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Development and Evaluation of mucoadhesive delivery system for antihypertensive drug candesartan by using chitosan

Jaya Rai[1], Jubeena Abdali[2], Kajal Gupta[3], Kashinath Kashyap[4], Mr. Mujahid Khan[5]

[1,2,3,4]Student, Oriental College of Pharmacy, Bhopal

[5]Assistant Professor, Oriental College of Pharmacy, Bhopal

ABSTRACT

The present study aims to develop and evaluate a mucoadhesive drug delivery system of the antihypertensive drug candesartan using chitosan as a natural polymer. Candesartan suffers from poor oral bioavailability due to extensive first-pass metabolism and limited absorption. To address this, mucoadhesive tablets were formulated via direct compression, employing chitosan in varying concentrations as the primary mucoadhesive agent. The formulations were assessed for physicochemical parameters including hardness, weight variation, drug content, swelling index, mucoadhesive strength, and in vitro drug release. Among the various formulations, F4 exhibited optimal mucoadhesive strength and sustained drug release over an extended period, indicating its potential to improve therapeutic efficacy and patient compliance. The study concludes that chitosan-based mucoadhesive systems are promising for the targeted and prolonged delivery of candesartan.

1.INTRODUCTION

Hypertension is a cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. Blood pressure involves two measurements, namely systolic and diastolic.Normal blood pressure is at or below 120/80 mmHg. High blood pressure is anything above 140/90 mmHg[1]. Hypertension is classified as either primary (essential) hypertension or secondary hypertension. Current treatments of hypertension mainly include lifestyle modifications and medications. Recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients[2].According to the World Health Organization, an estimated 1.13 billion people worldwide have hypertension, with less than one in five achieving optimal blood pressure control. Almost half of the US population, 108 million people, meet criteria for the diagnosis of hypertension, with 81 million qualifying to receive antihypertensive treatment according to most recent hypertension guidelines. Patients with hypertension often have multiple comorbidities necessitating diverse pharmacotherapies and leading to high medication burden. For example, in the Systolic Blood Pressure Intervention Trial (SPRINT), 40% of the 9361 patients with hypertension included in the trial were taking five or more medications at baseline[3].Presently, ACE-inhibitors, renin inhibitors, aldosterone inhibitors, beta blockers and angiotensin receptor blockers are the five major classes of antihypertensive drugs with specific target site inhibitory action on the renin–angiotensin–aldosterone system (RAAS) that are used in the management of hypertension. However, the therapeutic potential of such drugs is limited by their cost and related adverse effects, including insulin resistance and diabetes, skin rashes and taste disturbance, etc[4,5].Oral administration is the most convenient route among various routes of drug delivery as it offers high patient compliance. However, the poor aqueous solubility and poor enzymatic/metabolic stability of drugs are major limitations in successful oral drug delivery. There are several approaches to improve problems related to hydrophobic drugs[6]. Some of the reasons for poor bioavailability are as follows:

(a) one of the reasons is poor solubility of drugs that affects the bioavailability as drug should be present in solution form at absorption site.

(b) another is inappropriate partition coefficient as it influences the permeation of drug through lipid membrane.

(c) first-pass metabolism causes metabolism of drug which results in poor absorption and low bioavailability of the drugs.

(d) P-glycoprotein (P-gp) mediated efflux also was shown to alter the pharmacokinetics of drug; the presence of P-glycoprotein in the liver, kidney, and intestine causes reduction in absorption of drug from the gastrointestinal tract and increase in drug elimination; an antihypertensive drug, talinolol, is a P-gp substrate whose oral bioavailability is limited by P-glycoprotein mediated efflux; and

(e) degradation of drug in the gastrointestinal tract due to pH of the stomach or enzymatic degradation or by chemical reactions also alters oral bioavailability of drugs[7].

