Design and Development of Dexlansoprazole Buccal Tablets

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ABSTRACT

In the present study an attempt was made to formulate and evaluate a new Bucco adhesive tablets for buccal drug delivery of Dexlansoprazole in order to overcome bioavailability related problems, to reduce dose dependent side effects and frequency of administration. Different eight formulations of mucoadhesive buccal tablets were prepared by using HPMCK4M, Chitosan as mucoadhesive polymer in a different concentration by direct compression method. The prepared formulations were evaluated for pre compression and post compression parameters which revealed good flow properties of the blend and physical attributes of the prepared tablets were found to be practically within control limits. The swelling index was proportional to polymer content. The surface pH of all tablets was found to be satisfactory i.e. close to neutral pH hence, buccal cavity irritation should not occur with these tablets. Drug release and drug diffusion from the tablets were depended on the concentration and type of the polymer used in the formulation. FTIR studies showed the compatibility of drug with excipient. From the in-vitro drug release study it was found that formulation F5 has good drug release when compared to other formulations. The formulation F5 containing Dexlansoprazole, Chitosan as mucoadhesive polymer is the optimized formulation. The release data was treated with kinetic equation and it followed zero order release. The mechanism of drug release was found to be Fickians diffusion and followed anomalous release.

Keywords: Buccal tablets, Dexlansoprazole, HPMC K4M, Chitosan

INTRODUCTION:

Gastroesophageal reflux disease (GERD) is a chronic symptom of mucosal damage caused by stomach acid coming up from the stomach into the esophagus. GERD is caused by the changes in barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter. The most common symptoms include heart burn and regurgitation fig-1. Medications such as proton pump inhibitors, H2 receptor blockers and antacids are used in the treatment of GERD. DSP is a proton pump inhibitor drug used in the treatment of GERD. However, it is degraded in acidic stomach pH, thus lacking in pharmacological action of the drug.GERDis a common condition with a prevalence of 10–20% in the Western world and an annual incidence of 0.38–0.45%. The range of GERD prevalence estimate is 18.1–27.8% in North America and 8.8–25.9% in Europe. In the United States (US), 20% of the population experience GERD-related symptoms weekly and 7% daily. Several studies have demonstrated that patients with GERD have reduced health-related quality of life and work productivity. GERD is the most common outpatient gastroenterology diagnosis in the US with a concomitant significant economic burden.

Buccal Drug Delivery System:

Buccal drug delivery system is one such novel drug delivery system is that the mucoadhesive drug delivery system.

Dosage forms designed for mucoadhesive drug delivery should be small and versatile enough to be acceptable for patients and will not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release, good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Several peptides, including TRH, Insulin, Octreotide, Leuprolide, and Oxytocin, are delivered via the mucosal route, albeit with relatively low bioavailability (0.1–5%), owing to their hydrophilicity and enormous relative molecular mass, also because the inherent permeation and enzymatic barriers of the mucoadhesion. Each site of mucoadhesion has its own advantages and drawbacks alongside the basic property of prolonged residence of dosage form at that specific site. In buccal and sublingual sites, there's a plus of fast onset alongside bypassing the first pass metabolism, but these sites suffer from inconvenience due to taste and intake of food. In GIT, there's an opportunity for improved amount of absorption due to microvilli, but it's a drawback of acid instability and first-pass effects.

DEXLANSO PRAZOLE:

Dexlansoprazole, is used to treat gastroesophageal reflux disease. Effectiveness is similar to other proton pump inhibitors (PPIs). Dexlansoprazole is a new generation PPI used for the management of symptoms associated with GERD and erosive esophagitis

MATERIALS AND METHODS:

MATERIALS: Dexlansoprazole gift sample obtained from Sri Krishna Pharma ltd, HPMC, Chitosan and Magnesium stearate obtained from Yarrow Chem products Mumbai, Talc Central drug house (P) LTD.

