

# Modulation of pH-Independent Release of a Class II Drug (Domperidone) from a Polymeric Matrix Using Acidic Excipients

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## ABSTRACT

Drug release from polymeric matrix systems is the rate-limiting step for drug bioavailability and is determined by drug solubility; most drugs show pH-dependent solubility. Polymeric matrices remain in the gastrointestinal tract for a longer period of time and are exposed to environments of varying pH, which can adversely affect drug release. In the present study, the pH-independent drug release of domperidone was achieved by modifying the microenvironmental pH of a swollen polymeric matrix using acidic excipients (citric acid and tartaric acid). Matrices were prepared by a water-based, wet-granulation technique and evaluated for various official and unofficial parameters. In vitro drug release was studied using USP dissolution apparatus and pH 6.80 phosphate buffer as dissolution medium. Release kinetics was evaluated according to various mathematical models.

Results show that domperidone release can be effectively modified by inclusion of acidic excipients in the formulations. Acidic excipients modulated microenvironmental pH and avoided the effect of dissolution medium pH on drug release. The resultant formulations are easy to prepare and scale up for commercial manufacturing. Better pH-independent release, following zero-order kinetics, was achieved with tartaric acid.

**KEYWORDS:** Domperidone; polymeric matrix; citric acid; tartaric acid; pH-independent drug release; dissolution.

## INTRODUCTION

Hydrophilic matrix tablets are widely used for oral extended-release dosage forms because of simplicity, cost effectiveness, and reduced risk of systemic toxicity due to dose dumping (1). The rate-limiting step for drug bioavailability from a hydrophilic matrix system is dissolution. Fluids penetrate the matrix system, dissolve the drug, and diffuse it out of the matrix system in a controlled manner (2). The whole process is governed by drug solubility in the dissolution medium. Most of the drugs have pH-dependent solubility (1, 3), exhibiting varying release rates with changing pH in the gastrointestinal tract (GIT). Penetration of GIT fluids with varying pH causes conversion of the more ionizable drug (soluble form) to a less soluble form. Thus, the diffusion rate of the drug through the matrix is reduced. This conversion into an insoluble form depends on the  $pK_a$  value of the drug and the pH of the intestinal fluids (3, 4). It is desirable to achieve drug release independent of the environmental pH for making the required dose bioavailable (3, 4). As the pH of GIT fluids cannot be changed, an optimized pH in the dosage form can be used to modulate the release

rate of drugs exhibiting pH-independent solubility and to overcome the problem of varying drug release patterns in different pH environments. Modulation of the pH in the dosage form can modify the release rate of pH-dependent soluble drugs so that drug can be released at the desired rate irrespective of the environmental pH.

Various approaches have been made to improve the bioavailability of drugs with pH-dependent solubility. Most often cited are formulations of a solid dispersion with a water-soluble, rate-enhancing polymer such as polyethylene glycol (5), microencapsulation with hydrophilic polymers (6), and formation of inclusion complexes with a water-soluble material such as  $\beta$ -cyclodextrin (7). Another possible strategy is the incorporation of pH modifiers in the dosage form. Release of pH-dependent drug from matrix tablets can be successfully enhanced by maintaining the pH of the matrix in the desired range (8, 9). The release of weakly basic drugs is expected to be improved by inclusion of weak acids and vice versa. This will alter the microenvironmental pH within and in the close vicinity of the matrix system.

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Domperidone is a dopamine (D<sub>2</sub>) antagonist prescribed for the treatment of nausea and vomiting of various etiologies (10). The typical dose of domperidone is 10–40 mg daily and is 91–93% protein bound having an elimination half-life of 5–7 h. Domperidone is a weak base having pH-dependent solubility (11). It is practically insoluble in water and has good solubility in acidic pH, which is significantly decreased in alkaline pH (6). The melting point of domperidone is in the range of 244–246 °C, and its chemical structure is presented in Figure 1.

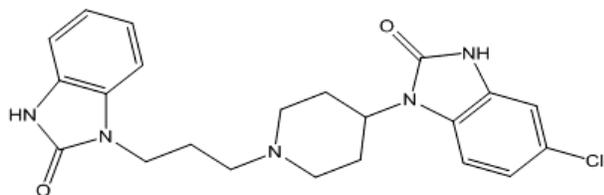


Figure 1. Chemical structure of domperidone.

