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Formulation and Characterization of Extended-Release Nevirapine Solid Dispersions Running Title: Extended Release Nevirapine Solid Dispersions

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Abstract:- The bioavailability of a drug is usually determined by its aqueous solubility and lipid permeability. Nevirapine is an antiretroviral drug that belongs to the BCS II with poor solubility but high permeability. This study was carried out to improve the dissolution of nevirapine and also to formulate extended-release nevirapine tablets. Nevirapine: PEG 4000 were combined in different ratios to produce physical mixtures and solid dispersions. Micromeritics studies were carried out on the particles of the solid dispersions and the physical mixtures. These physical mixtures and solid dispersions were then compressed into tablets. Micromeritic studies showed that the particles had fair to poor flow qualities, particle sizes were between 0 -20 µm. Organoleptic results showed round white tablets. The formulated tablets and the commercial brand passed the hardness test, PM1 and SD1only failed the friability tests. PM1 and the commercial brand displayed properties of an immediate-release tablet with disintegration times below 15 minutes and all drugs were released before 2 hours. Dissolution efficiency showed that the solid dispersion tablets with the highest concentration of polymer had the best DE. Compared with the physical mixture counterpart, the solid dispersions had a better dissolution and drug release. The PEG 4000 helped in extending the release of nevirapine drugs as seen by the extended-release of the nevirapine: PEG 4000 batches and the solid dispersion technique improved nevirapine dissolution.

Keywords:- *Nevirapine, dissolution, PEG 4000, solid dispersion, extended-release, physical mixtures, dissolution efficiency, dissolution profiles, polymer.*

I. INTRODUCTION

For a drug to be bioavailable, it has to be soluble in the body fluids and permeable to pass through the biological membrane lining[1]. Many drugs have been abandoned due to their poor aqueous solubility even though they have been proven to be therapeutically beneficial [2]. Several methods have been used to improve the solubility of drugs, for example, formulating with surfactants [3], using nanoparticles for drug delivery[4], use of liquid-solid compacts [5], using cyclodextrins, micelles [6], micro and nanoemulsions [7], liposomes [8], micronization [9], use of solid dispersions [2, 10, 11] etc. Solid dispersion has been described as the solid-state dispersion of one or more insoluble active ingredients in a hydrophilic carrier or matrix[10, 12]. It can be prepared by the melting method (fusion), solvent evaporation or melting solvent method. The idea is that the dispersed drug in the hydrophilic matrix easily dissolves in the gastrointestinal fluid unlike when in the natural drug form [10]. As the techniques in solid dispersion have improved so also the hydrophilic materials have been versatile ranging from crystalline sugar and urea to amorphous materials and polymers also with the addition of surfactants [10]. Extended drug release systems allow drugs to be released for a longer length of time. They are useful for increasing patient compliance with therapy, boosting the medicine's therapeutic benefits [13]and reducing side effects due to more consistent than fluctuating drug plasma levels [14]. Extended drug release formulation can be achieved by utilising different polymers, altering polymer end groups, incorporating other additives, manipulating the formulation technique etc [13].

Nevirapine is the first discovered non-nucleoside reverse transcriptase inhibitor (NNRTI) that is used in conjunction with nucleoside analogues to treat HIV-1 infection and AIDS [15]. It is a chemical compound that belongs to the dipyridodiazepinone family [16] and it belongs to the Biopharmaceutical classification system (BCS) II with poor aqueous solubility and a high degree of permeability. After oral administration, the peak plasma concentration is reached within 2 hours of administration [17]. It works by directly binding to reverse transcriptase (RT) and preventing RNA-dependent and DNA-dependent DNA polymerase activities by disrupting the enzyme's catalytic site. Nevirapine's activity does not compete with nucleoside triphosphates [18]. This study aimed to formulate extended-release nevirapine tablets with PEG 4000 in varying ratios using physical mixtures and solid dispersion methods and to compare the enhancement of nevirapine dissolution between the tablets made from physical mixtures and the tablets made from solid dispersions.

