

Full Length Research Paper

# Formulations of sustained release metformin hydrochloride tablet using combination of lipophilic waxes by melt granulation technique

Kamlesh Jayantilal Wadher<sup>1\*</sup>, Rajendra Baliram Kakde<sup>2</sup> and Milind Janrao Umekar<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Technology, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, 441002, India.

<sup>2</sup>University Department of Pharmaceutical Sciences, R. T. M. Nagpur University Nagpur, 440033 India.

Accepted 22 January, 2016

Metformin hydrochloride is recommended globally as first line therapy due to its favorable profile on morbidity and mortality associated with type- 2 diabetes mellitus. However, limitations of multiple dosing and risk of triggering gastrointestinal symptoms make its dose optimization difficult. The present study was designed to develop the oral sustained release metformin hydrochloride tablet formulation using lipophilic waxes viz. hydrogenated castor oil, stearic acid and glyceryl monostearate either alone or their combinations. The *in vitro* dissolution study was carried out using USP 22 apparatus I, basket method. The drug release kinetics demonstrated that hydrogenated castor oil sustained the release of metformin greater than stearic acid and glyceryl monostearate when used alone. Combination of hydrogenated castor oil with stearic acid (1:1) sustained the drug release ( $75.69 \pm 0.76\%$ ) greater than hydrogenated castor oil with glyceryl monostearate ( $86.45 \pm 0.96\%$ ) and stearic acid with glyceryl monostearate ( $92.29 \pm 0.76\%$ ) combinations. Kinetic modeling of *in-vitro* dissolution profiles revealed that metformin release ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport mechanisms. Applying Korsmeyer equation to *in-vitro* drug release data indicated that diffusion along with erosion could be the mechanism of drug release.

**Key words:** Hydrogenated castor oil, stearic acid, glyceryl monostearate, metformin matrix tablet, release kinetics.

## INTRODUCTION

Type-2 diabetes mellitus is a chronic progressive disorder characterized by defective insulin secretion and increased insulin resistance. It is widely accepted that it required intense and tight glycemic control to prevent several cardiovascular complications. Metformin hydrochloride is an orally administered biguanide, widely used in the management of type- 2 diabetes, a common disease that combines defects of both insulin secretion and insulin action (Stith et al., 1996). It is a hydrophilic drug which slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability is reported to be of 50-60% has relatively short biological

half life of 1.5-4.5 h (Dunn and Peters, 1995; Defang, 2005). However, frequent dosing schedule and risk of gastrointestinal symptoms makes its dose optimization complicated. Thus, it is reasonable to assume the requirement of sustained release metformin formulation to prolong its duration of action and to improved patient compliance.

Melt granulation is a process in which granulation is obtained by adding waxes, which melts/softens at relatively low temperature, and act as binding liquid (Sprockel et al., 1997). Melt granulation is simple and efficient technique that has many advantages over conventional methods (Taggart et al., 1984; Royce et al., 1996). Moreover, the melt granulation may be used to prepare controlled release granules by selecting suitable binders (Hamdani et al., 2002; Zhang and Schwartz, 2003).

Many waxes (e.g., stearic acid, mono-, di- and tri-glycerides,

\*Corresponding author. E-mail: [kamleshwadher@gmail.com](mailto:kamleshwadher@gmail.com).  
Tel: +91 7109 288650. Fax: +91 7109 287094.

glyceryl behenate, glyceryl monostearate, hydrogenated castor oil, etc.) have been extensively investigated for sustaining the release of various drugs (Voinovich et al., 2002). Hydrogenated castor oil is a white to slightly yellow fine powder obtained by hydrogenating castor oil using a catalyst. It has been used in pharmaceutical formulation or technology as a sustained-release coating material and hardening agent (Kibbe, 2000). Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant; it has also been suggested that stearic acid may be used as a sustained-release drug carrier (Rowe et al., 2003). Glyceryl monostearate, a white to cream coloured wax like solid is a lubricant for tablet manufacturing and used to form sustained release matrices for solid dosage forms (Kibbe, 2000; Rowe et al., 2003). Although, these waxes have been extensively used in preparation of sustained release formulation, their combinations in the melt granulation techniques largely remain unexplored.