Domperidone was selected as a model drug due to its pH-dependent solubility. When a controlled-release dosage form of a weakly basic drug having pH-dependent solubility is exposed to an environment of increasing pH, the drug in the dosage form precipitates and can no longer be released from the dosage form (6, 12). There is a need for pH-independent release of domperidone so that it can be converted into a slow-release dosage form to avoid frequent dosing and to maintain blood concentration within the therapeutic range.

The aim of the present study was to systematically and quantitatively investigate possibilities of modulating the release of domperidone from matrix tablets by modifying the microenvironmental pH within the matrix system. For this purpose, acidic excipients in various concentrations were used with polyvinylpyrrolidone as the matrix-forming material.

## MATERIAL AND METHODS

### Material

Domperidone (Ningbo Sansheng Pharmaceuticals Company, China) was procured from Medicraft Pharmaceuticals, Peshawar, Pakistan. Citric acid and tartaric acid (Merck KGA, Germany) were purchased from Sigma Chemicals, Pakistan. The other excipients, polyvinylpyrrolidone (PVP-K90, I.S.P. Technology, Texas), lactose (Kerry Biosciences, USA), and magnesium stearate (Peter Graven, Malaysia), were a kind gift from Ferozsans Laboratories, Pvt. Ltd, Nowshera, Pakistan. All the materials were of pharmaceutical grade. Tartaric acid and citric acid were pulverized through a 40-mesh sieve to reduce the particle size while the rest of the excipients were used as received.

### Preparation of Matrix Tablets

Polyvinylpyrrolidone K90 (PVP-K90) was used for the preparation of matrix tablets containing 10 mg of domperidone by a wet-granulation technique. Initially, acidifiers were used in different concentrations, keeping the quantity of polymer constant. In the second phase, the quantity of acidifier was constant and the quantity of polymer was increased gradually to sustain drug release for a longer period of time.

All the ingredients were accurately weighed using a digital balance (Shimadzu, Japan) according to their respective formulations as given in Table 1. Drug, release modifier (acidifiers), PVP-K90, and lactose were blended together in a laboratory-scale mixer. Wet-massing of the powder blend was performed using a sufficient quantity of purified water. The wet material was kneaded for 5 min, passed through a 10-mesh sieve, and dried in a hot-air drier at 60 ± 5 °C for 3 h. The dried mass was granulated through a 20-mesh sieve using rotary granulator (STC, China) and properly stored. Prior to compression, granules for each formulation were lubricated with magnesium stearate.

Table 1. Composition of Matrix Tablets of Domperidone

Ingredient <sup>a</sup>	BD-01	BD-02	BD-03	BD-04	BD-05	BD-06	BD-07	BD-08	BD-09	BD-10	BD-11
Domperidone	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67
PVP K90 <sup>b</sup>	13.33	13.33	13.33	13.33	13.33	13.33	13.33	26.66	33.33	26.66	33.33
Mg stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Lactose	78.00	71.33	64.67	58.00	71.33	64.67	58.00	44.67	38.00	44.67	38.00
Citric acid	–	6.67	13.33	20.00	–	–	–	–	–	20.00	20.00
Tartaric acid	–	–	–	–	6.67	13.33	20.00	20.00	20.00	–	–
Purified water	Q.S.										

<sup>a</sup> Quantities given as % w/w

<sup>b</sup> polyvinylpyrrolidone K90

Magnesium stearate was sifted through a 60-mesh sieve and blended with the granules in a laboratory-scale, double-cone mixer at 25 rpm for 5 min. The lubricated granules were compressed using a rotary compression machine ZP-19 (STC, China) fitted with 7-mm round, beveled-edged punches.

### Evaluation of Matrix Tablets

Matrix tablets from all the formulations were evaluated for various official and unofficial parameters.

#### Weight Variation and Thickness

Weight variation of the tablets from each formulation was calculated after determining the weight of 20 tablets individually (13) using a digital balance (Precisa, Switzerland).

The thickness of 10 randomly selected tablets was measured using a digital tablet tester (Pharma Test, Germany), and the mean and standard deviation were calculated.

#### Tablet Crushing Strength and Tensile Strength

Crushing strength was determined for 10 tablets, randomly selected from each formulation, using a digital tablet tester (Pharma Test, Germany), and the results are presented as mean  $\pm$  SD.

Tensile strength was calculated from the mean values of crushing strength, thickness, and diameter of the tablets (14) using the following equation:

$$T_s = \frac{2F}{\pi TD}$$

where  $T_s$  is the tensile strength of the tablet ( $\text{kg}/\text{mm}^2$ ),  $F$  is the crushing strength of the tablet (kg),  $T$  is the thickness of the tablet (mm),  $D$  is the diameter of the tablet (mm), and  $\pi$  is a constant (3.143).

