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Impact of superdisintegrants on the release of oro-dispersible tablets of losartan potassium: A comparative analysis

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ABSTRACT

The purpose of the present study was to study the impact of superdisintegrant on the release of Oro-Dispersible Tablet containing Losartan Potassium as a model drug using Natural and Synthetic Superdisintegrants. Various formulations were prepared by direct compression using different concentrations of natural superdisintegrant, Husk of *Plantago ovata* and synthetic superdisintegrants namely Kyron T-314, and croscarmellose sodium. The blends were evaluated for additive properties. Prepared tablets were evaluated for physical parameters and in vitro drug release. Dissolution profile suggested that tablet prepared with *Plantago ovata* husk and Kyron T-314 were capable of releasing up to 99 % drug within 15 minutes in phosphate buffer 6.8 pH, by an appropriate combination of excipients it is thus possible to obtain Oro-Dispersible Tablets using simple and conventional technique.

Keywords: Oro-Dispersible Tablet, *Plantago ovata* Husk, Kyron T-314, Croscarmellose sodium.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this problem, scientists have developed innovative drug delivery systems known as Orally Disintegrating Tablets. These are novel types of tablets that disintegrate/disperse/dissolve in saliva [1]. The demand for solid dosage forms that can be chewed, or rapidly dissolved or dispersed or dissolved/suspended in water prior to administration, particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form into a solution or suspension in the mouth without the need for water [1, 2]. The United States Food and Drug Administration define ODT as “a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.” The disintegration time for ODTs generally ranges from several seconds to about a minute [3]. The active agent can thus be rapidly dissolve in saliva and be absorbed through whatever membrane it encounters, during deglutination, unless it is protected from pregastric absorption [4]. To fulfill these requirements tablet must be highly porous, incorporating highly hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of matrix [5, 6]. The basic approach used in the development of the ODTs is the use of

superdisintegrants. Many approaches have been developed to manufacture ODTs. These include vacuum drying, direct compression, Lyophilization and molding. The direct compression is inexpensive and convenient for producing tablet of sufficient mechanical strength.

Losartan potassium is a potent highly specific angiotensin II type (AT₁) receptor antagonist with anti – hypertensive activity. It develops a gradual and long lasting effect as antihypertensive, becoming a new alternative to this frequent chronic disease treatment [7]. The disease in the blood pressure is produced by competitive antagonist action of AT₁ receptor and release of aldosterone and adrenaline from adrenal glands, renal action promoting salt and water reabsorption.

Polacrillin Potassium (KYRON T-314) is 2-methyl-2-propenoic acid polymer with divinylbenzene, potassium salt. It is a cation exchange resin used in oral pharmaceutical formulation as a tablet superdisintegrant. It appears as a cream colored, odorless and tasteless, free flowing powder [8]. The present study involved the comparison of properties of synthetic and natural superdisintegrant with newer superdisintegrant Kyron T-314.

MATERIALS AND METHODS

Materials

Losartan Potassium was gifted by, Cipla Mumbai. Croscarmellose sodium was procured from S.D. Fine Chemicals. Kyron T-314 was gifted by Corel Pharma Chem., *Plantago ovata* husk was procured from local market Sucralose was gifted by JK Sucralose; Starch 1500 X was gifted by Colorcon Asia Pvt.Ltd, Avicel PH102 was gifted by Vijlak Pharma Ltd, India. All other ingredients used were of analytical grade.

Method

Preparation of Losartan ODT

Tablets of Losartan Potassium were prepared by direct compression method. Starch 1500 X and Fumed silica were passed through 40 mesh screen, thereafter Losartan Potassium with Sucralose, Avicel PH 102, Stearic acid, Croscarmellose sodium / *Plantago ovata* husk/ Kyron T-314 were blended for 15 minutes with pestle and mortar. Magnesium stearate was further added and blended for additional 5 mins. Finally, each mixture were weighed and fed manually into the die of a single punch tableting machine, equipped with round beveled punches (12.0 mm), to produce the desired tablets [9]. Composition of Losartan Potassium ODT has been shown in the Table 1.

