

Formulation and Evaluation of Taste Masked Fast Disintegrating Tablets of Lisinopril

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Abstract: Basic goals in the development of taste masked orally disintegrating tablets are to increase patient compliance, ease of administration, safety and appropriate dosing. Orally disintegrating formulations also provide benefits for pharmaceutical companies like lifecycle management, line extension, market expansion, cost effective drug development programs. This technology has perceived faster onset of action (only if engineered for absorption in the oral cavity or stomach) as the dosage form is disintegrated prior to reaching the stomach and is ideal for acute diseases like hypertension and heart failure and particularly applicable to manage breakthrough symptoms. Fast dissolving tablets (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of drinking water. The FDT usually dissolve in the oral cavity in about 10 seconds to 3 minutes. Faster the drug goes into solution, the quicker absorption and onset of clinical effect.

Keywords: Fast dissolving tablets, disintegrates, beta-cyclodextrin, taste masked orally disintegrating tablets.

Introduction:

The oral route of drug administration is popular, convenient and widely accepted method of administering the drugs. For the past two decades, there has been enhanced demand for more patient compliant dosage forms. As a result, the demand for the technologies has been increased 3 fold annually. Oral route 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 patient compliance. Keeping in view the advantages of this delivery system, in the present study attempts were made to formulate taste masked orally disintegrating tablets of lisinopril which is used in acute diseases like hypertension and heart failure respectively. Taste masking of lisinopril was done by complex formation with beta-cyclodextrin by slurry method.

Materials and Methods:

β-cyclodextrins, Avicel, cellulose gel, Powdered talc, Magnesium Stearate. Tablet punching machine 8 station (Rimek Single pan electronic), Weighing

Balance (Toledo) Octagonal blender (Bectochem Engineers) Hardness Tester (Pfizer) Friability Tester (friabilator USP) (EF-2) (Roche) Thickness Tester (Digital Vernier Caliper) Mitutoyo Dissolution Tester USP (TDT – 08L Electro lab Particle size analyzer (Method : light scattering) Malvern Instruments Ltd. UV 1700 Spectrophotometer IR Spectrometer (Shimadzu) Stability control oven (Thermo lab), pH Meter (AP – 1 Plus) Analytical lab service Bulk density Apparatus (Campbell electronics).

Preformulation Studies ^{1,2,3}

Appearance Transferred approximately 2 g of the sample on a white piece of paper, spreaded the powder and examined visually.

Taste and odor: Very less quantity of lisinopril was used to get taste with the help of tongue as well as smelled to get the odor.

Loss on drying: Determined on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tared a glass stoppered, shallow weighing bottle that had been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty

bottle (W1). Put the sample in the bottle, replaced the cover, and accurately weighed the bottle and the contents (W2). By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature for constant weight. Upon opening the chamber, closed the bottle promptly, and allowed it to come to room temperature in a desiccator before weighing. Weighed the bottle (W3). The difference between successive weights should not be more than 0.5 mg. The loss on drying is calculated by the formula

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Determination of densities:

Apparent bulk density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduated cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formulae. Density = Mass/ Volume.

Tapped density: Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density test apparatus, was operated for a fixed number of taps. The tapped density was determined.

Percentage compressibility: Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by the following formula.

$$\% \text{ Compressibility} = \frac{\text{Tapped bulk density} - \text{Initial bulk density}}{\text{Tapped bulk density}} \times 100$$

Flow properties (Angle of repose): A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10 gm of sample powder was filled in funnel. Then funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured. The value of angle of repose was calculated by using the formula: $\tan \theta = h / r$, $\theta = \tan^{-1} h / r$. **Solubility:** A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system was vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in turns of ratio of solute and solvent. **pH:** Weighed and transferred accurately about 1.0 g of sample in a 20 ml clean and dried volumetric flask, dissolved in carbon dioxide free water and made up the volume to 20 ml with same

solvent, mixed. Determined the pH of freshly prepared solution by using precalibrated pH meter.

Identification, By IR: The IR spectrums of the sample and of the lisinopril working/reference standard in the range of 4000 cm^{-1} to 400 cm^{-1} were taken by preparing dispersion in dry potassium bromide under the same operational conditions. Superimposed these spectra. The transmission minima (absorption maxima) in the spectrum obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the lisinopril working/reference standard.

