

FORMULATION AND IN-VITRO PHYSICOCHEMICAL EVALUATION OF GLYCEROL-PLASTICIZED PVA/PVP FAST DISSOLVING ORAL STRIPS CONTAINING RABEPRAZOLE AND METOCLOPRAMIDE

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a common gastrointestinal condition that has a great impact on patients' quality of life. The tablets/capsules are the conventional dosage forms that tend to have a delayed therapeutic effect and may be subjected to degradation in the highly acidic stomach environment. The objective of this study is to develop and systematically test a fast dissolving oral strip containing two different drugs: proton pump inhibitor (Rabeprazole Sodium) and prokinetic agent (Metoclopramide Hydrochloride) with the goal of reducing the first-pass effect in the liver and providing rapid symptom relief.

Methodology: The solvent-film casting method was used for the fabrication of the FDOs. Polyvinyl Alcohol (PVA) was used as the main film forming polymer with Polyvinyl Pyrrolidone (PVP K30) as an optimum polymer for film elasticity. Glycerol was tested as a plasticizer at 5, 7.5 and 10% w/w. The preformulation compatibility was evaluated using Fourier Transform Infra Red Spectroscopy (FTIR). The strips produced were extensively tested for their surface morphology, mechanical properties (tensile strength, elongation, Young's modulus), weight uniformity, pH uniformity, moisture content, and in-vitro disintegration time (D.T), total dissolution time (T.), and time at which the gas reaches 100% (t. The percentage drug content, D), and percentage yield.

Results and Discussion: The FTIR spectra indicated that the structure and chemical compatibility of both the drugs remained intact in the polymeric matrix. The optimized strips presented a surface morphology with

light microscopy without the presence of any stickiness. Mechanical testing showed that the higher the concentration of glycerol, the lower the brittleness of the film, and the most ideal mechanical properties are obtained when the glycerol concentration is 75%. All formulations had an acceptable range for oral mucosa pH (6.38–6.92) and rapid disintegration (<30 seconds) to release the therapeutic doses.

Conclusion: Glycerol-plasticized PVA/PVP fast-dissolving oral strips are a stable, mechanically sound and highly patient-friendly option for GERD treatment compared to conventional treatment.

INTRODUCTION

Background

Gastroesophageal reflux disease (GERD) represents one of the most widespread chronic gastrointestinal conditions globally, affecting nearly 20% of the population in Western countries and showing an escalating prevalence across Asia [1]. GERD develops when the retrograde flow of acidic gastric content, pepsin, and bile acids into the esophagus causes troublesome symptoms or structural mucosal damage [3]. Clinical phenotypes range from non-erosive reflux disease (NERD) accounting for 60% of cases to erosive reflux disease (ERD) and dangerous premalignant states such as Barrett's esophagus [7]. Symptoms traditionally encompass debilitating heartburn and acid regurgitation, alongside atypical manifestations like chronic cough, asthma, and non-cardiac chest pain [3]. Standard clinical management relies heavily on effective acid suppression [2]. Proton pump inhibitors (PPIs), such as Rabeprazole Sodium, are widely recognized as first-line therapies due to their ability to covalently bind the H⁺/K⁺ ATPase pump on gastric parietal cells, causing a profound reduction in acid secretion [14]. However, monotherapy often falls short when underlying gastric motility abnormalities or delayed gastric emptying coexist [3]. Thus, combining a PPI with a gastroprokinetic agent like Metoclopramide Hydrochloride (a dopamine D2 and serotonin 5-HT3 receptor antagonist) offers a highly synergistic therapeutic approach that addresses both acid hypersecretion and delayed transit [3,10].

