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FORMULATION AND CHARACTERIZATION OF BUCCAL TABLETS OF LANSOPRAZOLE

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ABSTRACT

GERD is described as a "condition that develops when the reflux of stomach contents results in bothersome symptoms and/or complications." Buccal drug delivery has attracted a lot of interest and momentum since it provides outstanding benefits. The most often researched dosage type for buccal medication administration has been tablets. Therefore, the attempt has been made to formulate and characterize buccal lansoprazole tablets. In total nine different formulations were prepared. The result of pre-compression properties of Lansoprazole powder blend indicated that bulk density ranged from 0.342 to 0.358 gm/cm^3 while the tapped density vzried from 0.451 to 0.463 gm/cm^3. The Compressibility index extends from 22.84 to 25.00. The Hausner ratio varied from 1.293 to 1.333. Further the post compression parameters were analyzed by examining different parameters. The thickness among the formulations varied from 2.2±0.2 to 2.5±0.2 mm. The hardness stretched in between 4.2±0.1 kg/cm^2 to 4.8±0.2 kg/cm^2. The drug content among the formulation noted to be highest in F7 which is 99.95±0.14 %. The friability & weight variation ranged between 193±1 mg to 205±4 mg & 0.716±0.036 to 0.853±0.023%. The swelling index was observed to be maximum in case of F7 which is 110.25. The F7 formulation exhibited 98.85 % drug release in 12 hours. The *In-vitro* drug release data for optimized formulation F7 was exactly same which is 98.85%. Further mathematical models were applied and Regression analysis data was obtained. As the r^2 value observed to be highest which is 0.970 for Korsmeyer-Peppas the formulation F7 follows Korsmeyer-Peppas order release kinetics. Thus, lansoprazole was made into bioadhesive buccal tablets to prevent first pass metabolism and increase absorption.

Keywords: GERD, Lansoprazole, buccal medication, buccal drug delivery, bioadhesive, Mucoadhesive.

INTRODUCTION

GERD is described as a "condition that develops when the reflux of stomach contents results in bothersome symptoms and/or complications." The most typical sign of GERD is heartburn, which seven percent of Americans report having daily. It is expected that between 20 and 40 percent of people who have regular heartburn actually have GERD. Regurgitation and trouble swallowing are typical GERD symptoms in addition to discomfort. Additionally, GERD covers the pathologies that develop as the

condition worsens, such as Barrett's esophagus, Barrett's carcinoma, esophageal ulcer, and non-erosive esophageal reflux disease (NERD) [1-2].

The most typical GERD-related problems are heartburn, regurgitation, and difficulty swallowing, but GERD can also cause a wide range of additional symptoms. This understanding has resulted in a broader description of GERD-related symptoms, which can now encompass conditions like laryngitis, coughing, asthma, and dental erosions. In GERD, regurgitation or aspiration of gastric juice can lead to idiopathic pulmonary fibrosis, recurrent pneumonitis, tooth erosion, and chronic cough. Asthma, idiopathic pulmonary fibrosis, chronic hoarseness, nocturnal choking, chronic sinusitis, posterior laryngitis, and otitis media are other GERD symptoms. According to epidemiological data, between 34 and 89 percent of asthmatics also have GERD [3-4].

The production of acid is suppressed by drugs used to treat GERD. PPIs are thought to be the most successful treatment option for both erosive and nonerosive GERD. They could aid in esophageal lining recovery. The H2 blockers lessen stomach acid, but they are less effective at repairing the lining of the esophagus. Additionally, antacids can neutralize stomach acid since they are alkaline (bases). They are available over-the-counter and can be used to treat minor symptoms [5].

Buccal drug delivery has attracted a lot of interest and momentum since it provides outstanding benefits. In the recent years, there has been intense interest in the buccal route for systemic drug delivery employing mucoadhesive polymers to greatly enhance the performance of several medications. The most often researched dosage type for buccal medication administration has been tablets. Unlike normal tablets, buccal tablets are small, flat, and oval-shaped dose forms that don't cause any discomfort when swallowed or spoken. They become softer, stick to the mucosa, and remain there until the disintegration or release is finished [6-7].

