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FORMULATION AND CHARACTERIZATION OF SUSTAINED RELEASE BUCCOADHESIVE TABLETS OF LANSOPRAZOLE.

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ABSTRACT

The aim of this study was to formulate and investigate the in vitro performance of Lansoprazole .Lansoprazole can certainly be administered through the oral mucosa. The designed buccoadhesive tablets can overcome the disadvantage of extensive first pass effect and side effects of Lansoprazole. Lansoprazole, an acid proton-pump inhibitor similar to omeprazole, is used as an untiulcer drug in the treatment and maintenance of healing of duodenal or gastric ulcers, erosive and reflux esophagitis, NSAID-induced ulcer, Zollinger-Ellison syndrome, and Barrett's esophagus. Lansoprozole is active against Helicobacter pylori. Lansoprazole buccoadhesive tablets was formulate with following materials like Carboxy methyl cellulose, Carbopol 934P, Mannitol, Micro crystalline cellulose, Aspartame show better bioavailability.

KEYWORDS: Carboxy methyl cellulose, Carbopol 934P, Mannitol, Micro crystalline cellulose.

INTRODUCTION

Mucoadhesive Drug Delivery Systems

These may be defined as drug delivery systems, which utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting of drug to particular regions of body for extended periods of time. Hence buccal drug delivery systems are period of time. The mucoadhesive drug delivery system includes the following:[3] generally based on bioadhesive polymers which once hydrated adhere to the buccal mucosa and withstand salivation, tongue movements and swallowing for a significant.

1. Buccal drug delivery system.
2. Oral delivery system.
3. Vaginal delivery system.
4. Rectal delivery system.
5. Nasal delivery system.
6. Ocular delivery system

Buccal Drug Delivery System

Drug delivery via membranes of the oral cavity can be subdivided as follows.

- Sublingual delivery, in which the administration of drug via the sublingual mucosa to the systemic circulation.[3]
- Buccal delivery, in which the administration of drug via the buccal mucosa (the lining of cheek) to the systemic circulation via internal jugular vein.[3]
- Local delivery, for the treatment of conditions of the oral cavity, principally aphthous ulcers, fungal conditions and periodontal diseases by applications of the bioadhesive system either to the palate, or the cheek.[3]

These oral sites differ from each other, in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for desired period of time. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs and is convenient, accessible and generally well acceptable, which makes the oral mucosa. Finally the buccal site rather attractive for drug delivery.[3]

- Its ability to recover after local treatment is pronounced, and hence allowed a wide range of formulation to be used, e.g., bioadhesive ointment and patches.[3]
- The oral mucosa is accessible, so dosage forms can be administered and even removed from the site of application.[3]
- Since patients are well adapted to the oral administration of drugs in general, patient's acceptance and compliance is expected to be good.[3]
- According to its natural function the oral mucosa is routinely exposed to a multitude of different external compounds and, therefore, is supposed to be rather robust and less prone to irreversible irritation or

damage by dosage form, it's drug, excipients or additive.

Local delivery of drug to tissue of the oral cavity has a number of applications including the treatment of toothache, periodontal diseases, dental carries, bacterial and fungal infections and aphthous stomatitis.[3]

Overview of the Oral Cavity

The different anatomical regions of the oral cavity and mucosal tissues are shown in Figure no.3. The various target sites for drug delivery and absorption may include the upper and lower lips, gums, hard palate, soft palate, floor of the mouth (sublingual), tongue, and buccal mucosal tissue (cheek).The oral mucosal tissues can be divided into two types, namely, keratinized epithelium of the masticatory regions consisting of the gums palatal mucosa, and the inner side of the lips and non-keratinized regions consisting of the floor of mouth (sublingual) and the buccal mucosa. The differences between the two types of epithelia are:

- The superficial layer of the non-keratinized layer is rougher when compared to keratinized epithelium and.
- The elongated rate processes, which provide the attachment of epithelium to the underlying connective tissue, are deeper and narrower in keratinized epithelium as opposed to non keratinized epithelium.[3]

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.[3]

