Formulation and Evaluation of Mucoadhesive Buccal Patches Containing Cisplatin for Oral Cancer Therapy

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Abstract:
Oral cancer is a highly prevalent disease affecting millions worldwide. Major risk factors for oral cancer include tobacco and alcohol use, HPV infections, poor nutrition, and genetic susceptibility. The disease progresses through multiple genetic and epigenetic alterations involving tumor suppressors like p53, p16, and FHIT, along with oncogenes like EGFR, c-yc, K-ras, int-2, PRAD-1, and bcl leading to the development of premalignant lesions and subsequent tumors. Surgery, radiation, and chemotherapy are conventional therapies used against oral cancer, though they have numerous side effects.
Cisplatin, a genotoxic agent, is one of the most potent chemotherapy drugs, and has been widely used alone or in combination with other antineoplastic drugs or radiation therapy to treat various cancer types. However, this drug causes adverse effects that limit its therapeutic efficiency. To overcome such limitations of this drug and to find the new route of drug delivery systems based on microemulsions and nanoparticles have been explored toward modulating the enhanced permeability and retention effect and promoting cisplatin delivery to tumors.
Cancer chemoprevention, which represents one promising approach, is defined as the prevention, inhibition or reversal of carcinogenesis by intervention with chemically derived or naturally occurring dietary substances. The purpose of this study to prepare the buccal patches to treat oral cancer which should effective against the oral cancer and can use easily to the patient who should faced this problem. A buccal patches has been prepare and the chemical components are (carbopol 934, polyethylene glycol, glycerin, methyl paraben, propyl paraben, HPMC, Cisplatin, etc) were analyzed by high performance liquid chromatography in further study.

Keywords: Cisplatin, Buccal Patches, High Performance liquid chromatography, Anti-neoplastic etc.

Introduction

The oral route is the most favoured method of drug delivery for both patients and clinicians. However; it has drawbacks like hepatic first pass metabolism and enzymatic degradation in the gastrointestinal tract, making it unsuitable for certain drugs, particularly peptides and proteins. Hence, alternative absorptive mucosa is explored as potential sites for drug administration.
Cancer remains one of the most formidable challenges in modern medicine, with conventional treatments often struggling to balance efficacy against debilitating side effects. Chemotherapy, while a cornerstone of oncology, faces significant limitations due to its non-specific targeting, which damages healthy tissues alongside malignant cells. Among chemotherapeutic agents, cisplatin has been widely used since the 1970s for treating solid tumors such as lung, ovarian, and testicular cancers. Its mechanism of action involves the formation of DNA crosslinks that disrupt replication and transcription, triggering apoptosis in rapidly dividing cells. However, the clinical utility of cisplatin is severely constrained by dose-limiting toxicities, particularly nephrotoxicity, which affects up to 30% of patients.(1)
The drug's accumulation in renal tubular epithelial cells via organic cation transporters leads to oxidative stress, inflammation, and apoptosis, often resulting in acute kidney injury or chronic renal dysfunction. Neurotoxicity, ototoxicity, and bone marrow suppression further complicate treatment regimens, while intrinsic or acquired drug resistance in tumors diminishes therapeutic outcomes over time. These challenges underscore the urgent need for innovative strategies to enhance cisplatin's therapeutic index—improving its anticancer efficacy while minimizing harm to healthy tissues. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous benign. (2)

A critical unmet need exists for locoregional drug delivery systems that can maintain therapeutic concentrations at the tumour site while minimising systemic exposure. Buccal drug delivery directly addresses this challenge. Metastasis is the process by which malignant tumors invade adjacent tissues and spread to other parts of the body to develop into new malignancies. Malignant tumors are another name for cancerous tumors. Leukemias and other blood cancers typically do not produce solid tumors, although many other malignancies do. Neighboring tissues are not penetrated or spread by benign tumors. Malignant tumors may grow again after removal, whereas benign tumors typically do not. However, benign tumors can occasionally be rather large. Some, like benign brain tumors, can be lethal or produce severe symptoms.

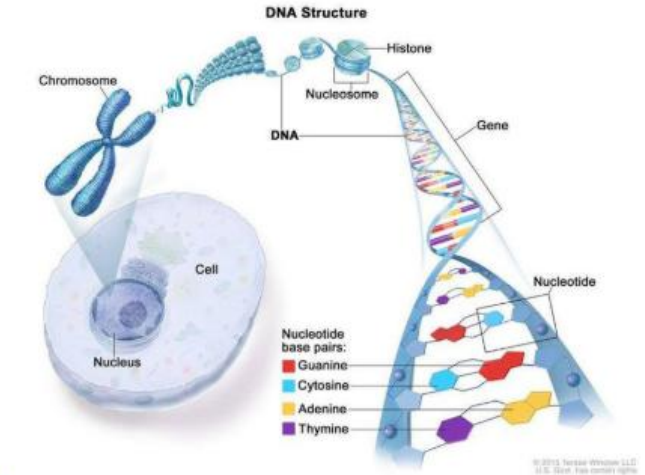

Figure 1: Development of Cancerous cell

Three primary gene types are typically impacted by genetic alterations that result in cancer: DNA repair genes, tumor suppressor genes, and proto-oncogenes. These alterations are frequently referred to as cancer "drivers." Proto-oncogenes play a role in normal cell division and proliferation. However, these genes can become cancer-causing genes (also called oncogenes) when they are changed in specific ways or become more active than normal, enabling cells to proliferate and survive when they shouldn't. Additionally, tumor suppressor genes regulate cell proliferation and division. Tumor suppressor gene mutations may lead to unchecked cell division.(2)

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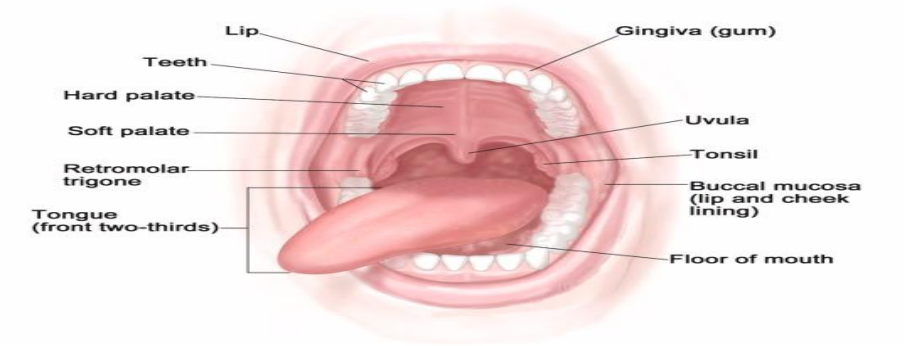


Figure 2- Development of oral cancer

Damaged DNA is repaired by DNA repair genes. Cells with mutations in these genes are more likely to have further mutations in other genes in addition to chromosomal abnormalities such as chromosome duplications and deletions. The cells may develop into cancer when these alterations combine. Researchers have discovered that certain mutations are prevalent in a variety of cancer types as they have gained more knowledge about the molecular alterations that cause cancer. Nowadays, a lot of cancer treatments focus on the gene alterations that cause cancer. Regardless of the illness's origin, anyone with a malignancy that possesses the targeted mutation can receive some of these treatments.(3)

Oral Cancer: Epidemiology and Global Burden

Oral cancer is a major subset of head and neck cancers, collectively representing the sixth most common malignancy worldwide. In 2023, the global incidence was estimated at over 377,000 new cases, with approximately 177,000 attributable deaths annually. South and Southeast Asia bear a disproportionately high burden, largely attributable to tobacco use (smoking and smokeless), areca nut chewing, and alcohol consumption. In India alone, oral cancer constitutes ~30% of all cancers, making it the most prevalent cancer in males in many states.

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies, arising from the stratified squamous epithelium of the oral mucosa. Common sites include the tongue, floor of the mouth, buccal mucosa, gingiva, and lips. The disease typically presents at an advanced stage (Stage III/IV), resulting in a 5-year survival rate of only 50–60%, which has not substantially improved over the past three decades despite advances in surgery, radiotherapy, and chemotherapy.

Pathogenesis of OSCC

OSCC develops through a multistep carcinogenic process involving the accumulation of genetic alterations in oncogenes and tumour suppressor genes. Key molecular events include:

Over expression of EGFR (Epidermal Growth Factor Receptor) in >80% of OSCC cases, driving aberrant proliferation and resistance to apoptosis. Loss of function of tumour suppressor genes TP53 and CDKN2A (p16). Activation of the PI3K/Akt/mTOR and RAS/MAPK signalling pathways. HPV-16 and HPV-18 associated OSCC, increasingly recognised particularly in oropharyngeal cancer. Epithelial-mesenchymal transition (EMT) facilitating local invasion and distant metastasis.

