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COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF FAST DISSOLVING TABLETS OF HYDROXYZINE HYDROCHLORIDE

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ABSTRACT

The main objective of the study was to compare the effect of natural and synthetic super disintigrants in the formulation of fast dissolving tablets of Hydroxyzine hydrochloride prescribed in the treatment of itching and as anti-anxiety agent. The mucilages were evaluated for physico-chemical parameters and they comply with the official specifications. The drug and excipients compatibility study by FTIR revealed no interaction between drug and excipients. Hydroxyzine hydrochloride tablets were prepared by direct compression method using different percentages of isabgol and hibiscus mucilages and synthetic super disintigrants like sodium starch glycolate and Kyron T-314 and were evaluated. The optimized formulations of isabgol (HI10), hibiscus (HH10) mucilages and kyron T-314 (HK3) showed less disintegration time of 29, 32 and 31 seconds respectively. The in-vitro drug release profile of all formulations was above 90% within 20 minutes. In comparison, formulation with isabgol (9%) and hibiscus mucilage (9%) showed less disintegration time than sodium starch glycolate but formulations with isabgol (2.4%) and hibiscus mucilage (2.4%) showed more disintegration time than Kyron T-314 (2.4%) and synthetic super disintigrant Kyron T-314 is used at low concentrations as natural super disintigrants can be used at higher concentrations as these are biodegradable, cheap, and biocompatible and less toxic.

Key words: Fast dissolving tablets, Hydroxyzine hydrochloride, Mucilage of isabgol, mucilage of hibiscus, Kyron t-314, sodium starch glycolate.

INTRODUCTION

Fast dissolving tablets (FDTs) are the novel dosage forms whish dissolve within few seconds in the mouth when comes in contact with the saliva without the need of water[1].The fast dissolving drug delivery technology started gaining popularity and acceptance because they are easy to administer and lead to better patient compliance. Hydroxyzine is antihistaminic drug with anti-cholinergic and sedative properties used to treat allergic reactions. Hydroxyzine can be administered orally or via intramuscular injection. When given orally, Hydroxyzine is rapidly absorbed from the gastro-intestinal tract [9, 10]. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintigrants in capsule and tablet formulations. The recommended concentration in a formulation as super disintigrants is 2-8 % [4, 6]. Kyron T-314 has very high swelling tendency of hydration either in contact with water or G.I. fluids causing fast disintegration without formation of lumps and thus acts as an effective tablet super disintigrants. It is used in concentration range of 0.2 to 2.5% [8].Hibiscus mucilage is obtained from the fresh leaves of *Hibiscus rosa-sinensis Linn* (Family: Malvaceae). Isabgol mucilage is obtained from the seeds of the plant *Plantago ovata* Forsk (Family: Plantaginaceae) [4, 5, 6].

MATERIALS AND METHODS

Seeds of isabgol were purchased from the Yarrow Chem products, Mumbai, Maharashtra, India and fresh leaves of hibiscus were collected from the local garden in Hyderabad. Hydroxyzine hydrochloride is purchased from Yarrow chem. Products, Mumbai, Maharashtra, India.

Isolation of mucilages

Isabgol: The seeds of isabgol were soaked in distilled water for 48 hours and boiled for few minutes for complete release of mucilage in to water. The contents were squeezed through muslin cloth. To the filtrate equal volume of acetone was added to precipitate the mucilage. The precipitated mucilage was separated and dried in oven at temperature less than 60˚c, powdered, sieved (#80) and stored in dessicator[11, 17].

Hibiscus: The fresh leaves of hibiscus were collected, washed with water to remove dirt and debris and dried. The powdered leaves were soaked in water for 5 to 6 hours, boiled for 30 minutes and kept aside for 1 hour for complete release of the mucilage in to water. The material was squeezed through eight fold muslin cloth bag. To the filtrate three volumes of acetone was added to precipitate the mucilage. The precipitated mucilage was separated and

dried in an oven at a temperature of less than 50˚c. Dried mucilage was powdered and passed through sieve number 80 and stored in dessicator.