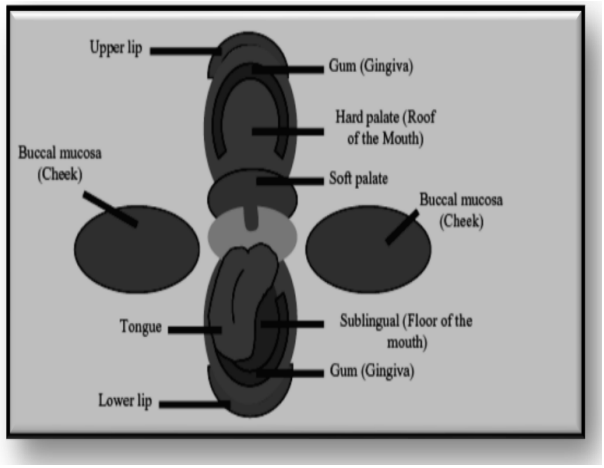

Figure Anatomic regions of oral cavity.

Drug Profile

Lansoprazole is a proton pump inhibitor which prevents the stomach from producing acid. It is manufactured by TAPPharmaceutical Products. Lansoprazole has been marketed for many years and is one of several PPI's available.

Proton-pump Inhibitors

Categories

- Anti-Infective Agents
- Anti-Infectives
- Anti-Ulcer Agents
- Enzyme Inhibitors

Lansoprazole, an acid proton-pump inhibitor similar to omeprazole, is used as an untiulcer drug in the treatment and maintenance of healing of duodenal or gastric ulcers, erosive and reflux esophagitis, NSAID-induced ulcer, Zollinger-Ellison syndrome, and Barrett's esophagus. Lansoprozole is active against Helicobacter pylori. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours. The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%.Following single-dose oral administration of PREVACID, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Formulation of Mucoadhesive Tablets of Lansoprazole

Preparation

In this work, direct compression method has been employed to prepare buccal tablet with CMC and Carbopol 934P as polymers because with the dry granulation and wet granulation the hardness of tablets has increased because of which rate of drug release got decreased. For one tablet accurately weighed 200 mg was used in the formulation.

Procedure: All the ingredients were accurately weighed and passed through mesh # 60. In order to mix all ingredients thoroughly Drug, polymers, mannitol, micro crystalline cellulose, Aspartame were blended geometrically in mortar and pestle for 10 minutes then magnesium stearate were mixed for 1-2 min.

The powder blends of various proportions were evaluated for angle of repose, Carr's compressibility index and compressed into tablets of diameter 8mm on Cadmach press16 Station machine. Using stainless steel flat surface dies and punches by maintaining individual tablet weight constant at 200 mg.

The Ethyl cellulose was placed on the prepared tablets from as an impermeable backing layer which was aimed to provide unidirectional drug release. The compositions of the prepared formulations are as specified in the table

Table Composition of Tablets

- Each tablet contains 20 mg of ethyl cellulose as a backing layer.
- All the weights are in mg.

Components(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Lansoprazole	30	30	30	30	30	30	30
Carboxy methyl cellulose	-	-	50	60	25	16.7	12.5
Carbopol 934P	50	60	-	-	25	33.3	37.5
Mannitol	20	20	20	20	20	20	20
Micro crystalline cellulose	96	86	96	86	96	96	96
Aspartame	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200

RESULTS

Characterization of Blend

The blends for Bucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content. Angle of repose was less than 35° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.0 for all the batches indicating excellent to good flow properties. The drug content was more than 98 % for all the blend of different formulations.

Table Physical Properties of Pre-compression Blend.

Formulatios	**Angle of repose (°)**	**Bulk Density (g/mL)**	**Tapped Density (g/mL)**	**Carr's Index (%)**	**Hausner's ratio**
F1	25.11	0.326	0.334	2.39521	1.02454
F2	24.6	0.334	0.348	4.022989	1.041916
F3	22.4	0.387	0.442	12.44344	1.142119
F4	26.3	0.331	0.338	2.071006	1.021148
F5	25.1	0.328	0.342	4.093567	1.042683
F6	29.3	0.452	0.516	12.4031	1.141593
F7	20.4	0.325	0.341	4.692082	1.049231

Physical Evaluation of Bucoadhesive tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 199.3 to 202.4mg. The hardness of the tablets ranged from 6.55 to 6.89kg/cm^2 and the friability values were less than 0.6% indicating that the Bucoadhesive tablets were compact and hard. The thickness of the tablets ranged from 2.50 to 2.64mm. All the formulations satisfied the content of the drug as they contained 98 to 101 % of Lansoprazole and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table Physical Evaluation of Bucoadhesive Tablets Microenvironment pH study.

