

Formulation and Evaluation of Mucoadhesive Matrix Tablets of Taro Gum: Optimization Using Response Surface Methodology

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Summary

The present study was aimed to formulate and evaluate oral controlled release mucoadhesive matrix tablets of taro gum incorporating domperidone as model drug. Tablets were prepared by direct compression and were evaluated for bioadhesive strength and *in vitro* dissolution parameters. A central composite design for 2 factors, at 3 levels each, was employed to evaluate the effect of critical formulation variables, namely the amount of taro gum (X_1) and PVP K 30 (X_2), on mucoadhesive strength, tensile strength, release exponent (n) and t_{50} (time for 50 % drug release). The mucoadhesive detachment force (evaluated using texture analyzer) was found to be 18.266, 54.684 and 65.904 N for A4, A5 and A6 batches of the formulated tablets.

The polynomial equation indicates that taro gum has dominating effect on mucoadhesive strength and both X_1 and X_2 have almost equal and comparable effect on tensile strength. The drug release follows first order kinetics (release of drug depends on remaining concentration of drug) and shows best linearity ($r^2 = 0.983$) with Higuchi model.

The release exponent (n) lies between 0.339 and 0.543 indicating drug release from the matrix tablets may be Fickian or non-Fickian (anomalous) depending upon the concentration of natural polymer. T_{50} was 58, 140 and 220 minutes for A7, A8 and A9 batches showing overriding potential of taro gum but still the effect of PVP K 30 is noteworthy. PVP K 30 has indirect effect on all the factors by increasing tensile strength and making the tablet firm and intact.

Key words: Gastro retentive, mucoadhesive, taro gum, response surface methodology, release mechanism

Formułowanie i ocena mukoadhezyjnych matryc tabletek gumy Taro: optymalizacja wyników przy zastosowaniu metody powierzchni odpowiedzi

Streszczenie

Celem pracy było formułowanie i ocena ustnie kontrolowanego uwalniania z mukoadhezyjnych matryc tabletek gumy Taro domperidon jako modelu leku. Tabletki były przygotowane przez bezpośrednią kondensację i oceniano właściwości bioadhezyjne i *in vitro* parametry rozpuszczalności. Centralny kompozyt składający się z 2 czynników, na 3 poziomach każdy, został użyty w celu oceny wpływu zmiennych decydujących preparatu, czyli ilości użytej Taro gumy (X_1), PVP K 30 (X_2), właściwości mukoadhezyjnych, wytrzymałości na rozciąganie, wykładników uwalniania i T_{50} (czas 50% uwalniania). Siła mukoadhezyjnego uwalniania (oceniana przy użyciu analizatora), wynosiła 18,266, 54,684 i 65,904 N dla A4, A5 i A6 sformułowanych partii tabletek.

Wyniki wykazały, że guma taro ma dominujący wpływ na mukoadhezyjne właściwości i zarówno X1 jak i X2 ma równy i porównywalny wpływ na wytrzymałość na rozciąganie. Uwalnianie leku następuje wg kinetyki pierwszego rzędu (uwalnianie leku w zależności od pozostałego stężenia w leku) i wykazuje najlepszą liniowość z modelem Higuchi. Wykładniki uwalniania znajdujące się między 0,339 i 0,543 wskazują, że uwalnianie z matrycy tabletek może być typowe i nietypowe, w zależności od koncentracji polimeru. t_{50} wynosił 58, 140 i 220 minut dla A7, A8, A9 partii pokazując nadrzędny potencjał gumy Taro, ale efekt PVP K 30 jest nadal godny uwagi. PVP K 30 ma pośredni wpływ na wszystkie czynniki poprzez zwiększenie wytrzymałości na rozciąganie i tworzenie tabletki twardą i nienaruszoną.

Słowa kluczowe: matryce mukoadhezyjne, guma taro, metoda powierzchni odpowiedzi, mechanizm uwalniania

INTRODUCTION

Naturally occurring polymers, being biocompatible and biodegradable, are currently extensively researched for the development of novel drug delivery systems. Oral route is the most favorable route of drug delivery and oral controlled release formulations are in demand because of their benefit viz. patient compliance and therapeutic advantages [1]. The main obstruction in the development of controlled release formulation is short gastric resident time [2, 3]. There are number of drugs like domperidone, ranitidine, theophylline those have narrow absorption window from upper intestine i.e. stomach and small intestine. Due to short gastric resident time less than 6 hr these drug reaches the non absorbing distal parts of intestine. Therefore main challenge is to prolong the resident time of drug in stomach and proximal small intestine. Gastro retentive drug delivery techniques are primarily controlled release 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. It helps to improve bioavailability, reduces drug wastage, improve solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like domperidone, papaverine).