For buccal drug delivery, monolithic and two-layered matrix tablets have been developed. Different techniques, such wet granulation or direct compression, can be used to make bioadhesive tablets. The tablets that are put into the buccal pouch for buccal drug delivery may disintegrate or erode; as a result, they must be manufactured and compressed with enough pressure only to produce a firm tablet. Water-impermeable substances, such as ethyl cellulose, hydrogenated castor oil, etc., may be employed either by compression or by spray coating to cover every face of the tablet aside from the one that is in touch with the buccal mucosa in order to enable or to achieve unidirectional release of the medicine. Prior to direct compression, the drug may, if necessary, be synthesized in specific physical states, such as

microspheres, to obtain particular desired qualities, such as increased activity and longer drug release [8-9].

For the short-term treatment of active gastric ulcers, active duodenal ulcers, erosive reflux oesophagitis, symptomatic gastroesophageal reflux disease, and non-steroidal anti-inflammatory drug (NSAID) induced gastric and duodenal ulcers, lansoprazole is used to decrease gastric acid secretion. It can be used to treat and maintain a number of gastrointestinal disorders, such as duodenal ulcers, gastric ulcers brought on by NSAIDs, and erosive esophagitis. In patients with a history of stomach ulcers and prolonged NSAID usage, lansoprazole inhibits the recurrence of gastric ulcers. The care of hypersecretory disorders, such as Zollinger-Ellison syndrome, benefits from it as is expected. When administered in combination with amoxicillin and clarithromycin (triple therapy) or by itself (dual therapy), lansoprazole is successful at getting rid of *H. pylori* [10-11]. Therefore, the purpose of this study is to formulate and characterize buccal lansoprazole tablets.

Materials & Methods

Chemicals and reagents

Ethanol, Methanol, HPMC K 15M, HPMC K 4 M, SLS, MCC 102, Mannitol, Mg Stearate and Ethyl cellulose were obtained from Loba chemie Pvt ltd.

Preparation of Bilayered buccal tablets of Lansoprazole core tablet

Various batches of BBT were prepared by changing the ratio of HPMC K15M, and HPMC 4 M. The drug-polymer combination was mixed and triturated for 15min (Table 1) in a glass mortar to obtain homogeneous mixture. The powder mixture equivalent to 150mg was then compressed directly using an 11mm diameter die in a single-stroke multistation tablet machine (Karnavati mini press, India). Upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact. Then 2 layers were compressed into a mucoadhesive bilayer tablet with a total weight of 200 mg/tablet [12].

Backing Layer

Ethyl cellulose granules were prepared by wet granulation using isopropyl alcohol as the granulating solvent. The wet mass was passed through mesh #8 and dried at 40°C for 1 h. The granules were then passed through mesh #22 and retained on mesh #44. The core tablet was transferred to the die cavity fitted with 10-mm flat punch. Ethyl cellulose granules (50 mg) were added and subsequently compressed at constant maximum compression force. The tablets were coated from the sides and bottom with ethyl cellulose as backing membrane such that only the top surface remained uncoated [13].

Table 1: Formulation of bilayered buccal tablets of lansoprazole

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	15	15	15	15	15	15	15	15	15
HPMC K 15M	25	30	35	25	30	35	12.5	15	17.5
HPMC K 4 M	-	-	-	10	15	20	12.5	15	17.5
SLS	4	4	4	4	4	4	4	4	4
MCC 102	96	91	91	96	76	66	96	91	86
Mannitol	5	5	5	5	5	5	5	5	5
Mg Stearate	5	5	5	5	5	5	5	5	5
Ethyl cellulose	50	50	50	50	50	50	50	50	50
Total	200	200	205	200	200	200	200	200	200

Evaluation of powder blend

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced, bulk density, true density and percent compressibility index have been measured [14].

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated [15].

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask.

The powder was dissolved in 5 ml of 6.8 pH Phosphate buffer and made up to volume with of 6.8 pH Phosphate buffer. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 296.0 nm using 6.8 pH Phosphate buffer.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach) [16].

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes [17]. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated [18].

Swelling Index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 6.8 pH Phosphate buffer was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2).