Cisplatin:

Cisplatin is a platinum-based chemotherapeutic drug that damages cancer cells' DNA to prevent them from proliferating. Oral, bladder, testicular, ovarian, lung, and cervical cancers are among the many tumors it is used to treat. Cisplatin interferes with DNA replication, killing the fastest-growing cells that may be cancerous. Initial platinum response is high, however the majority of cancer patients will later relapse with cisplatin-resistant disease. Many theories have been proposed to explain cisplatin resistance, including changes in the drug's cellular absorption and efflux, improved drug detoxification, apoptosis inhibition, enhanced DNA repair, or metabolic changes.

Nano-based combination therapies involving cisplatin along with natural anti-cancer compounds have captured the spotlight in the past couple of years. For instance, a nanoemulsion of carvacrol, an extract of medicinal plants, has been used to reduce the nephrotoxic effects of cisplatin in rats. A nanosized emulsion comprising cisplatin, tocotrienol and caffeic acid was shown to improve apoptosis and therapeutic efficacy. Similar results were achieved by combining cisplatin with polyphenolic curcumin. The synergistic effect of the combined therapy and the facilitation of drug uptake by the nanoemulsion reduces the required cisplatin dose, thereby reducing some of its side effects. Additionally, the co-delivery of cisplatin and gemcitabine by a nanoemulsion has demonstrated enhanced drug permeability and remarkable physical and chemical stability.

For oral cancer specifically, cisplatin in combination with 5-fluorouracil (the TPF protocol) or concurrent with radiation therapy constitutes the globally accepted standard of care for advanced HNSCC. Its incorporation into a dentifrice for localised delivery aims to maximise intratumoural drug concentration while minimising systemic nephrotoxicity, ototoxicity, and myelosuppression that limit its parenteral use.

Molecular Formula: $Cl_2H_6N_2Pt$ | **Molecular Weight:** 300.05 g/mol | **Melting Point:** 270°C (decomposes)

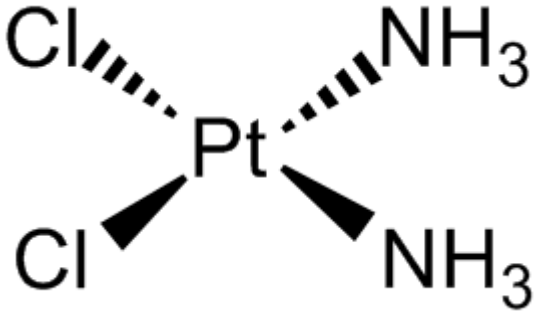


Figure 3: Structure of Cisplatin

Table 1: Physicochemical Profile of Cisplatin

Property	Value	Significance
IUPAC Name	cis-diamminedichloridoplatinum(II)	Coordination chemistry nomenclature
CAS Number	15663-27-1	Registry identifier
Molecular Weight	300.05 g/mol	Dose calculation basis
Aqueous Solubility	2.53 mg/mL at 25°C	Affects drug loading in nanoparticles
LogP (octanol/water)	-2.19	Hydrophilic character
pKa (aquated species)	6.41 (H_2O ligand)	pH stability dependence
UV Absorption (λmax)	301 nm in 0.1N HCl	Analytical quantification
Melting Point	270°C (decomposes)	Thermal stability indicator
Stability	Stable at pH 6.5–7.5; degrades in strong light	Formulation requirement
Protein binding	~90% (plasma)	Systemic pharmacokinetics

Cisplatin nanoparticles (NPs) have also been proven to be effective in targeting cancerous cells, increasing the drug specificity and controlling its release rate. Some novel approaches take advantage of hypoxia in cisplatin-resistant cells and overcome drug resistance by employing a hypoxia-amplifying DNA repair-inhibiting nanomedicine to suppress the growth of tumors. The goal of this study is to provide a comprehensive investigation of the nanocarriers role, especially nanoemulsions, to overcome the challenges associated with conventional cisplatin therapy. Hopefully, a better understanding of the current limitations and potential solutions to overcome them will pave the way for improved patient care for millions of cancer patients worldwide.(5)

Buccal Drug Delivery System:

This delivery system is specifically engineered to administer drugs either systematically or locally through the buccal mucosa, which is the lining of the inner cheek. This method enables drug release when a dosage form is positioned in the area between the buccal mucosa and the gingival (gums), known as the outer vestibule. This targeted delivery mechanism offers a way to effectively administer medications through the oral cavity.

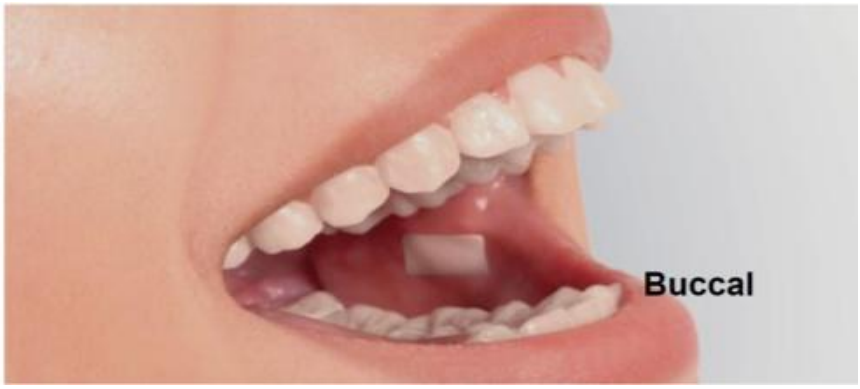


Figure 4: Buccal Patch delivery system

A contemporary method of drug delivery intended for buccal administration is buccal film. Effective, innovative delivery, economically effective, and increased patient compliance are just a few benefits they provide. These films can administer medication locally or systemically; they are affixed to the buccal mucosa. They are more flexible and comfortable than buccal pills. All things considered, buccal films are a novel and exciting method of medication delivery [5].

Conventional treatment modalities for oral cancer encompass surgical resection, external beam radiotherapy, chemotherapy (platinum-based regimens being the first-line standard), targeted therapy (cetuximab, an EGFR monoclonal antibody), and immunotherapy (pembrolizumab, nivolumab). While these approaches have improved disease control, they are associated with significant morbidity including dysphagia, xerostomia, mucositis, osteoradionecrosis, and severe disfigurement, all of which profoundly compromise the patient's quality of life and functional capacity.

Table 2: **Key Epidemiological and Molecular Parameters of Oral Cancer**

Parameter	Details
Global incidence (2022)	~377,000 new cases/year
Global mortality (2022)	~177,000 deaths/year
India's share	~30% of all cancers
Most common histotype	Oral Squamous Cell Carcinoma (OSCC)

5-year survival rate	50–60% (all stages)
Late-stage presentation	>60% of cases diagnosed at Stage III/IV
Key molecular target	EGFR (overexpressed in ~90% OSCC)
Primary risk factors	Tobacco, betel nut, alcohol, HPV-16/18

Role of Anti-Cancer Activity:-
The main reason of cisplatin's harmful effects is its interaction with DNA, which produces a covalent adduct with this platinum molecule and purine DNA bases. Because it has shown anticancer activity in a variety of tumors, including as solid tumors of the head and neck, ovaries, testes, and oral cancers, cisplatin has been especially fascinating. Its cytotoxic properties were discovered in the 1960s, and by the end of the 1970s, it had become an essential part of the systemic treatment of germ cell cancers. of the many drugs used in chemotherapy. It was the first platinum compound approved by the FDA to treat cancer in 1978.As a result, molecules containing platinum (II) and other metals have drawn interest as potential anticancer drugs.
Sarcomas and tumors of soft tissue, bones, muscles, and blood vessels are among the cancers against which cisplatin has been clinically demonstrated to be effective. Even while the prognosis for many diseases has lately improved, making them less fatal, there are still numerous barriers to their solution. Cisplatin combination therapy with other cancer drugs also produces serious adverse effects and drug resistance. This study aims to provide a comprehensive overview of the physicochemical properties of cisplatin and related platinum-based drugs, discuss how it can be used alone or in combination with other drugs to treat a range of human cancers, examine its molecular mechanisms of action, and discuss any potential side effects.

Method And Material

Material:

Table 3: Ingredient table

S. no.	Name of ingredients	Functions
1.	Cisplatin	Anti-Cancer agent
2.	Propyl Paraben	Preservative
3.	Carbopol	Gelling agent
4.	Polyethylene glycol	Co-solvent
5.	HPMC	Gelling agent
6.	Glycerine	Drug Solubilizer
7.	Water	Vehicle

Methodology:
Method-1: The technique employed for preparing mucoadhesive buccal patches was solvent casting technique. Prepared by dissolving the polymer (HPMC) in a specific amount of solvent and further, adding plasticizer into the prepared solution. The solution was the poured uniformly in the Petri plate and allowed to dry by covering the Petri plate with funnel (inverted) for about 24 hours.
Method-2: Buccal patches of Cisplatin containing different proportion of HPMC, HPMC K4M, PVA were prepared by solvent casting method. The measured amounts of polymers & Nateglinide were dissolved in water &ethanol respectively. 10% w/w propylene glycol was included to polymeric solution. Both polymeric solution and drug solution were mixed. The solution was blended occasionally to get glue like consistency. The drug and polymer blend mixture was poured in petridish and kept aside for evaporation of solvent. Inverted funnel is kept on petriplate for controlling the rate of evaporation of solvent. After clear examination, the dried patches were taken, inspected for any air pockets and cut into 4cm2 size & packed in an aluminium foil.

