CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.20578209

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE BUCCAL FILMS BY SOLVENT CASTING METHOD

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Abstract:
Buccal films (mucoadhesive) are a novel approach for the development of orally disintegrating dosage forms. They are thin, elegant in appearance and can be made into various sizes and shapes like rectangular or circular. The strips may be flexible or brittle, opaque or transparent. Buccal films are made up of various hydrophilic and hydrophobic polymers to provide rapid disintegration on the tongue without the need for water. The aim of the present study is to develop Buccal films of Tramadol Hydrochloride by enhancing drug dissolution in the oral cavity. The development of the films decreases the analgesic effect in less time and increases the patient's compliance. Tramadol Hydrochloride films were prepared using Hydroxy propyl methyl cellulose-E5, Hydroxy propyl methyl cellulose-E6, Hydroxy propyl methyl cellulose-E15 and sodium alginate as polymers. Therefore, the prepared films were evaluated for various parameters like physical appearance and surface texture of the film, thickness of the film, folding endurance, moisture uptake, uniformity of weight and drug content, swelling index, in vitro disintegration studies, and in vitro dissolution studies. Stability studies were also performed. Though all the formulations equally passed the evaluation parameters, it is concluded that buccal films containing 400 mg of sodium alginate as the polymer because of better dissolution profile.

Keywords: *Oral fast dissolving films, Tramadol Hydrochloride, Solvent casting method, Opioid analgesic.*

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Please cite this article in press **Afreen Banu** et al., **Formulation and evaluation of tramadol hydrochloride buccal films by solvent casting method**.., Indo Am. J. P. Sci, 2026; 13(06).

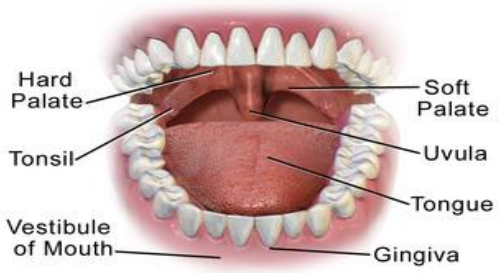
INTRODUCTION:

Buccal films are a thin, flexible drug delivery system that is placed inside the mouth against the cheek (buccal mucosa). The medicine is absorbed directly through the lining of the cheek into the bloodstream, avoiding the digestive system. [1]

Key Features: Very thin and flexible polymer film Placed on the inner cheek Fast or controlled drug release.

- Bypasses first-pass metabolism in the liver.
- Improves bioavailability of some drugs.
- Easy to use for children, elderly, and patients who have difficulty swallowing tablets.

The buccal mucosa is an ideal site for drug delivery because it has a rich blood supply and relatively high permeability compared with other oral tissues. Moreover, the buccal cavity is easily accessible and allows for easy placement and removal of the dosage form if necessary. Buccal films are designed to adhere to the mucosal surface, ensuring prolonged contact between the drug and the absorption site. This prolonged residence time enhances drug absorption and improves therapeutic effectiveness. [2]



Mouth

The preparation of tramadol buccal films generally involves techniques such as solvent casting or hot-melt extrusion. Among these, the solvent casting method is the most commonly used due to its simplicity and ability to produce uniform films. In this method, the polymer, drug, and other excipients are dissolved in a suitable solvent to form a homogeneous solution. The solution is then poured into a casting Mold and allowed to dry, forming a thin film. After drying, the film is cut into suitable sizes for administration. [3]

In addition to these advantages, buccal films also provide improved stability and accurate dosing. Each film contains a predetermined amount of the drug, ensuring consistent dosing and reducing the risk of dosing errors. The compact size and lightweight nature of buccal films also make them easy to carry and store, increasing their convenience for patients.[4]

In conclusion, tramadol buccal films represent a promising and advanced drug delivery system for effective pain management. [5]

MATERIALS AND METHODS:

Materials

The preparation of tramadol buccal films involves a variety of ingredients sourced from reputable suppliers. The active pharmaceutical ingredients, tramadol is supplied by MNS laboratories pvt. Ltd. Excipients such as HPMC E5, HPMC E6, peppermint oil, aspartame, poly ethylene glycol400 are procured from SSRCP.

