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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF HALOPERIDOL

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ABSTRACT

For the past four decades, the idea of mucoadhesion has been used to extend the controlled release effect as well as the contact time of multiple bioadhesive dosage forms through various mucosal routes. Haloperidol is an anti-psychotic drug. The present study focuses on the formulation and evaluation of mucoadhesive buccal tablets of haloperidol (HP) using the direct compression technique, aimed at improving oral bioavailability and sustaining drug release. Preformulation studies included physicochemical characterization, solubility analysis, and drug–excipient compatibility assessments using FTIR and DSC. Various formulations were developed employing polymers such as Carbopol 934p, HPMC K100M, ethyl cellulose, and chitosan in different ratios. The prepared tablets were evaluated for flow properties, hardness, friability, weight variation, drug content, swelling index, mucoadhesive strength, and in vitro release. Among the twelve formulations, F10 was identified as the optimized batch, showing excellent mucoadhesive strength (84%) and a sustained cumulative drug release of 97.22% over 12 h. Stability studies conducted under accelerated conditions (25 ± 2°C, 60 ± 5% RH) for six months confirmed the stability of the optimized formulation with no significant changes in physical or chemical properties. These findings suggest that mucoadhesive buccal tablets of Haloperidol represent a promising alternative to conventional dosage forms, with potential for improved therapeutic efficacy and patient compliance.

INTRODUCTION:

Drug delivery systems are intended to improve patient compliance and benefit by developing & targeting novel dosage forms [1]

Mucoadhesive drug delivery system

The oral mucosal drug delivery system (MDDS) bears the cost of an advantageous technique of dosing medicine, mainly to the patients with swallowing difficulties. Mucoadhesive delivery systems give an extended time of contact at the attached site, upgrade the patient's consistency, and lay a lower financial burden when contrasted with the other dose structures. The utilization of mucoadhesive polymers added to the compliance system in the controlled delivery. Though striking advancements have been made in mucoadhesive, there are various difficulties to be tended to in this field. However, more research work is needed in the novel mucoadhesive formulation, to understand mode of drug delivery in the clinical treatment of systemic and topical diseases [1,2]

For the past four decades, the idea of mucoadhesion has been used to extend the controlled release effect as well as the contact time of multiple bioadhesive dosage forms through various mucosal routes. The formulations based on the MDDS have shown improved bioavailability of numerous drugs. The use of mucoadhesive polymers has accomplished the critical interest in the formulation of sustained, extended, and prolonged release dosage forms. The Mucoadhesive Drug Delivery System (MDDS) enhances blood flow in mucosal cavities, thereby improving drug absorption. This route of administration offers significant advantages over conventional delivery methods, including bypassing first-pass hepatic metabolism and avoiding degradation by gastrointestinal enzymes and intestinal flora [2,3]

The polymers, either natural or synthetic macromolecules, strengthen the mucoadhesive dosage forms forming ideal to fit in contact with the mucosal surface. In recent years, the use of mucoadhesive polymers has emerged as a key strategy to prolong the residence time and enhance the localized effects of drug delivery systems on various biological mucosal membranes. This approach has garnered significant interest in the field of pharmaceutical technology [1,3].

The potential candidates for drug delivery by mucoadhesive dosage form to different sites includes oral, gastrointestinal, nasal, ocular, vaginal, and rectal. Buccal route found to be more suitable for the delivery of pharmaceutical agents using mucoadhesive polymers due to presence of relatively static and smooth surface on which various mucoadhesive dosage forms can be placed. Different dosage forms like films, tablets, gels, ointments and patches can be used for delivery of drug across the buccal mucosa. The drugs may be suitable candidates to be delivered via the oral cavity which are having short biological half-life, poor solubility, and permeability, susceptible to enzymatic degradation and for achieving sustain release effect [2,4]

The aim of the present study is to formulate, optimize, and evaluate mucoadhesive buccal tablets (BT) of haloperidol (HP) using the direct compression technique, with the intention of improving drug release and enhancing oral bioavailability.

MATERIALS AND METHODS

Preformulation studies

For the preformulation studies of drug, the physicochemical characterization of drug substance, selection of excipients, compatibility studies, and estimation of drug content in by UV-Visible Spectroscopy was carried out [5,6].

Physicochemical characterization

Drug was characterized and identified by its physical appearance, melting point, ultraviolet (UV) spectroscopy, solubility profile and infrared (IR) spectroscopy

Physical appearance

Description of the drug is the first line indication for purity for its identification. 1.0 g of HP was weighed and transferred into a clean, dry petri dish, and physical appearance, colour was observed visually.