Preparation of mixed blend of drug and excipients

All the ingredients were passed through mesh no #80. Required quantity of each ingredient was taken for each specified formulation (Table 1) and all the ingredients were subjected to grinding to a required degree of fineness. The powder blend was evaluated for flow properties [20].

Drug excipients compatibility study by FTIR

The spectrum analysis of pure drug and physical mixture of drug with excipients were subjected to IR spectral studies using FTIR spectrophotometer (FTIR 8400 S, Shimadzu, Japan)[21].

Angle of Repose [21, 22]

Angle of repose 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. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula,

θ = Tan-1(h / r)

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

Bulk density

Bulk density is defined as mass of the powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend in to graduated cylinder. The bulk volume (V*) and the 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 (100 tappings).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/Vt

Carr's index

Carr's index = (Tapped density - Bulk density)/Tapped density × 100.

The compressibility index (CI) and the Hausner's ratios (HR) were determined from the bulk and tapped densities according to the relationships.

Hausner's ratio

It is the ratio of tapped density to bulk density. This is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's ratio = *t/*d

*t =Tapped density *d=Bulk density.

Preparation of Hydroxyzine hydrochloride fast dissolving tablets

Fast dissolving tablets of Hydroxyzine hydrochloride were prepared by direct compression method. All ingredients were passed through sieve (# 60) separately to ensure better mixing. Super disintigrants were used separately in different proportions as shown in Table 1 and 2.Then all ingredients are weighed and mixed in geometrical order and compressed in to tablets of 50 mg. Batch of 50 tablets of each formulation was prepared for all the designed formulations using 4 mm flat face surface punches on a rotary machine (Rimek-1) [23].

Table 1: Formulations of Hydroxyzine hydrochloride containing isabgol and hibiscus mucilage powder

Formulation	Hydroxyzine HCl (mg)	Isabgol mucilage powder (mg)	Hibiscus mucilage powder (mg)	Lactose (mg)	Total weight of tablet (mg)
HI_1	10	0.4	-	22.6	50
HI_2	10	0.8	-	22.2	50
HI_3	10	1.2	-	21.8	50
HI_4	10	1.5	-	21.5	50
HI_5	10	2	-	21	50
HI_6	10	2.5	-	20.5	50
HI_7	10	3	-	20	50
HI_8	10	3.5	-	19.5	50
HI_9	10	4	-	19	50
HI_{10}	10	4.5	-	18.5	50
HH_1	10	-	0.4	22.6	50
HH_2	10	-	0.8	22.2	50

HH_3	10	-	1.2	21.8	50
HH_4	10	-	1.5	21.5	50
HH_5	10	-	2	21	50
HH_6	10	-	2.5	20.5	50
HH_7	10	-	3	20	50
HH_8	10	-	3.5	19.5	50
HH_9	10	-	4	19	50
HH_{10}	10	-	4.5	18.5	50

I = Isabgol mucilage, H = Hibiscus mucilage, H = Hydroxyzine Hcl, HI = Formulation of Isabgol mucilage, HH = Formulation of Hibiscus mucilage.

Note: *14 mg of mannitol, 2mg of aspartame, 0.5mg of talc, magnesium stearate were used in all formulations.*

Table 2: Formulations of Hydroxyzine hydrochloride containing kyron T-314 and sodium starch glycolate

Formulation	Hydroxyzine Hydrochloride(mg)	Kyron t-314(mg)	Sodium Starch glycolate(mg)	Lactose (mg)	Total Weight of tablet(mg)
HK1	10	0.4	-	22.6	50
HK2	10	0.8	-	22.2	50
HK3	10	1.2	-	21.8	50
HS1	10	-	0.4	22.6	50
HS2	10	-	0.8	22.2	50
HS3	10	-	1.2	21.8	50
HS4	10	-	1.5	21.5	50
HS5	10	-	2	21	50
HS6	10	-	2.5	20.5	50
HS7	10	-	3	20	50
HS8	10	-	3.5	19.5	50
HS9	10	-	4	19	50
HS10	10	-	4.5	18.5	50

K = Kyron T – 314, S = Sodium starch glycolate, H = Hydroxyzine HCl, HK = Formulation of KyronT-314, HS = Formulation of sodium starch glycolate.