Table 1: Composition of Losartan Potassium ODT

Ingredients	F ₀	FS ₁	FS ₂	FS ₃	FH ₁	FH ₂	FH ₃	FK ₁	FK ₂	FK ₃
Losartan Potassium	50	50	50	50	50	50	50	50	50	50
Avicel PH 102	3.01	2.51	2.01	1.51	2.51	2.01	1.51	2.51	2.01	1.51
Starch 1500 X	9.62	9.12	8.62	8.12	9.12	8.62	8.12	9.12	8.62	8.12
Croscarmellose sodium	-	1	2	3	-	-	-	-	-	-
Husk	-	-	-	-	1	2	3	-	-	-
Kyron T-314	-	-	-	-	-	-	-	1	2	3
Stearic acid	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64
Aerosil	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32
Magnesium stearate	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
Sucralose	1	1	1	1	1	1	1	1	1	1
Menthol	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25

In vitro evaluation of powder blends

Bulk density

A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density; results are expressed in (gm/ml) [10, 11].

$$\text{Bulk Density (BD)} = \frac{\text{Weight of the powder sample}}{\text{volume of the powder sample}}$$

Tapped density

The cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder, results are expressed in (gm/ml) [10, 11].

$$\text{Tapped Density (TD)} = \frac{\text{Weight of the powder sample}}{\text{volume of the tapped powder sample}}$$

Carr's index

An accurate weight of formula blend was poured into a volumetric cylinder to occupy a volume (V_0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). Carr's "percent compressibility" was calculated using the equation [10,11].

$$\text{Compressibility Index (CI)} = \frac{V_0 - V_f}{V_0} \times 100$$

Angle of repose

The angle of repose was measured by passing the prepared blend through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer, and the radius (r) of the cone base was also determined. The angle of repose (θ) was calculated from the formula [12, 20].

$$\theta = \tan^{-1} [h/r]$$

where θ is angle of repose.

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the formula [11].

$$\text{Hausners Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Swelling index

The study was carried out using a 100 ml stoppered graduated cylinder. The initial bulk volume of 1 gm of dried mucilage was recorded. Water was added in sufficient quantity to yield 100 ml of a uniform dispersion. The sediment volume of the swollen mass was measured after 24 hour, stored at room temperature. The swelling ratio was calculated by taking the ratio of the swollen volume to the initial bulk volume [13].

In vitro evaluation of the prepared tablets**Tablet weight variation**

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ± 1 mg by using Sartorius balance (BT 124 S). Weight control is based on a sample of 20 tablets. Determinations were made in triplicate [12].

Tablet thickness

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge [12].

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg/cm² is considered adequate for mechanical stability. Determinations were made in triplicate [12].

Tablet friability

Friability of the tablets was determined using Roche Friabilator (Electro lab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula [12].

$$F (\%) = \left(1 - \frac{W_0}{W} \right) \times 100$$

Where, W_0 is weight of the tablets before the test, W is the weight of the tablets after test

In vitro disintegration time

One tablet from each formulation was placed in USP tablet disintegration apparatus without disk, containing 900 ml of pH 6.8 phosphate buffer at $37 \pm 0.5^\circ \text{C}$, and the time required for complete disintegration was determined [16].

Wetting time

Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10 cm diameter. Ten mL of water at $37 \pm 0.5^\circ \text{C}$ containing eosin, a water-soluble dye, was added to the petri dish.

A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time [16, 17].

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 mL of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using following equation [16, 17, 18, 19].

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where, W_a = weight of tablet after absorption, W_b = Initial weight of the tablet

In vitro release studies

Drug release studies of the prepared Orodispersible tablets with semi synthetic and natural superdisintegrants were performed, in triplicate, in a USP Dissolution Apparatus II (Paddle type) (Electro lab TDT-08L, India). The dissolution test was performed using Phosphate buffer pH 6.8 at $37 \pm 0.5^\circ \text{C}$. The speed of rotation of paddle was set at 50 rpm. Aliquots of 1mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane ($0.45 \mu\text{m}$), and fresh dissolution medium was replenished immediately. Absorbance of solution was checked by UV spectrophotometer (Shimadzu-1800, Kyoto, Japan) at a wavelength of 278 nm and drug release was determined from standard curve ($R^2 = 0.999$).

Accelerated stability studies

Stability studies were carried out on optimized formulation. The tablets were stored at 40°C and 75% RH for duration of three months. After for every one month samples were withdrawn and tested for various parameters like hardness, drug content and in vitro drug release.

