Optimizing Organic Acid Blends for Microenvironmental pH Modulation in HPMC–Sodium Alginate Matrix Tablets to Enhance pH-Independent Sustained Release of Weakly Basic Drug.

Gaware Ravi Uttam[1]*,Kaliyaperumal Saravanan[2], Jadhav Suresh Laxman[3]

[1, 2]Department of Research, Bhagwant University, Ajmer, Rajasthan, India.

[3]Vishal Institute of Pharmaceutical Education & Research, Ale, Pune, Maharashtra, India

[1]ravi21gaware@gmail.com,

[2]kalyansar_mith@yahoo.co.in,

[3]suresh_jadhav007@yahoo.co.in

Abstract: **Weakly basic drugs show large changes in solubility at different pH levels in the gastrointestinal tract, which often leads to irregular or incomplete drug release and reduced bioavailability. In this study, we developed and optimized sustained-release matrix tablets of verapamil hydrochloride (120 mg) using HPMC K4M and sodium alginate. The main goal was to use combinations of organic acids to maintain an acidic microenvironment inside the tablet, so the drug could release consistently at all pH conditions.The tablets were prepared using two approaches—direct compression and dry granulation. Organic acids (malic, ascorbic, and fumaric acid) were added either inside the granules or outside them, or both, so that some acid released quickly while some continued to release over time. We assessed the assay, weight fluctuation, friability, tablet hardness, and powder characteristics. A two-stage dissolving procedure was used to examine drug release: two hours in simulated stomach fluid (pH 1.2) and then adjustment to simulated intestinal fluid (pH 6.8). UV spectroscopy was used to detect the concentration of verapamil at 278 nm.The powders showed satisfactory flow (Hausner ratio 1.235–1.271; Carr's index 19–21%), and the final tablets were strong and uniform (hardness 6.7–7.5 kg/cm², friability below 0.8%, drug content 98–99.5%). In dissolution studies, adding sodium alginate significantly reduced the initial release burst in acidic medium—falling from 49% in the alginate-free batch to 26–35% in alginate-containing formulations. Across 12 hours, total release ranged from 60% to 91%, depending on the acid type and how it was incorporated. The best performance came from formulation F9, which combined malic acid outside the granules and fumaric acid inside them, achieving about 91% release. This blend worked well because malic acid dissolved quickly and helped early drug release, while the slower-dissolving fumaric acid kept the microenvironment acidic even in intestinal pH, supporting continuous drug solubility.Overall, this work shows that carefully selected acid blends, placed strategically within the tablet, can create a controlled microenvironment that allows weakly basic drugs to release in a stable, pH-independent manner. The optimized formulation (F9) is a strong candidate for further development, including stability studies and in-vivo evaluation.**

Keywords: **pH independent release, weakly basic drug, HPMC, sodium alginate, microenvironmental pH.**

INTRODUCTION

The development of effective oral drug delivery systems faces significant hurdles when dealing with weakly basic drugs. These compounds inherently exhibit pH-dependent solubility, a characteristic that poses a considerable challenge to consistent drug release and absorption within the gastrointestinal (GI) tract [1]. Specifically, weakly basic drugs typically demonstrate high solubility in the highly acidic environment of the stomach, where the pH is low. However, their solubility dramatically decreases as the pH increases upon transit into the more neutral to weakly basic regions of the small intestine [2].This pronounced shift in solubility across the

varying pH conditions of the GI tract often leads to pH-dependent, incomplete, or erratic drug release from conventional extended-release formulations [3].As a result, the absorption of the drug may vary, leading to inconsistent and unpredictable bioavailability resulting in poor therapeutic outcomes [4]. Therefore, designing formulations that maintain a constant release profile across the gastrointestinal tract is crucial for improving therapeutic efficacy and patient compliance.

One promising approach involves the incorporation of organic acidifiers such as citric acid, fumaric acid, or succinic acid into the matrix. These acidifiers help modulate the microenvironmental pH within the matrix system, thereby maintaining drug solubility even when external pH rises. This microenvironmental pH modulation has been shown to prevent drug precipitation and enhance the release of weakly basic compounds under intestinal conditions [5,6]. Siepe et al. (2006) explored the incorporation of acidifying agents into matrix systems to maintain a favorable microenvironmental pH. This approach helps to stabilize the solubility of weakly basic drugs throughout gastrointestinal transit [5-9].Similarly, Dvorackova et al. (2010) investigated fumaric and succinic acid to improve dissolution profiles of weakly basic drug in simulated intestinal fluid [1].

