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EVALUATION OF OLEO-GUM RESIN AS DIRECTLY COMPRESSIBLE TABLET EXCIPIENT AND RELEASE RETARDANT

PRADEEP KUMAR* and INDERBIR SINGH

Chitkara College of Pharmacy, Chandigarh-Patiala National Highway,
Rajpura – 140401, Patiala, Punjab, India

Abstract: The present study was designed to study drug release retardant property of myrrh oleo-gum resin from tablets prepared by direct compression method (without binding agent). The tablets were evaluated for various physical tests viz. hardness, friability, tensile strength and drug content. Accelerated stability testing was carried out according to ICH guidelines. Batch F-VII showed 041 % friability, 6 kg/cm^2 hardness and 0.961 MN/m^2 tensile strength. *In vitro* dissolution studies were performed and different empirical models were applied to drug release data for evaluating the drug release mechanisms and kinetics. A criterion for selecting the most appropriate model was based on linearity (coefficient of correlation). The *in vitro* release data fit well to the Hixson Crowell model (r^2 value ranged from 0.9771 to 0.9945) indicating the drug release mechanism to be surface erosion, effected through water diffusion, polymer hydration, disentanglement and dissolution. In conclusion, myrrh-oleo-gum resin was found to be a suitable directly compressible tablet excipients having release modifying property.

Keywords: myrrh oleo-gum resin (MOGR), direct compression, sustained release, Hixson Crowell, erosion

The nontoxic behavior, easy availability, biodegradability and biocompatibility of natural polymers is making them more popular amongst formulation scientists for the development of oral controlled release dosage forms, which deliver significant advantages like better patient compliance, dose and side effects reduction, uniform drug levels maintenance and also an increase in safety margin for high potency drugs (1).

Myrrh 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.

Tramadol is a centrally acting analgesic. The chemical name for tramadol is (±)-cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol. Tramadol is marketed as a racemic mixture and at the receptor level has a weak affinity for the μ-opioid receptors (approximately 1/6th that of morphine). The (+)-enantiomer is approximately four times more potent than the (-)-enantiomer in terms of μ-opioid receptor affinity and 5-HT reuptake, whereas the (-)-enantiomer is responsible for noradrenaline reuptake effects (2). These actions appear to produce a synergistic analgesic effect, with (+)-tramadol exhibiting 10-fold higher analgesic activity than (-)-tramadol (3).

In the light of wide pharmaceutical application involving naturally occuring gums (4), waxes (5) and oily bases in drug delivery, the present study was designed to explore the potential of myrrh oleo-gum resin (MOGR) as a tablet excipient, primarily as a binder and release retardant. The tablets were prepared by direct compression method and subsequently characterised for various tablet parameters viz. weight variation, hardness, tensile strength, friability and content uniformity. Accelerated stability testing was carried out according to ICH guidelines (40^{o}C/75% RH). Furthermore, *in vitro* release studies were carried out to predict the effect of myrrh oleo-gum resin on release behavior of the drug from the dosage form. The drug release data were fitted into zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell semi empirical models to elucidate the release kinetics.

* Corresponding author: e-mail: pradeep.kumar@chitkara.edu.in; phone: 91-9888544148, 91-9216448444

Table 1. Formulation code table of the prepared MOGR tablets.

Formulation code	MCC (%)	$CaCO_3$ (%)	Diluent ratio	MOGR (mg)
F I	66	33	2	75
F II	75	25	3	75
F III	80	20	4	75
F IV	66	33	2	100
F V	75	25	3	100
F VI	80	20	4	100
F VII	66	33	2	125
F VIII	75	25	3	125
F IX	80	20	4	125

Table 2. Diffusion exponent (n) and drug release mechanism for cylindrical shape.

Diffusion exponent (n)	Mechanism of drug release
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
$n > 0.89$	Super case-II transport

MATERIALS AND METHODS

Tramadol hydrochloride was received as a gift sample from Indswift Ltd., Chandigarh, India. Vivapur-102 and Vivapress- CA 800 were gift samples from S. Zhaveri, Mumbai, India. Myrrh oleo-gum resin was purchased from Yarrow Chem, Mumbai, India. MOGR was powdered and passed through 60 # sieve for being used in the research work. Talc and magnesium stearate were procured from S D Fine Chemicals Ltd., Mumbai, India. All other chemical/reagents were of analytical grade and used as such.