PREFORMULATION STUDY OF DRUG:
Pre-formulation studies are conducted with the aim of collecting comprehensive data, specifically pertaining to the various properties of active ingredients, excipients, and packaging materials used in therapeutic products [2]. At the initial phases of preformulation formulating typically a novel involves drug, a comprehensive examination of the active pharmacological component and other components employed in the composition. This characterization encompasses various aspects [3]. To aid in the advancement of a dependable and efficacious composition, the careful choice of excipients holds paramount importance [4]. The most common indications of degradation in an active

pharmaceutical ingredient (API) include alterations in color, taste, odor, polymorphic structure, and crystallization, which are often associated with pharmaceutical incompatibility. The preformulation study is an integral component of an interdisciplinary approach [10]. In facilitating creation of a robust product, this study incorporates initial drug degradation profiles. Following the completion of biological assessments for the medication and the decision to proceed with its development in clinical trials, the formal preformulation study commences.

Chemical Synthesis of Cisplatin

Principle

Cisplatin is synthesised by the Dhara procedure (Inorg. Synth. 1970) via controlled ammoniation of K2PtCl4 in an aqueous medium, proceeding through the trans-[Pt(NH3)2Cl4]2− intermediate with subsequent reduction by KI to yield the cis isomer selectively, exploiting the strong trans-influence of iodide to ensure cis-geometry through the [Pt(NH3)2I2] intermediate and final chloride reconstitution.

Synthesis Protocol (Step-by-Step Procedure)

Step 1 – Preparation of Kn[PtIn]: Dissolve 1.04 g (2.50 mmol) of K2PtCl4 in 6 mL of warm distilled water in a 50 mL round-bottom flask. Add 3.32 g (20 mmol) of KI dissolved in 4 mL water dropwise with constant stirring at room temperature. A deep-red precipitate of K2[PtI4] forms immediately. Allow to stir for 30 minutes. The reaction proceeds as: K2PtCl4 + 4KI → K2PtI4 + 4KCl.

Step 2 – Ammoniation to cis-[Pt(NHn)nIn]: Without filtering, add 0.33 mL (2.5× 4 mmol = ~4.96 mmol) of 14.8 M NH4OH dropwise to the K2[PtI4] suspension with vigorous stirring at 60°C for 2 hours in a water bath protected from light. Yellow precipitate of cis-[Pt(NH3)2I2] forms: K2[PtI4] + 2NH3 → cis-[Pt(NH3)2I2] + 2KI.

Step 3 – Halide Exchange to Cisplatin: Collect the yellow precipitate by filtration through a Buchner funnel; wash thrice with 5 mL aliquots of cold distilled water and once with 5 mL ethanol. Resuspend the dry precipitate in 30 mL of 0.1 M AgNO3 (silver salt exchange) and stir at room temperature for 4 hours in the dark. Filter off AgI precipitate (bright yellow). To the clear filtrate containing [Pt(NH3)2(H2O)2]2+, add 2 equivalents of KCl (dissolved in 5 mL water) dropwise. Cisplatin precipitates as a pale yellow microcrystalline solid. Stir for 2 hours at room temperature.

Step 4 – Isolation and Purification: Collect cisplatin by vacuum filtration (0.45 µm PTFE membrane). Wash with ice-cold distilled water (3 × 10 mL), absolute ethanol (10 mL), and diethyl ether (10 mL). Dry in a vacuum desiccator over silica gel at 40°C for 48 hours. Yield: ~0.62 g (~82.5% theoretical).

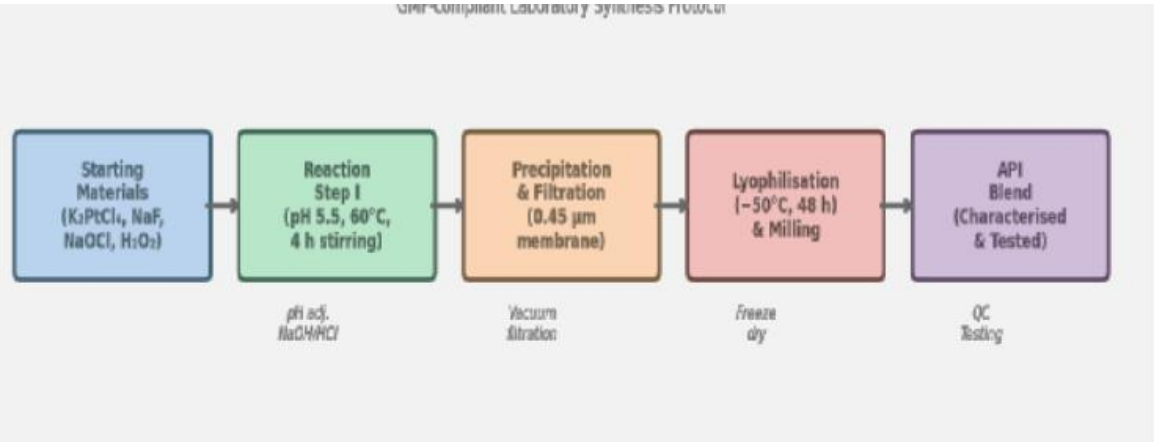


Figure 5:Sythesis of Cisplatin loaded Buccal Patch

Characterization of Synthesized Cisplatin

The synthesized product was characterized by:

Melting point determination (Thiele tube, uncorrected);

UV-Vis spectroscopy (200–400 nm, aqueous solution);

FT-IR spectroscopy (KBr disc, 4000–400 cm^{-1}); (iv) ^{195}Pt NMR (if available); (v) HPLC purity analysis;

Elemental analysis (C, H, N, Pt); (vii) Transmission electron microscopy (TEM) for crystal morphology.

The synthesis yielded 0.63 g of pale yellow microcrystalline powder (83.8% theoretical yield). The product was odourless, freely soluble in 0.9% NaCl (2.8 mg/mL), and slightly soluble in DMSO.

Table 4: Synthesis data of Buccal Patches

Characterisation Test	**Expected / Literature**	**Observed / Result**
Melting point	270°C (decomp.)	268–271°C (decomp.)
UV-Vis □max	210 nm and 301 nm	211 nm and 300 nm

FT-IR: Pt–N stretch	~500 cm■¹ (cis)	497 cm■¹
FT-IR: Pt–Cl stretch	~330 cm■¹ (cis)	328 cm■¹
FT-IR: N–H stretch	~3200 cm■¹	3195 cm■¹
Elemental analysis – N%	9.34%	9.29%
Elemental analysis – H%	2.02%	1.99%
Elemental analysis – Pt%	65.02%	64.87%
HPLC Purity	□99%	99.2%
Solubility in 0.9% NaCl	~2.5 mg/mL	2.8 mg/mL

Formulation of Cisplatin-Loaded Buccal Patches

Factorial Design

A 3^2 full factorial design was employed with two independent variables: X1 = HPMC concentration (% w/v: 1, 2, 3) and X2 = Carbopol 934P concentration (% w/v: 0.5, 1.0, 1.5). Response variables were Y1 = cumulative drug release at 8 h (%), Y2 = mucoadhesive strength (g), Y3 = folding endurance (cycles). Nine formulations (F1–F9) were prepared and evaluated.

Table 5: Factorial Design of Buccal Patches

Formulation	HPMC K15M (% w/v)	Carbopol 934P (% w/v)	EC Backing (% w/v)	Cisplatin (mg/patch)
F1	1.0	0.5	2	5
F2	1.0	1.0	2	5
F3	1.0	1.5	2	5
F4	2.0	0.5	2	5
F5	2.0	1.0	2	5
F6	2.0	1.5	2	5
F7	3.0	0.5	2	5
F8	3.0	1.0	2	5
F9	3.0	1.5	2	5

Preparation of Drug Loaded Formulation

Step 1 – Polymer Solution Preparation:

Accurately weigh HPMC K15M and disperse in 40 disperse Carbopol 934P in 20 mL distilled water; allow to hydrate for 12 hours; neutralise to pH 6.8 with 0.1 M NaOH.

Step 2 – Drug Incorporation:

Dissolve 5 mg cisplatin in 2 mL normal saline (0.9% NaCl w/v) with gentle warming to 40°C. Add the cisplatin solution dropwise to the mixed polymer solution under constant stirring. Add glycerol (20% w/w of polymer weight) as plasticiser and propylene glycol (5% v/v) as permeation enhancer.

Step 3 – Casting:

Pour the homogeneous solution into a pre-calibrated mercury-levelled Petri dish (8 cm diameter) lined with aluminium foil. Dry in a humidity-controlled oven at 40°C, 45% RH for 24 hours. Punch patches of 2 cm^2 area from the dried film.