Melting point

The melting point of HP was carried out by capillary method using a melting point apparatus.

Solubility studies [6-8]

The solubility of HP in various solvents like distilled water, methanol, ethanol, and phosphate buffer pH 6.8 were carried out individually. The HP (100 mg) was added in 100 mL of the various solvents in a volumetric flask and sonicated for 30 min. It was considered as stock solution; from it 1mL was taken and diluted to 10mL with same solvent and filtered through, 0.2 µm Whatman's filter paper. The absorbance was measured by UV spectrophotometer.

Study of analytical method for estimation of HP [9-12]

Preparation of phosphate buffer pH 7.4: The phosphate buffer pH 7.4 was prepared as per the specifications given in the Indian Pharmacopoeia

Preparation of 0.2M potassium dihydrogen phosphate solution: 27.218 of potassium dihydrogen phosphate was dissolved in 1000ml of distilled water to produce 0.2M solution of potassium dihydrogen phosphate.

Preparation of 0.2M NaOH solution: 8g of sodium hydroxide was dissolved in 1000ml

of distilled water to produce 0.2M sodium hydroxide solution.

Determination of wavelength of maximum absorption: A standard stock solution of haloperidol (100 µg/mL) was prepared by dissolving 10 mg of the drug in 10 mL of methanol in a 100 mL volumetric flask. The volume was then made up to the mark using phosphate buffer (pH 7.4). From this stock solution, a series of working standard solutions in the concentration range of 2–10 µg/mL were prepared by appropriate dilution with the same phosphate buffer. To determine the wavelength of maximum absorption (λ_{max}), a UV spectroscopic scan was carried out in the range of 200–400 nm, using phosphate buffer (pH 7.4) as the blank.

Drug-excipients compatibility studies by FTIR and DSC: The compatibility studies were conducted between drug and selected excipients by FTIR and DSC analysis.

Compatibility studies of the excipients by using FTIR spectroscopy: The drug-excipients compatibility studies are carried out to ensure, the interaction between the drug and polymer, when they are physically mixed together. HP was subjected for IR spectroscopic study (FTIR BRUKER). Spectra were taken after preparing the pellet with 2-3 mg of sample using potassium bromide in the ratio of 1:100 and were scanned from 4000-400cm-1. The FTIR spectra were scanned for pure drug, polymer, and drug-physical mixture individually to detect any appearance or disappearance of characteristic peaks.

Compatibility studies of the excipients by using DSC analysis: DSC analysis was performed using approximately 2 mg of the sample, placed in a T-zero aluminium pan and sealed with a T-zero aluminium lid using a T-zero press. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min. The samples were heated from 0°C to 300°C at a heating rate of 10°C/min, under nitrogen gas flow at 40 mL/min, and the corresponding thermograms were recorded. The thermal behaviour of the pure drug substance was compared with that of the physical mixture to assess potential interactions or compatibility between the drug and excipients.

***In vitro* evaluation of HP BT blend [12-14]**

Angle of repose: The angle of repose (θ) is defined as the maximum angle formed between the surface of a pile of powder blend and the horizontal plane, and it is an indicator of powder flowability. It was determined using the funnel method. A quantity of 20 g of the haloperidol powder blend was transferred into a funnel with an 8 mm orifice, which was initially blocked using a cotton plug. Upon removal of the plug, the powder was allowed to flow freely onto a flat surface, forming a conical heap. The height (h) and radius (r) of the heap were measured, and the angle of repose (θ) was calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r}$$

Where;
θ = Angle of repose,
h = height of HP blend,
r = radius of HP blend heap.

Bulk density and tapped bulk density: The loose bulk density (LBD) and tapped bulk density (TBD) of the haloperidol (HP) buccal tablet blend were determined using a standard method. An accurately weighed 20 g sample of the blend was transferred into a 100 mL graduated measuring cylinder. The cylinder was gently dropped onto a wooden platform from a height of 2.5 cm, three times at 2-second intervals. The initial volume occupied by the powder blend was noted as the bulk volume, and the loose bulk density was calculated using the formula:

$$LBD = \frac{\text{Weight of sample (M)}}{\text{Apparent volume of powder } (V_0)}$$

$$TBD = \frac{\text{Weight of sample (M)}}{\text{Tapped volume of powder (V)}}$$

The above data generated were used in calculating Carr's compressibility index and Hausner's ratio.

Carr's compressibility index

Carr's Compressibility Index is widely used as an indirect measure of flowability and is

influenced by several physical properties such as bulk density, particle size and shape, surface area, and moisture content of the powder blend. These characteristics collectively impact the compressibility and flow behaviour of the haloperidol buccal tablet (HP BT) blend.

