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Formulation and Evaluation of Fast Dissolving Tablet of Lisinopril

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ABSTRACT - Orodispersible tablets are useful in patients, such as pediatric, geriatric, bedridden or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquids orals or syrup, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attack or coughing for those who have an active life style. Fast onset of action- dispersible tablet has major advantage that the drug product is already in solution at that time it is consumed. Thus the absorption is faster and more complete than with conventional tablet. Lisinopril {(S)-1-[N2-(1-carboxy-3-phenylpropyl)-L proline] dihydrate} is a lysine analog of enalapril at, the active metabolite of enalapril. It is a long-acting, non sulfhydryl angiotensin-converting enzyme (ACE) inhibitor that is used for the treatment of hypertension and congestive heart failure in daily dosages of 10-80 mg. All the superdisintegrants such as crosscarmellose, crosspovidone, sodium starch glycolate were maintained in different concentrations in all the formulations. Microcrystalline cellulose was used as diluent. Here microcrystalline cellulose was also a superdisintegrant; each formulation was composed of drug and excipients in various proportions. This design techniques was used to optimized and obtain better formulation with respect to in vitro dispersion time , Drug release (%), Disintegration time. In vitro drug release showed that formula C- 5 (Crosspovidone) and S6 (sodium starch glycolate) had better % drug release as compare to other formulations. The faster disintegration may attribute to its rapid capillary activity and pronounce hydration with little tendency to gel formation. Thus these results can suggest that the disintegration time can be decreased by using wicking type of disintegrants.

Keywords: Orodispersible tablets, disintegration time, Crosspovidone, Sodium starch glycolate, Superdisintegrant.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, Pain avoidance and most importantly the patient compliance [1]. The most popular solid Dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the Swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

Fast dissolving tablets (FDT) are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapi-melts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva [2-6]. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopoeia adopted the term “or dispersible tablet” as a tablet that to be placed in the mouth where it disperses

Rapidly before swallowing**.** According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes [7-10]. The basic approach in development of FDT is the use of super disintegrants like cross linked carboxymethyl cellulose (Crosscarmellose), sodium starch glycolate (primo gel, explotab), polyvinylpyrollidone (Polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for

manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

Advantages of Fast Dissolving Tablets [11-18]

Administered without water, anywhere, any time. Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.

Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.

An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

Stability for longer duration of time, since the drug remains

Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Evaluation Parameters to Be Studied For Fast Dissolving Tablets [19-23]

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. The various evaluation testing includes tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

- **Size and Shape**

  The size and shape of the tablet can be dimensionally described, monitored and controlled.

- **Weight variation**:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

- **Drug Content Estimation**

Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to 100 ml flask. The powder was dissolved in pH 3.2.The sample was mixed by using Remi mixer for 5 minutes, after which it was filtered through Whatman filter paper. The filtered solutions after appropriate dilution (1 to 10 ml) with 0.1 N HCL were analyzed by validated UV Spectrophotometric method at Îmax 283nm.

- **Crushing Strength**

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

- **Friability test (F)**

The crushing test may not be the best measure of potential behavior during handling and pack-aging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab Friabilator". Ten pre weighed tablets were rotated at 25 rpm for 4 min, the tablets were then re weighed and the percentage of weight loss was calculated. The friability (F) is given by the formula.

F = (W initial – W final) / W initial × 100

- **In vitro dispersion time**

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

- **In Vitro disintegration time**

In Vitro disintegration time was performed by apparatus specified in USP at 50 rpm. Phosphate buffer 3.2, 900 ml was used as disintegration medium, and the temperature of which maintained at 37±2°C and the time in second taken for com complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. [13]

MATERIALS AND METHODS

Lisinopril was obtained as a gift sample from Aurbindo Pharmaceuticals, Hyderabad. Crosspovidone, sodium starch glycolate and microcrystalline cellulose was purchased from S. D. Fine Chemicals, Mumbai. All other materials used were of pharmaceutical grade.