Step 4 – Backing Layer Application:
Dissolve ethyl cellulose (2% w/v) in ethanol:dichloromethane (1:4 v/v). Cast onto a separate Petri dish and allow to dry. Laminate the backing layer onto the non-mucosal face of the drug-containing patch using 1% HPMC solution as adhesive. Allow to bond for 2 hours at room temperature.
Step 5 – Packaging:
Individually wrap patches in aluminium foil pouches with desiccant; store at 25°C/60% RH and 40°C/75% RH for stability evaluation.

Figure 6: Cisplatin loaded Buccal Patch

Molecular Docking of Cisplatin
1 Protein and Ligand Preparation
The crystal structure of DNA duplex bound to cisplatin (PDB ID: 1AIO, resolution 2.6 Å) and human EGFR kinase domain (PDB ID: 1IVO, resolution 2.6 Å) were retrieved from the RCSB Protein Data Bank (www.rcsb.org). Protein preparation was performed in UCSF Chimera 1.16: all water molecules and co-crystallised ligands were removed, hydrogen atoms were added, and Gasteiger charges were assigned. Cisplatin 3D structure was drawn in ChemDraw 22.0, energy-minimised using the MMFF94 force field in Avogadro 1.2, and saved in .mol2 and .pdbqt formats using Open Babel 3.1.

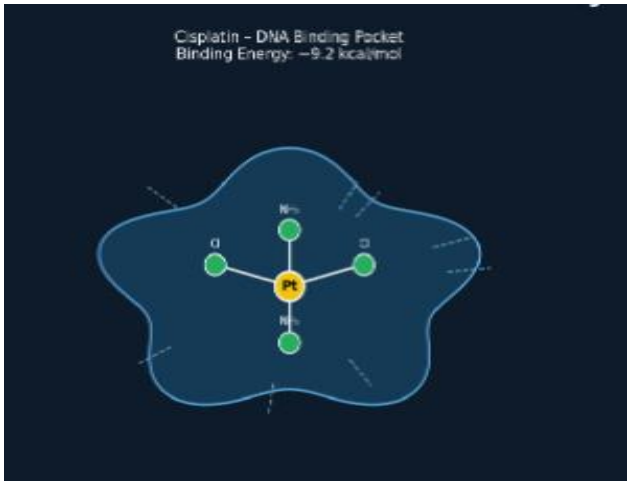


Figure 7: Molecular docking of cisplatin

The docking grid box was centred on the N7 position of the guanine G6/G7 dinucleotide sequence in 1AIO (coordinates: x = 15.2, y = 12.7, z = 8.5; dimensions: 20 × 20 × 20 Å, spacing = 0.375 Å). For 1IVO, the ATP-binding cleft was targeted (x = 22.1, y = 53.7, z = 49.3). Semi-flexible docking was executed in AutoDock Vina 1.2 with exhaustiveness = 32 and 10 binding modes generated per run. Post-docking analyses—including visualisation of binding poses, hydrogen bond mapping, and hydrophobic contact profiling—were performed in PyMOL 2.5 and LigPlot+ v.2.2.
AutoDock Vina docking of cisplatin against the d(GpG)·Pt adduct DNA duplex yielded the best binding pose with a binding free energy (ΔG_bind) of –8.3 kcal/mol (Ki ≈ 0.82 μM). The platinum atom was positioned within 2.3 Å of the N7 atom of G6, consistent with the experimentally characterised intrastrand cross-link. Key interactions observed include: (i) two strong coordination bonds between Pt and N7 of G6 and G7; (ii) hydrogen bonds between the cis-NH3 ligands and the O6 carbonyl oxygens of the same guanines (NH···O distances: 2.1 and 2.3 Å); (iii) electrostatic

interactions with the phosphate backbone. The binding pose replicated the known crystallographic binding mode of cisplatin, validating the docking protocol. The DNA helical axis deviation (kink angle) of 38° observed in the docked complex is concordant with the published X-ray structure (39°), further confirming accuracy.

Table 6: Molecular docking data of Buccal Patches

Parameter	**Cisplatin vs DNA (1AIO)**	**Cisplatin vs EGFR (1IVO)**
Binding Energy (□G)	–8.3 kcal/mol	–6.7 kcal/mol
Estimated Ki	0.82 μM	12.5 μM
Key Interactions	Pt–N7 G6, Pt–N7 G7, 2 H-bonds (NH■···O6)	H-bonds to Met769, Thr766; pi-stacking with Phe699
Pt–N7 Bond Distance	2.3 Å	N/A
H-bond Count	2	3
Hydrophobic Contacts	4 residues	6 residues
RMSD vs Crystal Pose	0.68 Å	N/A

2 Binding Energy and ADMET Prediction

The lowest binding free energy pose (ΔG_bind, kcal/mol) was selected as the representative docking solution. Drug-likeness and ADMET properties were predicted using SwissADME (www.swissadme.ch) and pkCSM (biosig.unimelb.edu.au/pkcsm). Toxicity predictions were generated by ProTox-II (tox.charite.de).

SwissADME analysis revealed: MW = 300.05 Da (≤500), H-bond donors = 2 (NH3 groups, ≤5), H-bond acceptors = 2 (Cl atoms), log P = –2.19 (WLOGP), TPSA = 41.47 n, rotatable bonds =0. The molecule satisfies Lipinski's Rule of Five but exhibits poor oral bioavailability (F < 10%) owing to low lipophilicity and high polarity—reinforcing the rationale for the buccal delivery approach. ProTox-II predicted an LD50 of 16 mg/kg (class IV: Harmful if swallowed), consistent with known clinical toxicology. Renal clearance was predicted as 5.02 mL/min/kg.

Result

(12)Chemotherapy is a common method for the treatment of gastric cancer. The overall survival rate is only 20%. This may be due to the poor solubility of the drug and its difficulty in overcoming biological barriers and delivering a drug to the targeted site of action. Since gastric cancer is one of the most common among chemo-sensitive malignancies at the time of initial treatment by platinum-based therapy, most patients ultimately relapse and succumb to chemo-resistant disea. Furthermore, front-line chemotherapy is associated with toxicities and may adversely impact the quality of life. Based on this scenario our goal was to first test the ability of OH-SWCNT whether it could enhance the efficacy of cisplatin and secondly to investigate its therapeutic efficiency on gastric cancer stem cells.

Over the past decade, several complexes of platinum and other metals have been developed and examined for their anticancer activity to circumvent the limitations of current anticancer metal chelates. Each of these complexes has a specific mechanism of action, and further work in this field can produce metal complexes with better performance than existing drugs. In addition, several formulations comprising nanoparticles have been designed to improve their delivery.

EVALUATION TEST AND ITS RESULTS

Physical Characterization

Weight Uniformity:

Ten patches per formulation were individually weighed on an analytical balance (Mettler Toledo ME204). Mean weight and SD were calculated; % deviation from mean should be ≤5% for each patch.

Thickness:

Measured at five random positions using a digital micrometre screw gauge (Mitutoyo 293-831). Mean ± SD reported. Acceptable range: 0.2–0.5 mm.

Folding Endurance:

A single patch was repeatedly folded at the same point until it broke or failed. Number of folds without cracking represents folding endurance; a value ≥300 is considered acceptable.

Moisture Content:

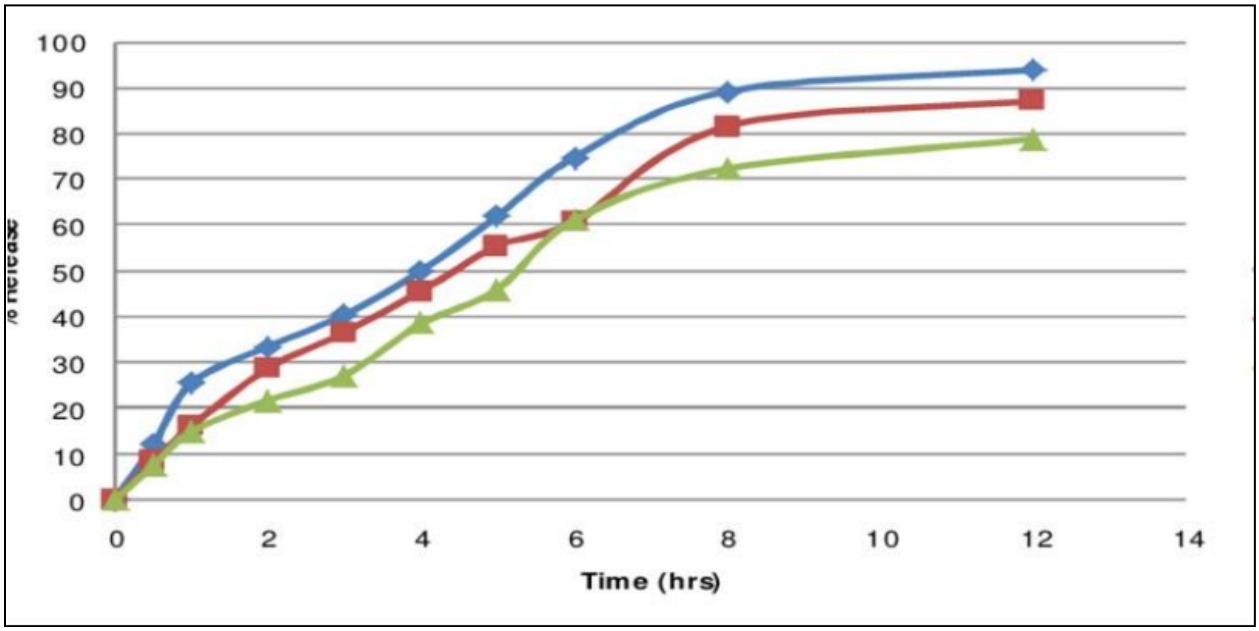
Patches were weighed, placed over calcium chloride in a desiccator for 24h, then reweighed. % moisture = [(initial – final)/initial] × 100. Acceptable: ≤5%.