Gastro retention is also used for achieving local delivery of drug to the stomach and proximal small

intestine [4]. Gastro retentive formulations could be designed based on approaches like: (a) floating [5]; (b) high density system; (c) bioadhesion [6]; (d) lowered motility of the GIT by concomitant administration of drugs or pharmaceutical excipients [7]; (e) swellable and expandable systems [8]. In the current study we have targeted at bioadhesion to the stomach mucosa. Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods by interfacial forces. When the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion [9]. The most widely investigated group of mucoadhesive is hydrophilic macromolecules containing numerous hydrogen bonds forming groups [10]. Once the dosage form firmly sticks to the mucosal surface, its gastric residence time is prolonging until it is removed by turnover of mucins or by some other means. Mucus is secreted from both non-specialized and specialized "Goblet" epithelial cells. Mucus glycoprotein chemically consist of large peptide backbone with pendent oligosaccharide side chains whose terminal end is either sialic or sulfonic acid. The presence of sialic acid and sulfate residues and its high charge density play an important role in bioadhesion [11].

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices [12]. Based on the principal of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms [13, 14].

Domperidone is an anti dopaminergic drug widely used in the treatment of motion-sickness. Domperidone is a chemically known as 5-chloro-1-(1-[3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)propyl]piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one. Its localization outside the blood-brain barrier and antiemetic properties has made it a useful adjunct in therapy for Parkinson's disease. The gastroprokinetic properties of domperidone are related to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. It is rapidly absorbed from the stomach and the upper part of the GIT by active transport, after oral administration, and few side effects have been reported. It is a weak base with

TABLE 2. Response parameters of various formulations prepared as per the experimental design

TABELA 2. Ocena według wybranych parametrów przygotowanych w doświadczeniu preparatów

Batch Code	Variable Levels in Coded Form		Mucoadhesion Strength (N)	Tensile Strength (MN/cm ²)	Release Exponent (n)	t ₅₀ (min)
	Taro gum % w/w (X ₁)	PVP K 30 % w/w (X ₂)				
A1	10 (-1)	5 (-1)	13.673	0.655	0.339	50
A2	20 (0)	5 (-1)	35.250	1.029	0.443	120
A3	30 (1)	5 (-1)	40.378	1.123	0.453	122
A4	10 (-1)	10(0)	18.266	0.842	0.358	56
A5	20 (0)	10(0)	54.684	1.217	0.471	132
A6	30 (1)	10(0)	65.904	1.404	0.502	180
A7	10 (-1)	15(1)	23.287	1.029	0.366	58
A8	20 (0)	15(1)	59.391	1.404	0.500	140
A9	30 (1)	15(1)	67.519	1.591	0.543	220

Experimental design

A Central Composite Design with $\alpha = 1$ was employed as per the standard protocol. The amount of taro gum (X₁) and the amount of PVP K 30 (X₂) were selected as the factors whose effect will be studied on the response variables. Table 2 summarizes the 9 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. Tensile strength, mucoadhesive force, n (release exponent), t₅₀ (time for 50 % drug release) were taken as response variables.

EVALUATION OF TABLETS

Physical parameters

The fabricated tablets were characterized for diameter and thickness (n = 20) using a screw gauge micrometer, hardness (n = 6, Monsanto hardness tester), weight uniformity (n = 20) and % friability (n = 20, Roche friabilator).

Measurement of tablet tensile strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direc-

tion and was measured using a Monsanto hardness tester. Tensile strength (T) is calculated using equation:

$$T = 2F / \pi dt$$

Where: F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Drug content

Twenty tablets were finely powdered; 50 mg of the powder was transferred to a 50 ml volumetric flask. Then the volume was made up with 0.1N HCl (pH 1.2) and shaken for 10 minutes to ensure complete solubility of drug. The mixture was centrifuged and 10 ml of the supernatant liquid quantified spectrophotometrically (Systronics 2202, India) at 284 nm after sufficient dilution.

In vitro drug release studies

The dissolution studies were carried out using eight stage USP dissolution apparatus, type II, (Lab India, DS 8000) at a speed of 50 rpm. Nine hundred millilitres of 0.1 N HCl (pH 1.2) as the dissolution medium, was placed in the cylindrical vessel, the apparatus assembled, and the dissolution medium equilibrated to 37 ± 0.5 °C. Aliquots of 5 ml were

withdrawn at different time intervals, filtered through cellulose acetate membrane (0.45 μm) and the content of domperidone was determined spectrophotometrically (Systronics 2202, India) at 284 nm. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced. The release studies were conducted in triplicates and the mean values were plotted versus time.

