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Original article

COMPARATIVE EVALUATION OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF FAST DISSOLVING TABLETS

P. K. LAKSHMI*, Y. NARENDRA, Swathi Latha REWANTHWAR, V. NEEHARIKA

G. Pulla Reddy College of Pharmacy, Department of Pharmaceutics, Mehdipatnam, Hyderabad 500 028 (AP), INDIA

Abstract

The main objective of this study was to prepare and evaluate fast dissolving tablets of Levocetrizine dihydrochloride with synthetic and natural superdisintegrants. Various formulations were prepared by direct compression using different concentrations of natural superdisintegrant i.e. isolated mucilage Hibiscus rosa sinensis Linn and synthetic superdisintegrants namely Kyron T-314, croscarmellose sodium and crospovidone. The compatibility studies between drug and excipients were carried out using FTIR spectroscopy. The blend was evaluated for additive properties. The tablets were evaluated for physical properties and in vitro drug release. From this study formulation containing Kyron T-314(2.4%) was found to possess better disintegration time (30 sec), water absorption ratio (95), and wetting time (34 sec). The in vitro dissolution of Kyron T-314 was found to have comparable release with other formulations of ODT with Hibiscus rosa sinensis Linn mucilage powder and croscarmellose sodium. natural superdisintegrants like Hibiscus rosa sinensis Linn mucilage powder showed better disintegrating property than the most widely used synthetic superdisintegrants like croscarmellose sodium. But Kyron T-314 was found to be better superdisintegrant among all; natural superdisintegrant like Hibiscus rosa sinensis Linn was also found to possess comparable properties of ODT like other synthetic superdisintegrants. An accelerated stability study on optimized formulation was performed as per ICH guidelines. It was found to be stable, with insignificant changes in the hardness, disintegration time, and in-vitro drug release pattern.

Key words: *Fast dissolving tablets, Levocetrizine dihydrochloride, Kyron T-314, Croscarmellose, Isolated mucilage of Hibiscus rosa sinensis, crospovidone.*

Hızlı Dağılan Tablet Formülasyonlarında Kullanılan Doğal ve Sentetik Süperdağıtıcıların Karşılaştırılmalı Değerlendirilmesi

Bu çalışmanın temel amacı sentetik ve doğal süperdağıtıcı içeren levosetirizin dihidroklorür hızlı dağılan tabletlerin hazırlanması ve değerlendirilmesidir. Direkt basım yöntemi ile doğal süperdağıtıcılardan Hibiscus rosa sinensis Linn müsilajı ve sentetik süperdağıtıcılardan Kyron T-312, kroskarmeloz sodium ve krospovidonun çeşitli konsantrasyonları kullanılarak bir çok formülasyon hazırlanmıştır. Etkin madde ve eksipiyanlar arasındaki geçimlilik çalışmaları FTIR spektroskopisi kullanılarak yapılmştır. Karışımın aditif özellikleri değerlendirilmiştir. Tabletlerin fiziksel özellikleri ve in vitro ilaç salım özellikleri değerlendirilmiştir. Bu çalışmada Kyron T-312 (%2,4) içeren formülasyonun daha iyi dağılma zamanına (30 s), su absorpsiyon oranı (95) ve ıslanma süresine (34 s) sahip olduğu görülmüştür. Kyron T-314'ün in vitro çözünme testinde Hibiscus rosa sinensis Linn mucilage tozu ve kroskarmeloz sodyum içeren formülasyonlar ile karşılaştırılabilir sonuçlar elde edilmiştir. Hibiscus rosa sinensis Linn müsilaj tozunun kroskarmeloz sodyum gibi çok yaygın kullanılan sentetik süperdağıtıcıdan daha iyi dağıtıcı özellik gösterdiği bulunmuştur. Ancak Kyron T-314'ün hepsi içinde daha iyi bir süperdağıtıcı olduğu görülmüştür. Hibiskus rosa sinensis Linn gibi doğal süperdağıtıcıların ODT gibi diğer sentetik süperdağıtıcılar ile karşılaştırılabilir özellikler gösterdiği bulunmuştur. Optimize edilmiş formülasyon için hızlandırılmış stabilite çalışmaları ICH kılavuzlarına göre yapılmış, formülasyon sertlik, dağılma zamanı ve in vitro salım özelliklerine göre stabil bulunmuştur.

Anahtar kelimeler: *Hızlı dağılan tabletler, Levosetirizin dihidroklorür, Kyron T-314, Kroskarmeloz, Hibiscus rosa sinensis'in izole müsilajı, Krospovidon*

***Correspondence:** E-mail: drlakshmisuresh@gmail.com

INTRODUCTION

Tablets are the most routinely used dosage form because it offers many advantages in terms of self administration, ease in manufacturing. But major disadvantage is incompliance with pediatric and geriatric patients, bedridden or developmentally disabled patients who have difficulty in swallowing (Dysphagia).They experience difficulty in swallowing conventional tablets. Oral dispersible tablets or fast dissolving tablets have developed to overcome all this disadvantages by the innovative discovery of scientists are defined.

They are defined as uncoated tablets intended to be placed in the mouth where they disperse readily within minutes before swallowing[1]. Due to the presence of super disintegrants, it gets dissolve quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Since the absorption is taking place directly from the mouth, bioavailability of the drug increases. Drug present in orodispersible tablets bypasses first pass metabolism.

Oral dispersible tablets (ODTs) are also called as orally disintegrating tablets, mouth dissolving tablets, rapid-dissolving tablets, fast-disintegrating, fast dissolving tablets (1,2).

Drug candidates suitable for oral dispersible tablet should posses following characteristics (3):

- No bitter taste
- Good stability in water and saliva.
- Dose should be as low as possible.

Unsuitable drug candidate for oral dispersible tablet should possess:

- Short half-life and frequent dosing.
- Drugs having very bitter taste.
- Required controlled or sustained release.

Drug chosen for the present study is levocetrizine dihydrochloride because of its application in allergic condition, fast onset of action and avoidance of water is highly desirable.

Levocetrizine dihydrochloride is an orally active H1-receptor antagonist. It is indicated for the relief of symptoms associated with perennial allergic rhinitis and for treatment of the uncomplicated skin manifestations of chronic idiopathic utricaria in adults and children 6 months of age and older.

