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# DESIGN AND EVALUATION OF CONTROLLED RELEASE MUCOADHESIVE BUCCAL TABLETS OF NIFEDIPINE.

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**ABSTRACT**
Nifedipine is a calcium channel blocker drug widely used in the treatment of hypertension. However, its extensive first pass metabolism results in poor bioavailability. The objective of present research work is to design and evaluate the controlled release of mucoadhesive buccal tablets of Nifedipine with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance. The tablets were prepared using Carbopol-934, Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC) as mucoadhesive polymers. Six formulations were developed with varying concentration of polymers. The tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, Surface pH, in-vitro studies like swelling, mucoadhesive strength and drug release. Formulation (F4) containing Carbopol-934 and HPMC K4M in the ratio of (2 : 4) showed good mucoadhesive strength (36.8) and maximum drug release of 97.1% in 10 hrs. Swelling increase with increase in concentration of HPMC K4M in tablets. Swelling pH was found to be 6.10. Formulation (F4) follows zero-order drug release. FTIR studied showed no evidence on interaction between drug and polymers. The results indicate that the mucoadhesive buccal tablets of Nifedipine may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability through buccal mucosa.

**Keywords:** Nifedipine hydrochloride, Mucoadhesive, Control release, Swelling index, HPMC, Carbopol and HEC etc.

## INTRODUCTION:

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But, after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability[1-4]. Within the oral route, the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism [5]. In the, oral cavity the delivery of drugs is classified into three categories:
*1.Sublingual delivery*, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
*2. Buccal delivery* it is the drug administration through mucosal membranes lining the cheeks (Buccal mucosa) and
*3. Local delivery* it is the drug delivery into the oral cavity [6, 7]. Among these routes, buccal delivery is suitable for administration of retentive dosage forms because of an excellent accessibility, an expanse of smooth muscle and immobile mucosa. So, buccal delivery of drugs is attractive alternative to the oral route of drug administration [8,9]. Buccal delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity).
Buccal drug delivery is the safer method of drug utilization because, drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability. The other advantages of buccal drug delivery include, low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless drug administration, easy drug withdrawal, possible to include the permeation enhancer/enzyme inhibitor or pH modifier in the formulation. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response.
Nifedipine (Dihydropyridine derivative) is a calcium channel blocker and widely used in the treatment of hypertension. It is 40-60% absorbed from oral route but undergoes first pass metabolism. The half life of Nifedipine is approximately 2-4 hours. Nifedipine was selected as model drug to avoid hepatic first pass metabolism and to improve bioavailability and to control the release of the drug from the tablets by matrix forming polymers, as the half life of drug is low.
In this investigation, buccoadhesive tablets of Nifedipine have been developed using Carbopol 934 and non-ionic polymer Hydroxy propyl methyl cellulose K4M (HPMC K4M) and Hydroxy Ethyl Cellulose. The main objective of this investigation is to study the effect of polymers combination and the effect of Drug**:** polymer ratio on drug release and other bioadhesive properties.

## MATERIALS AND METHODS:

### Materials:

Nifedipine was received as gift sample from AstraZeneca Ltd, Bengaluru, Karnataka. Carbopol-934, Hydroxy Propyl Methyl cellulose (HPMC), Hydroxy Ethyl Cellulose (HEC) were procured as gift samples from Karnataka fine chemicals Pvt. Ltd. Bengaluru, India. All other reagents and chemicals used of analytical grade.

### Preparation of Mucoadhesive buccal tablets

Mucoadhesive buccal tablets, each containing 20mgNifedipinewere prepared by direct compression method. Composition of various formulations employing Carbopol934P, HPMC K4M &HEC are shown in Table 1.

All the ingredients of tablets were blended in mortar with a pestle for 15 min to obtain uniform mixture. The blended powderwasthencompressedinto160mg tablets(at5-7 kg/cm2) on a single stoke, 10 station rotary tablet machine, with 8mm round shaped flat punch .

**TABLE: 1 Composition of Mucoadhesive Nifedipine buccal tablets:**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Nifedipine | 20 | 20 | 20 | 20 | 20 | 20 |
| Carbopol 934p | 25 | 42.5 | 60 | 25 | 42.5 | 60 |
| HEC | 60 | 42.5 | 25 | - | - | - |
| HPMC K4M | - | - | - | 60 | 42.5 | 25 |
| Sprayed dried Lactose | 35 | 35 | 35 | 35 | 35 | 35 |
| Mannitol | 17 | 17 | 17 | 17 | 17 | 17 |
| Magnesium Stearate | 5 | 5 | 5 | 5 | 5 | 5 |

**EVALUATION OF TABLETS**

The flow properties of blends (before compression) were characterized in terms of Angle of repose[10], Bulk density and tapped density [11], Carr's index[12]and Hausner's ratio[13] and evaluation of tablets can be divided into physical and chemical parameters. Physical appearance, Tablet size and thickness, Average weight of tablets, Hardness test, and chemical parameters like content uniformity, in vitro dispersion time and in-vitro drug release.