Despite their therapeutic efficacy, standard solid oral dosage forms like enteric-coated tablets and capsules possess inherent limitations [2]. They exhibit delayed systemic onset times, undergo aggressive hepatic first-pass metabolism, and are difficult to ingest for pediatric, geriatric, bedridden, or uncooperative patients [8]. To overcome these constraints, fast-dissolving oral strips (FDOs) have emerged as an elegant alternative [6]. Positioned on the tongue, these thin polymeric matrices rapidly hydrate and disintegrate within seconds upon contact with saliva [13]. The rich vascularization of the oral mucosa permits direct systemic absorption, effectively bypassing the first-pass hepatic pathway, safeguarding acid-labile drugs from gastric degradation, maximizing bioavailability, and providing rapid-acting clinical relief [4-6]. The shift towards patient-centric drug delivery systems has triggered broad optimization of thin-film technologies [8]. Studies have shown that thin films that dissolve rapidly in water reduce the risk of choking, while overcomes the volatility of liquid dosing. The formulation of such systems demands a close knowledge of chemistry of hydrophilic polymers, and of plasticization physics, to assure that the produced films have adequate mechanical stability during packaging and transport, and fast degradation rate in-vivo [11,13].

Polyvinyl Alcohol (PVA) is well known as an outstanding film-forming synthetic polymer, with a remarkable tensile strength, chemical resistance, non-toxicity and total biodegradability. But pure PVA films have high glass transition temperature (T_g≈87°C) which makes it difficult to use

unplasticized film structure [11]. Polyhydric alcohols are highly hygroscopic and are used to weaken the hydrogen bonds between chains of PVA [11,12]. Glycerol ($T_g \approx -83.15^\circ\text{C}$) is the most used. The elastic modulus is reduced and the film is extremely flexible and ductile due to this molecular modification that increases free volume [5,11]. In addition, mixing with other polymers as Polyvinyl Pyrrolidone (PVP K30) changes the matrix properties such as porosity and wetting properties, which directly affect the hydration rate upon exposure to the saliva [13].

New pharmacokinetic advances justify anti-secretory drugs combined with prokinetics [2,3]. Immediate-release profiles of the Rabepazole combinations have been investigated and it has been found that there is a linear relationship between the more rapid the systemic absorption and the more rapid the suppression of intra-esophageal acidity [2,9]. This quick suppression is crucial to avoid tissue damage caused by cytokines, and to avoid subsequent esophageal strictures or adenocarcinomas [2]. At the same time, prokinetic drugs have been proven worldwide to reduce the emptying time of the stomach, which is the most important physical cause of nocturnal acid reflux [3]. Therefore, today's formulation science is strongly focused on designing co-loaded, very thin film formulation with optimized bio-based plasticizers that provide enhanced pharmaceutical stability, appearance, and therapeutic effect [5,6].

2. Materials and Methods

2.1 Materials

Active Pharmaceutical Ingredients (APIs): Rabepazole Sodium (R.) is an Active Pharmaceutical Ingredient (API). The two drugs used at the same time are Metoclopramide

Hydrochloride (M.) and S.H) (Gift samples from Nexus Pharma, Karachi)

Polymeric Matrices & Excipients: Polyvinyl Alcohol (PVA), Polyvinyl Pyrrolidone (PVP K30), Glycerol, Ethanol, Menthol, Saccharin Sodium & Distilled Water.

Instrumentation: Digital Vernier Caliper (E252), Optika Microscope (B-510, Italy), Universal Testing Machine (TIRAtest 2810, Germany), Digital pH meter (AD-12), Hot Air Oven (Memmert), Jasco FTIR Spectrophotometer (FT-IR/4600), and UV/Visible Double Beam Spectrophotometer (AE-590-2D).

2.2 Methods

Preformulation FTIR Study: Separate KBr pellets were made for the pristine R.S, pristine M.H alone and an equal part drug mix (1:1). The pellets were compressed under a vacuum for 10 minutes at 20 MPa and then scanned in the range of 400 cm^{-1} to 4000 cm^{-1} [14].

Stock Solutions: The independent standard stocks were prepared using distilled water/ethanol: PVA (100 mg/mL, heated at 90°C under magnetic stirring conditions), Glycerol (100 mg/mL), PVP K30 (20 mg/mL), R.S (20 mg/mL), M.H (5 mg/mL), and Menthol (10 mg/mL in ethanol).

Pilot Formulations (Optimization of Glycerol): Casting runs were conducted with wide variations of plasticizer (10% to 50% w/w) to evaluate peeling clean ability, stickiness and base flexibility [11].