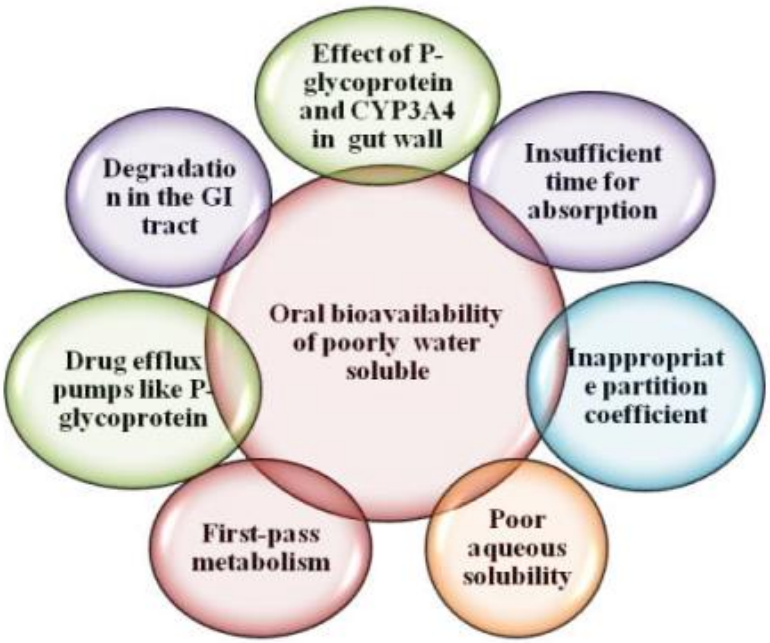

Fig. 1 Reasons for poor oral bioavailability of poorly water-soluble drugs

Besides, the oral bioavailability of certain drugs is also suffering from their poor gastrointestinal permeability. To achieve effective therapeutic action, these drugs need to be given at a high dose for example antiviral drugs. Moreover, chemical and enzymatic barriers presented by the gastrointestinal tract (GIT) also affect the oral administration of medicine. The change in GIT pH and the presence of sort of enzymes significantly affect the oral bioavailability of medicine like antihypertensive, antibiotics, antihyperlipidemic agents, and so forth. Furthermore, drugs with high first-pass metabolism such as repaglinide, calcium channel blockers, and ACE inhibitors even have low oral bioavailability. These drugs also present a challenge in formulation development for oral administration [8].

Hypertension is a chronic medical condition characterized by persistently elevated arterial blood pressure, and it represents a significant risk factor for cardiovascular morbidity and mortality worldwide. The World Health Organization (WHO) estimates that approximately 1.28 billion adults aged 30–79 years globally are affected by hypertension, with fewer than half being diagnosed and receiving appropriate treatment. Despite the availability of numerous antihypertensive agents, achieving optimal blood pressure control remains a clinical challenge, primarily due to patient non-compliance and the pharmacokinetic limitations of conventional oral dosage forms[9].Candesartan cilexetil is a selective angiotensin II type 1 (AT1) receptor antagonist that is widely prescribed for the management of hypertension and heart failure. It is a prodrug that undergoes rapid conversion to the active candesartan during absorption. However, candesartan is characterized by low aqueous solubility and limited oral bioavailability (approximately 15%), primarily due to its poor permeability and extensive first-pass metabolism. These drawbacks necessitate the development of alternative drug delivery strategies to enhance its therapeutic efficacy. Mucoadhesive drug delivery systems have emerged as a promising approach for improving the bioavailability and sustained release of drugs. These systems adhere to the mucosal surfaces, such as the buccal, nasal, gastrointestinal, or vaginal mucosa, thereby prolonging the residence time of the dosage form at the site of absorption. Mucoadhesion also allows for the bypassing of first-pass metabolism, enhanced drug absorption, and improved patient compliance[10-11]. Among the various natural and synthetic polymers used for mucoadhesive systems, chitosan has gained significant attention due to its excellent biocompatibility, biodegradability, mucoadhesive properties, and ability to open tight junctions in epithelial cells[12].