The basic approach in development of ODTs is use of disintegrants. It plays an important role in the disintegration and dissolution of ODT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates.

Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wettability and dispersebility of the system, thus enhancing the disintegration and dissolution. Care should be taken while selecting concentration of the superdisintegrant. Superdisintegrants are selected according to critical concentration of the disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of superdisintegrant which is above the critical concentration. At this concentration the disintegration time remains almost constant or even increases.

TECHNOLOGIES USED FOR ORAL DISPERSIBLE TABLET (4-9)

The technologies used to manufacture mouth dissolving tablets can be classified as

- Direct compression
- Sublimation
- Humidity treatment
- Sintering
- Wet granulation
- Dry granulation

- Melt granulation
- Spray drying

MATERIALS AND METHODS

Materials

Levocetrizine dihydrochloride was purchased from Seemed Labs Ltd; Hyderabad, India. Talc, Magnesium stearate, peppermint flavor was purchased from SD Fine – Chem Pvt Ltd; Mumbai, India. Croscarmellose sodium, Crospovidone and Spay dried lactose was procured from Natco Pharma Ltd, Hyderabad, India. Kyron T-314 was procured from Corel Pharma Chem Pvt Ltd; Mumbai, India. Aspartame was purchased from Otto Kemi Pvt Ltd; Mumbai, India. *Hibiscus rosa sinensis* was obtained from Local area of Hyderabad. Mannitol was purchased from Universal Laboratories Pvt. Ltd, Mumbai.

Isolation of mucilage

The fresh leaves of *Hibiscus rosa sinensis* were collected, washed with water to remove dirt and debris, and dried. The powdered leaves were soaked in water for 5-6 hr, boiled for 30 min, and kept aside for 1 hr. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the Mucilage in a quantity of three times the volume of the total filtrate. The Mucilage was separated, dried in an oven at a temperature < 50 °C, collected, dried again. The powder obtained was passed through a sieve (mesh no# 80), and stored for further use in desiccators (10).

Preparation of mixed blend of drug and excipients

All the ingredients were triturated individually in a mortar and passed through #60 mesh. Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except talc and magnesium stearate. At last magnesium stearate and talc were added as lubricant. The powder blend was evaluated for flow properties

Drug-excipient interaction studies

The physical mixture of pure drug sample and different excipients in the ratio 1:1 were subjected to IR spectral studies using FTIR spectrophotometer (FTIR 8400 S, Shimadzu, Japan).

Characterization of powder blends of active pharmaceutical ingredient and excipients (11)

Angle of repose

100 g of the blend was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel.
The interrelationship between the angle of repose and flow properties of powder are shown in the Table 2 Angle of repose is calculated by the following formula.

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

Where, θ = angle of repose, r=radius of the pile, h=height of the pile,

Bulk density

Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$*b = M/V*$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula.

$$*t = M/V_t$$

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Compressibility Index (C.I) which is calculated using the formula,

$$C.I\ (\%) = \frac{\text{Tapped Density} - \text{Bulk Density} \times 100}{\text{Tapped Density}}$$

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the using the formula,

$$\text{Hausner Ratio} = *t/*d$$

Where *t = Tapped Density, *d = Bulk Density

Compression of tablets

All ingredients were triturated individually in a mortar and passed through #60 mesh. Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed in to tablets containing 5 mg drug using 4.75 mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 50 mg (Table 1).

Evaluation of tablets

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging.

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Table 1. Tablet formulations of levocetrizine dihydrochloride containing different superdisintegrants.

Formulation	Levocetrizine Di HCl (mg)	Kyron T-314 (mg)	Mucilage powder (mg)	CP (mg)	CCS (mg)	Spray dried lactose (mg)	Mannitol (mg)	Aspartame (mg)	Total (mg)
LK1	5	0.2	-	-	-	31.8	10	2	50
LK2	5	0.4	-	-	-	31.6	10	2	50
LK3	5	0.6	-	-	-	31.4	10	2	50
LK4	5	0.8	-	-	-	31.2	10	2	50
LK5	5	1	-	-	-	31.0	10	2	50
LK6	5	1.2	-	-	-	30.8	10	2	50
LK7	5	1.4	-	-	-	30.6	10	2	50
LK8	5	1.6	-	-	-	30.4	10	2	50
LK9	5	1.8	-	-	-	30.2	10	2	50
LK10	5	2.0	-	-	-	30.0	10	2	50
LCS1	5	-	-	-	0.2	31.8	10	2	50
LCS2	5	-	-	-	0.4	31.6	10	2	50
LCS3	5	-	-	-	0.6	31.4	10	2	50
LCS4	5	-	-	-	0.8	31.2	10	2	50
LCS5	5	-	-	-	1.0	31.0	10	2	50
LCS6	5	-	-	-	1.2	30.8	10	2	50
LCS7	5	-	-	-	1.4	30.6	10	2	50
LCS8	5	-	-	-	1.6	30.4	10	2	50
LCS9	5	-	-	-	1.8	30.2	10	2	50
LCS10	5	-	-	-	2.0	30.0	10	2	50
LH1	5	-	0.2	-	-	31.8	10	2	50
LH2	5	-	0.4	-	-	31.6	10	2	50
LH3	5	-	0.6	-	-	31.4	10	2	50
LH4	5	-	0.8	-	-	31.2	10	2	50
LH5	5	-	1.0	-	-	31.0	10	2	50
LH6	5	-	1.2	-	-	30.8	10	2	50
LH7	5	-	1.4	-	-	30.6	10	2	50
LH8	5	-	1.6	-	-	30.4	10	2	50
LH9	5	-	1.8	-	-	30.2	10	2	50
LH10	5	-	2	-	-	30.2	10	2	50
LCP1	5	-	-	0.2	-	31.8	10	2	50
LCP2	5	-	-	0.4	-	31.6	10	2	50
LCP3	5	-	-	0.6	-	31.4	10	2	50
LCP4	5	-	-	0.8	-	31.2	10	2	50
LCP5	5	-	-	1.0	-	31.0	10	2	50
LCP6	5	-	-	1.2	-	30.8	10	2	50
LCP7	5	-	-	1.4		30.6	10	2	50
LCP8	5	-	-	1.6	--	30.4	10	2	50
LCP9	5	-	-	1.8	-	30.2	10	2	50
LCP10	5	-	-	2.0	-	30.0	10	2	50

LK= Formulations of Kyron, LH= Formulations of mucilage, LCP=Formulations of crospovidone, LCS= Formulations of croscarmellose sodium. **Note**: 0.5 mg of talc, magnesium stearate, and mint flavor were used in all formulations.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading noted.

