Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Research Article

FORMULATION, EVALUATION OF FAST DISSOLVING TABLET OF ANTI-HIV DRUGS AS FIXED DOSE COMBINATION: USE OF FREEZE-DRIED POWDER OF *ANNONA RETICULATA* AND COMPARISON WITH SYNTHETIC SUPERDISINTEGRANTS

Pingale Prashant L.*

Associate Professor, Department of Pharmaceutics, Gokhale Education Society's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005, India

*Corresponding Author Email: prashant.pingale@gmail.com

DOI: 10.7897/2277-4572.081124

Received on: 17/01/19 Revised on: 07/02/19 Accepted on: 09/02/19

ABSTRACT

The aim of the present research work was to prepare and evaluate fast dissolving tablets (FDTs) of fixed dose combination (FDC) of anti-HIV drugs Ritonavir and Lopinavir with a view to enhance patient compliance and minimizes the side effects. In the cited study, fast dissolving tablets of Ritonavir and Lopinavir were formulated by direct compression method using freeze dried powder *of Annona reticulata* (Custard apple) pulp as a natural disintegrants and synthetic superdisintegrants like Crospovidone, Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (Ac-di-sol) in different ratios with directly compressible mannitol as a diluent to improve the mouth feel. The prepared formulations were evaluated for various parameters including hardness, friability, drug content, *in vitro* dispersion time, wetting time, water absorption ratio, *in vitro* drug release studies, stability studies and excipients interaction studies. Among all the formulations, the formulation (F_{CA4}) containing 5% w/w pulp of *Annona reticulata* was the overall best formulation based on *in vitro* drug release studies. Stability studies on selected formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time. The final FDT was robust and disintegrated in 1 mL of fluid in 10 s with up to 4 tablets dissolving in 4 mL to achieve varying doses accommodated in a common teaspoon. From the above studies, it can be concluded that fast dissolving tablets of Ritonavir + Lopinavir can be prepared using different natural superdisintegrants for faster dispersion and disintegration in the mouth.

KEYWORDS: Fast dissolving tablets, fixed dose combination, Ritonavir, Lopinavir, *Annona reticulata*.

INTRODUCTION

The purpose of Novel drug delivery systems (NDDS) is to enhance safety and efficacy of drug by formulating a suitable dosage form for administration and to attain a better patient compliance. One such approach is fast dissolving tablets (FDT). FDT's were designed to enhance patient compliance by direct compression method[1]. AIDS is an ultimate output of HIV infection, if untreated for several years. As per World health Organization (WHO), 76% of all pregnant women living with HIV globally received medicines that prevent transmission to their babies in 2016 and more than 19.5 million people were receiving antiretroviral treatment by December 2016[2]. Antiretroviral (ARV) therapy has been shown to achieve high therapeutic efficacy in treating pediatric HIV disease. The delivery of affordable, child friendly and easy to store and administer ARV drugs are key to the successful management of HIV in children[3]. *Annona reticulata* i.e. Custard apple is rich of flavonoids, alkaloids, and acetogenins. It is easily available, low cost and non-toxic as compared to synthetic disintegrants[4]. In the present study, the fast dissolving tablets of Ritonavir and Lopinavir in fixed dose were prepared by direct compression method using natural and synthetic disintegrants to compare the efficiency of different natural and synthetic disintegrants.

MATERIALS AND METHODS

Materials: Ritonavir and Lopinavir were obtained as gift sample from Abbott Laboratories Ltd, Guwahati, India. *Annona reticulata* (Custard Apple) were purchased from local sources. Crospovidone (CP) was obtained as gift sample from Wockhardt Research Centre, Aurangabad, Maharashtra, India. Micro-crystalline cellulose (MCC) and Sodium Starch Glycolate (SSG) was gift sample from Alkem Labs Pvt. Ltd., Mumbai, Maharashtra, India. All the other chemicals were of analytical grade.

(A) (B) (C)

Fig. 1: Custard apple: A - Fruit, B - Pulp, C - Freeze Dried Powder

Compatibility study using FTIR method: The Fourier-transform infrared spectroscopy (FTIR) is used[1,5] to know the identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. KBr-pellet method is used to prepare pellets. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer (Bruker, Germany).

Extraction of *Annona reticulata* (Pulp powder): The pulp of the fruits was scraped off smoothly and obtained pulp was dried in sunlight. The dried mass was grinded in mixture to get fine powder and passed to mesh #60. The pulp powder was dried in oven at 50°C, powdered, passed through #60 mesh, weighed and stored in air tight well closed container[4].

