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Research Paper

A Review Article on Formulation and Evaluation of Floating cum Mucoadhesive fast Dissolving Film with Ramipril

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Abstract *- This study presents the formulation and evaluation of a novel pharmaceutical delivery system designed to enhance the therapeutic efficacy of ramipril, an antihypertensive medication. The formulation strategy involved the development of a fast dissolving film incorporating ramipril along with polymers and excipients selected for their ability to confer both floating and mucoadhesive properties. The formulation was optimized through a systematic screening of various polymer combinations and processing parameters to achieve the desired drug release profile and mechanical properties. Physicochemical characterization studies, including Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM), were conducted to assess the compatibility of the drug with the selected excipients and to characterize the surface morphology of the formulated films. In vitro dissolution studies were performed to evaluate the drug release kinetics under simulated physiological conditions, demonstrating sustained release characteristics over an extended period. Furthermore, the mucoadhesive properties of the film were evaluated using texture analysis to measure the force required to detach the film from mucosal surfaces. The optimized formulation exhibited excellent mucoadhesive strength, ensuring prolonged residence time at the site of absorption. Additionally, the floating behavior of the film was assessed in simulated gastric fluid, confirming its ability to remain buoyant in the stomach, thereby prolonging gastric residence time and enhancing drug absorption. Pharmacokinetic studies conducted in animal models revealed improved bioavailability and sustained plasma concentration profiles compared to conventional dosage forms. The developed floating cum mucoadhesive fast dissolving film offers a promising approach for enhancing the therapeutic efficacy of ramipril by improving drug absorption, bioavailability, and patient compliance.*

Keywords: *Ramipril, Fast dissolving film, Mucoadhesive drug delivery system, Antihypertensive*

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I. INTRODUCTION

Gastro-retentive dosage forms: Gastroretentive dosage forms constitute a pioneering approach in pharmaceutical formulation, designed to extend drug residence time within the stomach for enhanced drug absorption and sustained therapeutic effect. These formulations tackle challenges associated with erratic drug absorption and short gastric residence time, particularly beneficial for drugs with low solubility or absorption limitations. Employing various strategies such as floating systems, bioadhesive systems, expandable systems, and high-density systems, gastroretentive dosage forms ensure prolonged contact with the gastric mucosa, thus improving drug bioavailability, reducing dosing frequency, and ultimately enhancing patient compliance and therapeutic outcomes.

GRDD Devices are primarily site specific drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves:-

- Bioavailability
- Reduce drug wastage
- Improves solubility of drugs that are less

- soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine) Also helps in achieving local delivery of drug to the stomach and proximal small intestine

Advantages :

- Delivery of drugs with narrow absorption window in the small intestine region
- Reduced Frequency of Dosing with improved patient compliance
- Minimize the Fluctuation of drug concentrations
- Site specific drug delivery
- Enhances the Pharmacological effects

Disadvantages:

- Gastric emptying variability
- Gastrointestinal side effects
- Formulation complexity
- Limited Application
- Potential for drug –disease interaction.

ANATOMY OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract can be divided into three main regions namely

1. Stomach
2. Small intestine Duodenum, Jejunum and Ileum
3. Large intestine

The GIT is a continuous muscular tube, extending from the mouth to the anus, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. The organization of the GIT, from stomach to large intestine, is shown in Fig.1.

The stomach is a Jshaped enlargement of the GIT which can be divided into four anatomical regions: cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 litre when full 8 .