The final casting of Film Formulations: Nine ultimate formulations were systematically developed by varying the weights of polymer (100 mg, 125 mg, 150 mg) and glycerol threshold (5%, 7.5%, 10% w/w) [4,6], as explicitly structured below:

Table 1. Optimization matrix showing the concentrations of polymer (PVA), plasticizer (Glycerol), and other excipients used in the preparation of experimental formulations (Groups 1F, 2F, and 3F).

R.S Solution (mL)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
M.H Solution (mL)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
PVA Solution (mL)	1.0	1.25	1.5	1.0	1.25	1.5	1.0	1.25	1.5
Glycerol Solution (mL)	0.5	0.625	0.75	0.75	0.937	1.125	1.0	1.25	1.5

PVP K30 Solution (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Saccharin Sodium (mg)	10	10	10	10	10	10	10	10	10
Menthol Solution (mL)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Distilled Water (mL)	2.0	1.625	1.25	1.75	1.30	0.875	1.5	1.0	0.5
Total Volume (mL)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

Note: Series 1F, 2F, and 3F correspond to 5%, 7.5%, and 10% glycerol content variations relative to total formulation design proportions respectively.

All balanced formulations (7 mL each) were poured into smooth glass Petri dishes (23.74 cm²) and air dried for 24 hours at 40°C and then carefully removed and stored in a glass desiccator [6].

Physicochemical Testing Specifications:

- **Thickness & Weight Uniformity:** Measured on random locations using a digital micrometer caliper and an automated analytical electronic balance (n=6) [4].
- **Surface Tackiness:** Surface classification as tack-free, slightly tacky or very tacky, determined by compressing two strips against filter sheets [11].
- **Tensile Profilometry:** Carried out using strips (10×80 mm) in a TIRAtest testing system moving at 50 mm/min to obtain Tensile Strength (TS) (Newtons per mm width) and Elongation at Break (%EB) through:

$$T.S = \frac{\text{Initial Cross-Sectional Area (mm}^2\text{)} \times \text{Force at Break (N)}}{\text{Elongation at Break (mm)}}$$
- **pH and Moisture Content (%MC):** The pH and %MC of strips after they have been dissolved in 10 mL of neutral water were measured using a digital pH and moisture content electrode probe, respectively. %MC was determined by hot-air oven drying at 50°C for 24 hours [12].
- **In-Vitro Disintegration (D.T) & Dissolution (T.D):** Assessed by floating a strip with 1cm² area on top of 10 mL of distilled water at 37°C with low manual swirling [6,13].
- **Drug Content Uniformity:** The drug preparation was dissolved in 250 mL solution and analysed by UV-spectrophotometry at the λ_{max} of 284 nm for Rabepazole Sodium and 315 nm for Metoclopramide HCl [7,10].

3. Results and Discussion:

3.1 Preformulation Compatibility Analysis (FTIR)

FTIR profiling confirmed no significant chemical interactions between the drug molecules.

- **Metoclopramide HCl:** The diagnostic peaks were observed at 1460.81 cm⁻¹ (aromatic ring C-C stretching), 1263.15 cm⁻¹ (primary aromatic C-N stretching) and 1151.29 cm⁻¹ (secondary amine diethyl amino C-N stretching) and 1605.45 cm⁻¹ (conjugated ketone stretching) for H.
- **Rabepazole Sodium:** The sharp bands presented at 1471 cm⁻¹ (C-C aromatic vibrations), 1581.68 cm⁻¹ (C-N secondary amine stretching), 1296.89 cm⁻¹ (C-N indole ring stretching), and 1710.55 cm⁻¹ (carbonyl group of carboxylic acid).
- All main structural chemical identity bands were retained in the combination spectrum (Drug-Drug Combination Blend). The presence of a slight combination band at 1880.11 cm⁻¹ and 1680.17 cm⁻¹ shows that there is no chemical degradation between the two species but the two are in close physical proximity.

