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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF NOVEL BUCCAL MUCOADHESIVE TABLETS OF FELODIPINE

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ABSTRACT
The objective of this work was formulation and *in-vitro* evaluation of novel buccal mucoadhesive tablets of felodipine as core in cup to release and permeate the drug unidirectionally towards the buccal mucosa and to enter directly in to systemic circulation. The carbopol, sodium alginate, sodium carboxy methyl cellulose, guar gum and HMPC were used in the development of buccal cups in various proportions. Core tablet of drug was prepared by direct compression method. Mucoadhesive properties of mucoadhesive cups includes shear strength, tensile strength and peel strength were measured on freshly collected porcine buccal mucosa as substrate. Force of Adhesion (N) in shear strength, peel strength and tensile strength results for the adhesive cups composed of carbopol and HPMC (3:1) were 0.0398, 0.0384 and 0.0394 respectively. The novel tablets were evaluated in terms of content uniformity, weight variation, thickness, diameter, hardness, friability, swelling index, surface pH, mucoadhesion strength and time and *in vitro* release. The adhesive cups had residence time above 5 h were selected for further placing of core tablet. In the final tablet formulations FBT3 which composed of carbopol and HPMC in the ratio of 3:1 and in core 20 mg of carbopol showed the satisfactory results of *in-vitro* studies. The permeability coefficient (k_p) value for MC9 (3 parts of carbopol: 1 part of HPMC) was 0.055 cm/h and diffusion coefficient was 6.48 cm^2/h. The maximum % of drug (99.9 %) was permeated in 6 h study from FBT3 formulation. Cumulative % drug release from backing layer was also estimated and it observed that the drug releasing from back layer was not considerable (3.42 % for FBT3). Hence the results of this study signifying that the developed dosage form was a suitable alternative for delivery of felodipine in to blood circulation.
Keywords: Backing layer, felodipine, force of adhesion, mucoadhesive cups

INTRODUCTION

Mucoadhesive buccal drug delivery systems have turn into immensely interesting in the last 10-15 years. Their capability to bind to mucous membranes concerned awareness as a path for resolving the problem of less bioavailability of traditional drug delivery systems employed in the oral route and over surface of the eye or other organs where tissues movement or manufacture of various secretions avoids prolonged preservation of the medicinal agent[1]. The buccal delivery concept came out from the basic concept of increasing the efficiency of local treatment of infectious diseases of on the mucosa to efficient use of the intranasal and buccal routes of administration for systemic action of drugs. Advancement in bio adhesive drug delivery particularly, the formulation of novel, most-effective and mucosa-friendly polymer, are emerging new marketable and clinical benefits for carrying narrow absorption window drugs at site of action for maximum therapeutic benefit. Mucoadhesive DDS have been examined from various purposes, like creating of new mucoadhesives, device preparation, methods of mucus adhesion and permeation improvement[2]. Huge number of novel drug substances from the drug invention, mucoadhesive DDS playing a more important function in delivering these molecules[3].

Felodipine is a calcium channel blocker used as antihypertensive and anti anginal drug. According to biopharmaceutical Classification System, felodipine is class II drug, i.e., low solubility and high permeability. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration. In view of poor solubility and poor bioavailability of felodipine, in present study an attempt was made to develop novel novel buccal mucoadhesive tablets as core tablet in mucoadhesive cup system. The different mucoadhesive polymers were selected for preparing adhesive cups such as carbopol, sodium alginate, guar gum, SCMC and HPMC. The cups were evaluated for various mucoadhesive properties. The optimized adhesive cups were chosen for formulating novel tablets of felodipine. The tablets were performed for various *in-vitro* studies for understanding the pharmaceutical delivery requirements of the novel buccal tablets[4-9].

