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Design and release characteristics of sustained release tablet containing metformin HCl

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Metformin hydrochloride (metformin HCl) was formulated as a hydrophobic matrix sustained release tablet employing wax materials and the sustained release behavior of the fabricated tablet was investigated. Sustained release matrix tablets containing 500 mg metformin HCl were developed using different bees wax combinations. The tablets were prepared by wet granulation technique. The formulation was optimized on the basis of acceptable tablet properties and in vitro *drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. Statistically significant differences were found among the drug release profile from different bees wax combination matrices. The results of dissolution studies indicated that formulations F-III, F-IV and F-V (bees wax and cetyl alcohol combination matrices), exhibited drug release pattern very close to theoretical release profile. Applying kinetic equation models, the mechanism of release of the drug from the three formulations was found to be followed Higuchi model, as the plots showed high linearity, with correlation coefficient (R^2) value of 0.98 or more. Tablet matrices containing cetyl alcohol gave better release of the drug than other materials studied. However, the rate of release varied with amount of cetyl alcohol in the matrix. The 'n' value lies below 0.5 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release was the quasi Fickian. Therefore, the results of the kinetic study obtained permit us to conclude that the fabricated hydrophobic matrix tablets, in this case, delivers the drug through diffusion dominated mechanism.*

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INTRODUCTION

Metformin HCl is a biguanide oral antihyperglycemic (antidiabetic) agent. It is used as monotherapy as an adjunct to diet and exercise for the management of type 2 (non-insulin dependent) diabetes mellitus in patients whose hyperglycemia

cannot be controlled by diet alone (AFHS Drug Information, 2003a). It is slowly and incompletely absorbed from the gastrointestinal tract, with its absolute bioavailability reported to be about 50 to 60% (Sweetman, 2002). It is freely soluble in water. A traditional oral multiple release formulation releases the drug with undesirable peaks and troughs. These drawbacks can be overcome by designing a suitable sustained release metformin HCl preparation. Recently several studies have been carried out to investigate the pharmacokinetic and pharmacodynamic advantages of oral controlled release products of metformin HCl (Di Colo *et al.,* 2005; Hu *et al.*, 2006; Balasubramaniam *et al.*, 2007; Basak *et al.*, 2007).

The primary benefit of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug.

The objective of this study was to prepare sustained release metformin HCl tablets using hydrophobic wax materials, bees wax in combination with glyceryl monostearate, stearic acid or cetyl alcohol, to evaluate the *in vitro* release characteristics and to predict and correlate the release behavior of metformin HCl from the matrix. In order to elucidate release kinetics it is necessary to fit drug release data into a suitable model. The commonly adopted models for understanding the release of drugs from matrices are zero-order equation, first-order equation (Gibaldi, Feldman, 1967; Wagner, 1969), Higuchi equation (Higuchi, 1963) and Korsmeyer-Peppas simple exponential equation (Korsmeyer *et al.*, 1983; Peppas, 1985) models. These simple exponential equation models have been used to elucidate the mode of release.

MATERIAL AND METHODS

Material

Metformin HCl was obtained from New Drug and Chemical Company, Mumbai, India. Ethyl cellulose and stearic acid were purchased from the Dow Chemicals Company, Michigan, USA. Microcrystalline cellulose (MCC, Avicel pH 101) and cetyl alcohol were purchased from Coveral and Company, Chennai, India. Magnesium stearate and talc were procured from SD Fine Chemicals Ltd., Mumbai, India. Materials and excipients used in preparing tablets were Indian Pharmacopoeia grades. All other ingredients used throughout the study were of analytical grades and were used as received.

Estimation of metformin HCl

An ultraviolet (UV) spectrophotometric (Shimadzu 1601 UV/VIS spectrophotometer, Kyoto, Japan) method based on measurement of absorption at 232 nm in water was used for the estimation of metformin HCl (Indian Pharmacopoeia, 1996a). The method showed very good linearity (R^2 value 0.9998) in the concentration range of 0 - 20 µg/mL. 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.

Preparation of matrix tablets

Matrix tablets, each containing 500 mg metformin HCl were prepared by a conventional wet granulation technique. The composition of various formulations of the tablets with their codes is listed in Table I. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. The amount of bees wax was decreased gradually for formulation IV and V and the reduced amount of bees wax was replaced by cetyl alcohol. This was done to adjust drug release according predetermined limits (to be mentioned later). In each formulation, the amount of the active ingredient is 500 mg and the total weight of a tablet is 630 mg. A batch of 3000 tablets was prepared with each formula. The ingredients were passed through a 60 mesh sieve. A blend of all ingredients except glidant and lubricant was mixed for 8-10 min in a polythene bag. Particular attention had been given to ensure thorough mixing and phase homogenization.