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 100 rpm for 4 minutes 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

$$\mathbf{F\ \% = (1-W_0\ /W) \times 100}$$

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

Wetting time

Five circular tissue papers of 10-cm diameter were placed in a Petri dish with a 10-cm diameter. 10 ml of water at $37^0C \pm 0.5^0C$ 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. Six tablets from each formulation batch were tested randomly and the average reading noted.

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

$$\mathbf{R = W_a - W_b\ /W_b \times 100}$$

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Content uniformity

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 4mg was weighed and dissolved in 100 mL of 6.8 phosphate buffer, filtered and drug content analyzed spectrophotometrically at 231nm.

In-vitro disintegration time

Disintegration time was measured using a modified disintegration method. For this purpose, a petridish was filled with 10 ml of water at $37^0\ C \pm 0.5^0C$. The tablet was carefully put in the centre of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Swelling index

Swelling Index is the volume in milliliters that is occupied by 1 gm of drug or any adhering mucilage after it has swollen in an aqueous liquid for 3hours. The methods of studying swelling index for, *Hibiscus rosa sinensis* Linn, Crospovidone, Kyron T-314 and croscarmellose sodium were carried out. Swelling index was calculated from mean readings of three determinations.

Specific quantity of super disintegrant was taken in a 25 mL glass- stoppered measuring cylinder. The internal diameter of the cylinder should be about 16mm, the length of the graduated portion about 125 mm, marked in 0.2 mL division from 0 to 25 mL in an upwards direction. 25 mL of water was added and the mixture was thoroughly mixed for every 10 minutes for 1 hour. The mixture was allowed to stand for 3 hours at room temperature Measure

the volume in ml occupied by the material. Calculate the mean value of the individual determinations, related to 1g of the material.

$$\text{Swelling index (S.I.)} = \{(W_t - W_0) / W_0\} \times 100$$

Where, S.I. = swelling index. , W_t = Weight of superdisintegrants at time t. W_0 = Weight of superdisintegrant before immersion.

In vitro release

In-vitro drug release of levocetrizine dihydrochloride orodispersible tablets was determined using USP dissolution Apparatus II (Paddle type) (Electro lab TDT-08L). The dissolution test was performed using 900 ml 6.8 phosphate buffer at 37^0C ± 0.5^0C. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 5, 10, 15, 20, 25, and 30 min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 231 nm and drug release was determined from standard curve.

Accelerated stability studies

The optimized formulation was subjected to stability studies at 40^0C±2^0C/75%±2%RH for period of three months. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for three months. For every one month tablets were analyzed for the hardness, disintegration time, and drug content and in-vitro drug release.

RESULTS AND DISCUSSION

In the present study, Levocetrizine dihydrochloride fast dissolving tablets were prepared by using natural superdisintegrant namely isolated mucilage of *Hibiscus* and synthetic superdisintegrants namely Kyron T-314, Croscarmellose. IR spectroscopic studies revealed that drug was compatible with all the excipients (Fig 1a, 1b, 1c).