Note: *14 mg of mannitol, 2mg of aspartame, 0.5mg of talc, magnesium stearate were used in all formulations.*

Evaluation of tablets

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percentage deviation from the average weight was calculated [11, 12, 21].

Hardness

The strength of the tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break the tablet in to pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester) [11, 12].

Friability

Friability of the tablets was determined using Roche Friabilator (Electrolab, India).Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. The friability (%F) is given by the formula,

$$F\% = (1-W0/W)$$

Where, W0 is weight of the tablets before test and

W is the weight of the tablets after testing.

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. 10 ml of water at 37˚C ± 0.5˚C containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the surface of the tablets was noted as the wetting time [11, 22-24].

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish 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 [11, 12, 23].

Water absorption ratio R, was determined using the following equation

$$R = Wa – Wb / Wb$$

Where Wa = weight of the tablet after absorption

Wb = weight of the 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 10 mg of Hydroxyzine was weighed and dissolved in 0.1N hydrochloric acid, filtered and drug content was analyzed spectro-photometrically at 230 nm.

In-vitro disintegration time [11, 12, 20]

Disintegration time was measured using a modified disintegration method. For this purpose, a petridish was filled with 10 ml of water at 37˚c ± 0.5˚c. The tablet was carefully put in the center of the petridish and the time required for the tablet to completely disintegrate in to fine particles was noted.

In-vitro drug release [11, 12]

In-vitro drug release of Hydroxyzine hydrochloride fast dissolving tablets was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDT- 0.8L).The dissolution test was performed using 500 ml of 0.1N hydrochloric acid at 37˚c ± 0.5˚c .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, 30 minutes and the 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 230 nm and drug release was determined from standard curve.

Accelerated stability studies

The optimized formulation of Hydroxyzine hydrochloride was subjected to stability studies at 40˚c ± 2˚c/75% ± 2% RH for period of 3 months. Each tablet was individually wrapped in aluminum foil and packed in amber colored bottle and put at above specified condition in a heating humidity chamber for 3 months. For every one month tablets were analyzed for the hardness, disintegration time, drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION

The percentage yield of Isabgol mucilage was 17.5%, and Hibiscus mucilage was 15.8%. . IR spectroscopic studies revealed that drug was compatible with all the excipients (Fig1, 2, 3).