Therefore, present study was planned for formulation and *in-vitro* evaluation of sustained release matrix tablet of metformin hydrochloride by melt granulation technique using hydrogenated castor oil, stearic acid and glyceryl monostearate as meltable binders to reduce dosage regimen, better therapeutic efficacy and improved patient compliance with less toxicity.

## MATERIALS AND METHODS

### Materials

Metformin HCl was obtained from Universal Medicament (Nagpur, India). Microcrystalline cellulose (MCC, Avicel PH 101), stearic acid, glyceryl monostearate, were purchased from S. D. Fine Chem. Labs. (Mumbai, India). Hydrogenated castor oil was received as a gift sample from Shree Rayalaseema Alkalies and Allies Pvt. Ltd, (Chennai, India). All other ingredients used were laboratory reagents and used as such without further testing.

### Methods

#### Preparation of the tablets

Sustained release granules were prepared using wax as a retarding material. For the preparation of sustained release formulation, hydrogenated castor oil, stearic acid and glyceryl monostearate were used at three different concentrations by trial and error basis. Hydrophobic wax granules were prepared by melting waxes by heating at constant temperature of 75°C. Drug and diluents were gradually added to the molten mass with continuous stirring. The molten mixture was then allowed to cool and solidify at room temperature and pulverized in mortar and sized through a 16 mesh sieve. Prior to compression 5% (w/w), magnesium stearate was mixed with each batch of granules in poly bag for 5 min. A rotary tableting machine (Rimek Minipress I Ahmadabad, India), equipped with 14-mm flat faced circular punches was used to prepare tablets at a constant compression force. The composition with respect to waxes combination was selected on the basis of trial preparation of tablets. The composition of various formulations of the tablets with their codes is listed in Table 1.

### Evaluation of granules

The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausners index (United States Pharmacopoeia, 2000; Staniforth, 2000; Lachman et al., 1991).

### Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content (Wells, 2002; Martin, 2001). Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method (Indian Pharmacopoeia, 1996).

### In vitro drug release

Drug release studies were conducted using USP 22 dissolution apparatus I, basket type (Electrolab, Mumbai, India) at the speed of 100 rpm at 37 ± 0.5°C. The dissolution media used were 900 mL of 0.1 mol/L HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of prewarmed (37 ± 0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed by UV spectrophotometer after suitable dilution (Shimadzu UV-1700) at 233 nm (Basak et al., 2007). The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

### Analysis of release data

The data obtained from *in-vitro* drug release was fitted to mathematical equations of different kinetics model such zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) (Higuchi, 1963) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models (Korsmeyer et al., 1983).

### Drug release kinetics

In model-dependent approaches, release data were fitted to five kinetic models including the zero-order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), Peppas-Korsmeyer (Equation 4), and Hixson-Crowell (Equation 5) release equations to find the equation with the best fit using PCP Disso v3 software, Pune, India (Costa P, Lobo JMS, 2001).

$$R = k_1 t \text{-----} \quad (1)$$

$$\log UR = k_2 t / 2.303 \text{-----} \quad (2)$$

$$R = k_3 t \text{-----} \quad (3)$$

$$\log R = \log k_4 + n \log t \text{-----} \quad (4)$$

$$(UR)^{1/3} = K_5 t \text{-----} \quad (5)$$

**Table 1.** Composition of metformin HCl sustained release formulations.

Formulation Code	Ingredients (mg/tablet)					
	Metformin HCL	HCO	SA	GM	MCC	Mag. stearate
FI	500	100	-	-	396	4
FII	500	200	-	-	296	4
FIII	500	300	-	-	196	4
FIV	500	-	100	-	396	4
FV	500	-	200	-	296	4
FVI	500	-	300	-	196	4
FVII	500	-	-	100	396	4
VIII	500	-	-	200	296	4
FIX	500	-	-	300	196	4
FX	500	150	150	-	196	4
FXI	500	150	-	150	196	4
FXII	500	-	150	150	196	4

Where R and UR are the released and unreleased percentages, respectively, at time (t);  $k_1$ ,  $k_2$ ,  $k_3$ ,  $k_4$ , and  $k_5$  are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixon–Crowell model, respectively.

