SOLID DISPERSION OF NEBIVOLOL HYDROCHLORIDE IMPREGNATED BUCCAL PATCH: FORMULATION AND CHARACTERIZATION

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ABSTRACT

Objective: The objective of the present investigation was to design and characterize a mucoadhesive buccal patch of Nebivolol hydrochloride in order to administer a small dose of a drug to treat hypertension effectively and thereby avoiding disadvantages such as patient noncompliance and low bioavailability.

Methods: The buccal patches were prepared by solvent casting method. The polymers used to formulate patches were HPMC K 15 M, PVP K 30, and propylene glycol was used as plasticizer and ethanol as the solvent. The drug-polymer compatibility studied was conducted by FTIR.

Results: All the developed Patches had good transparency and stability. All formulated patches showed pH in the range of 6.49 to 7.22, and drug content was more than 90%. The folding endurance value showed that the patches are flexible and non-brittle. The in vitro residence time was found to be more than 30 min. Thickness, % moisture absorption, and % moisture loss values were in a normal range. The drug release study was conducted for 8 h, and it was found drug release was decreased with the increase in polymer concentration. The in vitro release profiles of the drug from all the formulations appeared to follow Korsmeyer Peppa’s exponential model, and release exponent (n) was found to be more than 0.45 so that the release can be characterized by Non-Fickian (anomalous) diffusion.

Conclusion: From the results, it was concluded that drug released from formulated buccal patches follows sustained release pattern, Hence can be used for the treatment of the hypertensive patient.

Keywords: Nebivolol hydrochloride (NBH), Mucoadhesive buccal patch, HPMC K 15 M

INTRODUCTION

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the arteries’ blood pressure is elevated. High blood pressure is present if it is often at or above 140/90 mm Hg. Hypertension is classified as either primary (essential) hypertension or secondary hypertension [1, 2]. The oral route is the most popular and convenient drug administration route. However, oral administration cannot achieve the maximum bioavailability of many drugs because of rapid or extrahepatic first-pass metabolism [3]. Among the different approaches to avoiding the first-pass metabolism, the buccal route seems convenient [4].

Buccal administration refers to a route of administration or topical route of administration. Drugs held or applied in the buccal area (in the cheek) diffuse through the oral mucosa (tissues that line the mouth) and enter directly into the bloodstream. Buccal administration may provide better bioavailability of some drugs and more rapid onset of action than oral administration. The medication does not pass through the digestive system and thereby avoids the first-pass metabolism. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments, and gels, have recently been developed. However, buccal patches offer greater flexibility and comfort than other devices. Besides, a patch can circumvent the relatively short residence time of oral gels on mucosa since the gels are easily washed away by saliva. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action. There are mainly 3 methods to prepare mucoadhesive buccal patch; they are solvent casting technique, hot-melt extrusion technique, and solvent evaporation method [5].

Polymers frequently used in the buccal delivery system are CMC, HEC, HPC, HPMC, MC, Chitosan, etc.

Nebivolol Hydrochloride (NBH) is a drug with low water solubility and high membrane permeability, as in class 2 in the Biopharmaceutical Drug Classification System. NBH is a beta-blocker that exerts its actions by exhibiting a high selectivity for B-adrenergic receptors and reducing peripheral vascular resistance by modulating nitric oxide release [6]. Nebivolol is indicated as medicine for Essential Hypertension but, it has some drawbacks like extensive first-pass metabolism, gastric irritancy, and low bioavailability. Further, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affect its absorption rate, resulting in a low and variable oral bioavailability. Formulation of poorly water-soluble drugs as solid dispersions leads to increased solubility and decreased gastrointestinal side effects. The resulted of that marked improvement in their dissolution rates and decreased gastrointestinal side effects. An increase often helps it in their relative bioavailability [7, 8]. So, to improve the solubility, bioavailability and avoid hepatic metabolism, in the present study, an attempt was made to develop solid dispersion loaded buccal patches of Nebivolol [9, 10]. NBH also has a low molecular weight and high partition coefficient, making it a suitable candidate for the buccal delivery system.