Carr's Compressibility index (%) = V - V0 / V X 100

Where;

V-Tapped volume of powder,

Vo-Apparent volume of powder.

Hausner's ratio: Hausner's ratio is an indirect index to measurement the ease of powder flow. It was calculated by the following formula;

Hausner's ratio = V/V0

Formulation development of HP BT: The composition of each tablet contains 10 mg of Haloperidol. Before direct compression, all the ingredients were screened through sieve no 60. HP was mixed manually with different ratios of polymers such as EC, Carbopol 934p, HPMC K-100 and Chitosan. This PVP K-30 (binder) was added and mixed for 10 min. The above blend was mixed with magnesium stearate and talc (lubricant) for 3 min. The tablets were compressed using a sixteen-station CEMACH rotary tablet-punching machine by the direct compression method.

RESULTS AND DISCUSSION

Melting point

The melting point of HP by the capillary method was found in the range of 145-150 °C and the average of three readings was found to be 146 °C.

Solubility studies

Based on the solubility data it can be inferred that the solubility in distilled water (22 µg/mL) < ethanol (41 µg/mL) < PH (pH 6.8) (58 µg/mL) <methanol (86 µg/mL).

Results of analytical methods for estimation of HP by UV

A calibration curve was constructed over the concentration range of 2–12 µg/mL by plotting concentration on the X-axis and the corresponding absorbance values on the Y-axis.

Stability studies for HP F10

The descriptions of the HP F10 at 0, 1, 2, 3, 6 months were checked. During the stability studies, there was no significant change in the physical appearance, hardness, friability, thickness, and weight variation. The drug content varied between 18.1±0.02 to 18.6±0.52 mg of the label claim. The results indicated that no significant changes were observed in the optimized formulation HP F10 during storage at 25 ± 2°C and 60 ± 5% relative humidity (RH) for a period of 6 months, demonstrating good stability under accelerated conditions.

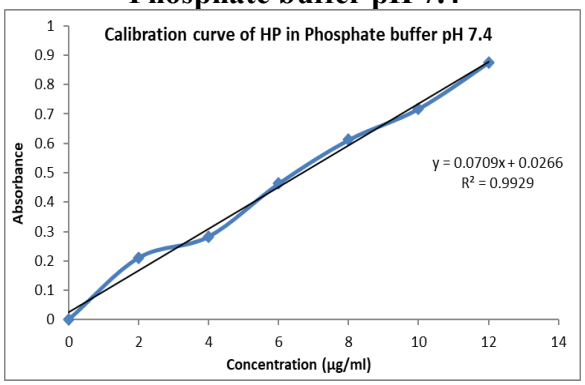
Table 1: Formulation chart

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	10	10	10	10	10	10	10	10	10	10	10	10
Carbopol 934p	20	25	30	35	20	25	30	35	20	25	30	35
Ethyl cellulose	60	55	50	45	--	--	--	--	--	--	--	--
HPMC K100M	--	--	--	--	60	55	50	45	--	--	--	--
Chitosan	--	--	--	--	--	--	--	--	60	55	50	45
PVP K-30	20	20	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight	125	125	125	125	125	125	125	125	125	125	125	125

Table 2: Absorbance value of drug in Phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance
0	0
2	0.211
4	0.283
6	0.463
8	0.612
10	0.718
12	0.875

Figure 1: Calibration curve of HP in Phosphate buffer pH 7.4



***In vitro* drug release**

Table 3: *In-vitro* dissolution profiles of HP Mucoadhesive formulations F1-F6

Time (h)	% Cumulative drug release*					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	25.77±0.15	27.18±0.04	27.54±0.07	29.13±0.07	31.21±0.06	29.46±0.044
1	39.57±0.21	35.76±0.01	34.50±0.05	32.45±0.02	33.86±0.06	31.30±0.01
2	44.45±0.13	38.83±0.02	39.10±0.14	37.16±0.03	39.76±0.01	36.44±0.03
3	52.65±0.16	45.88±0.06	44.34±0.04	46.12±0.09	43.72±0.04	40.43±0.05
4	61.22±0.09	53.87±0.01	53.38±0.05	52.24±0.04	47.26±0.03	44.65±0.02
5	69.85±0.13	60.07±0.08	61.02±0.009	57.46±0.01	53.89±0.02	51.25±0.03
6	76.21±0.005	71.03±0.02	65.58±0.09	61.35±0.04	59.64±0.001	56.72±0.01
7	84.23±0.04	77.07±0.002	74.64±0.03	67.30±0.007	64.88±0.08	61.73±0.02
8	89.16±0.03	84.15±0.09	79.63±0.02	70.29±0.06	70.24±0.03	66.61±0.05
9	95.14±0.03	87.38±0.07	87.15±0.05	76.37±0.06	76.74±0.01	72.37±0.03
10	95.59±0.06	92.31±0.03	94.38±0.03	82.19±0.05	82.36±0.02	76.87±0.09
11	96.12±0.02	92.87±0.04	94.85±0.009	87.52±0.01	87.24±0.02	79.94±0.07
12	----	93.30±0.03	95.38±0.039	88.00±0.004	87.74±0.03	80.43±0.04