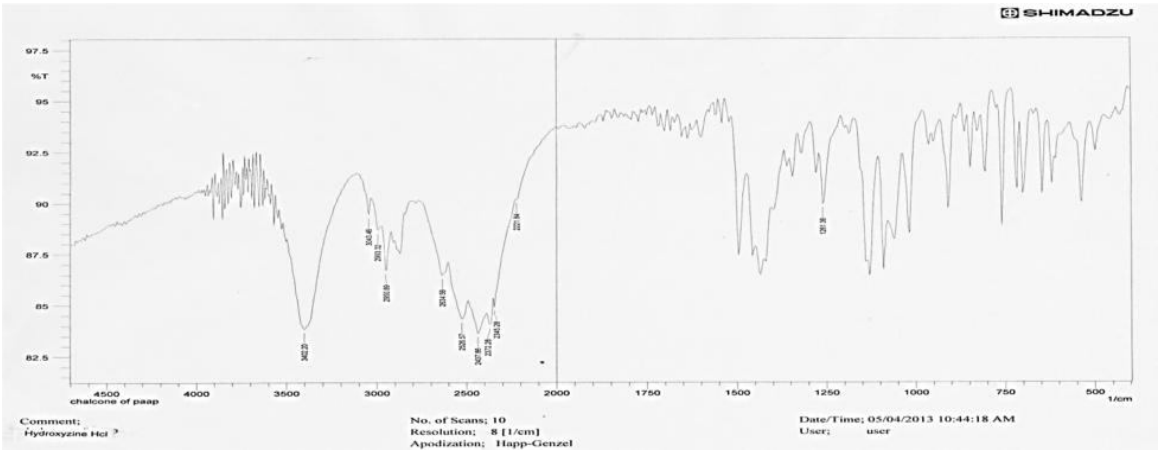

Fig 1: IR spectra of Hydroxyzine hydrochloride

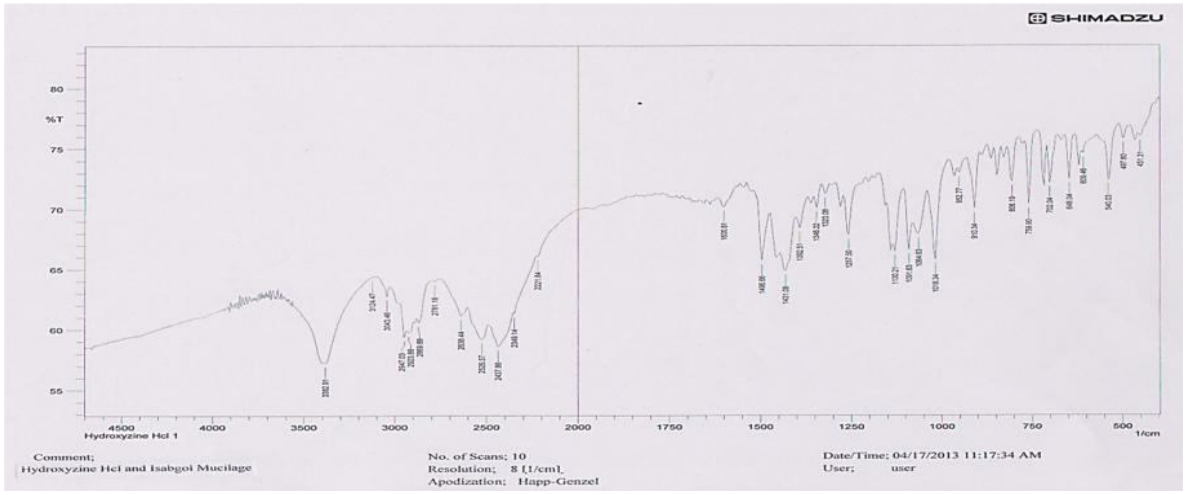

Fig 2: IR spectra of physical mixture of isabgol mucilage and Hydroxyzine

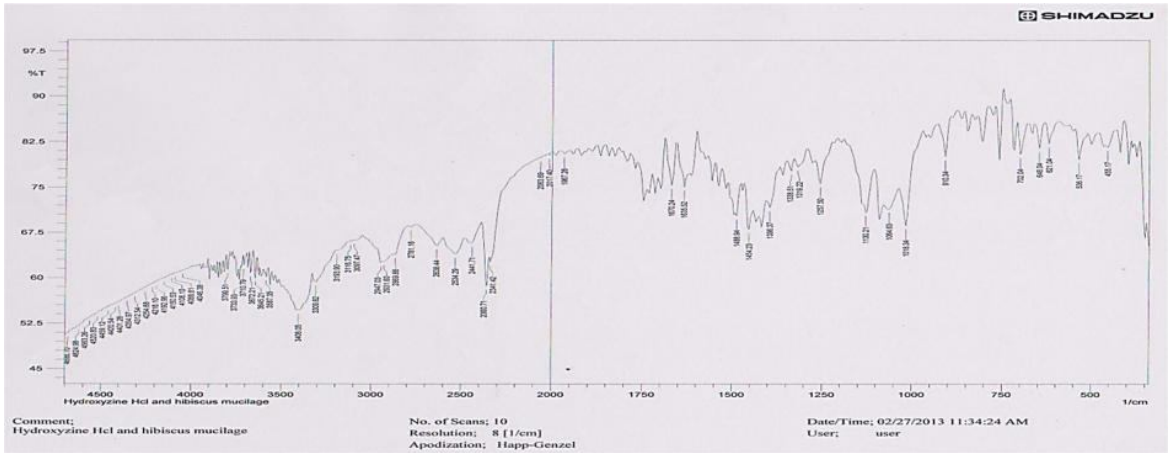

Fig 3: IR spectra of physical mixture of hibiscus mucilage and Hydroxyzine

The angle of repose of the powder blend of Hydroxyzine hydrochloride was in the range of 24.87±0.40 and 29.80±0.31g/cm3 showing that the powder blend was free flowing and can be used for direct compression. Bulk density was between 0.576±0.002 and