Present study aims to optimize a matrix tablet system using HPMC and sodium alginate for the controlled, pH-independent release of Verapamil HCl as a model weakly basic drug. In this study, organic acids—citric, succinic, and fumaric—are evaluated both individually using the direct compression method and in combinations using the dry granulation technique, where the acids are incorporated through intra- and extragranular addition to modulate the microenvironmental pH and sustain drug solubility in intestinal conditions. The objective is to design a robust formulation that ensures consistent drug release over 12 hours, independent of external pH, thereby enhancing drug bioavailability and therapeutic consistency.

MATERIAL & METHODS

Materials: Verapamil hydrochloride (Verapamil HCl) was generously supplied as a gift sample by Emcure Pharmaceuticals Ltd., Pune, India. Hydroxypropyl methylcellulose (HPMC K4M) was sourced from Colorcon Asia Pvt. Ltd., Mumbai, India, and sodium alginate was obtained from Loba Chemie Pvt. Ltd., Mumbai, India. Microcrystalline cellulose (Avicel PH 101), along with fumaric, citric, and succinic acids, was purchased from Research-Lab Fine Chem Industries, Mumbai, India. Aerosil, used as a glidant, and magnesium stearate, employed as a lubricant, were procured from SD Fine-Chem Ltd., Mumbai, India. Sodium triphosphate (STP), utilized for pH adjustment of the dissolution medium, was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. All remaining chemicals and reagents used in the study were of analytical grade. Simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 6.8) were freshly prepared with distilled water in accordance with the procedures described in the United States Pharmacopeia (USP).

Methods:

Preparation of calibration curve: By dissolving 10 mg of the medication in 100 ml of phosphate buffer (pH 6.8) to create a stock solution with a concentration of 100 µg/ml, a calibration curve for verapamil HCl was created. This stock was serially diluted using the same buffer to provide a range of working standard solutions (5–30 µg/ml). A UV–Visible spectrophotometer (Shimadzu UV-1900, Japan) was used to measure each solution's absorbance at 278 nm in comparison to a blank.[10-13]. A plot of absorbance versus concentration was constructed, and linearity was evaluated through the regression equation and correlation coefficient.

Preparation of verapamil hydrochloride matrix tablets:The contents of the various tablet formulations are shown in Table I. The direct compression approach was used to create the first six formulations (F1–F6). Verapamil HCl was blended with specified

quantities of HPMC K4M, sodium alginate, malic acid, ascorbic acid, fumaric acid and Avicel. The mixture was manually mixed and passed three times through an 80-mesh sieve to ensure uniformity, followed by lubrication with magnesium stearate and Aerosil. An eight-station rotary tablet press equipped with 9 mm flat-faced punches was used to compress the finished mixture into matrix tablets. Verapamil HCl, HPMC K4M, sodium alginate, and Avicel were used in the dry granulation (slugging) process to create the final three formulations (F7–F9). In F7, malic acid was added both intragranularly (35 mg, before granulation) and extra granularly (40 mg, after granulation). In F8, ascorbic acid was added in the same way. In F9, fumaric acid (35 mg) was added intragranularly, while malic acid (40 mg) was added extra granularly. After passing the slugs through a 60-mesh filter to create granules, they were lubricated with Aerosil and magnesium stearate before being compacted into matrix tablets using an eight-station rotary press equipped with 9 mm flat-faced punches.

Table I: Formulation table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil HCl	120	120	120	120	120	120	120	120	120
HPMC K4M	110	50	30	30	30	30	30	30	30
Sodium Alginate	0	60	80	80	80	80	80	80	80
Avicel PH 101	117	67	67	42	42	42	42	42	42
Malic Acid	0	50	50	75	0	0	75	0	35
Ascorbic Acid	0	0	0	0	75	0	0	0	0
Fumaric Acid	0	0	0	0	0	75	0	75	40
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

HPMC K4M: hydroxypropyl methyl cellullose K4M, * all quantities are in mg.