#### Statistical analysis

The data was subjected to ANOVA followed by Newman–Kuel's test and in all the cases  $p < 0.05$  was considered as significant. Correlation analysis reveals that  $p < 0.0001$ ,  $r = 0.845$  (F-X Vs F-XI) and  $p < 0.005$ ,  $r = 0.9792$  (FXI Vs FXII) and  $p < 0.0001$ ,  $r = 0.90$  (FX Vs FXII).

## RESULTS

### Evaluation of granules

The granules of proposed formulations were evaluated for LBD, TBD, compressibility index, angle of repose and Hausners ratio (Table 2). The results of LBD and TBD ranged from 0.355 to 0.461 and 0.412 to 0.530, respectively. Angle of repose of all the formulations was found to be in the range of  $31.15 \pm 0.61$  to  $35.13 \pm 0.63$  indicating good flow properties. Compressibility index and Hausners ratio ranges from, 12.6 to 17.9 and 1.14 to 1.23, respectively.

### Tablet characteristics

The physical parameters such as hardness, thickness, friability and weight uniformity of all the formulated tablets were given in Table 3. Hardness of all the tablets was in the range of  $7.01 \pm 0.90$  to  $8.26 \pm 0.56$  kg/cm<sup>2</sup>. The thickness and percentage friability ranged from  $4.42 \pm 0.02$  to  $4.65 \pm 0.07$  mm and  $0.098 \pm 0.17$  to  $0.326 \pm 0.12\%$ , respectively. All formulations showed less than 1% (w/w) friability which was within the prescribed limits

(Lachman et al., 1991).

### Drug release studies

*In vitro* drug release depends on several factors, such as the manufacturing process, the type of excipients and the amount of drug. The results of dissolution studies of formulations F -I, F-II, and F -III, composed of hydro-generated castor oil (10, 20 and 30%) are shown in Figure 1. Tablets F-I, F-II, and F-III released  $52.68 \pm 0.63\%$ ,  $37.91 \pm 0.42\%$ , and  $28.04\% \pm 0.23\%$  of metformin hydrochloride at the end of 2 h and  $98.29 \pm 0.61\%$ ,  $98.91 \pm 0.77\%$ , and  $78.80 \pm 1.08\%$  of drug at the end of 6, 9 and 12 h, respectively. The results of dissolution studies of formulations F-IV, F-V, and F-VI, composed of Stearic acid (10, 20 and 30%) are shown in Figure 2. Formulation F-IV, F-V, and F-VI, released  $38.08 \pm 0.35\%$ ,  $40.42 \pm 0.18\%$ , and  $10.76 \pm 1.41\%$  of metformin HCL at the end of 2 h and  $99.44 \pm 2.26\%$ ,  $98.48 \pm 1.37\%$ , and  $80.15 \pm 1.59\%$  of drug at the end of 6, 9 and 12 h, respectively.

The results of dissolution studies of formulations F-VII, F-VIII, and F-IX, composed of Glyceryl monostearate (10, 20 and 30%) are shown in Figure 3. Formulation F-VII, F-VIII, and F-IX released  $59.81 \pm 0.26\%$ ,  $44.97 \pm 0.21\%$ , and  $33.97 \pm 0.41\%$  of metformin HCL at the end of 2 h and  $98.29 \pm 1.06\%$ ,  $99.98 \pm 0.27\%$ , and  $95.29\% \pm 1.59\%$  of drug at the end of 6, 9 and 12 h, respectively. Formulations F-X, FXI and F-FXII composed of combination of HCO and SA (15%:15%), HCO and GM (15%:15%) and SA and GM (15%:15%), respectively are shown in Figure 3. Tablets –FX released  $10.99 \pm 0.49\%$  and  $75.69 \pm 0.76\%$ , metformin HCL at the end of 2 and 12 h, respectively. Tablets –FXI released  $51.16 \pm 0.89\%$  and  $86.45 \pm 0.96\%$ , metformin HCL at the end of 2 and 12 h, respectively. Tablets –FXII released  $42.87 \pm 0.79\%$  and  $92.29 \pm 0.76\%$ , metformin HCL at the end of 2 and 12 h, respectively.