RESULTS AND DISCUSSION**Drug-Excipients Compatibility Studies****FT-IR studies**

FT – IR studies were conducted by taking Drug Polymer in the ratio 1:1 to ascertain the compatibility between Losartan Potassium and the novel polymer i.e. Kyron T-314. The IR spectra revealed the presence of the characteristic peaks and relative intensities of Losartan Potassium. The characteristic peaks of drug such as of OH (3130.57), CH Stretching Aromatic (3003.27 cm^{-1}), CH Stretching Aliphatic (2963.12 cm^{-1}), C=O (1749 cm^{-1}), Al-CH-bend (1454.3 cm^{-1}), Ar-CH In plane Bending (1091.75 cm^{-1}), Ar-CH Out plane Bending (920.08 cm^{-1}), c-o-c Ether linkage (1193.98 cm^{-1}) appeared for the drug polymer physical mixture. Fig 1.

Evaluation of powder blend

The blend of all the batches were evaluated for parameters like angle of repose was found to be between 25.67 and 30.64 . Bulk density was found to be between 0.55 and 0.64 (gm/cc) and tapped density between 0.63 and 0.76 (gm/cc) . Carr's Index was found to be in between $8 - 17$, Hausner's ratio ranged between 1.09 and 1.20 . All the formulations showed good blend properties for direct compression technology as shown in Table 2.

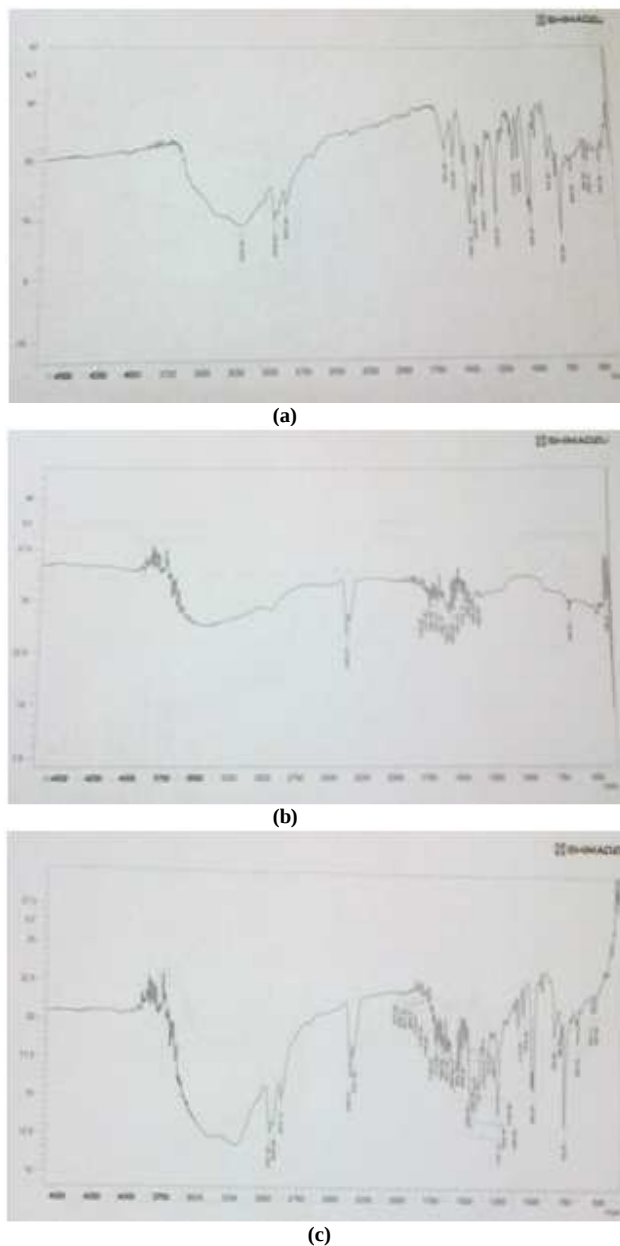


Fig. 1 FT-IR spectra of a) Losartan potassium, b) Kyron T-314, c) Physical mixture of Losartan Potassium and Kyron T-314