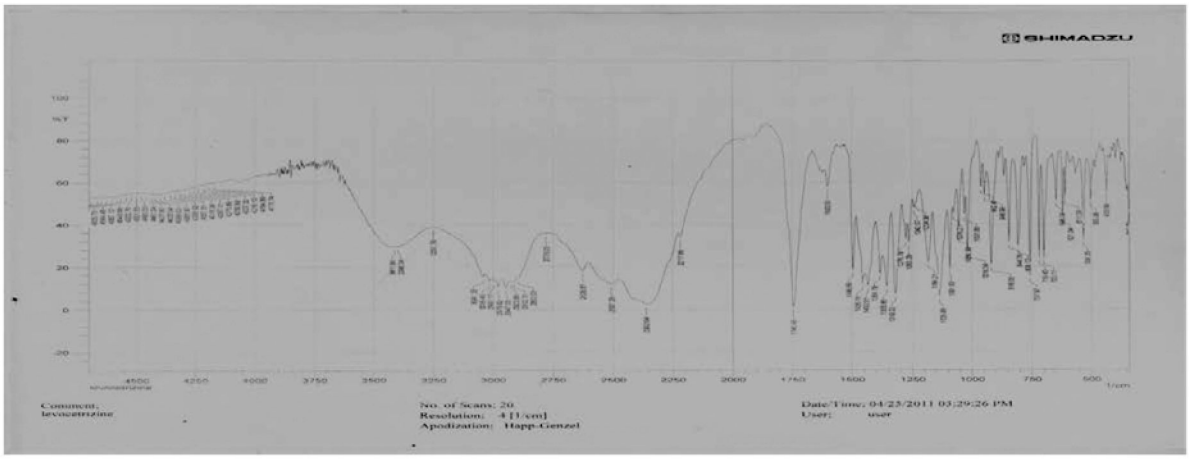

Figure 1a. IR spectra of levocetrizine dihydrochloride

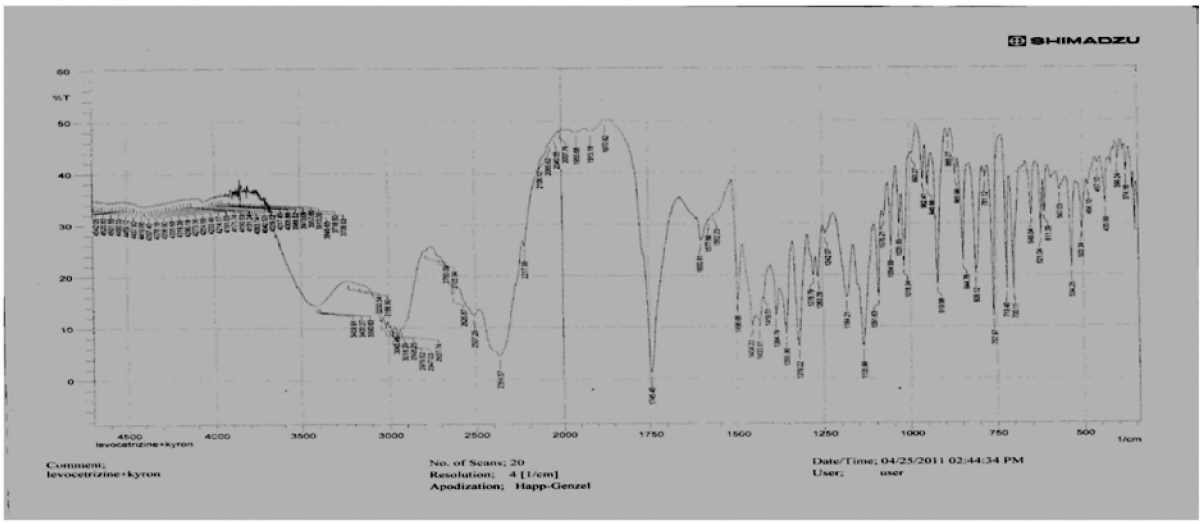

Figure 1b. IR graph of physical mixture of levocetrizine and kyron T-314

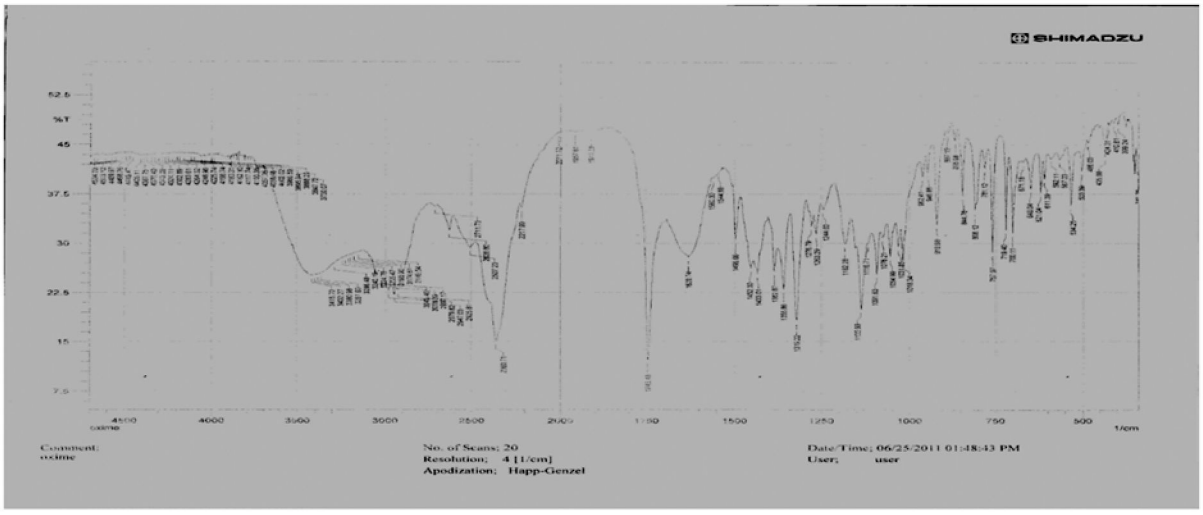

Figure 1c. IR graph of physical mixture of levocetrizine and mucilage of *Hibiscus rosa sinensis* Linn

The blend of all batches were evaluated for parameters like angle of repose was found to be between 23.01±0.58° to 26.26±0.61°. Hausner's ratio was found to be 1.17. Bulk density was found to be between 0.620±0.009 and 0.742±0.003 gm/cm^3 and tapped density was found to be between 0.661±0.003 and 0.757±0.009 gm/cm^3. Carr's index was in between 8.72±0.565 to 16.43±0.491 indicating that all batches of powder blends were having good compressibility. All the formulation showed good blend properties for direct compression and thus tablets were prepared by direct compression technology (Table 2).

The hardness of the tablets was found to be 2.90 ± 0.26 to 3.5 ± 0.27 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 2.52± 0.03 to 2.80± 0.002. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±10%. The drug content was found to be 99.11 to 105 %, indicating uniform distribution of drug in the tablets (Table 3).

The most important parameter that needs to be optimized in the development of fast dissolving tablets is disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 30 ± 1.25 to 103± 1.39 sec fulfilling the official requirements (<3 min) for dispersible tablets

Fig. 2 depicts disintegration behavior of tablets in water. This quick disintegration of the fast dissolving tablets were due to penetration of saliva into the pores of the tablets, which leads to the swelling of superdisintegrants to create hydrodynamic pressure for fast and complete disintegration of the tablets . It was observed that the disintegration time of the tablets decreased with increasing concentration of mucilage powder, croscarmellose sodium and crospovidone. However the disintegration time of tablets decreased with increasing concentration of Kyron T-314 up to 2.4%, but further increasing level of Kyron had no significant effect on disintegration time of tablets. Batch LK6 was selected as optimized batch containing 2.4 % concentration of Kyron T-314. It showed disintegration time of 30 seconds.

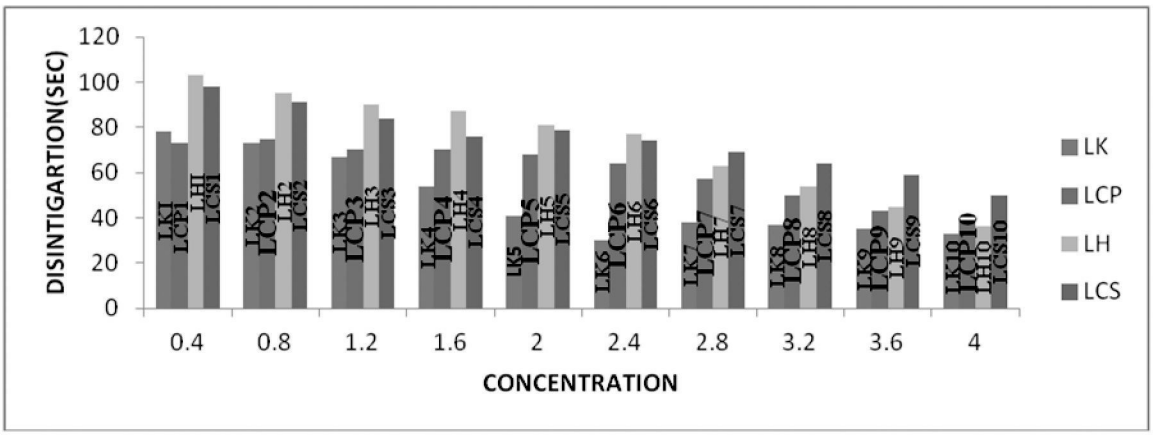

Figure 2. Disintegration time of different superdisintegrants with different concentrations.

