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Formulation and In-Vitro Evaluation of Elvitegravir Fast Disintegrating Tablets

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Abstract: Elvitegravir is an antiretroviral drug which belongs to BCS class-II of Biopharmaceutics classification. In the present work an attempt has been made to prepare solid dispersion of elvitegravir by using polyethylene glycol (PEG) and then compressing it along with suitable excipients to develop fast disintegrating tablets. Preparation of solid dispersions and then fast disintegrating tablets improves its solubility and then the absorption of drug. The solid dispersion (drug: PEG 6000, 1:3 ratio) used to prepare fast disintegrating tablet by direct compression method using superdisintegrants such as sodium starch glycolate, cross caramellose sodium and crospovidone. The precompression parameter of powder blends suggested good flowability and compressibility. The prepared tablets were evaluated for thickness, hardness, friability, weight variation, drug content, wetting time, water absorption ratio, i*n-vitro* disintegration time and dissolution studies. Among the various formulations tablets the batch F-6 prepared with 20 mg Crospovidone showed complete release of drug within 15 minutes. Hence fast dissolving tablets of elvitegravir by solid dispersion technique could be used to improve patient compliance.

Keywords: Elvitegravir; Polyethylene glycol; Solid dispersion; Fast disintegrating tablets; Sodium starch glycolate; Cross caramellose sodium; Crospovidone.

INTRODUCTION

There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs which include solid dispersion, solubilization using surfactant, the use of co-solvent, reduction of particle size, hydrotropy and the use of aqueous soluble derivatives or salts [1].

Among various technique solid dispersion (SD), is the most efficient technique and is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent or solvent fusion methods [2]. Many investigators have studied SDs of poorly water-soluble drugs with various pharmacologically inert carriers to increase the dissolution and oral absorption of poorly water soluble drugs [3, 4].

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids [5, 6]. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules [7]. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms [8]. Fast disintegration always requires fast absorption of water into the centre of the tablet. Thus, having open pore structures inside the tablets is very important for making fast dissolving tablets [9].

In the present study Elvitegravir a BCS class-II drug having an oral bioavailability of 20-30% is designed as solid dispersion in order to increase its solubility and then the solid dispersions are formulated into fast disintegrating tablet there by the

solubility and absorption of drug can be increased which leads to increased patience compliance.

MATERIALS AND METHODS

Materials

Elvitegravir was obtained from Chandra labs, Hyd. Polyethylene glycol was procured from ESSEL fine chem. Mumbai. Cross povidone, Sodium starch glycolate and Cross caramellose sodium were purchased from MYL CHEM Mumbai. Lactose monohydrate, Magnesium stearate and talc were purchased from S.D. Fine Chem. Ltd, Mumbai, India.

Methods

Preparation of fast dissolving tablets of solid dispersion by direct compression method [10]

Solid dispersion of PEG-6000 (1:3 ratio of drug: polymer) equivalent to 255mg of drug prepared by fusion method were taken and mixed with directly compressible diluent, super disintegrants and other excipients (as mentioned in the table-1) in a plastic container. Powder blend were directly compressed using 8mm, round-shaped flat punch in a multi station tablet compression machine (Cadmach, Ahmedabad, India).

Table-1: Composition of the tablet formulation

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Elvitegravir SD	255	255	255	255	255	255
Sodium Starch Glycolate	10	20	-	-	-	-
Cross Caramellose Sodium	-	-	10	20	-	-
Cross Povidone	-	-	-	-	10	20
Lactose Monohydrate	128	118	128	118	128	118
Magnesium Stearate	3	3	3	3	3	3
Talc	4	4	4	4	4	4
Total weight	400	400	400	400	400	400

Evaluation studies

Pre compression evaluation parameters [11]

Bulk density

Bulk density of powdered blend was determined by pouring gently through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

$$Bulk\ density = \frac{Weight\ of\ sample\ in\ grams}{volume\ occupied\ by\ the\ sample}$$

Tapped density

An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. Volume was noted and tapped density is calculated using following formula.

$$Tapped\ volume = \frac{Weight\ of\ sample\ in\ grams}{tapped\ volume}$$

Compressibility Index and Hausner ratio

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$Carr'sindex = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\mathbf{Tan\ \theta = h / r}$$
$$\theta = \text{Tan}^{-1}\ h / r$$

Where, θ = angle of repose, h = height, r = radius.
A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Post compression parameters

The quantitative evaluation and assessment of a tablets chemical and physical properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Weight variation test

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table-2: limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
From 130 to 324	7.5%
> 324	5%

Thickness and diameter

The thickness and diameter of 6 tablets were recorded during the process of compression using Vernier callipers.