Precompression studies: analysis of powder blend: A pre-compression study was carried out to evaluate the flow and compressibility of the powder blend by determining its bulk and tapped densities. Bulk density was measured by loosely filling a graduated cylinder and recording the initial volume, whereas tapped density was obtained by mechanically tapping the cylinder until a constant volume was reached. Using these values, the Hausner ratio and Carr's index were calculated[14-15].

Post compression studies: evaluation of compressed tablets: The hardness, thickness, friability, weight fluctuation, and drug content of the produced tablets were assessed. To provide sufficient mechanical strength, tablet hardness was determined using a Monsanto hardness tester and represented in kg/cm². Thickness was determined with a vernier caliper to confirm dimensional uniformity. The manufactured tablets were evaluated for hardness, thickness, friability, weight variation, and medication content. Tablet hardness was measured using a Monsanto hardness tester and expressed in kg/cm² to ensure adequate mechanical strength. Drug content was determined by finely powdering ten tablets, preparing a suitable dilution with buffer, filtering, and measuring absorbance on a UV–Visible spectrophotometer against the standard calibration curve of verapamil HCl. The percentage drug content was then calculated[14-15].

In-vitro drug release studies:The drug release study was carried out in simulated gastric fluid (SGF, pH 1.2)that was made following the USP standards & represents the ingredients of the stomach environment, during the first two hours of the release study. For the intestinal-phase study(SIF), we used sodium triphosphate (STP) to rapidly convert 0.1 N HCl (pH ≈1.2) to pH 6.8 in situ without removing dissolution vessels, preserving hydrodynamics. 18.7 g STP was added to each 900 mL vessel and the medium measured at pH 6.80 ± 0.05 before resuming dissolution. STP's high solubility and alkalinity provide reliable neutralization and

buffering (Katerina, 2013; Maskova, 2017), enabling a reproducible pH transition without changing volume or agitation [2,16]. At 1, 2, 4, 6, 8, 10, and 12 hours, samples were taken out of the dissolving jar, and each aliquot was quickly replaced with the appropriate amount of new buffer. Withdrawn samples were filtered to remove undissolved particles and analyzed by UV–Visible spectrophotometer at 278nm against standard calibration curves to determine cumulative percent drug release. Each formulation was evaluated using a minimum of six tablets, and the percentage of drug release was determined based on the average of these values[17-21]

RESULT & DISCUSSION

Calibration curve: The calibration curve of Verapamil HCl showed excellent linearity over 5–30 µg/mL, with a regression equation of y = 0.0496x – 0.0063 and R^2 = 0.9999 (Figure I). This confirms the method's suitability for quantitative analysis, making it reliable for drug estimation in dissolution and assay studies.