Formulations of Ritonavir and Lopinavir FDT's: FDT's of Ritonavir and Lopinavir were prepared by direct compression method[1,3,5]. Pulp of *Annona reticulata* (CA) as a natural disintegrants and CP or SSG as a synthetic superdisintegrants in various ratios and directly compressible mannitol as diluent to enhance the mouth feel. All the ingredients were passed through #60mesh separately. The drug and mannitol were mixed by small portion of both each time and blending it to get a uniform mixture and kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 8 mm size to get a tablet of 250 mg weight using a Karnavati tablet compression machine press 12 station rotary tablet compression machine. The tablets were prepared according to formulae given in table 1.

Table 1: Formulations of Ritonavir and Lopinavir FDT's prepared by direct compression method

Ingredient (mg)	FC_c	FC_1	FC_2	FC_3	FS_1	FS_2	FS_3	FCA_1	FCA_2	FCA_3
Ritonavir	20	20	20	20	20	20	20	20	20	20
Lopinavir	80	80	80	80	80	80	80	80	80	80
CP	-	5	10	15	-	-	-	-	-	-
SSG	-	-	-	-	5	10	15	-	-	-
CA	-	-	-	-	-	-	-	5	10	15
MCC	40	40	40	40	40	40	40	40	40	40
Aspartame	4	4	4	4	4	4	4	4	4	4
Flavour	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
Mannitol	100	95	90	85	95	90	85	95	90	85
Total Weight	250	250	250	250	250	250	250	250	250	250

FCc :- Control formulation without superdisintegrants
FC :- Formulation containing crospovidone
FS :- Formulation containing sodium starch glycolate
FCA :- Formulation containing custard apple pulp powder
1,2,3 :- Formulation code containing 2,4, 6 % of superdisintegrants of total tablet wt. respectively

Evaluation of Tablets

A. Pre-compression parameters of FDT granules

The prepared batches of formulations were evaluated for the pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio were shown in Table 2.

Bulk Density[5,6,7]: The term bulk density (rb) refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. Initially the weight of the measuring cylinder was tarred. Then, 4 gm presieved (40#) bulk drug were poured into the measuring cylinder using a funnel and weighed (M). Then volume of the powder (Vb) was taken. Bulk density of the granules was calculated using following formula.

$$rb = M/Vb$$

Tapped density[5,6,7]: Blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (Electrolab) (rt) was calculated using following formula.

$$rt = M/Vt$$

Angle of repose [5,6,7]: Angle of repose (a) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

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

Carr's Index[5,6,7]: Tapped and bulk density measurements can be used to estimate the Carr's index of a material. Carr's index (CI) was determined by,

$$\text{Carr's Index} = \text{Tapped density} - \text{bulk density} / \text{Tapped density} * 100$$

Hausner's ratio[5,6,7]: Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

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

B. Post-compression parameters of FDT

The prepared tablets were evaluated for parameters such as drug content uniformity, weight variation, hardness, friability, thickness, *in vitro* dispersion time, *in vitro* drug release and stability studies as shown in table 3.

Thickness: The thickness[5] of individual tablets is measured by using Vernier caliper (model-99MAC002M5, Mitutuyo, made in Japan).

Hardness: The hardness of prepared tablets was determined by using Monsanto hardness tester[5] and measured in terms of kg/cm^2.

Friability: Roche friabilator is used for the determination of friability[5] of tablets. Ten tablets were initially weighed (W_0) together and then placed in the chamber. The friabilator was operated for 100 revolutions (25 rpm, for 4 minutes) and the

tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W). The percentage of friability was calculated using the following equation.

$$\% \text{ Friability} = F = (1 - W/W0) \times 100$$

Where, W_0 and W are the weight of the tablets before and after the test respectively. The limit for percentage of friability should not be more than 1%.

Weight variation: The weight variation test was done by weighing 20 tablets individually using Shimadzu digital balance[5], calculating the average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

***In vitro* dispersion time[5]**: Tablet was added to 10 ml of phosphate buffer solution (pH 7.4) at 37±0.5°C. Time required for complete dispersion of a tablet was measured.

Wetting time[5]: A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d=6.5 cm) containing 6 ml of water. A tablet was put on the paper and the time for complete wetting was measured.

