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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET DILTIAZEM HYDROCHLORIDE

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Abstract:
New era of novel drug delivery system oriented towards increasing safety and efficacy of existing drug molecule through novel concepts like buccal drug delivery system. mucoadhesive buccal systems have carved a niche amongst the oral drug delivery systems due to the highest component of compliance they enjoy in patients especially the geriatrics and pediatrics. Buccal mucoadhesive tablet containing diltiazem HCl was prepared for treatment of hypertension. Buccal mucoadhesive tablet of diltiazem HCl were prepared by direct compression methods and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using carbopol, hydroxy propyl methyl cellulose (HPMC), and sodium alginate as mucoadhesive polymers in different concentration along with magnesium stearate and talc. Total six formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and invitro drug release. In-vitro dissolution studies are performed by using phosphate buffer pH 6.8 at 75 rpm by paddle method. Formulation F5 showed maximum release of 99.78% in 12hours. Formulation F5 showed maximum swelling index of 106.65 after 12hours. Formulation F5 follows Korsmeyer-Peppas order drug release. FTIR studies show no evidence on interaction between drug and polymers. The results indicate that suitable mucoadhesive buccal tablets with desired properties could be prepared.

Keywords: *Diltiazem hydrochloride, carbopol, hydroxy propyl methyl cellulose, Buccal mucoadhesive tablet*

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INTRODUCTION:

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is 'Dysphasia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like: Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally disabled persons, & Unavailability of water [1].The mucosa is considered as a potential site for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal tract (GIT) [2]. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism; drug degradation in gastro intestinal environment can be circumvented by administering a drug via buccal route [3, 4]. Moreover, buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore, mucoadhesive dosage forms were suggested for oral drug delivery, which includes adhesive tablets, adhesive gels, and adhesive patches [5]. Diltiazem HCl is extensively used either alone or in combination therapy to treat hypertension, atrial fibrillation and flutter, paroxysmal supraventricular tachycardia and for the treatment of stable and unstable angina pectoris [6]. It has short half-life of 2-3 h and bioavailability of 33-44% as only 40% of the oral dose reaches to systemic circulation in an unchanged form, mainly because of hepatic metabolism. The usual oral regimen is 30mg four times daily. Pharmacokinetic features of diltiazem HCl make it a potential candidate for buccal mucoadhesive once-a-day dosage form [7]. From the technological point of view, an ideal buccal dosage form must have three properties; it must maintain its position in the mouth for a few hours, release the drug in controlled fashion, and provide drug release in a unidirectional way towards mucosa.The aim of this study was design, development and characterization of a mucoadhesive controlled-release tablet of diltiazem HCl using some selective polymers like Carbopol, hydroxy propyl methyl cellulose and sodium alginate. Also, the interaction between polymers, drug-polymers, mucoadhesive and *in vitro* release characteristics of diltiazem HCl from different mucoadhesive matrix tablets was evaluated to assess the suitability of such formulations.

MATERIALS AND METHODS:

Materials:

Diltiazem HCl was a gift sample from Hetero Drugs Ltd., (Hyderabad, India). Carbopol, hydroxy propyl methyl cellulose and sodium alginate was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Magnesium stearate, talc and lactose were procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Preformulation studies:

Standardization of diltiazem HCl by UV-Visible spectrophotometry:

Accurately weighed 10 mg of drug was dissolved in 10 ml of phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with phosphate buffer pH 6.8 solution prepare suitable dilution to make it to a concentration range of 2-10µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Drug-excipients compatibility study:

FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of tablets of diltiazem HCl:

Buccal tablets of diltiazem HCl were prepared by direct compression [8] according to the formulae given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200 mg using 8 mm round

flat punches on a Rimek mini press 16 station rotary compression machine.

Table 1Various formulations of buccal tablets of diltiazem hydrochloride

Excipients (mg)	F1	F2	F3	F4	F5	F6
Diltiazem hydrochloride	30	30	30	30	30	30
HPMC K-4	25	50	75	25	50	75
Carbopol	-	-	-	25	50	75
Na Alginate	25	25	25	25	25	25
Magnesium stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Lactose	150	125	100	125	75	25
Total Weight	250	250	250	250	250	250

Evaluation of buccal tablets of diltiazem hydrochloride:

Precompression parameters:

Angle of repose (θ):

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h/r, \ \theta = \tan^{-1}(h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

Compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio:

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [9].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of tablets:

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 (- -) [10, 11].

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.

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 phosphate buffer pH 6.8 and made up to volume with of phosphate buffer pH 6.8. 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 234nm using of phosphate buffer pH 6.8 as blank.

Hardness:

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

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. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated[54].

