyclodextrin. The prepared complexes were characterized by FT-IR Studies and observed that there was no significant change observed.

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