Preparation of tablets

Vivapur-102 and Vivapress CA-800 (directly compressible ingredients, as diluent) and powdered MOGR were mixed thoroughly followed by additional mixing of lubricants/glidant (talc and magnesium stearate). All the batches were formulated by varying the diluent ratio (MCC : $CaCO_3$) and the amount of MOGR as detailed in Table 1. The tablet weight was kept at 255 mg for all the batches and were compressed using single stroke mutipunch tableting machine (AK Industries, Nakodar, India).

Table 3. Physical parameters of the formulated MOGR tablets.

Batch No.	Diameter (mm) n = 10	Thickness (mm) n = 10	Friability (%) n = 10	Hardness (kg/cm^2) n = 10	Tensile strength (MN/m^2) n = 10	Assay
F I	8.40 ± 0.02	4.80 ± 0.02	1.19 ± 0.03	2.50 ± 0.90	0.396 ± 0.025	97.5 ± 0.03
F II	8.44 ± 0.01	4.72 ± 0.04	1.61 ± 0.01	2.25 ± 0.41	0.347 ± 0.016	99.30 ± 0.06
F III	8.42 ± 0.02	4.74 ± 0.03	1.84 ± 0.01	1.25 ± 0.54	0.199 ± 0.032	98.4 ± 0.06
F IV	8.45 ± 0.03	4.75 ± 0.02	0.45 ± 0.02	4.10 ± 0.57	0.631 ± 0.041	97.9 ± 0.03
F V	8.44 ± 0.01	4.78 ± 0.01	0.72 ± 0.03	2.00 ± 0.21	0.319 ± 0.027	98.6 ± 0.02
F VI	8.41 ± 0.05	4.74 ± 0.01	1.64 ± 0.02	1.85 ± 0.12	0.280 ± 0.043	98.3 ± 0.02
F VII	8.42 ± 0.02	4.72 ± 0.02	0.41 ± 0.01	6.10 ± 0.48	0.961 ± 0.018	99.2 ± 0.05
F VIII	8.45 ± 0.02	4.80 ± 0.05	0.77 ± 0.02	5.50 ± 0.64	0.863 ± 0.039	102.4 ± 0.03
F IX	8.40 ± 0.03	4.76 ± 0.03	1.14 ± 0.05	2.75 ± 0.59	0.438 ± 0.025	98.5 ± 0.02

Table 4. Kinetic studies on MOGR tablets.

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
No.	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} ($h^{-1/3}$)
F I	0.8646	0.2732	0.9457	-0.0049	0.9742	6.1126	0.9678	1.0582	0.3340	0.9909	-0.0097
F II	0.8541	0.2782	0.9467	-0.0057	0.9691	6.2484	0.9686	1.0712	0.3182	0.9945	-0.0105
F III	0.8434	0.2833	0.9692	-0.0059	0.9632	6.3841	0.9693	1.1292	0.3029	0.9771	-0.0132
F IV	0.8551	0.2755	0.9647	-0.0059	0.9634	6.1838	0.9609	0.9632	0.0146	0.9894	-0.0108
F V	0.8509	0.2730	0.9839	-0.0051	0.9674	6.1364	0.9781	0.9709	0.0331	0.9855	-0.0101
F VI	0.8604	0.2743	0.9665	-0.0053	0.9724	6.1482	0.9652	1.0387	0.1574	0.9939	-0.0101
F VII	0.8621	0.2676	0.9773	-0.0053	0.9731	5.9937	0.9603	0.8656	0.1603	0.9920	-0.0102
F VIII	0.8685	0.2686	0.9880	-0.0046	0.9756	6.0010	0.9657	0.9187	0.0427	0.9900	-0.0095
F IX	0.8629	0.2744	0.9786	-0.0052	0.9731	6.1434	0.9684	0.9611	0.0275	0.9934	-0.0102

Table 5. Results of accelerated stability studies of MOGR tablets.