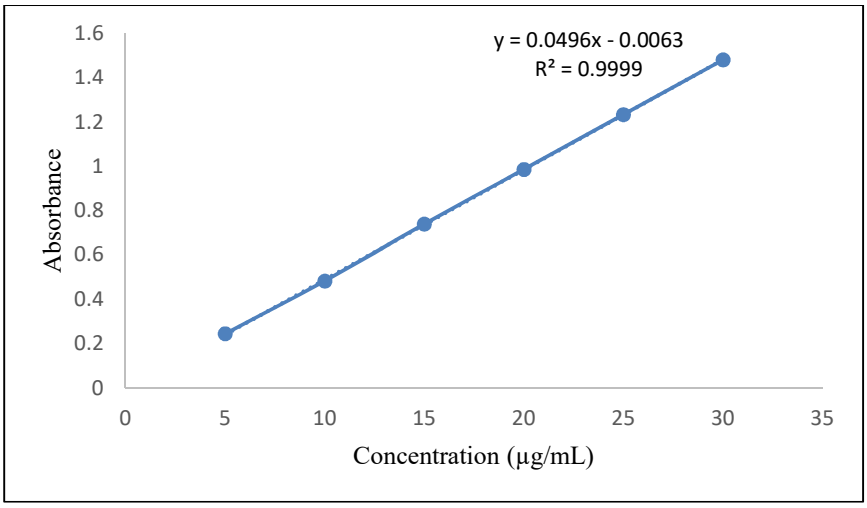

Figure I: Calibration curve in phosphate buffer

Precompression Characterization of Powder Blends:The pre-compression data (Table II) for all nine formulations showed generally acceptable powder flow characteristics, with bulk densities ranging from 0.435–0.471 g/cm³and tapped densities from 0.540–0.591g/cm³**.** Formulation F7 exhibited the lowest Hausner ratio (1.235) and the lowest Carr's index (19.0%), indicating the best flowability among the batches. The other formulations had Hausner ratios between 1.235–1.271 and Carr's index values of 19.0–21.3%, consistent with fair-to-good flow and compressibility. Although a couple of batches (F3 and F5) showed the highest compressibility (Carr's index = 21.3%), overall the blends demonstrated sufficient flow (Hausner ratio < 1.30 and Carr's index ≈ 19–21%) to support uniform die filling. These pre-compression properties suggest moderate interparticle friction but adequate flow for tablet compression, reducing the risk of weight variation and segregation.

Table II: Pre compression evaluation of powder mixture

Formulation	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner Ratio	Carr's Index (%)
F1	0.443±0.03	0.552±0.04	1.246	19.7
F2	0.471±0.05	0.589±0.02	1.250	20.0
F3	0.465±0.02	0.591±0.06	1.270	21.3
F4	0.447±0.01	0.558±0.03	1.248	19.8

F5	0.449±0.03	0.571±0.02	1.271	21.3
F6	0.439±0.07	0.557±0.05	1.268	21.1
F7	0.462±0.04	0.571±0.06	1.235	19.0
F8	0.457±0.05	0.569±0.07	1.245	19.6
F9	0.435±0.04	0.540±0.05	1.241	19.4

Evaluation of tablets: Table III summarizes the physical and content uniformity of nine verapamil HCl matrix tablet formulations (F1–F9). Hardness values (6.7–7.5 kg/cm²) indicate adequate mechanical strength with low variability. Thickness was consistent (4.11–4.17 mm), reflecting controlled compression. Friability values were low (0.42–0.74%), demonstrating robustness during handling; F6 exhibited the highest friability. Average tablet weights ranged narrowly (347–356 mg) with small standard deviations, confirming weight uniformity. Assay results showed drug content between 98.2% and 99.5% with minimal variation, indicating homogenous drug distribution and accurate dosing. Overall, all formulations met acceptable quality attributes for hardness, friability, weight, and assay.

Table III: Post compression evaluation

Formulation	Hardness(kg/cm^2)	Thickness(mm)	Friability(%)	Average weight(mg)	Drug content(%)
F1	7.5±0.3	4.12	0.45±0.32	356±2.2	99.5±0.2
F2	7.3±0.4	4.14	0.42±0.14	348±2.1	98.6±0.3
F3	6.9±0.2	4.13	0.59±0.23	353±4.5	99.2±0.4
F4	7.2±0.3	4.17	0.51±0.25	354±2.5	99.4±0.4
F5	7.1±0.5	4.16	0.67±0.35	347±3.9	98.2±0.5
F6	6.7±0.6	4.14	0.74±0.43	355±3.4	98.8±0.7
F7	7.4±0.4	4.15	0.52±0.16	349±2.9	99.5±0.6
F8	7.2±0.5	4.11	0.71±0.28	353±3.2	98.6±0.3
F9	7.1±0.6	4.13	0.57±0.46S	347±3.7	99.5±0.5

Overall Drug Release Pattern (F1-F9):The drug release profiles across all formulations (F1-F9) reveal distinct patterns influenced by their composition(Figure II). For example, by 2 h (end of SGF) cumulative release ranged from 26–49% across formulations, with F1 (no alginate or acid) showing the highest SGF release (49%) and malic-acid matrices (F3, F4, F7) showing only 26–28%.Formulations F1 and F2 generally exhibited initial burst release (49% & 45% respectively) compared to the other formulations, particularly within the first two hours in SGF. After 2 h, all formulations continued to release drug gradually. By 12 h, cumulative release ranged from 60–91%: the lowest was F1 (60%) and the highest was F9 (91%), with fumaric acid containing F6 (82%) and malic acid containing F7 (78%) intermediate. Formulation with only HPMC (no alginate/acid, F1) plateaued at 60%, whereas those with alginate and acidifiers continued releasing drug up to 12 h. These trends indicate that the matrix composition strongly influenced the release profile: the initial burst (<2 h) decreased and the extended-release phase became more pronounced as sodium alginate is included & type of acid is varied.

