



Development and evaluation of buccal film of norethindrone for birth-control

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ABSTRACT

Norethindrone is the class of progesterone which is used to prevent pregnancy. The plasma levels were considerably higher in women than men, especially at low dose levels. The plasma half-life of norethindrone is about 5 hrs in both sexes with single oral doses of 5 to 20 mg. Hence the present research work includes formulation of mucoadhesive buccal film of norethindrone with an objective to improve therapeutic efficacy, patient compliance and the bioavailability. In the present study five formulation of norethindrone were prepared as buccal film, by solvent casting technique. Sodium carboxymethylcellulose, hydroxylpropylmethylcellulose and polyvinylpyrrolidone were used as mucoadhesive polymers. Prepared films were evaluated for their weight, thickness, surface pH, swelling index, drug content uniformity, folding endurance *in vitro* release and permeation studies.

1. Introduction

Buccal drug delivery is an important route of drug administration. In the modern pharmaceutical field several bioadhesive mucosal dosage forms have been developed, which included adhesive tablets^[1,2,3], gels^[4,5], ointment^[6], patches^[7-9] and more recently films^[10] but the use of polymeric film for buccal drug delivery has not yet been widely investigated till now. Polymeric film for buccal drug delivery not only protect the tablet cores from environmental extremes but also very useful in improving appearance, masking the undesirable taste, and controlling the drug release. These unique properties associated with polymeric systems enhances the usefulness of polymeric buccal drug delivery systems in pharmaceutical world^[11]. Buccal film may also be preferred over the adhesive tablet in term of flexibility and comfort.

Formulation of fast dissolving buccal film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. In recent

application of fast dissolving buccal films, it has been made possible that vaccines can be provided to infants in impoverished area against rotavirus^[12].

Out of the various sites available for mucoadhesive drug delivery, buccal mucosa is the most suited one for local as well as systemic delivery of drugs. Its anatomical and physiological features like presence of smooth muscles with high vascular perfusion, avoidance of hepatic first pass metabolism and hence can potentially improve bioavailability are the unique features which make it as an ideal route for mucoadhesive drug delivery. Moreover, these dosage forms are economic and patient-friendly.

Norethindrone is a 19-Nortestosterone derivative, which is widely used to prevent pregnancy. It has very low bioavailability (46-65%) due to hepatic first pass metabolism^[13]. Hence to improve its therapeutic efficacy and bioavailability the drug may be administered by buccal route through buccal film. Buccal delivery of norethindrone may circumvent hepatic first pass metabolism and improve bioavailability. Hence the present work deals with the formulation and characterization of mucoadhesive buccal film of norethindrone using mucoadhesive polymer sodium carboxymethyl cellulose (SCMC), hydroxylpropyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP).

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2. Experimental section

2.1 Material and methods

Norethindrone was obtained as a gift sample from Cipla pharmaceutical Ltd. Secom, and PVP, HPMC (47 centipoises), SCMC (high viscosity grade) were obtained from Central Drug House, Mumbai. All the chemicals are of analytical grade and used without further purification.

2.2 Preparation of mucoadhesive buccal films

2.2.1 Preparation of polymer solution

For preparing the polymer solution 400mg of HPMC was weighed accurately and dissolved in 2 ml of distilled water. The beaker containing polymer and distilled water was kept aside for 5 min for swelling of the polymer. Further 3 ml of distilled water was added to the above polymer solution and the dispersion was stirred. One drop of glycerin was added to the polymer solution.

2.2.2 Preparation of drug solution

Norethindrone was accurately weighed in quantity such that 1 cm² film contained 40 mg and then dissolved in 1 ml of distilled water in a beaker.

