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DESIGN AND EVALUATION OF BILAYER SUBLINGUAL DRUG DELIVERY FOR ASPIRIN AND ISOSORBIDE MONONITRATE: A REVIEW

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ABSTRACT

In order to reduce myocardial damage and restore coronary perfusion following an acute myocardial infarction (AMI), antiplatelet and vasodilatory action must begin quickly. The sublingual method is appropriate for emergency medication delivery, avoids first-pass metabolism, and offers rapid systemic absorption. An new drug delivery strategy for dual-action therapy of ischemia episodes is the use of bilayer sublingual tablets that combine isosorbide mononitrate (ISMN, controlled or sustained-release) and aspirin (immediate-release). The pathophysiological basis of AMI, the need for sublingual drug administration, important excipients, formulation techniques, assessment criteria, and current developments in bilayer delivery systems for cardiovascular emergencies are all summarized in this brief study.

KEYWORDS: Myocardial Infraction, Sublingual Drug Delivery, Cardiovascular, Aspirin and Isosorbide Mononitrate.

1. INTRODUCTION

Myocardial infarction (MI) results from acute interruption of coronary blood flow, leading to myocardial ischemia and necrosis. Timely administration of antiplatelet and vasodilatory agents is essential for early reperfusion and reduction of morbidity. Traditional oral dosage forms are limited by slow onset and first-pass metabolism, making them unsuitable for emergency management.

Sublingual drug delivery bypasses gastrointestinal degradation and provides rapid systemic absorption. Bilayer tablets combine two different drug delivery kinetics—an immediate-release (IR) layer for fast onset and a sustained-release (SR) or mucoadhesive layer for prolonged action. The combination of Aspirin (antiplatelet) and Isosorbide mononitrate (vasodilator) offers a powerful therapeutic synergy for managing acute ischemic episodes.

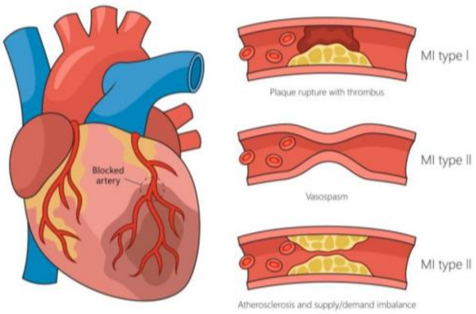


Fig. 1: Myocardial infarction.

Asprin The most used antiplatelet medication in the treatment of MI is aspirin, an irreversible cyclooxygenase-1 (COX-1) inhibitor. When taken early, aspirin inhibits platelet aggregation, stops thrombus from spreading, and lowers mortality via blocking the formation of thromboxane A_2. It is advised as a first-line treatment for both non-ST elevation MI (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).

Isosorbide mononitrate (ISMN) is a powerful arterial and venous vasodilator. It increases coronary blood flow, lowers preload and myocardial oxygen demand, and encourages smooth muscle relaxation by producing nitric oxide (NO). In ischemic heart disease, ISMN is utilized to enhance myocardial oxygenation, avoid angina attacks, and lessen chest pain.

Aspirin and ISMN work together in a clinically synergistic way to provide both quick relief from ischemia-induced chest discomfort and antithrombotic activity. However, traditional oral administration of these medications is linked to substantial first-pass metabolism, limited bioavailability, and delayed onset, especially for nitrates.

The formulation science, biopharmaceutics, evaluation criteria, difficulties, and technical developments in bilayer sublingual delivery for cardiovascular emergencies are highlighted in this study.

2. Myocardial Infarction: Pathophysiological Overview

The pathophysiology of MI involves a cascade of events including endothelial dysfunction, platelet activation, vasoconstriction, coagulation pathway activation, and subsequent myocardial cell death. Clinically, MI presents with classic symptoms such as acute chest pain, radiation to the arm or jaw, shortness of breath, diaphoresis, and hemodynamic instability. Since early restoration of coronary blood flow greatly lowers myocardial damage and increases survival chances, prompt intervention is essential.

MI is distinguished by

i. blockage of the coronary artery brought on by thrombosis or plaque rupture.
ii. Anaerobic metabolism and ATP depletion are caused by ischemia.
iii. inflammatory cascade activation, membrane rupture, and cellular necrosis.
iv. Vascular occlusion is increased by platelet aggregation.
v. Infarction caused by a decrease in coronary blood flow.

Early MI treatment requirements include

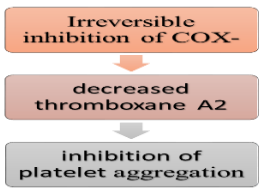
- Rapid coronary vasodilation → ISMN
- Immediate platelet inhibition → Aspirin
- Preventing more thrombus formation
- Improving the oxygen supply to the heart.

