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Sustained release Metformin Hydrochloride tablet using hydrogenated castor oil and stearic acid by melt granulation technique

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Abstract

The overall objective of this study was to develop a oral sustained release metformin hydrochloride tablet by using lipophilic waxes like Hydrogenated castor oil (HCO) and stearic acid(SA), alone or in combination using different diluents such as lactose, dicalcium phosphate and microcrystalline cellulose. Metformin hydrochloride has relatively short plasma half life, low absolute bioavailability. The need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma level for 8-12 h might be sufficient for daily dosing of metformin. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability. The in vitro dissolution study was carried out using USP 22 apparatus 2, paddle method. The drug release study revealed that HCO sustain the drug release more than that of SA. Combining HCO with SA sustained the drug release (75.69 ±0.76%) more than that of the HCO and SA for 12 h. At the same wax concentration, drug release from tablets decreased in order of Lactose > Microcrystalline cellulose > Di Calcium phosphate as diluents. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport.

Key words: Metformin hydrochloride, Hydrogenated castor oil, Stearic acid, Matrix tablets, Release kinetics

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INTRODUCTION

Sustained-release products have become important for the oral administration of many drugs because they give more consistent blood levels [1]. Wax matrices can be prepared by direct

compression, wet granulation fusion and melt granulation method [2, 3]. Melt granulation is the process in which granulation is obtained through the addition of meltable binder which melts or soften at relatively low temperature, after melting binder acts as binding liquid . Melt granulation technique fulfill today's Pharmaceutical industry need because it is simple, continuous and efficient and also has many advantages over conventional methods of granulation such as wet and dry granulation [4,5]. Furthermore, by selecting suitable binders, the melt granulation may be used to prepare controlled release granules [6]. Many waxes (e.g., stearic acid (SA) , mono-, di- and tri-glycerides, glyceryl behenate, Glyceryl monostearate , hydrogenated castor oil (HCO), etc.) have been extensively investigated for sustaining the release of drugs [7].

HCO is a white to slightly yellow fine powder obtained by hydrogenating castor oil using a catalyst. HCO has been used in pharmaceutical formulation or technology as a sustained-release coating material and hardening agent. SA 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. [8].

Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of and the type -II diabetes, is a common disease that combines defects of both insulin secretion and insulin action [19]. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract ,and the absolute bioavailability is reported to be of 50%-60%.[10].An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occurs during the initially period of treatment. The compound has relatively short plasma half life of 1.5-4.5 hours and the low absolute bioavailability of 50%-60% [11]. Side effects, short half lives, low bioavailability and the need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma level for 8-12 hrs might be sufficient for daily dosing for metformin sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances.

Hence present study was aimed towards formulation and invitro evaluation of sustained release matrix tablet of metformin hydrochloride by melt granulation technique by using HCO and SA as meltable binders and to study the effect of different diluents on the release rate.

MATERIALS AND METHODS

Materials

Metformin HCl was obtained from Universal Medicament Nagpur, India. Microcrystalline cellulose (MCC, Avicel pH 101), Stearic acid, Lactose and Di calcium phosphate were purchased from S. D. Fine Chem. Labs. (Mumbai, India), Hydrogenated castor oil was received as a gift sample from Shree Rayalaseema Alkalies & Allies Pvt. Ltd , (Chennai, India). All other ingredients used throughout the study were of analytical grades and were used as received.

Methods:

Estimation of metformin HCl

The analysis for the drug was carried out using UV/VIS spectrophotometer (Shimadzu 1700, Kyoto, Japan) at the y max of the drug which is 233 nm, using a quartz curette cell and against

an appropriate blank .All samples were appropriately diluted before reading the absorbance. The absorbance readings were converted to concentration in µg/mL by using an appropriate calibration curve.

Preparation of the granulates

Sustained release granules were prepared using wax as retarding material. For the preparation of sustained release formulation hydrogenated castor oil and stearic acid were used at three different concentrations at trial and error basis. Hydrophobic wax granules were prepared by melting waxes by heating. Drug and diluents were gradually added to the molten mass with continuous stirring .The molten mass was allowed to cool and then was sized with a 10 mesh sieve.

Preparation of the tablets

Prior to compression 5% (w/w) of magnesium stearate was mixed with each batch of granulates for 5 minutes in poly bag. A rotary tabletting machine (Rimek Minipress I Ahmadabad, India), equipped with 14-mm flat faced circular punches was employed 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. In each formulation, the amount of the active ingredient is 500 mg and the total weight of a tablet is 1000 mg. A batch of 30 tablets was prepared with each formula. The composition of various formulations of the tablets with their codes is listed in Tab.1.

