RESEARCH PAPER

Formulation and *in vitro* characterization of mucoadhesive buccal film incorporated with Doxazosin mesylate nanosuspension

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ABSTRACT

Introduction: Doxazosin mesylate, a selective α-1 adrenergic receptor antagonist and is used for the treatment of hypertension and benign prostatic hyperplasia. It is a BCS Class II drug and oral administration of the drug is associated with extensive first-pass metabolism and variable bioavailability of approximately 65%.

Aim & Objective: The main objective of this research work was to develop and evaluate Doxazocin mesylate mucoadhesive buccal films incorporated with nanosuspension for the enhancement of bioavailability.

Materials & methods: Initially, Doxazocin mesylate nanosuspension was prepared by a precipitation-ultrasonication method with varying concentrations of the polymer and was analyzed for its physical characters. Optimized nanosuspension was incorporated and sandwiched between a mucoadhesive layer and a backing layer to form three layered buccal films. They were evaluated further for their physical and bioadhesive parameters.

Results & Discussion: The Doxazocin mesylate mucoadhesive buccal films incorporated with nanosuspension showing good physical and mechanical properties. The mucoadhesive buccal film formulations were opaque with smooth surface structure. Weight of the all the developed films was found to be in the range of 23.71 ± 0.27 mg to 29.12 ± 0.21 mg. The surface pH of films ranged from 6.4 ± 0.4 to 6.8 ± 0.5. The optimized formulation was stable for 28 days.

Conclusion: Doxazocin mesylate loaded nanosuspension containing mucoadhesive buccal films were developed successfully using precipitation-ultrasonication method. The nanosuspension incorporation in mucoadhesive films showed increased release rate due to increased drug surface area, which was further responsible for the improvement in dissolution and bioavailability of the drug.

Keywords: Doxazocin mesylate, Zeta potential, Mucoadhesion, Buccal film

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INTRODUCTION

In addition to delivering drugs to the buccal mucosa for the treatment of oral disorders, buccal drug delivery systems provide a promising pathway for systemic distribution by absorption through the mucosa to the systemic circulation at a preset and regulated rate[1]. By preventing active medication loss from first-pass hepatic metabolism and overcoming premature drug breakdown caused by gastrointestinal tract pH and enzyme activity, absorption of medicinal drugs from the oral mucosa enhances systemic bioavailability[2]. Additionally, unlike the sublingual route, the buccal mucosa allows a dose form to be retained for a longer period of time, particularly when mucoadhesive polymers are used, without significantly interfering with speaking or chewing[3].

One of the most promising dosage forms for the development of medications that are sparingly soluble and water insoluble is nanosuspensions[4]. Hydrophobic drug particles in the nano range (100–1000 nm) are dispersed in a hydrophilic media (often water) to form nanosuspensions, which are stabilized by polymers, surfactants, or a combination of the two. Nanosuspensions' reduced particle radius and increased surface area result in an enhanced rate of dissolution, which may enhance the concentration gradient and, consequently, the absorption of highly permeable but poorly soluble medications[5]. To

exploit this potential benefit of a nanosuspension for buccal delivery, appropriate delivery devices are required to overcome the inherent demerit of low hold time of any liquid formulation such as nanosuspensions. A little portion of the dose is left for systemic absorption after traditional buccal devices, such as chewing gums, release a significant portion of the dose into buccal fluid that is ingested. In order to minimize medication loss into the buccal cavity, a triple layer buccal patch with a drug layer sandwiched between a mucoadhesive layer with an absorption promoter and a backing membrane would be optimal.

Doxazosin mesylate, a selective α-1 adrenergic receptor antagonist commonly associated with many side effects, had a major formulation development challenge and is still used for the treatment of hypertension and benign prostatic hyperplasia (BPH)[6]. It is a BCS Class II medication that requires frequent doses to maintain therapeutic plasma levels due to its significant first-pass metabolism and variable bioavailability of about 65%.

MATERIALS AND METHODS

Materials

Doxazosin mesylate was received as gift sample from Hetero Drugs, Hyderabad. Acetone, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP)-K 90, hydroxyl propyl methyl cellulose (HPMC) (15 cps), sodium carboxy methyl cellulose (Na CMC), Methanol, PEG 400, Tween 80 and EC from S.D fine chem. All other chemicals used were of pharmaceutical grade. HPLC grade methanol was obtained from Merck. Triple distilled water was obtained from Milli-Q water purification system (Millipore).