MATERIALS AND METHODS

Felodipine was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad, Telangana, India. Sulfobutyl ether β-Cyclodextrin (SBE-β-CD) was gifted by Cydex Pharma Inc., USA. Carbopol, Sodium carboxy methyl cellulose (SCMC), Sodium alginate, Guar gum, Hydroxypropyl methyl cellulose (HPMC) and Hydroxy ethyl cellulose were utilized from institution resources. Methanol, talc, microcrystalline cellulose procured from Karnataka fine Chem. Industries, Bangalore, Karnataka, India. Porcine buccal mucosa, for determining buccoadhesive strength and *ex-vivo* permeation studies, was procured from a local slaughter house. All other materials used were of analytical grade.

Formulation of Novel Buccal Mucoadhesive Tablets

Novel buccal mucoadhesive tablets were prepared in a three-step process involving preparation of adhesive cups, core tablets and Novel buccal mucoadhesive tablets.

Preparation of granules

The granules for compression of adhesive cups were prepared by wet granulation method. In formulation of adhesive cups,

the respective mucoadhesive substance was mixed with the microcrystalline cellulose, 10 % w/v PVP solution was used as granulating agent and then passed through sieve # 18. Granules were dried in a tray drier at 50 ± 10^0C for 6 hours, passed through sieve # 22. The granules were mixed uniformly with calculated quantities of saccharin, vanillin and talc.

Compression of adhesive cups

Granules were compressed in a 10-station rotary table top mini press by using specially fabricated projected upper punch of 4.4 mm outer diameter and 2.8 mm inner diameter. The die volume and compression force was so adjusted to get thickness (1.2 mm) and hardness (4 kg/cm^2) for all the batches.

Preparation of Felodipine Core Tablets

Core tablets were formulated by direct compression method by mixing Felodipine, microcrystalline cellulose, respective mucoadhesive substance, and purified talc. 35 mg of the mixture was weighed and directly compressed using 2.8 mm flat faced punches at the compression force to get tablets with the thickness of 0.8 mm.

Formulation of buccal core tablets in mucoadhesive cups

Finally, novel core tablets in adhesive cups were prepared by inserting core tablets into the respective cups manually and compressed with little force using 4.5 mm flat faced punches.

Evaluation of Mucoadhesive Cups

***In-vitro* Residence time of adhesive cups**

In vitro residence time was determined using a modified USP disintegration apparatus. The disintegration medium composed of 800 ml isotonic phosphate buffer pH 6.6 maintained at 37^{o}C. The adhesive cup was pressed over the excised bovine buccal mucosa for 30 seconds that was secured to the surface of a glass slab and allowed for five minutes. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the adhesive cups was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the adhesive cup from the mucosal surface was recorded (mean of triplicate determinations).

Measurement of bio adhesive strength of the Adhesive cups

Bio adhesive strengths such as peel, shear and tensile strengths of adhesive cups were measured by specially designed and fabricated instruments using freshly excised bovine (goat) and porcine buccal mucosa as substrates. The experiments were performed within 3 hours of procurement of the mucosa. Buccal mucosa obtained from slaughter house soon after sacrifice was kept in Krebs buffer at 4°C. The underlying tissue was dissected out and the mucosa along with the adherent mucus was stored in isotonic phosphate buffer (pH 6.6) at 37°C for about 15 minutes before the commencement of experiment. The backside of the Adhesive cup was fixed to the movable block by the synthetic adhesive. It was pressed manually for 30 seconds over the buccal mucosa secured on the fixed block. After 5 minutes, water was added the hanging basket through the burette at constant flow until the complete detachment of Adhesive cups from mucosa takes place. The shear, tensile and peel strengths depend on the direction of pulling. The procedure was repeated for five times (n = 5). The force of adhesion and the bond strength were calculated as

$$\text{Force of adhesion (N)} = \frac{\text{Weight (g)}}{1000} \times 9.81$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area of cup (m2)}}$$

Evaluation of novel felodipine tablets

Uniformity of weight and thickness

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation. The thickness of the tablets of 10 tablets of each formulation measured using screw gauge.

Content uniformity

Three tablets of each formulation were powdered using a mortar and a pestle. Aliquots of the crushed tablets equivalent to 50 mg of felodipine were weighed and required amount of distilled water was added to extract the drug. This suspension was shaken for 6 hour and volume was made up to 100 ml with distilled water, filtered through whatmann filter paper, 2 ml of filtrate were diluted to 50 ml with distilled water. The samples were analyzed in spectrophotometer at 364 nm.