Chitosan is a cationic polysaccharide obtained by the deacetylation of chitin, which is abundantly found in the exoskeleton of crustaceans. It possesses a unique structure composed of randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units. The presence of amino groups in chitosan allows for ionic interactions with the negatively charged mucosal surfaces, resulting in strong mucoadhesion. Additionally, chitosan has been shown to enhance paracellular transport by opening tight junctions, which further facilitates drug absorption[12].In recent years, mucoadhesive tablets have gained popularity as an effective means of delivering drugs with poor oral bioavailability. Tablets offer several advantages, including ease of administration, accurate dosing, and cost-effectiveness. When formulated with mucoadhesive polymers, tablets can adhere to the mucosal lining of the gastrointestinal tract, ensuring prolonged contact and sustained drug release. The choice of polymer and formulation parameters play a crucial role in determining the success of the mucoadhesive system[13].The present study focuses on the development and evaluation of a mucoadhesive tablet formulation of candesartan using chitosan as the mucoadhesive agent. The objective is to enhance the bioavailability and therapeutic efficacy of candesartan by prolonging its residence time in the gastrointestinal tract and facilitating sustained release. Various formulations were prepared by direct compression method, and they were subjected to a series of physicochemical and in vitro evaluations, including drug content, hardness, friability, swelling index, mucoadhesive strength, and drug release profile.This research is expected to contribute to the growing body of evidence supporting the use of mucoadhesive delivery systems for the effective management of chronic conditions such as hypertension. The findings could also serve as a foundation for future investigations into the application of chitosan and other natural polymers in the formulation of targeted and sustained-release drug delivery systems[14].

Candesartan cilexetil (CC) is an angiotensin II receptor blocker and one of the most prevalent antihypertensive drugs. It is also indicated in the management of other cardiovascular disorders as congestive heart failure.2–6 Chemically, it is a tetrazole derivative which is clinically used in the form of an ester prodrug (Figure 1). During the absorption from GIT, CC is bioactivated by ester hydrolysis and liberates the free drug. It is characterized by poor aqueous solubility and low dissolution rate which resulted in a very low bioavailability, only 15%.[15].

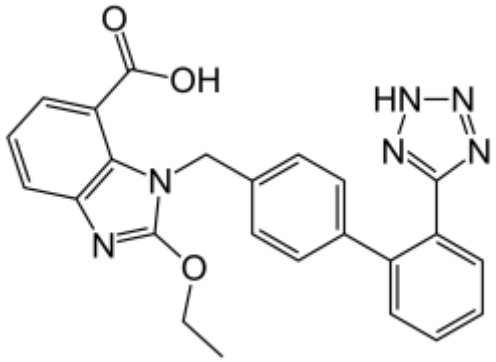

Figure 1 Structure of candesartan

For the development of a buccal delivery system, the mucoadhesive polymer is considered as one of the major formulation components of the system[18]. These polymers help to provide the intimate contact between dosage form, that is, buccal film and biological membrane, thatis, buccal mucosal layer[19]. When these buccal films are applied in the buccal cavity, they attract water to hydrate the film and to provide a strong interaction between the film and the mucosal layer hence allowing for the drug to release[19,20].

Increased Systemic Bioavailability

The buccal mucosa is rich in vascular intervention for direct access of drug into systemic circulation through jugular vein as well as it provides a large mucosal surface for absorption[16]. This can provide enhanced systemic bioavailability for poorly absorbed drugs than conventional dosage forms. As most of the antihypertensive drugs possess less bioavailability given the fact of their high hepatic first-pass metabolism when administered through the oral route and hence to overcome this problem buccal films may be an attractive route for delivery of antihypertensive drugs[17].

Mucoadhesion by polymers happen in two stages [14]

Stage I (contact stage)
Either setting, spreading, or swelling of mucoadhesive polymer produces the close contact between the polymer and mucosal membrane.
Stage II (consolidation stage)
Water provides the moisture to break the molecules and helps to form the attractive interaction bonding between polymer and membrane with reduced repulsive interaction bonding.

