



## Formulation and Evaluation of Controlled Release Mucoadhesive Matrix Tablets: Assessment of Myrrh Oleo Gum Resin as a Natural Pharmaceutical Excipient

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### ABSTRACT

Mucoadhesive polymer owing to its binding capacity with gastric mucin prolongs the gastric residence time and thereby increased drug bioavailability. In the present study, oral controlled release mucoadhesive matrix tablets have been developed for domperidone as model drug using natural mucoadhesive material myrrh oleo gum resin (MOGR). The tablets were formulated with the natural polymer in different concentration (5, 10, 15 and 20 % w/w) employing direct compression technology. The prepared batches were evaluated for tablet parametric test (drug assay, diameter, thickness, hardness and tensile strength), swelling index, mucoadhesive strength (using texture analyser) and in vitro drug release studies. Accelerated stability studies were also conducted on all the prepared batches. The tensile strength increases from  $0.973 \pm 0.09$  to  $1.687 \pm 0.11$  MN/m<sup>2</sup> and mucoadhesive strength from 19.868 to 49.778 N with the increase in natural polymer concentration from 5 to 20 % (M1 to M4). Swelling index of natural polymer was testified towards proliferation by together increasing gum concentration and the time period. The release kinetic and mechanism of release were calculated by fitting in vitro release data in various models demonstrating that release follows zero order and Hixson Crowell cube root law. The release exponent (n) ranges in between 0.5889 to 0.7389 indicating multiple release mechanisms possibly the combination of diffusion and erosion. Accelerated stability studies demonstrate no significant change in the tensile strength, mucoadhesive strength and drug assay. These research outcomes clearly specify the potential of MOGR to be used as binder, release retardant and mucoadhesive natural material in tablet formulations.

**Keywords:** Myrrh oleo gum resin, binder, release retardant, mucoadhesion, drug release mechanism.

### INTRODUCTION

Domperidone is synthetic benzimidazole compound that act as dopamine D2 receptor antagonist drug widely used in the treatment of motion-sickness. 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 good solubility in acidic pH but in alkaline pH solubility is significantly reduced. Oral controlled release dosage forms containing drug, which is a weak base, are exposed to environments of increasing pH and poorly soluble freebase may get precipitated within the formulation in the intestinal fluid. Precipitated drug is no longer capable of being released from the formulation. It is absorbed orally, but bioavailability is only 15% due to first pass metabolism. It is eliminated seven hours after single oral

administration reaches at peak concentration within 30 minutes following oral administration also favors development of a sustained release formulation.<sup>[1-2]</sup>

The drugs with a narrow absorption window in the GIT or acting locally in the stomach, the principal challenging task is not only to prolong drug release but the retention of the dosage form in the upper GIT. This results in a higher bioavailability, reduced time intervals for drug administration and thus a better patient compliance.<sup>[3]</sup> Various approaches for gastro retentive dosage forms have been proposed including floating dosage forms like single and multiple unit gas generating systems, hollow microspheres, hydrodynamically balanced systems, swelling or expanding systems, mucoadhesive systems and other gastroretentive dosage forms.<sup>[4]</sup> Mucoadhesive drug delivery systems (MDDS) are used to immobilize a drug delivery device on a specific site for targeted release and optimal drug delivery due to intimacy and duration of contact. These effects may improve bioavailability of the drug to be delivered.<sup>[5]</sup> Several theories have been proposed in order to explain the

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mucoadhesive phenomenon includes: the electronic theory, [6] the wetting theory, [7] the adsorption theory, [8] the fracture theory [9-10] and the diffusion theory. [11] Taking into account all these theories, the process involved in the formation of mucoadhesive bonds can be divided in four basic steps: wetting and swelling of the polymers; interpenetration of the mucoadhesive polymer chains and entanglement of the polymer and mucin chains; interfacial interaction of functional groups; and formation of weak chemical bonds. Myrrh oleo gum is a reddish-brown resinous material, the dried sap of a number of trees, but primarily from *Commiphora myrrha*. Myrrh is most commonly used in Chinese medicine for rheumatic, arthritic and circulatory problems. In pharmacy, myrrh is used as an antiseptic and is most often used in mouthwashes, gargles and toothpastes for prevention and treatment of gum disease. MOGR is already explored as tablet binder and drug release retardant. [12] The present study was aimed at formulation and evaluation of controlled release mucoadhesive matrix tablets of domperidone using MOGR. The prepared batches were evaluated for tablet parametric test (drug assay, diameter, thickness, hardness and tensile strength), swelling index, mucoadhesive strength (using texture analyzer), in vitro drug release studies and accelerated stability studies. Release kinetic and mechanism of release was found by fitting the in vitro data in various models.