**Table 2.** Physical properties of the granules containing metformin HCl as a SR formulation.

Formulation	L.B.D.	T.B.D.	Angle of repose	Carrs index	Hausners ratio
FI	0.380	0.440	30.31±0.35	13.6	1.16
FII	0.374	0.448	34.35±0.18	16.5	1.19
FIII	0.357	0.420	31.60±0.15	15.0	1.17
FIV	0.450	0.530	31.13±0.79	15.1	1.17
FV	0.386	0.437	35.13±0.23	11.6	1.13
FVI	0.417	0.508	32.70±0.63	17.9	1.22
FVII	0.430	0.523	31.15±0.61	17.8	1.22
FVIII	0.371	0.438	32.15±0.43	15.3	1.18
FIX	0.399	0.492	34.83±0.63	18.9	1.23
FX	0.461	0.530	32.15±0.33	13.0	1.49
FXI	0.355	0.421	33.15±0.43	15.6	1.85
FXII	0.360	0.412	32.83±0.63	12.6	1.14

**Table 3.** Physical properties of the prepared sustained release metformin HCl matrix tablets.

Formulation code	Hardness† (kg/cm <sup>2</sup> )	Friability† (%)	Weight variation* (%)	Drug content* (%)	Thickness† (mm)
FI	7.25 ± 0.52	0.232 ± 0.16	1002.28 ± 9.13	98.13	4.65 ± 0.07
FII	7.58 ± 0.38	0.198 ± 0.29	1001.58 ± 5.13	99.34	4.54 ± 0.03
FIII	7.37 ± 0.25	0.098 ± 0.17	1002.24 ± 9.46	92.73	4.45 ± 0.07
FIV	7.17 ± 0.53	0.145 ± 0.10	998.23 ± 11.13	99.19	4.55 ± 0.08
FV	8.10 ± 0.61	0.259 ± 0.21	1003.28 ± 5.13	99.34	4.51 ± 0.07
FVI	8.26 ± 0.56	0.260 ± 0.09	1001.28 ± 6.13	96.34	4.53 ± 0.02
FVII	7.01 ± 0.90	0.271 ± 0.02	998.38 ± 7.13	97.34	4.66 ± 0.02
FVIII	7.15 ± 0.68	0.226 ± 0.12	1001.08 ± 3.13	98.74	4.48 ± 0.02
FIX	8.76 ± 0.56	0.260 ± 0.09	1001.28 ± 6.13	96.34	4.53 ± 0.02
FX	7.15 ± 0.68	0.326 ± 0.12	1003.08 ± 3.13	99.74	4.42 ± 0.02
FXI	7.65 ± 0.68	0.256 ± 0.12	1002.28 ± 4.13	99.44	4.44 ± 0.02
FXII	8.06 ± 0.56	0.240 ± 0.09	1001.26 ± 8.13	98.34	4.58 ± 0.02

\*All values are expressed as  $M \pm SE$ ,  $n = 20$ , † All values are expressed as  $M \pm SE$ ,  $n = 10$ .

## Drug release kinetics

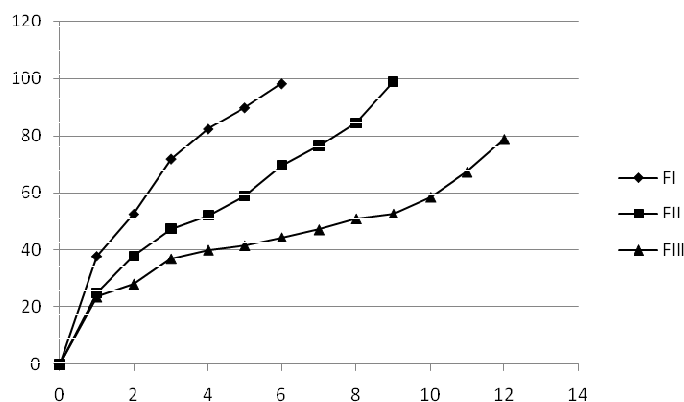
To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations. The data was analyzed by the regression coefficient method and regression coefficient value ( $r^2$ ) of all batches as shown in Table 4. The drug release from F-VI, F-VII and F-X formulation followed Hixson – Crowell's cube root model. F -II, F-IV and F-V formulation, followed Korsmeyer-Peppas model; F-I, F-III, F-XIII, F-IX, F-XI and F-XII formulation followed Higuchi model release kinetics which is indicated by the correlation coefficients ( $r^2$ ) value.