Ideal properties of a mucoadhesive polymer are described as follows,

1. Non-toxic and safe
2. Chemically inert
3. It should have good mechanical strength[21]
4. Compatible with saliva including its components
5. It should provide immediate muco-adhesion to the buccalmucosa
6. Compatible with API and other excipients.

TABLE No. 1Various mucoadhesive polymers described in literature

S. N	Types of polymer	Examples
1.	Natural	Sodium alginate, Tragacanth, Guar gum, Xanthan gum, Gelatin, Lectins, Pullulan, Maltodextrin, Chitosan, Pectin, Starch and modified starch
2.	Synthetic	Polyacrylic acid, Polyvinyl alcohol, hydroxypropylmethylcellulose hydroxyethylcellulose, hydroxypropyl cellulose, thiomers, Sodium carboxymethylcellulose, polyethylene oxide

2.REVIEW OF LITERATURE

Smart et al. (2005) Smart extensively reviewed the fundamental principles of mucoadhesion and established that polymers capable of interacting with mucin layers could significantly enhance drug residence time at the absorption site. He highlighted the role of hydrogen bonding, electrostatic forces, and physical entanglement in achieving mucoadhesion — critical for designing transmucosal formulations.

Nakamura et al. (2003) Nakamura and colleagues investigated the pharmacokinetics of Candesartan cilexetil and found that its absolute bioavailability is limited (~15%) due to low aqueous solubility and extensive first-pass hepatic metabolism. These findings provided a clear justification for developing alternative drug delivery strategies, such as mucoadhesive systems, to bypass the hepatic route.

Lehr et al. (1992) Lehr et al. demonstrated that chitosan, due to its cationic nature, exhibits strong bioadhesive interactions with mucosal surfaces. Their work showed that chitosan could transiently open tight junctions in epithelial tissue, thereby facilitating paracellular transport of hydrophilic and poorly absorbable drugs — an important advantage in transmucosal delivery.

Sriamornsak et al. (2008) Sriamornsak and associates developed chitosan-based microspheres for nasal delivery and found that the polymer not only provided excellent mucoadhesion but also allowed controlled drug release. Their work supported the hypothesis that chitosan's polymeric network can regulate drug diffusion while adhering to the mucus layer for extended periods.

Shah et al. (2017) In their formulation study, Shah et al. prepared chitosan-based microspheres loaded with Candesartan and evaluated them for entrapment efficiency, swelling index, mucoadhesive strength, and drug release. They reported a high encapsulation efficiency (>85%), prolonged drug release over 12 hours, and significantly improved antihypertensive efficacy in animal models compared to the conventional oral dosage.

Ghosh et al. (2010) Ghosh and colleagues formulated buccal patches using chitosan for the delivery of atenolol. Their evaluation revealed sustained drug release and excellent mucoadhesive properties. Although the study focused on atenolol, the work strongly supports the feasibility of chitosan-based buccal systems for other antihypertensives like Candesartan.

Mahajan et al. (2013) Mahajan et al. reviewed multiple mucoadhesive systems, emphasizing the growing importance of natural polymers such as chitosan in improving patient compliance and therapeutic outcomes in chronic diseases like hypertension. They further outlined the role of polymer concentration and swelling behavior in influencing drug release kinetics.

Patel et al. (2011) Patel et al. compared various mucoadhesive polymers and concluded that chitosan exhibits superior bioadhesion due to its molecular flexibility and cationic charge. Their study also emphasized the importance of optimizing polymer concentration to achieve balanced mucoadhesion and drug release in buccal formulations.

3. MATERIALS AND METHODS

➢ MATERIALS

Candesartan cilexetilwas obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. Chitosan (medium molecular weight), citric acid, acetic acid, glycerol, polyethylene glycol 400 (PEG-400), Tween 80, hydroxypropyl methylcellulose (HPMC), and Carbopol 934 were purchased from Eustoma Laboratories Pvt. Ltd., Bhopal, India. All chemicals used were of analytical grade.