## MATERIAL AND METHODS

### Material

Domperidone was received as gift sample from Helios Pharmaceuticals, Baddi, India. Vivapur-102 was gift sample from S. Zhaveri, Mumbai, India. Myrrh gum was procured from Yarrow Chem, Mumbai, India. Talc and magnesium stearate were purchased from S. D. Fine Chemicals Ltd. Mumbai, India. All other chemicals and reagents were of analytical grade and were used as such.

### Preparation of Domperidone Tablets

Oral controlled release mucoadhesive matrix tablets containing 30 mg domperidone were prepared by direct compression technology. The investigated formulations are shown in Table 1. The respective powders (drug, polymers viz. myrrh gum and vivapur 102, talc and magnesium stearate) were passed through a 200 mesh sieve. The powders were blended thoroughly using a pestle and mortar. Then, 200 mg of each mixture was weighed and fed manually into the die of a single stroke multi punch tableting machine (AK Industries, India) fitted with 8.40 mm flat faced punch and die set possessing 50 ton compression force. Before compression, the surface of die and punch were lubricated with magnesium stearate.

**Table 1: Composition of domperidone tablets**

Ingredients(mg)	M1	M2	M3	M4
Domperidone	30	30	30	30
Myrrh oleo gum resin	10	20	30	40
Vivapur 102	156	146	136	126
Talc	2	2	2	2
Mg. Stearate	2	2	2	2

## Evaluation of Formulated Tablets

### Friability

Twenty tablets of each batch were weighed and put into the friabilator drum. After 100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust

and weighed. Friability was calculated from the following formula.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

### Tablet Crushing Strength

A Monsanto tablet hardness tester was used to measure the force needed to fracture the tablets. The dimensions (the diameter and the thickness) and the weight of the tablets were determined using calibrated vernier caliper. For measuring the hardness of the tablets, the plunger of the hardness tester was driven down at a speed of 20 mm/min. Tensile strength for crushing (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 Uniformity

Ten tablets were weighed individually, crushed and the drug was extracted in 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45  $\mu$ m) and the drug content was determined by UV/Vis double-beam spectrophotometer (Systronics 2202, India) at a wavelength of 284 nm after a suitable dilution.

### Swelling Index

Swelling study of individual polymers and combinations was carried out using eight stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm and 0.1 N HCl was used as medium, temperature was maintained at 37 $\pm$  0.5  $^{\circ}$ C. Weight of individual tablet was taken prior to the swelling study ( $W_1$ ). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours ( $W_2$ ). Percent hydration (swelling index) was calculated as shown in table 4 using following formula,

$$\text{Swelling Index} = (W_2 - W_1) \times 100 / W_2$$

Where  $W_1$ :- initial weight of tablet,  $W_2$ :- weight of hydrated tablet.

### Ex-vivo Mucoadhesive Strength Determination

Mucoadhesion studies of designed formulations were carried out using texture analyser (TAXT plus, Stable Micro Systems, UK). Freshly excised porcine stomach mucosa was obtained from the local slaughter house. The tissue was placed in simulated gastric fluid and oxygen is provided using aerator. The mucosal tissue was cut in small piece (2 $\times$ 2cm) and held using clips on a holder. The tissue in holder was immersed in simulated gastric fluid maintained at 37 $^{\circ}$ C. The designed tablet was attached to the probe (stainless steel cylindrical probe with 10 mm diameter) using double sided tape. The probe was lowered at a speed of 0.5 mm/s until the tablet made contact with mucosal tissue. A constant force of 1 N was applied for 60 s, after which the probe was withdrawn at a speed of 0.5 mm/s to the distance of 15 mm. Peak detachment force was used to establish mucoadhesive strength using texture exponent software. The test was conducted in triplicate.