Spectroscopic Analysis of Lisinopril

Method of Estimation of Lisinopril

In the present work, Lisinopril was estimated by UV- Visible Spectrophotometric method using dissolution media (Distilled water/Simulated saliva)

Composition of phosphate buffer pH 6.8

KH_2PO_4	12Mm (1.6g)
NaCl	40Mm (2.3g)
$CaCl_2$	1.5mM (o.17g)
NaOH	To pH 6.8

Preparation of stock solution

- Lisinopril (100 mg) was dissolved in 100 ml of simulated saliva to obtain a stock solution of 1000 µg/ml.
- 10 ml of the stock solution was taken in 100 ml volumetric flask and the volume was made with simulated saliva to obtain 100 µg/ml
- Aliquots of 0.1, 0.2, 0.3 to 1 ml of the solution was prepared and serially diluted with simulated saliva to 10 ml to get 2, 4, 6, 8, 10, 12 µg/ml
- The absorbance of each solution was measured at maxima of 206nm against phosphate buffer pH 6.8 as blank
- The assay was performed in triplicate and average absorbance was considered. The results are shown in Figure 1 and Table 1.

RESULTS AND DISCUSSION

- The Hardness for the formulation containing crosspovidone and sodium starch glycolate decreases with increase in concentration of superdisintegrant and decrease in concentration of MCC. This shows that the more the concentration of superdisintegrant the minimum it attains the hardness. It shows and assures MCC to be a direct compressible diluent.
- The Disintegration time for the formulation containing crosspovidone and sodium starch glycolate decreases with increase in concentration of superdisintegrant and decrease in concentration of MCC. This shows that the more the concentration of superdisintegrant the quicker the tablet disintegrates in phosphate buffer pH 6.8.
- Both wetting time and weight variation for the formulation containing crosspovidone and sodium starch glycolate decreases with increase in concentration of superdisintegrant and decrease in concentration of MCC.
- The Friability for the formulation containing crosspovidone and sodium starch glycolate decreases with increase in concentration of superdisintegrant.
- In-vitro dissolution study for the formulation containing crosspovidone and sodium starch glycolate showed good release

- The formulations S6 containing sodium starch glycolate as superdisintegrant and C5 containing crosspovidone as superdisintegrant were found to show better results**.**

CONCLUSION

From all the above experimental observations it was concluded that the formulation containing crosspovidone and sodium starch glycolate fulfilled the official requirements of a Fast Dissolving tablet. On comparing all the formulations it was concluded that crosspovidone as superdisintegrant showed better results if taken alone.

Concentration (mcg/ml)	**Absorbance**
2	0.104
4	0.207
6	0.305
8	0.404
10	0.507
12	0.602

Table 1. Calibration curve of Lisinopril using pH 6.8 buffer at 206 nm

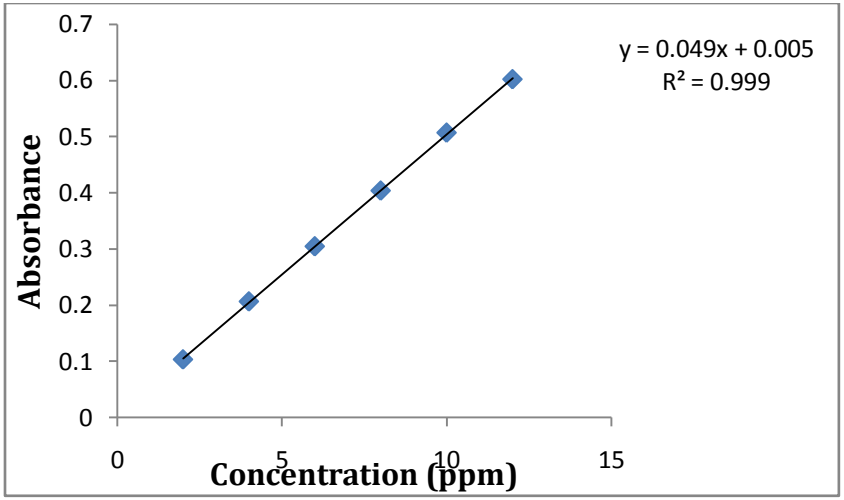

Figure 1. Standard graph of Lisinopril using pH 6.8 buffer at 206 nm

FORMULATION DESIGN OF LISINOPRIL FDT USING CROSSPOVIDONE (XPV) AS SUPERDISINTEGRANT

Ingredient	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**
Lisinopril	4	4	4	4	4	4
Micro crystalline cellulose (mg)	50	40	30	20	10	0
XPV (mg)	0	10	20	30	40	50
Mannitol (mg)	44	44	44	44	44	44
Magnesium Stearate (mg)	1	1	1	1	1	1