3. Rationale for Combining Aspirin and ISMN in a Sublingual Bilayer Tablet

Aspirin (Acetylsalicylic acid)

- Essential for rapid antithrombotic effect.

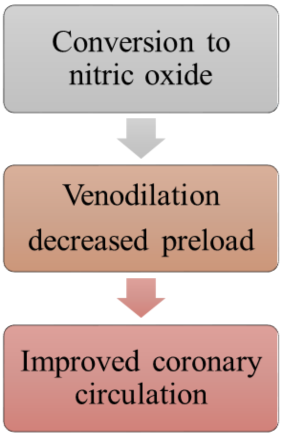
MECHANISM



Isosorbide Mononitrate (ISMN)

- Provides relief from ischemic chest pain and prevents recurrent ischemia.

MECHANISM



4. Need for a Bilayer Sublingual Drug Delivery System

The bilayer sublingual drug delivery system is designed to meet the dual therapeutic requirements of immediate platelet inhibition and sustained vasodilation. In this approach, aspirin is incorporated in the immediate-release layer to provide rapid antiplatelet action, while isosorbide mononitrate (ISMN) is formulated in the sustained-release or mucoadhesive layer to ensure prolonged vasodilatory effect. This combination offers several important benefits, including a faster onset of action along with an extended duration of therapeutic effect. It also improves patient compliance by reducing dosing frequency and enhances bioavailability through avoidance of first-pass metabolism, thereby allowing a lower dose to achieve the desired effect. Moreover, this bilayer sublingual system has significant potential for use as a pre-hospital emergency therapy in the early management of cardiovascular events.

Immediate platelet inhibition	Aspirin	IR
Sustained vasodilation	ISMN	SR / mucoadhesive

4.1 Benefits of the combination include

- Faster onset + longer duration
- Better patient compliance
- Lower dose required because of enhanced bioavailability
- Potential pre-hospital emergency therapy.

5. Formulation Design of Bilayer Sublingual Tablets

5.1 Immediate-Release Aspirin Layer

API	Aspirin
Super disintegrants	Crospovidone, Croscarmellose sodium
Diluents	Mannitol (provides cooling and sweetness), MCC
Flavors & sweeteners	Peppermint, Aspartame
Binders	PVP
Lubricants	Mg stearate (used minimally)

Functional Objectives

- Disintegration ≤ 30 seconds
- Complete dissolution within 5–10 minutes
- Palatable mouthfeel.

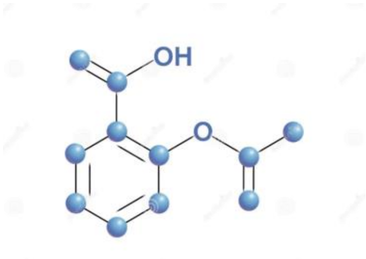


Fig. 2: Chemical sturcture of ASPRIN.

5.2 Sustained/Mucoadhesive ISMN Layer.

Lubricants	Minimal Mg stearate
Mucoadhesive enhancers	Chitosan, Carbopol
Diluents	MCC, Mannitol
Polymers	HPMC K4M Carbopol 934P Sodium alginate Chitosan

FUNCTIONAL OBJECTIVES

- Increase residence time (≥ 30–60 minutes)
- Provide controlled release of ISMN
- Maintain neutral surface pH

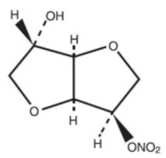
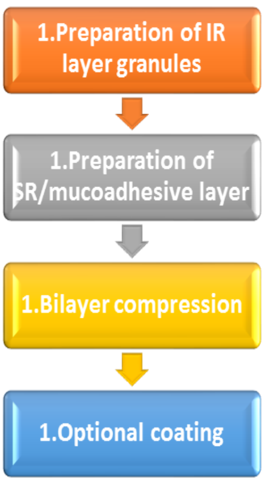


Fig. 3: Chemical structure of ISMN.