Surface pH

The surface pH of the buccal tablets was determined in order to find out the possibility of any side effects in buccal environment. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to buccal pH as possible, The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing 2 % w/v agar medium (pH 6.8 ± 0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 minute. A mean of three readings were recorded.

Swelling index

Three tablets from each batch were weighed individually and placed separately in a thoroughly cleaned Petri dish containing 5 ml of pH 7.2 phosphate buffer. At regular intervals the tablets were removed and weight was noted. The swollen tablets were reweighed and swelling index was calculated by using the formula:

$$\text{Index of swelling (S.I)} = [(W2-W1)/W1] \times 100$$

Here, W1- original weight of tablet, W2- Final tablet weight

***In-vitro* dissolution studies**

In vitro dissolution studies of felodipine tablets were conducted in Phosphate buffer (pH 6.6, 250 ml) at 37°C by paddle method at 100 rpm by using USP XXII Electro Lab eight spindle dissolution apparatus.

Study of dissolution rate

Felodipine tablets were fixed at the bottom surface of dissolution chamber exposing the core tablets to the dissolution medium. Samples were withdrawn at regular time intervals for four hours and felodipine content was estimated by measuring at 434 nm using UV/VIS Spectrophotometer. The dissolution profiles of the mean of the six replicates at each data points were determined.

Table 1: Formulation of Muco Adhesive Cups

Form. Code	Polymer compositions (%)					
	Cp	SCMC	Sod. algnate	HPMC	Guar gum	HEC
MC1	100	-	-	-	-	-
MC2	-	100	-	-	-	-
MC3	-	-	100	-	-	-
MC4	-	-	-	100	-	-
MC5	-	-	-	-	100	-
MC6	-	-	-	-	-	100
MC7	75	25	-	-	-	-
MC8	75	-	25	-	-	-
MC9	75	-	-	25	-	-
MC10	75	-	-	-	25	-
MC11	75	-	-	-	-	25
MC12	25	75	-	-	-	-
MC13	-	75	-	25	-	-
MC14	-	-	75	-	25	-
MC15	-	-	75	-	-	25
MC16	50	50	-	-	-	-
MC17	50	-	50	-	-	-
MC18	50	-	-	50	-	-
MC19	50	-	-	-	50	-
MC20	50	-	-	-	-	50
MC21	25	-	-	75	-	-
MC22	-	25	-	75	-	-
MC23	-	-	-	75	25	-
MC24	-	-	25	75	-	-

*Saccharin (2 % w/w), Vanillin (1 % w/w) and Talc (1 %) was used as sweetener, flavor and lubricant. 10 % w/v solution of PVP was used as granulating agent

Table 2: Formulation composition of Core Tablets

Code	Polymer compositions (mg)								
	Felodipine	Carbopol	SCMC	Sod. Alg.	HPMC	Guar gum	Chitosan	MCC	Talc
CP1	5	10	-	-	-	-	-	19.5	0.5
CP2	5	15	-	-	-	-	-	14.5	0.5
CP3	5	20	-	-	-	-	-	9.5	0.5
CP4	5	25	-	-	-	-	-	4.5	0.5
SC1	5	-	10	-	-	-	-	19.5	0.5
SC2	5	-	15	-	-	-	-	14.5	0.5
SC3	5	-	20	-	-	-	-	9.5	0.5
SC4	5	-	25	-	-	-	-	4.5	0.5
SA1	5	-	-	10	-	-	-	19.5	0.5
SA2	5	-	-	15	-	-	-	14.5	0.5
SA3	5	-	-	20	-	-	-	9.5	0.5
SA4	5	-	-	25	-	-	-	4.5	0.5
HP1	5	-	-	-	10	-	-	19.5	0.5
HP2	5	-	-	-	15	-	-	14.5	0.5
HP3	5	-	-	-	20	-	-	9.5	0.5
HP4	5	-	-	-	25	-	-	4.5	0.5
GG1	5	-	-	-	-	10	-	19.5	0.5
GG2	5	-	-	-	-	15	-	14.5	0.5
GG3	5	-	-	-	-	20	-	9.5	0.5
GG4	5	-	-	-	-	25	-	4.5	0.5
CS1	5	-	-	-	-	-	10	19.5	0.5
CS2	5	-	-	-	-	-	15	14.5	0.5
CS3	5	-	-	-	-	-	20	9.5	0.5
CS4	5	-	-	-	-	-	25	4.5	0.5

