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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF NEVIRAPINE

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ABSTRACT

Objective: The present research work was to formulate fast disintegrating tablets of Nevirapine. **Methods:** The formulation was developed with different concentrations of super disintegrants such as sodium starch glycolate, croscarmellose sodium and crosspovidone. Nevirapine fast disintegrating tablets were prepared by direct compression. All the ingredients were passed through 60# mesh sieve separately and collected. The drug weighed along with the other excipients and was mixed in geometrical order. This mixture was compressed using flat face 10mm oval shaped punch to get tablet of 500mg weight using tablet compression machine. **Results:** Fast disintegrating tablet showed a significant influence on disintegration and dissolution studies. Effect of super disintegrant on dispersion time and *in vitro* release has been studied. Fast disintegrating tablets containing crosspovidone showed excellent *in vitro* dispersion time and drug release as compared to other formulations. The cumulative % drug release profile of Fdt-6 formulation was found to be maximum when compared with other formulations. **Conclusion:** It is concluded that the formulated FDT tablets of Nevirapine using crosspovidone was capable of exhibiting immediate release properties. Among all the formulations Fdt 6 prepared with crosspovidone as disintegrant exhibited least disintegration time. As the concentration of superdisintegrant in the formulations increased the disintegration time was found to decrease. From the characterization of fast disintegrating tablets of Nevirapine it can be concluded that formulation containing crosspovidone is most acceptable. Fast disintegrating tablets of Nevirapine are a therapeutically effective, economical, commercially feasible approach for the therapeutic benefit of HIV patients.

KEYWORDS: Fast disintegrating tablets, Nevirapine, Super disintegrants, Anti retroviral therapy.

INTRODUCTION

Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Fast disintegrating tablets are also called as mouth-disintegrating tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick disintegrating etc. Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva.

Fast disintegrating dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. This fast disintegrating tablet disintegrates instantaneously when placed on tongue and releases the drug dissolves or disperses in the saliva. Fast disintegrating tablets are useful in patients, like paediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style.[1,2,3] Fast disintegrating tablets are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething, and to those who cannot swallow intact sustained action tablets/capsules.

According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of superdisintegrants like cross povidone[4], cross linked carboxymethyl cellulose (Croscarmellose), sodium starch glycolate (Primogel, Explotab) etc.,[5,6,7] which provide instantaneous disintegration of tablet after putting on

tongue, their by release the drug in saliva A fast-disintegrating drug delivery system, in most cases, is a tablet that dissolves or disintegrants in the oral cavity without the need of water or chewing. Most fast-disintegrating delivery system films must include substances to mask the taste of the active ingredient.

The technologies utilized for fabrication of MDDDS include lyophilization, moulding, direct compression and cotton candy process, spray drying sublimation, mass extrusion, nanonization and quick dissolve film formation. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. In the recent past, several new advanced technologies have been introduced for the formulation of mouth disintegrating tablets (MDTs) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients.[8,9,10,11]

MATERIALS AND METHODS

Table 1: List of Materials

S.No	Materials	Property	Manufactures
1	Nevirapine	Pure drug	KP laboratories, Hyderabad
2	Lactose	Diluent	SD fine chemicals
3	Sodium saccharin	Sweetening agent	SD fine chemicals
4	Cross povidone	Super disintegrant	Nikite chemicals industries
5	Sodium cross carmellose	Super disintegrant	Nihal trader pvt,ltd
6	Sodium starch glycolate	Super disintegrant	Nikite chemicals industries
7	Magnesium stearate	Glidant	SD fine chemicals
8	Talc	Lubricant	SD fine chemicals
9	Mannitol	Taste masking agent	SD fine chemicals

Table 2: List of Equipment

S.No	Equipment	Name
1	Dissolution test apparatus	Lab India
2	Vernier caliper	Edison
3	Digital pH meter	Rimek
4	Roche Friabilator	Biotechnics India
5	Melting apparatus	Polmon
6	Monsanto hardness tester	Sisco
7	Rotary punching machine	Karnavati
8	Sieves (60#)	Jayant
9	UV- visible double beam spectrophoto meter	Elico

Preparation method of Nevirapine fast disintegrating tablets using super disintegrant

Nevirapine fast dissolving were prepared by direct compression. All the ingredients were passed through 60# mesh sieve separately and collected. The drug weighed along with the other excipients and was mixed in geometrical order. This mixture was compressed using flat face 10mm oval shaped punch to get tablet of 500mg weight using ten station karnavati tablet compression machine.