F.Code	**Hardness (kg/cm2)**	**Thickness (mm)**	**Weight (mg)**	**Friability (%)**	**Drug content *(%)**
F1	6.72	2.54	201.6	0.53	99.12±2.47
F2	6.86	2.50	202.4	0.42	101.22±0.88
F3	6.55	2.64	200	0.54	98.28±1.99
F4	6.61	2.52	201.5	0.47	98.35±1.14
F5	6.86	2.55	201.6	0.42	99.32±0.58
F6	6.82	2.58	199.4	0.46	100.24±1.05
F7	6.89	2.53	199.3	0.48	99.53±1.32

F CODE	Surface pH
F1	6.5
F2	6.3
F3	6.3
F4	6.5
F5	6.7
F6	6.3
F7	6.8

Table: Results of Microenvironment pH study

The surface pH of all formulations was found to be within ±1 units of neutral pH. The values are tabulated in the table no. Hence these formulations should not cause any irritation in buccal cavity.

Swelling Index

Table Results of Percent swelling Index.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	10.21	14.32	12.93	8.71	12.93	11.62	7.87
3	30.47	36.76	33.52	22.37	28.31	32.15	19.34
6	80.69	80.07	80.21	57.24	79.47	77.28	60.85
8	101.5	103.8	88.31	100.9	93.83	98.02	99.17

The swelling behavior of a buccal adhesive system is an important properties uniform and prolonged release and effective mucoadhesion. The swelling index study indicated that the rate of swelling was directly proportional to carboxy methyl cellulose and Carbopol 934 content. Swelling index was calculated with respect to time. The swelling index gives an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption.

Formulation Code	Bioadhesive strength	Mucoadhesion time
F1	26.62	8
F2	31.57	>8
F3	22.39	6
F4	25.32	7.2
F5	21.26	6
F6	24.34	7
F7	25.39	8

Table Bioadhesive Strength and Mucoadhesion time

Ex vivo residence time was determined by using sheep buccal mucosa. The mucoadhesion time is important to know how long the tablet could able to stick to the buccal mucosa. This adhesion time relates to the release rate of drug. The mucoadhesion time is as follows F2>F1>F7>F8 >F6>F4>F5. The bioadhesive tablet is important for good mucoadhesion. Bioadhesion characteristics are affected by the type and ratios of bioadhesive polymers carboxy methyl cellulose, Carbopol 934P were used. F1,F2 as carbopol concentration increases bioadhesive strength increases, F3,F4 as carboxy methyl cellulose increases bioadhesive strength increases, F5-F7 as the ratio of carboxy methyl cellulose: carbopol 934P increases the bioadhesive strength increases, the results revealed that the highest detachment force was observed in formulation F2 containing carbopol 934P, indicating that as the concentration of carbopol increases bioadhesion force also increases. This may cause damage to the buccal mucosa during the time of termination.

Table L: In-vitro drug release study.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	25	17	34	26	34	30	34
2	34	26	46	38	45	41	40
3	45	32	50	48	53	50	49
4	52	38	79	69	76	67	64
5	68	50	82	76	81	79	76
6	74	66	96	84	92	81	81
7	80	72	--	90	--	94	89
8	92	84	--	94	--	--	97

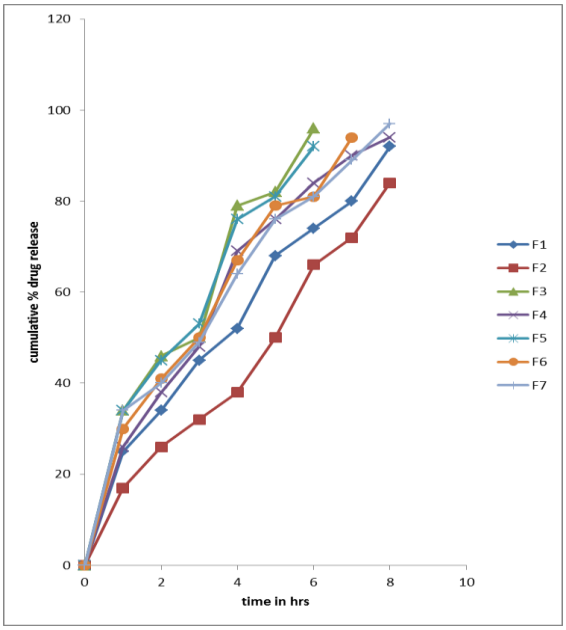

Figure: In-Vitro Drug Release for Formulations.