Evaluation of granules

The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, Compressibility index and drug content [12, 13]. Angle repose (θ) of granules was determined by the funnel method. The diameter and height of the powder cone were measured and angle of repose was calculated using the equation:

$$\text{Tan } \theta = h/r,$$

Where h and r are the height and radius of the powder cone.

LBD and TBD were determined by cylinder method using the equations

LBD = weight of the powder/ volume of the packing;

TBD = weight of the powder/tapped volume

The compressibility index or Carr's index (CI) of the granules was determined by using the following equation:

$$\text{Carr's index} = [(TBD-LBD) \text{ X } 100)]/TBD.$$

Hausners ratio was related to interparticle friction and could be used to predict powder flow properties. Hausners values of the prepared granules ranged from 1.12 to 1.25 were thought to indicate good flow properties [14].

Table 1: Composition of Various Trial Formulations for the Metformin HCl Sustained release tablet

formulation	Ingredients (mg/tab)						
Code	**Metformin HCL**	**HCO**	**SA**	**MCC**	**Lactose**	**DCP**	**Mag.stearate**
FI	500	100	-	396	-	-	4
FII	500	200	-	296	-	-	4
FIII	500	300	-	196	-	-	4
FIV	500	-	100	296	-	-	4
FV	500	-	200	196	-	-	4
FVI	500	-	300	96	-	-	4
FVII	500	200	100	196	-	-	4
VIII	500	150	150	196	-	-	4
FIX	500	150	150	-	196	-	4
FX	500	150	150	-	-	196	4

Table 2: Physical properties of the Metformin HCl stained release granules

formulation	L.B.D.	T.B.D.	Angle of Repose	Carrs Index	Hausners Ratio
FI	0.380	0.440	30.31±0.35	12.4	1.14
FII	0.374	0.448	34.35±0.18	16.8	1.25
FIII	0.307	0.400	31.60±0.15	18.1	1.24
FIV	0.450	0.530	31.13±0.79	15.4	1.18
FV	0.386	0.417	35.13±0.23	17.4	1.14
FVI	0.417	0.508	32.70±0.63	17.5	1.22
FVII	0.371	0.410	31.45±061	15.6	1.20
FVIII	0.401	0.430	32.15±0.33	12.8	1.28
FIX	0.390	0.412	32.83±0.63	13.8	1.26
FX	0.420	0.400	31.18±0.41	14.8	1.19

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. 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 [14, 15].

***In vitro* drug release studies**

Drug release studies were conducted using USP dissolution apparatus I, basket type (Electrolab, Mumbai, India) at a rotational speed of 100 rpm at at 37±0.5 ºC. The dissolution media used were 900 mL of 0.1mol/L HCl for first 2 hours 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 ºC) fresh dissolution medium was replaced to maintain the volume constant.

Table 3: Physical properties of the metformin HCl Sustained release tablet

Formulation Code	Hardness† (kg/cm2)	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	4.452±0.07
FIV	7.17±0.53	0.145±0.10	998.23±11.13	99.19	4.55±0.08
FV	8.91±0.71	0.259±0.21	1003.28±5.13	99.34	4.51±0.07
FVI	8.76±0.56	0.260±0.09	1001.28±6.13	96.34	4.53±0.02
FVII	8.01±0.90	0.301±0.02	1001.38±9.13	98.34	4.60±0.02
FVIII	7.15±0.68	0.326±0.12	1003.08±3.13	99.74	4.42±0.02
FIX	7.82±0.51	0.313±0.13	999.28±9.13	95.44	4.81±0.04
FX	6.77±0.52	0.198±0.08	1002.88±2.34	94.64	4.67±0.06