The manufacturing process utilizes several key pieces of equipment's like weighing balance, magnetic stirrer, casting substrate, hot air oven, desiccator, micro meter screw gauge, sonicator are procured from the Smt. Sarojini Ramulamma College of Pharmacy, Seshadri Nagar, Mahabubnagar-509001, Telangana, India.

Methodology

Analytical method for Tramadol Hydrochlorid:

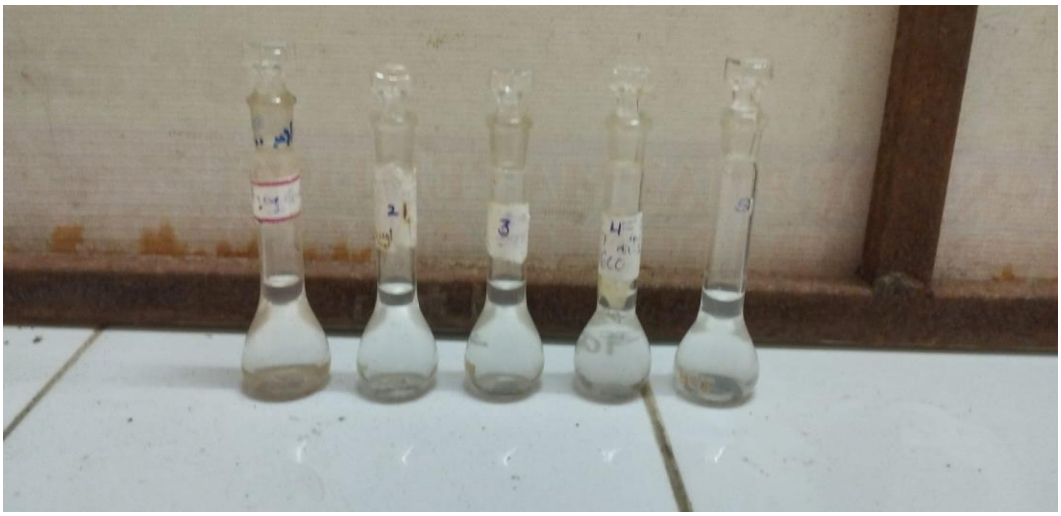
Stock solution/ standard solution

The tramadol has aqueous solubility. The solubility was determined in distilled water and phosphate buffer pH 6.8.

Calibration curve in 0.1 N tramadol Hydrochloride

Accurately weigh 10 mg of Tramadol using a digital balance. Transfer the weighed drug into a 100 ml volumetric flask. Add a small quantity of phosphate buffer (pH 6.8) or distilled water to dissolve the drug. Shake the flask gently until the drug is completely dissolved. Make up the volume up to the 100 ml mark with the same solvent. Mix the solution well to obtain a uniform stock solution. The samples were subjected to UV spectrophotometric analysis and were scanned for absorption maxima (λ max) in the range of 200 - 400 nm using UV spectrophotometer in an appropriate medium.[6]

Dispersion of Tramadol



Preparation of buccal films by solvent casting method

Buccal films are prepared via the solvent casting method by dissolving film-forming polymers (e.g., HPMC, PVA) and API in a solvent, adding a plasticizer (e.g., propylene glycol), casting the mixture onto a mold, and evaporating the solvent. The technique is praised for its simplicity, low cost, and ability to create flexible mucoadhesive films.[7]

Formulation Composition

INGREDIENT NAME	F1	F2	F3	F4	F5	F6
Tramadol	400mg	400mg	400mg	400mg	400mg	400mg
HPMC E5	200mg	300mg	400mg	-	-	-
HPMCE6	-	-	-	200mg	300mg	400mg
PEG 400	2mg	3mg	4mg	2mg	3mg	4mg
Aspartame	50mg	50mg	50mg	50mg	50mg	50mg
Peppermint oil	1ml	1ml	1ml	1ml	1ml	1ml
Distilled water	25ml	25ml	25ml	25ml	25ml	25ml
total weight	678mg	779mg	880mg	678mg	779mg	880mg