### In-vitro Drug Release Studies

Dissolution tests were performed in USP dissolution eight dissolution apparatus II (paddles) (Lab India, DS 8000) at 37 $\pm$ 0.5 $^{\circ}$ C. The baskets were rotated at a speed of 50 rpm. The test was performed in 37 $\pm$ 0.5 $^{\circ}$ C with a rotation speed of 50 rpm using 900 ml of 0.1 N HCl, pH 1.2, as a dissolution medium. According to the sampling plan, samples of 5 ml were withdrawn till 24 h and immediately replaced with an equal volume of the respective dissolution medium maintained at 37 $\pm$ 0.5 $^{\circ}$ C. Test samples were filtered through

Whatman filter paper No. 41 (Whatman Paper Limited, UK), and assayed for domperidone at 284 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (Systronics 2202, India). The tests were conducted in triplicates and the mean values were plotted versus time.

#### Kinetic Analysis

To analyze the *in-vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi<sup>[13]</sup> described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion Eq. (3). The Hixson-Crowell cube root law<sup>[14]</sup> Eq. (4) describes the release from systems where there is 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.

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

Where,  $C_0$  is the initial concentration of drug and  $K$  is first order constant.

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

Where,  $K$  is the constant reflecting the design variables of the system.

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

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.

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) and *cube root of drug % remaining in matrix vs. time* (hixson-crowell cube root law).

#### Mechanism of Drug Release

Korsmeyer *et al.*<sup>[15-16]</sup> *log cumulative % drug release vs. log time* (korsmeyer model), 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:

$$M_t / M_\infty = k_{KP} t^n \quad (6)$$

Where  $M_t / M_\infty$  is fraction of drug released at time  $t$ ,  $k_{KP}$  is the rate constant and  $n$  is the release exponent. The  $n$  value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices. 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 plasticization 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.

#### Stability Studies

Accelerated stability testing was carried out according to ICH guidelines (40°C/75% RH). One hundred tablets of each batch were securely packed in HDPE bottles and kept in a stability chamber. Tablets were evaluated at 0 day, 3 and 6 months for tensile strength, mucoadhesive strength and drug assay.

## RESULTS AND DISCUSSION

### Drug Content and Physical Properties

Prepared tablets were evaluated for parametric tests (Table 2). The drug content in various formulations was varied between  $99.52 \pm 0.13$  and  $99.96 \pm 0.17\%$ . Maximum diameter and thickness of prepared tablets were  $9.02 \pm 0.05$  mm and  $4.00 \pm 0.05$  mm respectively. Hardness values of formulated tablets were ranging between  $5.5 \pm 0.40$  and  $9.3 \pm 0.60$  kg/cm<sup>2</sup>. The formulation does not include binding agent, these findings designate towards the binding property of MOGR. Friability of prepared tablets ranges between  $0.01 \pm 0.01$  to  $0.08 \pm 0.01$ . Tablet crushing strength increases from  $0.973 \pm 0.09$  to  $1.687 \pm 0.11$  MN/m<sup>2</sup> (M1 to M4) with increasing the polymer concentration 5 to 20% (M1 to M4). This enhancement in crushing strength directs towards extensive binding potential of MOGR, which is in accordance to the previous finding,<sup>[12]</sup> in concentration dependent manner.

### Swelling Index

The percentage water uptake of the formulations (M1-M4) was calculated (Table 3). The results show swelling index increases through raising polymer concentration as well as time duration. Through rising polymer concentration from 5 to 20% (M1-M4), swelling index after 12hr was increased from 56.24 to 67.81% and by increasing time duration from 2 to 12hr in formulation M4, swelling index was found to be raises from 36.50 to 67.81%. This tremendous swelling index points towards the hydrophilic potential of MOGR. Swelling of natural gum plays vital role in both mucoadhesive property and release retardant activities. The increase in mucoadhesive strength by raising polymer concentration possibly will be owing to extensive swelling of the gum supporting in the interpenetration of polymeric chains with the mucin presents on the gastric mucosa. Swelling of the polymer stands crucial for the development of sound matrix for retarding the release of drug from the formulation.