*Felodipine has taken in the form of β-cyclodextrin (SBE-β- CD) complex in all formulations

Table 3: *In-vitro* shear, peel, and tensile strength of mucoadhesive cups

Code	Shear srength		Peel strength		Tensile strength	
	Force of Adhesion (N)	Bond strength (N/m^2)	Force of Adhesion (N)	Bond strength (N/m^2)	Force of Adhesion (N)	Bond strength (N/m^2)
MC9	0.0398	4175.139	0.0384	4130.190	0.0394	4190.105
MC10	0.0385	4075.114	0.0382	4102.175	0.0386	4121.135
MC11	0.0270	3825.130	0.0285	3758.136	0.0282	3832.182
MC16	0.0318	3965.142	0.0313	3836.175	0.0363	3852.136
MC17	0.0365	3775.135	0.0308	3785.121	0.0375	3682.145
MC19	0.0375	3846.174	0.0341	3896.165	0.0336	3895.161
MC23	0.0325	4012.158	0.0323	4011.185	0.0339	4058.135
MC24	0.0348	3725.028	0.0354	3803.012	0.0352	3708.075

Table 4: Human acceptability studies of various parameters

Parameters observed	FBT3	FBT7	FBT9	FBT11	FBT12	FBT18
Duration of stay of the dosage form	90 %	100 %	90 %	100 %	100 %	90 %
Intactness at the affixed site	Yes	Yes	Yes	Yes	Yes	Yes
Duration of maintenance of its structural integrity	100 %	100 %	100 %	100 %	90 %	90 %
Palatability	80 %	90 %	100 %	100 %	100 %	90 %
Effect on salivary secretion	No	No	No	No	No	No
Discomfort due to swelling or stickiness	No	No	No	No	No	Yes
Irritation during and after removal of dosage form	Slight	No	No	No	No	Slight
Feeling of dryness	Yes	No	No	No	Yes	No

Table 5: Correlation coefficients (R^2) and exponent for release mechanism values *in-vitro* dissolution studies of felodipine buccal tablets

F. code	Zero order	First order	Higuchi model	Korsmeyer-Peppas-rel. mechanism	Best fit model
FBT1	0.989837	0.94753	0.978026	0.879302	Zero order
FBT2	0.992295	0.94020	0.967498	1.004529	Zero order
FBT3	0.997838	0.94693	0.961478	1.021867	Zero order
FBT4	0.992864	0.94985	0.973782	0.926234	Zero order
FBT5	0.999679	0.98859	0.968109	0.946193	Zero order
FBT6	0.990162	0.95223	0.979391	0.858757	Zero order
FBT7	0.987037	0.92143	0.96872	1.000551	Zero order
FBT8	0.990833	0.95386	0.980331	0.850485	Zero order
FBT9	0.997261	0.94218	0.96659	0.988388	Zero order
FBT10	0.992483	0.92168	0.958158	1.140677	Zero order
FBT11	0.999307	0.95171	0.958047	1.034805	Zero order
FBT12	0.998979	0.94502	0.957711	1.060465	Zero order
FBT13	0.988882	0.9460	0.978386	0.874904	Zero order
FBT14	0.995872	0.96073	0.972839	0.921058	Zero order
FBT15	0.994629	0.95112	0.970474	0.940209	Zero order
FBT16	0.994179	0.92822	0.953155	1.174511	Zero order
FBT17	0.999104	0.98982	0.949447	1.094075	Zero order
FBT18	0.997966	0.93958	0.960642	1.060408	Zero order
FBT19	0.988746	0.94932	0.980316	0.850872	Zero order
FBT20	0.996754	0.95816	0.968021	0.973495	Zero order
FBT21	0.992547	0.92633	0.96518	1.050234	Zero order
FBT22	0.996511	0.93397	0.952561	1.17179	Zero order
FBT23	0.998475	0.94694	0.960984	1.032455	Zero order
FBT24	0.998227	0.94613	0.961856	1.018826	Zero order