MATERIALS AND METHODS

Materials

Nebivolol Hydrochloride was a gift sample Cipla Pharma Ltd. (Bangalore, India). Hydroxy propylmethyl cellulose (K15 M) was obtained from Yarrow chemical products (Mumbai, India) and Polyvinyl pyrrolidone K 30 (PVP K30) was obtained from Central drug house (P) Ltd. (Delhi, India). Ethanol was obtained from Merck specialties Private Limited, (Mumbai, India). Propylene glycol 800 was obtained from Sisco laboratories (Mumbai, India). All other chemicals used were of analytical grade and procured from Hi media laboratories (Mumbai, India).
Fabrication of nebivolol solid dispersion infused buccal patch

The buccal patches containing Nebivolol solid dispersions were prepared by incorporating solid dispersions of Nebivolol in a different composition of Hydroxypropyl methylcellulose (HPMC) K15 M polymer. Solid dispersions of Nebivolol were prepared as by Shah I et al., in that 1:7 ratio of drug and PVP K 30 was taken. Different percentages of HPMC K 15 M were taken and dissolved in 20 ml of ethanol. The beakers containing polymer solution were kept aside for 24 h for swelling of the polymer. Further, 5 ml of ethanol was added to it, and the dispersion was stirred. Then propylene glycol was added to the polymer solution and mixed well. Accurately weighed amounts of Nebivolol loaded solid dispersion were taken, added slowly in the polymeric solution, and stirred on the magnetic stirrer to obtain a uniform solution. This solution was then made up into 30 ml using ethanol, and then the solution was poured on the Petri dish of diameter 9 cm and kept for drying. These were left undisturbed at room temperature for one day. After drying, medicated patches of 2×2 cm² were cut using a sterile stainless steel borer; each film containing 10.0 mg of the drug. The cut patches were used for further studies [6,11]. The composition of different formulation showed in table 1.

Drug excipient compatibility studies

To determine whether there are any interactions between the drug and excipients, FTIR spectroscopic analysis was performed using the instrument BRUKER Alpha II in the region of 2000 to 400 cm⁻¹. All individual components of drug, drug-polymer mixture and patch were analysed.

Characterization of buccal mucoadhesive patches

Weight variation

A weight variation test was carried out using digital balance (Mettler-Toledo), by weighing three films containing a specific amount of drug from each formulation. The standard deviations (SD) were calculated from the individual weight of the film [11-13].

Film thickness

The thickness of the films was determined using a micrometer screw gauge. Thickness of 10 films of each formulation was determined and the average was calculated.

Content uniformity of patches

To make sure uniform distribution of NBH in film, a content uniformity test was performed. The film was added to 100 ml of Sorenson's phosphate buffer (SPB) pH 6.4 contained in a 250 ml beaker. The glass slab brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down until it broke. The number of times the film could be folded at the same place until it broke. The film samples, which broke at the point of clamping and not between the clamps, were not included in the calculation. Triplicate results for each film were considered. Tensile strength can be computed from the applied load included in the calculation. Triplicate results for each film were considered.

Surface pH study

The surface pH of the patch was determined in order to investigate the possibility of any side effects (in vivo). The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5±0.2) for 15 min at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [11, 13].

Percentage moisture absorption

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. Buccal films were weighed and placed in a desiccator containing 100 ml of a saturated solution of aluminum chloride and 7.45±5% RH was maintained. After three days the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using this formula [14].

| Formulation coed | Solid dispersion equivalents to 10 mg of nebivolol | HPMC K 15 M (mg) | Propylene glycol (%) | Aspartame (mg) | Peppermint oil (ml) | Ethanol |
|------------------|-----------------------------------------------|------------------|----------------------|---------------|-------------------|---------|
| F1               | 80                                            | 20               | 30                   | 0.25          | 0.02              | Q.S.    |
| F2               | 80                                            | 25               | 30                   | 0.25          | 0.02              | Q.S.    |
| F3               | 80                                            | 30               | 30                   | 0.25          | 0.02              | Q.S.    |
| F4               | 80                                            | 35               | 30                   | 0.25          | 0.02              | Q.S.    |
| F5               | 80                                            | 25               | 20                   | 0.25          | 0.02              | Q.S.    |
| F6               | 80                                            | 25               | 40                   | 0.25          | 0.02              | Q.S.    |

Percentage moisture loss

To evaluate the integrity of the patches in dry conditions percentage moisture loss test was carried out. The patches were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The formula used to find out the percentage moisture loss is:

\[ \% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \]

Tensile strength

Tensile strength was measured using tensile analogy tester (model TKG, FSA, India). Films free from air bubbles or physical imperfections were selected for tensile testing. The two clamps of the tensile tester were adjusted such that the distance between them is 3 cm by moving the upper clamp. During measurement, the strips were pulled by top clamp at a rate of 100 mm/min; the force applied was measured until the film was broken. The film samples, which broke at the point of clamping and not between the clamps, were not included in the calculation. Triplicate results for each film were considered. Tensile strength can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film using the following equation [15].

\[ \text{Tensile strength} = \frac{\text{Maximum force}}{\text{Area}} \]

Folding endurance

A small strip of film was cut evenly and separately folded at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the folding endurance [16].