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II. MATERIALS AND METHOD

Nevirapine, Microcrystalline cellulose (from Qualikems, India), Lactose (Kermel, China), Sodium lauryl sulphate (LobaChem, India), Aerosil, PEG 4000, Magnesium stearate (Legend Industries, India), n-hexane (JHD, India) Ethanol (JHD, China), Hydrochloric acid (LobaChem, India).

A. *Preparation of Physical Mixtures*

Nevirapine was mixed with PEG 4000 at various ratios as shown in Table 1 in a mortar for about an hour with continual trituration.

B. *Preparation of Solid Dispersion by Kneading Method*

Nevirapine: PEG 4000 dispersions were made at the ratios shown in Table 1. A weighed amount of medicine and carrier (Nevirapine and PEG 4000 respectively) was put in a mortar and triturated for 10 minutes using a pestle. A little amount of 50% alcohol was added to the mortar and the mixture was triturated until the 50% alcohol had evaporated. After that, a screen was used to filter the dry dispersion.

C. *Formulation of Nevirapine Tablets*

The remaining excipients – microcrystalline cellulose and lactose – were added to each of the physical mixtures and solid dispersions batches mixtures in the proportions specified in Table 2 and mixed using a mortar. Magnesium stearate was added to each batch just before compression with a punching machine to make spherical tablets.

D. *Preliminary Tests*

- *Test for compatibility:* The possibility of any interaction between the drug and the carriers during the preparation of the physical mixtures and solid dispersion was assessed by carrying out Fourier transform infrared spectroscopy (FTIR) of drug and polymer alone (Nevirapine alone and PEG 4000 alone) as well as for the combination of drug and polymer.
- *Evalutaion of Powder Properties:* The optical microscopy approach was used to examine the particle size of each of the batches. Bulk, tapped and particle density, Hausner's quotient, Carr's index, flow rate and angle of repose of each batch were analysed using described methods [19].

E. *Evaluation of Tablet Properties*

Organoleptic tests, weight uniformity tests, hardness tests, friability tests, and disintegration tests were done using previously described methods [19].

F. *Dissolution Tests*

The paddle dissolution apparatus (Erweka DT 600, Germany) was used for the dissolution test at a speed of 50 rpm and a temperature of 37 ± 0.5 ºC. The dissolution fluid was 900 mL of 0.1 N HCl. At intervals of 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, 360, 420, and 480 minutes, 5 mL of the dissolution medium was withdrawn and replaced each time with 5 mL of the pure dissolution medium. The withdrawn samples were filtered using a Whatman 110 mm filter paper. The filtrates were assayed using a UV spectrophotometer (6405 UV Jenway) at a wavelength of 258 nm.

Method of Preparation	Drug to Carrier	Drug to Carrier Ratio	Batch
Physical Mixtures	NEV: PEG 4000	1:0	PM1
	NEV: PEG 4000	1:0.5	PM2
	NEV: PEG 4000	1:1	PM3
	NEV: PEG 4000	1:2	PM4
Solid Dispersion	NEV: PEG 4000	1:0.5	SD1
	NEV: PEG 4000	1:1	SD2
	NEV: PEG 4000	1:2	SD3

Tale 1: Drug To Carrier Ratio Of Nevirapine And Peg 4000

NEV = Nevirapine , PEG 4000 = Polyethylene glycol 4000

Batches/ Ingredients	PM 1 (mg)	PM 2 (mg)	PM 3 (mg)	PM 4 (mg)	SD 1 (mg)	SD 2 (mg)	SD 3 (mg)
Nevirapine	72	72	72	72	72	72	72
PEG 4000	-	36	72	144	36	72	144
Lactose (qs)	250	250	250	250	250	250	250
MCC	25	25	25	25	25	25	25
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil	3	3	3	3	3	3	3

Table 2: Formulation Code For Physical Mixtures And Nevirapine Solid Dispersions Tablets

A. *Analysis of Data*

- Statistical analysis: Microsoft Excel Lte and GraphPad Prism version 6 were used for ANOVA tests. A p–value of ≤ 0.05 was considered significant.
- The area under the curve (AUC): This was calculated for using the Excel add-in DD-solver version 1 software. AUC can be calculated using the trapezoidal method thus:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 t_i - 1)(y_i - 1 + y_i)}{2} \quad (1)$$

t_i = i^{th} time point and y_i is the percentage dissolution of the product at time =t_i

- Dissolution efficiency (DE): This is determined using the area under the dissolution curve to a specific time (t) and is denoted as the size of the rectangle represented by 100% dissolution in the same period (t). The trapezoidal equation below can be used but, in this study, we used the Excel add-in DD-solver version 1 software [3, 20, 21] to calculate DE.

$$DE = \frac{\int_{t1}^{t2} y.dt}{y_{100}(t_2 - t_1)} * 100\% \quad (2)$$

y = percentage dissolution of the product , t_1 and t_2 = 2 different time points.