0.689±0.003g/cm3 and Tapped density was between 0.689±0.003 and 0.789±0.006g/cm3. Hausner's ratio was between 1.109±0.009 and 1.192±0.007. Compressibility index was between 10.807±0.97 and 20.441±0.83.All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology. The hardness of the tablets was 1.9±0.05 to 3.2±0.15 kg/cm2 and friability was below 1% indicating good mechanical resistance. The drug content was 96.55% to105.42%. The most important parameter that needs to be optimized in the development of oro-dispersible tablets is the disintegration time of tablets. In the present study disintegration time of all batches were in the range of 29±1.89 to 110±1.48 sec fulfilling the official requirements (3 min) for dispersible tablets.

Evaluation of Hydroxyzine hydrochloride tablets prepared with isabgol mucilage and hibiscus mucilage

Formulation	Weight variation (mg)****	Hardness ($Kg/cm^{2)}$	Thickness (mm)***	Friability (%)*	Wetting time (sec)**	water absorption ratio **	DT(sec) **	Content uniformity (%)*
HI1	49±0.83	2.3±0.12	2.42±0.04	0.37±0.12	69±1.29	103±1.67	79±1.12	99.4±1.23
HI2	51±1.26	2.9±0.2	2.49±0.05	0.61±0.14	61±1.26	108±1.56	70±1.24	99.55±0.79
HI3	50±0.92	2.8±0.12	2.62±0.02	0.43±0.18	58±1.20	115±1.34	59±1.28	100.4±0.68
HI4	50±0.97	3.2±0.15	2.41±0.04	0.65±0.22	57±1.23	116±1.27	61±1.14	99±0.58
HI5	51±0.90	2.8±0.05	2.59±0.02	0.58±0.14	55±1.64	116±1.33	60±1.34	99.25±0.89
HI6	51±1.16	3.1±0.10	2.51±0.05	0.57±0.30	51±1.85	118±1.21	58±1.13	96.85±1.10
HI7	51±1.02	1.9±0.05	2.50±0.03	0.52±0.18	47±1.57	120±1.92	50±1.58	99.1±0.73
HI8	50±1.10	2.7±0.2	2.53±0.02	0.33±0.09	36±1.45	122±1.13	47±1.34	99.57±1.12
HI9	49±0.86	2.9±0.10	2.61±0.05	0.81±0.22	33±1.28	126±1.82	38±1.40	98.42±0.64
HI10	50±0.85	2.9±0.12	2.54±0.03	0.52±0.18	28±1.32	132±1.28	29±1.81	102.3±0.96
HH1	51±1.05	3.1±0.62	2.60±0.03	0.61±0.12	81±1.41	99±1.28	96±1.82	97.7±0.89
HH2	49±0.62	2.8±0.16	2.53±0.07	0.68±0.04	69±1.97	104±1.81	87±1.34	99.25±0.92
HH3	51±1.02	3.1±0.24	2.51±0.02	0.36±0.12	66±1.26	107±1.45	70±1.70	98.1±0.24
HH4	50±0.96	2.8±0.57	2.48±0.04	0.46±0.24	67±1.81	108±1.34	72±1.29	97±0.89
HH5	51±0.93	3.0±0.39	2.51±0.04	0.74±0.18	61±1.52	111±1.23	66±1.97	98.42±0.96
HH6	51±1.24	2.9 ±0.16	2.49±0.06	0.56±0.07	58±1.52	115±1.62	65±1.37	97.25±0.77

HH7	49±1.15	2.7±0.24	2.65±0.07	0.52±0.18	49±1.86	117±1.43	59±1.06	99.1±0.82
HH8	50±1.06	2.7±0.20	2.58±0.01	0.81±0.22	44±1.63	120±1.86	51±1.11	99.55±2.15
HH9	51±1.64	2.8±0.16	2.53±0.08	0.55±0.30	35±1.18	123±1.52	40±1.24	98.95±1.12
HH10	52±1.80	3.0±0.48	2.47±0.01	0.54±0.06	31±1.32	127±1.12	32±1.60	99.4±2.19

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

HI = Formulations of Hydroxyzine hydrochloride with isabgol mucilage.