3.2 UV spectrophotometric Calibration Curves

- **Rabepazole Sodium:** λ_{max} =284 nm (Linear concentration working range: 1 to 10 µg/mL).
- **Metoclopramide HCl:** λ_{max} =315 nm (Linear concentration working range: 2 to 18 µg/mL). Both drugs displayed high linearity with regression coefficients (R²>0.999).

3.3 Physical Morphology and Thickness Profiles

The following observations have been made about the physical morphology and thickness profiles: The aesthetic optical transparency, even

distribution of gloss and smooth mouthfeel were confirmed by visual inspection with all cast films. The matrices exhibited excellent uniformity

under high resolution light microscopy (40× magnification lens) with no drug crystallization or phase separation.

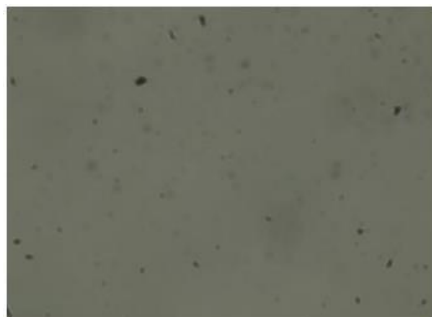


Figure 1: 1Fa image by 40X lens



Figure 1: 1Fb image by 40X lens



Figure 1: 1Fc image by 40X lens

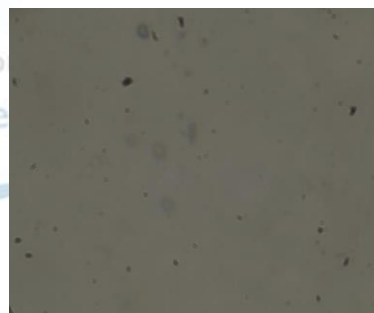


Figure 2: 2Fa image by 40X lens



Figure 2: 2Fb image by 40X lens

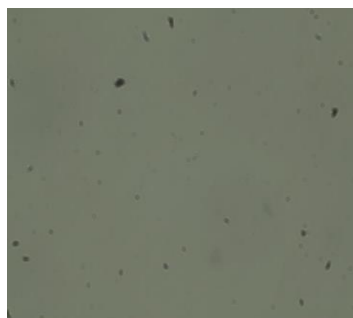


Figure 2: 2FC image by 40X lens

Figure 1 & 2 Light microscopy images (1Fa, 1Fb, 1Fc vs 2Fa, 2Fb, 2Fc) under 40X power magnification showing isotropic polymer structure and absence of drug aggregates.

The measured physical and mechanical dimensions of the final formulations are detailed below:

Table 2. Influence of PVA and glycerol concentration variations on film thickness, surface tack, and mechanical strength.

1Fa	0.11±0.01	Tack-Free	42.15	8.5%
1Fb	0.13±0.02	Tack-Free	45.60	6.2%
1Fc	0.15±0.01	Tack-Free	49.32	4.1%
2Fa	0.12±0.01	Tack-Free	31.45	22.4%
2Fb	0.14±0.03	Tack-Free	34.80	18.2%
2Fc	0.16±0.02	Tack-Free	38.12	12.6%
3Fa	0.12±0.02	Slightly Tacky	18.22	58.0%
3Fb	0.15±0.01	Slightly Tacky	22.41	44.3%
3Fc	0.17±0.02	Tacky	25.10	31.5%

The mechanical and physical evaluation reveals that increasing PVA concentration across batches (a to c) significantly enhances thickness and tensile strength while reducing elongation. Conversely, higher glycerol levels (Groups 1F to 3F) act as a plasticizer, drastically increasing percentage elongation up to 58.0% (3Fa) but

inducing an undesirable surface tackiness.