The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propria and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit 9

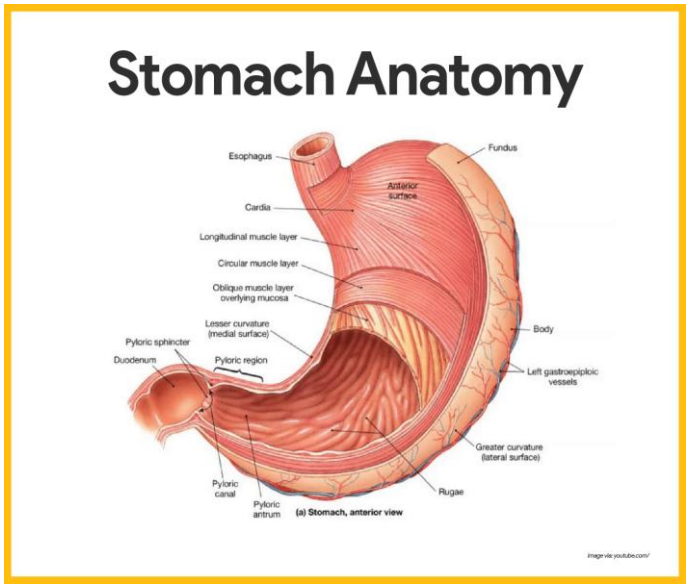


Fig.1. ANATOMY OF THE GASTROINTESTINAL TRACT

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY
Anatomically the stomach is divided into 3 regions:

- Fundus
- Body,
- Antrum pylorus.

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase)
2. Phase II (preburst phase)
3. Phase III (burst phase)
4. Phase IV

Phase I (basal phase): It is a quiescent period lasting from 30 to 60 minutes with no contractions.
Phase II (preburst phase): It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase
Phase III (burst phase) : This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ‘‘house-keeper wave,’’ sweep gastric contents down the small Intestine
Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.
After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase 2 of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled towards the pylorus in a suspension from. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.13 Scintigraphic studies determining gastric emptying rate revealed that orally administered controlled released dosage forms are subjected to complications that of short gastric residence time and unpredictable gastric emptying rate.

Mucoadhesive-
Mucoadhesion has drawn a lot of attention in pharmaceutical technology since the early 1980 Mucoadhesive systems have the potential to be used as drug carriers since they can increase contact with the epithelial barrier by extending their period of residence at the absorption site. A drug carrier system must be attached to a particular biological area in order for mucoadhesion, also known as bioadhesion, to occur. When a pressure-sensitive adhesive comes into contact with a surface (in this case, the mucus membrane), the two materials become adherent. Two Different forces that are further explicated in the mucoadhesion section hold these two surfaces together during the therapy time. Bioadhesion in biological systems can be categorized into three type,

1. Adhesion between two biological stages, such as platelet aggregation and wound healing.
2. Attachment of a biological phase to an artificial substrate, such as cell adhesion to culture dishes and biofilm development on prosthetic devices and inserts.
3. Attachment of a synthetic material to a biological substrate, such as the adherence of sealants to dental enamel and synthetic hydrogels to soft tissues.

Based on their characteristics and interactions with mucus, mucoadhesive polymers can be simply grouped into three general classes:

1. **Water-Soluble Polymers**: These polymers can bind tightly to the mucus layer because they are soluble in water. They effectively moisten the mucus thanks to their ideal polarity. The contact makes it easier for the polymer to adhere to the mucosal surface, facilitating mucoadhesion.
2. **Contrary to water-soluble polymers**, water-insoluble polymers are not soluble in water but nevertheless have the ability to cling to the mucus layer. They are joined by cross-linking agents to from a growing network. They can intersect with the mucus while retaining their integrity thanks to this structure.
3. **Swellable Networks with Cross-Linking Agents**: Polymers having both water-soluble And water-insoluble components fall under this category.

4.

THEORIES OF MUCOADHESION-

1-Wettability Theory: The "spreadability" of an active drug delivery system is defined by the wettability hypothesis as the degree to which a mucoadhesive polymer may adhere to a biological membrane. The wetting theory relates to liquid systems that have an attraction for the surface and spread over it. This affinity can be discovered via measurement techniques. Such as the contact angle. This hypothesis is applicable for organizations with low viscosity or liquid mucoadhesive properties.