2.2.3 Preparation of Films

Buccal films of norethindrone were made by solution casting method. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The whole solution was poured into the plastic petri dish placed over a flat surface. Inverted funnel was placed over the dish to avoid sudden evaporation. The mould containing polymeric solution of drug was kept for 12 hrs at room temperature for drying. After drying, the films were tested for possible imperfections. They were covered with the wax paper and preserved in desiccators till the evaluation tests were performed. Films were examined in order to select the film having the best characteristics. Five formulation have been formulated by the similar method although they are varied in their composition (Table 1)

Table 1. Composition of mucoadhesive buccal film of norethindrone

Formulation polymer	F1	F2	F3	F4	F5
HPMC	2%	1%	–	–	–
PVP	–	–	5%	2%	–
SCMC	–	–	–	–	2%
Ethanol or water	20	20	20	20	20

2.3 Characterization of mucoadhesive buccal films

2.3.1 Thickness

Three films of every formulation were weighed individually in a digital balance and the mean weight was calculated. The mean value of film thickness was calculated by measuring thickness of three films of each formulation at three different places using Micrometer Screw Gauge.

2.3.2 Folding endurance

Folding endurance was determined by repeatedly folding a small strip of size (2 x 2 cm) of film at the same place till it broke. The mean value (three reading and standard deviation) of folding endurance (the number of time, the film could be folded at the same place without breaking) were show in Table 2.

Table 2. Physical evaluation of mucoadhesive buccal film of norethindrone

Formulation code	Swelling index (2h)	Thickness	Content (mm)	Folding endurance	Surface pH
F1	31.81	9mm	17.7	295	6.71
F2	21.33	9mm	18.3	279	6.41
F3	17.12	9mm	19.5	179	6.62
F4	28.03	9mm	19.0	162	6.51
F5	25.34	9mm	18.2	280	6.85

2.3.3 Drug content uniformity

To determine the drug content uniformity, three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.6 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 217 nm in a UV spectrophotometer (Lambda 25, Perkin Elmer). The average of drug contents of three films was taken as final reading.

2.3.4 pH of films

To determine surface pH of films, buccal films were left to swell for 1 hr on the surface of the agar plates. Agar plates were prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer (pH 6.6) under stirring and then poured the solution into the petri dish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film.

2.3.5 Swelling properties

For studying swelling properties, a drug-loaded film of 10x10 mm² was weighed on a pre-weighed cover slip. It was kept in a Petri dish and 50 ml of pH 6.6 phosphate buffer was added. After every 30 min, the cover slip was removed and the films were weighed. The difference in the weight gives the weight increase due to absorption of water and swelling of film. The percent swelling, % S, was calculated using the following equation^[14,15]

$$\text{Percent swelling (\% S)} = (X_t - X_o/X_o) \times 100$$

Where X_t is the weight of the swollen film after time t, X_o is the initial weight of the film.

2.3.6 In-vitro release study

For the *in-vitro* release study the USP XXIV six station dissolution apparatus type 1 (DA-6DR, Veego Ltd., India) with 900 ml of pH 6.6 phosphate buffer (dissolution medium) was used. One film of each formulation was fixed to the central shaft using a cyanoacrylate adhesive. During the release study the temperature and rotation was carried out for 2 hrs. After every 5 min, samples were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 227 nm.

2.3.7 Ex-vivo permeation study

The *ex-vivo* permeation studies of mucoadhesive buccal films of norethindrone through an excised layer of porcine buccal mucosa (washed in isotonic phosphate buffer (pH 6.6) after excising and trimming from the sides) were carried out using the modified Franz diffusion cell^[15,16]. A 2.0 cm diameter film of each formulation under study was placed in intimate contact with the excised porcine buccal mucosa and the top of the assembly was covered with aluminum foil. The receptor compartment was filled with 100 ml of pH 7.4 phosphate buffer

with a Teflon bead placed inside and were stirred with a magnetic stirrer. The temperature of the instrument and contents was maintained at 37±1⁰C. The samples were withdrawn at every hour, filtered, diluted suitably and then analyzed using UV spectrophotometer at 227 nm.

3. Result and discussion

Buccal films of nonathindone were prepared by solvent casting technique with the use of mucoadhesive polymers such as PVP, HPMC and SCMC. The prepared films were evaluated for different physicochemical tests such as weigh variation, thickness, content uniformity, swelling index, surface pH, in vitro residence time, and in vitro drug release studies.