Batch	Hardness (Kg/cm^2)				Friability (% w/w)				Assay (%)			
No.	0 D	6 W	3 M	6 M	0 D	6 W	3 M	6 M	0 D	6 W	3 M	6 M
F I	2.50 ± 0.9	2.45 ± 0.5	2.45 ± 0.7	2.50 ± 0.8	1.19 ± 0.03	1.23 ± 0.02	1.22 ± 0.04	1.26 ± 0.03	97.5 ± 0.03	98.1 ± 0.07	97.7 ± 0.05	96.7 ± 0.08
F II	2.25 ± 0.41	2.25 ± 0.4	2.20 ± 0.9	2.20 ± 0.8	1.61 ± 0.01	1.63 ± 0.05	1.61 ± 0.02	1.57 ± 0.03	99.3 ± 0.06	99.1 ± 0.08	99.7 ± 0.07	98.8 ± 0.09
F III	1.25 ± 0.54	1.25 ± 0.8	1.25 ± 0.7	1.30 ± 0.8	1.84 ± 0.01	1.89 ± 0.06	1.82 ± 0.03	1.85 ± 0.01	98.4 ± 0.06	98.6 ± 0.10	98.8 ± 0.07	99.1 ± 0.09
F IV	4.10 ± 0.57	4.00 ± 0.4	4.10 ± 0.4	4.10 ± 0.6	0.45 ± 0.02	0.45 ± 0.01	0.45 ± 0.06	0.48 ± 0.04	97.9 ± 0.03	97.6 ± 0.05	97.3 ± 0.11	98.4 ± 0.08
F V	2.00 ± 0.21	2.00 ± 0.2	2.05 ± 0.4	2.05 ± 0.3	0.72 ± 0.03	0.78 ± 0.05	0.73 ± 0.04	0.74 ± 0.05	98.6 ± 0.02	98.6 ± 0.08	98.4 ± 0.04	98.5 ± 0.02
F VI	1.85 ± 0.12	2.00 ± 0.3	1.90 ± 0.5	2.00 ± 0.2	1.64 ± 0.02	1.67 ± 0.01	1.69 ± 0.03	1.58 ± 0.07	98.3 ± 0.02	98.7 ± 0.09	98.3 ± 0.10	98.0 ± 0.08
F VII	6.10 ± 0.48	6.20 ± 0.5	6.20 ± 0.4	6.20 ± 0.4	0.41 ± 0.01	0.43 ± 0.03	0.43 ± 0.02	0.40 ± 0.02	99.2 ± 0.05	99.8 ± 0.13	99.3 ± 0.10	98.5 ± 0.06
F VIII	5.50 ± 0.64	5.55 ± 0.6	5.55 ± 0.5	5.60 ± 0.7	0.77 ± 0.02	0.78 ± 0.05	0.78 ± 0.04	0.77 ± 0.05	102.4 ± 0.03	102.2 ± 0.07	101.8 ± 0.04	100.8 ± 0.05
F IX	2.75 ± 0.59	2.65 ± 0.4	2.70 ± 0.6	2.70 ± 0.5	1.14 ± 0.05	1.16 ± 0.04	1.11 ± 0.06	1.12 ± 0.05	98.5 ± 0.02	98.2 ± 0.09	98.4 ± 0.05	99.1 ± 0.08

D = day, W = week, M = month

Determination of content uniformity

The tramadol HCl matrix tablets were tested for their drug content. Twenty tablets were finely powdered; 400 mg of the powder was accurately weighed and transferred to a 50-mL volumetric flask. Then, the volume was made up with 0.1 M HCl and shaken for 10 min to ensure complete solubility of the drug. The mixture was centrifuged (Remi, India) and 10 mL of the supernatant liquid was diluted 20 times with 0.1 M HCl, and after centrifugation the absorbance was determined spectrophotometrically (Systronics 2202 model, India) at 272.5 nm.

Physical properties of tablets

The formulated tablets were evaluated for diameter, thickness, hardness and friability.

Diameter and thickness

A calibrated vernier caliper was used for diameter and thickness evaluation of the tablets.