6. Manufacturing Process of Bilayer Sublingual Tablets

Aspirin, super disintegrants (like sodium starch glycolate or croscarmellose sodium), diluents (like microcrystalline cellulose), and an appropriate binder (like PVP K-30) must all be precisely weighed in order to prepare the aspirin immediate-release (IR) layer granules. To increase homogeneity during mixing, the weighed aspirin is first run through a #40 sieve to achieve uniform particle size and shatter lumps. To ensure uniformity, the excipients are also filtered via the same sieve. To keep the moisture-sensitive medication from degrading, the aspirin and diluent are carefully combined in a dry state using a tumbling or planetary mixer. Since aspirin is prone to hydrolysis in the presence of water, the binder solution is made separately after obtaining uniform mixing by dissolving PVP K-30 in isopropyl alcohol or a hydroalcoholic medium. To create a cohesive wet mass that can be granulated, the binder solution is gradually added to the dry mixture while being constantly stirred. After that, the wet mass is run through a #12 or #16 sieve to produce uniformly sized moist granules. To stop aspirin from thermally degrading, these granules are equally distributed on trays and dried in a tray drier at a regulated temperature (40–45°C). The granules are dried and then run through a finer filter (#20 or #24) to break up agglomerates and guarantee homogeneous, free-flowing granules. Lastly, to avoid over-lubrication, lubricants like magnesium stearate and glidants like talc or aerosil are added and gently combined for a brief period of time. The resultant IR granules are appropriate for compression as the first layer of the bilayer sublingual tablet because they have good flowability, compressibility, and quick disintegration qualities.

Step-by-step technique



7. Evaluation Parameters

A number of assessment criteria were applied to the aspirin and isosorbide mononitrate (ISMN) bilayer sublingual tablets to guarantee its effectiveness, safety, and quality. The tablets were first inspected for appearance, with color, texture, smoothness of the surface, and any obvious flaws noted. To ensure consistency between batches, thickness and diameter were measured with a digital Vernier caliper. To ascertain the mechanical strength necessary to endure handling stress, hardness testing was done using a Monsanto or Pfizer hardness tester. Tablets were rotated for a predetermined number of revolutions using a Roche friabilator to measure friability; a weight loss of less than 1% was deemed acceptable, demonstrating adequate resistance to abrasion. To verify dose consistency, the weight variation test was carried out by weighing individual tablets and comparing them to the average batch weight in accordance with pharmacopeial standards. In order to verify that the actual drug content of both aspirin and ISMN stayed within 95–105% of the label claim, the tablets were crushed, appropriate dilutions were made, and the results were analysed using UV spectroscopy or HPLC.

In order to evaluate the tablet's capacity to quickly absorb saliva—a critical component for sublingual administration—the wetting time and water absorption ratio were also calculated. A USP disintegration device was used to assess the in vitro disintegration time, which shows how quickly aspirin's immediate-release layer degrades under physiological settings. For sublingual tablets, disintegration within 30 to 60 seconds is ideal. Additionally, USP Type II (paddle) equipment was used for in vitro dissolution investigations to assess the release profile of both layers. While the ISMN layer was watched for a controlled or sustained release pattern based on formulation design, the IR layer of aspirin was anticipated to release more than 80% of the drug within 5–10 minutes. By looking for distinctive peaks, FTIR analyses were conducted to find any drug–excipient interactions. Stability studies were carried out at accelerated circumstances (40°C ± 2°C/75% RH ± 5%) in accordance with ICH recommendations to assess changes in physical appearance, drug content, disintegration time, and dissolution profile over a period of one to three months. Together, these factors guaranteed that the bilayer sublingual tablets had the necessary therapeutic efficacy and pharmaceutical grade.

8. DISCUSSION

In order to treat acute myocardial infarction (AMI) quickly and effectively, a bilayer sublingual tablet with an immediate-release (IR) layer of aspirin and a controlled/sustained-release (SR/CR) layer of isosorbide mononitrate (ISMN) was developed. The formulation method was designed to provide a continuous release of ISMN to assure extended vasodilation and enhanced coronary blood flow, while delivering aspirin rapidly to accomplish immediate antiplatelet activity. To maximize the final product, a number of preformulation, formulation, and assessment characteristics were methodically evaluated throughout the study. Uniform thickness, diameter, hardness, and friability were among the acceptable physical characteristics of the bilayer tablets. Without sacrificing disintegration performance, hardness values were sufficient to preserve layer adhesion. Sufficient mechanical integrity was indicated by friability values that were below 1%. The weight variation data showed homogeneous granule dispersion during compression and were within pharmacopeial limitations. With readings falling within the allowed range of 95–105%, drug content analysis for both layers verified that the formulation procedure ensured consistent dosage.

9. CONCLUSION

Aspirin and ISMN-containing bilayer sublingual tablets are a novel and clinically useful medication delivery system for quick MI treatment. Effective pharmacodynamic synchronization is made possible by the combination of an early antiplatelet impact and a prolonged vasodilatory action. Bilayer systems are a possible substitute for traditional oral or injectable therapy because to technological developments in mucoadhesive polymers, tablet engineering, and sublingual drug administration. These systems have a great deal of potential to become frontline therapies in the early treatment of MI with additional optimization and clinical investigation.

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11. Conflict of Interest: No Conflict of Interest.

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