III. RESULTS AND DISCUSSION

A. Preliminary analysis

The FTIR and DSC showed that the active drug and polymer were compatible. As seen in Figures 1, 2 and 3.

Fig. 1: FTIR analysis of nevirapine pure sample

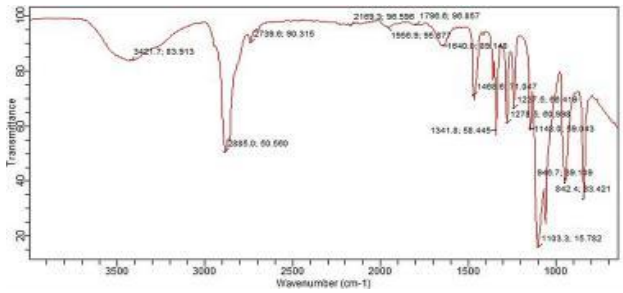

Fig. 2: FTIR analysis of PEG 4000

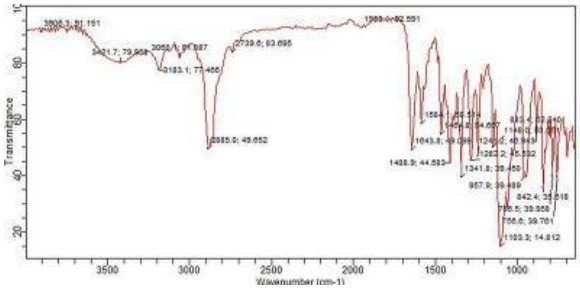

Fig. 3.FTIR of Nevirapine and PEG 4000 in a ratio of 1:1

B. Powder Properties

Figure 4 shows the solid dispersions (SD1-SD3) had the most particles within 10 m, but the physical mixtures had more particles within the greater particle range of 120 -160 m, even though a one-way ANOVA at $p > 0.05$ revealed no significant variation in particle sizes across batches.

The granule particle size is an essential feature that can impact the compression and compaction qualities of tablets, as well as their bioavailability [22, 23]. The particle size range of 120 -160 µm had more physical mixtures than the solid dispersions meaning that the solid dispersions had more fines and were of smaller particles (0 – 20 µm), which belongs to the group of fine powders. This correlates with previous literature which has stated that solid dispersions yield smaller particle sizes [24, 25]. This shows the technology of solid dispersion reduces the particle size more than using physical mixtures of a drug. It has been shown that micronization of powder particles improves the dissolution of medications [25].