Hardness

Ten tablets from each batch were examined using Monsanto hardness tester.

Friability

For friability tests, ten tablets were weighed (W1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were then reweighed (W2) and the percentage of friability (%F) was calculated.

$$\% F = W1 - W2 / W1 \times 100$$

Friability below 0.8% is usually considered satisfactory.

Determination of tensile strength

The tensile strength (T) of tablet, which is a measure of the stress necessary to cause diametral fracture of the compact, was determined from the mean data obtained from the hardness test carried out on the tablets (n = 10) using the Mosanto hardness tester according to Brook and Marshal (6). The T values were computed from equation below (7):

$$T = 2 P/ \pi D t$$

where P is the load applied on the tablet that causes tensile fracture of the tablet of diameter, D, and t is the tablet thickness.

***In vitro* drug release studies**

The matrix tablets were subjected to the paddle dissolution method using 900 mL of phosphate buffer solution pH 7.4 ± 0.2 as the dissolution medium. The dissolution test was performed at 100 rpm and the temperature was set at 37 ± 1°C. At predetermined time intervals over an 8-hour period, 4 mL samples were withdrawn, centrifuged, and assayed spectrophotometrically at 272.5 nm. After each sampling, equal volume (4 mL) of fresh buffer solution with the same temperature was replaced. All experiments were run 3 times, and the calibration curve specifications were $y = 0.006x \pm 0.005$ ($r^2 = 0.9998$, n = 9).

Kinetic studies

The *in vitro* drug release data of the formulated batches of the MOGR tablets were fitted into the following models and respective plots were made: zero order kinetic model (cumulative % drug release *vs*. time); first order kinetic model (log cumulative of % drug remaining *vs*. time); Higuchi model (cumulative % drug release *vs*. square root of time); power law (log cumulative % drug release *vs*. log time) and Hixson-Crowell model (cube root of drug % remaining in matrix *vs*. time.

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 (8) 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 (equation 4) correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets (9). The power law (10) (equation 5) describes the influence of polymeric hydration and swelling on drug release rate.

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

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

$$\log C = \log C_0 - k_1 t / 2.303 \quad (2)$$

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

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

where, k_H 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.

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

where, M_t/M_∞ is the fraction of drug released, k_{KP} is the release rate constant, n is the diffusional release exponent indicative of the drug release mechanism (Table 1), and t is the dissolution time.

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 and after 6 weeks, 3, 6 and 12 months for hardness, disintegration time, dissolution rate and assay.

RESULTS AND DISCUSSION

All the batches of MOGR tablets were formulated under similar conditions to avoid processing variables. The prepared tablets were evaluated for various physical parametric tests. The diameter and thickness of the prepared tablets was found to be 8.43 ± 0.02 mm and 4.75 ± 0.05 mm, respectively. The diluent ratio and amount of MOGR was found to have a significant effect on friability, hardness and tensile strength of the prepared tablets. Friability is an important factor in tablet formulation to ensure that the tablet can stay intact and withhold its form from any outside force of pressure. The % friability was found to increase from 1.19 – 1.84 (**F I – F III**)