Kinetic and mechanism of release analysis

In vitro release data was examined through various kinetic models to describe the release kinetics. The zero order model (equation 1) describes concentration independent drug release rate from the formulation, whereas the first order model (equation 2) describes concentration dependent drug release from the system. Higuchi [20] described the release of drugs based on Fickian diffusion as a square root of time dependent process from swellable insoluble matrix (equation 3), whereas the Hixson-Crowell cube root law [21] (equation 4) correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets.

$$C = k_0 t \quad (1)$$

where, k_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - k_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and k_1 is first order constant.

$$Q = k_H t^{1/2} \quad (3)$$

where: k_H is the rate constant for Higuchi equation.

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (4)$$

where: Q_t is the amount of drug released in time t , Q_0 is the initial amount of the drug in tablet and k_{HC} is the rate constant for Hixson-Crowell rate equation.

Korsmeyer et al [22, 23] derived a simple relationship which described drug release from a polymeric system (equation 5) to find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model:

$$M_t / M_\infty = k_{KP} t^n \quad (5)$$

where M_t/M_∞ is fraction of drug released at time t , k_{KP} is the Korsmeyer-Peppas rate constant and n is the release exponent. The n value is used to characterize different release mechanisms.

The following plots were made: cumulative %

drug release vs. time (Zero order kinetic model); log cumulative of % drug remaining vs. time (First order kinetic model); cumulative % drug release vs. square root of time (Higuchi model); log cumulative % drug release vs. log time (Korsmeyer-Peppas model) and cube root of drug % remaining in matrix vs. time (Hixson-Crowell cube root law).

Ex vivo bioadhesive strength determination

Mucoadhesion testing of the sample tablets was carried out using a texture analyzer (TAXT plus, Stable MicroSystems, UK) with 50 N load cell equipped with mucoadhesive holder. A tablet was attached to the cylindrical probe (10 mm in diameter) by double-sided adhesive tape. Porcine gastric mucosa was utilized as the model membrane for mucoadhesive strength determination of various formulations. The tissue (about 20 X 20 mm) was equilibrated for 15 min at 37.0 ± 0.5 °C before placing onto the holder stage of mucoadhesive holder. The probe with the tablet attached was lowered at a rate of 0.5 mm/s until a contact with the membrane was made. A contact force of 1N was maintained for 60 s, and the probe was subsequently withdrawn at a 0.5 mm/s to the distance of 15 mm. By using the texture analyzer, the maximum force required to separate the probe from the tissue (i.e. maximum detachment force; F_{max}) could be detected directly from Texture Exponent 32 software.

Data analysis and rationale of optimization model

Various Response Surface Methodology computations for the current optimization study were performed employing Design Expert software (Version 8.0.4.1, Stat-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation 1.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 \quad (6)$$

Where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_7 are the coefficients computed from the observed experimental values of Y ; and X_1 and X_2 are

the coded levels of the independent variable(s). The terms X_1X_2 and X_i^2 ($i = 1$ to 2) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of ANOVA provision in the Design Expert software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations. Also, the 3-D response surface graphs and the contour plots were generated by the design expert software.

Real time stability studies

Real time stability studies were carried out by keeping the formulated tablets at regular climatic condition (at varying temperature and humidity of summer and winter of Punjab, India). One hundred tablets of each batch were packed in HDPE bottles and kept in an isolated chamber in laboratory. Tablets were evaluated at 0 day and after 3 and 6 months for drug assay, tensile strength and mucoadhesive strength.

RESULT AND DISCUSSION

Drug assay and physical evaluation

The assessment parameters of the prepared batches of tablets are documented in table 3. The as-

sayed content of drug in various formulations varied between 98.54 ± 0.46 and 100.5 ± 0.31 percent. All the formulated batches pass the weight variation test. Thickness between 4.00 ± 0.1 and 4.00 ± 0.2 mm, hardness between 3.5 and 8.5 Kg/cm², and friability ranged between 0.12 and 0.01. Thus, all physical parameters of the compressed matrices were within the permissible limits of USP.

In vitro drug release

The release from the controlled release mucoadhesive matrix tablet comprising of the drug and natural polymer, could follow three steps. First step can be the penetration of the dissolution medium in the tablet matrix (hydration). Second step could be the swelling with subsequent dissolution and/or erosion of the matrix and followed by the third step comprising of the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium. *In vitro* drug release profile (figure 1) shows decline in % drug release from 77.02 to 67.57 (A1 to A9), which point towards release retardant effect of taro gum with the increasing concentration of PVP K 30. Taro gum has direct effect on release of drug by formation of matrix and at higher concentration through diffusion and erosion, in contrast PVP K 30 has indirect effect by providing more tensile strength and prevent the tablet from disintegration and stay it firm.