3.4 Physicochemical Quality Metrics

All formulations fell perfectly within acceptable pharmaceutical guidelines regarding weight uniformity, biological surface pH safety, moisture retention ratios, and high drug content assays:

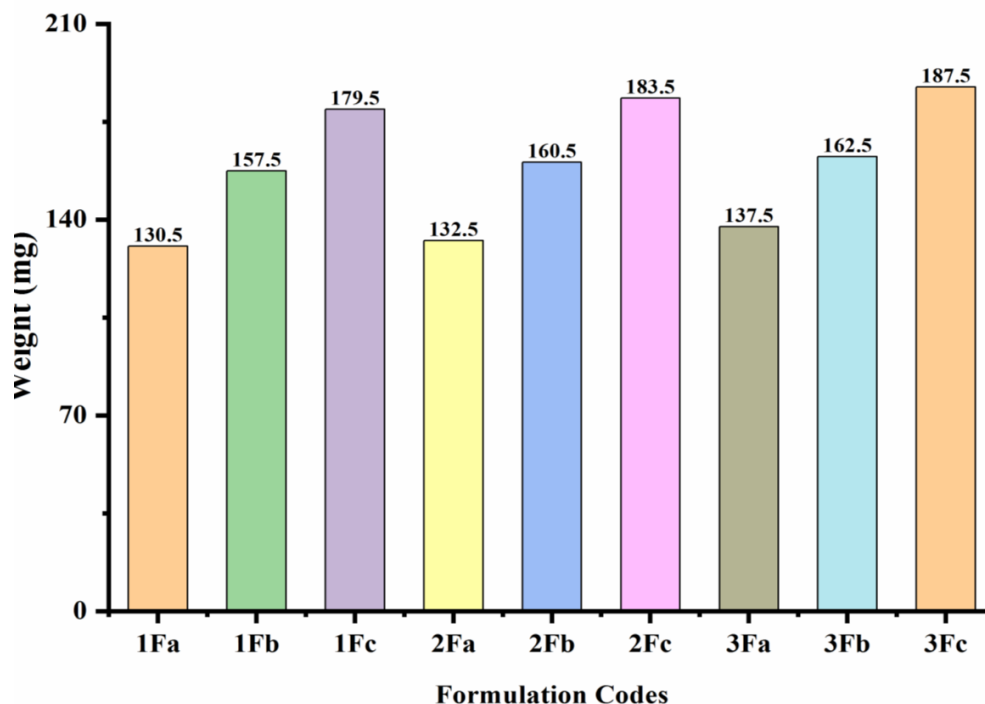


Figure 3. Comparative evaluation of the physical weight variation across different experimental PVA formulation codes (1Fa to 3Fc).

Figure 3 shows a progressive increase in weight is observed within each group from 'a' to 'c' (e.g., 1Fa to 1Fc), corresponding to higher concentrations of PVA and glycerol.

Additionally, increasing baseline glycerol levels across the distinct groups (1F to 3F) results in a concurrent upward trend in formulation weigh.

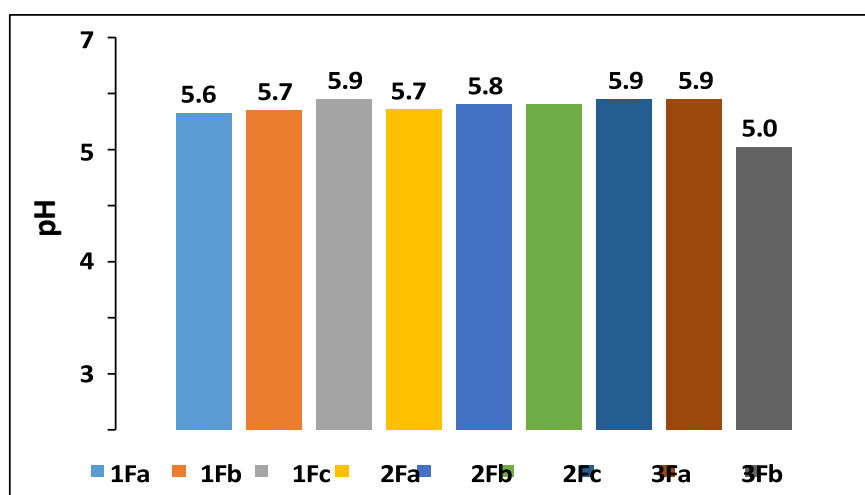


Figure 4. Surface pH profiles of the prepared PVA-based formulations (1Fa to 3Fc) indicating compatibility with physiological mucosal limits.