Friability

Total of 6 tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula:

$$\%\ Friability = \frac{weight\ of\ the\ tablets\ before\ test - weight\ of\ the\ tablets\ after\ test}{weight\ of\ the\ tablets\ after\ test} \times 100$$

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter 6.5 cm) containing 6ml pH 6.8 phosphate buffer. A tablet was put on the paper, and the time for complete wetting was measured. The wetted tablet was then weighed. The water absorption ratio (R) was determined using formula as,

$$R = \frac{Weight\ of\ tablet\ after\ absorption - Weight\ of\ tablet\ before\ absorption}{Weight\ of\ tablet\ before\ absorption} \times 100$$

In-vitro disintegration time

The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. The time taken for the complete disintegration of the tablet is noted.

In-vitro dissolution studies

In-vitro dissolution study was performed by using USP dissolution testing apparatus- 2 (Paddle method). Weighed tablets from different batches were kept in a flask of the dissolution apparatus containing 900 ml of 6.8 pH Phosphate buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (5 ml) was withdrawn at specific time

intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 313 nm against Suitable blank using UV-visible spectrophotometer [12-14].

Stability studies

Stability studies were carried out according to ICH guidelines by exposing the formulations F6 in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30, 60 and 90 days and analyzed for change in drug content, dissolution and disintegration time.

RESULTS AND DISCUSSION

Precompression parameters

Bulk densities and tapped densities of various formulations were found to be in the range of 0.73 to 0.76 (g/cc) and 0.80 to 0.88 (g/cc) respectively. Carr's index and hausner's ratio of various formulations were found to be in the range of 7.113 % to 7.57% and 1.06 to 1.32 respectively. The values for angle of repose were found in the range of 32.43º-39.32º. From the results it was concluded that the powder blends has good to fair flow properties and these can be used for tablet manufacture.

Table-2: Results of recompression evaluation of powder blend

Formulation	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of repose
F1	0.73	0.87	7.126	1.16	26.28º
F2	0.74	0.80	7.577	1.32	26.21º
F3	0.74	0.88	7.113	1.18	25.16º
F4	0.74	0.81	7.414	1.09	26.32º
F5	0.75	0.83	7.499	1.10	25.43º
F6	0.76	0.82	7.320	1.06	25.46º

Post Compression evaluation

Hardness test

Tablets of each batch were checked by using Monsanto hardness tester and the data's were shown in table-3. The results showed that the hardness of the tablets was in range of 3.5 to 3.8 Kg/cm^2.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the table 3. The average friability of all the formulations lies in the range of 0.40 % to 0.58 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the table 3. The average weight of the tablet is approximately 400 mg, so the permissible limit is ±7.5%. The results of the test showed that, the tablet weights were within pharmacopoeial limit.

Drug content (%)

The drug content was above 97% for all formulations.

Table-3: Post compression evaluation results for F1 – F6

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)	Drug content (%)
F1	3.6±0.002	0.42±0.01	396±0.99	2.20±0.01	97.80±0.01
F2	3.8±0.001	0.40±0.04	398±0.97	2.11±0.04	98.12±0.08
F3	3.7±0.01	0.40±0.02	407±0.98	2.13± 0.04	98.16± 0.07
F4	3.6±0.004	0.42± 0.05	400±0.96	2.16±0.09	99.10±0.09
F5	3.5±0.03	0.45±0.03	405±0.97	2.19±0.09	99.05±0.05
F6	3.5±0.009	0.46±0.09	401±0.92	2.21±0.05	99.40± 0.07

In- vitro disintegration time

Tablets of each batch were evaluated for *in-vitro* disintegration time and the data were shown in the table 4. The results showed that the disintegration time of prepared tablets were in the range of seconds.