TABLE 3. Assessment of prepared tablets

TABELA 3. Właściwości przygotowanych preparatów

Batch	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm ²)	Tensile Strength (MN/cm ²)	Friability (%)	Drug content (%)
A1	8.5± 0.3	4.0± 0.1	3.5± 0.5	0.665± 0.1	0.12± 0.02	98.97± 0.57
A2	8.5± 0.2	4.0± 0.2	5.5± 0.25	1.029± 0.07	0.12± 0.02	99.92± 0.32
A3	8.5± 0.3	4.0± 0.1	6.0± 0.60	1.123± 0.12	0.09± 0.01	99.27± 0.64
A4	8.5± 0.1	4.0± 0.1	4.5± 0.40	0.842± 0.08	0.08± 0.01	100.5± 0.31
A5	8.5± 0.2	4.0± 0.2	6.5± 0.50	1.217± 0.13	0.05± 0.02	98.54± 0.46
A6	8.5± 0.2	4.0± 0.2	7.5± 0.30	1.404± 0.095	0.03± 0.01	99.11± 0.67
A7	8.5± 0.3	4.0± 0.1	5.5± 0.60	1.029± 0.09	0.04± 0.02	99.36± 0.39
A8	8.5± 0.1	4.0± 0.2	7.5± 0.70	1.404± 0.13	0.01± 0.01	98.80± 0.27
A9	8.5± 0.1	4.0± 0.2	8.5± 0.50	1.591± 0.1	0.02± 0.01	98.67± 0.87

Kinetic analysis and mechanism of release data

The mechanism of drug release from matrices containing swellable polymers is a complex phenomenon. Some systems may be classified as either purely diffusion or erosion controlled, while other systems exhibit a combination of these mechanisms. Based on various mathematical models, the magnitude of the release exponent “n” indicates the release mechanism (ie, Fickian diffusion (case I), case II transport, or anomalous transport). The value of $n \leq 0.45$ indicates a classical fickian diffusion-controlled (case I) drug release, $n = 0.89$ indicates a case II relaxational release transport; non-Fickian, zero-order release and $n > 0.89$ indicates super case II (increased plastici-

zation at the relaxing boundary) type of release. Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport. The n and r^2 values for various formulations are given in table 4. In the zero order plot (figure 1, table 4) the r^2 value was 0.745 and the first order (figure 2, table 4) gave 0.960 describing the drug release rate to be dependent on concentration of drug. The best linearity was found in Higuchi equation (figure 4, table 4) ($r^2 = 0.983$), indicated that the drug release mechanism from these tablets was diffusion controlled. To explore the release pattern, results of the in vitro dissolution data were fitted to the Korsmeyer and Peppas equation (figure 3, table 4). The tabulated data (table 4) shows