**Table 2: Appraisal of prepared tablets**

Parameters	M1	M2	M3	M4
Diameter (mm)	8.40±0.06	8.40±0.02	8.40±0.03	8.40±0.05
Thickness (mm)	4.00±0.02	4.00±0.05	3.99±0.01	3.99±0.04
Hardness (kg/cm <sup>2</sup> )	5.5±0.40	7.0±0.80	8.55±0.60	9.3±0.60
Tensile strength (MN/m <sup>2</sup> )	0.973±0.09	1.238±0.15	1.551±0.11	1.687±0.11
Friability (%)	0.08±0.01	0.05±0.02	0.03±0.02	0.01±0.01
Drug content (%)	99.91±0.12	99.52±0.13	99.96±0.17	99.62±0.31

**Table 3: Swelling index of various batches**

Batch	Swelling Index (%)			
	2 h	4 h	8 h	12 h
M1	20.12	37.40	49.14	56.24
M2	25.92	44.12	51.06	60.33
M3	29.57	50.50	58.33	63.41
M4	36.50	55.55	60.50	67.81

### Ex-vivo Mucoadhesive Strength

The mucoadhesive strength increases from 19.868 to 49.778 N with the increase in MOGR concentration from 5 to 20 % shown in Fig. 1. The raise in mucoadhesive strength may be due to increase in availability of adhesive sites of natural polymer with mucin tends to increase in bond strength. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. Swelling of natural polymer based initiation of deep

**Table 4: Release kinetic studies of formulated tablets**

Batch	Zero order		First order		Higuchi		Korsmeyer- Peppas			Hixson- Crowell	
	$r^2$	$K_0(h^{-1})$	$r^2$	$K_1(h^{-1})$	$r^2$	$K_H(h^{1/2})$	$r^2$	$n$	$K_{KP}(h^{-n})$	$r^2$	$K_{KP}(h^{-n})$
M1	0.8118	0.0713	0.9515	-0.0015	0.9639	2.9422	0.8984	0.5889	0.3381	0.9938	-0.0031
M2	0.8654	0.062	0.9418	-0.0011	0.9836	2.5051	0.9119	0.5915	0.2197	0.9615	-0.0026
M3	0.898	0.0595	0.9098	-0.0011	0.9901	2.3663	0.9677	0.6313	0.0226	0.9417	-0.0025
M4	0.9772	0.0562	0.8554	-0.0010	0.9659	2.1171	0.9967	0.7389	-0.4477	0.9023	-0.0024

**Table 5: Results of accelerated stability studies in MOGR tablets**

Batch	Parameter(months)								
	Tensile strength			Mucoadhesive strength			Drug Assay		
	0	3	6	0	3	6	0	3	6
M1	0.973±0.098	0.960±0.07	0.966±0.17	13.673	12.543	11.28	99.91± 0.12	99.90± 0.29	99.79± 0.66
M2	1.238± 0.15	1.235±0.09	1.230±0.05	18.052	19.732	15.402	99.52± 0.13	99.80± 0.42	99.37± 0.28
M3	1.551±0.11	1.523±0.13	1.540±0.15	23.287	22.400	19.763	99.96± 0.17	99.79± 0.39	99.87± 0.22
M4	1.687±0.10	1.680± 0.11	1.677±0.13	40.378	38.750	35.264	100.1±0.31	99.93± 0.62	100.02± 0.43