As illustrated in Figure 4, most formulations exhibit a stable pH ranging closely between 5.65 and 5.90, which is generally safe and non-irritating for biological tissues. However, a

noticeable drop to 5.05 is observed for batch 3Fc, indicating a slightly more acidic profile compared to the other batches.

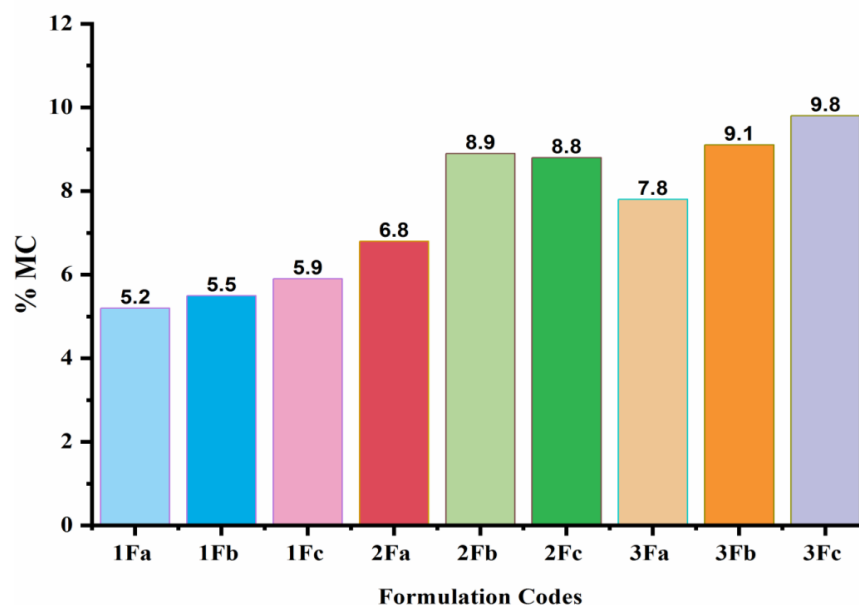


Figure 5. Percentage moisture content (%MC) profiles of the prepared PVA-based formulations (1Fa to 3Fc), showcasing the impact of varying excipient ratios.

Figure 5 presents the percentage moisture content generally rises within each subgroup from 'a' to 'c' and increases progressively across groups (1F to 3F). This upward trend directly

correlates with increasing concentrations of glycerol and PVA, reflecting their inherent hygroscopic properties and water-retention capacity.

Table 3. Consolidated physicochemical evaluation parameters, disintegration-dissolution kinetics, and drug assay percentages for the prepared formulation batches (1Fa to 3Fc).

1Fa	45.2±1.2	6.42	5.20%	16s	34s	98.4%	99.1%
1Fb	52.1±2.1	6.51	5.50%	22s	45s	97.2%	98.5%
1Fc	58.4±1.8	6.38	5.90%	28s	58s	99.0%	97.6%
2Fa	46.8±1.5	6.65	6.80%	14s	28s	98.1%	99.3%
2Fb	54.3±2.4	6.70	8.80%	19s	39s	96.5%	98.0%
2Fc	61.2±1.9	6.58	8.90%	25s	51s	97.8%	98.8%
3Fa	48.1±2.0	6.88	7.80%	11s	22s	99.2%	96.9%
3Fb	56.0±1.7	6.92	9.10%	15s	31s	98.7%	97.2%