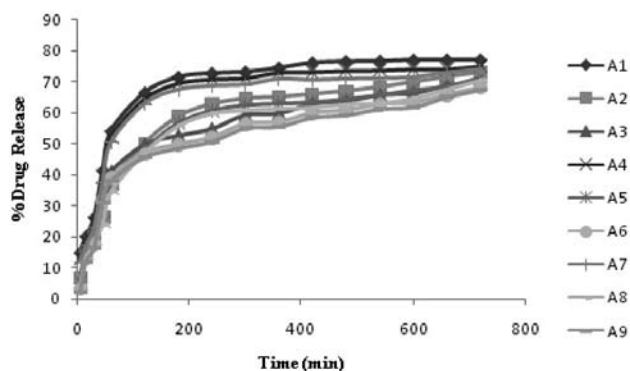


FIG. 1. Zero order release model of domperidone from taro gum tablets

Ryc. 1. Procent uwalnianego domperidonu z tabletek w zależności od czasu

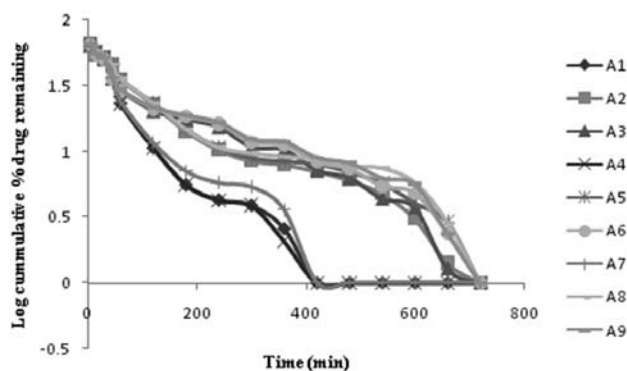


FIG. 2. First order release model of domperidone from taro gum tablets

Ryc. 2. Procent pozostałego domperidonu z tabletek w zależności od czasu

Table 4. Release kinetic studies of formulated tablets

Tabela 4. Ocena kinetyczna przygotowanych tabletek wg wybranych wskaźników

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	r^2	$k_0(h^{-1})$	r^2	$k_1(h^{-1})$	r^2	$k_H(h^{1/2})$	r^2	n	$k_{KP}(h^{-n})$	r^2	$k_{HC}(h^{-n})$
A1	0.608	0.070	0.879	-0.002	0.932	33.09	0.900	0.339	0.996	0.919	-0.005
A2	0.736	0.077	0.960	-0.002	0.976	34.39	0.943	0.443	0.673	0.911	-0.004
A3	0.739	0.071	0.960	-0.002	0.983	31.58	0.894	0.453	0.629	0.918	-0.004
A4	0.597	0.069	0.875	-0.002	0.966	31.18	0.894	0.358	0.935	0.841	-0.004
A5	0.733	0.076	0.938	-0.002	0.963	31.76	0.933	0.471	0.587	0.883	-0.004
A6	0.742	0.070	0.946	-0.002	0.972	34.49	0.869	0.502	0.487	0.894	-0.003
A7	0.602	0.068	0.900	-0.002	0.917	34.33	0.893	0.366	0.901	0.820	-0.004
A8	0.728	0.075	0.907	-0.001	0.89	35.01	0.921	0.500	0.501	0.860	-0.004
A9	0.745	0.070	0.931	-0.001	0.931	32.99	0.847	0.543	0.376	0.884	-0.003

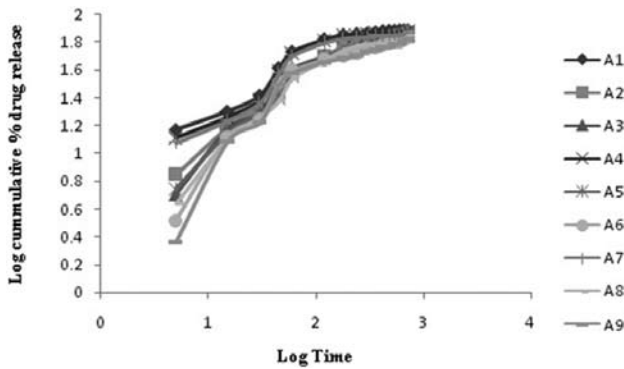


FIG. 3. Korsmeyer-Peppas model for mechanism of drug release

Ryc. 3. Model Korsmeyer-Peppas dla mechanizmu uwalniania leku

that values of n are between 0.339 and 0.543. This implies that release may be fickian or non fickian (anomalous) depending upon polymer concentration. Higher concentration of natural polymer shifts the release pattern from fickian to non fickian. This indicates that at low natural polymer concentration only diffusion is dominating mechanism of release shifting to combination of diffusion and erosion based drug release mechanism when polymer concentration is increased.

The value of kinetic constant (k_{KP}), which is a direct function of matrix solubility was found to decrease {0.996 to 0.629 (A1 to A3)} with increase in taro gum concentration. This could be due to increase in viscosity of polymeric mixture and governance of polymeric chain entanglement with subsequent increase in polymeric concentration. Additionally increase in PVP concentration was found to decrease the kinetic constant {0.629, 0.487, 0.376 (A3, A6, A9)} which may be due to binding potential of PVP keeping the polymeric chains intact for prolonged period of time.

Mathematical modelling

Mathematical relationships generated using multiple linear regression analysis for the studied response variables are expressed in equation (7) – (10) in terms of coded factors:

$$\text{Mucoadhesive strength} = 54.03 + 18.94X_1 + 10.15X_2 + 4.38 X_1 X_2 - 13.10 X_1^2 - 5.38 X_2^2 \quad (7)$$

$$\text{Tensile Strength} = 1.21 + 0.25 X_1 + 0.20 X_2 - 0.024 X_1 X_2 - 0.13 X_1^2 + 0.016 X_2^2 \quad (8)$$

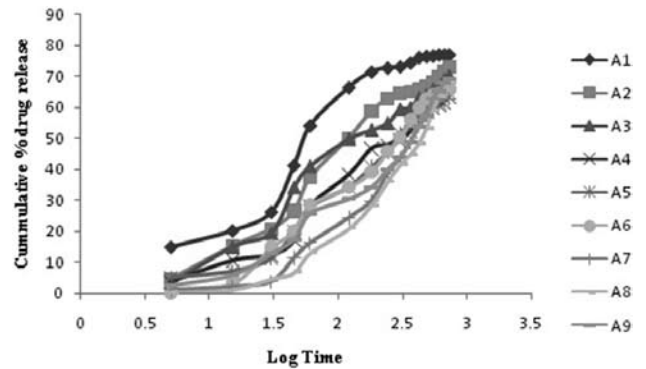


FIG. 4. Higuchi release model of domperidone from taro gum tablets

Ryc. 4. Model Higuchi dla mechanizmu uwalniania leku

$$\text{Release exponent } (n) = 0.47 + 0.069 X_1 + 0.029 X_2 + 0.016 X_1 X_2 - 0.048 X_1^2 - 2.500E-003 X_2^2 \quad (9)$$

$$t_{50} = 129.15 + 54.88X_1 + 21.00 X_2 + 22.50 X_1 X_2 - 22.31 X_1^2 + 4.06 X_2^2 \quad (10)$$