**Hardness:** The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted[14,15].

**Friability:** Ten tablets were weighed and placed in a Roche friabilator (Veego, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured[16].

**Weight variation:** Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±10% [17].

**Content uniformity:** Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 20mg of Nifedipine equivalent of mixture was present in extract was determined usingUVSpectrometerat235nm. The results presented inTable3.

**Surface pH:** The surface pH of the buccal tablets was determined in order to investigate the possibility of any in *vivo* side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg *et al* was used. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing ittoequilibratefor1min.Theresultsareshownin Table3.

**Invitro welling studies:** The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a Petri-dish containing 5ml of phosphate buffer at pH6.8 for 12hrs, the tablets were taken out from the Petri-dish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula and results are summarized in Table4.

Swelling Index (SI)= ( Wt-Wo) / Wo X 100

Where,

SI= Swelling index.

Wt= Weight of tablets after time at't'.

Wo = Weight of tablet before placing in the beaker.

**Invitro Mucoadhesive Study:** The rabbit buccal mucosa was cut into pieces and washed with phosphate buffer pH6.8.A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37ºC±0.5ºC), so that it just touches the mucosal surface. The buccal tablets were suck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5gms, was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in the position for 1min contact time. Mucoadhesive strength was assessed in terms of weight (gms) required to detach the tablet from the membrane. Mucoadhesive strength which was measured as force of adhesion in Newton's by using following formula was used (Table 3),

Force of adhesion (N) = Mucoadhesive strength/ 100 X9.81

**In-vitro drug release profile:** The United States of Pharmacopoeia (USP) XXIV rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 900ml of phosphate buffer (pH6.8). The release was performed at 37ºC±0.5ºC, with rotation speed of 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (1, 2 and3…10hrs) and volume was replaced with the fresh medium. The samples were filtered through Whatman filter paper and analysed after appropriate dilution by UV spectrophotometry at 235 nm. The experiments for different formulations (F1 to F6) were conducted in triplicate and average values were recorded and found the release kinetics such as zero order, first order, Higuche and Hixcon crowell were determined & the data are shown in Table 4.

**RESULTS AND DISCUSSION**

Before designing various formulations, the drug polymer-excipient compatibility studies were conducted by FTIR spectroscopy and the results are presented in Fig.1& Fig.2. The results indicate that they were no chemical incompatibility between drug-polymer, polymer- polymer and polymer- excipients.

Total six different formulations (F1 to F6) of Nifedipine buccal tablets were prepared by direct compression techniques using various proportions of polymers and excipients. Inorder to select the best formulations, various

evaluation parameters were checked and subjected to Invitro dissolution studies and their release profiles.

**Hardness:**

The hardness of tablets of different formulation (F1 to F6) was determined as per standard procedure. The average hardness of tablets was found to be 5 to7 kg/cm. None of the formulations showed deviation for any of the tablets tested.

**Thickness of tablets:**

The average thickness of tablets (F1 to F6) determined and results are presented in Table 2. The maximum and minimum average thickness of tablet was found to3 mm and2.5mm respectively. None of the formulation (F1toF6) deviated from the standards.

**Friability:**

Friability was performed for all the batches (F1 to F6). None of the formulation (F1toF6) deviated from the standards.

**Table2: Weight variation, thickness and friability of Nifedipine buccal tablets**

| Formulation code | Average weight of tablet (mg) | Thickness in mm | Friability |
|---|---|---|---|
| F1 | 162.4 | 2.7 | 0.352 |
| F2 | 162.1 | 2.5 | 0.298 |
| F3 | 163.3 | 3 | 0.368 |
| F4 | 161.5 | 2.5 | 0.278 |
| F5 | 162.4 | 2.7 | 0.289 |
| F6 | 160.5 | 2.5 | 0.358 |

**Content uniformity:**

The content uniformity of the entire tablet (F1toF6) was evaluated and the results are presented in Table3. The maximum percentage of drug content from the different formulations was found to be 100.12 and minimum percentage of drug content was found to be 98.6%. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

**Surface pH:**

The surface pH of tablets of each formulation (F1 toF6) was tested and the results are provided in table-3. The maximum and minimum pH values of the formulations were found to be 6.10 and 5.59 respectively. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

**In vitro drug release profile:**

The drug release pattern was studied for all formulations (F1toF6) for 10 hrs following standard procedure and the results are provided in Fig.5. The drug release pattern of buccal Mucoadhesive tablets varied according to their type and ratio of polymers. The most important factor affecting the rate of release from buccal tablet is the drug and polymer ratio. The formulation F1, F2 and F3 contained the drug, Carbopol 934p and HEC polymers in the ratio of 1:2:4, 1:3.4:3.4 and 1: 4: 2 respectively.