3Fc	63.5±2.3	6.81	9.80%	21s	42s	96.1%	98.2%
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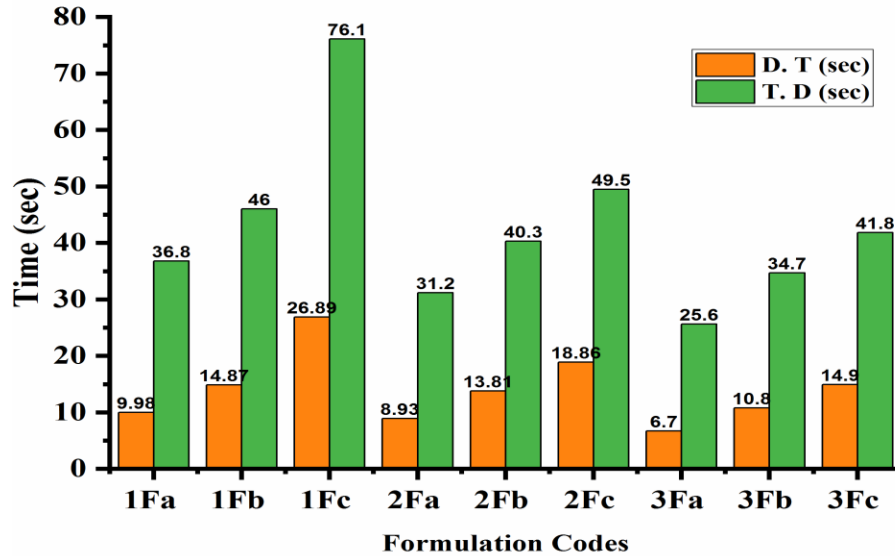


Figure 6. Evaluation of disintegration time (D.T) and dissolution/degradation time (T.D) profiles across the prepared PVA formulation codes (1Fa to 3Fc).

As presented in Figure 6, both D.T and T.D rise progressively within each subgroup from 'a' to 'c', driven by higher PVA concentrations. Conversely, increasing the glycerol ratio across

groups (1F to 3F) leads to faster structural breakdown, notably reducing the maximum T.D from 76.1 seconds (1Fc) to 41.8 seconds (3Fc).

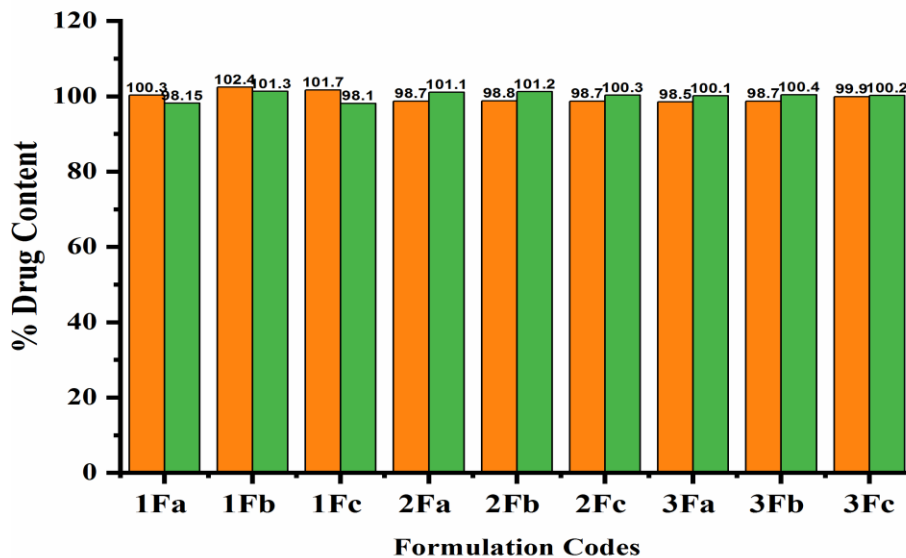


Figure 7. Percentage drug content uniformity of Metoclopramide Hydrochloride and Rabeprazole Sodium across the prepared PVA-based formulation codes (1Fa to 3Fc).

Figure 7 showed that entirely batches demonstrate excellent drug content uniformity, with values for both Metoclopramide Hydrochloride and Rabeprazole Sodium remaining tightly clustered near 100% (ranging from 98.15% to 102.4%). This confirms that variations in polymer and plasticizer concentrations did not negatively impact the homogenous distribution of either active ingredient.

Discussion:

Oral strips need to be carefully optimized to have the required mechanical strength and dissolution rates to develop as fast-dissolving products. PVA gives the film its structural framework, and the addition of PVP K30 creates some amorphous regions in the polymer network that help to increase the rate of water entering the film when it is hydrated.