The values obtained for the main effects of each factor in equations (7), (9) and (10) reveals that the amounts of taro gum (X_1) has a more dominant role for the response variables viz. mucoadhesive strength, release exponent and t_{50} . Both X_1 and X_2 , whereas (Equation 8), have a comparable effect on the values of tensile strength.

Mucoadhesion strength

The response surface plot demonstrate (figure 6) the effect of taro gum on mucoadhesive strength, as observed with porcine mucosa, increased from 13.673 to 40.378 and from 23.287 to 67.519 at low and high level of PVP respectively, as the concentration of taro gum was increased, which clearly point towards the mucoadhesive potential of taro gum. The polynomial equation (7) clearly indicates that mucoadhesive strength was increased from 13.673 to 23.287 and from 40.378 to 67.519 at low and high levels of taro gum respectively, as the concentration of PVP was increased. Increasing the amount of natural polymer results in augmentation of bioadhesive strength, which may be due to the availability of more adhesive sites and polymer chains for interpenetration with the mucin. Table 2 specifies the potentiating effect of increasing PVP concentration on the mucoadhesive strength. This could be attributed to increase in ten-

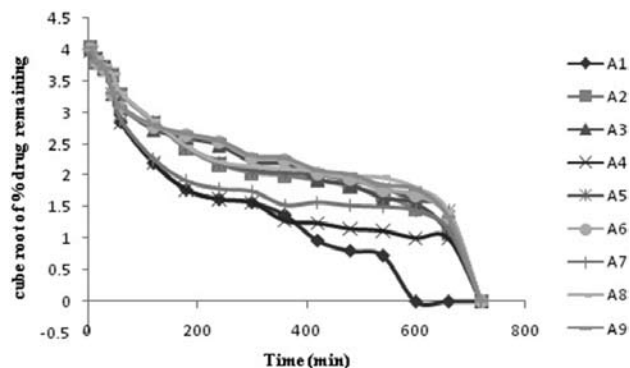


FIG. 5. Hixson-Crowell cube root plots of domperidone from taro gum tablets

Ryc. 5. Hixson-Crowell wykres dla mechanizmu uwalniania leku

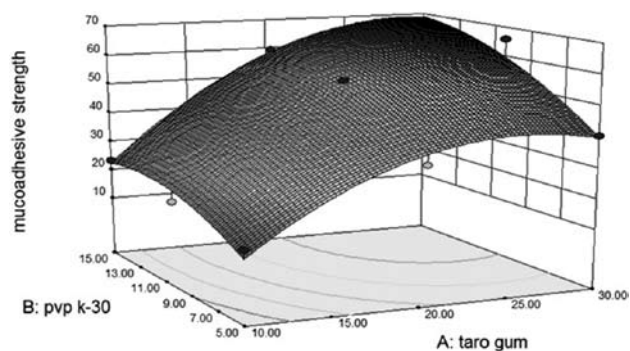


FIG. 6. Response surface plot showing the influence of amount of taro gum and PVP K 30 on mucoadhesive strength

Ryc. 6. Pole powierzchni odpowiedzi pokazującej wpływ wartości taro gum i PVP K 30 na właściwości mukoadhezyjne

sile strength of the prepared tablets, which is sufficient to keep the formulation intact, and thereby enhancing the contact time of the tablet with the mucosal surface.

Tensile strength

The response surface plot (figure 7) illustrate that the value of tensile strength increased from 0.655 to 1.123 and from 1.029 to 1.591 at low and high level of PVP respectively, as the concentration of taro gum was increased. 3 D plots point up, that the value of tensile strength increased from 0.655 to 1.029 and from 1.123 to 1.591 at low and high levels of taro gum respectively, as the concentration of PVP was increased. From the equation (8), it could be recognized that both the polymer has almost equal and compa-