Determination of mucoadhesive strength

The working of a double beam physical balance formed the basis of the bioadhesion test assembly. The left pan was removed and hung with a stainless steel chain. A Teflon block with 1.5 in height and 1.5 in diameter was hung with the stainless steel chain to balance the weight of the other pan. The height of the total set up was adjusted to accommodate a glass container or beaker below it leaving a head space of about 0.5 cm in between. Block of 2 in height and 1.5 in diameter was kept inside the glass vessel, which was then positioned below the top hung Teflon block. Suitable weights were added on the right pan to balance the beam of the balance.

The porcine gastric mucosa was attached with the mucosal side upward onto the lower Teflon block which was then placed in the glass vessel. Sufficient simulated gastric fluid was filled into the beaker so that the surface of the fluid just touches the mucosal surface to Teflon block.

A tablet was fixed to the bottom portion of the cylindrical shaped base with 'feviquick' glue. The string with tablet was hung in such a way that the tablet was just in contact with the surface of the mucosal side of pig stomach when the balance was in a balanced position. The balance was left in a balanced position for fixed time of 5 minutes and then slowly weights were increased on the right pan until the tablet detaches from the surface of the intestinal mucosa. The weights on right side pan gave the mucoadhesive strength of the tablet in grams.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 6.8 pH Phosphate buffer was set into the dissolution flask maintaining the temperature of 37 ± 0.5^0C and rpm of 75. One Lansoprazole tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 296.0 nm using spectroscopy.

RESULTS & DISCUSSION

In total nine different formulations were prepared. The result of pre-compression properties of Lansoprazole powder blend indicated that bulk density ranged from 0.342 to 0.358 gm/cm^3 while the tapped density vzried from 0.451 to 0.463 gm/cm^3. The Compressibility index extends from 22.84 to 25.00. The Hausner ratio varied from 1.293 to 1.333. Further the post compression parameters were analyzed by examining different parameters. The thickness among the formulations varied from 2.2±0.2 to 2.5±0.2 mm. The hardness stretched in between 4.2±0.1 kg/cm^2 to 4.8±0.2 kg/cm^2. The drug content among the formulation noted to be highest in F7 which is 99.95±0.14 %. The friability & weight variation ranged between 193±1 mg to 205±4 mg & 0.716±0.036 to 0.853±0.023%. The swelling index was observed to be maximum in case of F7 which is 110.25. The Mucoadhesive strength was examined by estimating force of adhesion. The maximum force of adhesion was observed again in F7 which is 4.45. The degree of adhesion between the epithelial surface and/or mucus and a polymeric component included in the formulation is referred to as mucoadhesive strength. The soaking of the polymer, interpenetration, and mechanical attachment between the polymer and mucus are the three main phases of the

mucoadhesion process. The length of contact with mucus, type of biological membrane, swelling behavior of the polymer, average molecular weight, concentration, and composition of the polymer being employed all have a significant impact on the strength of mucoadhesion.

The last and most important step was to assess the % Cumulative Drug Release. The F7 formulation exhibited 98.85 % drug release in 12 hours. The *In-vitro* drug release data for optimized formulation F7 was exactly same which is 98.85%. This means that the concentration of SCMC has a significant impact on the drug release profile. The ability of HPMC K 15M and HPMC K 4 M to absorb more water is anticipated to cause the polymer matrix to significantly swell, allowing the medication to release out quickly.

Further mathematical models were applied and Regression analysis data was obtained. The r^2 value obtained for zero order, first order was 0.865 & 0.961 respectively while the r^2 value for Higuchi and Korsmeyer-Peppas was observed to be 0.965 & 0.970 respectively. As the r^2 value observed to be highest for Korsmeyer-Peppas the formulation F7 follows Korsmeyer-Peppas order release kinetics.

According to this study, all of the developed formulations were suitable. The outcomes of the physical tests on the formulations were acceptable and met the requirements.