Mainly seen excipients in FDT are as follows at least one disintegrant, a diluent, a lubricant and optionally, a swelling agent, a permeabilizing agent, sweeteners and flavorings.

Table 3: Formulation of Nevirapine fast disintegrating tablets

Ingredient	Category	Batch Code					
		F1	F2	F3	F4	F5	F6
Nevirapine	Anti-viral	200	200	200	200	200	200
S.S.G	Super disintegrant	25	50	-	-	-	-
CCS	Super disintegrant	-	-	25	50	-	-
CP	Super disintegrant	-	-	-	-	25	50
Sodium saccharin	Sweetner	20	20	20	20	20	20
Magnesium stearte	Glidant	30	30	30	30	30	30
Talc	Lubricant	30	30	30	30	30	30
Mannitol	Taste masking agent	80	80	80	80	80	80
Lactose	Diluents	115	90	115	90	115	90
Total weight of tablet (mg)		500	500	500	500	500	500

EVALUATION

I. Pre Compression Parameters

A. Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane.[12] The angle of repose can range from 0° to 90°. It is related to the density, surface area and shapes of the particles and the coefficient of friction of the material.

The fixed funnel method was employed to measure the angle of repose.[13] A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\theta = \tan^{-1}(h / r)$$

where θ = angle of repose

B. Bulk Density

Density is defined as weight per unit volume Bulk density, ρb, is defined as the mass of many particles of the material divided by the total volume they occupy and is expressed in grams per cubic centimeter (g/cm^3).[13] The total volume includes particle volume, inter-particle void volume and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled. The bulk density of a powder is determined by measuring the volume of a known mass of powder sample, that may have been passed through a sieve, into a graduated cylinder (Method A), or by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup (Method B) or a measuring vessel (Method C).

The bulk density was calculated, in grams per ml, using the formula:

(M) / (Vo)

Where M = Total weight of the powder blend,

V_0 = bulk volume of the powder blend

C. Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped 100 times, then tapped volume was measured and tapped density was calculated, to the nearest graduated unit.

The tapped density was calculated, in gm per ml, using the following formula.

$(M) / (V_f)$

Where M = Total weight of the powder blend

V_f = Tapped volume of the powder blend

D. Compressibility Index

The **Carr index** (also: Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr.

The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. It is determined from the bulk and tapped densities.[13] In a free-flowing powder, the bulk density and tapped density would be close in value; therefore, the Carr index would be small. On the other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore, the Carr index would be larger.

The Carr index is calculated by the formula

$$C = 100(1 - \rho_B/\rho_T),$$

Where, ρ_B is the freely settled bulk density of the powder and

ρ_T is the tapped bulk density of the powder.

E. Hausners Ratio

The Hausners ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900–1995). A Hausners ratio greater than 1.25 is considered to be an indication of poor flowability. The Hausners ratio is calculated by the formula.

$$H = \frac{\rho_T}{\rho_B}$$

Where $\rho_B$is the freely settled bulk density of the powder and

ρ_T is the tapped bulk density of the powder.

II. Post Compression Parameters

A. Hardness

It is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The breaking point of a tablet is based on its shape. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester.[14] The hardness is usually measured in terms of kg/cm^2.

B. Friability

The friability test was carried out in an instrument called the Roche friabilator**.** It is expressed in percentage (%). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min.[3]

After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

C. Weight Variation

Weight variation was carried out to ensure that, each of tablets contains the proper amount of drug. The test was carried out by weighing the 20 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weights to the average.[15]

The percentage of weight variation is calculated by using the following formula:
% Weight variation = (Average weight-Individual Weight) / Individual Weight × 100.

Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopeia and none deviates by more than twice that percentage.

D. Disintegration time
Select one tablet from each formulation and placed in a petriplate containing 10 ml of Phosphate buffer (pH 6.8) as a disintegrating medium. The time taken for the tablet to get disintegrate in the medium was noted.

E. Wetting Time
A tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5cm) containing 6 ml of Sorenson's buffer pH 6.8 and the time for complete wetting is measured.

F. Water absorption Ratio
A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of Sorenson's buffer pH 6.8.[16] A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$$R = 10 (Wa / Wb)$$

Where, **Wa** is weight of tablet before water absorption
Wb is weight of tablet after water absorption.

G. *In vitro* dispersion time
In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. The time required for the tablet to get dispersed in the solution was noted.

***H*. *In vitro* dissolution test**
Dissolution test for Nevirapine was carried out as per USP method for dissolution test for tablets and capsules using apparatus II[2] (paddle type). Dissolution medium used was 900 mL of 0.1N Hcl, rotating at 50 rpm at 37±0.5`C. An aliquot of 5mL of samples were withdrawn at different time periods and replaced with fresh solvent.[3] These samples were filtered. Absorbance of the resulting solution was measured at 313 nm (experimental λmax for Nevirapine in 0.1N HCl). Percent drug release was calculated.

RESULTS AND DISCUSSION
All these formulations were evaluated for micrometric properties before going to compression and were tabulated in table 5. Bulk density, was found in the range of (0.484-0.512gm/cm^3) and the tapped density between (0.572-0.620 gm/cm^3). The compressibility index was found between (15.66-18.18) which indicates a fairly good flow ability of the powder blend. The good flow ability of the powder blend was also evidenced with angle of repose in the range of (22.14-24.16) which is below 30^0 indicating good flow properties of the granules.

Tablets were prepared using direct compression technique. All batches of tablets were evaluated for various physical parameters and were tabulated in table 6. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The average weight of the prepared tablet was found 490 to 500 mg. All the tablets were exhibit in white colour, odourless, smooth surface with zero defects. A tablet requires certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The friability of all the formulation was found to be less than 1.0%. The hardness of the prepared tablet varied from 3.5 to 3.9kg/cm^2 which have satisfactory strength to withstand the mechanical shocks. The % drug release of different batches with time shown in table 8. All the formulations showed no significant variation in all the parameters under the test.

Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablets. All the formulations were evaluated for the influence of disintegrants and their concentrations on the characteristics of rapid disintegrating tablets mainly in terms of disintegration time and dissolution studies. Among all the formulations, the batch prepared using crosspovidone (Fdt 6) showed better disintegration time of 15sec. The formulations (Fdt6) with crospovidone showed more than 90% drug release within 30 min.

Table 4: Standard graph values of Nevirapine

S.No	Concentration (µg/ml)	Absorbance
1	0.2	0.0506
2	0.4	0.1023
3	0.6	0.1456
4	0.8	0.1961
5	1	0.2479

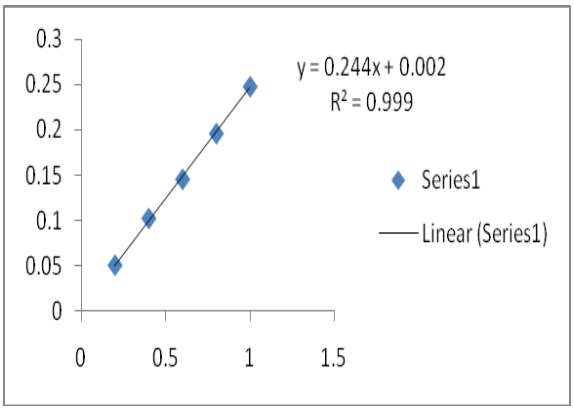

Figure 1: Standard graph for Nevirapine

Table 5: Pre compression parameters of Nevirapine powder blend

S.No	Bulk density (g/ml)	Tapped density(g/ml)	Angle of repose	Carr's index(%)	Hausner's ratio
Fdt1	0.484±0.008	0.572±0.002	24	18.181	1.181
Fdt2	0.506±0.004	0.600±0.008	24.16	15.666	1.185
Fdt3	0.504±0.006	0.610±0.006	22.64	17.377	1.210
Fdt4	0.512±0.002	0.612±0.008	23.12	16.339	1.195
Fdt5	0.510±0.002	0.620±0.004	22.16	17.741	1.215
Fdt6	0.506±0.008	0.607±0.004	22.14	16.639	1.199