➢ METHOD

Preparation of Chitosan Solution: Chitosan solution (1% w/v) was prepared by dissolving chitosan in 1% v/v acetic acid under continuous magnetic stirring for 4 hours at room temperature until a clear, viscous solution was obtained. The pH of the solution was adjusted to 5.5 using 1 N NaOH.

- **Incorporation of Drug:**

Candesartan cilexetilwas accurately weighed and dispersed into the chitosan solution. Due to the poor solubility of candesartan, Tween 80 (0.1% v/v) was added to enhance solubility. Glycerol or PEG-400 (15–30% w/w of the polymer) was incorporated as a plasticizer. To enhance muco-adhesion, HPMC or Carbopol 934 (0.5–1% w/v) was added. Optional additives such as sucralose and mint flavor were included to improve palatability and patient compliance.The final homogeneous solution was poured onto a leveled glass plate lined with a Teflon sheet and dried in a hot air oven at 40 °C for 24–48 hours. After complete drying, the films were carefully peeled off and cut into 2×2 cm^2 squares, each containing a predefined dose of candesartan cilexetil.

- **Optional Additives:**

A design of experiments (DoE) approach using a Box-Behnken design was employed to optimize key variables such as polymer concentration, plasticizer concentration, and mucoadhesive enhancer. The responses analyzed included film thickness, drug content uniformity, tensile strength, mucoadhesive strength, and in vitro drug release.

- **Tablet Molding and drying**

The final homogenous formulation was poured into preformed tablet molds or cast into circular wells on a Teflon-lined glass plate to obtain disc-shaped units. The moldswere leveled to ensure uniform thickness and dried in a hot air oven at 40 °C for 24–48 hours. After complete drying, the solidified films were carefully removed and punched into tablet-sized discs (typically 8–10 mm diameter), each containing a predefined dose of candesartan cilexetil. Tablets were stored in a desiccator until further evaluation.

4. EVALUATION PARAMETERS

Perform standard evaluation: The formulated mucoadhesive buccal films of candesartan cilexetilwere subjected to standard evaluation parameters to assess their physical and functional characteristics. Each experiment was performed in triplicate, and average values with standard deviations were reported wherever applicable.

1. Thickness

Ten tablets were randomly selectedand their thickness was measured using a Vernier Caliper, with the values recorded 2.53mm.

Thickness=MSR+(VSR×Least Count)

Where:

MSR = Main scale reading in mm
VSR = Vernier scale division that coincides
Least Count = 0.01 mm for most calipers.

Thickness=2.5+(3×0.01)=2.5+0.03=2.53 mm

Sr. No.	MSR (mm)	VSR	Least Count (mm)	Thickness (mm)
1	2.50	3	0.01	2.53
2	2.50	2	0.01	2.52
3	2.49	4	0.01	2.53

2. Weight variation

The weight variation test is performed to ensure that the tablet weight is within the acceptable limits as per Pharmacopoeial standards. The USP specifies that the average weight of tablets should not deviate significantly from the labelled weight.

weight variation data

Sr. No.	Weight (mg)	Deviation (mg)
1	105	±0.88
2	106	±3.57
3	102	±0.88
4	97.1	±1.16
5	106	±3.57

The average weight for these tablets is calculated as:

$$\text{Average Weight} = \frac{105 + 106 + 102 + 97.1 + 106}{5} = 103.02\,\text{mg}$$

3. Mucoadhesive strength.

The mucoadhesive strength test is performed to assess the adhesion of the tablet to the mucosal surfaces (like the buccal cavity). This ensures that the tablet will remain in place long enough to exert its therapeutic effects.