* Mean ± S.D (n=3)

Table 4: Results of the stability studies for HP F10

Description	Storage conditions (25°C ± 2°C/60% RH ± 5%)				
	Initial	After 1 month	After 2 months	After 3 months	After 6 months
Physical appearance	Off white colour tablet	Off white colour tablet	Off white colour tablet	Off white colour tablet	Off white colour tablet
Hardness 2(Kg/cm)	5.9±0.34	5.84±0.34	5.75±0.34	5.57±0.34	5.57±0.34
Friability (%)	0.29±0.12	0.28±0.12	0.30±0.12	0.29±0.12	0.28±0.12
Thickness (mm)	5.26±0.03	5.26±0.03	5.26±0.03	5.26±0.03	5.26±0.03
Weight variation (mg)	2.39±0.33	2.35±0.33	2.29±0.33	2.26±0.33	2.21±0.33
Drug content (mg) label claim	99.36±0.63	99.26±0.63	99.21±0.63	99.±18.63	99.10±0.63

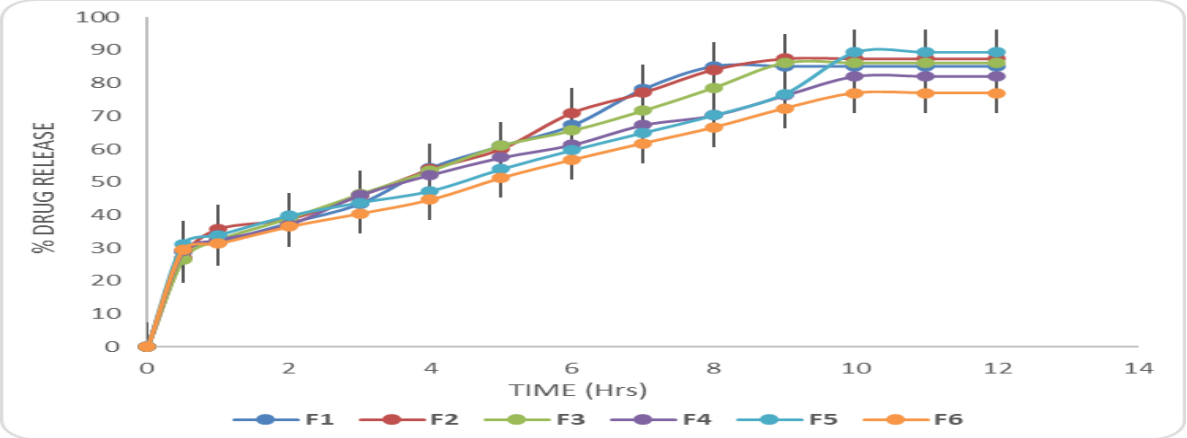


Figure 2: *In-vitro* dissolution profiles of formulations F1-F6

CONCLUSION

The present study aimed to formulate and evaluate mucoadhesive buccal tablets of Haloperidol (HP) using the direct compression technique, with the objective of enhancing drug release and oral bioavailability. Preformulation studies included physicochemical characterization of the drug substance, excipient selection, drug–excipient compatibility studies, and drug content estimation via UV-Visible spectroscopy. The flow properties of the Haloperidol powder blend were evaluated by measuring the angle of repose, bulk and tapped density, Carr's compressibility index, and Hausner's ratio. The tablets were prepared by direct compression and evaluated for key parameters including hardness, friability, weight variation, drug content, in vitro mucoadhesion, swelling index, and in vitro drug release. Among the twelve formulations developed, Formulation F10 was identified as optimized, exhibiting excellent mucoadhesive strength (84%) and a cumulative drug release of 97.22% over 12 hours. Stability studies conducted at 25 ± 2°C and 60 ± 5% RH for 6 months showed no significant changes in the formulation, confirming the stability of HP F10 under accelerated storage conditions.

Conflicts of interest

The authors declare no conflict of interest.

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