Evaluation of Buccal Films

Preformulation studies of Buccal films

Surface pH

Surface pH Evaluation Surface pH measures the acidity or alkalinity of the top layer of a material, which is critical for corrosion resistance, biocompatibility, and adhesion. Methodology: Often evaluated using electrochemical tests, such as open circuit potential or potentiodynamic polarization, to determine the stability of the surface passive film.17-4 PH Stainless Steel: Corrosion studies show that 17-4 PH forms a stable, protective passive layer in acidic to neutral environments. Factors Affecting pH: Surface roughness, contamination, and the degree of passivation directly influence the surface's chemical behavior, with rougher surfaces (often due to corrosion) having lower pH stability. [8]

Tensile strength

Tensile Strength Evaluation Tensile strength (or Ultimate Tensile Strength- UTS) measures the maximum stress a material can withstand before breaking.17-4 PH SS Performance: As-Sintered/Built: ~1000–1100 MPa, depending on manufacturing techniques. Heat Treated (H900): Yield strength increases significantly, often exceeding 1300 MPa, with tensile strength sometimes reaching 1.35 GPa. Manufacturing Influence: Additively manufactured (SLM/DMLS) 17-4 PH parts can show superior or similar tensile properties to wrought counterparts when properly treated. Surface Effects: High surface roughness from manufacturing or corrosion introduces stress concentrators, which lower the overall tensile strength.

% Elongation

(Ductility) Evaluation% Elongation measures the material's ductility—how much it can s**tre**tch before breaking.17-4 PH SS Performance: As-Built: Typically, 8% to 10%.H900 Heat Treatment: The high strength (H900) condition often results in reduced ductility (around 7–8%) due to increased brittleness. Overaged (H1150): Higher ductility (higher elongation percentage) but lower strength. Ductility Loss: Corroded specimens with higher surface roughness can experience substantial

reductions in elongation (up to 80% loss in capacity).[9]

Physical appearance and surface texture
Physical appearance refers to the visual characteristics and overall presentation of a product.

Color
Uniformity of color, absence of mottling, fading, or darkening (stability indicating)

Shape and Dimensions
Measurement of size, diameter, and thickness (e.g., within $\pm$5% for tablets)

Clarity/Transparency
Evaluated for solutions to detect turbidity or particulates

Surface Condition
Examination for defects like cracks, capping, sticking, chipping, or swelling.

Odor
Detection of characteristic odors indicating degradation (e.g., acetic acid in aspirin).

Surface Texture/Gloss
Visual assessment of surface shine or roughness. Impurity/Contamination: Identification of foreign matter.

Surface texture
Surface texture consists of the small-scale, geometric deviations of a surface from its nominal form. It is commonly divided into roughness (high frequency) and waviness (lower frequency). Surface texture: Surface texture refers to the measurable topographical characteristics—roughness, waviness, and lay—that define the physical deviations of a material's surface from a perfectly flat plane. It impacts functional performance, including friction, wear, lubrication, and aesthetics, and is analyzed through profiling techniques to ensure quality control.[9]

Key Components of Surface Texture
Roughness
Fine, closely spaced irregularities created by production processes like cutting or grinding.

Waviness
More widely spaced deviations, often caused by vibrations, heat treatment, or deflections during manufacturing.

Lay
The dominant direction of the surface pattern, determined by the production method.

Flaws
Random defects (cracks, scratches) that occur occasionally.

Thickness
Thickness measurement tools include calipers, micrometers, and ultrasonic gauges, selecting the right one depends on precision needs and accessibility. Micrometers and feeler gauges are ideal for direct contact measurements, while non-contact methods like laser sensors or coating thickness gauges are used for fragile or single-side access, such as measuring pipe wall thickness.[10]

Common Thickness Measurement Tools
Ultrasonic Thickness Gauges
Measure material thickness (e.g., metal, plastic) without needing access to both sides, utilizing high-frequency sound waves.

Micrometer's & Screw Gauges
Offer high-precision, direct contact measurements for thin sheets of metal.

Feeler Gauges
A set of stainless-steel blades used to check gap widths or thicknesses between components. Digital Thickness Gauges/ Caliper: Portable tools (often LCD) designed for measuring leather, paper, cloth, or thin metal sheets. [11]

Coating Thickness Gauge
Specialized tools to measure paint, powder coating, or plating thickness on steel or non-ferrous metals.