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

Table 4: In - vitro release kinetics parameters of Metformin HCL Matrix Tablet

formulation	zero order		First order		Higuchi		Hixon-crowell		Korsmeyer-peppas		
	r2	k	r2	k	r2	k	r2	K	N	r2	K
FI	0.918	18.99	0.9924	-0.5349	0.9977	40.286	0.9924	-0.115	0.5462	0.996	37.720
FII	0.953	12.44	0.8129	-0.2924	0.983	28.970	0.9318	-0.064	0.5936	0.993	24.377
FIII	0.862	6.624	0.929	-0.103	0.972	19.445	0.9287	-0.029	0.4381	0.928	21.72
FIV	0.977	15.324	0.8288	-0.4622	0.9782	34.272	0.9513	-0.093	0.7151	0.951	24.515
FV	0.946	11.602	0.8418	-0.2853	0.9846	29.43	0.9455	-0.056	0.6800	0.945	21.51
FVI	0.984	6.8245	0.9749	-0.1102	0.9519	19.565	0.9875	-0.030	0.9710	0.987	7.49
FVII	0.986	6.698	0.9794	-0.1072	0.9494	19.141	0.9901	-0.030	0.8944	0.990	8.457
FVIII	0.978	7.549	0.9845	-0.1321	0.9594	21.697	0.9945	-0.035	0.9409	0.9945	8.868
FIX	0.972	8.382	0.9864	-0.1651	0.9665	24.164	0.9960	-0.042	0.8241	0.9960	12.536
FX	0.959	4.533	0.983	-0.0584	0.966	13.104	0.977	-0.017	0.8201	0.980	6.8405

The samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. [16]. The dissolution test was repeated thrice. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Analysis of release data

The release data obtained were treated according to 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**)** [17] and korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models. [18]

Release Kinetics

In model-dependent approaches, release data were fitted to five kinetic models including the zero-order (Eq. 1), first order (Eq. 2), Higuchi matrix (Eq. 3), Peppas–Korsmeyer (Eq. 4), and Hixson–Crowell (Eq. 5) release equations to find the equation with the best fit using PCP Disso V3 software Pune, India [19]

$R = k_1 t$ ---------- Eq. 1

$\log UR = k_2 t / 2{:}303$ ---------- Eq. 2

$R = k_3 \sqrt{t}$ ---------- Eq. 3

$\log R = \log k_4 + n \log t$ ---------- Eq. 4

$(UR)^{1/3} = K_5 t$ ---------- Eq. 5

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 studentized range test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA).

RESULTS AND DISCUSSION

Analytical method validation:

The UV scanning of metformin HCL showed a maximum absorbance at 233 nm. There was no sifting in λ max for the drug at various pH values. The calibration curves of metformin HCL was linear in different dissolution media at various pH values. The correlation coefficient (r^2) was higher than 0.9998. When standard drug solution was assayed for number of times (n=6) the relative error (accuracy) and the relative standard deviation were found to be 0.8% and 0.47% respectively.

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 0.307± 0.05 to 0.450 ± 0.02 and 0.400 ±0.03 to 0.530 ± 0.05 respectively. The value obtained lies within the acceptable range. Angle of repose of all the formulations was found to be in the range of 25.31 ±0.79 to 26.82 ±0.23 indicating good flow properties. Compressibility index and Hausners ratio ranges from, 12.3±0.01 to 17.4 ±0.03 and 1.14 to 1.22 respectively. Granules with Carr's index values around 21% and below are considered to have fair and excellent flow properties [14].

Tablet characteristics:

Table 3 gives the physical parameters such as hardness, thickness, friability and weight uniformity of all the fabricated tablets. Hardness of all the tablets were in the range of 7.76±0.56 to 8.50±0.32 kg/cm$^{2.}$ The thickness and percentage friability ranged from 4.41±0.07to 4.50±0.02 mm ±.and 0.198±0.008 to 0.298 ± 0.243 % respectively. All formulations showed less than 1% (w/w) friability which was within the prescribed limits [20]. According to the Pharmacopoeial recommendation for tablets weighing more than 324 mg, ±5% deviation from the mean weight is acceptable. As the results show, the average weight deviation percentage of 20 tablets taken from each formulation was less than ±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%. As the concentration of lipophilic binder increases, cold welding of waxes increases in melt granules and therefore tablet hardness increases.

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 .In this work the effect of some diluents on metformin release was also studied. The results of dissolution studies of formulations F-I, F-II, and F-III, composed of HCO (10%, 20% and 30%) are shown in Figure 1. Tablets F-I, F-II, and F-III released 52.68 ±0.63%, 37.91 ±0.42%, and 28.04% ±0.23% of metformin HCL at the end of 2 h and 98.29 ±0.61%, 98.91 ±0.77%, and 78.80% ±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 SA (10%, 20% and 30%) are shown in Figure 2. Formulation F-IV, F-V, and F-VI, released 38.08±0.35%, 40.42 ±0.18%, and 10.76% ±1.41% of metformin HCL at the end of 2 h and 99.44 ±2.26%, 98.48 ±1.37%, and 80.15% ±1.59% of drug at the end of 6, 9 and 12 h respectively. Formulations F-VII and F-VIII composed of combination of HCO and SA (10:20% and 15:15% respectively) are shown in Figure 3. Tablets –VII and F-VIII released 10.99 ±0.99% and 13.20 ±0.76%, metformin HCL at the end of 2 hours; and 75.69 ±0.74% and 83.99% ±0.67% of drug at the end of 12 h respectively. The results of dissolution studies of formulations F-IX and F-X, composed of Lactose and Di Calcium phosphate as a diluents are shown in Figure 4. Formulation F-IX and F-X released 18.57 ±0.65% and 9.46% ±1.13% metformin HCL at the end of 2 hours; and 92.23 ±0.87% and 50.70 % ±0.76% of drug at the end of 12 hours respectively.