#### Tablet Friability

The friability of tablets from each formulation was determined as per the official method (13) using a single drum friabilator (Faisal Engineering, Pakistan).

#### Tablet Moisture Content

The moisture content of tablets from each formulation was determined gravimetrically, in triplicate, according to the official method (14) using a helium moisture analyzer (Mettler Toledo, Switzerland).

#### Tablet Wetting Time

Tablet wetting time was determined by placing a tablet on doubled-folded filter paper (Whatman Grade 2, Sigma Aldrich) soaked in 5 mL of pH 6.80 phosphate buffer. The time for complete soaking of the tablet was determined in triplicate using a digital stopwatch (Sony, Japan), and results are presented as mean  $\pm$  SD.

#### Domperidone Content of Matrix Tablets

The domperidone content of the matrix tablets was determined according to the *British Pharmacopoeia* (13) using methanol as a solvent and blank. The absorbance of sample and standard solutions was measured at 384 nm using a double-beam UV-vis spectrophotometer (Perkin Elmer, U.S.A.), and drug content was calculated using following equation:

$$\% \text{ Drug content} = \frac{A_{\text{sample}}}{A_{\text{std}}} \times 100$$

where  $A_{\text{sample}}$  is the absorbance of the test solution and  $A_{\text{std}}$  is the absorbance of the standard solution.

#### In Vitro Drug Release

In vitro drug release was studied for six tablets, randomly selected from each formulation, using USP Apparatus 2 (paddle method) at a rotation speed of 50 rpm. Phosphate buffer pH 6.8 (900 mL) at  $37 \pm 2$  °C, was used as the dissolution medium. Samples (5 mL) were withdrawn at various time intervals, filtered, and analyzed for drug content in triplicate using a double-beam UV-vis spectrophotometer. Results are presented graphically as mean  $\pm$  SD.

#### Kinetics of Drug Release

Drug release kinetics was studied for the formulations containing a fixed quantity of the acidifier with varying polymer content by various mathematical models considering the quantity of domperidone released at various time intervals (0–250 min). The best-fit model was determined by plotting the results of in vitro drug release according to the various mathematical models, such as the zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas, and calculating  $r^2$  values:

Zero-order:  $Q_t = Q_0 + k_0 t$

First-Order:  $\log C = \log C_0 - K_1 \frac{t}{2.303}$

Higuchi:  $Q_t = k_2 t^{1/2}$

Hixson–Crowell  
Cube Root:  $W_0^{1/3} - W_t^{1/3} = k_h t$

Korsmeyer–Peppas:  $\frac{Q_t}{Q_\infty} = K_p t^n$

Table 2. Post Compression Evaluation of Matrix Tablets<sup>a</sup>

Formulation	Weight Variation (%)	Thickness (mm)	Crushing Strength (kg)	Tensile Strength (kg/mm <sup>2</sup> )	Friability (%)	Moisture Content (%)	Drug Content (%)
BD-01	± 2.37	3.21 ± 0.05	4.35 ± 0.31	0.123	0.45	2.69 ± 0.09	101.72 ± 0.16
BD-02	± 4.18	3.16 ± 0.03	4.22 ± 0.17	0.121	0.30	2.37 ± 0.06	98.29 ± 0.09
BD-03	± 2.95	3.28 ± 0.06	4.20 ± 0.22	0.116	0.30	2.93 ± 0.03	101.75 ± 0.13
BD-04	± 2.87	3.14 ± 0.02	4.45 ± 0.09	0.129	0.15	2.17 ± 0.09	100.73 ± 0.11
BD-05	± 3.61	3.00 ± 0.01	4.44 ± 0.12	0.135	0.30	2.05 ± 0.03	101.26 ± 0.07
BD-06	± 4.39	3.21 ± 0.06	4.03 ± 0.11	0.114	0.30	2.63 ± 0.10	98.81 ± 0.06
BD-07	± 2.05	3.28 ± 0.08	3.59 ± 0.09	0.099	0.30	2.44 ± 0.06	100.39 ± 0.12
BD-08	± 4.72	3.27 ± 0.04	4.88 ± 0.10	0.136	0.45	2.01 ± 0.03	102.30 ± 0.11
BD-09	± 3.06	3.69 ± 0.03	7.01 ± 0.08	0.173	0.15	2.38 ± 0.01	101.59 ± 0.26
BD-10	± 4.2	3.21 ± 0.05	5.45 ± 0.15	0.154	0.30	2.31 ± 0.08	98.90 ± 0.17
BD-11	± 3.83	3.26 ± 0.03	6.81 ± 0.08	0.190	0.45	2.52 ± 0.09	101.67 ± 0.14