Table 2. Preformulation characteristics of the powder blend of all formulations.

Formulation	Angle of repose (θ)*	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Hausner's ratio *	Compressibility Index (%) *
LK1	24.68±0.81	0.647±0.008	0.674±0.007	1.149±0.013	11.89±0.931
LK2	24.52±1.05	0.632±0.002	0.661±0.003	1.142±0.009	13.10±0.855
LK3	25.12±0.68	0.620±0.009	0.742±0.002	1.170±0.005	12.51±0.435
LK4	23.86±0.95	0.628±0.003	0.757±0.009	1.133±0.019	14.19±1.019
LK5	23.59±0.67	0.634±0.007	0.751±0.004	1.151±0.003	13.50±1.025
LK6	25.18±1.09	0.667±0.003	0.738±0.012	1.142±0.007	14.50±0.335
LK7	24.97±0.53	0.651±0.010	0.721±0.010	1.149±0.008	10.25±0.620
LK8	24.35±0.86	0.639±0.005	0.725±0.007	1.139±0.015	11.51±0.628
LK9	25.28±1.03	0.742±0.003	0.736±0.004	1.127±0.011	12.86±0.925
LK10	23.76±0.63	0.629±0.006	0.718±0.003	1.129±0.007	10.42±0.240
LH1	24.21±0.82	0.645±0.018	0.748±0.006	1.143±0.017	13.13±1.739
LH2	24.68±0.78	0.654±0.008	0.735±0.008	1.134±0.009	14.38±0.169
LH3	24.89±0.53	0.661±0.005	0.743±0.007	1.127±0.005	11.56±0.936
LH4	25.21±0.96	0.637±0.012	0.727±0.003	1.123±0.006	12.78±0.286
LH5	25.64±1.10	0.630±0.015	0.718±0.006	1.129±0.008	12.89±1.010
LH6	25.85±0.69	0.648±0.004	0.737±0.005	1.150±0.021	14.13±0.243
LH7	23.01±0.58	0.654±0.004	0.749±0.009	1.131±0.019	15.67±0.421
LH8	24.34±0.74	0.665±0.009	0.765±0.004	1.134±0.004	16.43±0.491
LH9	25.11±0.39	0.629±0.014	0.692±0.007	1.126±0.019	11.98±1.524
LH10	24.95±0.87	0.623±0.007	0.712±0.003	1.139±0.007	12.76±0.332
LCSI	26.26±0.61	0.648±0.006	0.732±0.003	1.125±0.012	12.06±0.195
LCS2	24.34±0.35	0.631±0.003	0.743±0.006	1.129±0.018	11.43±0.731
LCS3	24.18±0.71	0.639±0.008	0.747±0.005	1.127±0.007	11.67±0.439
LCS4	23.59±0.89	0.662±0.007	0.734±0.009	1.135±0.009	8.72±0.565
LCS5	25.26±0.27	0.651±0.004	0.755±0.003	1.142±0.005	10.49±0.939
LCS6	24.37±0.67	0.658±0.006	0.738±0.010	1.149±0.007	11.34±0.351
LCS7	24.87±0.91	0.636±0.010	0.745±0.013	1.132±0.013	11.25±0.310
LCS8	23.69±0.78	0.627±0.005	0.696±0.017	1.118±0.009	11.29±0.297
LCS9	25.13±0.93	0.619±0.013	0.728±0.007	1.126±0.015	11.37±0.432
LCS10	24.97±0.85	0.643±0.005	0.690±0.009	1.135±0.011	10.51±1.238
LCPI	24.63±0.69	0.625±0.009	0.679±0.005	1.109±0.016	12.19±0.386
LCP2	24.86±0.73	0.615±0.002	0.668±0.013	1.082±0.009	13.39±0.587
LCP3	24.71±0.76	0.643±0.009	0.734±0.006	1.125±0.005	11.09±0.720
LCP4	25.19±0.41	0.631±0.003	0.727±0.009	1.132±0.008	10.18±1.310
LCP5	23.27±0.92	0.650±0.007	0.739±0.004	1.136±0.010	15.57±0.553
LCP6	24.49±1.09	0.632±0.003	0.737±0.012	1.129±0.015	14.91±0.239
LCP7	25.11±0.78	0.658±0.010	0.728±0.010	1.095±0.011	14.33±0.247
LCP8	26.18±0.53	0.631±0.005	0.758±0.007	1.116±0.009	13.58±0.333
LCP9	25.71±0.69	0.629±0.003	0.791±0.004	1.129±0.007	12.97±0.741
LCP10	23.86±0.85	0.677±0.006	0.725±0.003	1.085±0.016	12.81±0.937

Values are expressed as Mean ±SD, *n = 3

Table 3. Evaluation of tablets.