Laser Sensors
Used for high-resolution, non-contact measurement of materials like steel strips or plastic films.
Wire Gauges: Used for measuring the diameter or thickness of wire and metal sheets.

Moisture content
Moisture uptake is the process by which materials—particularly polymers, composites, and fibers—absorb or adsorb water from their environment, leading to increased weight, potential swelling, and degraded material properties. It is heavily influenced by humidity, temperature, and material porosity, often analyzed using Fiskian diffusion models or gravimetric analysis.

Key Aspects of Moisture Uptake Mechanisms
Water uptake occurs through diffusion into the bulk material and interfacial storage within voids. It is commonly driven by network polarity, were polar groups form hydrogen bonds with water molecules. Influencing Factors: Increased temperature accelerates absorption rates. High relative humidity increases the equilibrium moisture content, which

can be measured using sorption isotherms. Effects on Materials: Moisture uptake reduces mechanical properties, causes swelling, and can lead to irreversible damage like chemical degradation or hydrolysis. Measurement Methods: Gravimetric Analysis: Simple weight gain measurement to determine moisture content. Dynamic Vapor Sorption (DVS): Measures moisture sorption/desorption.

Drug content uniformity [12]
The drug content uniformity test is a USP/pharmacopeial quality control procedure ensuring each dosage unit (tablet, capsule, etc.) contains the intended amount of API, with little variation. It requires assessing 10-30 units, typically ensuring 85–115% of the label claim, to confirm consistent distribution and safety.

Key Aspects of the Content Uniformity Test
Purpose
To confirm the consistency of API distribution within a batch, ensuring every tablet/capsule is close to the target label claim.

Methodology
Typically, 10 units are tested, measuring the API content of each. If necessary, another 20 are tested (total 30).

Acceptance Criteria (USP)
Based on the Acceptance Value (AV). The requirement is typically that the AV of the first 10 units is (), though it can go to 30 units.

Formula **AV =|M-X|+KS**
M=Reference value (target content). • X=Mean individual content. • K=Acceptability constant (e.g., 2.4 for 10 units). • S=Standard deviation.

Fail Criteria: The batch fails if individual units fall outside 85-115% of the target in a way that exceeds the calculated AV limit.

Swelling index
A swelling index measures the volume increase of a material (like plant mucilage, soil, or coal) upon absorbing liquid or heating, usually expressed as the volume in milliliters occupied by 1 gram of material after swelling. It acts as a quality indicator for drug purity, bentonite expansion, or coal coking properties.

Key applications and methods [13]
Herbal Materials/Drugs (e.g., Isabgol): Measures the ability of mucilage to swell in water. Usually, 1 g of drug is shaken with water in a 25 ml stoppered cylinder, allowed to stand for 4 hours, and the volume is measured.

Bentonite/Clay
A high swelling index (e.g.,) indicates good quality bentonite. Coal (Free Swelling Index- FSI): Evaluates coking properties by measuring volume increase when heated.

Soil Engineering
Measures the deformation behavior of expansive soils using a consolidation test (oedometer) to calculate the swelling index.

General Formula
swelling index = final volume– initial volume by initial volume.

***Invitro* disintegration time**
The in vitro disintegration test is a pharmacopeial quality control procedure that measures the time (typically $\le$15-30 min) required for solid oral dosage forms—like tablets or capsules—to break into smaller particles in a fluid medium at. It ensures that the medication breaks down to enable subsequent dissolution and absorption in the body.

Key Aspects of the Disintegration Test:
Apparatus Setup
The test uses a basket-rack assembly with six cylindrical glass tubes (often with 10-mesh screens), which moves up and down (29-32 cycles/min) in a 1-liter beaker containing a test medium.

Disintegration Definition
A tablet is considered disintegrated when no residue remains on the screen, or only a soft mass (with no palpable, un-wetted core) or insoluble coating remains. **Media Used:** Usually water, simulated gastric fluid (pH 1.2), or simulated intestinal fluid (pH 6.8), maintained at to mimic body conditions.

Methodology
Generally, one tablet is placed in each of the six tubes. A guiding disc may be added to prevent floating.

Types of Dosage Forms
This test applies to uncoated tablets, plain-coated tablets, capsules, and enteric-coated preparations (which must not disintegrate in acid for 1-2 hours).

