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DEVELOPMENT AND *IN-VITRO* EVALUATION OF CARVEDILOL LOADED MUCOADHESIVE BUCCAL TABLET

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ABSTRACT

Buccal delivery is considered to be an important alternative to theper oral route for the systemic administration of drugs. The aim of the study was to develop and evaluate mucoadhesive buccal tablets of Carvedilol for systemic delivery. Carvedilol mucoadhesive buccal tablets were prepared by direct compression method using ethyl cellulose and mucoadhesive polymers namely, Sodium alginate, Hydroxyl propyl cellulose and Methylcellulose. FTIR and DSC analysis were carried out to investigate the drug polymer interactions. All the formulations were subjected to evaluation of physicochemical parameters such as hardness, thickness, friability, surface pH, swelling index and weight variation. The mean surface pH of the prepared tablets was found to 6-7.04 which is favorable for oral mucosa. *In-vitro* drug release studies demonstrated that Carvedilol release from the selected tablets followed diffusion kinetics with a maximum drug release and it is confirmed that the tablet has the ability to deliver the drug. The present study indicates enormous potential of erodible mucoadhesive buccal tablet containing Carvedilol for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism.

1. INTRODUCTION

Oral drug delivery system is one of the most popular and preferred route of drug administration due to its high patient compliance and ease of administration[1]. This is due to that the buccal area has an immobile surface with rich blood vessel and presence of saliva acts as a good dissolution medium[1]. On top of that, buccal route administration could avoid hepatic first pass metabolism to result in drastic improvement of bioavailability of drug and it is applicable for both local and systemic delivery system as retentive dosage form[2], without compensating any patient compliance.

In this research, the anti-hypertensive drug selected as model drug is carvedilol.

Materials and methods

Carvedilol was gifted from Dr. Reddy's Laboratories Ltd., Hyderabad, Sodium alginate, hydroxyl propyl cellulose, methyl cellulose and ethyl cellulose were purchased from *Shasun Pharmaceuticals* Ltd., *Puducherry*. Other excipients such as mannitol, talc and magnesium stearate used and all other reagents used were of analytical grade.

Construction of calibration curve of Carvedilol

To prepare the stock solution, 10 mg of Carvedilol was weighed accurately and dissolved in phosphate buffer (pH 6.8). It was then transferred into a 100 mL volumetric and topped up with phosphate buffer. Carvedilol of concentrations 1 μg/mL, 2 μg/mL, 3 μg/mL, 5 μg/mL, 7 μg/mL and 10 μg/mL were prepared from stock solution and used to construction the calibration curve. The apparatus used was Shimadzu UV mini 1240 spectrophotometer. The λmax was determined at 241nm. The UV spectrum is as shown in Fig.1.

Formulation of carvedilol mucoadhesive buccal tablets

The Carvedilol bilayer buccal tablets were formulated in two consecutive steps by direct compression method. Firstly, all the excipients including drug and mucoadhesive polymers accurately weighed and mixed uniformly about 20 minutes in a glass mortar. Then magnesium stearate (lubricant) and talc (glidant) were incorporated and mixed thoroughly for 3 minutes. By using 9 station rotary machine, 9 mm, flat punch, the 100 mg of powder blend was slightly compressed at single to form a single layered tablet. Secondly, final compression was made by adding ethyl cellulose 50 mg to get a final mucoadhesive bilayer tablets weighing 150 mg. The composition of buccal tablet was given in table no 1.

Physico-chemical evaluation of Carvedilol mucoadhesive buccal tablet:

1. Thickness

Ten tablets were randomly chosen from each batch and the thickness was calculated by using vernier calipers (Mitutoyo Corporation, Japan.) and the mean values were noted in table no 2.

2. Weight variation

Ten tablets were randomly chosen from each batch individually weighed and the mean values were noted in table no 2. It was measured by employing the formula.

$$\%\ \text{Weight variation} = \frac{\text{Average weight - Individual weight}}{\text{Average weight}} X100$$

3. Hardness

The tablets hardness was measured using Monsanto hardness tester (Singhala scientific industries, Ambala) to identify its ability to withstand the pressure. The 3 randomly chosen tablets from each batch were measured and the reports were noted in table no 2.