Wetting time (seconds) and Water absorption ratio (%)

Tablets of each batch were subjected to wetting time and water absorption ratio was shown in the table 4. The results showed that the wetting time of prepared tablets were in the range of

seconds and water absorption ratio was found to be in the range of 83.92 to 100.58.

Table-4: Evaluation of specific tablets for formulations F1 – F6

Formulation	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio mean
F1	20.16	31.45	88.92
F2	18.48	30.63	83.50
F3	20.11	18.30	93.98
F4	19.48	29.98	94.66
F5	12.12	17.82	96.52
F6	11.42	12.02	100.58

In- vitro dissolution studies

Finally, the tablets were evaluated for *in-Vitro* dissolution studies in simulated gastric fluid and the results were shown in the table 5. Formulations F1 showed 63.8% of drug release with 10mg of SSG, F2 showed 59.5% of drug release with 20mg of SSG, F3 which contain 10mg of CCS showed 88.7% of drug release within 15min, F4 showed 93.2% of drug release with 20mg of CCS, F5 showed 87.8% of drug release with 10mg of CP and finally F6 showed 98.7% of drug release with 20mg of CP. This result exhibit a direct relationship between concentration of superdisintegrants and drug release. Among the various formulations tablets of batch F6 prepared with 20mg CP showed complete release of drug within 15 minutes.

Table-5: *In- Vitro* drug release for the formulations

Time (minutes)	F1	F2	F3	F4	F5	F6
5	49.7±0.12	36.8±0.01	43.9±0.15	62.1±0.04	41.9±0.24	61.8±0.24
10	55.8±0.15	49.9±0.08	68.7±0.07	71.7±0.08	63.2± 0.25	78.1±0.28
15	63.8±0.04	59.5±0.09	88.7± 0.19	93.2± 0.09	87.8± 0.26	**98.7± 0.29**

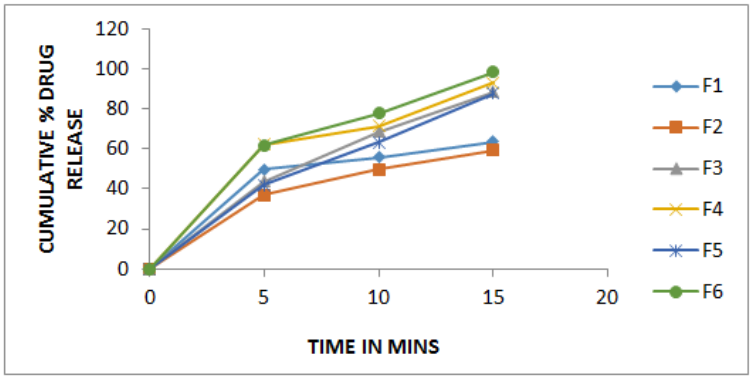

Fig-1: Graph for in-vitro drug release of developed formulations

Stability Studies

The optimized formulation was subjected to stability studies as per ICH guidelines for a period of 3 months. There was no significant change observed in the formulations during the stability studies

Table-6: Stability Studies for the formulations

Time	Assay		Cumulative % drug release at 15 min	
	25±2ºc and 65±5%RH	40±2ºc and 75±5%RH	25±2ºc and 65±5%RH	40±2ºc and 75±5%RH
First day	99.2	100.50	99.5	96.9
30 days	98.5	99.4	97.4	96.2
60 days	98.2	98.75	96.9	95.9
90 days	98.1	98.5	96.7	95.5

CONCLUSION

Solid dispersion tablets for an antiretroviral drug Elvitegravir were successfully prepared by direct compression method using super disintegrants such as sodium starch glycolate, crosspovidone and crosscarmellose sodium. Formulating elvitegravir as

solid dispersion increasing its solubility, and then converting into tablet dosage form ie., fast disintegrating tablets helps the drug to quickly release from the dosage form and be available in the oral cavity where absorption of drugs is usually high due to more vasculature. In this present work solid dispersion tablets were successfully developed which enhances the solubility, with fast release and achieving good patient compliance.

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