Table: 1 Composition of Bucco adhesive tablets containing Dexlansoprazole

Ingredients(mg)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Dexlansoprazole	30	30	30	30	30	30	30	30
HPMC K4M	50	100	150	200				
Chitosan					50	100	150	200
Mannitol	166	116	66	16	166	116	66	16
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2

METHOD OF PREPARATION:

Buccal tablets of Dexlansoprazole using HPMC K4 and Chitosanwas prepared by Direct compression method. Drug, polymer and excipients were weighed accurately according to the batch formula and mixed in the order of ascending weights and blended for 10 min by triturating in a glass mortar & pestle. After uniform mixing of ingredients, Magnesium stearate and talc was added and again mixed for 2 min. Final lubricated blend equivalent to the compressed in to tablets using 4 mm round flat punches on 10-station rotary tablet compression machine (Rimek). mucoadhesive tablet with a total weight of 200 mg/tablet.

EVALUATION OF BUCCAL TABLETS:

Determination of angle of repose (θ): A glass funnel is held in place with a clamp and place a graph paper below it. Approximately weighed quantity of powder is poured through the funnel keeping the orifice of the funnel blocked by the thumb. A gap of 6.4 mm is maintained between the bottom of the funnel stem and the top of the powder pile. Again, the powder is poured through the funnel keeping the orifice of the funnel blocked by the thumb. The height of the heap is measured. The circumference of the heap is marked by pencil and diameter is determined with the help of scale and finally the radius is determined and the angle of repose is calculated using the formula.

$\tan \theta = h/r$

Where,

θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Determination of Bulk Density and Tapped Density:
20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals for 100 tapping. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formula.
Bulk density = W / VO Tapped density = W / VF
Where, W = weight of the initial granules
VO = Initial volume of the granules
VF = Final volume of the granules.

Hausner's Ratio:
It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.
Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's Index):
The flow ability of powder can be evaluated by comparing the bulk density and tapped density of powder and the rate at which it packed down. Compressibility index is calculated

$$\text{Compressibility index}(\%) = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} X100$$

Post-compression Parameters:
Appearance, colour, and odour of tablets Organoleptic properties such as taste, colour, odour was evaluated. Ten tablets from each batch were randomly selected and taste tested, colour visually compared and odour checked.

Weight variation:
All prepared Dexlansoprazole buccal tablets were evaluated for weight variations as per USP monograph. Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight was calculated, individual tablet weight was then compared with the average value to find out the deviation in weight and percent variation of each tablet was calculated.

Tablet hardness:
The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its strength or hardness. The hardness of ten randomly selected buccal tablets was measured by using Monsanto hardness tester which measures the pressure required to break diametrically placed tablets by applying pressure with coiled spring and expressed in Kg/cm2.The mean and standard deviation values were calculated and reported.

Friability:
Friability was performed by using Roche Friabilator to determine friability It is expressed in terms of percentage (%). For friability testing 10 tablets from each batch were randomly selected, initially weighed and transferred into Friabilator apparatus that revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inches with each revolution. At the end of test (after 100 revolution), tablets were dedusted, reweighed and percentage loss was determined. % friability was then calculated by the following formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets - final weight of tablet}}{\text{Initial weight of tablets}} X\ 100\%$$

Content Uniformity:
Five tablets from each formulation were powdered individually and a quantity equivalent to 30 mg of Dexlansoprazole was accurately weighed and extracted with a suitable volume of 6.8 pH buffer. Each extract was

suitably diluted and analysed spectrophotometrically at 285 nm.

Swelling study:
The swelling behaviour of a dosage form was measured by studying its weight gain or water uptake. Buccal tablets were weighed (W0) and placed separately in petri dishes with 5ml of phosphate buffer pH 6.8. At the interval of 1,2,3,4,5,6,7 and 8 hours, tablets were removed from the petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (Wt) and the swelling index (SI) were measured in terms of percent weight gain, as given by the following formula:

$$SI = \frac{(Wt-W0)}{W0} X\ 100$$

Where, SI= Swelling index
W0 =Initial weight of dosage form
Wt =Weight of dosage form at time t