Methods

Preparation of Doxazosin mesylate nanosuspensions

The anti-solvent precipitation–ultrasonication approach was used to create doxazosin mesylate nanosuspensions[7]. Solutions comprising 20, 30, 40, and 60 mg/ml of doxazosin mesylate were made by dissolving the medication in acetone. To create anti-solvent solutions with different PVA concentrations (0.1%, 0.15%, 0.2%, 0.5%, and 1% w/v), PVA was dissolved in water. Before being used, the anti-solvent was chilled down below 3°C in an ice water bath. A magnetic stirrer was used to continuously mix the organic drug solution (2 ml) into a beaker filled with aqueous PVA solution (20 ml). Because the drug was insoluble in water, it precipitated out right away, creating submicron particles. A probe sonicator was used to further reduce the size of this precipitated drug suspension. Drug suspension, in an ice bath, was probe sonicated at 90% amplitude for different time intervals (4, 8, 12, 16 and 20 min). The nanosuspension obtained was concentrated by centrifugation at 16000 rpm for 40 min in an ultracentrifuge. After centrifugation, supernatant was replaced with 2 ml of 0.2% PVA solution. Solid residue was redispersed using a bath sonicator.

Characterization of Doxazosin mesylate nanosuspension

Particle size, size distribution and zeta potential

The fundamental and crucial factor for characterizing nanoparticles is their size. It establishes the particles size and size distribution. Photon correlation spectroscopy (PCS) is used to quantify the particle size at room temperature using a Zetasizer (Nano ZS 90, Malvern Instruments, and Malvern, UK). To obtain the ideal kilo counts per second (Kcps) of 50–200 for measurements, 100 µl of the prepared NS formulation was diluted to 5 ml with double-distilled water. The sample was taken straight from the device and used for size measurement. Zeta potential testing was also done using the same equipment.

Entrapment efficiency

The amount of doxazosin mesylate entrapped in the nanosuspension was calculated by centrifuging the nanosuspension at 20,000 rpm, decanting the supernatant, and twice washing the sediment with distilled, deionized water. The amount of medication unentrapped in the supernatant was measured using a UV spectrophotometer set to 246 nm. The amount of drug that was entrapped was determined by deducting the amount of drug that was not entrapped from the total amount of drug that was added to create the nanosuspension. The study was conducted in triplicate, and the average results were presented[8].

Preparation of Doxazosin mesylate nanosuspension incorporated mucoadhesive buccal film

Preparation of nanosuspension incorporated buccal film constituted of three distinct layers, i.e., mucoadhesive layer, nanosuspension containing layer and backing membrane. All the three layers were prepared by a solvent casting method.

Preparation of mucoadhesive layer

The weighed amount of polymer was dispersed in 15 ml distilled water with continuous stirring using a magnetic stirrer and the final volume was adjusted to 20 ml. Following levigation with glycerine (15% of dry polymer weight), one drop of Tween 80 was added to the resultant polymeric solution. After being left overnight to create a bubble-free solution, the mixture was cast onto glass Petri dishes with a diameter of 10 cm and heated to 40°C for 24 hours in a hot air oven. To preserve their integrity and elasticity, the prepared films were wrapped in aluminum foil and kept in an airtight glass container[9].

Table 1: Optimization of Mucoadhesive Layer

Polymer	Formulation code	Polymer concentration (%v/v)	Permeation enhancer (Tween 80)	Optimized concentration & Batch
HPMC	**M1-F3**	**1-3%**	**1 drop**	**2 (M2)**
Na CMC	M4-M6	1-3%	1 drop	2 **(M5)**
PVA	M7-M9	1-3%	1 drop	3 **(M9)**
Sodium alginate	M10-M12	1-3%	1 drop	1 **(M10)**
PVP-K90	M13-M15	1-3%	1 drop	2 **(M14)**

Preparation of nanosuspension containing layer

A gel was formulated by dispersing a weighed quantity of HPMC (15 cps) and carbopol 934P as film-forming polymers in 20 ml of Doxazosin mesylate nanosuspension while continuously stirring with a magnetic stirrer. To this resulting gel, 15% PEG 400 w/v was added as a plasticizer and then was casted onto glass Petri dishes (10 cm diameter) and kept in vacuum desiccators for drying up to 24 h[10]. To preserve their integrity and flexibility, the created films were wrapped in aluminum foil and kept in an airtight glass container.