The Invitro cumulative drug release profile of formulations F1, F2, F3 at 10 hrs showed 86.54%, 85.48% and 84.1% drug release respectively. Similarly the formulations F4, F5, and F6 contained drug, Carbopol 934p and HPMC K4M polymers in the ratio of 1:2:4, 1:3.4:4.3 and 1:4:2 respectively. The *invitro* cumulative drug release profile of formulations F4, F5 and F6 at 10hrs showed 97.1%, 95.41% and 93.17% drug release respectively.

It was concluded that by increasing the concentration of Carbopol 934p in the formulations (F1toF6), the drug release rate from the tablet was found to be decreased, but when the concentration of secondary polymers HEC and HPMCK4M is increase, the drug release rate was found to be increased. This may be attributed to increased hydration followed by increased swelling of polymers with increase in concentration.

The overall data on the in vitro dissolution studies closely indicated that among the six formulations, the formulation F4 was found to be the best with high percentage of drug release (97.1). The cumulative drug release of formulations containing Carbopol 934p with secondary polymers was found to be in order of F4>F5>F6>F1>F2>F3.

**Table 3: Content uniformity, surface pH, Mucoadhesive strength, Mucoadhesive force of Nifedipine buccal tablets:**

| Formulation code | %Drug content | Surface pH | Mucoadhesive strength (g) | Mucoadhesive force (N) |
|---|---|---|---|---|
| F1 | 99.2 | 5.9 | 28.8 | 2.79 |
| F2 | 98.6 | 5.8 | 29.2 | 2.86 |
| F3 | 99.13 | 6.0 | 32.4 | 3.17 |
| F4 | 100.12 | 6.10 | 36.5 | 3.58 |
| F5 | 99.2 | 5.59 | 34.5 | 3.38 |
| F6 | 98.8 | 5.9 | 30.5 | 2.99 |

**Table 4: Drug release kinetics studies of Nifedipine buccal tablets:**

| Formulation code | Zero order (R2) | First order (R2) | Higuchi (R2) | Hixon-Crowell (R2) |
|---|---|---|---|---|
| F1 | 0.9911 | 0.9091 | 0.8171 | 0.9249 |
| F2 | 0.9860 | 0.8950 | 0.7940 | 0.9090 |
| F3 | 0.9920 | 0.8990 | 0.8310 | 0.9450 |
| F4 | 0.9940 | 0.7840 | 0.9260 | 0.9030 |
| F5 | 0.9831 | 0.8184 | 0.8490 | 0.8810 |
| F6 | 0.9870 | 0.8150 | 0.8980 | 0.9010 |

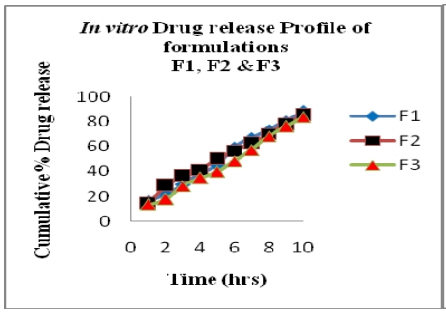


**Fig.1: drug release profile of F1, F2, F3.**

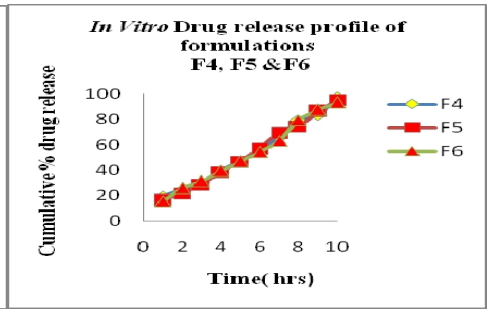


**Fig.2: Drug release profile of F4, F5, F6.**

## Kinetic treatment to dissolution data

Kinetic studies i.e. zero-order, first order and Higuchi and Hixcon- Crowell were conducted for all formulations and the data is shown in table 4.The value of regression correlation co-efficient (R2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release.

## CONCLUSION

The overall studies indicated that the polymers Carbopol 934p and HPMC K4M in the ratio of 2:4 showed satisfactory Mucoadhesive properties. Among the 6 formulations, the formulation F4 using these polymers in the above ratio with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F4 will be useful for buccal administration for the treatment of anti-hypertensive. So, the Mucoadhesive buccal tablets of Nifedipine may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Nifedipine through Buccal mucosa.

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