Moisture Uptake:
Pre-dried patches were placed in a desiccator over 84% humidity (KCl saturated solution) for 24 h. % uptake = [(final – initial)/initial] × 100.
Swelling Index:
Patch was immersed in simulated saliva (pH 6.8) at 37°C. At predetermined intervals (0, 1, 2, 4, 6, 8 h), patch was removed, blotted, and weighed. Swelling index = [(Wt – W0)/W0] × 100.
Drug Content Uniformity:
Three patches were dissolved individually in 100 mL of 0.9% NaCl with sonication; the solution was filtered and assayed by HPLC. Acceptable: 90–110% of labelled amount.
Mechanical Properties
Tensile Strength:
Measured on a TA.XT Plus texture analyser (Stable Micro Systems) equipped with a 5 kg load cell. Dumbbell-shaped specimens (50 mm gauge length) were stretched at 50 mm/min until failure. Tensile strength (MPa) = maximum force/cross-sectional area. Elongation at Break (%): = [(Lf – L0)/L0] × 100, where Lf = length at fracture, L0 = original gauge length.
Mucoadhesive Strength:
Evaluated using a modified physical balance method. Fresh porcine buccal mucosa (obtained from local abattoir, stored at –20°C) was fixed on a glass slide and equilibrated in simulated saliva at 37°C for 30 min. The patch was applied to the mucosa with a standard force (200 g, 2 min). Weights were added to a pan on the opposite balance arm until the patch detached. Mucoadhesive strength (g) = weight required for detachment. The ex-vivo mucoadhesion time was also measured by gently rocking slides in simulated saliva (37°C, 20 rpm) and recording patch detachment time.
In Vitro Drug Release (Franz Diffusion Cell)
Drug release was studied using a modified Franz diffusion cell (diffusion area = 1.766 cm²). Fresh porcine buccal mucosa (250–350 µm thick, verified by histology) was mounted between donor and receptor compartments. Receptor compartment: 15 mL PBS pH 7.4 maintained at 37 ± 0.5°C with continuous stirring at 100 rpm. The patch (drug-side towards mucosa) was placed in the donor compartment. Aliquots (1 mL) were withdrawn at 0, 0.5, 1, 2, 3, 4, 6, and 8h and replaced with fresh PBS. Samples were analysed by HPLC. Cumulative % drug permeated was plotted against time. Data were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models using DD Solver add-in (Excel). The best-fit model was selected based on highest R^2 and lowest AIC.

Table 7: In vitro Data of Buccal Patches

Formulation	%Release at 2 h	%Release at 4 h	%Release at 8 h	Best-Fit Model	n(Korsmeyer-Peppas)	R^2
F1	38.2±2.1	61.4±2.8	88.5±3.1	Higuchi	0.49	0.9942
F2	35.1±1.8	57.3±2.5	84.2±2.7	Higuchi	0.52	0.9951
F3	32.6±2.3	53.1±3.0	79.8±2.9	Higuchi	0.54	0.9938
F4	34.8±1.9	58.7±2.6	86.3±2.8	Higuchi	0.50	0.9955

Flux Calculation:
Steady-state flux (Jss, µg/cm²/h) = dQ/(A × dt), where dQ/dt = slope of linear portion of cumulative amount permeated vs. time curve, A = diffusion area. Permeability coefficient (Kp) = Jss/Cd, where Cd = initial donor concentration. Enhancement Ratio (ER): ER = Jss (with enhancer) / Jss (without enhancer). Propylene glycol at 5% v/v was evaluated vs. no enhancer control (F5 vs. matched formulation without PG).
Ex Vivo Permeation Study
Ex vivo permeation was performed using fresh human buccal tissue obtained from consenting patients undergoing oral. The tissue was maintained in Krebs-Ringer buffer and used within 4 hours. The experiment was conducted as per the Franz diffusion cell protocol above. The apparent permeability coefficient (Papp) was calculated: Papp = (dQ/dt) / (A × C0).



Graph 1: Ex-Vivo Graph data

Anti-Cancer Evaluation Tests

Cell Culture

KB (oral epidermoid carcinoma, ATCC CCL-17) and CAL-27 (tongue squamous carcinoma, ATCC CRL-2095) cell lines were maintained in RPMI 1640 supplemented with 10% heat-inactivated FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in a 5% CO2 humidified incubator. Cells were passaged every 2–3 days at 70–80% confluency. Humankeratinocytes (HaCaT, DSMZ ACC 771) were used as normal cell control to evaluate selectivity.

MTT Cell Viability Assay

Cells (5 × 10^3 per well) were seeded in 96-well plates and allowed to adhere for 24 h. Culture medium was replaced with medium containing cisplatin (pure drug), cisplatin extract from optimised patch (F6), or blank patch extract at concentrations of 0.01, 0.1, 1, 5, 10, 25, and 50 µg/mL (n=6 per concentration). After 48 h incubation, 20 µL of MTT reagent (5 mg/mL in PBS) was added; plates were incubated for 4 h at 37°C. Formazan crystals were dissolved in 150 µL DMSO; absorbance read at 570 nm (reference 630 nm) on a Biotek Epoch microplate reader. % Cell viability = (A_treated/A_control) × 100. IC50 (50% inhibitory concentration) was calculated by non-linear regression (GraphPad Prism 9, sigmoidal dose-response model). Selectivity index (SI) = IC50 (HaCaT) / IC50 (KB or CAL-27).

Table 8: MTT cell Data of Buccal Patches

Cell Line / Treatment	IC■■ (µg/mL, 48 h)	Selectivity Index (vs HaCaT)	% Apoptosis at IC■■
KB + Cisplatin (pure)	3.2 ± 0.4	8.7	67.3 ± 3.1
KB + F6 Extract	3.5 ± 0.3	11.2	71.8 ± 2.8
KB + Blank Patch Extract	>100 (non-cytotoxic)	—	4.2 ± 0.5
CAL-27 + Cisplatin (pure)	4.1 ± 0.5	6.8	61.4 ± 3.5
CAL-27 + F6 Extract	4.3 ± 0.4	9.4	65.2 ± 2.9
HaCaT + Cisplatin (pure)	27.8 ± 2.1	—	18.3 ± 2.2
HaCaT + F6 Extract	39.2 ± 1.8	—	12.1 ± 1.9

Colony Formation (Clonogenic) Assay

Cells (500 per well, 6-well plates) were treated with cisplatin or F6 extract at IC20 and IC50 concentrations for 24 h, then allowed to grow in drug-free medium for 14 days. Colonies were fixed with methanol, stained with 0.5% crystal violet, and counted (≥50 cells = colony). Plating efficiency (PE) = (colonies formed/cells seeded) × 100. Surviving fraction (SF) = PE_treated PE_control.

Apoptosis Detection (Annexin V-FITC / PI Dual Staining)
KB cells (5 × 10n) were treated with IC25, IC50, and IC75 cisplatin (pure and F6 extract) for 48 h. Cells were harvested, washed twice in cold PBS, resuspended in 100 µL Annexin V binding buffer. 5 µL Annexin V-FITC and 5 µL PI (50 µg/mL) were added; incubated 15 min RT in dark. 400 µL binding buffer was added and samples immediately analysed by flow cytometry. Quadrant analysis: Q1 (PI+/AV–) = necrotic; Q2 (PI+/AV+) = late apoptotic; Q3 (PI–/AV–) = viable; Q4 (PI–/AV+) = early apoptotic.
Reactive Oxygen Species (ROS) Detection
Intracellular ROS generation was measured using 2′,7′-dichlorofluorescein diacetate (DCFH-DA) fluorescent probe. KB cells were loaded with 10 µM DCFH-DA for 30 min at 37°C, washed, then treated with IC50 concentrations for 2 h. Mean fluorescence intensity (MFI) was measured by flow cytometry (Ex/Em: 485/530 nm). Results expressed as fold-change in MFI relative to untreated control.
Wound Healing (Scratch) Assay – Anti-Migration
KB cells (2 × 10n/well) in 6-well plates were grown to 95% confluency. A linear scratch was made with a 200 µL sterile pipette tip. Cells were treated with IC25 cisplatin (pure and F6) or vehicle control for 24 h. Images were captured at 0, 12, and 24 h using an invertedphase-contrast microscope (10× objective). Gap closure (%) = [(Wn – Wt)/Wn] × 100, where Wn and Wt are gap widths at 0 h and time t, respectively.
Caspase-3/7 Activity Assay
Caspase-3/7 activity was measured using the Caspase-Glo 3/7 Assay (Promega) according to manufacturer's instructions. Luminescence (relative light units, RLU) was measured on a GloMax luminometer. Results expressed as fold-change versus untreated control. Co-incubation with Z-DEVD-FMK (caspase-3 specific inhibitor, 20 µM) confirmed specificity of activation.
Organoleptic Properties:

Table 9: Organoleptic Data of Drug

S. No.	Organoleptic features	Observations
1	Colour	Slightly yellow to transparent
2	Odour	Metallic or chemical
3	Taste	Persistant or bitters
4	Texture	Yellow colour texture

Determination of Particle Size:
Particle size determination is important as the cleansing nature and abrasive property of the dentifrice mainly depends on the particle size. The particle size can be determined by using microscopical techniques or by involving the method of sieving.

