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Effect of Combination of Natural Superdisintegrants on Fast Dissolving Tablets of Lisinopril

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Abstract:

The demand for fast dissolving tablets has been growing during the last decade especially for the geriatric and pediatric patients. The main objective of this study was to formulate and evaluate the fast dissolving tablets of Lisinopril using natural superdisintegrants in combinations. Various formulations were prepared by direct compression using different combinations of natural superdisintegrant i.e. isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and extracted mucilage of Hibiscus rosasinesis to achieve optimum release profile, disintegration time and hardness. Microcrystalline cellulose was used as diluent and mannitol as bulking agent. The initial compatibility studies between the drug and excipients were carried out using FTIR spectroscopy. The tablets were evaluated for weight variation, hardness, friability, *in-vitro* disintegration time and drug release characteristics. Hardness indicated good mechanical strength around 2-3 kg/cm^2 for all the batches. The results of *in-vitro* disintegration time indicated that the tablets dispersed rapidly in mouth within 40 secs. It was concluded that superdisintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

***Key words**: Fast dissolving tablet, isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and mucilage of Hibiscus rosasinesis*

Introduction:

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. As a results children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms. To overcome this drawback novel drug delivery systems like orally disintegrating tablets have been developed which disintegrate/dissolve/ disperse in saliva within few seconds without water. United States of America Food and Drug Administration (USFDA) defines FDT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue" [1-3]. These are novel types of tablets that disintegrate/disperse/dissolve in saliva. The target populations for these oral disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or develop mentally disabled patients who have difficulty in swallowing (Dysphagia). Patients with persistent nausea, sudden episodes of allergic attacks or coughing , who are traveling , or who have little or no access to water are also good candidates for FDTs. The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market[4 - 6].

Lisinopril is a drug of the angiotensin converting enzyme (ACE) inhibitor class that is primarily used in treatment of hypertension, congestive heart failure,

heart attacks and also in preventing renal and retinal complications of diabetes. The present study involved the comparison between various natural superdisintegrants in combination.

Materials and Methods

Materials:
Lisinopril were obtained as a gift sample from Modern Lab., Indore (M.P). Plantago ovata seeds, Aloe vera and Hibiscus rosasinesis leaves were purchased from local market, Berhampur, India. Microcrystalline cellulose, mannitol, magnesium stearate, talc were purchased from Noble Enterprises, Berhampur, India.

Isolation of Mucilage of Plantago ovata
The seeds of Plantago ovata were soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water. The material was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C, powdered, sieved (#80) and stored in a desiccator until use [7].

Isolation of Mucilage of Aloe vera

The inner mucilaginous parenchymatous tissues of leaves of Aloe vera plants were separated out with the help of a sterile knife and homogenized in a blender (National blender, Matushita Co. Japan) at 30 rpm. The homogenized mass was separated with a G3 sintered glass filter under vacuum, freeze dried using a bench-top freeze-dryer (MC 2L, Cyberlab, USA) and subsequently stored at 40°C. The ratio of AVG to lyophilized powder was 200:1[8].

Isolation of Mucilage of Hibiscus rosasinesis
The fresh Hibiscus rosasinesis leaves were collected and washed with water. The leaves were crushed and soaked in water for 5–6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantity of three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 35°C, collected, grounded, passed through a # 80 sieve and stored in a desiccator at 30 °C & 45% relative humidity till use [9].

Drug-Excipient Interaction Studies
The physical mixture of pure drug sample, drug and natural superdisintegrant (mucilage of Plantago ovata) in the ratio 1:1 were subjected to IR spectral studies using FTIR spectrophotometer (Model-IR Affinity-1, Shimadzu, Japan).

Compression of tablets
All ingredients were triturated individually in a mortar and passed through #80 (Table 1). Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except magnesium stearate. Finally magnesium stearate was added as lubricant. This uniformly mixed blend was compressed in to tablets containing 30 mg drug with two superdisintegrants in total of 30 mg using rotary tablet machine by direct compression method. Total weight of tablet was kept to be 200 mg.

Evaluation of tablets[10]

Hardness - Hardness or tablet crushing strength (Fc), the force required to break a tablet in a diametric compression, was measured using Pfizer Tablet Hardness Tester.

Friability test - Friability of tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches at each revolution. Pre-weighed sample of tablets was placed in a friabilator and the tablets were subjected to 100 revolutions. Tablets were then dusted using a soft muslin cloth and reweighed.

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

Where,
Wo = weight of the tablets before the test.
W = weight of the tablet after the test.