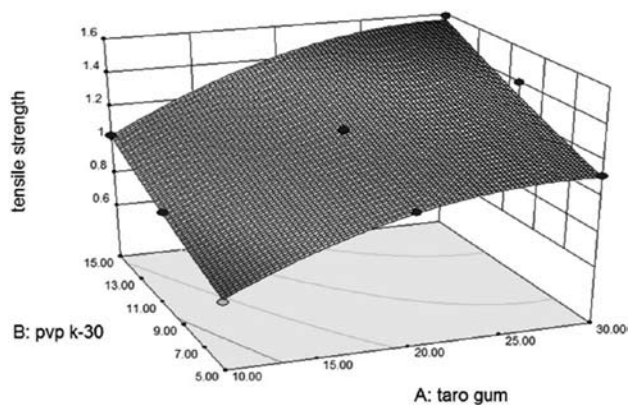


FIG. 7. Response surface plot showing the influence of amount of taro gum and PVP K 30 on tensile strength

Ryc. 7. Pole powierzchni odpowiedzi pokazującej wpływ wartości taro gum i PVP K 30 na wytrzymałość na rozciąganie

nable effect on the tensile strength, which indicates binding potential of taro gum, in concentration dependent manner. Elevated polymer concentration delivers supplementary tensile strength on the formulated tablets.

Release exponent

The response surface plot (figure 8) point up that the value of release exponent (n) increased from 0.339 to 0.453 and from 0.366 to 0.543 at low and high level of PVP respectively, as the concentration of taro gum was increased. From 3 D plots it may palpable that

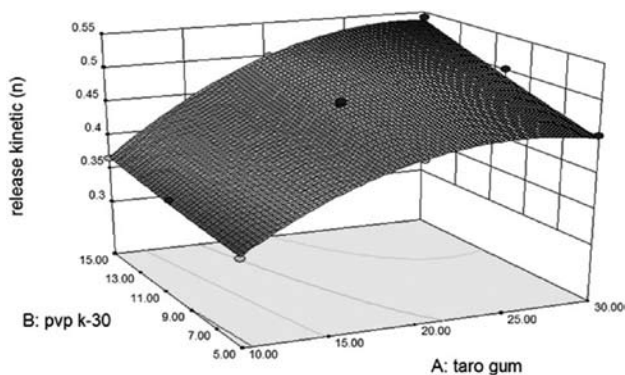


FIG. 8. Response surface plot showing the influence of amount of taro gum and PVP K 30 on release exponent

Ryc. 8. Pole powierzchni odpowiedzi pokazującej wpływ wartości taro gum i PVP K 30 na parametry uwalniania

the value of release exponent (n) increased from 0.339 to 0.366 and from 0.453 to 0.543 at low and high levels of taro gum respectively, as the concentration of PVP was increased. Equation (9) suggests that taro gum has significant effect on the release pattern relatively than PVP, indicating concentration dependent effect of natural polymer on the drug release mechanism from matrix tablet.

t_{50} (time for 50% drug release)

The response surface plot (figure 9) exemplify that the value of t_{50} increased from 50 to 122 min and from 58 to 220 min at low and high level of PVP respectively, as the concentration of taro gum was increased. It may apparent from 3 D plots, that the value of t_{50} increased from 50 to 58 min and from 122 to 220 min at low and high levels of taro gum respectively, as the concentration of PVP was increased. Equation 5 indicates towards governing responsibility of taro gum in the release of drug moreover PVP shows noteworthy outcome in controlling the release of drug from tablets. The enhancement in t_{50} with increase in natural polymer concentration may be ascribed to increase in polymer chain density leading to pronounced chain entanglements and/or interpenetrations, thereby hindering the transport of drug molecules through the matrix. These findings point towards release retardant potential of taro gum in formulation of matrix tablets.

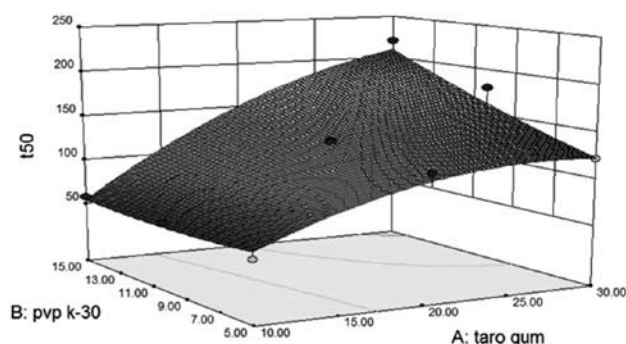


FIG. 9. Response surface plot showing the influence of amount of taro gum and PVP K 30 on t_{50}

Ryc. 9. Pole powierzchni odpowiedzi pokazującej wpływ wartości taro gum i PVP K 30 na t_{50}

Real time stability studies

Effect of real time storage conditions on the drug assay, tensile strength and mucoadhesive strength of various batches of domperidone tablets are shown in

table 5. It was evident that there was no significant modification in the drug assay, tensile strength and mucoadhesive strength after 3 months but significant effect were pragmatic after 6 months, this possibly will be owing to the altering circumstance and amalgamation of moisture which may perhaps be owed to the water assimilation capacity of taro gum, make the tablets lesser tensile and eventually lower the mucoadhesive strength. Although drug assay has no concern with these happening therefore remains unchanged.