Table 2: Optimization of nanosuspension containing layer

Formulation Code	HPMC (15CPS) (%w/v)	Carbopol 934P (mg)	Permeation enhancer (Tween 80)
NS1	2	20	1 drop
NS2	**3**	**40**	**1 drop**
NS3	4	60	1 drop
NS4	5	80	1 drop
NS5	6	100	1 drop

Preparation of backing membrane

A magnetic stirrer was used to continuously mix a weighed amount of ethyl cellulose in 15 milliliters of chloroform. To create a clear, bubble-free solution, 30% PEG 400 w/v was added to the resulting polymeric solution and set aside. In order to completely remove the chloroform, this solution was cast onto glass Petri dishes and dried for up to 24 hours in vacuum desiccators[11]. To preserve their integrity and flexibility, the produced films were wrapped in aluminum foil and kept in an airtight glass container to prevent moisture loss.

Table 3: Optimization of Ethyl Cellulose Baking Layer

Formulation code	Ethyl cellulose (% w/v)	Chloroform (ml)	PEG 400 (% w/v)
BL1	1	15	1
BL2	**2**	**15**	**1**
BL3	3	15	1
BL4	4	15	1
BL5	5	15	1

Final composite formulation

The three layers listed above are combined to create the final mucoadhesive buccal formulation. The nanosuspension-containing layer was affixed to the backing membrane on one side and the mucoadhesive layer on the other by spraying chloroform. The composite was sliced to a size of 2 cm^2 and placed between two stainless steel stabs in vacuum desiccators for 24 hours after the mucoadhesive side was covered with a peelable polyethylene film. To preserve their integrity and flexibility, the produced films were wrapped in aluminum foil and kept in an airtight glass container to prevent moisture loss.

Characterization of buccal films

The buccal films were evaluated for their physical, mechanical and bioadhesive parameters followed by *in vitro* drug release studies.

Weight variation

A digital weighing balance was used to weigh four films from each batch of formulation separately and then collectively. The average weight and weight variation of the films were then noted[12].

Thickness

Four films of each combined layer formulation were taken and the thickness of the film was measured using a screw gauge at different points of the plane surface. The average film thickness was calculated[13].

Folding endurance

The folding endurance was measured by hand. A tiny strip of film measuring 2 cm2 of each formulation was obtained and folded at the same location till it breaks. The value of folding endurance was

determined by how many times a film could be folded in the same spot. Three determinations were averaged[14].

Surface pH

The surface pH of the film was determined by allowing the film to swell by keeping it in contact with 1 ml of phosphate buffer (pH 6.8) for 1 h in a glass Petri dish. The surface pH was noted by bringing a combined glass electrode near the surface of the film for 1 min using a pH meter. The pH was recorded and average of three determinations was calculated [15].

Drug content uniformity

The three-layered film was dissolved in 100 milliliters of an isotonic phosphate buffer (pH 6.8) and homogenized for two hours with sporadic shaking to assess the drug content homogeneity. A 0.45 mm Whatman filter paper was used to filter the resultant solution after an aliquot (5 ml) was removed and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml. Spectrophotometric analysis was then used to determine the drug content[16].

Swelling studies

The 1.5 cm diameter patch sample was weighed before being placed in a porcelain dish with 15 ml of artificial saliva. The patch was gently wiped with absorbent tissue to eliminate any extra moisture at predetermined intervals, and it was then weighed again. The film's weight increased at each interval until it reached a constant weight. The following formula was used to determine the degree of swelling.

Swelling index = W_t- W_0/W_0

Where, Wt is weight of the patch at time t and W_0 is weight of the patch at time zero.

***In vitro* mucoadhesion test**

A modified balance method was used to measure the buccal film's mucoadhesive strength[16]. After being collected, fresh sheep buccal mucosa from a slaughterhouse was kept at 4°C in Krebs' buffer pH 7.4. Using appropriate glue, a 1 cm^2 piece of cleansed sheep buccal mucosa was adhered to the beaker's bottom flat surface with the mucosal aspect facing up. The test films were adhered to the lower flat side of the hanging glass assembly to the balance's left arm, which had previously been balanced by holding a 5 g weight on each side. After blotting the mucosa's surface with Whatman filter paper and adding 25 µl of pH 7.4 Krebs' buffer solution, 5 g of weight was taken out of the right pan. As a result, the glass assembly and the 5 g film were dropped over the membrane. This was left alone for three minutes before being rebalanced with five grams of weight on the right side. The weights were then gradually added until the film barely broke away from the membrane's surface. The bioadhesive strength was determined by adding weight to break the adhered film from the mucosa. Each formulation was tested on three films, and the average of the three films was computed.