<sup>a</sup> Results are presented as mean ± SD

where  $Q_0$ ,  $Q_t$ , and  $Q_\alpha$  are the amounts of drug release at times 0,  $t$ , and  $\alpha$ , respectively;  $C_0$  and  $C_t$  are the concentrations of drug initially and at time  $t$ ;  $W_0$  and  $W_t$  are amounts of drug remaining in dosage form initially and at time  $t$ ; and  $k_0$ ,  $k_1$ ,  $k_2$ ,  $k_h$ , and  $k_p$  are the rate constants for the respective models.

## RESULTS AND DISCUSSION

### Physical Parameters of the Matrix Tablets

Matrix tablets of domperidone were compressed using 7.00-mm round punches at a compression weight of 150 mg/tablet. Tablets from all the formulations were smooth and shiny without any sticking or picking. As shown in Table 2, the weight variation of the tablets was low. The highest weight variation was observed for BD-08 (±4.72%) and is within the official limits (13). Matrix tablets were prepared by a wet-granulation technique using a large quantity of PVP K-90. The resultant granules had very efficient flow resulting in a narrow range of weight variation.

The thickness of the tablets was within the range of 3.00–3.70 mm. Proper lubrication of the granules resulted in a smooth surface.

The moisture content of the tablets was determined gravimetrically in triplicate, according to USP (14), and was less than 3% w/w. The highest moisture content was observed for BD-03 (2.93 ± 0.06% w/w). All the formulations had optimum moisture content as evident from the physical shape and mechanical strength of the tablets.

Friability of the tablets was determined according to the British Pharmacopoeia (13) and was within the official

limit (<0.80%) for all the formulations.

Tablets from all the formulations were of sufficient hardness. The crushing strength of the tablets was within the range of 4.00–7.50 kg and increased with the quantity of polymer. The highest crushing strength was observed for BD-09 (7.01 ± 0.22 kg,  $n = 10$ ) containing 33.33% (w/w) of the polymer. The higher binding effect of PVP resulted in an increased crushing strength of the tablets.

The tensile strength of the tablets was calculated on the basis of mean crushing strength and thickness of the tablets. As shown in Table 2, tablets from all the formulations had higher tensile strength. The lowest tensile strength was observed for BD-07 (0.099 kg/mm<sup>2</sup>).

The domperidone content for all the formulations was determined in triplicate, and results are presented as mean ± SD in Table 2. For all the formulations, domperidone content was in the range of 98–102.50% indicating uniform mixing of drug and excipients.

### Selection of Acidifiers for Modulation of Microenvironmental pH

Acidifiers used for modulation of the microenvironmental pH of the matrix tablets were selected on the basis of acid strength and water solubility. An acidifier with good acid strength will produce remarkable changes in the microenvironmental pH of the gel layer surrounding the matrix irrespective of the penetrating fluid. With reduced solubility, an acidifier will not diffuse out of the matrix quickly and will remain there for a longer period of time to control the microenvironmental pH.

In the present study, two acidifiers, citric acid and tartaric acid, were selected to control the microenvironmental pH of the PVP matrix for achieving pH-independent release. Both of the acidifiers are commonly used in pharmaceuticals and are cost effective and safe.

Citric acid is a short-chain organic tricarboxylic acid having an average molecular weight of 192.124 g/mol. Experimental water solubility of citric acid is 592 mg/mL (15), and the predicted solubility is 105.99 mg/mL (predicted by ALOGPS). The pH of a 0.1 N aqueous solutions is 2.2.

Tartaric acid is a crystalline solid, short-chain dicarboxylic acid with an average molecular weight of 150.087 g/mol and water solubility of 1.33 g/mL (20 °C). Some of the characteristics of citric acid and tartaric acid are summarized in Table 3.