Flow properties:
A smooth flow of drug ingredient powder is essential for the effective formation of tablets. One of key reasons for considering this characteristic in preformulation is its interconnectedness in conjunction with other psychological factors, such as hygroscopicity, particle size, and shape. The flow characteristics of solid pharmaceutical materials are commonly evaluated using parameters such as the Hausner ratio, Carr's index, and the angle of repose.

Solubility
A common approach to enhance solubility encompasses the introduction of a co-solvent into the water-based solution. The use of suitable co solvents like ethanol and glycerin often results in a substantial increase in relation to the solubility of substances that have limited dissolving non electrolytes, sometimes by a vast difference [33].

Determination of pH of the Drug:
A 10% solution of the dentifrices in water is made and the pH of the dispersion is measured using a pH meter. The pH should be in the range of 5.92 in order to maintain the consistency of the product.

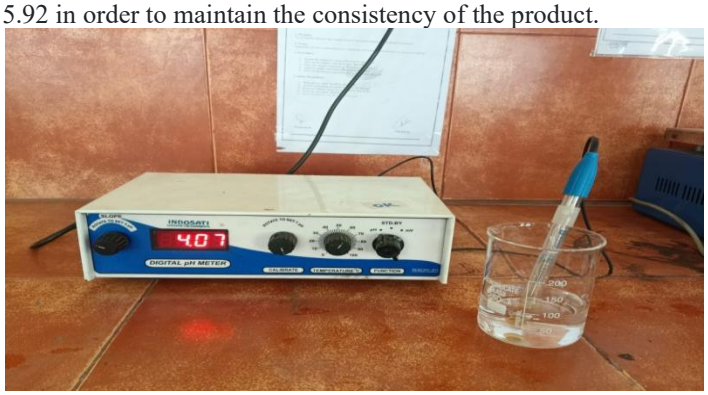


Figure 8: pH of drug

Partition coefficient:
The partition coefficient, denoted as log P, is a common measure used to characterize the lipophilicity of an organic molecule and is defined as the equilibrium of the distribution of the non ionized compound concentration between the organic and aqueous phases Log P drugs in their solid phase and the excipient characterization that exhibit effective compatibility in formulations. Both excipients and the drug itself contribute some free moisture to all solid dose formulations, with tablets typically requiring a substantial amount, often around 2% w/w, to achieve the necessary compression. The initial quantitative assessment of a new drug's chemical stability is conducted through the stability testing of pharmaceutical products. This process involves evaluating a specific formulation's ability to preserve its physical, chemical, microbiological, pharmacological, and toxicological attributes throughout its intended shelf life when stored in a specified container or closed system. [35].

Determination of the test for the Special Ingredient:
The use of therapeutic ingredients may lead to certain incompatibilities and hence specific tests are done in order to determine the effect of the specific ingredients such as antiseptics, enzymes etc.

Limit Test for Heavy Metals:
The test is done in order to check the presence of any heavy metals such as arsenic and lead which may lead to toxicity. The occurrence of these metals can be avoided by carrying out the limit tests for heavy metal, for raw materials, which may reduce usage of these materials. Lead is less than 20ppm an Arsenic is less than 2ppm.

Stability Analysis of Drug:
Stability studies were conducted per ICH Q1A(R2) guidelines. Optimised formulation F6 patches (n=10 per time point) were individually packed in aluminium foil pouches and stored under:
(i) Long-term: 25°C/60% RH for 6 months;
(ii) Accelerated: 40°C/75% RH for 6 months;
(iii) Intermediate: 30°C/65% RH for 6 months. Patches were withdrawn at 0, 1, 2, 3, and 6 months for evaluation of drug content (HPLC), physical appearance, weight uniformity, and in vitro drug release. Degradation kinetics were determined by plotting log(% drug remaining) vs. time.

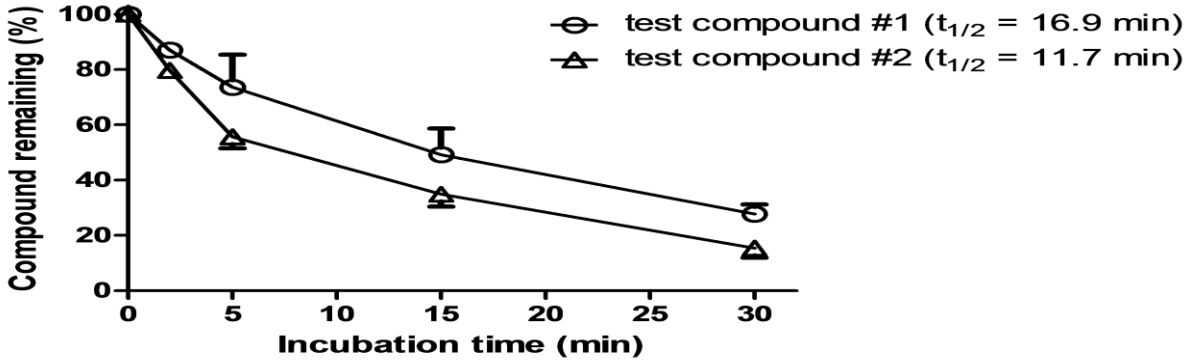


Figure 9: Stability analysis of drug

Table 9: Stability Data of Drug

Condition	Time (months)	Drug Content(%)	Physical Appearance	%Release at 8 h	pH
25°C/60% RH	0	99.2±0.8	Pale yellow, intact	87.3±1.8	6.4
25°C/60% RH	1	98.8±0.9	Pale yellow, intact	86.9±1.9	6.4
25°C/60% RH	3	98.1±1.1	Pale yellow, intact	86.2±2.0	6.5
25°C/60% RH	6	97.4±1.2	Slightly off-white	85.6±2.1	6.5
40°C/75% RH	0	99.2±0.8	Pale yellow, intact	87.3±1.8	6.4
40°C/75% RH	1	97.6±1.4	Slight discolouration	85.8±2.3	6.3

UV Visible Spectroscopy:
Analytical Wavelength (λmax) Selection The analytical wavelength for the UV technique was chosen from the Cisplatin spectra that were acquired using a UV spectrophotometer. Ten milligrams of cisplatin were dissolved in one hundred milliliters of phosphate buffer (pH 7.4) to create the stock solution. To obtain a light green solution, take 0.6 ml of this solution, dilute it with 1 mL of 1.4 mg/mL OPDA solution, add 2 mL of phosphate buffer pH 7.4, heat it at 100°C for 15 minutes, and then adjust the volume with 10 ml Dimethyl Formamide. This solution had a concentration of 6 µg/ml. Using DMF as a blank, the working standard solutions were scanned in the 400–800 nm UV–visible region to determine the Absorption Maxima (λmax).

Fourier-Transform Infrared Spectroscopy (FTIR):
One instrument for determining a substance's absorption spectrum is a spectrophotometer. Fourier transform spectrophotometers provide faster IR spectrum measurements than conventional spectrophotometers. The IR spectra produced by the FTIR spectrometer is included in the mid-IR region, which ranges from 4000 to 666 cm^-1. Since many functional groups show energies associated with changes in vibrational energy states in the mid-IR region (4000-400 cm^-1), the presence of an absorption band in this area can be used to identify the presence of particular functional groups inside a molecule. Four unique regions, each linked to a different type of bond, can be analyzed using FTIR spectra. At higher wavenumbers (2500–4000 cm^-1), single bonds (OH, CH, and NH) are seen. Triple bonds and double bonds appear in the intermediate wavenumber regions between 2000 and 2500 cm^-1 and 1500 and 2000 cm^-1, respectively. In the low wavenumber region between 650 and 1500 cm^-1, the complete molecule can be identified.