Surface pH :
The surface pH of the tablet was determined to investigate the effect of pH on the bioadhesion and possible side effects of the tablets in vivo. This was determined by allowing the tablet to swell in 10 ml of phosphate buffer (pH 6.8) for 2 hrs. A combined glass pH electrode was brought in contact of the swollen tablet and the pH was measured after 1 min equilibrium

In-vitro drug release study:
The USP type- II rotating paddle method was used to study the drug release from the tablet. The dissolution medium consisted of 900ml of sodium phosphate buffer pH 6.8. The release study was performed at 37± 0.50C, with a rotation speed of 50 rpm. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 6.8 and were analysed spectrophotometrically at 285nm

Stability studies:
Optimized formulation F5 was stored at 40° ± 2°C/75% RH ± 5% RH in stability chamber for 3 months. The optimized formulation stored in the sealed aluminum foil and was analyzed for every 30 days.

RESULTS AND DISCUSSION:

PREFORMULATION STUDIES:

Drug description
Description of drug were showed on below Table no:2

Table 2: Description about drug

Drug	Dexlansoprazole
Nature	Solid
Colour	White
Odour	Odourless

Solubility Analysis
Solubility studies were carried out in different solvents and observations were showed Table no:3

Table no:3 Solubility profile of Dexlansoprazole:

Solvent	Solubility
Methanol	Very soluble
0.1 N HCl	Very soluble
Phosphate buffer pH 6.8	Freely soluble
Water	Partially soluble

Solubility analysis is important because the drug has to dissolve in the solvents and also in the dissolution medium used. Dexlansoprazole was found to be very soluble in Methanol and0.1N HCL, freely soluble in Phosphate buffer pH 6.8 and partially soluble in water.

Melting Point determination:

Melting point were carried out and observations were showed Table no: 4

Table 4: Melting point of Dexlansoprazole

Sample	Melting point of sample in literature	Melting point of sample experimented determine*
Dexlansoprazole	140^{o}C	140^{o}C ± 1

Melting point of the obtained Dexlansoprazole was found to be 140^{o}C ± 1, that is within the standard range of 140^{o}C, which showed that the procured pure drug is Dexlansoprazole which is free from impurities.

Drug and excipients compatibility studies by FT- IR Spectroscopy

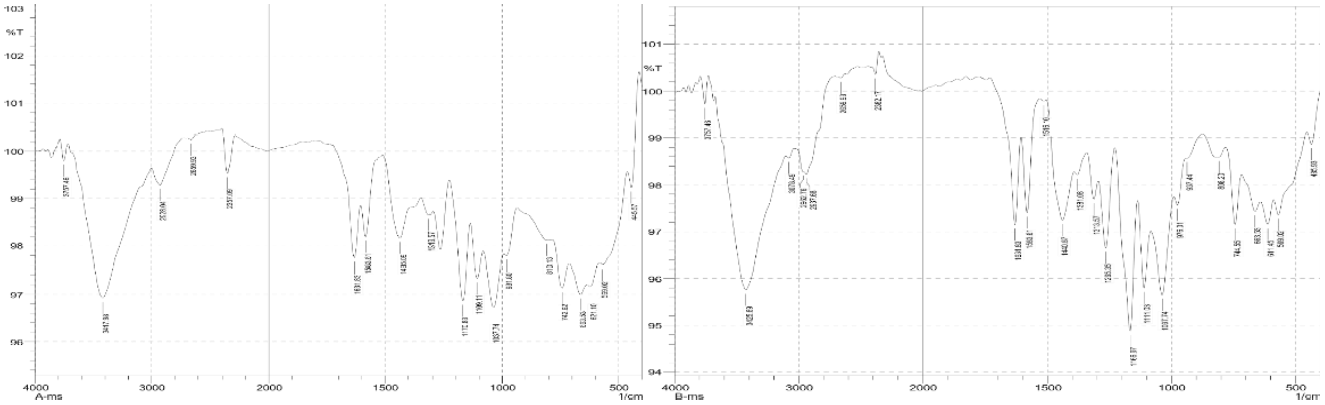


Fig: 3 FT-IR Spectrum of pure drug Dexlansoprazole
Fig:4 FT-IR Spectrum of Dexlansoprazole +HPMC K4M