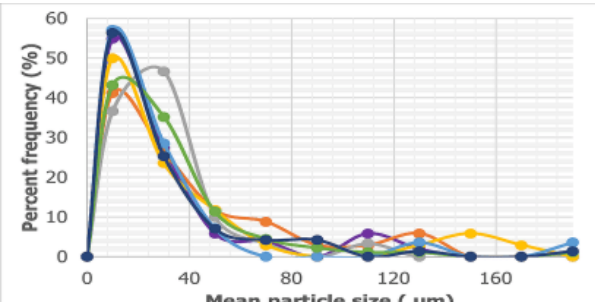

Fig. 4.Particle size analysis of the different batches of tablet

BATCH	BULK DENSITY (mg/ml)	TAPPED DENSITY (mg/ml)	HAUSNER'S RATIO	CARR'S INDEX	TRUE DENSITY (mg/ml)
PM 1	0.500 ± 0.013 a	0.537 ± 0.032 a	1.073 ± 0.044 a	25.850 ± 3.875 a	2.192 ± 0.020 a
PM 2	0.537 ± 0.032 a	0.883 ± 0.044 a	1.652 ± 0.160 a	39.074 ±5.836b	2.198 ± 0.312 a
PM 3	0.526± 0.020 a	0.909± 0.015 a	1.727 ± 0.042a	42.105±1.44 b	3.465 ± 0.808 a
PM 4	0.577 ± 0.019 a	0.812 ± 0.037 a	1.408 ± 0.096 a	28.758 ± 4.935a	1.819 ± 0.227 a
SD 1	0.583 ± 0.020 a	0.733 ± 0.032 a	1.258 ± 0.084 a	20.289 ± 5.287 c	2.889 ± 0.970 a
SD 2	0.551 ± 0.009 a	0.750 ± 0.016 a	1.363 ± 0.026 a	26.602 ± 1.437 a	2.381 ± 0.289 a
SD 3	0.566 ± 0.019 a	0.674 ± 0.013 a	1.192 ± 0.055 a	15.959 ± 3.889 d	2.174 ± 0.207 a

Table 3: Physicochemical and flow properties of different batches of nevirapine granules

a, b, c, d = Tukey post hoc test across the rows after a one-way ANOVA.

Table 3 shows that apart from Carr's index that shows differences between some batches all other physicochemical characteristics of the batches were not significantly different. The physicochemical parameters of the granules are not significantly different, as shown in Table 3. The Hausner's ratio and the Carr's index, which represent granule flowability[26] were better for the solid dispersions than the physical mixtures, with Batch SD3 having the best flowability. The SDs had lower particle sizes, which gave them superior flowability, according to the particle size study. This is consistent with prior research, which has demonstrated that smaller particles flow better [27]. Poor flow property is indicated by a Carr's index of more than 20 and a Hausner's ratio greater than 1.25[26]. The high Hausner's ratio and Carr's index, of all the granules, show that they did not have adequate flow properties.

C. Tablet Evaluation

The formulated tablets were spherical, white, and odourless. The results of the tablet quality test are shown in Table 4. The strength of the commercial brand utilised was different. Apart from the disintegration time, none of the other parameters was significantly different from the commercial tablet. Modified release tablets are designed to disintegrate gradually, either to produce delayed and prolonged dissolution in the GI tract or to achieve selective absorption across the GI tract [28] Looking at Table 4, it can be seen that all of the tablets had a disintegration time of more than 15 minutes and less than 2 hours, except Batch PM1 and commercial brand, which had a disintegration time of less than 15 minutes (which is within the limit for an immediate release tablet). The PM1 and commercial brand's quick disintegration time might be due to the lack of PEG 4000 in their composition, resulting in a shorter disintegration period. Smaller particles take longer to swell than bigger particles, which has a direct impact on disintegration time, with slower disintegration observed in powder beds with smaller particles, especially if the powder bed is polydisperse rather than monodispersed [28]. The crushing strength of the tablets does not differ significantly. The crushing strength test, which has a limit of 4 -8 KgF, was passed by all batches.

D. Drug Release Profile

Figures 5–7 demonstrate that the batches of tablets without PEG 4000 (PM 1 and the commercial brand) had an instantaneous release, but the other batches had drug release that lasted more than 2 hours. Among the solid dispersions, SD3 with the most PEG 4000 had the greatest dissolution as well as the most consistent/steady extended-release. After an initial burst release, the commercial brand likewise showed a persistent release, as seen by the graphs in Figures 5 and 6. The physical mixtures and the solid dispersions, though mostly showed no significant difference ($p > 0.05$) in dissolution as seen in Table 5, the solid dispersions still showed superior dissolution profiles as can be seen from the derived dissolution efficiency of the dissolution profiles.

The commercial brand had a burst release of around 75% in only 5 minutes of dissolution testing, but the inclusion of PEG 4000 reduced the effect of burst release since the formulations with PEG 4000 had a little amount of drug released in just 5 minutes and the amount of drug released progressively grew. PEG 4000 has been shown over time to be an inert excipient with good qualities like drug compatibility, low antigenicity, hydrophilicity etc. It has been used in drug delivery in several works to control the rate of drug release [29, 30]. A burst release is unwanted in drug delivery as it tends to increase the risk of side effects or unwanted effects from the drug. Moreover, there is the scare that such unprecedented shoot in the concentration of the drug in the system could reach toxic levels. PEG 4000 encourages extended drug release because if forms a matrix during drug delivery which slows the release of the drug from the matrix but the hydrophilicity of PEG 4000 ensures that all the drug is completely released.