Table 3. Comparison of Acidifiers Used for Modulation of Microenvironmental pH

Characteristic	Citric Acid	Tartaric Acid
Molecular weight (g/mol)	192.126	150.087
Acid strength	Tricarboxylic	Dicarboxylic
Water solubility (g/mL)	0.6	1.33
pH	2.2 (1% w/v solution)	2.2 (1.5% w/v solution)

### In Vitro Drug Release from Matrix Tablets

In the present study, polyvinylpyrrolidone (PVP-K90) was used as a matrix-forming polymer. PVP is a white amorphous, free-flowing hygroscopic powder with a weak characteristic odor. It is a nonionic water-soluble polymer and forms a viscous gel layer in contact with water (16). The dissolution medium penetrates the inner portions of the matrix layer-by-layer, and drug is released in a controlled manner. The rate of drug release from the PVP matrix is controlled by diffusion of drug through the gel layer and erosion of the gel layer.

### Effect of Acidifier Concentration on Drug Release

The solubility of domperidone was determined in purified water, 0.1 N HCl (pH 1), and pH 6.8 phosphate buffer. Domperidone is highly soluble ( $509 \pm 48.7 \mu\text{g/mL}$ ) at pH 1, while its solubility significantly decreases ( $3.8 \pm 0.4 \mu\text{g/mL}$ ) at pH 6.8. In vitro drug release was studied at pH 6.8 without any pH switch because our aim was to modulate drug release only at a basic pH.

Three levels of acidifiers (6.66%, 13.33%, and 20.00% w/w) were selected on the basis of their weight–weight ratio to the drug and studied at a fixed polymer concentration (13.33% w/w).

A significant increase in domperidone dissolution rate was observed in the presence of acidifiers, as compared with matrix without acidifier. Acidifiers created an acidic pH in the microenvironment of the gel layer, irrespective of the pH of dissolution medium, resulting in an enhanced dissolution rate.

During the wet-granulation process, dissolved acidifier distributed around nondissolving particles of the polymer and formed a layer on drying, while undissolved acidifier remained entrapped among the polymer particles and modulated microenvironmental pH inside the matrix gel (4, 17).

The effect of acidifier on the dissolution rate of domperidone was more pronounced during the initial 60 min and reduced with the passage of time due to outward diffusion of the acidifiers. Reducing the solubility of the acidifier or any other approach for reducing its outwards diffusion will keep the acidifier inside the matrix for a longer time producing a sustained pH-modulating effect.

At a fixed polymer quantity, domperidone exhibited acidifier-dependent drug release. A maximum of 57.02% drug released from the matrix in one hour. The drug release rate was higher during the initial 15 min and decreased with the passage of time.

With an increase in the concentration of citric acid up to 20% of total tablet weight, the dissolution rate of domperidone increased accordingly, and more than 90% of the drug was released (Figure 2). The rate of drug release was higher during the first 60 min at higher citric acid concentration and reduced with the depletion of citric acid, indicating that the rate of drug release was higher as long as citric acid remained inside the matrix.

Due to the lower acid strength of tartaric acid, the increase in drug release was lower compared with citric acid, and 50.39% drug released at a 6.66% (w/w) concentration (Figure 3). An increase in the concentration of tartaric acid increased drug release but was lower than that with citric acid.

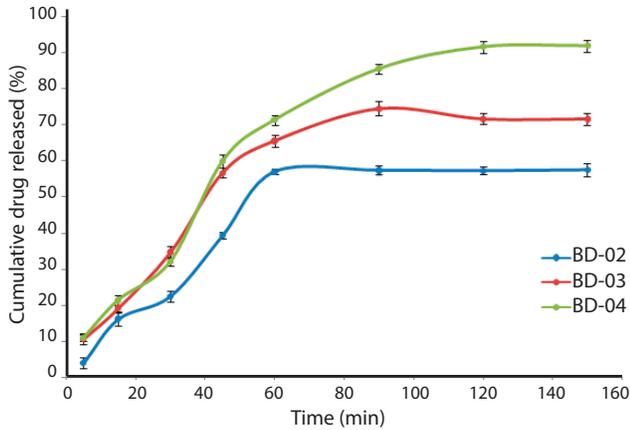


Figure 2. Dissolution profiles of domperidone matrix tablets containing varying citric acid and constant polymer concentrations.

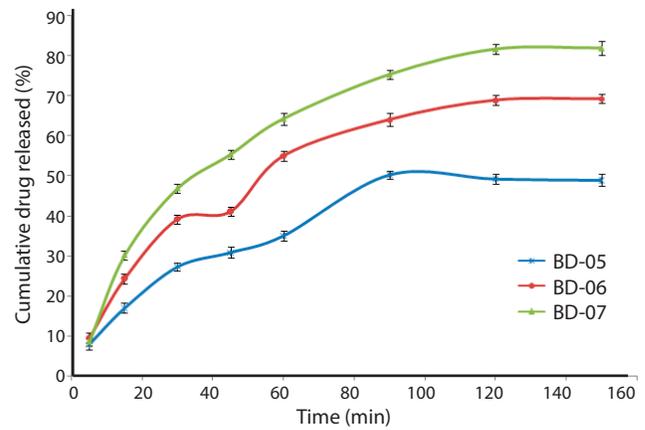


Figure 3. Drug release profiles of matrix tablets with varying tartaric acid and constant polymer concentrations.