Effect of different drug : wax ratio (FI-FVI) on release profile of metformin HCL was studied and the decrease in drug release rate was observed when HCO and SA content in the matrix were increased (Fig 1 & 2).It may be due to the slower penetration of dissolution medium in matrices due to increased liophilicity of waxy substances **[7].** In formulations FVII and FVIII containing different combinations of HCO and SA the release of metformin HCL get more retarded than that of HCO and SA alone, it may be due to higher lipophilicity offered by combination of waxes (Fig.3).

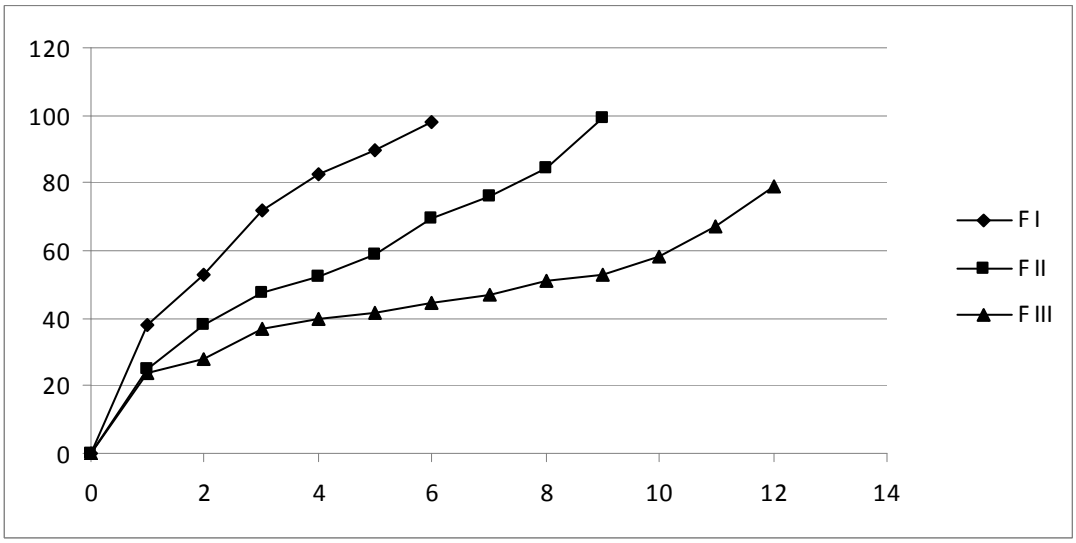

Figure 1: In vitro cumulative release of metformin from formulation F-I (–♦–), F-II (–■–) & F-III. (–▲–) . Each point represents mean ± SD, n=3