Talc (mg)	1	1	1	1	1	1
Total (mg)	100	100	100	100	100	100

Table 2. Formulation of Lisinopril FDT

	C1	C2	C3	C4	C5	C6
Hardness (kg/cm^2)	4.0833±0.116	3.816±0.11	3.433±0.08	3.283±0.075	3.016±0.098	2.866±0.08
DT (secs)	60.83±0.75	53.6±0.8	46.3±0.81	39.5±0.54	30±0.89	23.8±0.75
Friability (%)	0.633±0.008	0.605±0.005	0.568±0.01	0.531±0.007	0.488±0.009	0.445±0.01
Wetting time (secs)	59.1±0.7	44.5±1.04	37.6±1.2	32.8±0.7	25±0.8	16.6±0.51
Dispersion time (secs)	42.6±0.5	36.1±0.7	32±0.8	27.3±0.8	23±0.6	17.3±0.5
Drug content (%)	99.6±0.5	100±0.8	99.3±1	99.8±0.7	100.3±0.8	99.5±1.0
Weight variation (%)	100.33±0.81	99.66±0.81	99.5±1.22	100±0.8	100.5±1.04	100.16±0.7

Table 3 Evaluation Parameters for the formulation design of Lisinopril FDT using crosspovidone (xpv) as superdisintegrant

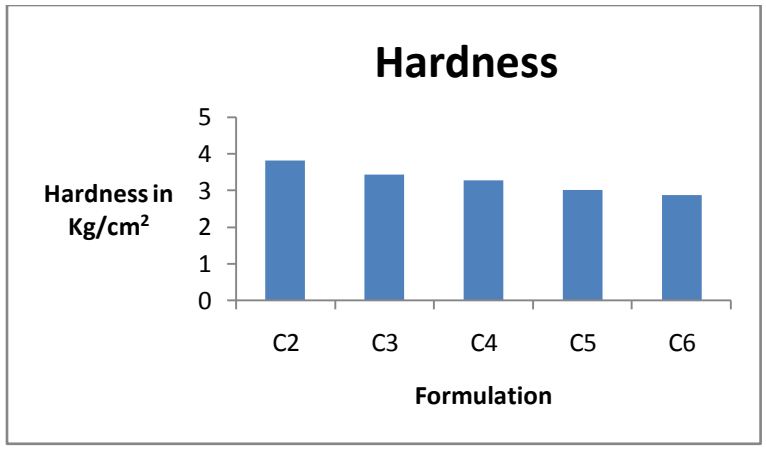

Figure 2. – Bar diagram showing Hardness for the formulation design of Lisinopril FDT using crosspovidone (xpv) as superdisintegrant

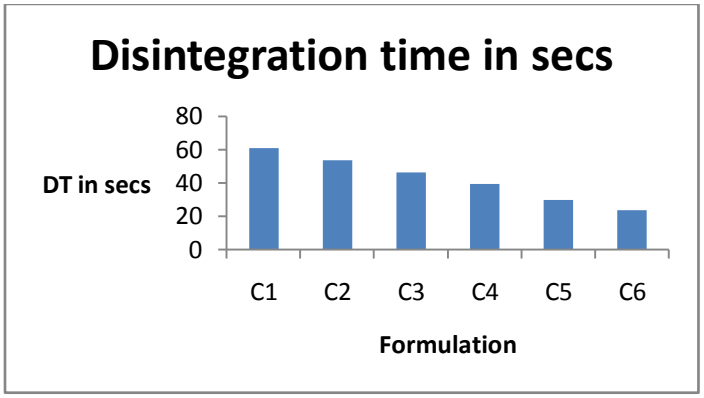

Figure3. – Bar diagram showing DT for the formulation design of Lisinopril FDT using crosspovidone (xpv) as superdisintegrant