***In vitro* drug release studies**

A shaking incubator rotating at 100 rpm was used to conduct in vitro drug release experiments using the dialysis bag method. The dissolution medium was methanolic phosphate buffer (pH 6.8), which is a 90:10 ratio of methanol to phosphate buffer 6.8. Each dialysis bag (pore size: 12 kD, Sigma Chemical Co., St. Louis, MO) contained four milligrams of medication in buccal film. The dissolution medium had a volume of 200 ml and a temperature of 37.0 ± 0.2°C. At predetermined time interval, samples (2 ml) were withdrawn, replaced with same volume of fresh media, filtered and assayed for drug content at 246 nm against blank using a UV-Visible spectrophotometer. Mean results of triplicate measurements and standard deviation were reported.

Mechanism of release kinetics

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson–Crowell. R^2 values were determined by regression formed by the index of linearity.

Stability Studies

Accelerated stability testing was performed on the optimized formulation. To determine the impact of temperature on the drug content in formulation, the investigation was carried out at 37°C and 45°C. Films were placed in glass Petri plates covered with aluminum foil and stored for a month at 37±0.5°C and 45±0.5°C in an incubator. After 7, 14, 21 and 28 days, changes in the bioadhesive patch appearance and medication content were examined[17].

Results and discussion

Formulation and optimization of Doxazosin mesylate nanosuspension

Nanosuspensions were prepared according to the procedure mentioned and further, it was optimized on the basis of particle size of the nanosuspension.

Table 4: Optimization of Doxazocin mesylate nanosuspension based on particle size and drug entrapment efficiency

Formulation Code	Drug concentration (mg/ml)	Stabilizer concentration (%w/v)	Particle size (nm)	Zeta potential (mV)	Drug entrapment (%)
NS1	4	0.2	291.3	-	81.4±

			±1.21	19.01 ±1.01	0.12
NS2	8	0.4	185.2 ±0.31	-27.42 ±0.32	95.1± 0.04
NS3	12	0.6	285.3 ±2.03	-23.16 ±0.54	80.5± 0.15
NS4	16	0.8	272.7 ±1.23	-21.71 ±0.03	78.4± 0.12
NS5	20	1	288.1 ±0.27	-24.01 ±1.25	82.3± 0.21

Characterization of Doxazosin mesylate nanosuspension

In vitro characterization included parameters such as size and size distribution and particle charge.

Particle size and distribution

Using a Zeta sizer (Nano ZS 90, Malvern Instruments, and Malvern, UK), photon correlation spectroscopy was used to determine the particle size and size distribution of the Doxazosin mesylate nanosuspension. All of the produced formulations were determined to be between 185.2 and 291.3 nm in size. This suggests that the technique used produced consistent Doxazosin mesylate particles within the required size range for buccal formulation.

Surface charge on particle

The physical stability of a nanosuspension can be inferred from its zeta potential. Every formulation was expected to have a zeta potential between -19.01±1.01 and -27.42±0.32. According to the study, all of the created nanosuspension formulations had sufficient stability due to the existence of a polymer interfacial coating on the drug particles[18].

Preparation of nanosuspension incorporated mucoadhesive buccal film of Doxazosin mesylate

Using optimized mucoadhesive films with optimal drug nanosuspension integrated gel (NS2) and the optimized backing membrane (BL2), five batches of mucoadhesive buccal formulations (D1 to D5) were created. The buccal formulation was created by joining and compressing them. The mucoadhesive quality of the sandwiched layer (drug gel layer) made with HPMC and carbopol 934P, which imparted adhesivity and accommodated enough doxazosin mesylate nanocrystals, allowed them to be firmly attached. For ease of use, the formulation was divided into 2 cm^2 pieces[19].

Characterization of mucoadhesive buccal film formulation

Physical characterization

The mucoadhesive buccal film formulations have been evaluated for various physical characteristics. The mucoadhesive buccal film formulations were opaque with smooth surface structure. Weight of the all the developed films was found to be in the range of 23.71 ± 0.27 mg to 29.12 ± 0.21 mg. Folding endurance test indicated no crack even after 300 times folding, revealing satisfactory flexibility of the films. The surface pH of films ranged from 6.4 ± 0.4 to 6.8 ± 0.5. These values were found to be around the saliva pH (range 6.2 to 7.6) confirming the compatibility of the films with buccal mucosa and no risk of mucosal damage or irritation on usage[20].

Drug content uniformity

Mucoadhesive buccal films were found to have an average Doxazosin mesylate concentration of 4.13 ± 0.12 mg/cm^2. The range of drug content uniformity values was 87.21 ± 2.34% to 97.32 ± 2.31%. The drug was evenly dispersed throughout the movie, according to the content uniformity results[21].