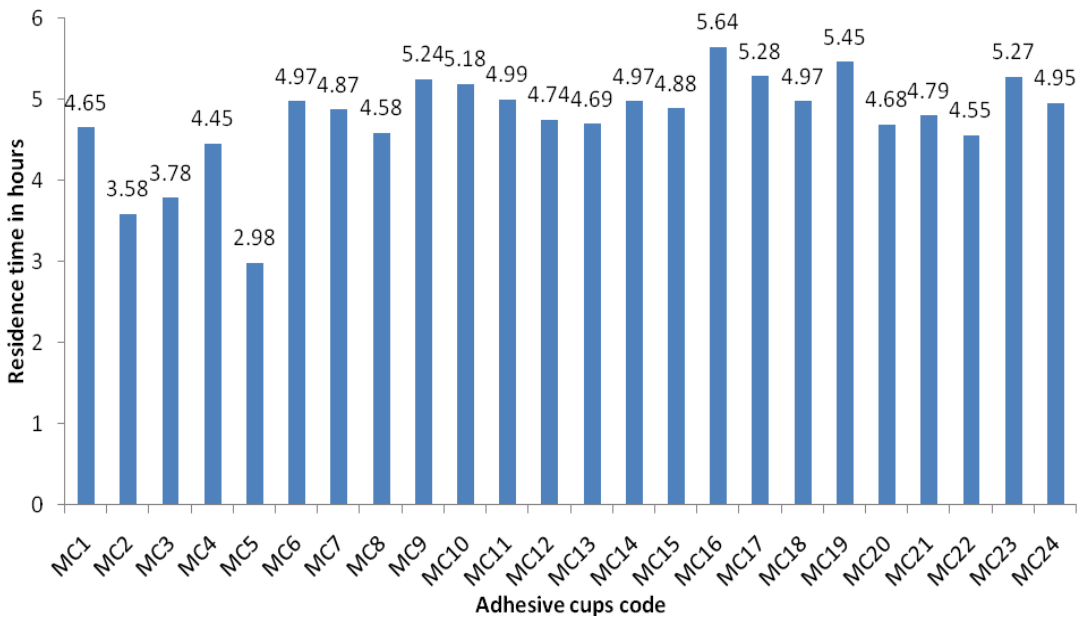

Figure 1: *In-vitro* residence time chart of adhesive cups

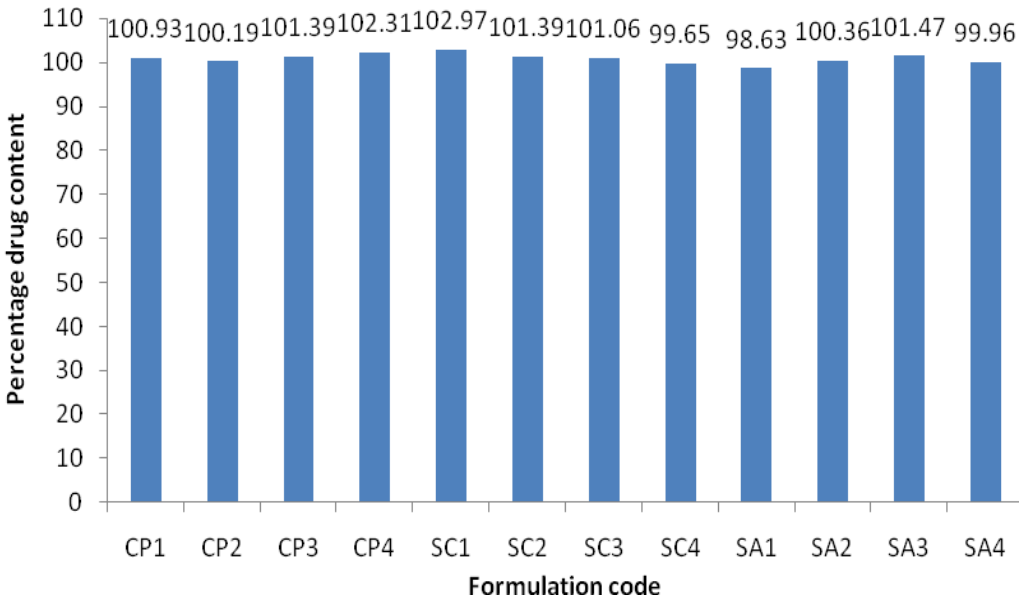

Figure 2: Percentage drug content of felodipine core tablets

Study of unidirectional release

Felodipine tablets were fixed to the internal wall of the dissolution chamber after wetting the surface by directing the core tablets towards the wall. Dissolution medium pre warmed to 37°C was poured into the chamber carefully after five minutes and the paddle was rotated at 50 rpm. Samples were withdrawn at regular time intervals for four hours and felodipine content was estimated at 364 nm.

RESULTS AND DISCUSSION

The present work aimed to develop novel buccoadhesive tablets to release the felodipine at site of administration in unidirectional pattern for extended period of time without wash of drug by saliva. The tablets were prepared in three steps. The prepared tablets were evaluated for different parameters. The thickness of tablets falls between 0.817 ± 0.032 to 0.993 ± 0.015 mm and weight variation percentage was below 1 %, suggesting its suitability for ease of administration without any discomfort. Weight variation and drug content uniformity studies suggest uniform mixing, validation of manufacturing process and its reproducibility. Results such as percent friability (0.28 ± 0.20 to 0.94 ± 0.17) and hardness (4.02 ± 4.32to 4.86 ± 3.97 kg/cm^2) were found to be within the recommended values of Indian Pharmacopoeia. Adhesive cups were studied for their mucoadhesive strengths by using the specially fabricated apparatus Tensile, shear and peel strengths were calculated after five minutes of contact time and results represented in Table 7. The observed surface pH of the formulations was found to be in the range of 6.48 ± 0.021 to 6.68 ± 0.24. The results show that there is no significant difference in the surface pH of all the formulations that indicates no irritation in the buccal mucosa. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. Swelling index was calculated with respect to time up to 6 h. All the formulations shown comparable swelling index and concentrations of carbopol and HPMC in 3:1 ratio gave the maximum swelling percentage. The formulations are producing complete release of drug at the end of 6 h. The release rate depends on the swelling index and buccoadhesive strength, which may varies with characteristics and composition of matrix forming polymers in the formulations. In general the rate of drug release was increased by increasing proportions of hydrophilic polymer. The maximum cumulative percentage release of felodipine obtained from formulation FBT3 in 6 h due to optimum concentrations of carbopol and HPMC which in turn increases in swelling index and buccoadhesive strength. The correlation coefficient values (r) indicate that the kinetic of drug release was of zero order. The mechanism of drug release by Peppas model indicates the super case II transport evidenced with diffusion exponent values (n). It was found that less than 3.7 % of drug diffused through the backing layer in four hours of study. The results suggest that the mucoadhesive material under investigation has not allowed the drug to diffuse through its backing layer enabling unidirectional release pattern.

CONCLUSION

From the above mentioned results it can be concluded that the formulation of novel buccal tablets of felodipine were prepared by direct compression method by using polymers like Carbopol 934 P, SCMC, sodium alginate and HPMC either alone or in combinations and all the formulations were evaluated for the various parameters which showed satisfactory results with good swelling index and buccoadhesive strength. Buccoadhesive bi layer tablets of felodipine could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improves patient compliance hence, felodipine might be a right and suitable candidate for oral controlled drug delivery via buccoadhesive bi layer tablets for the therapeutic use.

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