Batch	Mean weight (mg)±SD	Thickness (mm)±SD)	Diameter (mm)±SD	Disintegration time (mins)±SD	Crushing Strength (KgF)±SD	FRIABILITY (%)
PM 1	**249.4 ± 0.01**	**4.682 ± 0.133**	**8.673 ± 0.070**	**0.896 ± 0.683**	**5.3 ± 0.350**	**5.38**
PM 2	**249.7 ± 0.01**	**4.654 ± 0.080**	**8.834 ± 0.180**	**29.001 ± 4.108***	**4.7± 0.632**	**0.95**
PM 3	**248.5 ± 0.01**	**4.383 ±0.099**	**8.826 ± 0.129**	**14.138 ± 2.340***	**4.7 ± 0.580**	**0.11**
PM 4	**249.2 ± 0.01**	**4.56 ±0.101**	**8.877 ± 0.027**	**20.637 ± 2.214***	**6.0±0.369**	**0.12**
SD 1	**253.9 ± 0.01**	**4.458 ± 0.127**	**8.718 ± 0.089**	**27.747 ± 2.192***	**5.4 ± 0.394**	**1.82**
SD 2	**249.8 ± 0.01**	**4.399 ± 0.092**	**8.849 ± 0.094**	**17.172 ± 2.131***	**5.5 ± 0.624**	**0.91**
SD3	**253.1 ± 0.01**	**4.858 ± 0.080**	**8.857 ± 0.037**	**14.387 ± 1.122***	**5.6 ± 0.658**	**0.05**
Commercial	**800.8 ± 0.0046**	**6.677 ± 0.0343**	**10.358 ±0.048**	**1.8 ± 0.471**	**6.7 ± 0.034**	**0.09**

Table 4: Comparison of tablet properties of the different batches of formulated nevirapine tablets and the marketed commercial brand

Key: * shows a significant difference between test batches and the commercial brand

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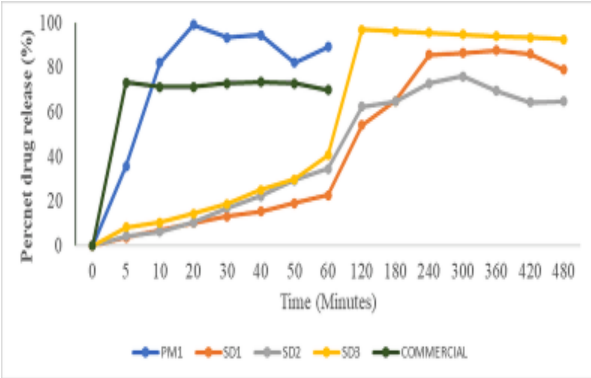

Fig. 5.Drug release of the solid dispersion tablets, the commercial brand tablet and PM1 (without PEG 4000)

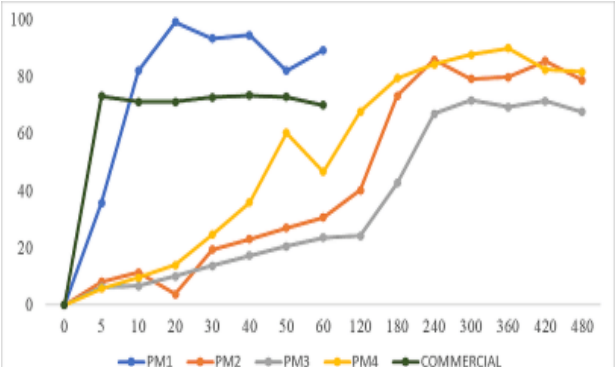

Fig. 6.Drug release of the physical mixtures, the commercial brand tablet and PM1 (without PEG 4000)