4. Friability

The Roche friability test apparatus (Campbell Electronics, Mumbai) measured the tablets friability. In the apparatus, twenty preweighed tablets were kept and operated for 25 rpm/4 minutes and the tablets were weighed again. It was measured by employing the formula and the reports were noted in table no 2.

$$\%\ \text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

5. Uniformity of Drug content

From each batch 20 randomly chosen tablets were finely powdered and powder equivalent to 6.25mg of carvedilol was weighed exactly and dissolved in 50 ml of methanol and contents were shaken thoroughly. The volume was made up to 100 ml with phosphate buffer (pH 6.8) and then 0.1 ml was transferred to 10ml volumetric flask and the volume was adjusted with phosphate buffer (pH 6.8). The absorbances were analysed on a UV/Vis spectrophotometer (Lab India) at 241 nm. Drug content was measured from a standard calibration curve and the reports were noted in table no 2.

6. Surface pH:

The test was performed by tablets were kept to swell in 1 ml of distilled water (pH 6.8) in small beakers, and the pH was noted after 1 h by keeping the electrode in contact with the swollen tablets allowing it to equilibrate for 1 minute. The mean pH of five measurements was shown in the table no.2.

7. Swelling Index (%S)

This test is carried out by hot agar solution 5% w/v was transferred to petri plates and kept to solidify. Then from each batch 6 tablets were weighed and kept over the surface of the agar and placed at 37ºC for 3 hrs in the incubator and the hydrated tablet was reweighed.

Component	T1	T2	T3	T4	T5	T6
Primary layer (core layer containing drug)						
Carvedilol (mg)	6.25	6.25	6.25	6.25	6.25	6.25
Sodium alginate (mg)	30	15	7.5	-	-	-
Hydroxyl propyl Cellulose (mg)	-	-	-	30	15	7.5
Methyl cellulose (mg)	-	-	-	-	-	-
Mannitol (mg)	70	85	92.5	70	85	92.5
Magnesium stearate (mg)	2	2	2	2	2	2
Talc (mg)	1.75	1.75	1.75	1.75	1.75	1.75
Secondary layer (Backing layer)						
Ethyl cellulose (mg)	40	40	40	40	40	40
Total weight (mg)	150	150	150	150	150	150

Table 1: Formula of Carvedilol mucoadhesive buccal tablets

Formulation Code						
Physico-Chemical parameters	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
Uniformity of Weight	148.2±1.22	150.1±1.13	148.7±1.33	148.2±1.21	148.2±1.21	149.2±1.61
Surface P^H ± SD	7.040.11	7.02±1.20	6.9±0.61	7.1± 1.11	6.9±1.32	6.6±0.54
Assay ± SD	98.15±1.32	99.02±2.12	99.92±1.11	98.92±1.02	99.04±2.1	99.94±1.21
Thickness ± SD	2.02±0.03	2.12±0.22	2.03±0.12	2.02±0.05	2.31±0.03	2.27±0.08
Hardness ± SD	4.1±0.02	4.0±0.03	3.9±0.35	4.3±0.01	4.1±0.41	4.0±0.82
Friability ± SD	0.41±0.02	0.42±0.09	0.43±0.01	0.40±0.03	0.41±0.12	0.42±0.09
Swelling Index ± SD	41.02±1.22	40.11±2.31	39.01±1.33	41.31±1.22	40.20±3.11	40.01±2.11