Water absorption ratio: Test was done with the same procedure as that of wetting time. In this test initial weight of tablet was taken before placing on petri dish. After complete wetting the wetted tablet was then weighed. Water absorption ratio, R was determined using the equation,

$$R = 100(Wb - Wa) / Wa$$

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

***In-vitro* drug release for drug Content:** *In vitro* drug release of Lopinavir and Ritonavir from prepared tablets was determined using USP Dissolution Apparatus II (Paddle type) (model, TDT081, Electrolab). The dissolution test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5^0C. The speed of rotation of paddle was set at 50 rpm. At a predetermined time, interval (5 min), 5 ml samples were withdrawn, filtered through Whatman filter paper. Absorption of solution was checked by UV spectrophotometer (model, 25, PerkinElmer lambda) at 258 nm and 245 nm for Lopinavir and Ritonavir respectively[8].

RESULTS AND DISCUSSION: A total of 10 formulations including a control formulation FCc (without superdisintegrant) were designed. All the blends were free flowing having all pre-compression parameters in range as per USP as given in USP shown in Table 2.

Table 2: Pre-compression parameters of formulations prepared by direct compression method

Ingredient (mg)	FC_c	FC_1	FC_2	FC_3	FS_1	FS_2	FS_3	FCA_1	FCA_2	FCA_3
Bulk Density (gm/cc)	0.60	0.54	0.53	0.53	0.54	0.51	0.51	0.55	0.52	0.52
Tapped Density (gm/cc)	0.70	0.66	0.63	0.62	0.65	0.62	0.62	0.67	0.63	0.65
Angle of repose (^{0})	29.14	26.15	25.84	25.31	25.41	25.37	25.31	25.14	25.81	25.31
Carr's Index (%)	14.29	18.18	15.87	14.52	16.92	17.74	17.74	17.91	17.46	20.00
Hausner's Ratio	1.17	1.22	1.19	1.17	1.20	1.22	1.22	1.22	1.21	1.25

Table 3: Post-compression parameters of formulations prepared by direct compression method

Ingredient (mg)	FC_c	FC_1	FC_2	FC_3	FS_1	FS_2	FS_3	FCA_1	FCA_2	FCA_3
Thickness (mm)	3.12 ±0.16	3.18 ±0.97	3.19 ±0.72	3.20 ±0.73	3.20 ±0.78	3.21 ±0.71	3.21 ±0.64	3.21 ±0.73	3.22 ±0.81	3.23 ±0.76
Hardness (Kg/cm^3)	3.12 ±0.14	3.22 ±0.25	3.23 ±0.69	3.24 ±0.54	3.31 ±0.47	3.41 ±0.49	3.32 ±0.71	3.53 ±0.17	3.56 ±0.94	3.61 ±0.46
Friability (%)	0.69 ±0.17	0.71 ±0.16	0.73 ±0.19	0.74 ±0.19	0.71 ±0.23	0.72 ±0.23	0.75 ±0.17	0.71 ±0.27	0.72 ±0.24	0.72 ±0.25
In-vitro dispersion time (Sec.)	95.12 ±0.76	45.12 ±0.49	32.14 ±0.47	25.10 ±0.19	48.21 ±0.49	41.12 ±0.43	36.15 ±0.46	47.12 ±0.42	43.25 ±0.43	38.15 ±0.39
Wetting time (Sec.)	100.14 ±0.97	45.93 ±0.91	40.13 ±0.93	25.14 ±0.96	46.21 ±0.78	40.89 ±0.89	37.12 ±0.94	49.21 ±0.83	41.23 ±0.78	37.21 ±0.86
Water absorption ratio (%)	68.14 ±0.18	71.15 ±0.94	84.98 ±0.94	92.12 ±0.93	71.12 ±0.45	74.15 ±0.76	81.12 ±0.71	73.14 ±0.63	78.14 ±0.79	83.41 ±0.14
Ritonavir content (%)	78.15 ±0.98	73.15 ±1.96	79.24 ±1.78	87.21 ±1.69	87.12 ±1.14	91.14 ±1.03	94.12 ±1.17	84.14 ±0.79	93.14 ±0.97	99.47 ±1.12
Lopinavir content (%)	76.47 ±1.04	73.17 ±1.11	79.18 ±1.17	86.76 ±0.96	73.14 ±1.13	78.19 ±1.09	84.73 ±1.07	84.17 ±1.07	91.17 ±1.17	99.18 ±1.23
Weight variation (mg, ± %)	231.25 to 268.75 mg (within USP specified limits of ±7.5%)									

Tablets obtained were of uniform weight (due to uniform die fill) with acceptable variation as per USP specifications. Drug content, hardness, water absorption ratio and wetting time were found to be in the satisfactory range as shown in Table 3. Friability value of prepared tablets was found to be less than 1% (an indication of good mechanical resistance of tablets). Drug release was determined from standard curve. A drug release of Lopinavir and Ritonavir is shown in figure 2 and 3 respectively.