Formulation	Weight variation (mg) ****	Hardness (kg/cm^2) *	Thickness (mm) ***	Friability (%) *	Wetting time(sec) **	Water absorption ratio **	DT (sec) **	Content uniformity (%)*
LK1	50± 1.36	3.2±0.38	2.68±0.05	0.31±0.16	76±1.21	109±1.31	78±1.18	105±0.71
LK2	51±0.71	3.3±0.35	2.52±0.03	0.33±0.21	73±1.28	110±1.18	73±1.34	99.95±0.56
LK3	50±1.53	3.1±0.24	2.57±0.02	0.36±0.19	72±1.42	113±1.15	67±1.03	99.80±0.55
LK4	49±1.98	3.3±0.21	2.62±0.03	0.32±0.18	56±1.81	125±1.28	51±1.81	99.32±1.45
LK5	49±1.26	3.2±0.12	2.65±0.04	0.34±0.09	46±1.12	115±1.96	42±1.05	99.82±1.12
LK6	52±0.86	3.0±0.38	2.70±0.02	0.25±0.16	34±0.98	95±1.75	30±1.25	100.98±1.10
LK7	50±0.79	3.1±0.26	2.72±0.02	0.29±0.37	42±1.35	118±1.36	38±1.86	99.92±1.24
LK8	51±0.94	3.4±0.18	2.78±0.03	0.30±0.22	41±1.79	121±1.27	37±1.93	99.24±0.58
Lk9	50±1.18	2.9±0.52	2.61±0.04	0.32±0.31	39±1.61	120±1.89	35±1.28	99.85±0.86
LK10	52±0.93	3.2±0.54	2.77±0.03	0.33±0.29	43±1.21	126±1.76	33±1.36	99.75±0.89
LH1	5O±1.35	3.2±0.31	2.54±0.02	0.39±0.19	84±1.75	110±1.31	103±1.39	99.42±0.64
LH2	51±1.21	3.1±0.26	2.61±0.05	0.37±0.21	80±1.69	115±1.56	95±1.24	99.36±0.92
LH3	52±1.095	3.3±0.21	2.73±0.03	0.33±0.17	74±1.89	114±1.75	90±1.75	99.52±0.89
LH4	53±0.86	3.4±0.38	2.68±0.02	0.34±0.31	68±1.31	118±1.28	87±1.69	99.23±0.82
LH5	51±1.45	3.3±0.18	2.71±0.03	0.35±0.26	70±1.46	124±1.37	81±1.37	99.11±0.77
LH6	51±1.19	3.2±0.22	2.65±0.07	0.31±0.33	66±1.53	129±1.95	77±1.18	99.89±0.69
LH7	50±0.98	3.1±0.20	2.76±0.02	0.33±0.35	60±1.78	120±1.09	63±1.96	99.99±1.27
LH8	51±0.86	3.4±0.31	2.68±0.04	0.31±0.37	57±1.63	124±2.31	54±1.73	99.89±2.15
LH9	50±1.24	3.5±0.27	2.79±0.02	0.35±0.15	51±1.48	123±1.27	45±1.68	100.19±2.19
LH10	50±0.78	3.2±0.23	2.75±0.06	0.31±0.29	45±1.27	135±1.38	36±1.26	99.52±1.12
LCS1	50± 1.35	3.2±0.21	2.69±0.03	0.35±0.24	78±1.35	115±1.41	98±1.68	99.87±1.65
LCS2	50±1.65	3.0±0.36	2.80±0.02	0.36±0.18	78±1.43	118±1.38	91±1.25	99.98±0.69
LCS3	51±1.08	3.1±0.35	2.63±0.04	0.37±0.21	68±1.21	117±1.25	84±1.18	99.89±1.23
LCS4	52±1.95	3.1±0.28	2.68±0.06	0.33±0.28	63±1.18	119±1.29	76±1.34	99.39±1.45
LCS5	51±1.28	3.2±0.23	2.74±0.02	0.32±0.16	61±1.26	120±1.37	79±1.21	99.82±1.12
LCS6	49±1.39	3.3±0.26	2.70±0.03	0.31±0.31	60±1.19	124±1.81	74±1.03	99.98±0.90
LCC7	50±1.86	3.4±0.31	2.72±0.05	0.31±0.23	57±1.39	129±1.76	69±1.47	99.86±0.89
LCS8	51±1.76	3.2±0.11	2.77±0.03	0.33±0.28	57±1.42	133±1.65	67±1.28	99.24±0.58
LCS9	49±1.95	3.1±0.18	2.65±0.02	0.34±0.23	48±1.59	131±1.59	59±1.22	101.13±0.86
LCS10	50±1.45	3.0±0.15	2.79±0.02	0.35±0.17	42±1.31	125±1.31	50±1.65	100.31±0.69
LCP1	50±1.35	3.0±0.33	2.65±0.04	0.34±0.31	79±1.09	126±1.67	73±1.28	99.68±0.62
LCP2	51±1.78	2.9±0.26	2.74±0.03	0.37±0.26	77±1.26	125±1.54	75±1.07	99.66±0.82
LCP3	53±0.61	3.2±0.64	2.71±0.03	0.33±0.64	74±2.08	125±1.27	70±0.81	99.76±0.89
LCP4	51±1.21	3.0±0.58	2.69±0.02	0.31±0.58	64±1.48	123±1.79	68±0.97	99.43±0.72
LCP5	52±0.84	3.1±0.21	2.78±0.06	0.31±0.21	68±1.32	120±1.35	64±1.36	99.37±0.77
LCP6	51±1.13	3.2±0.18	2.76±0.02	0.35±0.18	63±1.68	116±1.56	57±1.58	99.99±0.69
LCP7	50±1.36	3.2±0.11	2.68±0.04	0.31±0.11	47±1.51	127±1.83	55±1.34	99.84±1.27
LCP8	49±1.54	3.0±0.09	2.73±0.02	0.30±0.09	46±2.29	120±1.39	50±1.10	99.82±1.15
LCP9	50±1.12	3.1±0.20	2.77±0.03	0.34±0.20	41±1.36	128±1.27	43±2.09	99.91±2.19
LCP10	49±1.75	2.9±0.26	2.78±0.04	0.29±0.26	37±1.19	105±1.19	39±1.48	100.12±0.22

Values are expressed as Mean ±SD, *n=3, **n = 6, ***n=10, ****n= 20

It was observed that less disintegration time was observed when Kyron T-314 was used as superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with mucilage of *Hibiscus rosa sinensis* Linn, crospovidone and croscarmellose sodium, thereby possibility of enhancing the bioavailability (18). Mucilage of *hibiscus* showed more disintegration time than Kyron T-314, crospovidone but less disintegration time was observed with mostly used superdisintegrants croscarmellose sodium. As reported in the literature references mucilage of *Hibiscus rosa sinensis* Linn powder showed better disintegrating property than the most widely used synthetic super disintegrants like Ac-di-sol (19). The study further revealed a poor relation between the swelling index and disintegrating efficiency of all the superdisintegrants used in the study. The formulation LK6 was found to be the best, as this formulation showed less disintegration time and possessing good tableting properties. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of KyronT-314 in bringing about faster disintegration. The rank order given for disintegration time parameter for various superdisintegrants were given as given as Kyron T-314(LK6) > crospovidone (LCP10) > *Hibiscus rosa sinensis* (LH10) > crospovidone (CP10). The formulation containing Kyron T-314 at all percentages were found to be significant in comparison to Croscarmellose sodium (P=0.002/ F= 13.15). The Results of other disintegrants were found to be insignificant with P=0.005 using Anova (Minitab 16 statistical software, USA).