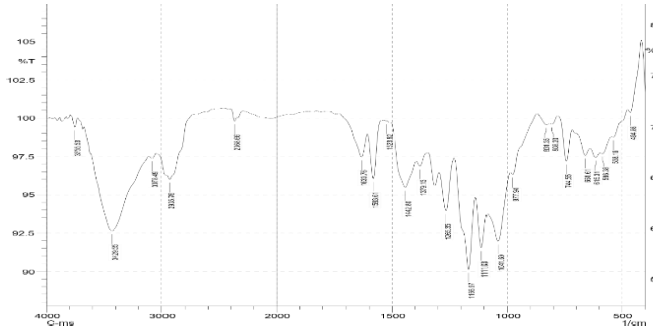


Fig:5 FT-IR Spectrum of Dexlansoprazole+Chitosan

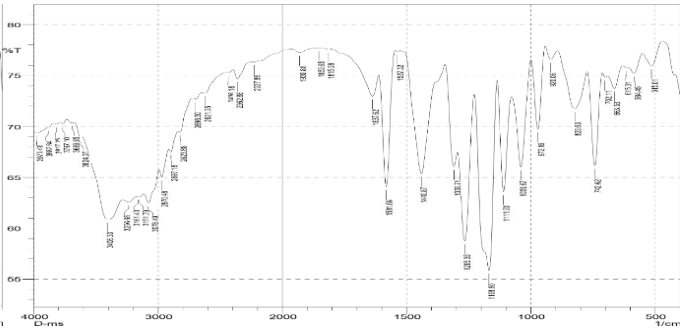


Fig:6 FT-IR Spectrum of Dexlansoprazole + all polymers

Precompression evaluation parameters for powder mixture:

The results are showed in table no:7

Table no:5 Precompression parameters results for formulation F1-F8

Formulation code	Formulation Code				
	Bulk density (g/cm^3)	**Tapped density (g/cm^3)**	**Angle of repose (°)**	**Carr's index%**	**Hausner's ratio**
F1	0.55	0.62	26.56	11.24	1.12
F2	0.58	0.66	27.47	12.12	1.13
F3	0.52	0.58	23.45	10.34	1.11
F4	0.55	0.62	27.01	11.29	1. 12
F5	0.55	0.62	24.17	11.29	1.12
F6	0.58	0.66	26.64	12.12	1.13
F7	0.62	0.71	26.56	12.67	1.07
F8	0.66	0.71	27.47	12.67	1.14

Post compression evaluation parameters:

The results of post compressional evaluation parameters are shown in table no:8

Table no:6 Post compression parameters results for formulation F1-F8

Formulation code	Formulation Code					
	Thickness(mm)	**Hardness (kg/cm^2)**	**%Friability**	**Weight variation (mg)**	**Drug content (%)**	**Surface pH**
F1	3.7	3.8	0.25	201	85.33	5.22
F2	4.2	4.2	0.3	201	83.41	5.43
F3	4.0	4.1	0.5	200	85.17	5.60
F4	3.9	4.2	0.5	200	80.82	5.9
F5	4.0	4.0	0.25	201	98.12	6.21
F6	3.8	4.1	0.15	201	97.88	6.47
F7	3.7	4.2	0.75	200	93.0	6.10
F8	4.7	4.2	0.65	201	88.65	6.17