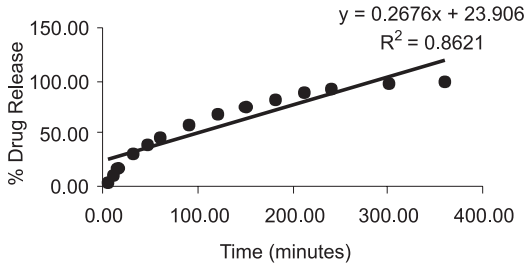

Figure 1. Zero order release model of tramadol from MOGR tablet

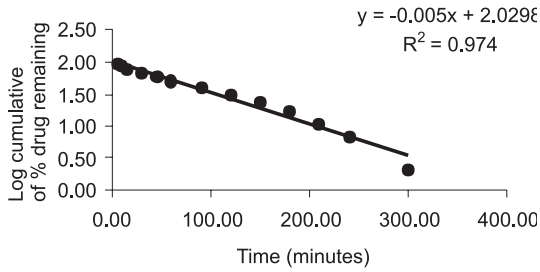

Figure 2. First order release model of tramadol from MOGR tablet

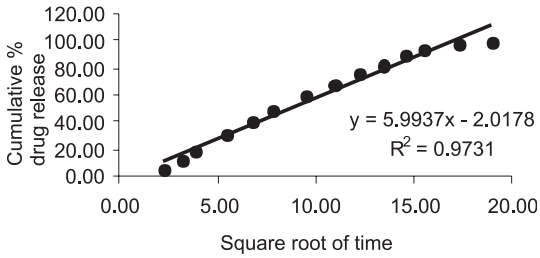

Figure 3. Higuchi release model of tramadol from MOGR tablet

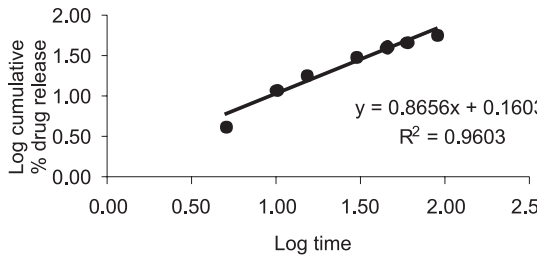

Figure 4. Korsmeyer-Peppas model for mechanism of drug release (first 60% drug release)

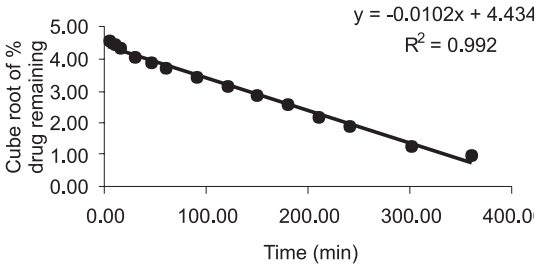

Figure 5. Hixson-Crowell cube root plots of tramadol from MOGR tablet

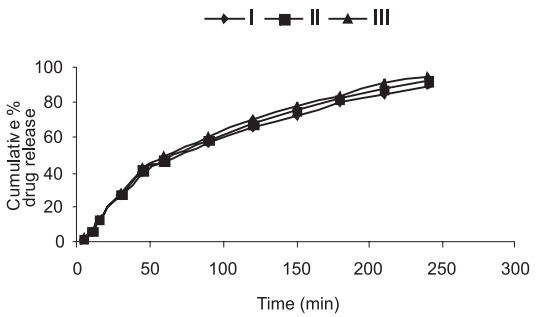

Figure 6. Drug release profile of tramadol from MOGR tablet

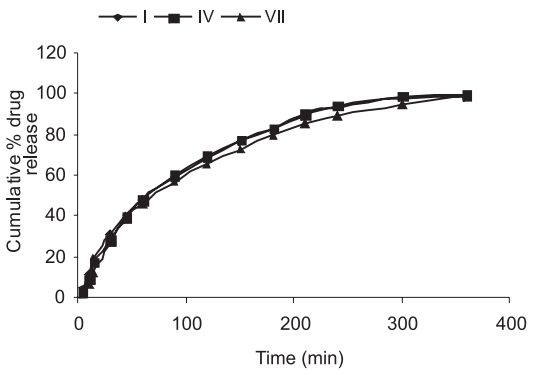

Figure 7. Drug release profile of tramadol from MOGR tablet

to 0.45 – 1.64 (**F IV** – **F VI**) and 0.41 – 1.14 (**F VII** – **F IX**), indicating the dependence of friability on diluent ratio. As the diluent ratio is increasing, i.e., the amount of $CaCO_3$ is decreasing, the tablets are becoming more prone to friability losses, clearly representing the need of optimum diluent ratio in formulating MOGR tablets. Tablet hardness or tablet

breaking force, which measures the tablet mechanical integrity, was found to decrease from 2.25 – 1.25 (**F I – F III**), 4.00 – 1.80 (**F IV – F VI**) and 6.00 – 2.75 (**F VII – F IX**), demonstrating the effect of diluent ratio on hardness. As the diluent ratio is decreasing, i.e., the amount of MCC is decreasing, the tablet hardness is substantially increasing. Hence, diluent ratio was found to directly affect the hardness and friability of the prepared MOGR tablets. Appropriate MCC to $CaCO_3$ ratio is required for sufficient strength in the dosage form. As hardness was found to be effected by the diluent ratio, similarly, tensile (hardness derived parameter) was also effected by diluent ratio. Tensile strength ranges were: 0.396 – 0.199 (**F I – F III**), 0.631 – 0.280 (**F IV – F VI**) and 0.961 – 0.438 (**F VII – F IX**).