The *in-vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity ( $r^2 = 0.98$  to  $0.99$ ) (Higuchi et al., 1961). To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation (Korsmeyer et al., 1983).

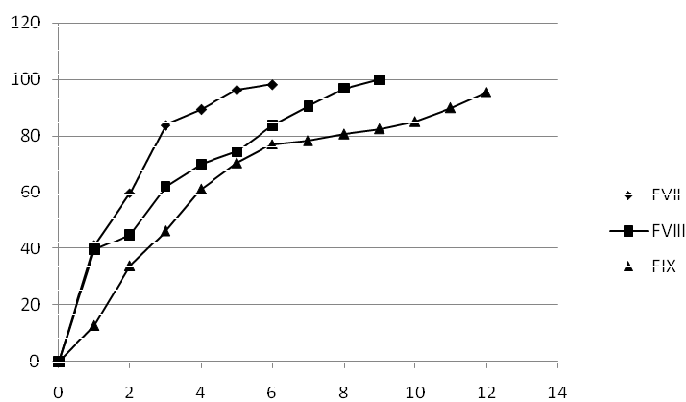
## DISCUSSION

In the present study, the matrix system of hydrophilic metformin hydrochloride was developed by melt granulation techniques. The granules of proposed formulations were evaluated for LBD, TBD, compressibility index, angle of repose and Hausners ratio. The value obtained for LBD, TBD and Hausners ratio lies within the acceptable range. Hausners ratio of the prepared granules ranged from 1.13 to 1.85 which was thought to indicate good flow properties of the prepared granules as a result of increasing particle sizes owing to granulation. (Lachman et al., 1991) The results of angle of repose indicating good flow property of granules. Granules with Carr's index values around 21% and below are considered to have fair and excellent flow properties (Wells, 2002).

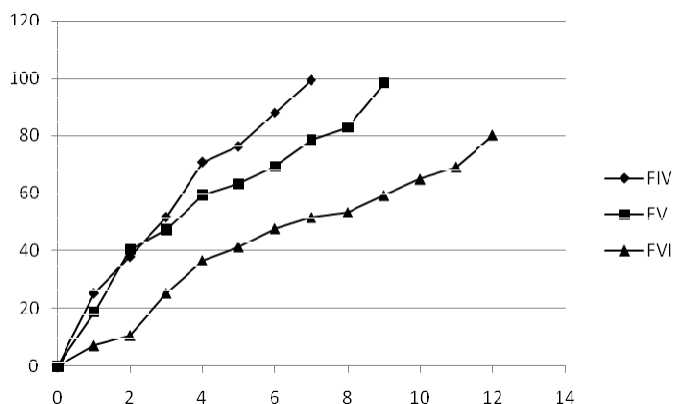
Tablets of all the formulations were subjected to many physical parameters such as hardness, thickness, friability



**Figure 1.** *In vitro* cumulative release of metformin from formulation F-I (—), F-II (—) and F-III (—). Each point represents mean  $\pm$  SD, n=3.



**Figure 3.** *In vitro* cumulative release of metformin from formulation F-VII (—), F-VIII (—) and F-IX (—). Each point represents mean  $\pm$  SD, n=3.



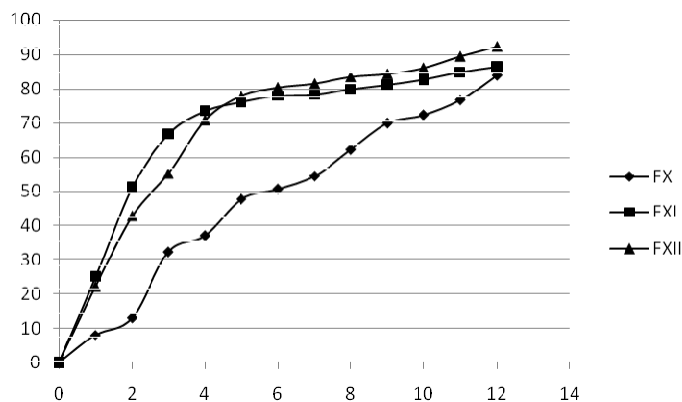
**Figure 2.** *In vitro* cumulative release of metformin from formulation F-IV (—), F-V (—) and F-VI (—). Each point represents mean  $\pm$  SD, n=3.