Formulation of Orally Disintegrating Tablets of Lisinopril (10 mg)^{4, 5, 6, 7, 8}

Preparation of fast disintegrating tablets^{9, 10, and 11}

Required quantity of lisinopril was weighed and sifted through # 40 ASTM SS sieve. Other ingredients like beta-cyclodextrin, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and talc were weighed, sifted and kept separately. Complexation with beta-cyclodextrin was done. Initially, Drug: beta-cyclodextrin ratio was 1:5. Slurry of beta-cyclodextrin was prepared by taking beta-cyclodextrin: water (5 gm: 5 ml), stirred for 30 minutes. Drug was added, stirred for 2 hours, dried it. Lubricated with magnesium stearate by tumbling for 10 minutes, finally compressed the lubricated powder base on rotary tablet compression machine plain round punches.

Evaluation of Lisinopril Orally Disintegrating Tablets^{12, 13}

Weight variation test: Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial Specification, tablets with an average weight between 80-250 mg, the percentage deviation should not be more than 7.5%, and tablets with an average weight 250 mg or more, the percentage deviation should not be more than 5.0%. **Friability test** Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum was rotated at a speed of 25 rpm for 4 minutes and reweighed the tablets. %Friability was calculated by the following formula.

$$\%F = 100 \frac{(W_0 - W)}{W}$$

Where, F = Friability, W_0 = Initial Weight, W = Final weight

Hardness Pfizer hardness tester was used for the determination of the hardness. For each formulation 5 tablets were determined. **Thickness** of the tablets was determined using scrooges. 5 tablets from each formulation and average were calculated.

Disintegration test: Placed one tablet in each of the six tubes of the basket and operated the apparatus, using water maintained at 37°C as the immersion fluid. Noted down the time to complete disintegration of tablets. **Wetting time:** Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing 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. **Dissolution study** Dissolution media 900 ml 0.1N HCl, Apparatus : USP II (Paddle) Speed 50 rpm, Temperature 37°C ± 0.5°C Time For 10, 20, 30, 40, 50, 60 minutes λ_{\max} 246 nm. **Stability studies:** Selected formulations were subjected to stability studies as per I.C.H guidelines. 25 °C analyzed every month for a period of one month. 40 °C analyzed every month for a period of one month. 60 °C analyzed every month for a period of one month.

Results and Discussion

Preformulation Studies, Organoleptic properties

Loss on drying: 0.24% that is in the limit. **Angle of repose:** 46.231° show good flow. **Bulk density and tapped density:** 0.312 5 and 0.3846 gm/ml respectively. **Powder compressibility:**

Compressibility index and Hausner ratio 44.7 and 1.8 respectively. **Solution properties pH of the solutions:** 4.91 which is in the specified limit 4.3 – 5.3

Solubility: Freely soluble. **Evaluation of Lisinopril (10mg) Tablets: Weight variation test** Average tablet weight 300.0 mg and % Deviation is maximum 2.28 - 0.33 Complies as per IP specification. **Friability:** less than 0.72 the results indicate that the percentage losses were not more than 1.0%. So the tablet complies as per IP specifications. **Thickness average 4.23 mm** The results indicate that the tablets are suitable for packing.

Hardness between 3.9 to 4.5 The results indicate that the tablets are mechanically strong and are in limit. **Disintegration time: in between 50 to 53 second** the results indicate that disintegration time of tablets is within 1 minute. **Wetting time:** in between 19 to 22

second. **Dissolution Study in 0.1N hydrochloric acid:** is 99% in 60 min the results indicate that the tablet complies as per IP specifications. **Assay (Estimation of lisinopril by UV method):** Limit: Not less than 90% and not more than 110% of the stated amount of the Lisinopril. 97.60%. The results indicate that the tablet complies as per IP specifications. **FTIR studies:** The FTIR spectra of the pure drug and physical mixture of drug were recorded in between 400 to 4000 (cm⁻¹). No peaks are obtained which interfere with the main drug peaks. No compatibility was found. **Stability Studies: Storage condition:** Tablets were stored at 40°C ± 2°C for a storage period of 8 days, 15 days and 30 days, at 25°C ± 2°C for 30 days and at 60°C ± 2°C for 15 days and 30 days. **Hardness** was increases with time increases but in all cases, hardness is within the limit. **Disintegration time:** at various storage conditions increases but maximum 54 second which is less than 1min (specification of IP). Dissolution studies shows there is no large difference in dissolution data of formulations at initial and after specified storage period. **Assay (%):** Results show there is no significance difference in assay data of formulations at initial and after specified storage period.