In vitro residence time

The in vitro residence time was determined using a locally modified USP disintegration apparatus (Disintegration tester, Electrolab, Mumbai, India). The disintegration medium was composed of 300 ml of phosphate buffer pH 6.4 maintained at temperature 37±2°C. A segment of pig buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive film with backing membrane was hydrated from film surface using 15 µl phosphate buffer pH 6.4 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and
Drug release kinetics of each formulation were subjected and the average cumulative percentage drug release was determined [15]. For drug release three intervals 3 ml of samples was withdrawn and replaced with fresh ml of PB pH 6.8 phosphate buffer solution. At predetermined time intervals 3 ml of samples was withdrawn and replaced with fresh medium. After appropriate dilutions with simulated saliva was assayed spectrophotometrically at 281 nm. For drug release three films of each formulation were subjected and the average cumulative percentage drug release was determined [15].

**Drug release study of the buccal patch**

**In vitro release study**

The drug release studies were performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37±1°C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessel containing 500 ml of PB pH 6.8 phosphate buffer solution. At predetermined time intervals 3 ml of samples was withdrawn and replaced with fresh medium. After appropriate dilutions with simulated saliva was assayed spectrophotometrically at 281 nm. For drug release three films of each formulation were subjected and the average cumulative percentage drug release was determined [15].

**Drug release kinetics**

To study drug release kinetics of buccal patches formulation, data obtained from in vitro release studies were plotted in various kinetic models: zero order (see Equation: 1) as cumulative percentage of drug released versus time, first order (see Equation: 2) as log cumulative percentage of drug remaining versus time [17].

Zero-order equation Q = K0 t

First order equation lnQ = ln Q0 + K1 t

Where Q is the percentage of drug release at time t, K0 and K1 are the coefficients of the equation.

**Mechanism of drug release**

Mechanism of drug release from oral patches was evaluated by subjecting the data obtained from in vitro drug diffusion studies in Higuchi's model (see Equation: 3) as cumulative percentage of drug released versus the square root of time and Korsmeyer–Peppas' model (see equation: 4) as log cumulative percentage drug released versus log time [17].

Higuchi equation Q = Kt1/2

Korsmeyer and peppas equation Q = Kp n t

Kp is constantly incorporating structural and geometrical characteristics of the release device and n is the release exponent indicate the release mechanism.

**RESULTS AND DISCUSSION**

Buccal patches loaded with Nebivolol solid dispersion were prepared by solvent casting method. The prepared buccal patches were transparent, smooth, uniform and flexible as shown in fig. 1, except F6, which was tackier and non-uniform.

**Fig. 1: Buccal patch of nebivolol solid dispersion**

**IR spectroscopy**

The major IR peaks (wave number, cm⁻¹) of pure drug and optimized formulation F3 are given below: Pure NBH: 3397.75, 3187.33, 2903.02, 2845.37, 1749.30,1491.9, 1213.14, 1074.73; Optimized Formulation F3: 3312.97, 3188.78, 2923.41, 2735.69, 1740.33, 1488.83, 1209.09, 1069.62. The result showed that the principle IR peak of pure drug and an optimized formulation F3 were almost similar, signifying no interaction between drug and polymer during formation of patch [18].

**Table 2: Weight variation, thickness, surface pH and % drug content of developed buccal mucoadhesive patch**

| Table 2: Weight variation, thickness, surface pH and % drug content of developed buccal mucoadhesive patch |
|------------------------------------------------------------------------------------------------|
| **Formulation** | **Weight variation (mg)±SD** | **Thickness (µm)±SD** | **Surface pH ±SD** | **Drug content (%)±SD** |
| F1 | 86.3±0.28 | 67.0±0.94 | 9.1±0.9 | 95.17±0.96 |
| F2 | 104.5±0.19 | 89±0.81 | 6.87±0.09 | 92.20±0.76 |
| F3 | 109.0±0.36 | 97±0.95 | 6.64±0.06 | 94.09±1.21 |
| F4 | 114.7±0.32 | 107±1.63 | 6.51±0.11 | 90.88±1.09 |
| F5 | 101.6±0.21 | 84±1.24 | 6.49±0.08 | 91.02±0.99 |
| F6 | 102.1±0.24 | 88±0.47 | 7.22±0.06 | 88.45±1.22 |