and weight uniformity. All the formulation showed thickness in the range of  $4.42 \pm 0.02$  to  $4.65 \pm 0.07$  mm. All formulations showed less than 1% (w/w) friability which was within the prescribed limits (Lachman et al., 1991). According to the Pharmacopoeial recommendation for tablets weighing more than 324 mg,  $\pm 5\%$  deviation from the mean weight is acceptable. Weight variation test revealed that all the tablet were within the range of pharmacopoeial limit. As the results show, the average weight deviation percentage of 20 tablets taken from each formulation was less than  $\pm 0.5\%$ , and all the formulations met the requirement. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%. All the formulation showed reasonably good hardness value of 7 - 8 kg/cm<sup>2</sup>. As the concentration of lipophilic binder increases, cold welding of waxes increases in melt granules and therefore tablet hardness increases.

Effect of different drug:wax ratio (FI-FIX) on *in vitro* release profile of metformin hydrochloride was studied and the decrease in drug release rate was observed when hydrogenated castor oil, stearic acid and glyceryl monostearate content in the matrix were increased (Figure 1, 2 and 3). It may be due to the slower penetration of dissolution medium in matrices due to increased liophilicity of waxy substances (Hamdani, 2003). Initial burst release from the matrix could probably be attributed to the dissolution of drug from the surface of the tablet. Further, penetration of solvent molecule was hindered due to the hydrophobic coating of the hydrogenated castor oil on the drug particle leading to the slow release for a prolonged period (Yonezava, 2001).

In the present study, combination of waxes in controlling the release rate of metformin hydrochloride was also examined. Formulations F -X contains different combination of hydrogenated castor oil with stearic acid 1:1 (w/w); F-XI contains different combinations of hydrogenated castor oil with and glyceryl monostearate 1:1(w/w), respectively and formulation F-XII containing different combination of stearic acid with glyceryl monostearate 1:1 (w/w). The release of metformin hydrochloride from the combinations get more retarded than that of alone wax content, it may be due to higher lipophilicity offered by combination of waxes. Result also showed that among meltable waxes combination of hydrogenated castor oil with stearic acid provide more sustained effect than that of combination of hydrogenated castor oil with glyceryl monostearate and stearic acid with glyceryl monostearate (Figure 4).

The preference of a certain mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release. Successive evidence of the relative validity of diffusion and first order models obtained by analyzing the data using the following equation of Korsmeyer and Peppas (1983):



**Figure 4.** *In vitro* cumulative release of metformin from formulation F-X (—●—), F-XI (—■—) and F-XII (—▲—). Each point represents mean  $\pm$  SD, n=3.

$$Mt/M = K \cdot t^n$$

Where  $Mt/M$  is the fraction released by the drug at time  $t$ ,  $K$  is a constant incorporating structural and geometric characteristic and  $n$  is the release exponent characteristic for the drug transport mechanism. When  $n = 0.5$  fickian diffusion is observed and the release rate is dependent on  $t$ , while  $0.5 < n < 1.0$  indicate anomalous (non-fickian) transport and when  $n = 1$ , the release is zero order. The formulations showed good linearity ( $r^2 = 0.92$  to  $0.99$ ) with slope ( $n$ ) between  $0.4180 - 0.9710$  which appears to indicate a coupling of diffusion and erosion mechanisms—so called anomalous diffusion.

Therefore, the release of drug from the prepared tablets is controlled by the swelling of the polymer followed by drug diffusion through the swelled polymer and slow erosion of the tablet. From the release exponent in the korsmeyer-peppas model, it can be suggested that the mechanism that led to the release of metformin hydrochloride was an anomalous transport with constant release rate adequate for a sustained release dosage form. The correlation ( $r^2$ ) was used as an indicator of the best fitting for each of the models considered (Table 4). Correlation data shows that among the waxes hydrogenated castor oil and in combinations hydrogenated castor oil with stearic acid 1:1 (w/w) was found to be more significant.

## CONCLUSIONS

The approach of the present study was to make an evaluation of wax materials as sustained release matrix for water soluble metformin hydrochloride and to access the kinetics of drug release mechanism. Results of the present study demonstrated that tablet formulated with hydrogenated castor oil sustain the release more than that of stearic acid and glyceryl monostearate. Combination of hydrogenated castor oil and stearic acid provide

more sustained effect than the combination of hydrogenated castor oil with glyceryl monostearate and stearic acid with glyceryl monostearate. Diffusion coupled with erosion might be the mechanism for the drug release. The hydrophobic wax matrix tablet is a promising approach to achieve appropriate sustained release dosage.