Uniformity of weight:

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

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 phosphate buffer pH 6.8 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). Percent hydration (swelling index) was calculated as shown in Table 7.4 using the following formula:

$$\text{Swelling index} = (W_2 - W_1) \times 100/W_2$$

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

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 phosphate buffer pH 6.8 was set into the dissolution flask maintaining the temperature of 37±0.5^{0}C and rpm of 75. One Diltiazem hydrochloride tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 12 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37^{0}C) was supplanted each time with a similar amount of the sample and takes the absorbance at 234 nm using spectroscopy.

Mathematical treatment of *in-vitro* release data:

The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

1. Zero-order kinetics: The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$\mathbf{Q_t = Q_o + K_o\, t}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

2. First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

3. Higuchi model: Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.

The simplified Higuchi model is expressed as:

$$Q = K_H . t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms such as transdermal systems and matrix tablets with water-soluble drug.

4. Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for fickian diffusion and higher values of n, between 0.5 and 1.0, or n =1.0, for mass transfer following a non-fickian model. In case of a cylinder n =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where M_t/M_∞ < 0.6

should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (*l*) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_{\infty}} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_{\infty}} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as Power Law, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms [12-14].

RESULTS AND DISCUSSION:

The λ_{max} of diltiazem HCl was found to be 234nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 10-50µg/ml. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility index and Hauser's ratio of all the formulations was found to be within the range and showing that the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3.

All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 4.2±0.4 to 4.7±0.3kg/cm^2 and the friability values were less than 0.9% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.11±0.09 to 3.16±0.08mm. All the formulations satisfied the content of the drug as they contained 98.62±0.17 to 99.85±0.23% of diltiazem HCl and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The swelling index is the parameters which are used to study the swelling ability of the polymer. The swelling index is affected considerably by the polymer concentration. As the polymer is increased the swelling index is increased, this might be due to increased absorption of the water in the polymeric matrix. Both the polymer is of hydrophilic nature having ability to hold water within it Table 4. The tablets were evaluated for *in vitro* dissolution studies in phosphate buffer pH 6.8 for 12 hrs. The results of the optimized formulation F5 showed maximum drug release i.e. 99.78% at the end of 12hrs. The results of release studies of formulations F5 was shown in Table 5. The *in vitro* drug release data of the optimized formulation F5 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer's models was maximum i.e. 0.967 hence indicating drug release from formulations was found to follow Korsmeyer's models kinetics Table 6.

Table 2 Result of pre-compression properties of diltiazem hydrochloride

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner's ratio
F1	0.385	0.485	20.619	1.260
F2	0.345	0.452	23.673	1.310
F3	0.374	0.483	22.567	1.291
F4	0.356	0.469	24.094	1.317
F5	0.372	0.489	23.926	1.315
F6	0.356	0.469	24.094	1.317

Table 3 Results of post compression properties of diltiazem hydrochloride buccal tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.12±0.09	4.5±0.2	250±5	0.754±0.015	98.85±0.23
F2	3.15±0.10	4.7±0.3	255±4	0.658±0.023	98.78±0.21
F3	3.16±0.08	4.6±0.3	248±5	0.821±0.041	99.12±0.25
F4	3.11±0.09	4.5±0.4	250±2	0.756±0.036	98.65±0.14
F5	3.14±0.07	4.3±0.2	249±4	0.825±0.047	99.85±0.23
F6	3.12±0.08	4.2±0.4	251±3	0.814±0.031	98.62±0.17

Table 4 Results of swelling index of diltiazem hydrochloride buccal tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	23.65	48.85	68.85	75.56
F2	29.95	49.98	70.12	79.98
F3	30.25	50.23	73.32	83.12
F4	29.95	52.32	74.45	81.12
F5	36.65	62.23	82.26	106.65
F6	30.25	58.89	78.84	95.56

Table 5 *In-vitro* drug release data for optimized formulation F5

Time (hr)	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	23.32	1.368	76.68	1.885
1	1.000	0.000	35.65	1.552	64.35	1.809
1.5	1.225	0.176	46.52	1.668	53.48	1.728
2	1.414	0.301	55.42	1.744	44.58	1.649
3	1.732	0.477	65.44	1.816	34.56	1.539
4	2.000	0.602	73.32	1.865	26.68	1.426
6	2.449	0.778	86.65	1.938	13.35	1.125
8	2.828	0.903	93.32	1.970	6.68	0.825
12	3.464	1.079	99.78	1.999	0.22	-0.658

Table 6 Regression analysis data of diltiazem hydrochloride buccal tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F5	0.834	0.934	0.949	0.967

CONCLUSION:

The study suggests that the mucoadhesive tablet of diltiazem hydrochloride was prepared using carbopol, Na alginate and HPMC providing regulated release up to 12h. The tablet demonstrated ample mucoadhesive strength. Formulation F5 were found to be the best formulations to achieve the aim of this study. The study can, therefore enable the formulator to reach and quantify the optimum, decreasing experimentation during formulation. Further work is recommended to support its efficacy claims by long term Pharmacokinetic and Pharmacodynamic studies in human beings.

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