**Weight variation, film thickness, surface pH, and content uniformity of patches**

The results of weight variation, film thickness, surface pH and content uniformity are represented in table 2. The weights and thickness of different formulations were ranged between 86.3±0.28 mg to 114.7±0.32 mg and 67±0.94 µm to 107±1.3 µm, because of different concentration of polymer and plasticizer. As an acidic or alkaline pH may cause irritation to the buccal mucosa, an attempt was made to keep the surface pH as close to neutral as possible. The surface pH of formulations was found to be in the range of 6.49±0.08 to 7.22±0.06, which was well within range of neutral pH and has not cause irritation and ultimately achieves patient compliance. All the formulations exhibited fairly uniform drug content ranging from 88.45±1.22 % to 95.17±0.96 %, Formulation procedures involving fewer processing steps, no major drug loss was observed during the preparation of the films.

**Percentage moisture loss and moisture absorption**

The percentage moisture loss was found to be between 3.48±0.23 to 6.63±0.33 and percentage moisture absorption was found to be 3.9±0.10 to 5.71±0.33, as shown in table 3. The result revealed that the moisture absorption and loss was found to increase with increasing concentration of hydrophilic polymers as well as increase the concentration of hydrophilic plasticizer. The optimum moisture content in the formulations helps the film to remain stable, non-brittle and free from completely drying. Optimum values of moisture absorption in F3 formulation indicate less chance of microbial contamination and maintain integrity through the films shelf life [19,20].

**Tensile strength, folding endurance and in vitro residence time**

Tensile strength is defined as the maximum stress applied at a point at which the film specimen breaks. The tensile strength measures the ability of a patch to withstand rupture. As the concentration of
hydrophilic polymer HPMC K 15 M was increased, there is increase in tensile strength, as shown in table 3.4. Polymers contain large number of chain of molecules and between these chains, homopolar bond and other types of bonds are possible. These bonds are either strong or feeble, depending on the nature of the polymer. According to the bonds formed force required to break the bonds and rupture the patch will differ. The mean value of tensile strength of patch containing different concentrations of HPMC K 15 M was found to vary between 4.11±1.51 to 8.55±0.90 kg/mm² (F1 to F4). As the concentration of plasticizer propylene glycol was increased (20 to 40 %) there is an increase in tensile strength (Patel and Poddar 2009), as shown in formulation F4, F3 and F5. The mean value of tensile strength of patch containing different concentration of plasticizer was found to be 4.32±1.27, 7.72±0.40 and 8.28±0.65 kg/mm² for formulation F4, F3 and F6, respectively. Presence of a plasticizer in the formulation helps in imparting strength to the films by lubrication effect of the plasticizer and reduction of the cohesive force between chain molecules of polymer. As a result, tensile strength of the films will be reduced. The formulation F3 showed optimum tensile strength which indicates less probability of rupture.

Release rate is controlled by more than one mechanism i.e. Diffusion non–fickian (anomalous) diffusion, which may indicate that the drug release was best fitted to zero order as the plot indicates highest linearity regression coefficient (R²) when compared to first-order kinetic model. The mechanism of drug release from buccal patches was studied by fitting the data into Higuchi model and korsmeyer peppa’s exponential model. The corresponding in vitro release plot of Korsmeyer-peppa’s equation indicated good linearity of regression coefficients (Patel and Poddar 2009). Release exponent (n) was found to be more above 0.45, so that the release can be characterized by non-fickian (anomalous) diffusion, which may indicate that the drug release rate is controlled by more than one mechanism i.e. Diffusion coupled with erosion mechanism [22, 23].