## REFERENCES

- Basak SC, Rahman J, Ramlingam M. (2007). Design and *in vitro* testing of a floatable gastroretentive tablet of metformin hydrochloride. *Pharmazie*, Eschborn, 62 : 145-148.
- Costa P, Lobo JM. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci.* 2001;13:123-133.
- Defang O, Shufang N, Wei L (2005). *In vitro* and *in vivo* evaluation of two extended Release preparations of combination metformin and glipizide. *Drug Dev. Ind. Pharm.* 31: 677–685.
- Dunn CJ, Peters DH (1995). Metformin: A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs*, 49: 721-749.
- Hamdani J, Moes AJ, Amighi K (2002). Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *Int. J. Pharm.* 245: 167–177.
- Higuchi T (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drug dispersed in solid matrices. *J. Pharm. Sci.* 52: 1145–1149.
- Indian Pharmacopoeia (1996). 4ed New Delhi: The Controller of Publications. 2, pp.736
- Kibbe AH (2000). Handbook of pharmaceutical excipients. London, UK: American Association and The Pharmaceutical Society of Great Britain. pp. 94–537.
- Korsmeyer RW, Peppas NA (1983). Macromolecular and modeling aspects of swelling controlled system. In: Roseman, T.J., Mansdorf, S.Z. (eds.) *Controlled Release Delivery Systems*. Dekker, New York, NY, pp. 77–101
- Lachman L, Liberman HA, Kanig LJ (1991). *The Theory and Practice of Industrial Pharmacy*, pp 67-69, 296-302, 316-318
- Martin A, (2001). *Micromeritics*. In: *Physical Pharmacy*. Philadelphia, PA: Lippincott Williams & Wilkins. pp 423-454.
- Rowe RC, Sheskey PJ, Weller PJ (2003). *Handbook of Pharmaceutical excipients*. Pharmaceutical Press, American Pharmaceutical Association. pp106 -671
- Royce A, Suryavanshi J, Shah U, Vishnupad K (1996). Alternative granulation technique: Melt granulation. *Drug. Dev. Ind. Pharm.*; 22: 917– 924.
- Sprockel OL, Sen M, Shivanand P, Prapaitrakul W ( 1997). Melt extrusion processes for manufacturing matrix drug delivery systems. *Int. J. Pharm.* 155: 191-199.
- Staniforth, J (2002). Powder Flow, In Aulton ME (eds) *Pharmaceutics- The science of dosage form design*, Churchill livingstone. pp 198-210.
- Stith BJ, Goalstone ML, Espinoza R, Mossel C, Roberts D, Wiernsperger N (1996). The antidiabetic drug metformin elevates receptor tyrosine kinase activity and inositol 1, 4, 5-triphosphate mass in *Xenopus oocytes*. *Endocrinology*, 137: 2990–2999.
- Taggart CM, Ganley JA, Sickmuller A, Walker SE (1984). The evaluation of formulation and processing conditions of a melt granulation process. *Int. J. Pharm.*, 19: 139 -148.
- United States Pharmacopoeia XXIV NF 19(2000). United States Pharmacopoeial Convention, Rockville. Pp 1913-1914, 2235-2236.
- Voinovich D, Moneghini M, Perissutti B, Filipovic-Grcic, J, Grabnar I (2000). Preparation in high-shear mixer of sustained-release pellets by melt pelletisation. *Int. J. Pharm.*, 203: 235–244.
- Wells J (2002). *Pharmaceutical preformulation: The physiochemical properties of drug substances*. In: Aulton ME. (eds.) *Pharmaceutics the science of dosage form design*, London: Churchill Livingstone. pp 247.
- Yonezava Y, Ishida S, Sunanda S (2001). Release from or through a wax

matrix system: I, basic release properties of the wax matrix system.

Chem Pharm Bull. 49:1448-51

Zhang Y, Schwartz JB (2003). Melt granulation and heat treatment for wax matrix controlled drug release. Drug Dev. Ind. Pharm. 29: 131-138.