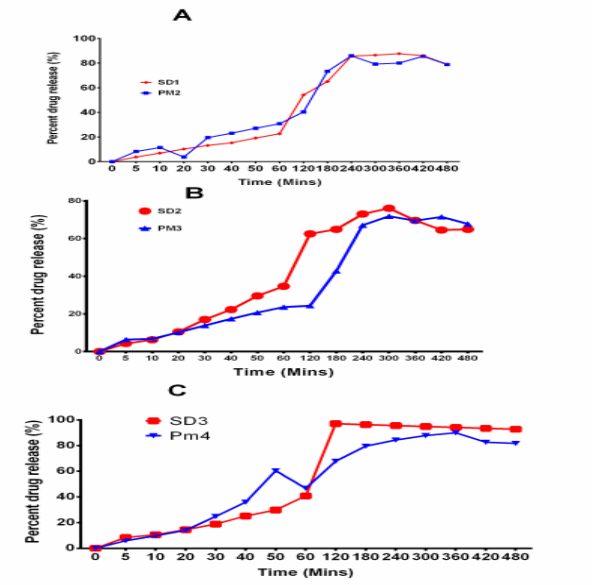

Fig. 7.Drug release curves comparing the physical mixtures with the solid dispersions.

E. Analysis of Dissolution Profiles

Table 5 shows the highest DE for batch SD3 compared with the other batches formulated with PEG 4000. In all cases, the solid dispersions had greater dissolution efficiencies compared with the same concentrations of the drug: polymer in physical mixtures. PM2 = 64.53%, SD1 = 66.10 %. This shows that formulating tablets from solid dispersions using PEG 4000 as the hydrophilic polymer enhances its dissolution than when it is formulated from a physical mixture. The formulated SDs could have improved the dissolution of the nevirapine tablets in several ways. Molecular dispersion of the drug in the hydrophilic carrier leads to smaller particle sizes leading to enhancement of drug dissolution. As can be seen from Figure 1 the SDs had smaller particle sizes than their physical mixture counterpart, which will have promoted dissolution enhancement. Kneaded SDs are usually amorphous formulations that will not require as much energy like a crystal lattice for the drug to disintegrate and dissolve. Finally, the PEG 4000 (a hydrophilic polymer), increased the wettability of the drug and also improved the dissolution of drug.

Batches	Time (minutes)						AUC_{60}	DE (%)
	5	30	60	240	300	480		
PM 1	35.81 ab	93.45 a	89.43 a				82.27	82.27 #
PM 2	8.22 a	19.52 b	30.81 b	85.93 ab	79.26 bc	78.89 bc	16.95	64.53
PM 3	6.33 a	13.83 b	23.61 b	67.07 d	71.86 c	67.76 c	13.67	50.79
PM 4	5.87 a	24.78 b	46.74 b	84.35 abc	87.83 ab	81.74 ab	28.13	73.07
SD 1	3.74 a	13.21 b	22.68 b	85.71 ab	86.49 ab	79.09 bc	12.74	66.10
SD 2	4.28 a	16.98 b	34.64 b	73.02 bcd	76.08 bc	64.87 d	17.24	59.70
SD3	8.38 a	18.87 b	40.81 b	95.61 a	94.89 a	92.75 a	20.14	82.31
Commercial	73.26 b	72.92 a	70.05 ab				69.32	69.32 #

Table 5: Statistical analysis of the dissolution curve at selected time points

Key: Letters show the significant difference in the dissolution profiles after a Tukey post hoc test with a significance level p = 0.05. At 240 minutes to 480 minutes, batches PM1 and the commercial brands had stopped releasing their drugs.

= DE (dissolution efficiency) for PM1 and commercial brand were taken at 60 minutes while the other batches were taken till 480 minute.

IV. SUMMARY AND CONCLUSION

Nevirapine is an antiretroviral BCS II drug with high lipophilicity and poor aqueous solubility. The aim of the research was to formulate extended-release nevirapine tablets using PEG 4000 as the hydrophilic polymer. A comparison was made of the nevirapine: PEG 4000 combinations as physical mixtures and solid dispersions. It was seen that the solid dispersions had better dissolution characteristics. The PEG 4000 was able to prolong the release of the nevirapine from the tablets and reduce the incidence of a bursr release.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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