Three different proportions (75, 100, 125 mg / tablet) of MOGR were selected to study its effect on the physical parameters of the prepared tablets. Overall improvement in friability, hardness and tensile strength of the tablets was seen as the amount of MOGR was increasing in the formulation, demonstrating the binding capacity of MOGR in the dosage form. As no other binder was included in the formulation, MOGR was found effective in providing sufficient strength to the formulation ingredients. Batch **VII** (diluent ratio 2 and MOGR 125 mg / tablet) was found to be good enough amongst all formulated batches, showing 0.41% friability, 6 kg/cm^2 hardness and 0.961 MN/m^2 tensile strength.

***In vitro* dissolution studies**

The release of tramadol from the prepared MOGR tablet formulations was analyzed by plotting the cumulative percent drug released *vs*. time as shown in Figures 6 and 7. Simple visual observation of the plots reveals a gradual release of the active substances from the matrix tablet. The drug release at first 60 min ranges from 46.11 to 48.67%; at 120 min from 65.75 to 70.44%; and at 240 min from 89.32 to 95.00%, respectively, for all the prepared experimental batches.

In the present study, MOGR has been used as release retardant excipient to modify the release of drug from the tablet matrix. Being an oleo-gum resin, MOGR is supposed to reduce the drug release due to a reduction in the penetration of the solvent molecules into the matrix structure. The proposed drug release phenomenon from the MOGR matrix tablets may be explained in three steps. First step could be the penetration of the dissolution medium in the tablet matrix (hydration) followed by the consequent dissolution or erosion of the matrix and finally, the transport of the dissolved drug from the parts of the eroded tablet matrix to the surrounding dissolution medium. It is evident from the drug release profiles (Figure 7) that as the proportion of MOGR is increased in the formulation, the release process of tramadol slows down.

Kinetics of drug release

As shown in Figures 1–5, plots drawn according to various semiempirical kinetic models, were giving linear relationship. In the zero order plot (Fig. 1, Tab. 4) the r^2 value obtained is 0.8621 and the first order (Fig. 2, Tab. 4) gave 0.9740 describing the drug release rate relationship with the concentration of drug. The best linearity was found in Hixson Crowell cube root plot (Fig. 5, Table 4) ($r^2 = 0.9920$) indicating the involvement of erosion / dissolution based release of drug from the MOGR tablet matrix.

Mechanism of drug release

To explore the release pattern, results of the i*n vitro* dissolution data were fitted to the Korsmeyer and Peppas equation. The value of release exponent (n) ranges from 0.8656 to 1.1292 (Table 4) amongst the formulated batches, indicating drug release governed by super case II transport, which includes polymer disentanglement and erosion (Table 2). It is evident that dissolution or erosion of the MOGR matrices would account for the increasing values of n. Furthermore, drug release kinetics of the formulations corresponds best with the Hixson-Crowell model, demonstrating the drug-release mechanism to be predominantly surface erosion, effected by water diffusion, polymer hydration, disentanglement and dissolution.

Accelerated stability studies

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

CONCLUSION

The present research was carried out to study the binding and release retardant properties of MOGR in tablet dosage form prepared by direct compression method and to carry out mechanistic study for understanding the drug release mechanism. *In vitro* release studies demonstrated that the release of drug from all prepared formulations was generally sustained. Drug release kinetics revealed

that the formulations follow Hixson-Crowell model, indicating erosion as a predominant drug release mechanism for MOGR based tablets. Being of natural origin, MOGR could be positively explored for its release retardant property in various dosage forms.

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