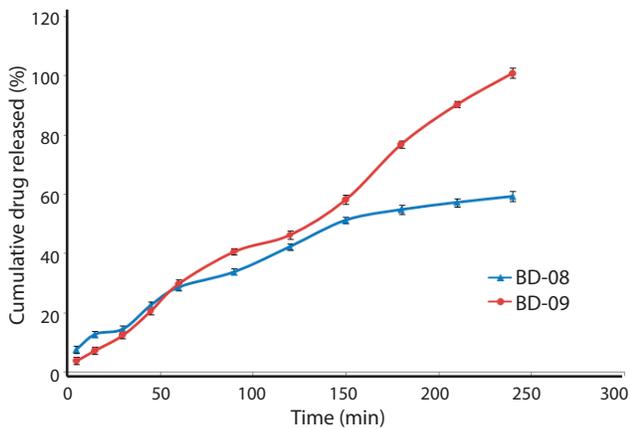


Figure 4. Effect of polymer concentration on drug release from matrices containing citric acid in a fixed concentration.

### Effect of Polymer Concentration

An increase in polymer concentration at a fixed acidifier concentration (20% w/w) resulted in a linear drug release for longer duration (Figure 4). At a lower polymer concentration (26.66% w/w), drug release extended for 240 min and reached 59.30% (BD-08). An increase in polymer concentration up to 33.33% of total tablet weight extended drug release for 240 min at a higher rate, and 100% drug was released (BD-09). Drug release was linear, and no burst effect was observed as the acidifier remained inside the matrix and released at a slower rate due to the thick gel layer.

Better control was achieved with tartaric acid (Figure 5) than with citric acid due to its low water solubility. Tartaric acid dissolves slowly and diffuses out of the matrix at a lower rate than citric acid, maintaining the pH of the gel layer on the acidic side for a longer period of time, thus regulating domperidone release. Lower polymer

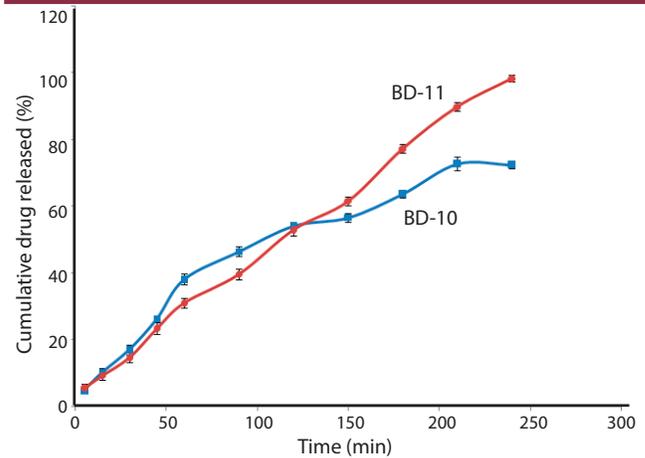


Figure 5. Effect of polymer concentration on drug release from matrices containing a fixed tartaric acid concentration.

concentration (26.66% w/w) extended drug release for 210 min, releasing 72.91% drug. An increase in polymer concentration up to 33.33% extended drug release for 24h at a constant rate. A maximum of 98.42% drug released within 24 h (BD-11).

At a higher polymer concentration, a more viscous gel layer was formed and a relatively longer time was required for polymer chain elongation and erosion of the gel layer. Due to a viscous gel layer formed by higher polymer concentration, the release rate of the acidifier from the polymer was reduced. As a result, the acidifier remained in the matrix for a longer time and maintained the acidic pH of the microenvironment, providing an extended-release modulating effect.

Acidifiers increased drug release from the matrix by preventing the drop in drug solubility due to changes in pH of the dissolution medium and providing an environment

of pH control within the gel layer (4, 17). As long as the pH of the microenvironment of the gel layer is maintained within the desired range, drug will keep dissolving.