Table 2: In vitro evaluation data of Powder blends

Formulatic	Bulk Density (gm/cc)	Tapped Density (gm/cc) $\pm$ SE	Angle of Repose	Carr's index $\pm$ SE	Hausner's Ratio
F ₀	0.55 $\pm$ 0.010	0.63 $\pm$ 0.006	30.64	12.69	1.14
FC ₁	0.60 $\pm$ 0.015	0.72 $\pm$ 0.011	29.55	16.66	1.20
FC ₂	0.59 $\pm$ 0.005	0.69 $\pm$ 0.011	28.78	14.49	1.16
FC ₃	0.61 $\pm$ 0.005	0.73 $\pm$ 0.006	26.76	16.43	1.19
FH ₁	0.63 $\pm$ 0.015	0.76 $\pm$ 0.003	29.00	17.10	1.20
FH ₂	0.64 $\pm$ 0.006	0.76 $\pm$ 0.009	30.65	15.78	1.18
FH ₃	0.64 $\pm$ 0.009	0.70 $\pm$ 0.009	25.67	08.57	1.09
FK ₁	0.65 $\pm$ 0.010	0.71 $\pm$ 0.004	27.89	08.45	1.09
FK ₂	0.63 $\pm$ 0.010	0.70 $\pm$ 0.011	28.35	10.00	1.11
FK ₃	0.63 $\pm$ 0.006	0.71 $\pm$ 0.009	26.34	11.26	1.12

Value are expressed as Mean $\pm$ SD *n = 3 F₀ = Control formulation, FC₁₋₃ = Formulation of Croscarmellose sodium, FH₁₋₃ = Formulation of Plantago ovata Husk, FK₁₋₃ = Formulation of Kyron T-314

Swelling Index

The swelling index of Husk, determined in phosphate buffer pH 6.8 was 84 %. There was a significant change in swelling by the end of the study, which indicated that the mucilage had excellent swelling properties, Table 3.

Table 3: Swelling Index comparison of Natural and semi synthetic Superdisintegrant

Name of Superdisintegrant	Swelling Index (% V)
Kyron T-314	88
Plantago ovata husk	84
Croscarmellose sodium	75

Evaluation of oro-dispersible tablets

Results for hardness, friability, content uniformity, and disintegration time are indicated in Table 4. and were found to be well within the limits. The hardness of the tablets was found to be between 3.23 and 4.95 kg/cm² and friability was found to be below 1 % which indicated good mechanical resistance. The drug content was found to be in the range 98.77±1.00 to 99.93±1.01.

Table 4: *In vitro* evaluation data of Losartan Potassium Oro Dispersible Tablets

Formulation	Thickness (cm)	Weight Variation (mg)***	Hardness (Kg/Cm ²)*	Friability (%w/w)*	Disintegration Time (secs)**	Drug content (%)	Water absorption ratio (%)**	Wetting Time (secs)
F ₀	2.31 ±0.24	65±1.00	3.23	0.33	145	98.77±1.00	32±0.40	170
FC ₁	2.33 ±0.15	64±1.15	4.88	0.36	35	99.93±1.01	57±0.55	50
FC ₂	2.31±0.11	64±1.00	4.90	0.35	32	99.90±0.11	55±0.41	41
FC ₃	2.28±0.17	65±1.15	4.86	0.35	28	99.34±1.10	75±0.12	38
FH ₁	2.63±0.24	64±1.11	4.81	0.35	25	99.57±0.61	63±0.51	30
FH ₂	2.60±0.24	64±1.05	4.90	0.35	26	99.67±0.14	77±0.63	30
FH ₃	2.53±0.22	65±0.86	4.95	0.36	27	99.36±0.40	79±0.64	33
FK ₁	2.34±0.21	64±1.28	4.34	0.45	16	99.59±0.20	80±0.66	26
FK ₂	2.30±0.20	65±0.95	4.67	0.48	18	99.36±0.12	81±0.45	30
FK ₃	2.34±0.24	66±1.04	4.54	0.40	19	99.30±0.12	80±0.55	31