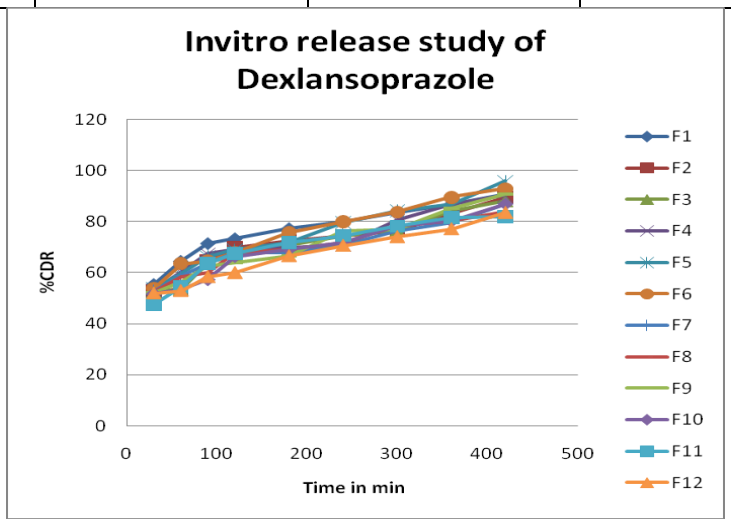
Swelling index:
The swelling indices of the various buccal formulations are table no:9

Table:7 Swelling index of the Dexlansoprazole buccal tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	25.0	20.0	17.5	10.0	30.0	28.5	20.0	15.0
2	35.0	27.5	25.0	23.5	45.5	46.0	29.5	28.5
3	45.0	35.0	35.0	31.0	51.5	55.5	37.5	35.0
4	50.0	42.5	43.5	43.5	60.0	62.5	45.0	43.5
5	65.0	50.0	51.5	46.0	74.5	73.5	57.5	63.5
6	75.0	60.0	64.01	52.5	83.0	84.5	65.0	76.0
7	88.5	77.5	70.01	60.0	92.0	91.5	75.0	84.0
8	92.0	87.5	82.5	75.0	98.0	95.0	91.5	87.0

Table 8: *Ex-vivo* Mucoadhesive strength, Force and Retention Time

Formulations	Mucoadhesive strength	Mucoadhesive force	Retention Time
F1	30.20	2.90	45min
F2	32.14	3.15	1.13min
F3	34.18	3.35	1.35min
F4	29.14	2.85	1.55min
F5	32.17	3.15	3.45min
F6	36.14	3.54	3.30min
F7	31.05	2.94	3.10min
F8	28.65	2.81	2.50min



***In-vitro* drug release study**
Kinetics of drug release
Table:9 Kinetics modelling data:

Formulation	Kinetic Drug Release		Mechanism Of Release		
	Zero Order	First Order	Higuchi	Korsemeyer Peppas	
	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2	Slope 'n' value
F5	0.67175	0.44925	0.89735	0.7845	0.4252

STABILITY STUDIES RESULTS:

Three months of stability study for best formulations were carried out as per procedure Formulation F5 was analysed for organoleptic properties and other various post compression study.

Table:10 Stability data of selected F5 & F6 formulation stored at 40°C ± 2°C and 75 ± 5% RH

No of Days	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	pH	Swelling index	%Drug Content	% CDR
0	4.0	4.1	0. 25	6.25	98.0	98.0	95.00
30	4.1	4.0	0.26	6.30	98.12	97.95	94.85
60	4.12	4.1	0.26	6.45	98.3	97.90	94.70

CONCLUSION:

Mucoadhesive buccal tablets of Dexlansoprazole prepared by direct compression method. All the formulations were evaluated for hardness, thickness, friability, weight variation, drug content estimation, surface pH determination, swelling index, in-vitro drug release, ex-vivo mucoadhesive strength, mucoadhesive force and residence time and short-term stability study.

FTIR studies revealed no interaction between the drug and excipients. The prepared formulations were evaluated for precompression and post compression parameters which revealed good flow properties of the blend and physical attributes of the prepared tablets were found to be practically within control limits. The swelling index was proportional to polymer content. The surface pH of all tablets was found to be satisfactory i.e. close to neutral pH.

The in-vitro drug release study of majority of formulation showed more than 50% of drug release in 6 hrs. As the concentration of polymer increases the retarding of drug release also increased. The in-vitro drug release study of formulation F5&F10 containing Dexlansoprazole, chitosan as mucoadhesive polymer has good drug release, when compared to other formulations and was considered as optimized formulation.

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