Swelling studies

In a pH 6.8 phosphate buffer solution, the films were seen to swell. The order of the comparative swelling in the various formulations was D1 > D4 > D5 > D2 > D3. Because there were more hydroxyl group molecules in films D1 containing HPMC, swelling was more noticeable[22].

***In vitro* mucoadhesion strength**

The modified balancing method was used to determine the mucoadhesive strength for each formulation. Formulations D1, which comprised HPMC, had higher bioadhesive strength than films containing sodium alginate, PVA, and Na CMC (D2, D3, D4 and D5). Additionally, it was found that bioadhesive strength increased with polymer concentration[23].

In vitro release studies

For all formulations, the *in vitro* drug release of the nanosuspension-incorporated buccal film was conducted for six hours in methanolic PBS pH 6.8. At the end of six hours, the percentage of medication released from all formulations from D1 to D5 was 95.13%, 87.02%, 76.32%, 81.24%, and 85.31%. Only after four hours did all formulations show between 49% and 63% of the medication release. D1 delivered the most medication of all the formulations in less than six hours. The following is the order of retardation times for various films: D1 > D2 > D5 > D4 > D3. The reason might be due to water permeability characteristics of the film prepared out of different polymers. Lower the water permeability

coefficient the greater the sustained drug release characteristics observed. Swelling of polymers may be an additional factor which controlled the release rate[24].

Mechanism of release kinetics

To determine the drug release of the created formulations, the in vitro release profiles of each formulation were subjected to a kinetic analysis for fitting into different models, including zero-order, first-order, Higuchi and Peppas exponential equations. Plots for Higuchi release kinetics were found to be linear in both situations. Exponent values (n) in the *ex vivo* permeation profile indicated that the drug was released and penetrated by the diffusion mechanism after super case-II transport[25-28].

Table 5: Characterization of buccal films

Formulation code	Weight variation (mg)	Thickness (mm)	Swelling (%)	Content uniformity (%)	Surface pH	Folding endurance
D1	23.71 ± 0.27	0.38 ±0.13	42.5 ±1.51	97.32 ±2.31	6.8 ±0.5	>300
D2	29.12 ± 0.21	0.47 ±0.05	29.2 ±1.34	89.01 ±1.26	6.5 ±0.2	>300
D3	25.35 ±0.32	0.49 ±0.13	25.4 ±0.67	91.24 ±2.32	6.6 ±0.3	>300
D4	21.19 ±1.31	0.54 ±0.19	36.2 ±0.31	85.13 ±1.23	6.4 ±0.4	>300
D5	24.21 ±0.28	0.59 ±0.21	30.2 ±0.25	87.21 ±2.34	6.5 ±0.1	>300

Table 6: *In-vitro* mucoadhesion strength

Formulation code	Mucoadhesive strength (gm)	Force of adhesion
D1	16.2±1.01	0.17±0.04
D2	11.5±1.12	0.14±0.01
D3	12.3±1.02	0.15±0.03
D4	14.1±1.12	0.16±0.02
D5	13.7±1.05	0.12±0.01

Table 7: Stability study of optimized formulation

Days	Drug content	Surface pH	Appearance
7	97.32±2.31	6.8±0.5	Opaque & smooth
14	97.21±1.03	6.8±0.3	Opaque & smooth
21	97.03±1.24	6.8±0.4	Opaque & smooth
28	97.16±1.12	6.8±0.2	Opaque & smooth

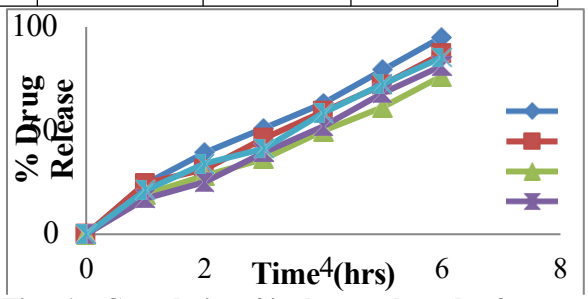

Fig. 1: Cumulative % drug released of Doxazocin mesylate mucoadhesive buccal films

CONCLUSION

Doxazosin mesylate nanosuspension was developed and optimized based on its characters. Then it was incorporated into hydrophilic films to prepare a suitable formulation for buccal drug delivery. The nanosuspension incorporation in mucoadhesive films showed increased release rate due to increased drug surface area. From the study, it can be concluded that the prepared nanosuspension incorporated mucoadhesive buccal films are capable of minimizing the shortfalls of Doxazosin mesylate oral administration.

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