Value are expressed as Mean ± SD, ***n = 20, **n = 6, *n = 3

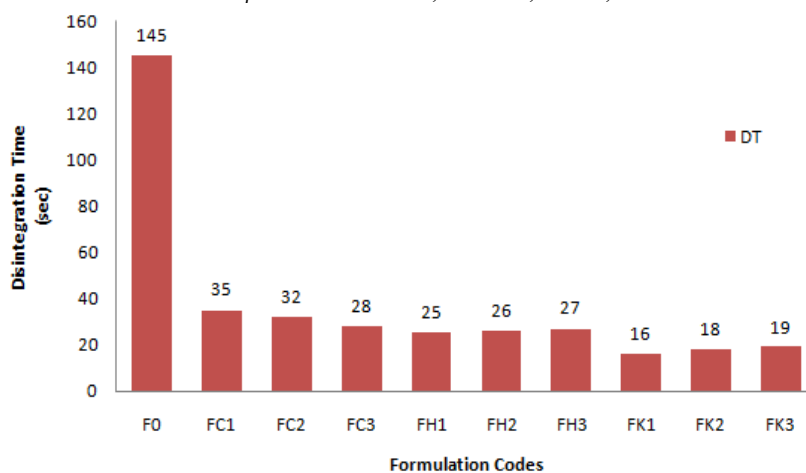


Fig 2. Disintegration time of different formulations at different concentration

In-vitro disintegration

The most important parameter that needs to be optimized in the development of oro-dispersible tablets is the disintegration of tablets. In the present study disintegration time of all the batches were found to be in the range of 25 to 27 secs for formulations having *Plantago ovata* Husk as superdisintegrant fulfilling the official requirements (3mins) while in the range of 16 to 19 secs for formulations having Kyron T-314 as superdisintegrant, whereas formulations having Cross-carmellose sodium showed DT between 28 to 35 secs. The control formulation showed disintegration time of 145 secs as depicted in the figure Fig 2. The rapid disintegration of the oral dispersible tablets

were due to penetration of saliva into the pores of the tablets, which leads to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. Formulation (FK₂) with superdisintegrant (Kyron T-314) in 3% concentration was selected as optimized formulation, as it showed less disintegration time of 18 secs, which may be due to faster swelling rate upon contact with water and also the problem of lump formation was also not reported. Kyron T-314 was effective at concentration i.e. 3 % and next best DT was shown by *Plantago ovata* Husk at concentration i.e. 3 %.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients therefore it was used as a measure to correlate with disintegration time in oral cavity. Since the dissolution process of a tablet depends upon the wetting time, followed by disintegration it could be predicted that wetting time can be the cause of disintegration, which can be attributed by the fact that aqueous medium might have penetrated into the tablet and have replaced the adsorbed air on the particle, which in turn should have weakened the intermolecular forces between the bonds and finally broken the tablet into the fine dispersion. The wetting time was in the range of 30 to 24 sec for Husk, whereas 15 to 16 sec for Kyron T-314, it can be depicted by the relation shown in the Figure 3.