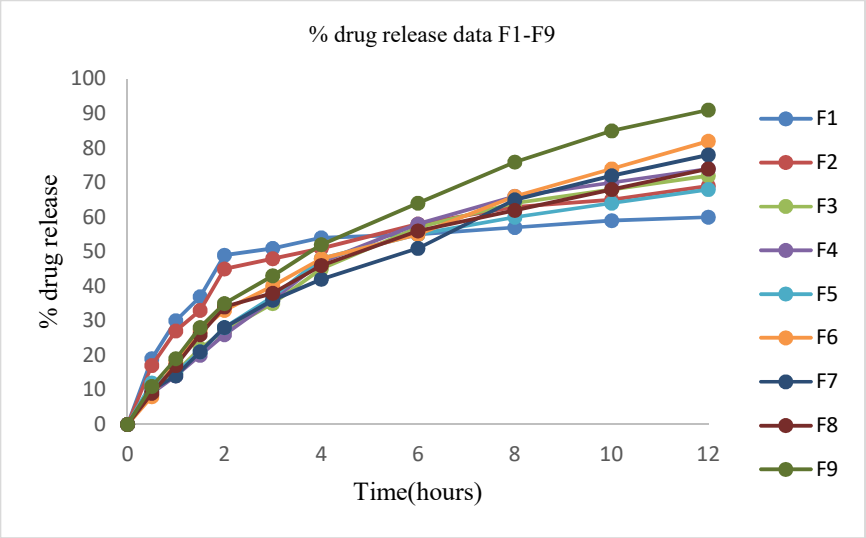

Figure II: %drug release F1-F9

Synergistic effect of HPMC & Sodium alginate:Sodium alginate is a pH-sensitive polyanion (pKa ≈ 3.4–4.4). In the highly acidic gastric environment (pH 1.2) its carboxyl groups are protonated, converting the sodium salt into insoluble alginic acid that forms a dense, cohesive gel barrier and markedly retards drug diffusion[17,18]. This effect is evident at the end of the SGF phase (2 h): F1 released 49% while alginate-containing formulations released only 26–35% (F3 = 27%; F4 = 26%), demonstrating alginate's ability to suppress the initial burst release(Figure III).Upon transition to intestinal fluid (pH 6.8) the alginate carboxylates deprotonate, the polymer chains acquire negative charge, and electrostatic repulsion drives swelling and hydration[18,19]. The hydrated, more porous gel increases aqueous channel formation and facilitates drug release, producing higher release in SIF. This is reflected in the drug release profiles and by 12 h the effect is pronounced, F1 attains only 60% cumulative release, whereas alginate containing batches reach substantially higher values (F2- 69% to F9- 91%).

Thus, the dual polymer strategy yields a desirable two-phase behavior: alginate's insoluble gel at gastric pH minimizes early burst, while its ionization and swelling in intestinal pH convert the same matrix into a more permeable network that sustains and enhances verapamil release through 12 h.