2. **Adsorption Theory**: Adsorption theory established van der Waals' and hydrogen bond forces for adhesive contacts. After a first contact angle between the exteriors, the mucoadhesive material adheres due to superficial forces acting between the molecules of two surfaces. Collaboration through the contact occurs as a result of compact covalent bonding, according to the chemisorption idea.

3 **Fracture Theory**: The strength necessary to distinguish both surfaces from each other, according to this approach, is linked to the bonding links between the systems. This "fracture theory" conveys polymer impartiality strength from mucus to the strength of their sticky bond.

4- **Diffusion Theory**: This theory describes the time-dependent migration of mucoadhesive polymer chains into the mucus stratum's glycoprotein chain network, as seen in. This is a two-way diffusion approach in which permeation amount is determined by the diffusion coefficients of polymers that are mutually related. While many variables are considered in such operations, the essential qualities that have a significant impact on diffusion include cross-linking density, molecular weight, chain flexibility extension capacity of both networks, and temperature.

5.**Mechanical Theory:** According to mechanical theory, adhesion is caused by a mucoadhesive liquid filling the imperfections on a rough surface. Furthermore, roughness increases the interfacial area available to contacts, assisting in energy dissipation, and might be considered the most essential aspect of the process. The way adhesion happens isn't the same for everything. We have different ideas about how it works. These ideas help us figure out important things about how to make these systems.

6- Electronic Theory: Every surface possesses a distinctive electrical configuration and structural characteristics. This system relies on alterations in electronic arrangements or structures. It posits that bonding arises from the exchange of electrons between the polymer arrangement and the mucous membrane epithelium, leading to the formation of a double layer characterized by electric charges at the interface of the mucoadhesive system and the mucus.

Mechanism of Floating cum mucoadhesive fast dissolving film

Floating mucoadhesive fast dissolving films work by floating on gastric fluid, adhering to the gastrointestinal mucosa, rapidly dissolving upon contact with saliva or gastrointestinal fluids, and releasing the drug for improved absorption and bioavailabiliy**.**

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS There are many parameters related to stomach's anatomy and physiology that are needed to be considered in the development of gastroretention dosage forms.

Particle size Should be in the range of 1-2 mm to pass through the pyloric valves into the small intestine.

Density Density of dosage form should be in range of 1g/cm3 to 2.5g/cm3 Size should be greater than 7.5 mm in diameter.

Shape of dosage forms Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/ inch2 show 90-100 % gastric retention times (GRT).

Single unit/multiple unit Multiple units are preferable because of predictable release profile, coadministration of different units, larger safety margins.

Food intake GRT is longer in fed states.

Nature, calorie content Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.

Frequency of intake GRT increases 400 times due to low frequency of MMC Posture Varies between spine and upright ambulatory states.

Gender Females have shorter GRT than males.

Nature of drug Drugs with impact on gastro intestinal transit time e.g. Codeine and pharmacokinetic agents e.g. metclopramide, cisapride increases GRT. 20

Drug Profile :

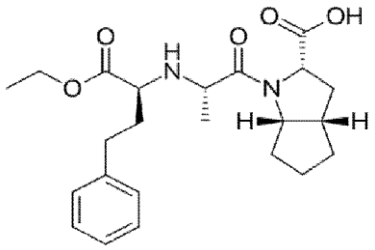
Ramipril –

Drug Type: Approved by US-FDA

Description: Ramipril belongs in a class of drugs called angiotensin converting enzyme (ACE) inhibitors. ACE

inhibitors are used for treating high blood pressure, heart failure and for preventing kidney failure due to high blood pressure and diabetes. ACE is important because it is an enzyme responsible for producing the chemical, angiotensin. Angiotensin causes muscles in most arteries, including the arteries of the heart, to contract, thereby narrowing the arteries and elevating blood pressure. ACE inhibitors such as Ramipril lower blood pressure by reducing the production of angiotensin, thereby relaxing arterial muscle and enlarging arteries. When the blood pressure is lower, the heart - including the failing heart - does not have to work as hard to pump blood. The arteries supplying the heart with blood also enlarge during treatment with ACE inhibitors. This increases the flow of blood and oxygen to the heart, further improving the ability of the heart to pump blood.
Chemical IUPAC Name: (2S,3aS,6aS)-1 [(S)-N-[(S)-1-Carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta [b]pyrrole-2-carboxylic acid, 1-ethyl ester
Chemical Formula: C23H32N2O5