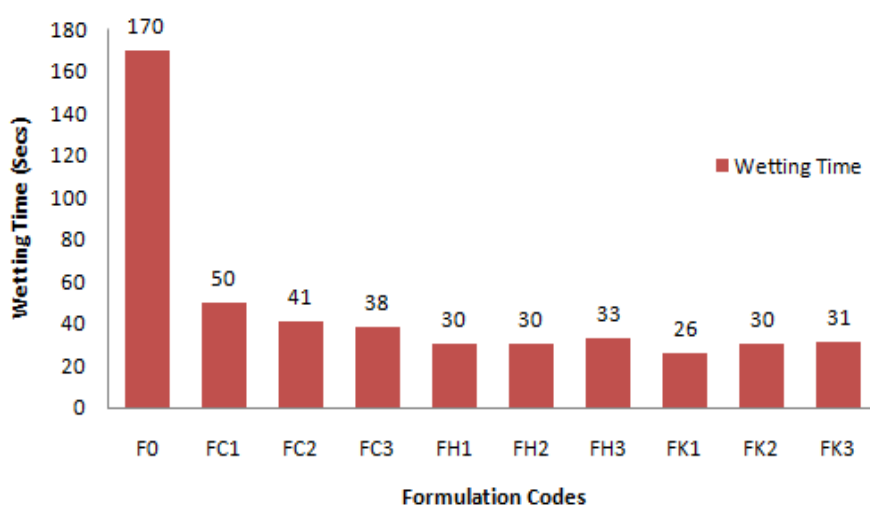


Fig 3. Wetting time of different formulation with different concentration

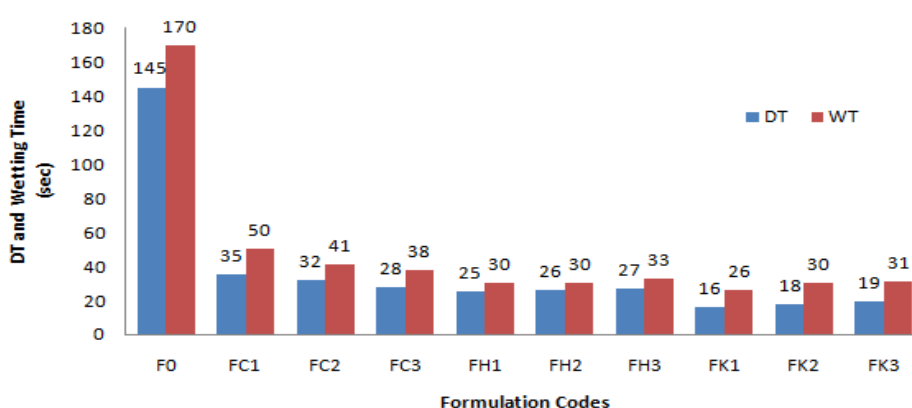


Fig 4. Disintegration Time and Wetting Time of different formulations

Water-absorption ratio

Water absorption ratio was performed for ensuring the moisture sorption and water uptake properties of superdisintegrants. It was observed that water absorption ratio increased to a considerable extent and disintegration and wetting time was decreased when superdisintegrant concentration was increased. The water absorption ratio of the formulated tablets were found in the range of 63 – 79% for formulation having Husk, while for Kyron T-314 it was in the range of 80 – 81 %. As shown in the Figure 4.

In – vitro drug release

The in-vitro drug release studies were performed on the formulations prepared using either natural or semi synthetic superdisintegrants, drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The percent drug release from the optimized (FK₂) Oro Dispersible tablets of Losartan Potassium using Kyron T-314 as superdisintegrants presented 99 percent release in 25 min, whereas the control formulation (C₀) which was devoid of any of superdisintegrant presented complete drug release in about 35 min.. The percentage cumulative drug release has been shown in the Figure 5.

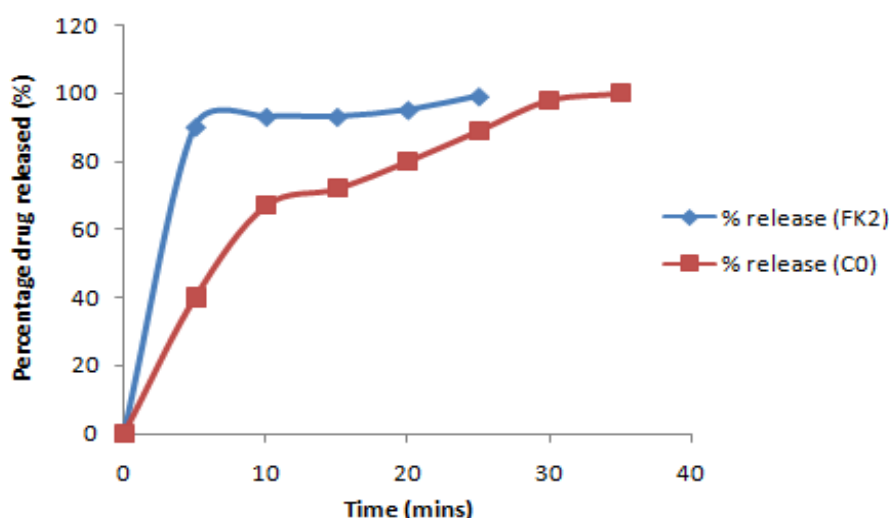


Fig 5. Comparison of in vitro drug release of optimized FK₂ with control C₀ formulations

Stability studies

The stability of the optimized formulation was known by performing stability studies for three months at accelerated conditions of 40°C±75 % RH on optimized formulation. The formulation was found to be stable, with insignificant change in the hardness, disintegration time, and *in vitro* drug release pattern the data have been given in Table 5.

Table 5: Stability study data for optimized formulation FK₂

Parameters	Time in months			
	0 (Initial)	1 st month	2 nd month	3 rd month
Hardness (kg/cm ²)	4.67	4.51	4.49	4.502
Disintegration time (sec)	18	15	16	15
Drug content (%)	99.36	99.45	99.10	99.09
<i>In vitro</i> drug release (%)	100	99	98	99

CONCLUSION

Oro dispersible tablets transform into easy-to-swallow suspension on contact with the saliva, after ingested in mouth. These are particularly useful for pediatric or geriatric patients, can be taken without liquids and facilitate treatment of Hypertension. The developed formulations have suitable characteristics that distinguish them from common solid dosage forms, such as rapid disintegrating, combining advantages of both liquid and conventional tablet formulations, ease of swallowing and possible taste-masking components for an acceptable taste in the mouth. From the results obtained it can be concluded that Kyron T-314 showed sufficient promise to warrant its use as superdisintegrant, as shown by the faster in-vitro release from the formulations containing it as superdisintegrant.

From this study, results revealed that it is possible to enhance dissolution rate by using direct compression technique using different concentrations of Kyron T-314, Plantago ovata husk as superdisintegrants.

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