Time in mins	C1	C2	C3	C4	C5	C6
0	0	0	0	0	0	0
5	26.83	27.98	33.45	23.67	21.98	21.11
10	39.89	37.13	47.98	38.43	45.56	33.77
20	57.87	59.11	65.55	59.88	61.19	48.89
30	84.81	76.98	79.19	79.91	76.37	72.98
40	92.32	88.17	91.78	86.55	89.94	88.98
50	99.08	98.87	99.98	98.76	99.94	99.11

Table 4. - In-vitro drug release study for the formulation design of Lisinopril FDT using crosspovidone (xpv) as superdisintegrant

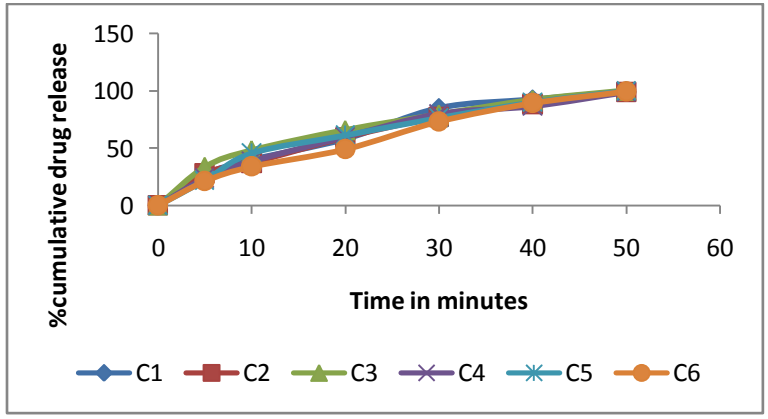

Figure 4. - %cumulative drug release for the formulation design of Lisinopril FDT using crosspovidone (xpv) as superdisintegrant

FORMULATION DESIGN OF LISINOPRIL FDT USING SODIUM STARCH GLYCOLATE (SSG) AS SUPERDISINTEGRANT

Ingredient	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**
Lisinopril	4	4	4	4	4	4
Micro crystalline cellulose (mg)	50	40	30	20	10	0
SSG (mg)	0	10	20	30	40	50
Mannitol (mg)	44	44	44	44	44	44
Magnesium Stearate (mg)	1	1	1	1	1	1
Talc (mg)	1	1	1	1	1	1
Total (mg)	100	100	100	100	100	100

Table 5. - Formulation of Lisinopril FDT

Parameters	Hardness (kg/cm^2)	DT (secs)	Friability (%)	Wetting time (secs)	Dispersion time (secs)	Drug content (%)	Weight variation (%)
S1	4.5±0.08	61.5±0.54	0.65±0.01	60.1±1.16	43.6±0.81	99.6±0.8	99.8±1.1
S2	4.4±0.07	54.5±1.04	0.61±0.01	44.8±1.16	37.5±1.04	99.8±0.9	99.5±1.04
S3	4.41±0.1	47.1±0.75	0.57±0.008	38.1±1.4	32.8±1.1	99.1±1.1	99.3±1.3
S4	4.2±0.08	40.3±1.03	0.52±0.012	33.6±1.2	28.1±0.7	100.3±1.0	100.3±0.8
S5	4.1±0.09	30.8±1.16	0.47±0.01	25.6±1.03	23.5±0.54	100.6±0.5	101.1±0.7
S6	3.7±0.10	24.5±1.04	0.44±0.01	17.1±0.75	16.3±0.8	100±1.2	100.5±1.0

Table 6. – Evaluation Parameters for the formulation design of Lisinopril FDT using Sodium starch glycolate (SSG) as superdisintegrant