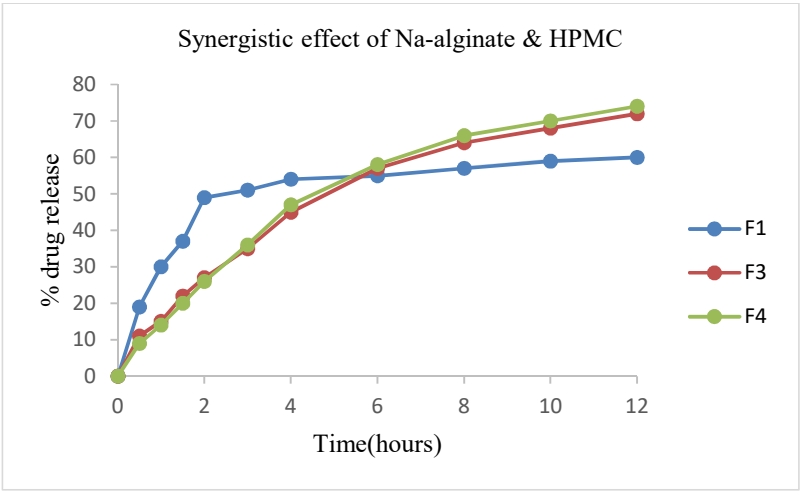

Figure III: Synergistic effect of Na-alginate & HPMC

Effect of organic acids: Batches containing malic acid(F2-F4) showed promising drug release (63-66% at 8 hours) for first few hours in SIF but their release slowed after 8 hours (69-74% at 12h), likely due to the rapid dissolution of malic acid and loss of acid reservoir. In contrast Fumaric Acid Formulation (F6) showed the higher cumulative drug release, (F6- 82% at 12 hours) indicating sustained and complete release.Notably, the dual-acid formulation F9 (35 mg malic + 40 mg fumaric) achieved ~91% release, the highest of all – suggesting an additive or synergistic effect of combined acids(see intragranular discussion below). In contrast, ascorbic acid containing batch (F5) gave only 68% cumulative release, the lowest among the acid-modified systems(Figure IV).

Several reasons account for the better performance observed with fumaric acid.First, fumaric acid is a strong acid (pKa≈3.0) but has very low solubility in near-neutral medium (≈10 mg/ml at pH 6.8), whereas malic acid (pKa≈3.4) is highly soluble (~561 mg/ml)[8,17].Thus, fumaric acid remains in the gel layer throughout dissolution and continuously acidifies it, whereas malic acid dissolves away rapidly once the medium changes to pH 6.8. Similar trends have been described in the studies of Siepe et al(2006) and Streubel et al(2000)[2,5]**.** In practice, we observed that malic acid tablets lost their acid reservoir after ~8 h, so their microenvironmental pH rose and release slowed. By contrast, fumaric-acid tablets sustained a low internal pH, prolonging verapamil solubility and diffusion in the intestinal phase. Ascorbic acid (pKa≈4.2) [Ref] is weaker acid and more soluble than fumaric, so F5 showed only modest improvements over other matriceswith F5 reaching 68% at 12 hours.

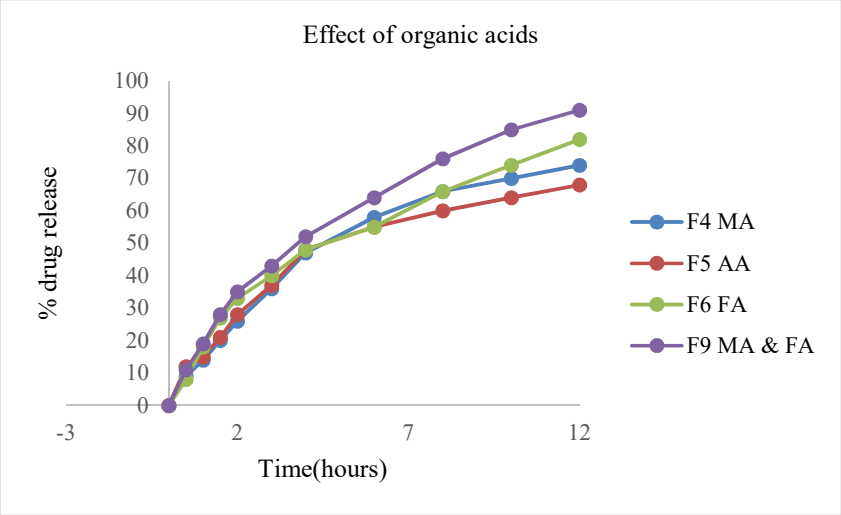

Figure IV: Effect of organic acids

Effect of Intragranular vs. Extragranular Acid Placement:The placement of tablet excipients — intragranular vs. extragranular, affects their availability and duration of action. Intragranular addition (before granulation) embeds the excipients in the granule core so it is released slowly as the matrix hydrates and erodes, whereas extragranular addition (during lubrication) positions it at or near the surface so it dissolves rapidly. Accordingly, we split the organic acid between extragranular (for immediate pH modulation) and intragranular fractions (for sustained microenvironmental acidification), combining early acidifying action with prolonged local pH control to promote more consistent pH-independent drug release. However, when the same organic acid was incorporated in both intragranular and extragranular fractions, only a slight improvement in cumulative release was observed. For instance, with malic acid, intragranular placement in F7resulted in slightly higher cumulative release (78% at 12 h) compared to the direct compression