Difference from Dissolution Testing: Disintegration
Focuses on the physical breaking down of the dosage form into smaller pieces (desegregation).

Dissolution
Measures the rate and amount of the active pharmaceutical ingredient (API) that dissolves in the medium over time

Purpose
Disintegration is a faster, simpler, and more routine quality control test, while dissolution provides better data on how the drug is released for absorption.

***Invitro* dissolution studies**
In vitro dissolution studies measure the rate and extent of drug release from formulations (e.g., tablets, capsules) under standardized, simulated physiological conditions. These studies are critical for quality control, predicting in vivo drug performance, and comparing formulation efficiency. Key factors include USP apparatus selection, media pH, and sink conditions.

Key Aspects of In Vitro Dissolution Studies
Purpose
Quality Control (QC): Ensures batch-to-batch consistency and detects manufacturing errors. Formulation Development: Distinguishes between different formulation types. In Vivo Prediction: Evaluates how drugs dissolve in the gastrointestinal (GI) tract. Biowaivers: Supports regulatory approval to waive human bioequivalence studies.

Common Apparatus (USP)
Apparatus 1 (Basket): Commonly used for capsules and floating dosage forms. Apparatus 2 (Paddle): Most common for tablets. Apparatus 3/4: Reciprocating cylinder and flow-through cell, used for modified-release or low-solubility drugs.

Methodology Factors
Dissolution Media
Typically, 500, 900, or 1000 mL, designed to simulate GI fluid pH (e.g., gastric juice, intestinal fluid). Sink Conditions: Maintained to ensure the drug concentration remains low enough not to limit dissolution, typically less than of saturation solubility. Temperature: Usually maintained at 37 ± 0.5ºC to simulate body temperature.

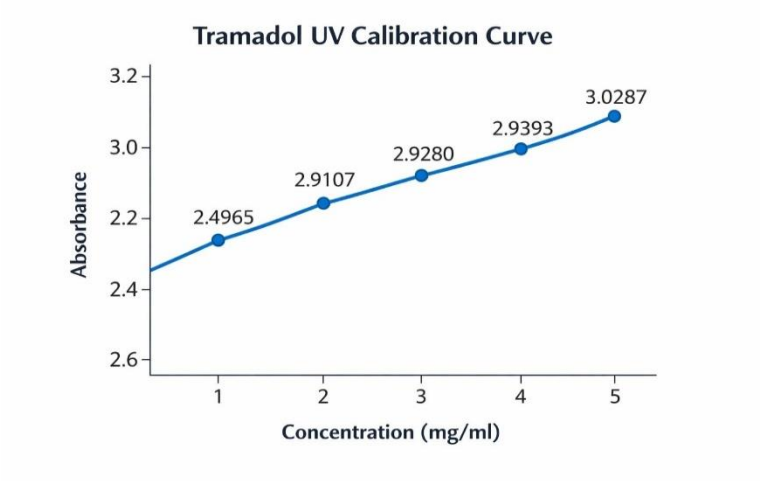
RESULTS AND DISCUSSION:

Construction of calibration curve
The results of absorbance for all the prepared concentrations were scanned in UV Visible spectrophotometer between the wavelengths 200 to 400nm and the λ max was determined as 203mn.

Table calibration data

Concentration Ratio	Absorbance
1ml	2.965
2ml	2.9107
3ml	2.9280
4ml	2.9393
5ml	3.0287

Observation for graph of diethylcarbamazine citrain 0.1n HCL (275nm)
After the Preformulation studies of active ingredients and Excipients, incompatibility and stability studies were carried out.



Evaluation of films for physical parameters

Formulation	Wt.(mg)	Thickness (mm)	Folding endurance	Moisture uptake
F1	52.3±0.8	0.82±0.05	140	Nill
F2	49.5±1.2	0.78±0.04	190	Nill
F3	51.8±0.9	1.02±0.03	150	Nill
F4	46.9±1.0	0.72±0.06	130	Nill
F5	44.7±0.7	0.70±0.05	120	Nill
F6	48.6±0.6	0.85±0.04	170	Nill

Evaluation of films for Drug content & performance

Formulation	Drug content (%)	Disintegration time(sec)	Swelling index (%)
F1	95.2%	28sec	60.1%
F2	92.8%	18sec	55.4%
F3	93.5%	38sec	63.2%
F4	94.6%	21sec	57.8%
F5	92.3%	17sec	62.5%
F6	93.0%	35sec	61.7%

Tramadol buccal films

The drug and excipients properly evaluated with different concentration by using surface ph., tensile strength, %elongation, physical appearance, thickness, folding endurance, moisture uptake, drug content uniformity, swelling index, invitro disintegration time, invitro dissolution study.