### Effect of Admixed Acid on pH of the Dissolution Medium

The dissolution rate of the matrix tablets was determined using pH 6.8 phosphate buffer as the dissolution medium (900 mL). The highest amount of acidifier used in the formulation of matrix tablets for pH modulation was 20% (w/w) of the total tablet weight (30 mg/tablet); that is, 30 mg of acidifier was available to be released into the dissolution medium from one tablet during the determination of dissolution rate. The pH of the dissolution medium was checked at different intervals to evaluate the effect of released acid on the pH of the dissolution medium. Results are presented in Table 4.

Table 4. Effect of Acidifiers on Dissolution Medium pH

Time (min)	pH of Medium <sup>a</sup>	
	Tartaric Acid	Citric Acid
0	6.80 ± 0.10	6.80 ± 0.10
60	6.41 ± 0.20	6.00 ± 0.20
After completion	6.10 ± 0.10	5.70 ± 0.20

<sup>a</sup> Mean ± SD

The pH of the dissolution medium remained unaffected at lower acidifier concentration, as shown in Figure 6, and dropped significantly at higher concentration (20.00% w/w). A decrease in the pH of the dissolution medium was more pronounced with citric acid (5.70 ± 0.20, *n* = 3) than with tartaric acid (6.10 ± 0.10, *n* = 3).

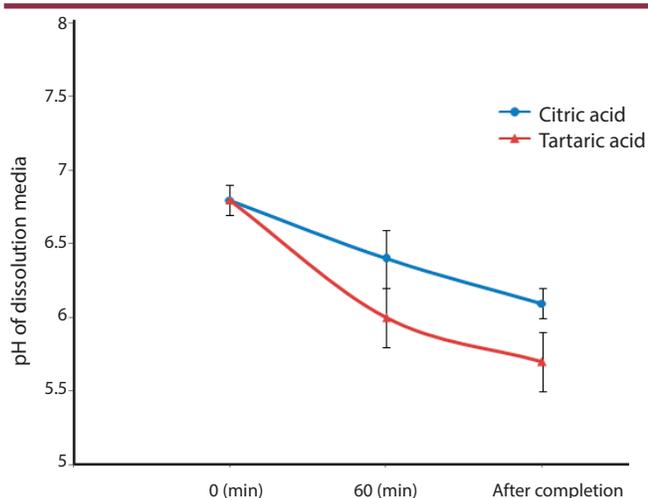


Figure 6. Effect of acidifiers on the pH of dissolution medium.

Monitoring the pH of the dissolution medium provides an indication of the amount of dissolved acid. A shift in the pH of the dissolution medium to the acidic side indicates a release of acidifier from the matrix but is detectable only when large amounts of the acidifiers are used producing marked changes in dissolution medium pH.

### Effect of Acidifier Nature on Drug Release (Comparison of Acidifiers)

Two acidifiers (citric acid and tartaric acid) were studied for modulation of the microenvironmental pH of the PVP matrix containing domperidone. The acidifiers have different acid strengths and water solubilities. Citric acid is a tricarboxylic acid, and a 1% w/v aqueous solution has a pH of 2.20, while the same pH is obtained with a 1.50% w/v solution of tartaric acid. On the basis of ionic strength, both acidifiers were expected to produce different effects on enhancing the dissolution rate of domperidone.

The acidifiers exhibited a concentration-dependent effect on the dissolution rate of domperidone from matrix tablets. A burst release was observed initially with tartaric acid at lower polymer concentration. In the case of citric acid, no burst release was observed, and the amount of drug released during the initial 50 min was lower than that of tartaric acid. Maximum drug release was higher with citric acid (76.88 ± 0.19%, *n* = 3) than with tartaric acid (72.91 ± 0.27%, *n* = 3).

Both acidifiers produced a different effect on the pH of the dissolution medium when used at the maximum concentration. Citric acid reduced the pH of the dissolution medium to 5.70 ± 0.02 (*n* = 3), while with tartaric acid, the pH of the medium was 6.10 ± 0.10 (*n* = 3), indicating that citric acid was more effective in reducing the pH of the dissolution medium.

### Kinetics of Drug Release

Drug release kinetics was studied for the formulations containing fixed quantities of acidifiers (20% w/w) and variable polymer concentrations (26.66% and 33.33%, w/w). The goodness of fit was evaluated on the basis of the *r*<sup>2</sup> values as presented in Table 5.