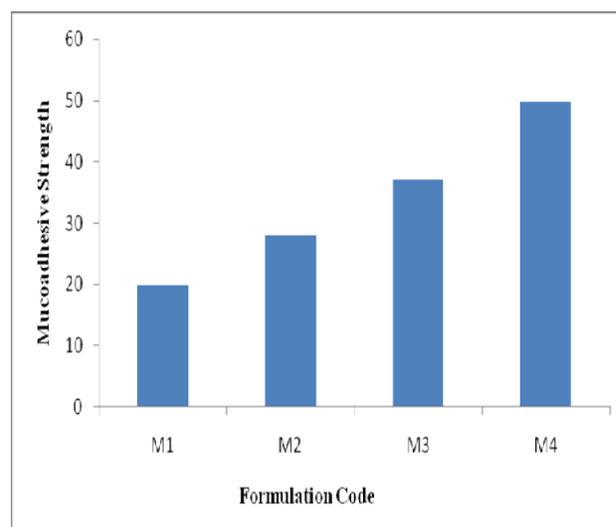
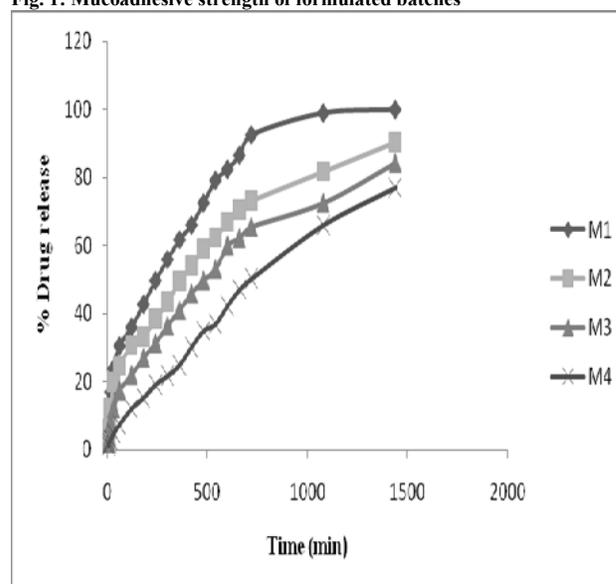
contact with the mucous layer permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction and the building of secondary bonds favouring both chemical and mechanical interactions.

#### Drug Release Profile and Kinetic Analysis

The drug release profile of controlled release mucoadhesive matrix tablet formulations M1-M4 obtained by varying concentration of MOGR was shown in Fig. 2. Release profile clearly indicates that with increasing the concentration of MOGR, drug release rate decreases which may be due to formation of sound matrix gel. The *in-vitro* drug release was found to be decreased from 99.99 to 76.98 % (M1 to M4) with increasing polymer concentration from 5 to 20% in duration of 24 h. The fall in drug release with increase in MOGR concentration may be credited to decrease in porosity of the matrices and increase in drug diffusion path length of the polymeric matrices. These statistics clearly indicate towards matrix forming property and release retardant belonging of MOGR tablets. The *in vitro* drug release data was analysed for establishing kinetic of drug release. Zero order, first order, Higuchi model, Hixson and Crowell were tested for selected finest batches. The highest correlation coefficient ( $r^2$ ) gives idea about model best fitted to the release data. The zero order plot (Fig. 2, Table 4) the  $r^2$  value obtained is 0.9772 and the first order (Fig. 3, Table 4) gave 0.9515 indicating the dissolution rate of the drug is independent of the amount of drug available for dissolution and diffusion from the matrix. The best linearity was found in Hixson Crowell cube root plot (Fig. 6, Table 4) ( $r^2=0.9938$ ) indicating the involvement of erosion/dissolution based release of drug and change in surface area and diameter of the matrix tablets with time. The mechanism of drug release from polymer-based matrices is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms. The mechanism of drug release was evaluated by fitting 60% drug release data into korsmeyer peppas model. The value of release exponent 'n' ranges in between 0.5889 to 0.7389 (Table 4) amongst the formulated batches showing release follows non fickian (anomalous) mechanism means both diffusion and erosion responsible for release of drug from matrix tablets. Absorption of dissolution media by matrix tablets causes swelling and subsequent polymer relaxation leading to the formation of channels and pores for the diffusion of drug from the formulation. Simultaneous erosion of the polymer matrix is also contributing towards the drug release.

#### Accelerated Stability Studies

Table 5 shows the effect of accelerated storage conditions on the tensile strength, mucoadhesive strength and drug assay of various batches of MOGR tablets. It was evident from the results that there was no significant change in the tensile strength, mucoadhesive strength and drug assay observed with any batch of prepared tablets kept under accelerated storage conditions.