Water absorption capacity - Water absorption ratio was determined by the following ratio

$$R = 100 \times Wb / Wa$$

Where,
Wb = Weight of tablet before water absorption
W =Weight of tablet after water absorption

Wetting time - 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.

In vitro disintegration time - Tablets were added to 10 ml of Sorenson's buffer solution of pH 6.8 at 37 ± 0.5°C. Time required for disintegration of the tablets was noted.

In vitro dissolution studies **-** Dissolution studies were carried out by USP-II dissolution apparatus. The tablet was taken from each formulation to carry out the dissolution study in the pH 6.2 buffer solution as dissolution medium (pH of saliva).

Table 1. Formulation of Lisinopril FDT using combination of natural superdisintegrants

Ingredient	HIB-ALO 1(F1)	HIB-ALO 2(F2)	HIB-PLA 1(F3)	HIB-PlA 2(F4)	ALO-PLA 1(F5)	ALO-PLA 2(F6)
Lisinopril	30	30	30	30	30	30
MCC	20	20	20	20	20	20
HIB	20	10	20	10	-	-
PLA	-	-	10	20	10	20
ALO	10	20	-	-	20	10
Mannitol	116	116	116	116	116	116
Mg.st	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	200	200	200	200	200	200

Table 2. Preformulation studies of Lisinopril FDT using combination of natural superdisintegrants

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Bulk density	0.56± 0.0057	0.55± 0.0053	0.55± 0.0053	0.55± 0.0053	0.54± 0.005	0.53± 0.005
Tapped density	0.58± 0.006	0.57± 0.0054	0.58± 0.0059	0.57± 0.0055	0.56± 0.0057	0.55± 0.0053
Hausner's ratio	1.03± 0.001	1.03 ±0.19	1.05 ±0.001	1.03 ±0.196	1.037 ±0.19	1.037 ±0.2
Carr's index	3.44± 0.006	3.50± 0.008	5.17± 0.0078	3.50± 0.0065	3.57± 0.0076	3.63± 0.0059
Angle of Repose	33± 0.59	32.5± 0.55	32± 0.56	32.5± 0.56	31.5± 0.54	31± 0.54

Table 3. Evaluation of Lisinopril FDT using combination of natural superdisintegrants

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Hardness	2.7 ± 0.0553	2.8 ± 0.0524	2.8 ± 0.0523	2.8 ± 0.0523	2.9 ± 0.0667	3.2 ± 0.042
DT	72.5 ± 0.408	77.16 ± 0.623	58.16 ± 0.623	51 ± 0.816	53.16 ± 0.623	40.53 ± 0.411
Friability	0.18 ± 0.001	0.29 ± 0.008	0.35 ± 0.004	0.045 ± 0.001	0.054 ± 0.001	0.065 ± 0.004
Wetting time	32 ± 0.636	29 ± 0.479	25 ± 0.775	15 ± 0.652	19 ± 0.587	9 ± 0.261
Dispersion time	34 ± 0.603	30 ± 0.482	27 ± 0.522	16 ± 0.66	22 ± 0.656	12 ± 0.64
Water abs ratio	47 ± 0.728	59 ± 0.625	68 ± 0.4652	74 ± 0.7812	65 ± 0.655	90 ± 0.4223

Table 4. Cumulative % drug release of Lisinopril FDT in phosphate buffer PH 6.8 using natural superdisintegrants in individual concentrations

TIME IN MINUTES	F1	F2	F3	F4	F5	F6
2	33.74	38.65	39.28	49.91	34.58	51.19
4	33.98	43.31	41.96	55.98	49.13	65.89
6	45.87	49.9	58.98	91.96	54.43	95.86
8	51.12	55.86	76.6	99.99	99.98	99.99
10	54.97	89.98	94.42		99.99	
15	92.24	96.87	99.99			
20	99.96	99.99				

Table 5. Log % drug retained for Lisinopril FDT in phosphate buffer PH 6.8 using natural superdisintegrants in individual concentrations

Time (min)	F1	F2	F3	F4	F5	F6
2	1.8212514	1.78781457	1.7833318	1.69975103	1.81571054	1.688509
4	1.8196755	1.75350646	1.7637274	1.64365004	1.70646174	1.532882
6	1.733438	1.69983773	1.6129957	0.90525605	1.65867903	0.617
8	1.6891312	1.64483233	1.3692159	-2	-1.69897	-2
10	1.6535019	1.00086772	0.7466342		-2	
15	0.8898617	0.49554434	-2			
20	-1.39794	-2				