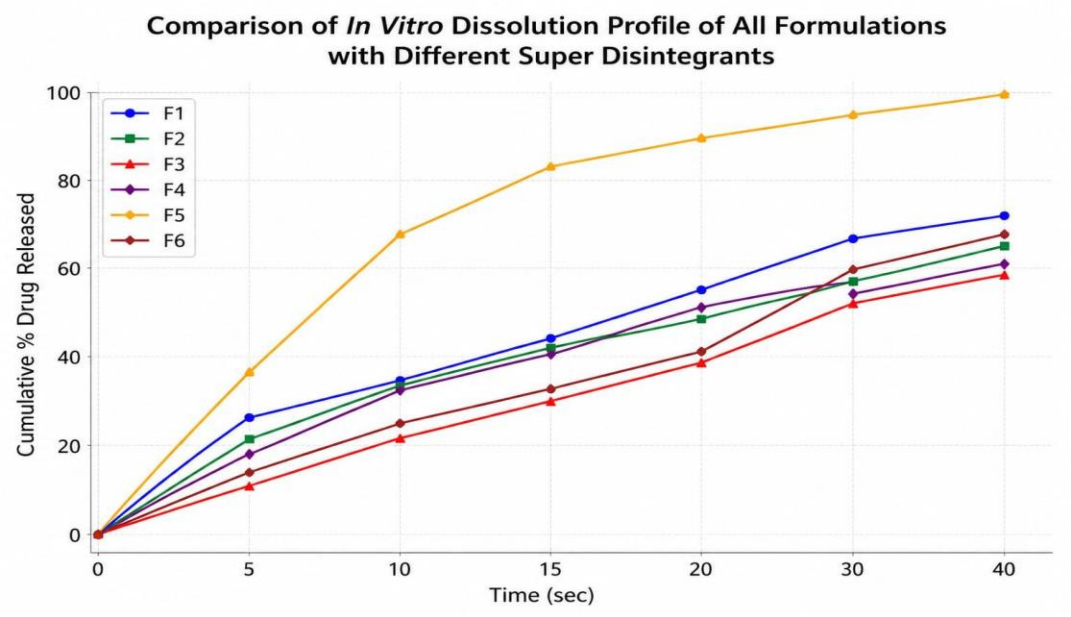
The prepared buccal films are characterized by surface ph., tensile strength, % Elongation, physical appearance, thickness, folding endurance, moisture uptake, drug content uniformity, swelling index, in-vitro disintegration time, in-vitro dissolution study. By following the procedures as per pharmacopeia to check the stability of thin film during transportation Packaging and storage. The result obtained in all the formulations studies were within pharmacopeia standards. The results were tabulated.

Post formulation

Formulation code	Thickness	Disintegration time	Wetting time	%water absorption ratio	Drug content
F1	0.82±0.05	28sec	17	90	95.2%
F2	0.78±0.04	18sec	18	114	92.8%
F3	1.02±0.03	38sec	22	91	93.5%
F4	0.70±0.06	21sec	16	84	94.6%
F5	0.70±.05	17sec	13	119	92.3%
F6	0.85±0.04	35sec	18	75	93.0%