Chemical Structure:



Average Molecular Weight: 416.5106
State: Solid
Melting Point: 109ºC
Experimental Water Solubility: 3.5mg/L
Predicted Water Solubility: 3.90e-02 g/l
Solubilizing solvent: Freely soluble in methanol, sparingly soluble in water.
Drug Category: Drugs affecting the renin-angiotensin system
Excipients:

- Carbopol-934,
- Hydroxypropyl methylcellulose (HPMC), and
- Ethyl cellulose (EC)

Common Ingredients: Active Pharmaceutical Ingredient (1-25%): Variety of APIs can be delivered through fast dissolving films. Potent drugs are the best candidates for incorporation in fast dissolving film. It is useful to use micronized API as it improves the texture of the film and also results in better dissolution and uniformity in the fast dissolving film. Many APIs, which are potential candidates for fast dissolving film technology, has a bitter taste which makes the formulation unpalatable, especially for pediatric preparations. Thus before incorporating such APIs in fast dissolving films, the taste masking is an essential step. Various methods can be used to improve the palatability of the formulation, but the simplest method is mixing and co-processing of bitter tasting API with flavoring or sweetening agent e

1. **Film Forming Polymer** (40-50%): To prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film-forming capacity. The polymer that is to be used should be non-toxic, non-irritant, and devoid of leachable impurities. It should have good wetting and spreadability property. It should exhibit sufficient peel, shear, and tensile strengths. It should be readily available and should not be very expensive
2. **Plasticizer (0-20%):** Plasticizer helps to improve the flexibility of films and reduces the brittleness of the films. However, inappropriate use of plasticizer may lead to film cracking, splitting, and peeling. Common plasticizers that can be used are glycerol, propylene glycol, etc.
3. **Sweetening Agents (3-6%):** Sweeteners have become an important part of the formulation that disintegrates or dissolves in the oral cavity. Both natural, as well as artificial sweeteners, can be used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they provide good mouth feel and cooling sensation. However, the use of natural sugars should be restricted in people who are on a diet or in diabetic patients. Due to this reason, artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate, and aspartame are artificial sweeteners.
4. **Saliva Stimulating Agent (2-6%):** The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving films. Generally, acids which are used in the preparation of food can be used as salivary stimulants such as citric acid, malic acid,

lactic acid, ascorbic acid, and tartaric acid .

5. **Flavouring Agents (0-10%)**: The acceptance of an orally disintegrating or dissolving formulation by an individual depends on the flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10min. The selection of flavor depends on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors, while the younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils, while vanilla, cocoa, coffee, chocolate, and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are a few examples of fruit essence type .

6. **Colouring Agents (1%):** FD & C approved coloring agents are used for fast dissolving films like titanium dioxide.