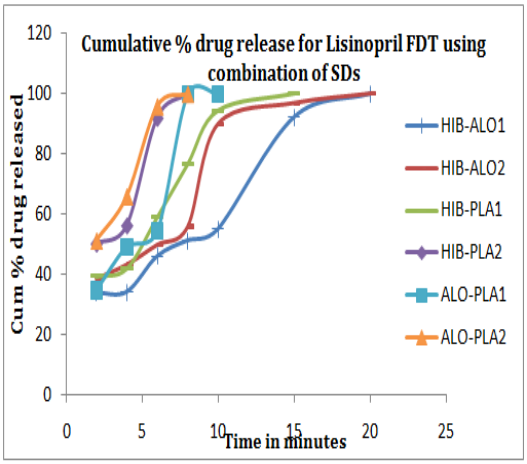

Figure 1: Cumulative % drug release of Lisinopril FDT in phosphate buffer PH 6.8 using natural superdisintegrants in individual concentrations

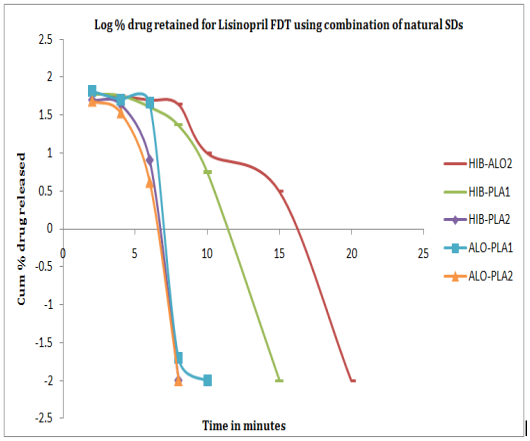

Figure 2. Log % drug retained for Lisinopril FDT in phosphate buffer PH 6.8 using natural superdisintegrants in individual concentrations

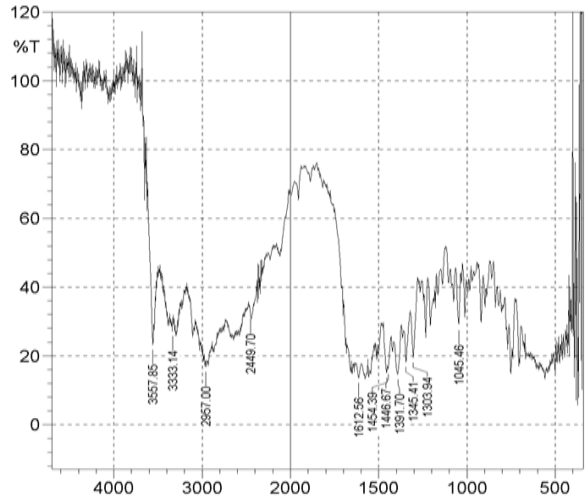

Figure 3. FTIR spectra for pure drug Lisinopril

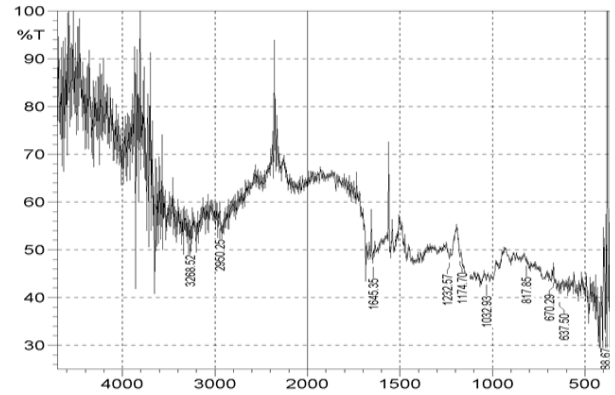

Figure 4. FTIR spectra for pure Plantago ovate

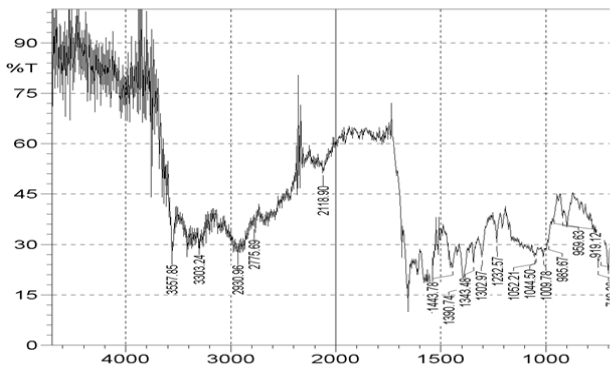

Figure 5. FTIR spectra for optimized formulation (F6)