Table 2: Result of pre-compression properties of Lansoprazole powder blend

F. Code	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Compressibility index	Hausner ratio
F1	0.352	0.462	23.81	1.313
F2	0.345	0.452	23.67	1.310
F3	0.358	0.463	22.68	1.293
F4	0.348	0.451	22.84	1.296
F5	0.342	0.456	25.00	1.333
F6	0.349	0.453	22.96	1.298
F7	0.348	0.451	22.84	1.296
F8	0.353	0.463	23.76	1.312
F9	0.358	0.463	22.68	1.293

Table 3: Results of post compression properties of Lansoprazole bilayer tablets

Formulation code	Thickness* (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	2.3±0.1	4.8±0.2	205±4	0.785±0.025	98.85±0.32
F2	2.2±0.2	4.6±0.3	198±2	0.853±0.023	98.78±0.21
F3	2.4±0.2	4.3±0.2	200±4	0.845±0.025	98.95±0.25
F4	2.3±0.1	4.2±0.1	196±6	0.865±0.024	97.95±0.26
F5	2.4±0.2	4.8±0.2	194±5	0.716±0.036	98.85±0.21
F6	2.5±0.2	4.3±0.2	202±4	0.765±0.036	99.05±0.20
F7	2.4±0.2	4.8±0.1	198±3	0.782±0.041	99.95±0.14
F8	2.4±0.2	4.6±0.2	195±2	0.763±0.036	98.78±0.23
F9	2.5±0.1	4.7±0.2	193±1	0.765±0.035	98.65±0.24

Table 4: Results of Swelling Index of Lansoprazole bilayer tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	40.25	65.85	87.74	98.85
F2	49.95	62.25	86.65	97.85
F3	46.65	61.25	81.14	96.65
F4	52.23	69.98	86.65	101.25
F5	55.65	72.25	87.75	102.32
F6	57.78	69.11	87.74	101.85
F7	68.98	89.98	96.65	110.25
F8	67.74	85.95	92.25	105.45
F9	68.15	83.32	90.74	103.65

Table 5: Results of determination of Mucoadhesive strength

S. No.	Formulation Code	Force of Adhesion
1.	F1	2.36
2.	F2	2.45
3.	F3	2.54
4.	F4	3.21
5.	F5	3.52
6.	F6	3.41
7.	F7	4.45
8.	F8	4.05
9.	F9	4.11

Table 6: *In-vitro* drug release study of bilayer tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	34.45	32.25	30.45	24.45	22.23	20.23	17.75	15.25	13.25
1	52.23	55.65	51.12	36.65	35.65	32.23	26.65	20.23	18.85
1.5	65.59	63.32	56.65	43.32	41.25	38.85	38.89	33.32	32.69
2	86.65	81.12	79.98	55.78	53.32	51.14	46.67	41.15	39.98
3	98.85	93.36	89.98	73.36	74.45	59.98	59.98	55.65	51.45
4	-	99.12	98.65	83.32	86.65	76.65	68.74	67.78	65.58
6	-	-	-	99.12	99.74	88.89	79.98	75.56	71.12
8	-	-	-	-	-	98.85	88.89	83.32	82.23
12	-	-	-	-	-	-	98.85	91.74	89.45

Table 7: *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	17.75	1.249	82.25	1.915
1	1	0	26.65	1.426	73.35	1.865
1.5	1.414	0.301	38.89	1.590	61.11	1.786
2	2	0.602	46.67	1.669	53.33	1.727
3	2.449	0.778	59.98	1.778	40.02	1.602
4	2.828	0.903	68.74	1.837	31.26	1.495
6	3.464	1.079	79.98	1.903	20.02	1.301
8	0.707	-0.301	88.89	1.949	11.11	1.046
12	1	0	98.85	1.995	1.15	0.061

Table 8: Regression analysis data of Lansoprazole tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2			
F7	0.865	0.961	0.965	0.970

Conclusion

Lansoprazole was made into bioadhesive buccal tablets to prevent first pass metabolism and increase absorption. These are made using the direct compression technique. All of the formulations tested for a variety of physicochemical parameters produced positive outcomes. According to the findings, formulation F7 had the greatest in-vitro drug release. Additionally, research on the optimized formulations' ex vivo permeability, swelling, and moisture absorption have shown that they are acceptable for buccal distribution. The most effective formulation is F7, which followed the Korsemeyer and Peppas release kinetics and controlled by the Super Case II diffusion mechanism.

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