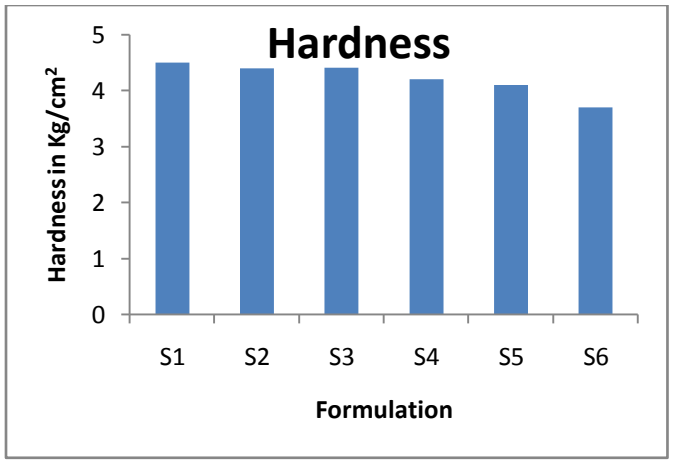

Figure 5. – Bar diagram showing Hardness for the formulation design of Lisinopril FDT using sodium starch glycolate (SSG) as superdisintegrant

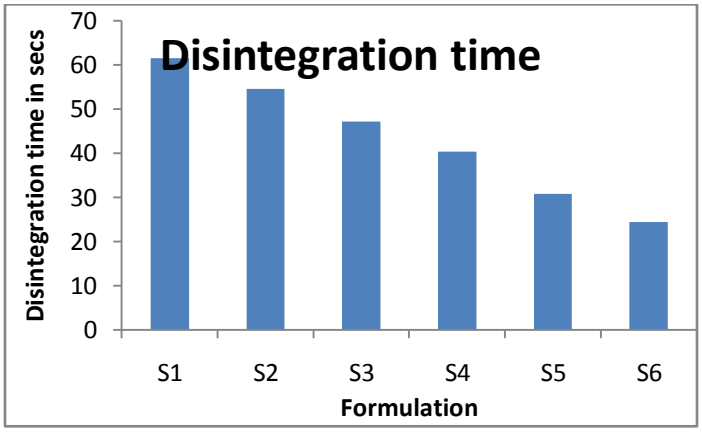

Figure 6. – Bar diagram showing DT for the formulation design of Lisinopril FDT using sodium starch glycolate (SSG) as superdisintegrant

Time in minutes	S1	S2	S3	S4	S5	S6
0	0	0	0	0	0	0
2	49.83	51.28	44.04	54.47	41.72	51.28
3	53.02	67.87	51.08	67.23	54.47	67.87
5	67.72	75.49	78.98	76.51	69.90	75.49
10	78.25	83.09	85.98	88.88	79.12	83.09
15	89.54	91.54	92.54	92.43	89.99	91.54
30	97.32	99.97	99.65	98.06	99.89	99.97

Table 7. - In-vitro drug release study for the formulation design of Lisinopril FDT using sodium starch glycolate (SSG) as superdisintegrant

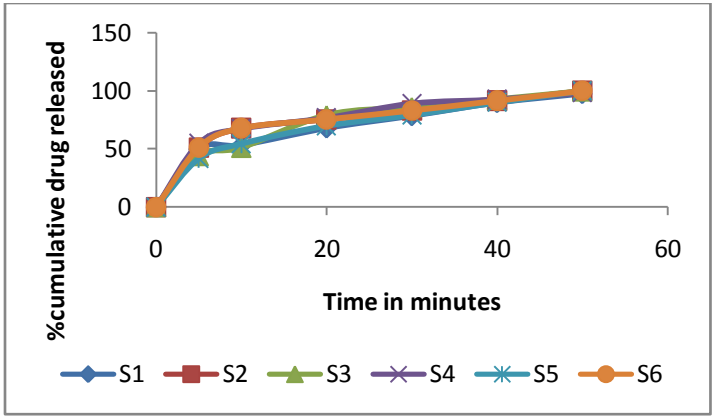

Figure 7. - %cumulative drug release for the formulation design of Lisinopril FDT using sodium starch glycolate (SSG) as superdisintegrant

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