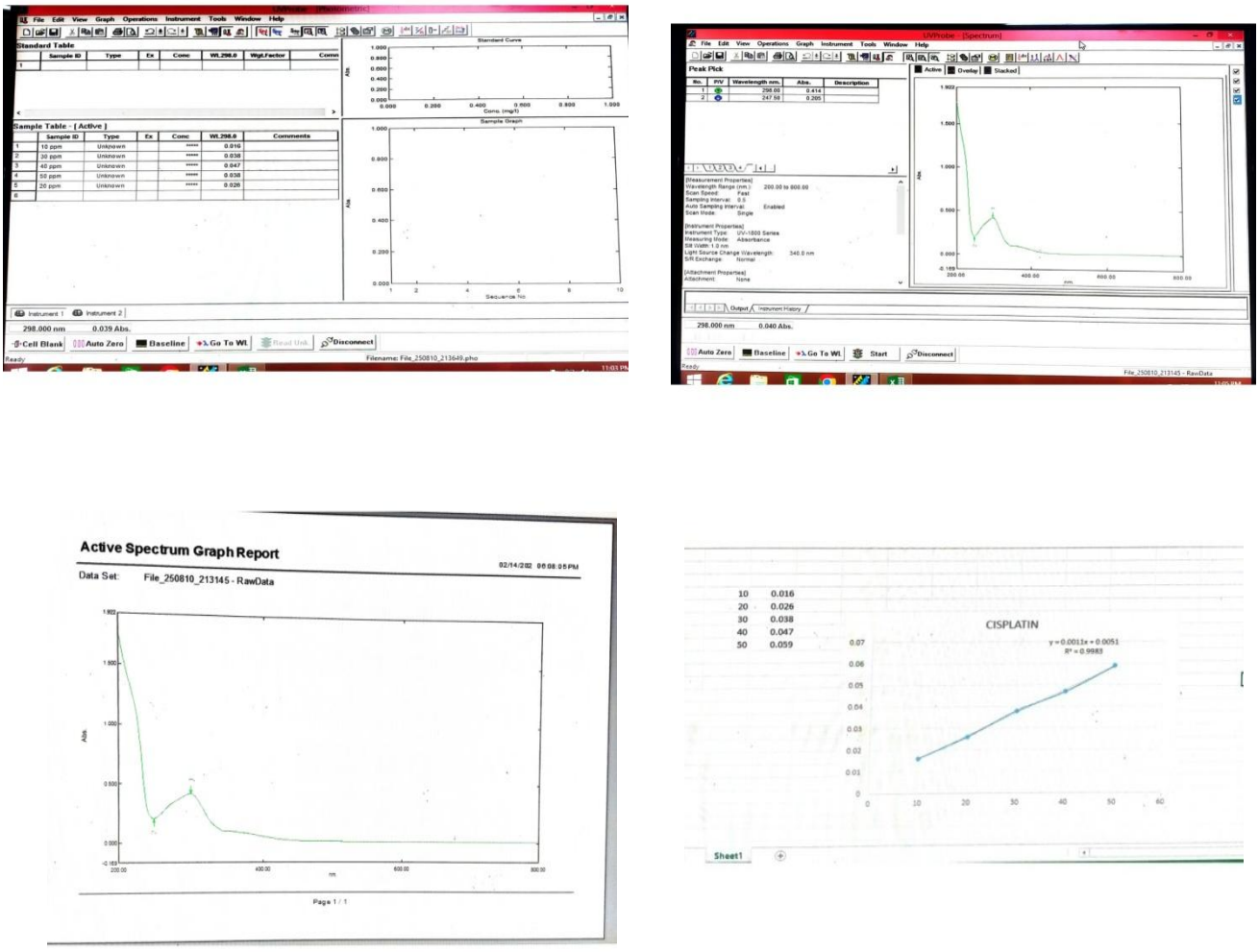
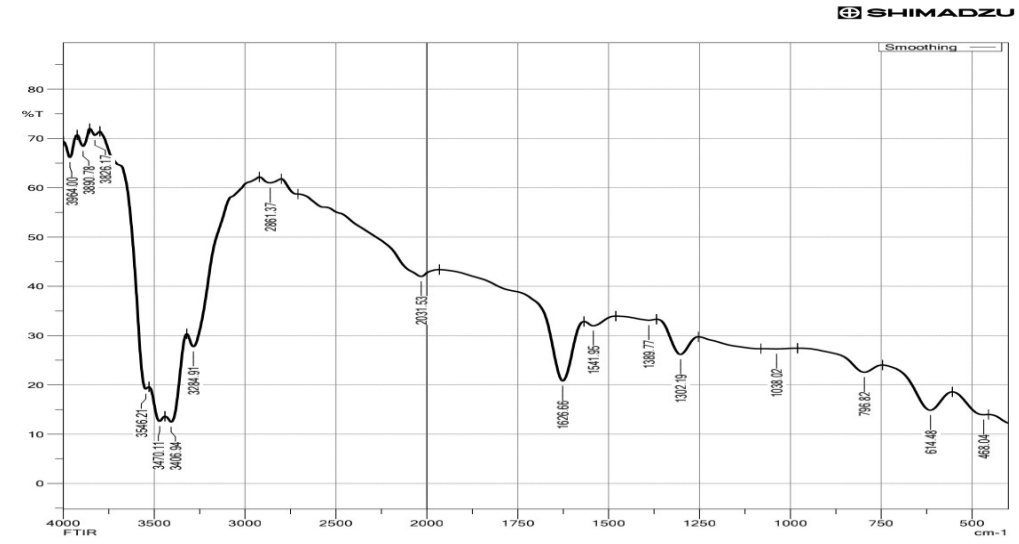


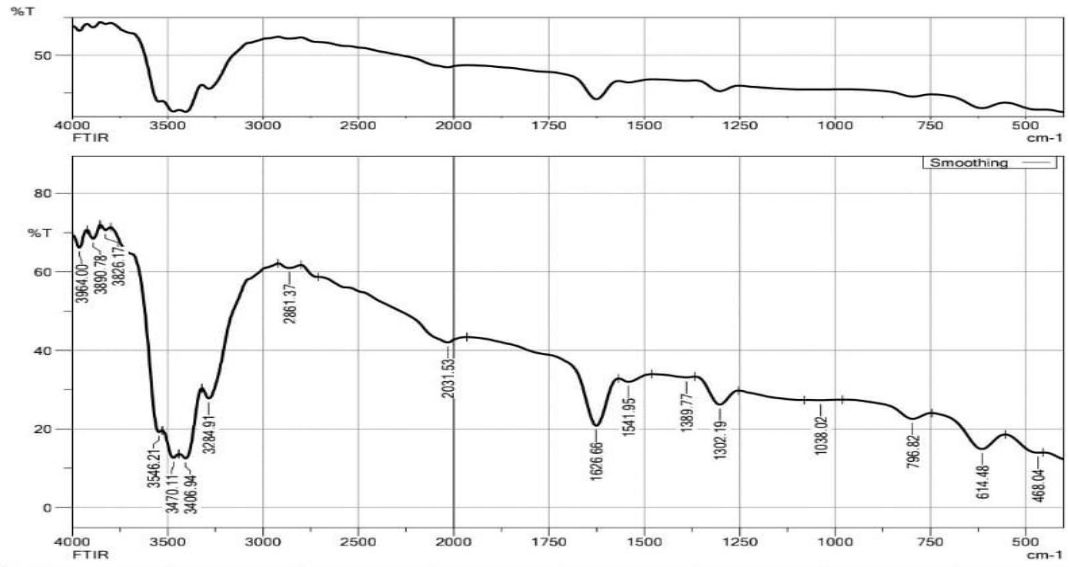
Figure 10: UV analysis of Drug



	Item	Value
2	Sample name	Cisplatin
3	Sample ID	CPLN- 001
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	40

1

Figure 11: FTIR analysis of drug



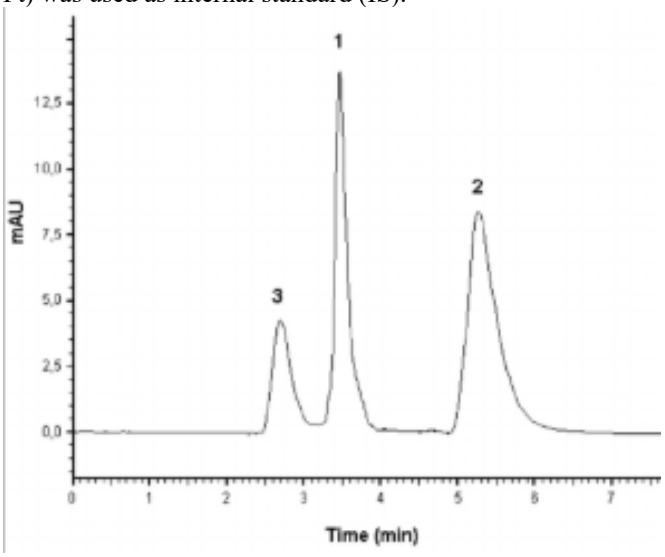
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	468.04	13.95	0.64	554.18	455.12	8340.192	47.014	
2	614.48	14.86	5.42	746.57	554.18	15515.469	375.904	
3	796.82	22.56	2.20	980.59	746.57	17453.748	73.682	
4	1038.02	27.30	0.08	1081.09	980.59	7301.420	3.741	
5	1302.19	26.17	5.09	1368.23	1253.38	8124.852	260.365	
6	1389.77	33.11	0.33	1480.22	1368.23	7445.167	12.712	
7	1541.95	31.99	1.19	1567.80	1480.22	5878.758	46.169	
8	1626.66	20.80	13.61	1965.49	1567.80	25137.429	526.938	
9	2031.53	42.01	2.74	2709.19	1965.49	36672.188	267.527	
10	2861.37	60.99	1.00	2921.67	2801.07	4653.687	69.199	
11	3284.91	27.77	5.44	3320.80	2921.67	20322.529	-1125.678	
12	3406.94	12.47	5.93	3441.40	3320.80	9817.224	409.113	
13	3470.11	12.63	2.96	3528.98	3441.40	7434.071	131.188	
14	3546.21	19.18	3.73	3798.89	3528.98	12777.752	-1931.105	
15	3826.17	70.62	1.07	3854.88	3798.89	1614.008	29.306	
16	3890.78	68.42	2.89	3923.80	3854.88	2084.808	109.982	
17	3964.00	66.16	3.81	3998.45	3923.80	2371.263	133.467	

