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RESEARCH ARTICLE

Formulation Development and Evaluation of Fast Dissolving Oral Films of Nebivolol

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ABSTRACT

Oral films dissolve rapidly along with drug in mouth and majority of the drug is absorbed through buccal/oral mucosa in to systemic circulation avoiding first pass metabolism. Hypertension is a major cause of concern not just in the elderly but also in the youngsters. An effort was made to formulate a fast dissolving film containing Nebivolol which is used in the treatment of hypertension with an objective to rapid dissolution of drug and absorption which may produce the rapid onset of action and provides the convenient means of administration to those patient suffering from difficulty in swallowing such as paediatrics, geriatric and uncooperative mentally ill patients and also improve the bioavailability of the drug. The fast dissolving oral film were prepared using different polymers like Sodium starch glycolate, Hydroxy propyl methyl cellulose, Croscarmellose sodium and Tween 80 by solvent casting method. The fast dissolving oral film evaluated for folding endurance, swelling index, surface pH, *in vitro* disintegration time, drug content, drug polymer compatibility (IR Study), and *in vitro* drug release. The physical appearance and folding endurance properties were found to be good and electron microscopy shows that films are clear, colourless with smooth surface without any scratches. The drug content showed uniform mixing of drug in all prepared fast dissolving films. The *in vitro* drug release in optimized formulation F9 was found to be 69.56 % in 5 min. Drug release obeys the first order kinetics. The prepared films were stable. Hence it can be inferred that the fast dissolving oral film of nebivolol may produce the rapid action thereby improving bioavailability and enhance the absorption by avoiding the first pass effect.

Keywords: Fast dissolving oral films, Nebivolol, Sodium starch glycolate, Hydroxy propyl methyl cellulose, Croscarmellose sodium and Tween 80

Introduction

Fast dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages [1,2]. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract [3,4]. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms [1-4]. These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance.

Nebivolol is a cardioselective β-blocker used in the management of hypertension [5,6]. Nebivolol undergoes extensive metabolism in the liver after its oral administration, which results in very poor bioavailability (approximately 12%). Oral administration of nebivolol also reported to cause gastrointestinal disturbances and abdominal or stomachache. In an attempt to improve the bioavailability, efficacy and to minimise the side effects associated with oral administration, we have prepared fast dissolving film of nebivolol

MATERIALS AND METHODS

Materials

Nebivolol was a gift sample from Micro Labs Ltd. Bangalore. Hydroxylpropyl methylcellulose (HPMC), Sodium starch glycolate (SSG), Croscarmellose sodium (CS) and Tween 80 were purchased from S. D. Fine-Chem, Mumbai and all other chemicals used were of analytical grade.

Preparation of fast dissolving oral film of Nebivolol

Oral fast dissolving film was prepared by solvent casting method. Aqueous solution (A) was prepared by dissolving film forming polymer, in specific proportion in distilled water and allowed to stirred for 3 hours and kept for 1 hour to remove all the air bubble entrapped or remove bubbles. Aqueous solution (B) was prepared by dissolving the pure drug, sweetener, and plasticizer in specific proportion in distilled water. The aqueous solution A and B were mixed and stirred for 1 hour. The solutions were casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and were dried in the oven at 45^{o}C for 12 hours [7]. The film was carefully removed from glass plates and cut according to size

required for testing. The films were stored in an air tight container till further use. Two film forming agents and one co-film forming were selected. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. Concentration of film forming agent is optimized on the basis of thickness and appearance of film. The compositions of the formulations were shown in table 1.

Table 1: Formulation of Nebivolol oral fast dissolving films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	5	5	5	5	5	5	5	5	5
HPMC	150	200	250	150	200	250	150	200	250
Ethyl Cellulose	25	25	25	25	25	25	25	25	25
Glycerin	-	-	-	-	-	-	-	-	-
PEG-400	10	10	10	10	10	10	10	10	10
SSG	20	20	20				10	7.5	15
CCS	-	-	-	20	20	20	10	7.5	15
Aspartame	5	5	5	5	5	5	5	5	5
Citric acid	10	10	10	10	10	10	10	10	10
DM water qs to	-	-	-	-	-	-	-	-	-

Characterization of fast dissolving oral films by IR Spectroscopy

The samples of the fast dissolving films were prepared inthe form of KBr pellets and subjected for the scanning in the range of 4000 cm-1 to 400 cm-1 using FTIR spectrophotometer.

Evaluation of fast dissolving oral films

Nebivolol films were evaluated for the following properties-

Physical appearance and surface texture of the film

This parameter was evaluated by doing visual inspection of films and texture of films.

Thickness of film

The thickness of patches was measured at three different places using a absolute digimetic (Mitutoyo) from Medreich Lab, Bangalore.

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

Folding endurance is determined by repeated folding of the whole film at a particular place till the film breaks. Folding endurance value is computed by the number of times the film resists from breaking up.

Moisture uptake

The moisture uptakes by the films are determined by exposing the films to an environment of 40°C with 75% relative humidity for 1 week. The uptake of moisture by the films was calculated as the measure of the percent increase in weight.