Conclusion:

Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are the Fast disintegrating tablets. And for that lisinopril was chosen a choice drug candidate. Since it is drug prescribed especially in elderly patients as antihypertensive. And also it is given in the conditions of heart failure and heart attack. The drug is slightly bitter taste in nature and produces non compliance to patient's especially geriatric patients. It concluded that beta cyclodextrins were useful for masking the taste as well as enhancing the solubility of the drug. Super disintegrants were helpful in formulation of the Fast dissolving tablets. crosscarmellose Sodium is suitable for the formulation of the FDTs

Table: 1

Storage condition	25° C ± 2° C	40° C ± 2° C	60° C ± 2° C			
Storage period	30 days	8 days	15 days	30 days	15 days	30 days
Sl. No.	Hardness	Hardness	Hardness	Hardness	Hardness	Hardness
1	4.2	4.3	4.3	4.2	4.2	4.1
2	4.3	4.3	4.2	4.1	4.3	4.1
3	4.2	4.2	4.2	4.1	4.3	3.8
4	4.2	4.4	4.2	4.2	4.0	4.0
5	4.1	4.2	4.3	3.9	3.9	4.3
6	4.1	4.2	4.2	4.3	4.1	4.1
7	3.9	4.1	4.1	4.0	4.0	4.0
8	4.0	4.4	4.1	4.2	4.1	3.9
9	4.1	4.3	4.0	4.1	4.1	4.1
10	4.0	4.3	4.1	4.1	4.2	4.1
Hardness range	3.9-4.3	4.1-4.3	4.0-4.3	3.9-4.3	3.9-4.3	3.8-4.3

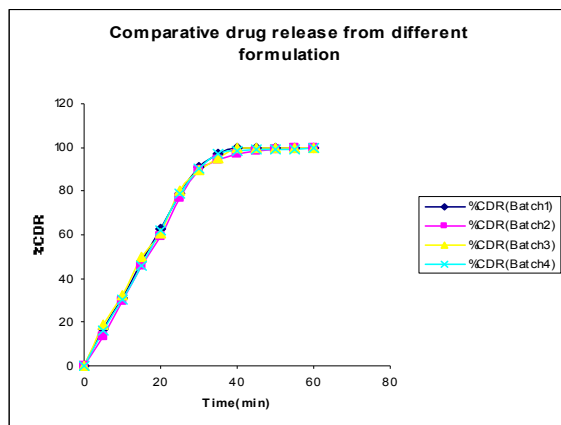
Effect on hardness on various storage conditions(temperature& duration

Table: 2

Batch No.	Tablet weight (X)mg	Average tablet weight (X_1) mg	% Deviation $(X - X_1 / X) * 100$
1	0.307 - 0.301	300.0	2.28 - 0.33
2	0.298 - 0.304	300.0	0.67 -1.33
3	0.295 - 0.300	300.0	1.69 - 0.00
4	0.302 - 0.304	300.0	0.67 - 1.33

Weight variation test table

Graph: 1



References:

1. Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig., the theory and practice of Industrial Pharmacy, 3rd edition, a) Ch-8, Preformulation ,171-194Pp., b) Ch-11,Tablets, by Gilbert S. Banker, 293,296-303, c) Ch-26, Kinetic Principles and testing, by Patrick Deluca, 760-800Pp.
2. Herbert A. Lieberman, Leon Lachman, and Joseph B.Schwartz, Pharmaceutical dosage forms: Tablets volume 1, 2nd edition, Ch: 1, Preformulation testing, 1 to 56 Pp.
3. Fabio Baldi, Peter Malfertheiner, Lansopraole fast disintegrating tablet:- A new formulation for an established proton pump inhibitor.
4. Robert H. Bagner, Meghan F. Wilkosz, Fast dissolving tablets, USPharmacist.
5. David Brown., "orally disintegrating tablets- Taste over speed", Drug delivery technology, September-2003, Vol 3(6).
6. www.pharmainfo.com – Taste masking of pharmaceuticals.htm Cyclodextrin- Wikipedia, the free encyclopedia
7. Suresh Sarasija and Pandit V., Preparation and evaluation of mouth dissolving tablets of Salbutamol sulphate, Indian journal of pharmaceutical science, Volume- 69, 2007.
8. B. S. Kuchekar, Atul C. Badhan, Mouth dissolving tablet:- A novel drug delivery system, pharmaceutical times, volume-35, June 2003.
9. James Swarbrick, Anya M. Hillery, Andrew W. Lloyd, Drug Delivery and Targeting; For Pharmacists and Pharmaceutical Scientists, 2001.
10. Herbert A. Liberman, and L. Lachman., Pharmaceutical dosage forms: Tablets, vol-1,2nd edition, revised and expanded, Ch-4, 195-245 Pp.
11. Rxlist.com- Heart Failure
12. The E-Tongue in pharmaceutical industry, AAPS exhibition: Booyh 442.