This rapid disintegration of the FDTs was due to the penetration of saliva into the pores of the tablet, which lead to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. The amount of Superdisintegrant crospovidone (Formulation with code FC), Sodium starch glycolate (Formulation with code FS) and freeze-dried powder of *Annona reticulata* - Custard apple (Formulation with code FCA) were similar in proportion i.e. 5, 10 and 15 mg.

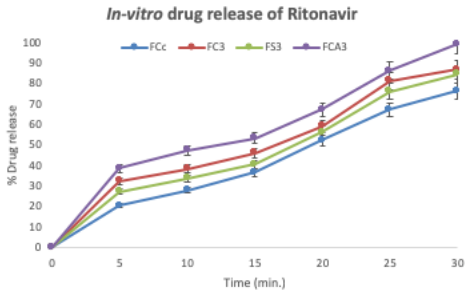

Figure 2: *In-vitro* drug release of Ritonavir using synthetic superdisintegrants and freeze-dried powder of *Annona reticulata*

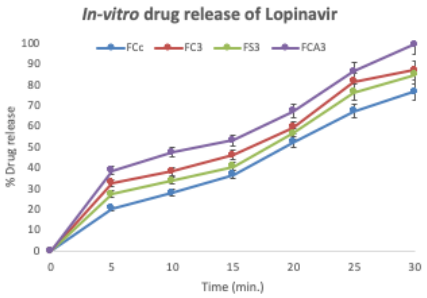

Figure 3: *In-vitro* drug release of Lopinavir using synthetic superdisintegrants and freeze-dried powder of *Annona reticulata*

CONCLUSION

In the present study, it can be concluded that fast dissolving tablets of Ritonavir and Lopinavir can be prepared by using pulp of *Annona reticulata* which shows better drug release and disintegration time as compared to tablets prepared by synthetic super disintegrants like crospovidone and sodium starch glycolate.

REFERENCES

1. Shirsand SB, Suresh S, Swamy PV, Para MS, Kumar DN. Formulation design of fast disintegrating tablets using disintegrant blends. Indian journal of pharmaceutical sciences. 2010Jan;72(1):130.
2. World Health Organization. HIV/AIDS data and statistics. http://www.who.int/hiv/data/en/ accessed on 19.10.2018.
3. Phelps BR, Rakhmanina N. Antiretroviral drugs in pediatric HIV-infected patients. Pediatric Drugs. 2011 Jun 1;13(3):175-92.
4. Shirsand SB, Shilashri VJ, Gumate RT. *Annona reticulata* Pulp Powder as a Disintegrant in Design of Fast Dissolving Tablets. Journal of PharmSciTech. 2016. 6(1): 34-39.
5. Yadav ND, Pingale PL, Tatane SR. Comparative study on effect of natural and artificial superdisintegrants in the formulation of fast dissolving aspirin tablet. Journal of Pharmacy Research. 2010 Jul;3(7):1594-7.
6. Marshall K, Lachman N, Liberman HA, Kanig J. The theory and practice of industrial pharmacy. Edition. 1987; 3:66-99.
7. Ansel HC, Popovich NG, Allen LV, Pharmaceutical dosage forms and drug delivery system, 8th edition, New Delhi, B.I. Waverly Pvt. Ltd, 1995,189-94, 235-36.
8. Devineni J., Rangani V., Nunna S. New sensitive UV spectrophotometric method for simultaneous estimation of Lopinavir and Ritonavir in fixed dose combination as softgels. International Journal of Pharmaceutical Development and Technology. 2016. 7(1): 25-30.

How to cite this article:
Pingale Prashant L. Formulation, evaluation of fast dissolving tablet of anti-HIV drugs as fixed dose combination: Use of freeze-dried powder of *Annona reticulata* and comparison with synthetic superdisintegrants. J Pharm Sci Innov. 2019;8(1):38-41.
http://dx.doi.org/10.7897/2277-4572.081124

Source of support: Nil, Conflict of interest: None Declared