Numerical optimization

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. Upon comprehensive evaluation of the feasibility search and subsequently exhaustive grid searches, the formulation composition with taro gum concentration of 30% and the amount of PVP K 30 was 15%, fulfilled maximum requirements of an optimum formulation, desirability 0.972, because of maximum mucoadhesive strength and better regulation of release rate. The optimized formulation was evaluated for various dependent variables. The response values were calculated and compared to the corresponding predicted values. Table 6 lists the values of the observed responses and those predicted by mathematical models along with the percentage prediction errors. The prediction error for the response parameters ranged between 2.45 and 4.51%. Drug release from the optimized formulation was found to follow non fickian (anomalous) behavior and was characterized by the Higuchi kinetic model.

CONCLUSION

The research findings of the study clearly point towards the concentration dependent mucoadhesive and release retardant potential of taro gum in the formulation of gastro retentive mucoadhesive matrix tablets. Drug release kinetics study revealed that the formulation follows higuchi equation and a concentration (taro gum) dependent transformation from fickian to non fickain drug release mechanism was observed. The dependent variables *viz.* mucoadhesive strength, tensile strength, release exponent (n) and t_{50} could be modulated by varying the critical formulation variables, namely, the amounts of taro gum and PVP K 30. High degree of prognosis ob-

TABLE 5. Real time stability studies

TABELA 5. Ocena wytrzymałości na rozciąganie mukoadhezyjnych parametrów w zależności od czasu

Batch	Parameter(months)								
	Tensile strength			Mucoadhesive strength			Drug Assay		
	0	3	6	0	3	6	0	3	6
A1	0.665± 0.1	0.664± 0.07	0.656± 0.17	13.673	12.543	11.28	98.97± 0.57	98.90± 0.70	98.67± 0.5
A2	1.029± 0.07	1.027± 0.05	1.003± 0.03	35.250	34.500	31.873	99.92± 0.32	99.80± 0.62	99.97± 0.22
A3	1.123± 0.12	1.123± 0.1	1.091± 0.17	40.378	38.250	35.264	99.27± 0.64	99.7± 0.32	99.57± 0.42
A4	0.842± 0.08	0.840± 0.15	0.820± 0.25	18.260	16.750	15.376	100.5± 0.31	99.97± 0.50	98.5± 0.43
A5	1.217± 0.13	1.215± 0.20	1.117± 0.15	54.684	52.540	48.093	98.54± 0.46	98.45± 0.22	98.84± 0.48
A6	1.404± 0.095	1.400± 0.076	1.280± 0.08	65.904	62.920	58.278	99.11± 0.67	99.35± 0.40	98.90± 0.76
A7	1.029± 0.09	1.025± 0.15	0.923± 0.05	23.287	21.865	19.903	99.36± 0.39	99.58± 0.65	98.56± 0.93
A8	1.404± 0.13	1.334± 0.16	1.215± 0.20	59.391	58.280	54.804	98.80± 0.27	99.02± 0.15	98.40± 0.72
A9	1.591± 0.1	1.590± 0.18	1.398± 0.15	67.519	64.290	60.289	98.67± 0.87	97.12± 0.78	97.42± 0.43

TABLE 6. Comparison of experimentally observed responses of the optimized taro gum formulation with predicted responses

TABELA 6. Porównanie obserwowanych doświadczalnie odpowiedzi z wartościami przewidywanymi

Response parameters	Constraints Set	Observed value	Predicted value	Error (%)
Mucoadhesive Strength (N)	Maximize	65.9	69.0179	4.51
Tensile Strength (MN/cm ²)	Maximize	1.507	1.56756	3.86
Release Kinetic (n)	Maximize	0.552	0.53875	2.45
t ₅₀	Maximize	201	209.278	3.95

tained using the response surface methodology indicates that a 2-factor central composite design is quite efficient in optimizing drug delivery systems. Being of natural origin, taro gum could be optimistically explored for its mucoadhesive strength and release retardant property in various dosage forms.

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Acknowledgement

The authors are grateful to Dr. Madhu Chitkara, Vice Chancellor, Chitkara University, Patiala, Punjab, India, Dr. Ashok Chitkara, Chairman, Chitkara Educational Trust, Chandigarh, India and Dr. Sandeep Arora, Dean, Chitkara University, Patiala, Punjab, India, for support and institutional facilities.

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