Uniformity of drug content

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved I in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer.

Surface pH of films

The surface pH was evaluated by using digital pH meter. The prepared oral film was slightly wet using water. The pH was measured by bringing the combined glass electrode in contact with surface of the films.

***In-vitro* disintegration study**

Disintegration Tester (Electronic India) was employed for the *in-vitro* disintegration study of the fast dissolving oral. One piece of the prepared film was placed in each of the six tubes of the basket. The disc was added to each tube and the apparatus was run using 900 ml of pH 6.8 phosphate buffer solutions as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute in distilled water maintained at 37±0.5°C. The time in seconds was measured and recorded for complete disintegration of the oral film with no palatable mass remaining in the apparatus.

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C with stirring speed of 75 rpm in 900 ml 0.1 N Hydrochloric acid. Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of 0.1 N HCl. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Nebivolol was determined using UV-Visible spectrophotometer at 244 nm. The results were presented as an average of three such concentrations.

Stability studies

The aim of stability testing is to provide prominent evidence on how the quality of drug substance or drug product may varies with time under the influence of a variety of environmental factors like temperature, humidity and light and to establish retest period for the drug substance or a shelf life for the drug product and recommended storage condition. Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve

method. The % assay of tablets was found to slightly decrease at higher temperature.

Results and Discussion

It was clear from the FTIR spectrophotometric observations that the characteristics absorption bands for different functional groups and bonds of the drug and its polymer that is most of the cases there is no appreciable change in the position of the bands. Even if negligible deviation exists, it's due to the different types of the polymers used for the study. Hence it is clear that the drug has not undergone any type of structural change or any chemical reaction with the polymers and other excipients used. Therefore it can be concluded that in the present investigation there is no interaction of the drug with the polymers and the excipients used.

The weight of the prepared films was determined using digital balance and the average weight of the all the films was given in table 2. All the films are within the weight range of 110.20 ± 0.110 to 116.80 ± 1.210 mg indicates that all the films are in uniform weight with minimum standard deviation. All the films are free from the moisture uptake and there is no evidence of moisture attack in the prepared films. The thickness of the film was measured using screw gauge micrometer. The thickness was almost uniform in all the formulations and values ranges from 52.00 ± 0.057 mm to 56.45 ± 0.100 mm. The standard deviation values indicated that all the formulations were within the range. Nine formulations with variable concentration of po lymer were prepared by solvent casting method and evaluated for physicochemical properties and in-vitro drug release. The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation in order to determine the mechanism of drug release table 3. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e 0.992 hence indicating drug release from formulations was found to follow First order release kinetics fig 3. Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The %Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of tablets was found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits.

Therefore formulation remains stable for sufficient time.

Table 2: Evaluation of fast dissolving oral film of Nebivolol

Formulation code	Folding endurance	Disintegrating time	Tensile strength in kg/cm²	Percentage of Moisture Content
F1	More than 250	46±2	0.648±0.1	0.50±0.05
F2	More than 250	35±2	0.546±0.2	0.56±0.06
F3	More than 250	42±3	0.745±0.1	0.52±0.04
F4	More than 250	41±2	0.845±0.2	0.55±0.05
F5	More than 250	44±3	0.859±0.1	0.54±0.04
F6	More than 250	41±2	1.115±0.2	0.52±0.05
F7	More than 250	32±3	1.256±0.1	0.53±0.06
F8	More than 250	36±2	0.987±0.3	0.51±0.07
F9	More than 250	30±2	0.845±0.2	0.53±0.06

Conclusion

A successful attempt was made to develop oral fast dissolving films of nebivolol. From the results it was observed that drug and different polymer combination ratio influence the thickness, folding endurance, drug content as well as the drug release pattern of fast dissolving oral film of nebivolol. Hence, the fast dissolving oral film of nebivolol are expected to provide clinician with a new choice of safe and more bioavailable formulations in the management of hypertension. The study reveals satisfactory results with a further scope of pharmacokinetic and pharmacodynamic evaluation.

Table 3: Results of *in-vitro* release study of optimized formulation F9

S. No.	Time (Min.)	% CDR
1	1	45.56
2	2	55.69
3	5	69.56
4	10	92.56
5	15	100.02

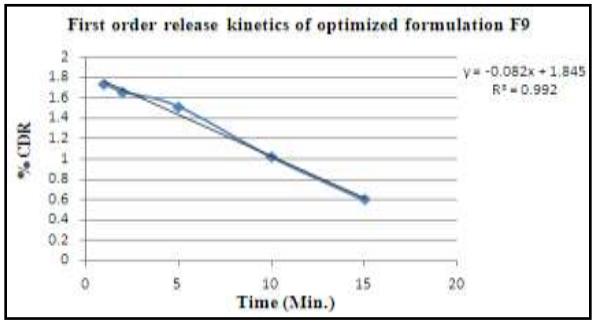

Figure 1: First order release kinetics of optimized formulation F9

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