The mechanical evaluation profiles show a very strong correlation with glycerol plasticizer concentration. The strips had high tensile strength, but limited elongation at break (%EB) for the 1F series (5% w/w glycerol). This means that the matrix is very rigid and the polymer chains do not flow easily, so cutting the film can provoke brittle fracture. This brittleness was overcome by increasing the glycerol content to 7.5% (w/w) (2F series). Glycerol molecules fit in between the PVA chains, thereby canceling out the PVA inter-chain cohesive forces and increasing the free-volume of the matrix. This led to considerable improvement in %EB and still remaining with acceptable structural integrity. The plasticizer was however raised to 10% w/w (3F series), where excessive amounts of moisture from the atmosphere were absorbed (the glycerol is very hygroscopic). This resulted in some undesirable surface tackiness and marked loss of mechanical strength, leading to handling difficulties.

The in-vitro disintegration data indicates there is a direct relationship to polymer thickness and plasticizer concentration. The disintegrations of the formulations with lower polymer densities (1Fa, 2Fa, 3Fa) were much faster than

disintegrations of thicker formulations (1Fc, 2Fc, 3Fc). The 2F series (7.5% w/w plasticizer) was the series that provided the best balance of performance. It showed fast disintegration (<20 seconds) and total dissolution (<45 seconds) which is in the ideal range for fast dissolving systems.

Most importantly, the surface pH of the 2F series was close to neutral (between 6.51 and 6.70) reducing the possibility of irritation to the oral mucosa at the local level. A uniform distribution of both Rabeprazole Sodium and Metoclopramide Hydrochloride was confirmed from drug content analysis in the films, in accordance with USP standards. The formulation 2Fb (125mg of PVA and 7.5% glycerol) was found to be most promising in terms of mechanical strength, storage stability and fast disintegration.

Limitations of the Study: While this study successfully establishes the mechanical viability and rapid breakdown kinetics of the co-loaded PVA/PVP oral strips, certain long-term parameters remain outside the current scope. First, the in-vitro disintegration and dissolution testing were conducted using static distilled water setups rather than simulated human saliva environments under dynamic mucosal flow rates. Second, although the chemical stability of the dual-drug combination was verified via preformulation FTIR, long-term accelerated stability profiling under varied international climatic zones (ICH guidelines) is still required to confirm shelf-life. Finally, in-vivo pharmacokinetic evaluation in animal or human models is necessary to definitively confirm that this formulation successfully bypasses hepatic first-pass metabolism and delivers superior bioavailability compared to commercial enteric-coated oral tablets.

Conclusion

Successful formulation of fast dissolving oral strips co-loading of Rabeprazole Sodium and Metoclopramide Hydrochloride was made by the solvent casting technique in this study. The excellent physicochemical compatibility between

the two active ingredients in the polymer matrix was confirmed by preformulation FTIR spectroscopy. Extensive mechanical and quality evaluations showed that formulation parameters, such as 7.5% w/w glycerol plasticizer concentration and PVA/PVP polymeric matrix, gave strips with optimal tensile durability, very low surface tackiness, safe physiological pH values, and fast disintegration times (<20 seconds). Thus, this thin-film system is a potential means to circumvent hepatic first pass metabolism and potentially a more rapid, effective and patient-friendly treatment modality for the clinical treatment of gastroesophageal reflux disease (GERD).

Declarations

Ethics Approval and Consent to Participate:

This article does not contain any studies with human participants or animal subjects performed by any of the authors. Consequently, ethical approval and formal consent protocols were not required for this laboratory-based formulation study.

Consent for Publication: All authors read and approved the final manuscript and grant consent for its publication in the *Journal of Pharmaceutical Innovation*.

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Conflict of Interest: The authors declare that they have no known competing financial interests, personal relationships, or institutional conflicts that could have appeared to influence the work reported in this paper.

Data Availability Statement: The raw physicochemical datasets, FTIR spectra, and microscopy images generated during the current study are available from the corresponding author upon reasonable academic request.

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