Table 3: Tensile strength, folding endurance, % moisture absorption and Moisture loss of developed formulations of betamethasone sodium phosphate

| Formulation | Percentage moisture absorption±SD | Percentage moisture loss±SD | Folding endurance±SD | Tensile strength Kg/cm²±SD | In vitro residence time |
|-------------|-----------------------------------|-----------------------------|----------------------|-----------------------------|------------------------|
| F1          | 3.90±0.19                         | 3.48±0.23                   | 32±3.87              | 4.11±1.51                   | >30                    |
| F2          | 4.09±0.32                         | 5.73±0.39                   | 59±2.83              | 5.34±0.95                   | >30                    |
| F3          | 5.50±0.21                         | 6.81±0.50                   | 93±3.58              | 7.72±0.40                   | >30                    |
| F4          | 5.71±0.33                         | 6.32±0.33                   | 158±4.37             | 8.55±0.98                   | >30                    |
| F5          | 4.45±0.53                         | 4.20±0.31                   | 76±2.01              | 4.32±1.27                   | >30                    |
| F6          | 5.23±0.43                         | 5.33±0.42                   | 135±4.02             | 5.28±0.65                   | >30                    |

*mean±SD (n=3)*

**In vitro drug release studies**

In vitro release of all formulation were performed and results are shown in fig. 2 and 3. The maximum percentage of drug released from the formulations F1 to F4 was found to be 95.88±3.03, 92.29±2.72, 90.18±2.59, and 75.88±2.43 at the end of 480 min. It was found that increase in the concentration of polymer significantly decreased the drug release. The slow drug release mechanism for improved polymer concentration may have providing the matrix permeability due to change in the morphology of the polymer. Improved polymer concentration may have providing the matrix with greater tortuosity and deprived water porosity for diffusion of drug [20,21]. In vitro release of drug also depends on nature of plasticizer. As the concentration of hydrophilic plasticizer was increased, the release of drug was also found to be increased, as shown in fig. 2. It may be due to quick absorption of water by formation of large number of hydrogen bonds and helped in faster diffusion of drug from the system. Formulation F5, F3 and F6 were contained different concentrations of plasticizer i.e. 20, 30 and 40 % respectively and maximum drug release at the end of 480 min was found to be 62.15±2.39, 90.18±2.59 and 93.18±1.19 respectively.

![Fig. 3: In vitro release studies of buccal patches of nebivolol contains different concentration of propylene glycol [mean±SD (n=3)]](image)

Based on physicochemical properties, in vitro residence time and in vitro drug release studies, formulation F3 was found to be optimized. Tensile strength of formulation F3 was sufficient to maintain the integrity of the film and it showed adequate residence time to keep the film at the site of administration. From in vitro drug release study, it was found that F3 showed maximum release (90.18±2.59) at the end of 30 min which was the prerequisite for the achievement of therapeutic action. However, formulations F1 and F2 containing lower concentration of HPMC K 15 M showed more...
release compared to F3 at the end of 480 min but tensile strength was lesser than F3. But formulations F4 containing high concentration of HPMC K 15 M showed less release and high tensile strength compared to F3. Formulation F6 also showed more drug release compared to F3, since it content higher amount of plasticizer, but it was rejected because of its sticky nature.

### Table 4: Kinetic parameter for in vitro drug release from buccal patches of nebivolol

| Kinetic model | F1 | F2 | F3 | F4 | F5 | F6 |
|---------------|----|----|----|----|----|----|
| Zero Order    | R² | 0.9701 | 0.987 | 0.9917 | 0.9932 | 0.9939 | 0.9683 |
|               | K  | -0.161 | -0.162 | -0.167 | -0.145 | -0.13 | -0.14 |
| First Order   | R² | 0.941 | 0.9495 | 0.9444 | 0.9806 | 0.9826 | 0.955 |
|               | K  | -0.0027 | -0.0021 | -0.002 | -0.0012 | -0.0011 | -0.0022 |
| Higuchi       | R² | 0.9886 | 0.986 | 0.9806 | 0.9885 | 0.9862 | 0.9917 |
|               | K  | 4.488 | 4.45 | 4.5654 | 3.9959 | 3.5718 | 3.924 |
| Korsmeyer Peppas model | R² | 0.9911 | 0.9889 | 0.9831 | 0.9972 | 0.9966 | 0.9938 |
|               | K  | 0.5059 | 0.5434 | 0.6208 | 0.7361 | 0.6341 | 0.4238 |
| n              | 0.6267 | 0.49 | 0.2688 | 0.102 | 0.1362 | 0.8256 |

### CONCLUSION

The buccal patches are very comfortable due to nonirritating to tissue and can be easily apply and remove. The buccal patches of Nebivolol required lower dosage compared to conventional tablets and able to deliver a drug over 6 hr continuously. Results illustrate the drug release was decreases with polymer and increases plasticizer.

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Nil

### AUTHORS CONTRIBUTIONS

All authors have contributed equally.

### CONFLICT OF INTERESTS

Declared none

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