Fig. 3 depicts the relation between the concentrations of superdisintegrants and wetting time. The most important parameter that is needed to optimize during the development of ODTs is disintegration time, wetting time is related to inner structure of tablet and hydrophobicity of components (20).

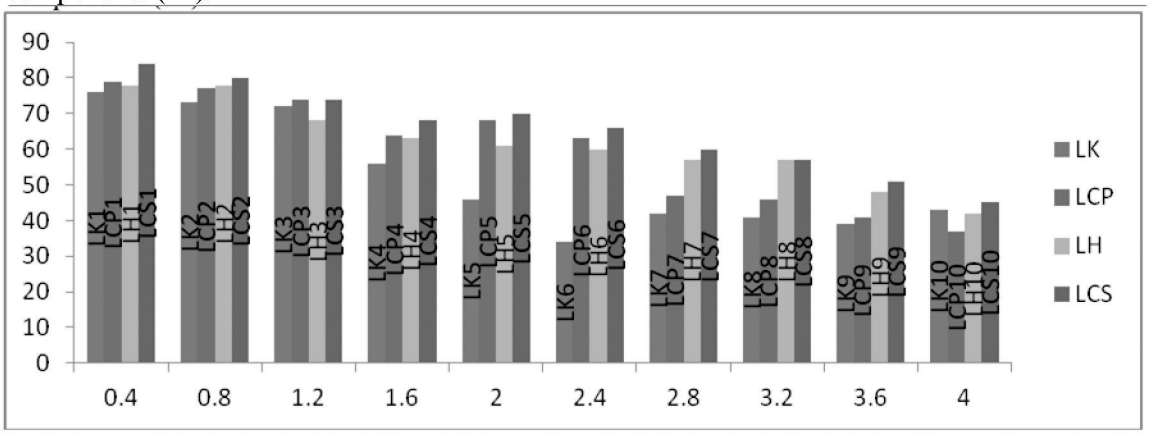

Figure 3. Wetting time of different superdisintegrants with different concentrations

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, it could be assumed that wetting was the only cause of disintegration.

Kyron T-314 is an anion exchange resin used in oral pharmaceutical formulation and it swells rapidly when wetted. This indicates that aqueous medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bonds and breaks the tablet into fine particles. The Wetting time/ disintegration time decreases with increase in the concentration of superdisintegrants[20]. The wetting time of the formulated tablets were found to be in the range of 34 ± 0.98 to 84± 1.75 sec. The rank order given for wetting time parameter for various superdisintegrants were given as Kyron T-314(LK6) > crospovidone (LCP10) >

Hibiscus rosa sinensis (LH10) > crospovidone (CP10) .The results were found to be insignificant with P=0.213using Anova (Minitab 16 statistical software, USA).

Fig 4 depicts the relation between the concentration of superdisintegrants and water absorption ratio. Water absorption ratio was performed to know the moisture sorption and water uptake properties of superdisintegrants.

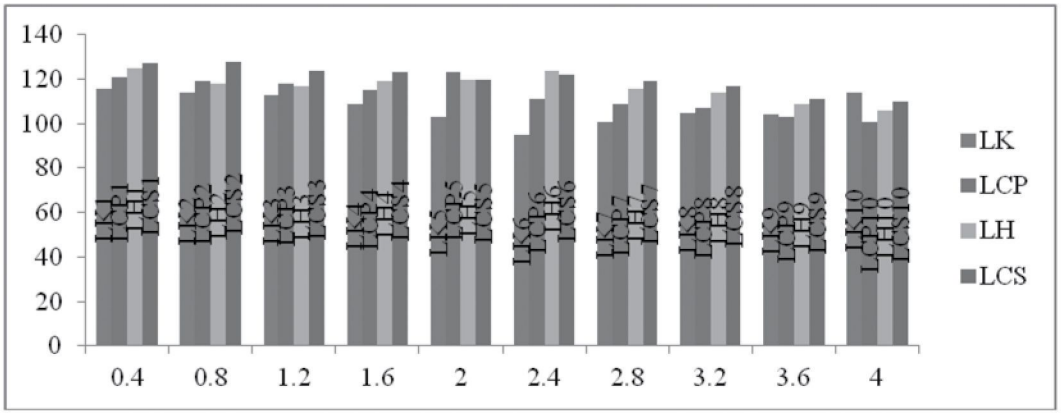

Figure 4. Water absorption ratio of different superdisintegrants with different concentrations

Water absorption ratio was increased and disintegration time and wetting time was decreased with an increase in concentration of superdisintegrants. The water absorption ratios of the formulated tablets were found in the range of 95±1.75 to 135±1.38.

The rank order for water absorption ratio parameter for various superdisintegrants were given as Kyron T-314(LK6 2.4)> crospovidone (LCP10 4 %)> mucilage of *Hibiscus rosa sinensis* (LH10 4 %)> croscarmellose sodium (LCS10 4 %). The results were found to be insignificant with P=0.114 using Anova (Minitab 16 statistical software, USA).

Fig 5 depicts in vitro drug release profile of different superdisintegrants at same concentration.