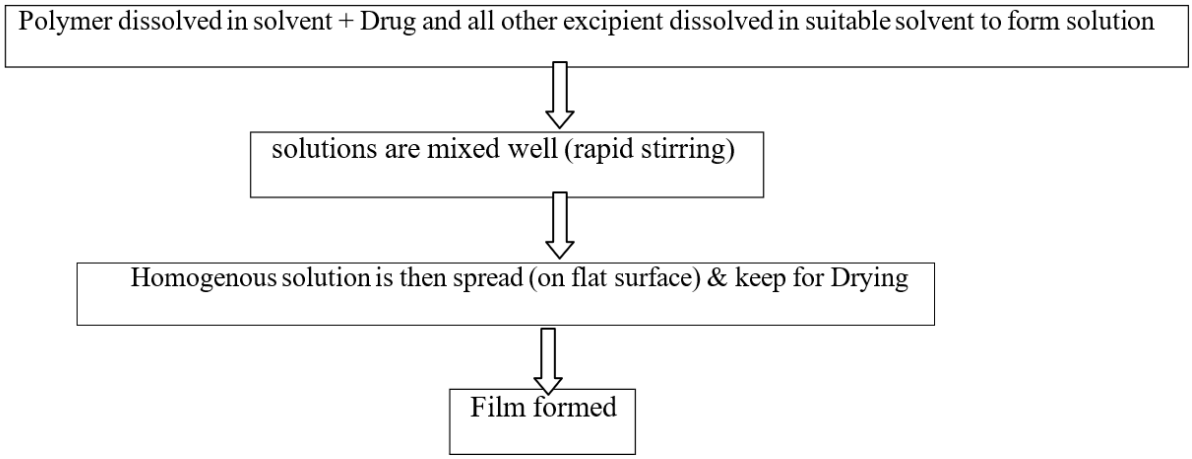
7. **Surfactants**: Surfactants act as solubilizing or wetting or dispersing agent in the formulation so that the film gets dissolved within seconds and releases active agent quickly. Some of the commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens, etc. One of the most important surfactants is Polaxamer 407 that is used as solubilizing, wetting, and dispersing agent

Methodology: Method of preparation of FDF

There are five methods for the preparation of FDF: -

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

Solvent casting method: - In suitable solvent, watersoluble polymers are dissolved and in another suitable solvent, the drug along with other excipients is dissolved, then both solutions are mixed well and casted into the petri plate and kept for drying.



Evaluation parameter –

1- Floating Properties: Assess the film's ability to float on the gastric fluid, typically measured by the floating lag time, duration of floating, and floating strength.

2- Mucoadhesive Properties: Evaluate the film's ability to adhere to the mucosal surface, including mucoadhesive strength and duration of adhesion.

3- Disintegration Time: Measure how quickly the film disintegrates upon contact with the dissolution medium, reflecting its fast-dissolving nature.

5. Drug Release Profile: Analyze the release of the active ingredient(s) from the film over time, ensuring controlled and sustained release if necessary.

6. Physical Characteristics: Evaluate the film's appearance, thickness, flexibility, and uniformity.

7. Mechanical Properties: Assess mechanical strength, elasticity, and toughness to ensure proper handling and administration.

8. Stability Studies: Conduct stability testing under various conditions (temperature, humidity, etc.) to

assess shelf-life and storage requirements.

9. **In vitro and In vivo Studies:** Perform studies to evaluate the film's performance in simulated physiological conditions and in animal or human models.
10. **Biocompatibility and Safety:** Ensure the film's ingredients are safe for mucosal contact and do not cause irritation or adverse reactions.
11. **Pharmacokinetic Parameters:** Measure drug absorption, bioavailability, and pharmacokinetic profiles to understand the film's efficacy and performance in vivo.

By evaluating these parameters comprehensively, you can assess the quality, efficacy, and safety of the floating cum mucoadhesive fast dissolving film for potential pharmaceutical applications.

II. Conclusion

In conclusion, the formulation and evaluation of the floating cum mucoadhesive fast dissolving film with Ramipril showcase its potential as a promising drug delivery system. The developed film exhibited favorable characteristics including rapid disintegration, prolonged residence time, and sustained drug release, indicating its suitability for enhanced bioavailability and therapeutic efficacy. Physicochemical characterization confirmed its suitability for oral administration with satisfactory mechanical strength and mucoadhesive properties. Moreover, in vitro dissolution studies demonstrated sustained drug release, suggesting potential benefits in reducing dosing frequency and maintaining steady plasma drug levels. Future pharmacokinetic studies in animal models and long-term stability assessments would provide further insights into its in vivo performance and storage stability. Overall, the findings underscore the potential of this formulation as a novel approach for improving the treatment of cardiovascular diseases with Ramipril, warranting further research and clinical validation**.**

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