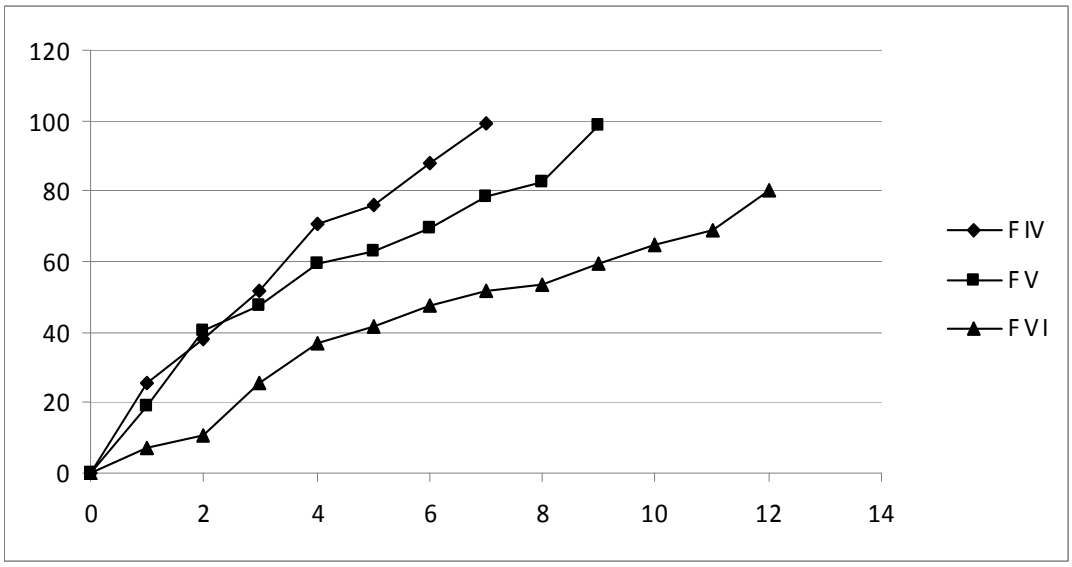

Figure 2: In vitro cumulative release of metformin from formulation F-IV (–♦–), F-V (–■–) & F-VI. (–▲–) . Each point represents mean ± SD, n=3

In formulations F-IX and F-X microcrystalline cellulose (MCC) was replaced by Lactose and calcium dihydrogen phosphate (DCP) respectively and it was found that use of lactose (FIX) produces a higher release of drug and lowest with DCP (FX) as compared to MCC (Fig.3). It may be due to rapid solubility of lactose and a tendency to form pores in matrix which allow the dissolution medium to penetrate the matrix and dissolve the drug. The release rate of drug was lowest with FX formulation as, DCP is insoluble, non-swelling and also the tablets were found to remain intact throughout the dissolution process.

At the same wax concentration, drug release from tablets decreased in order of Lactose> MCC> DCP as diluents. The observed difference in dissolution profiles of these three formulations due to difference in the solubility , swell ability and density of the diluents.

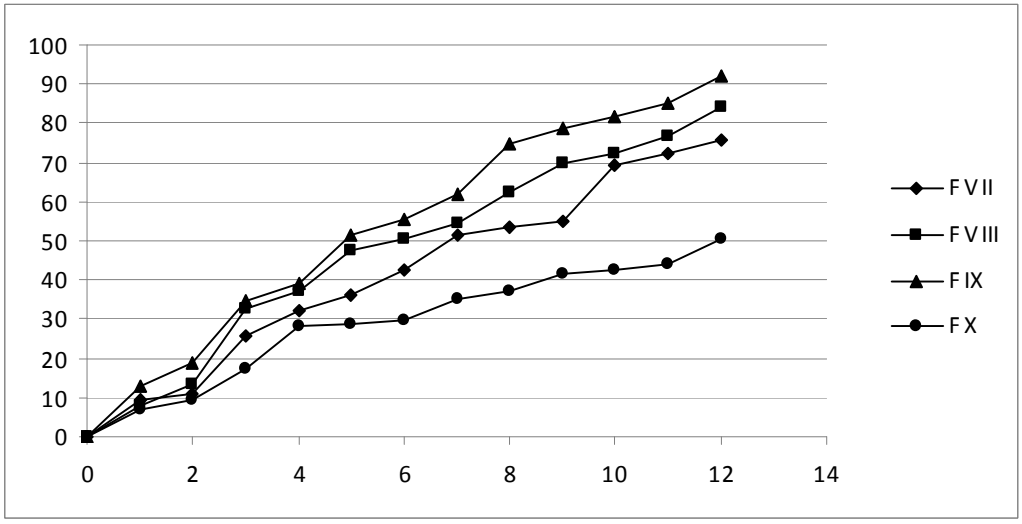

Figure 3: In vitro cumulative release of metformin from formulation F-VII (–♦–), F-VIII (–■–), F-IX. (–▲–) & FX. Each point represents mean ± SD, n=3. Each point represents mean ± SD, n=3

Drug release kinetics:

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations .The data were analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches were shown in Table 4. To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations .The data were analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches as shown in Table 4. The drug release from FVI, FVII, FVIII and FIX formulation followed Hixson –Crowell's cube root model. FII, FIV and IX formulation, followed Korsmeyer-Peppas model. Formulation FX followed first order kinetics. FI, FIII, formulation followed Higuchi model release kinetics which is indicated by the correlation coefficients (r2) 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=0.98to 0.99) [17]. To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation [18]. The formulations showed good linearity (r^2 = 0.92 to 0.98) 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.

CONCLUSION

Results of the present study demonstrated that tablet formulated with HCO sustain the release more than that of SA. Combination of HCO and SA provide more sustained effect than that of individual meltable wax. At the same wax concentration, drug release from tablets decreased in

order of Lactose> MCC> DCP as diluents. Diffusion coupled with erosion might be the mechanism for the drug release.

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Declaration of interest
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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