In-vitro drug release study

The In-vitro drug release study has been done for various formulations (F1-F7). The different ratios of polymers were used. The results shown that as the proportion of

polymers in the formulation increases, cumulative percent drug released was found to be reduced. Among the seven trial batches, formulation F_1 F2 and F_4 have released 92%, 84, and 94% drug release in 8th hr respectively, F_3, F5 formulations have drug release of 96% and 92% drug release in 6th hr respectively where as F6 Showed a drug release of 94% of drug release in 7thhr respectively. Among all F7 was optimized based on sustained drug release and highest drug release at 97% at 8th hr.

Table: Drug Release Kinetics for Optimized Formula F7.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	11.03333333	-0.16253538	34.28384413	1.341505423
Intercept	14.75555556	2.098924492	-3.22582004	0.908560506
Correlation	0.973389083	-0.94577699	0.992233863	0.746513988
R 2	0.947486307	0.894494094	0.98452804	0.557283134

Table Ex-vivo drug permeation studies for F7.

Time	F7
1	10.03
2	15.8
3	23.18
4	33.27
5	44.89
6	58.76
7	70.04
8	85.01

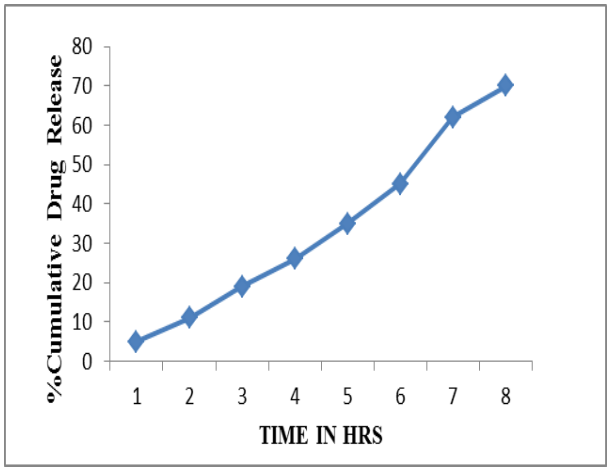

Figure For permeation studies of formulation F7.

The drug permeation was slow and steady, 85.01% of drug could permeate through the buccal membrane in 8 hours.

Drug release kinetics

In-vitro drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release.

From the above data, it can be seen the formulation, F7 have displayed zero order release kinetics ('r^2 value of 0.9475). From Higuchi's and Peppas data, it is evident that the drug is released by non-Fickian diffusion mechanism.

The values of 'r' for Higuchi's equation of factorial formulations have r^2 value of 0.984. This data reveals that drug release follows non-Fickian diffusion mechanism. This is because as the proportion of polymers in the matrix increased there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths.

Stability Studies

Table 16: Stability studies of Lansoprazole bucoadhesive tablet (F7) at room temperature.

Time	Colour	Assay		Cumulative % drug release		Surface pH	
		25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	White	99.73	99.73	97	97	6.8	6.8
30 days	White	97.93	97.85	96.38	96.31	6.8	6.8
60 days	White	97.83	97.65	96.25	96.16	6.8	6.8
90 days	White	97.76	97.49	96.05	96.82	6.8	6.8

Results from stability studies indicate that the formulated lansoprazole bucoadhesive tablet are stable for a period of 3 months under 2 different conditions at 25±2^{0}c, 65±5% RH and 40±2^{0}c and 75±5% RH. There were no remarkable changes were observed during the period of storage.

CONCLUSION

It can be concluded that Lansoprazole can certainly be administered through the oral mucosa. The designed buccoadhesive tablets can overcome the disadvantage of extensive first pass effect and side effects of

Lansoprazole. This increased and predictable availability of Lansoprazole from designed formulation may result in substantial dose reduction of the dosage form when the drug is administered through oral mucosa so that it will be economical to the patient. Further work is recommended to support its efficacy claims by pharmacokinetic and pharmacodynamic studies in human beings.

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