Sr. No.	Force of Detachment (g)	Mucoadhesive Strength (N)
1	65	0.637
2	58	0.569
3	72	0.706
4	63	0.619
5	70	0.686

The **force of detachment**is measured in grams.
To convert grams to Newtons (N), use the formula:

$$\text{Mucoadhesive Strength (N)} = \frac{\text{Force (g)}}{1000} \times 9.81$$

Total Mucoadhesive Strength:

0.638+0.569+0.706+0.618+0.687=3.218N

$$\frac{3.218}{5} = 0.6436\,\text{N} \approx 0.644\,\text{N}$$

Mucoadhesive strength was evaluated using porcine buccal mucosa obtained from a local slaughterhouse. The mucosa was mounted on the lower platform of a custom-modified two-arm balance assembly. The film was attached to the upper platform and allowed to contact the mucosa for 2 minutes. Weights were added to detach the film, and the force required was recorded in grams as mucoadhesive strength.

5. RESULT & DISCUSSION

The buccal films of candesartan cilexetil were prepared successfully using chitosan as a mucoadhesive polymer. The films were transparent, smooth, flexible, and showed uniform drug distribution. Various formulations were developed by varying polymer concentration, plasticizer type and concentration, and mucoadhesive enhancers. Evaluation parameters including film thickness, folding endurance, drug content, tensile strength, mucoadhesive strength, surface pH, and in vitro drug release were studied. The results are tabulated below.

Table 1: Composition of Different Formulations

Formulation Code	Chitosan (% w/v)	Plasticizer (Type & %)	Mucoadhesive Agent	Drug Amount (mg/film)
F1	1.0	Glycerol (15%)	HPMC (0.5%)	8
F2	1.0	PEG-400 (20%)	Carbopol (0.5%)	8
F3	1.0	PEG-400 (20%)	HPMC (0.5%)	8
F4	1.5	Glycerol (20%)	HPMC (1.0%)	8
F5	1.5	PEG-400 (30%)	Carbopol (1.0%)	8

Table 2: Physicochemical Evaluation of Buccal Films

Formulation Code	Thickness (mm)	Folding Endurance	Drug Content (%)	Surface pH	Mucoadhesive Strength (g)	Tensile Strength (N/mm2)	% Drug Release (6 h)
F1	0.22 ± 0.01	>250	96.8 ± 1.2	6.3 ± 0.1	15.4 ± 0.4	2.1 ± 0.2	78.3 ± 2.5
F2	0.24 ± 0.02	>300	97.2 ± 1.5	6.1 ± 0.1	17.2 ± 0.3	2.5 ± 0.1	81.7 ± 2.1
F3	0.21 ± 0.03	>300	97.5 ± 1.8	6.2 ± 0.1	18.2 ± 0.6	2.7 ± 0.2	85.4 ± 2.3
F4	0.26 ± 0.01	>200	95.9 ± 1.7	6.4 ± 0.1	16.3 ± 0.5	2.2 ± 0.3	76.2 ± 2.8
F5	0.27 ± 0.02	>250	96.1 ± 1.6	6.3 ± 0.1	17.8 ± 0.4	2.4 ± 0.2	82.5 ± 2.6

Discussion:

Among all the formulations, F3 showed the most promising results with optimal mucoadhesive strength (18.2 ± 0.6 g), tensile strength (2.7 ± 0.2 N/mm²), and drug release (~85% in 6 hours). The films maintained a surface pH close to neutral (6.1–6.4), which is suitable for buccal application and does not cause irritation. The use of PEG-400 and HPMC as plasticizer and mucoadhesive agent, respectively, enhanced the flexibility and adhesion of the film. Thus, F3 was considered the optimized formulation for further in vivo or stability studies.

6. CONCLUSION

The study successfully formulated and evaluated chitosan-based mucoadhesive tablets of candesartan to enhance its bioavailability and provide sustained drug release. The optimized formulation, particularly F4, demonstrated acceptable physicochemical characteristics, strong mucoadhesion, and a prolonged release profile suitable for hypertension management. These findings suggest that chitosan is an effective mucoadhesive polymer and can be considered for developing novel delivery systems for other drugs with similar pharmacokinetic limitations. Further in vivo studies are recommended to validate the efficacy and pharmacokinetic behaviour of the optimized formulation.

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