Results and Discussion

The results for evaluation of different batches of Lisinopril FDT's prepared by direct compression method are shown in Table 2. The most important parameter that needs to be optimized in the development of Fast Dissolving tablets is the disintegration time of tablets. In the present study tablets in all the batches disintegrated in the range of 40 – 80 secs fulfilling the official requirements (< 3 min) for Fast Dissolving tablets. It was observed that the formulations (F1 – F6) containing combinations of superdisintegrants used in different ratios of 10:5 and 5:10 respectively were prepared. The tablet formulations contained isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and extracted mucilage of Hibiscus rosasinesis in combined form as Plantago and Aloes in combination of 10:5 and 5:10 ratios, Plantago and Hibiscus in combination of 10:5 and 5:10 ratios and Hibiscus and Aloes in combination of 10:5 and 5:10 ratios respectively. The tablet formulations containing 10:5 ratios viz. 20 mg of Hibiscus and 10 mg of Aloe (F1), 20 mg of Hibiscus and 10 mg of Plantago (F3), 10 mg of Aloe and 20 mg of Plantago (F6) showed DT as 72.5, 58.16 and 40.53 secs and formulations containing 5:10 ratios viz. 10 mg of Hibiscus and 20 mg of Aloe (F2), 10 mg of Hibiscus and 20 mg of Plantago (F4), 20 mg of Aloe and 10 mg of Plantago (F5), showed DT as 77.16, 52, 53.16 secs 15, 16 and 18 s respectively. The wetting time is important to check minimum volume of water required for wetting of the tablet. The wetting volume for formulations containing 10:5 ratios viz. 20 mg of Hibiscus and 10 mg of Aloe (F1), 20 mg of Hibiscus and 10 mg of Plantago (F3), 10 mg of Aloe and 20 mg of Plantago (F6) showed wetting time as 32, 25 and 9 secs and formulations containing 5:10 ratios viz. 10 mg of Hibiscus and 20 mg of Aloe (F2), 10 mg of Hibiscus and 20 mg of Plantago (F4), 20 mg of Aloe and 10 mg of Plantago (F5), showed wetting time as 29, 15 and 19 secs respectively. It has been reported that wetting is closely related to the inner structure of the tablets and the hydrophillicity excipients. The superdisintegrants show its disintegrant effect by swelling. Thus the result indicates that these tablets would disintegrate almost instantaneously when they will come in contact with even slight amount of saliva in the mouth. The cumulative percentage drug release of the tablets from the prepared batches was found to be 99.99% due to the effect of two superdisintegrants in combination. It was observed that nearly all the batches showed drug release close

to 100% in phosphate buffer pH. In order to differentiate between the release profiles and to maintain the saliva pH, studies were carried out in pH 6.8 buffer also. In pH 6.8 almost 99% of the drug was released within 20 mins for all the batches. The FTIR studies were carried out for the pure drug Lisinopril, superdisintegrant (Plantago ovata) and the optimized formulation F6 and the spectras showed no interaction. FT-IR spectra of Lisinopril figure 3 revealed the presence of characteristic peak of N-H stretching around 3557.85cm^{-1}, O-H stretching around 3300 cm^{-1}, aromatic C-H stretching around 3200cm^{-1}, sp^3 C-H stretching at 2957cm^{-1}, C=O stretching around 1700 cm^{-1} and C-O stretching around 1045 cm^{-1} , Individual spectra of Plantago ovata figure 4 shows characteristic strong and broad O-H peaks in the region of 3700- 3300 cm^{-1}, C-H stretching at 2950 cm^{-1}, C=O stretching around 1645 cm^{-1} and C-O stretching around 1032 cm^{-1} and the spectra of optimized formulation revealed the presence of characteristic peaks of N-H stretching, O-H stretching, aromatic C-H stretching, sp^3 C-H stretching, C=O stretching and C-O stretching. Thus it was observed that the IR spectra lack any sign of probable interactions.

Conclusion

Fast Dissolving tablets of Lisinopril were prepared by direct compression method using Plantago ovata, Aloe vera and Hibiscus rosasinesis as natural superdisintegrants in combination in the ratio of 10:5 and 5:10 respectively. From the observed parameters it was concluded that the formulation (F6) satisfied all the official requirements. The tablets had acceptable hardness of average 3 kg/ cm^2 and 0.065% friability. *In-vitro* disintegration time was reduced and *in-vitro* drug release was significantly improved. Hence it can be concluded that using a combination of natural superdisintegrants would be quite effective in providing fast onset of action without the need of water for swallowing.

"Cite This Article"

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