Among the four formulations, a zero-order release of domperidone from polymeric matrix was achieved with BD-09 (*r*<sup>2</sup> = 0.976) containing tartaric acid (20% w/w) and PVP-K90 (33.33% w/w). Due to relatively lower water solubility, tartaric acid remained entrapped in the polymeric matrix system for a longer time and achieved

Table 5. Mathematical Modeling of Drug Release Kinetics from Formulations Containing Varying Polymer Concentrations

Formulation	Zero Order	First Order	Higuchi	Hixson Crowell	Korsmeyer Peppas		Release Mechanism
	$r^2$	$r^2$	$r^2$	$r^2$	$r^2$	$N$	
BD-08	0.956	0.832	0.984	0.974	0.979	0.568	Non Fickian Diffusion
BD-09	0.976	0.790	0.987	0.995	0.990	0.882	Non Fickian Diffusion
BD-10	0.943	0.748	0.986	0.975	0.987	0.734	Non Fickian Diffusion
BD-11	0.952	0.776	0.987	0.979	0.984	0.682	Non Fickian Diffusion

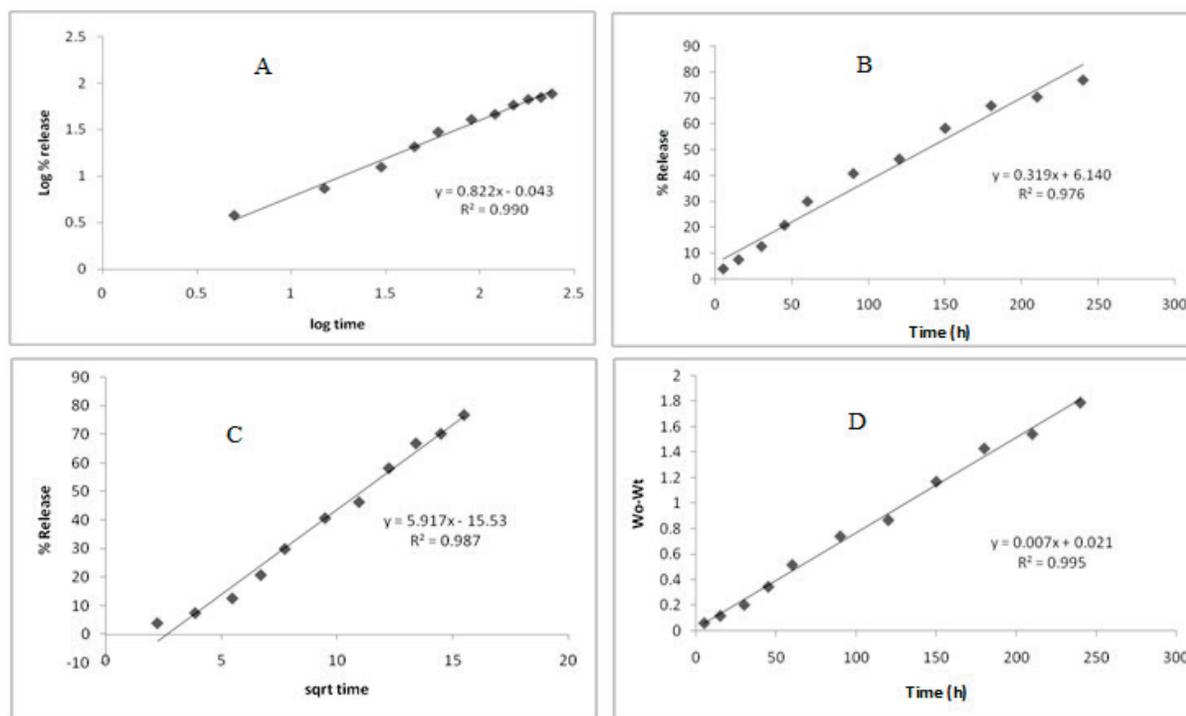


Figure 7. Graphical presentation of in vitro drug release data according to (A) Korsmeyer, (B) zero-order, (C) Higuchi, and (D) Hixson-Crowell models.

zero-order release of domperidone. The in vitro drug release profile of BD-09 exhibited best fit for the rest of the mathematical models as shown in Figure 7. The  $n$  value of the drug release data calculated according to the Korsmeyer–Peppas equation (0.882) showed that drug release was diffusion controlled.

## CONCLUSION

A pH-independent drug release can be achieved by modifying the microenvironmental pH of a polymeric matrix by including acidifiers (citric acid and tartaric

acid) in the formulation. Use of an acidifier results in the release of drug with pH-dependent solubility following zero-order kinetics, irrespective of the pH of dissolution medium.

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## CONFLICT OF INTEREST

The authors claim no conflict of interest.

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