Table 6: Post compression parameters of Nevirapine oral disintegrating tablets

Formulation code	Hardness (kg/cm^2)	Weight variation(g)	Friability (%)	Disintegration time(sec)
Fdt1	3.88±0.05	0.49±0.011	0.10±0.011	43
Fdt2	3.92±0.04	0.50±0.010	0.13±0.008	60
Fdt3	3.82±0.06	0.50±0.008	0.14±0.008	58
Fdt4	3.90 ±0.06	0.50±0.010	0.11±0.011	25
Fdt5	3.64±0.08	0.49±0.011	0.14±0.014	20
Fdt6	3.54±0.05	0.50±0.011	0.12±0.008	15

Table 7: Post compression parameters of Nevirapine oral disintegrating tablets

Formulation code	Wetting time(sec)	Water absorption ratio	Drug content uniformity (%)
Fdt 1	48	5.30	199.8±0.82
Fdt 2	46	4.20	200.4±0.89
Fdt 3	47	4.18	200.2±0.97
Fdt 4	46	4.84	200.0±0.89
Fdt 5	45	5.12	199.9±0.89
Fdt 6	43	4.35	200.1±0.89

Table 8: Drug release profile of Nevirapine oral disintegrating tablet

Time(min)	Fdt 1	Fdt 2	Fdt 3	Fdt 4	Fdt 5	Fdt 6
0	0	0	0	0	0	0
5	30.82	31.34	30.18	31.00	32.05	34.06
10	42.74	45.68	40.64	43.63	42.96	46.66
15	50.61	56.72	40.59	54.32	56.63	60.21
20	59.02	63.92	56.24	60.12	66.72	76.42
25	62.0	66.76	60.12	63.13	77.16	80.16
30	68.16	71.65	65.18	66.64	80.18	90.37
60	70.02	82.74	68.02	80.72	92.00	96.72

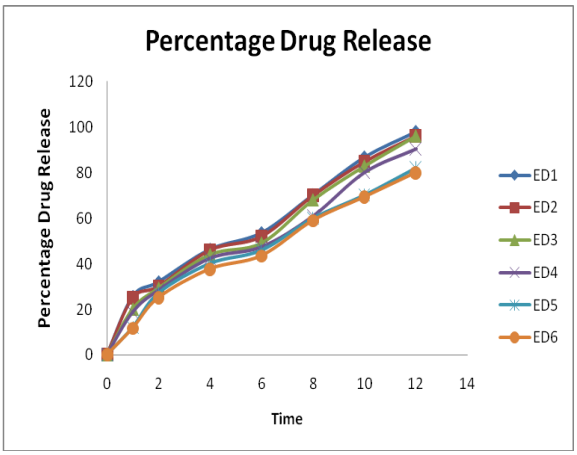

Figure 2: Percentage drug release graph of Nevirapine

CONCLUSION

Based on above results and discussion, it is concluded that the formulated FDT tablets of Nevirapine using crosspovidone was capable of exhibiting immediate release properties. Among all the formulations Fdt 6 prepared with crosspovidone as disintegrant exhibited least disintegration time. As the concentration of superdisintegrant in the formulations increased the disintegration time was found to decrease.

From the characterization of fast disintegrating tablets of Nevirapine it can be concluded that formulation containing crosspovidone is most acceptable. Fast disintegrating tablets of Nevirapine are a therapeutically effective, economical, commercially feasible approach for the therapeutic benefit of HIV patients.

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