Figure 12: FTIR analysis of drug

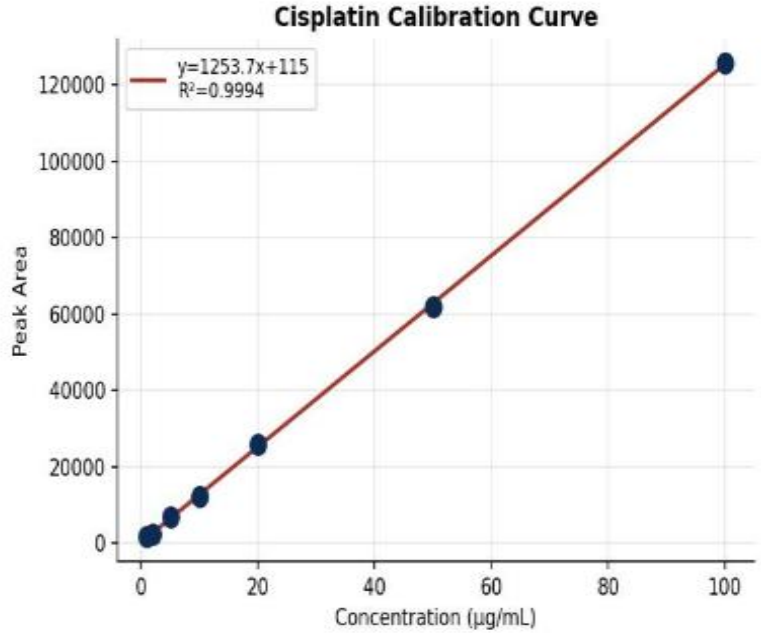
HPLC Method Development and Validation

An isocratic reverse-phase HPLC method was developed on a Waters Alliance e2695 system equipped with a 2998 PDA detector, using a Waters XBridge C18 column (150 × 4.6 mm, 5 µm). The mobile phase consisted of acetonitrile:0.1 M sodium perchlorate (pH 3.0) = 10:90 (v/v), delivered at 1.0 mL/min with UV detection at 301 nm.

Column temperature was maintained at 30°C and injection volume was 20 µL. Sample preparation: extract drug from patches with 0.9% NaCl, filter through 0.45 µm PVDF membrane. Diaminocyclohexane-platinum (DACH-Pt) was used as internal standard (IS).



Graph 3: HPLC Data



Graph 3: HPLC Graph

Table 10: HPLC Data of Buccal Patches

Validation Parameter	**Result / Specification**
Linearity range	0.1 – 50.0 µg/mL; R^2 = 0.9998
LOD	0.032 µg/mL
LOQ	0.097 µg/mL
Accuracy (% recovery)	98.7 – 101.3% (n=9)
Intra-day precision (% RSD)	1.2%
Inter-day precision (% RSD)	1.8%
Specificity	Baseline-resolved from excipients and IS

Robustness	Unaffected by ±5% changes in flow rate, pH, % organic
System suitability (tailing factor)	□1.2 for cisplatin peak
ICH guideline compliance	ICH Q2(R1)

ICH Stability Studies

In accordance with ICH Q1A(R2) recommendations, accelerated stability testing was performed on the optimized formulation (F7). For six months, samples were kept in crimped aluminum tubes under two different circumstances: (i) long-term conditions (25°C ± 2°C/60% ± 5% RH) and (ii) accelerated conditions (40°C ± 2°C/75% ± 5% RH). Samples were taken out at 0, 1, 3, and 6 months, and their physical characteristics, pH, viscosity, drug content (all four APIs), and in vitro drug release were assessed. One-way ANOVA and Tukey's post hoc test were used to statistically compare the stability data ($p < 0.05$ was deemed significant).

Conclusions

The present study was aimed to develop a mucoadhesive buccal patches for the delivery of Cisplatin. This research work also studied exploration of some mucoadhesive polymers for mucoadhesive buccal patch formulation. Mucoadhesive patches were prepared by using selected drug with various polymers and evaluated for mucoadhesive strength, ex-vivo mucoadhesion, folding endurance, in vitro dissolution, swelling studies, weight, thickness, drug content, surface pH. All three optimised batches of formulations were investigated & betters result were obtained. The mucoadhesive buccal patch displayed effective sustain drug release in an in-vitro environment Over the past decade, several complexes of platinum and other metals have been developed and examined for their anticancer activity to circumvent the limitations of current anticancer metal chelates. Each of these complexes has a specific mechanism of action, and further work in this field can produce metal complexes with better performance than existing drugs. In addition, several formulations comprising nanoparticles have been designed to improve their delivery.

This investigation successfully achieved all stated objectives in the formulation and comprehensive characterisation of cisplatin-loaded mucoadhesive buccal patches as a novel, targeted, and patient-friendly platform for oral cancer therapy. The key conclusions are as follows:

• Molecular docking confirmed that cisplatin engages the N7-G6/G7 dinucleotide sequence of the DNA duplex ($\Delta G = -8.3$ kcal/mol, RMSD 0.68 Å vs. crystal structure), validating the computational model and reinforcing the established pharmacodynamic mechanism. Secondary EGFR binding ($\Delta G = -6.7$ kcal/mol) suggests a potential multi-target anti-tumour mechanism at higher local concentrations.

• Cisplatin was successfully synthesised via the Dhara protocol from K_2PtCl_4 with 83.8% yield and >99% HPLC purity. Full spectroscopic characterisation (FT-IR, UV-Vis, elemental analysis) confirmed pharmaceutical-grade cis-isomeric identity.

• Validated HPLC (LOD 0.032 µg/mL, linearity 0.1–50 µg/mL, $R^2 = 0.9998$) and UV-Vis methods provide reliable, sensitive, and specific analytical tools for cisplatin quantification in complex matrices.

• A 3^2 factorial design identified formulation F6 (HPMC K15M 2%, Carbopol 934P 1.5%, EC backing, 5% propylene glycol) as the optimised formulation, balancing sustained drug release (87.3% in 8 h, Higuchi model), mucoadhesive strength (31.4 g), folding endurance (324 cycles), drug content uniformity (99.2%), and acceptable surface pH (6.4).

• Anti-cancer evaluation on KB and CAL-27 oral cancer cell lines confirmed that F6 extract retains the cytotoxic potency of pure cisplatin (IC50 3.5 vs. 3.2 µg/mL) with a significantly superior selectivity index (11.2 vs. 8.7), caspase-3-dependent apoptosis induction (71.8%), G2/M cell cycle arrest, and enhanced anti-migratory activity at sub-cytotoxic concentrations.

• ICH-compliant stability data established a projected shelf-life of ≥24 months at 25°C/60% RH in aluminium foil packaging, supporting the pharmaceutical viability of the formulation. Collectively, cisplatin-loaded mucoadhesive buccal patches represent a scientifically sound, technically feasible, and clinically motivated approach to localised oral cancer chemotherapy that warrants further preclinical development and, ultimately, clinical translation.

Future Scope

• In vivo pharmacokinetic and pharmacodynamic studies in hamster cheek pouch OSCC model and rabbit buccal absorption model to quantify systemic vs. local drug exposure.

• Nanoparticle-embedded buccal patches: incorporation of cisplatin-loaded PLGA nanoparticles or liposomes within the patch matrix to further sustain release and enhance intracellular delivery via endocytosis.

• Co-delivery systems: incorporation of cetuximab (anti-EGFR monoclonal antibody) or Cisplatin into the buccal patch for synergistic chemo-targeted therapy.

• 3D-printed buccal patches with patient-specific geometry and programmable drug-release kinetics using hot-melt extrusion FDM technology.

• Clinical Phase I safety and tolerability study in OSCC patients with cisplatin buccal patches as adjunct to radiotherapy, with formal assessment of local drug concentrations, systemic PK, mucositis scoring, and quality-of-life metrics.
• Bioinformatics investigation of platinum resistance pathways (MMR deficiency, ERCC1 upregulation) in tumour specimens from patch-treated patients to inform rational combination strategies.

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