**Fig. 1: Mucoadhesive strength of formulated batches****Fig. 2: Zero order release model of domperidone from MOGR tablets**

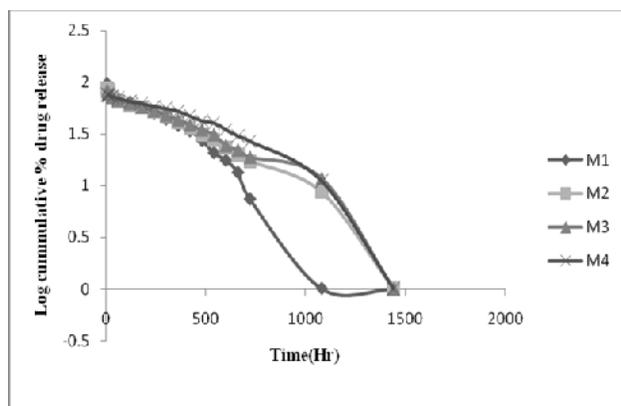


Fig. 3: First order release model of domperidone from MOGR tablets

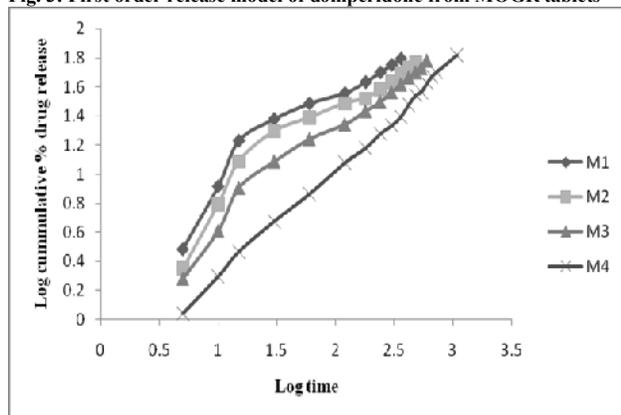


Fig. 4:Korsmeyer-Peppas model for mechanism of drug release

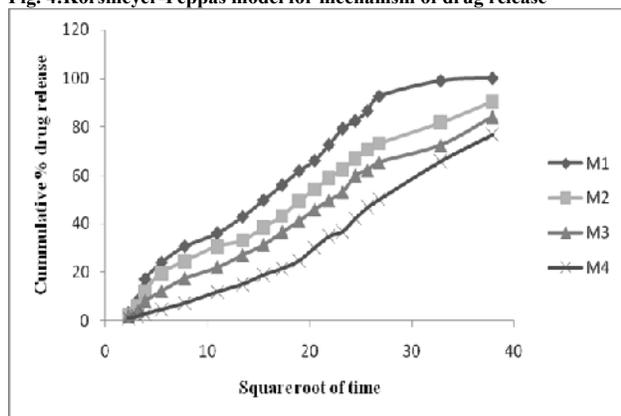


Fig. 5: Higuchi release model of domperidone from MOGR tablets

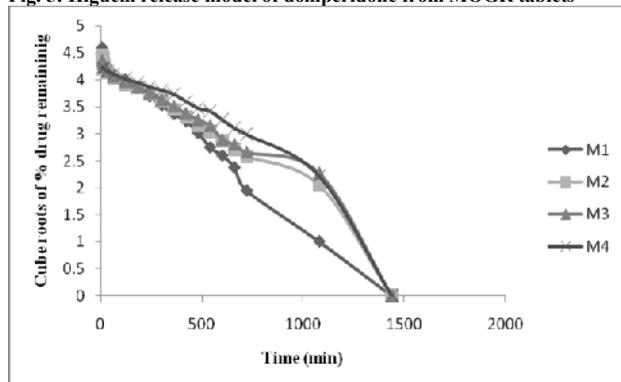


Fig. 6: Hixson-Crowell cube root plots of domperidone from MOGR tablets

The research findings of the study clearly point towards the concentration dependent mucoadhesive, release retardant and binding potential of myrrh oleo gum resin in the formulation of controlled release mucoadhesive matrix tablets. Natural materials being readily available, cost effective, eco-friendly, biodegradable and biocompatible due to their natural origin can be extensively used in the field of drug delivery. It can be concluded that natural polymer myrrh oleo gum resin can be used as binder, release retardant and mucoadhesive agent for its pharmaceutical applications in other pharmaceutical dosage forms.

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