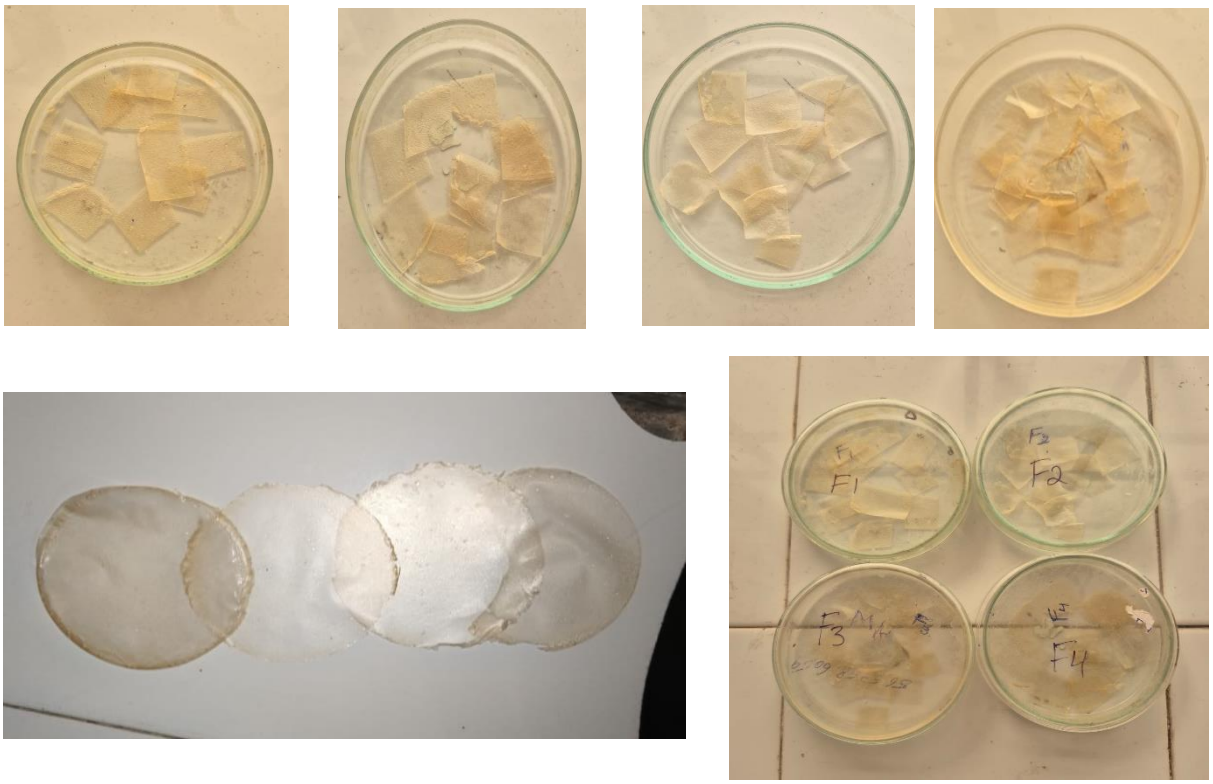
In-vitro drug release

Time(sec)	F1	F2	F3	F4	F5	F6
0	00	00	00	00	00	00
5	26.45	22.17	11.25	19.94	36.44	16.28
10	34.44	34.30	22.06	33.57	68.32	26.99
15	43.83	42.78	30.63	41.21	83.23	34.36
20	55.54	49.53	39.09	51.60	89.76	43.87
30	67.64	57.01	53.11	57.21	95.45	61.47
40	72.88	66.79	59.22	64.57	99.90	68.77



Comparison of in Vitro dissolution profiles of all formulations of different super disintegrants

Tramadol buccal films (F1, F2, F3, F4, F5)



CONCLUSION:

Buccal films of Tramadol Hydrochloride were successfully prepared using the solvent casting method with different concentrations of polymers (HPMC E5 and HPMC E6). All six formulations (F1–F6) were evaluated for various physicochemical and performance parameters.

The prepared films showed good physical appearance, uniform thickness, adequate folding endurance, and acceptable weight variation, indicating uniformity of formulation. Drug content in all formulations was found to be within acceptable limits, confirming uniform drug distribution.

In-vitro disintegration studies revealed that all films disintegrated rapidly, indicating their suitability for fast drug release and quick onset of action. Among all formulations, F5 showed the least disintegration time, making it more effective for immediate drug release.

In-vitro dissolution studies demonstrated that drug release varied with polymer concentration. F6 exhibited the highest drug release, while formulations with lower polymer concentration showed comparatively slower release.

Among all the formulations, F5 was selected as the optimized formulation. This is because F5 showed the fastest disintegration time (92.3%), and a good swelling index (62.5%). These parameters indicate rapid drug release and effective performance, making F55 the best formulation among all**.**

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