HH = Formulations of Hydroxyzine hydrochloride with hibiscus mucilage.

Evaluation of Hydroxyzine hydrochloride tablets prepared with KyronT-314 and sodium starch glycolate

Formulation	Weight variation (mg)****	Hardness ($Kg/cm^{2)}$	Thickness (mm)***	Friability (%)*	Wetting time (sec)**	water absorption ratio **	DT (sec)**	Content uniformity (%)*
HK1	49±1.24	2.9±0.37	2.50±0.03	0.68±0.29	67±1.35	114±1.56	74±1.29	101.42±0.99
HK2	50±1.23	2.9±0.16	2.57±0.01	0.58±0.19	42±1.60	119±1.30	51±1.89	97.2±0.68
HK3	51±1.43	3.0±0.53	2.44±0.05	0.30±0.13	29±1.30	124±1.67	31±1.97	100.25±0.89
HS1	49±1.43	2.8±0.22	2.53±0.07	0.54±0.12	103±1.85	87±1.46	110±1.48	99.45±1.23
HS2	50±0.85	3.1±0.28	2.49±0.08	0.27±0.19	95±1.49	94±1.18	102±1.29	97.7±1.45
HS3	51±1.04	2.7±0.57	2.52±0.03	0.56±0.33	89±1.30	99±1.27	95±1.80	98.3±1.12
HS4	50±1.12	2.7±0.48	2.61±0.08	0.38±0.23	85±1.56	101±1.81	88±1.34	99.4±1.10
HS5	50±1.05	2.8±0.53	2.55±0.02	0.65±0.33	81±1.47	103±1.79	86±1.15	97.5±0.43
HS6	51±0.99	3.0±0.17	2.49±0.06	0.52±0.15	65±1.62	105±1.75	79±1.95	98.2±2.19
HS7	49±1.06	3.0±0.24	2.63±0.04	0.38±0.12	59±1.24	109±1.62	67±1.11	97.9±0.73
HS8	51±1.01	2.9±0.39	2.55±0.06	0.81±0.22	48±1.24	116±1.38	54±1.39	99.8±0.69
HS9	52±1.84	3.0±0.32	2.52±0.02	0.68±0.29	40±1.17	119±1.54	48±1.97	98.6±1.23
HS10	51±1.19	2.9±0.69	2.51±0.03	0.79±0.8	34±1.49	123±1.47	40±1.34	96.55±1.45

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

HK = Formulations of Hydroxyzine hydrochloride with Kyron T-314

HS = Formulations of Hydroxyzine hydrochloride with sodium starch glycolate.

It was observed that the disintegration time of the tablets were decreased with increase in concentration of mucilages and sodium starch glycolate up to 9% and Kyron T-314 up to 2.4% (Kyron T-314 was used at concentration range of (0.2 –2.5%.) Formulation HI10, HH10 and HK3 were selected as optimized batches containing isabgol and hibiscus mucilages (9%) and Kyron (2.4%) as super disintigrants with least disintegration time of 29, 32 and 31seconds. These formulations were compared with formulation of sodium starch glycolate 40sec (9%). In comparison KyronT-314 (2.4%) showed less disintegration time compared to isabgol (2.4%), hibiscus (9%) mucilages and sodium starch glycolate (9%). Isabgol and hibiscus mucilages both at 9% showed less DT than sodium starch glycolate (9%). Hence, formulations of Hydroxyzine with isabgol (HI10), hibiscus (HH10) mucilages and Kyron T-314 (HK3) were found to be better super disintigrants as these showed less disintegration time and good tabletting properties.

CONCLUSION

From the study, it was concluded that natural super disintigrants like *Plantago ovata and Hibiscus rosa-sinensis* mucilages showed better disintegrating property than synthetic super disintigrant sodium starch glycolate and Kyron T-314. Though kyron T-314 (2.4%) was found to be better super disintigrant among all, natural super disintigrants isabgol (9%) and hibiscus mucilages (9%) were found to possess comparable disintegrating properties like kyron T-314 (2.4%) at higher concentrations, as these natural super disintigrants has an advantage of being less toxic, low cost, biocompatible and possessing less side effects.

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