3.1 Thickness

All the films showed uniform thickness. The film thickness was observed to be in the range of 9 mm to 9.5 mm and average thickness found was about 9 mm. The weights of different formulation were found to be in the range of 58±1.97 mg to 86±0.77 mg.

3.2 pH of films

The acidic or alkaline pH may cause irritation to buccal mucosa and may affect the drug release and degree of hydration of polymers. Therefore the surface pH of buccal film was determined to optimize both drug release and mucoadhesion. The surface pH of all formulations was within ±0.5 units of the neutral pH and hence no mucosal irritation were expected and ultimately achieve patient compliance.

3.3 Folding endurance

Folding endurance was measured manually by folding the film repeatedly at a point till they broke. Films did not show any cracks even after folding for more than 285 times. Hence it was taken as the end point. The folding endurance was found to be in the range of 295 to 162. The values were found to be optimum to reveal good film properties.

3.4 Drug content uniformity

The result of content uniformity indicated that the drug was uniformly dispersed; the content was in range of 17.7 to 19.5 mg/cm².

3.5 Swelling properties

The swelling of the films were observed in pH 6.6 phosphate buffer solution. The comparative swelling in different formulations were in order of F1>F4>F5>F2>F3. Swelling was more pronounced in films F1 which containing HPMC. The percentage swelling of F5 and F4 was reduced considerably by the PVP. As the drug was uniformly dispersed in the matrix of the polymer, a significantly good amount of drug was loaded in all the formulations.

3.6 In-vitro release study

In vitro release studies of various formulations were performed using pH 6.6 phosphate buffer as dissolution medium. The drug concentration was determined spectrophotometrically at 227 nm. Significant difference was observed in the release pattern of norethindrone films containing PVP, HPMC and SCMC (fig. 1). It was observed that during dissolution, SCMC containing films swelled forming a gel layer on the exposed film surfaces [17,18]. The loosely bound polymer molecule in these films was readily eroded, allowing the easy release of norethindrone as compared to PVP. After two hours the release was found to be in the range of 91.02 to 26.33 %. The rank order of drug release after 2 hrs was found to be 91.02>90.34>50.16>48.95>26.33 for formulations F2>F1>F4>F3>F5, respectively.

It was also concludes that formulation F1 (HPMC) and F4 (PVP) showed good swelling, a convenient residence time as well as promising drug release. On the basis of release pattern, swelling and residence time, F1 and F4 formulation were chosen for *ex-vivo* study.

3.7 Ex-vivo permeation study

In *ex-vivo* study, drug permeation through the porcine buccal mucosa was determined for formulation F1 and F4. The drug permeation was found to be 82.48 % in case of F1 and 90.68% in F4 [after 10 hrs]. The drug permeation decreased in *ex-vivo* study in comparison of *in-vitro* release. This decrease in drug diffusion may be due to the lesser permeability of porcine mucosa and also the presence of a backing membrane in the *ex-vivo* study, which make the release unidirectional. The backing membrane restricting the contact of the film with the receptor fluid to one side alone slows down the water uptake, swelling and disruption of the matrix. That's why releasing lesser amount of drug in specified time, compared to the one without the backing membrane. The correlation coefficient values were found to be 0.9852 and 0.9667 for F1 and F4. From the above mentioned data it may be concluded that the release kinetics followed zero order. The Higuchi Plots of F1 and F4 were found to be almost linear with correlation coefficient values of 0.932 and 0.956. This proves that the drug permeation followed the matrix diffusion process.

4. Conclusion

The results of all the physical characterization of all formulations (F1-F5) were found to be satisfactory. The results of the study show that therapeutic levels of nonethindrone can be delivered by the buccal route. The present study concludes that these erodible mucoadhesive buccal films containing nonethindrone can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. Films exhibited controlled release over more than 2 h. It was concluded that the films containing 40 mg of nonethindrone in hydroxypropylmethylcellulose 4% w/v (formulation F1), showed good swelling, a convenient residence time and

promising controlled drug release, thus can be selected for the development of buccal film for effective therapeutic uses. Further, the study may be extended for assessing the *in vivo* release and *in vitro-in vivo* correlation.

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