batch F4 (74%). In the case of fumaric acid, however, intragranular incorporation in F8 produced a lower release (74%) than the corresponding direct compression batch F6 (82%). Notably, F9 (extragranular malic acid + intragranular fumaric acid) produced the highest drug release (91% at 12 h), among all other batches(Figure V).

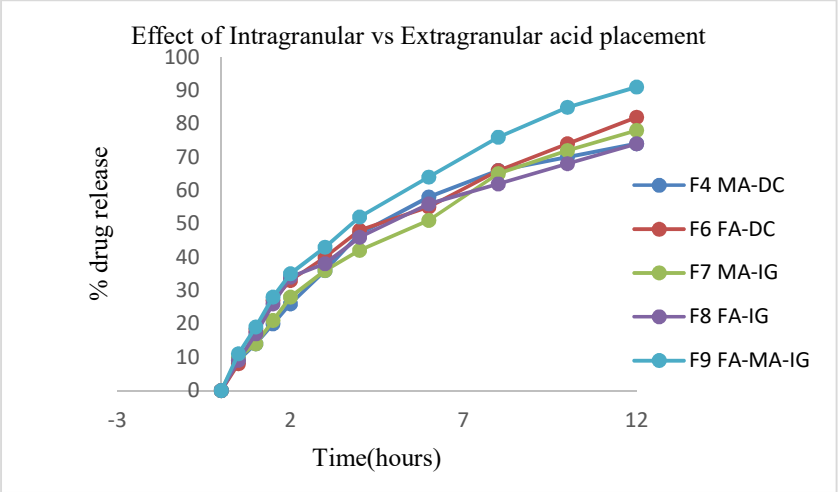

Figure V: Effect of Intragranular vs Extragranular acid placement

This improvement likely reflects complementary actions: extragranular malic acid, being highly water-soluble, dissolves rapidly at the tablet surface to produce immediate pH modulation to accelerate early drug solubilization; intragranular fumaric acid, entrapped in the granule coreand has low aqueous solubility, so it is released slowly and sustains a lowered microenvironmental pH during the intestinal phase.These complementary actions are likely responsible for the improved cumulative release of F9.

CONCLUSION

This study confirms that microenvironmental pH modulation using organic acids within HPMC–sodium alginate matrices is an effective approach for achieving pH-independent controlled release of verapamil hydrochloride. The addition of sodium alginate reduced the initial burst in acidic medium and supported sustained drug release through its ionization-based swelling behavior. Organic acids played a key role in maintaining an acidic environment around the drug, improving solubility across changing gastrointestinal pH conditions. Among all formulations, the dual-acid blend in F9—extragranular malic acid combined with intragranular fumaric acid—provided the most consistent 12-hour release profile (approximately 91%). This optimized performance resulted from the rapid action of malic acid and the prolonged acidifying effect of fumaric acid. Overall, the study demonstrates that carefully selecting and positioning organic acids can overcome the pH-dependent solubility limitations of weakly basic drugs. The optimized formulation is suitable for further stability testing and in-vivo evaluation.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Mr. Ravi Gaware carried out the overall conceptualization and study design, prepared the matrix tablet formulations, performed all laboratory experiments, analyzed the in vitro release data, and developed the tables, figures, and initial manuscript draft. Dr. K. Sarvanan provided essential guidance and expert supervision throughout the research, offering scientific insights, helping refine the experimental protocol, and critically reviewing the results. His contribution was central to maintaining methodological quality and scientific rigor. Dr. Suresh Jadhav, as co-guide, supported the selection and justification of excipients, contributed to the interpretation of dissolution data, and assisted in improving the manuscript's technical clarity and academic presentation. All authors reviewed and approved the final manuscript.

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