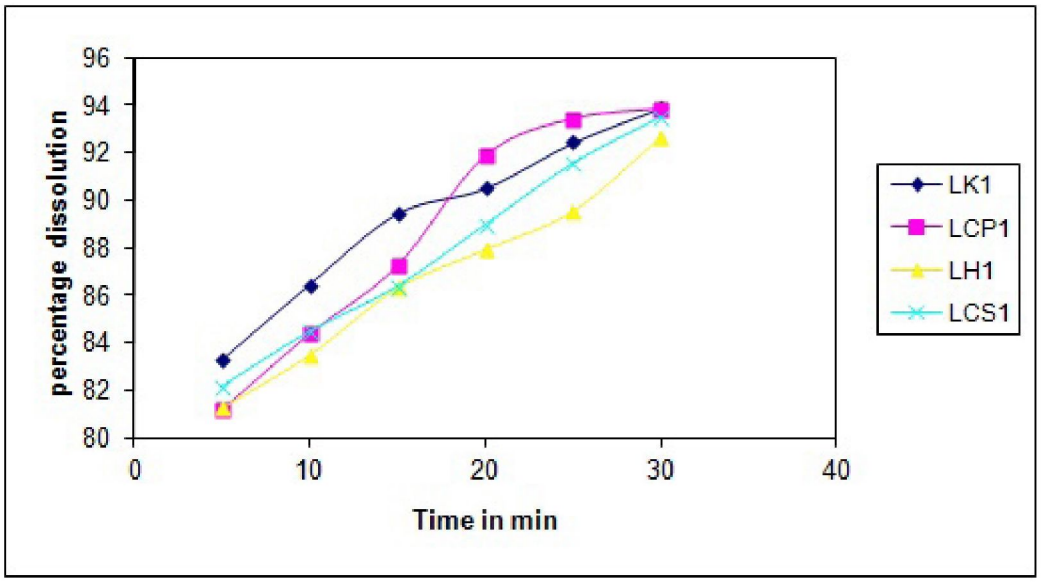

Figure 5. Dissolution profile of levocetrizine dihydrochloride orodispersible tablets of LK1, LCP1, LH1, LCS1 (0.4 %).

In vitro dissolution study of formulations containing different superdisintegrants with 0.4 % concentrations showed drug release of 86.44±2.28 % (LK1), 84.36±0.57 % (LCP1), 83.46±2.45 % (LH1) and 84.45±0.35 % (LCS1) at t_{10}. Overall Kyron-T314 containing batches showed good dissolution property with insignificant difference ($P>0.05$, using one-way Anova Minitab 16 statistical software, USA) in dissolution profile, when compared to other superdisintegrants at the same 0.4 % concentration. In significant difference in dissolution of same concentration of different superdisintegrants might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium, but Kyron T-314 has much effect on dissolution when compared to other.

Figure 6 depicts Comparison of dissolution profile of different superdisintegrants with different concentration. In vitro drug release of all formulations showed above 90 % at t_{30}. In vitro dissolution study of different superdisintegrants with different concentrations (0.4 % to 4 %) showed variable drug release. In these set of formulations, Kyron T-314 (2.4 %) batch showed 99.69±0.49 %, the highest dissolution property within t_{30}. On the contrary crospovidone (4 %) and *Hibiscus rosa sinensis* Linn (4 %) showed 98.75±1.34 % and 98.57±0.45 % release within 30 min respectively. Croscarmellose containing batch showed (4 %) 98.03±0.46. Lower percentage of (2.4 %) Kyron T-314 was comparable to 4 % of crospovidone, *Hibiscus rosa sinensis* Linn and croscarmellose.

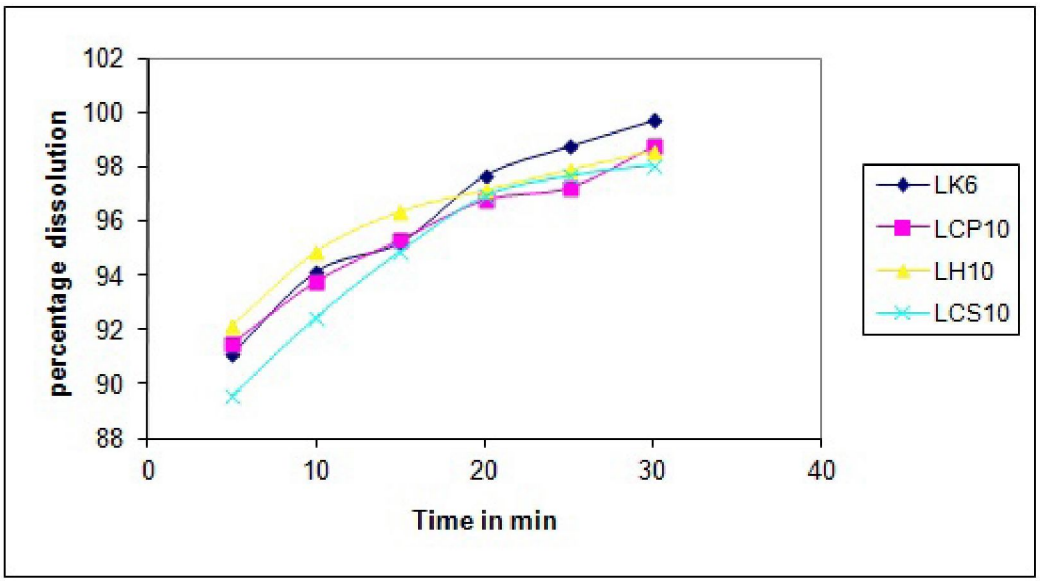

Figure 6. Comparative *in vitro* dissolution profile of LK6, LCP10, LH10, and LCS10

In vitro dissolution of formulations of LK6, LCP10, LH10 and LCS10 were compared. Formulation LK6 showed better dissolution property when compared to other formulation (99.69 %). The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium (21). The results were found to be insignificant with P=0.891/F=0.31 using Anova (Minitab 16 statistical software, USA).

The stability study of optimized formulation (LK6) was conducted for three months at accelerated conditions of 40±2^{0}C/75±2 % RH. The formulation was found to be stable, with insignificant change in the hardness, disintegration time, and drug content and in-vitro drug release.

Table 4. Stability data of optimized formulation Lk6.

Parameters	Time in months			
	0 (Initial)	**1st month**	**2nd month**	**3rd month**
Hardness (kg/cm^2)	3.0±0.36	3.0.±0.24	2.8±0.18	2.9±0.41
Disintegration time (sec)	30±0.606	31±0.724	29±0.597	33±0.639
Drug content (%)	100.35±0.38	99.98±0.69	100.18±1.06	99.96±0.73
In vitro drug release (%)	99.69±0.25	99.52±0.19	99.64±0.31	99.61±0.28

CONCLUSION

From the present study, it can be concluded that natural superdisintegrant like *Hibiscus rosa sinensis* Linn mucilage powder showed better disintegranting property than the most widely used synthetic superdisintegrants like croscarmellose sodium. Though Kyron T-314 was found to be better superdisintegrant among all; natural superdisintegrant like *Hibiscus rosa sinensis* was also found to possess comparable properties like other synthetic superdisintegrants. Also, it is cheap, biocompatible, and biodegradable and can be used as one of the excipient in the formulation of ODT.

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