Table 2: Physiochemical parameters of carvedilol mucoadhesive buccal tablets

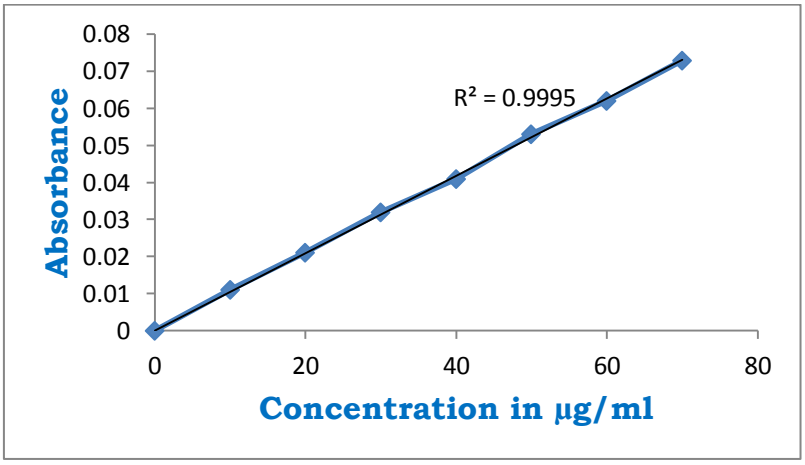


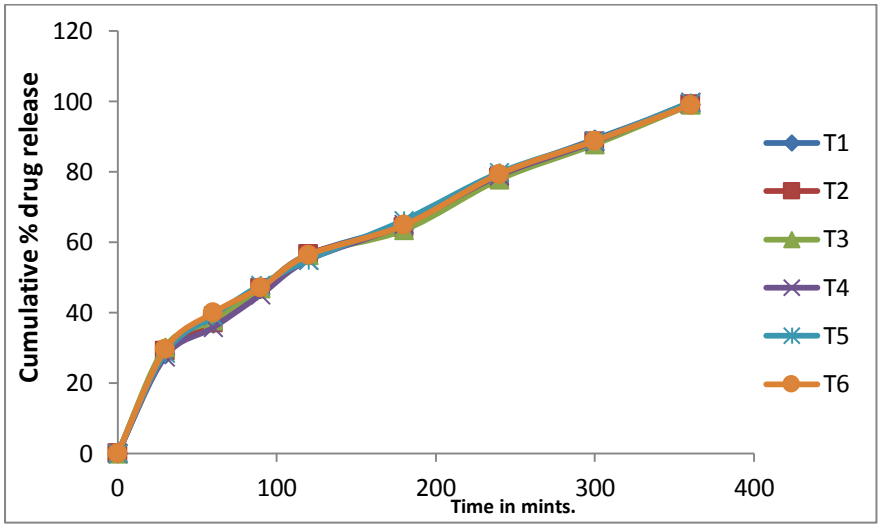
Fig.1: Calibration curve of carvedilol

The % of moisture absorbed was measured by employing the formula: % S = [(Final weight - Initial weight)/Initial weight] × 100. The reports obtained were shown in table no 2.

In Vitro Drug Release Dissolution Studies

It was carried out by USP 28, type II dissolution test apparatus. The phosphate buffer (P^H 6.8), 500 ml of was employed as the dissolution medium, at 37.0 ± 0.5ºC, and 50 rpm was used. Backing layer of the buccal tablet was attached to the paddle with water proof adhesive tape. Samples (5 ml) were withdrawn at 0.5, 1, 1.5,2,3,4, 5 and 6 hrs periods and replaced with same amount of fresh medium for sink condition. The samples were filtered through 0.45-µm Whatman filter paper and measured. The drug concentrations were analysed spectrophotometrically at 241 nm. The works were carried out in triplicate and it showed in Fig, 2

Fig.2: *In vitro* drug release dissolution profiles of carvedilol mucoadhesive buccal tablets



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RESULT AND DISCUSSION

All the physiochemical parameters results are shown in Table 2. All the tablets prepared according to the formulation had complied with the weight variation acceptance criteria. The thickness of all tablets are very uniform at approximately 2.20±0.03 mm. Hardness obtained ranged from 3.9-4.3 kg/cm^2 and content uniformity ranged from 98.15-99.94. The percentage weight loss in friability test ranged from 0.430 – 0.40%. All the test results had shown that the tablets had fulfilled the standard official requirements. The surface pH obtained ranged from 6.60 – 7.02, which is within the buccal environment pH range of 6.2 – 7.4, indicating that the buccal tablets formulated would not cause any buccal irritation as all formulation have very similar pH nature with the buccal environment. The swelling index ranged from 39 – 41.02, indicating that the hydrated gel forming polymers are able to form a good matrix upon exposure to wet surface.

In Vitro Drug Release Dissolution Studies

The backing ethyl cellulose layer of all tablets remained intact with the swollen polymer matrix until the release of minimal 80% drug concentration. For T1 batch, the drug release profile had achieved 89.3% by the 5th hour and the average T50 was 2.5 hours. The F2 and F3 batches only achieved 88.6% and 87.86% drug release by the 5th hour. For all batches(T1-T6), the drug release profile had achieved more than 85% by the end of 6th hour The dissolution profiles of all formulations are shown in Fig.2.

CONCLUSION

All the formulations showed no chemical interaction between drug and polymer, thus they are compatible to each other. All the formulated buccal tablets passed the weight variation test. The friability test results were less than 1%. The surface pH results were all within the buccal environment pH range indicating that the formulation would not result in any pH related irritation. All the prepared formulations

were showing good and satisfactory results in all the evaluation parameters. Further studies of different mucoadhesive polymer at various concentrations can be used to prepare and optimize the sustained release buccal tablets. Also, *in vivo* studies using animals or human can be carried out for further analysis.

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