TABLE I - Formulae of Metformin HCl SR Matrix Tablets

Ingredients mg/tab.	Formulations				
	F-I	F-II	F-III	F-IV	F-V
Metformin HCl	500	500	500	500	500
MCC	15	15	15	15	15
Ethyl cellulose	24	24	24	24	24
Bees wax	50	50	50	42.5	37.5
Glycerin monostearate	30	-	-	-	-
Stearic acid	-	30	-	-	-
Cetyl alcohol	-	-	30	37.5	42.5
Magnesium stearate	6	6	6	6	6
Talc	5	5	5	5	5
Total	630	630	630	630	630

Granulation was done manually with a solution of calculated quantity of ethyl cellulose in sufficient solvent blend containing isopropyl alcohol and methylene chloride in 1:1 ratio. The wet masses were passed through a 12 mesh sieve and the wet granules produced were first air dried for 10 min and finally at 45-50 ºC in a tray drier for 2 hours. The dried granules were sized by a 20 mesh sieve and mixed with 8% (150g /batch) of fines (granules passed through a 20 mesh sieve). Magnesium stearate and talc were added as glidant and lubricant and blended for 10 min in a twin-shell blender. Granules thus obtained were compressed into tablets on a 23-station rotary Cadmach machine (Cadmach, Ahmedabad, India) at a constant compression force using 15/32 mm standard round punches. Just before compression, the surfaces of the die and punches were lubricated with magnesium stearate. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Evaluation of granules

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 (Carter, 1986), Tan θ = h/r, where h and r are the height and radius of the powder cone. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using the equations (Shah *et al.,* 1997), LBD = weight of the powder/ volume of the packing; TBD = weight of the powder/tapped volume. The compressibility index of the granules was determined by Carr's index (Carr, 1965) using the equation, Carr's index = [(TBD-LBD) X 100)]/TBD.

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 (Indian Pharmacopoeia, 1996b).

In vitro drug release studies

In vitro drug release from tablets was studied using a USP 24 dissolution apparatus type 2 (USP 2000) (Tab-Machine, Mumbai, India) at 100 rpm. The study was carried out in 900 mL 0.1N HCl at 37±0.5 ºC for first 2 hours and then in 900 mL of phosphate buffer (pH 6.8)

TABLE II - Properties of the granules

Formulation	Angle of repose	Tapped bulk density (g/mL)	Loose bulk density (g/mL)	Compressibility index
F-I	32.80 (0.07)	0.645 (0.05)	0.492 (0.07)	22.92 (0.09)
F-II	30.06 (0.09)	0.636 (0.03)	0.496 (0.04)	21.97 (0.10)
F-III	31.33 (0.05)	0.632 (0.07)	0.502 (0.05)	20.86 (0.11)
F-IV	32.97 (0.11)	0.641 (0.04)	0.501 (0.07)	21.54 (0.06)
F-V	29.06 (0.13)	0.637 (0.08)	0.498 (0.03)	21.86 (0.09)

Figures in the parentheses represent ±SD, n=3

TABLE III - Properties of compressed metformin matrix tablets

Formulation	Weight mg ± SD (n=20)	Hardness kg/cm^2 ± SD (n=3)	Thickness mm ± SD (n=5)	Friability %	Drug content % ± SD (n=3)
F-I	632.3 (2.53)	4.2 (0.30)	5.56 (0.05)	0.68	98.60 (0.23)
F-II	629.4 (2.97)	3.7 (0.10)	5.24 (0.04)	0.59	99.70 (0.17)
F-III	630.9 (1.83)	4.7 (0.20)	5.15 (0.07)	0.45	97.37 (0.42)
F-IV	633.6 (3.53)	5.1 (0.31)	5.51 (0.02)	0.61	97.92 (0.23)
F-V	632.6 (2.21)	4.1 (0.21)	5.50 (0.06)	0.62	101.05 (0.35)

All figures in the parentheses represent ±SD; n is specified in each column head

from 3 to 8 hours. Sink condition was maintained for the whole experiment. Ten millilitres of the sample was withdrawn at regular intervals and the same volume of pre-warmed (37±0.5 ºC) fresh dissolution medium was replaced to maintain the volume constant. 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 Shimadzu 1601 UV/VIS spectrophotometer (Kyoto, Japan) at 232 nm. The content of metformin HCl was calculated taking 798 as value A (1%, 1 cm) at 232 nm. The predetermined drug release requirement, based on a method described earlier (Basak *et al.* 2004) and in order to provide theoretical release of metformin HCl (calculated using available pharmacokinetic data) (AHFS Drug Information 2003b, Scheen 1996) was set at between 30-50% at 1 hour, between 45-65% at 3 hours, between 60-85% at 6 hours and not less than 80% at 8 hours. The dissolution test was repeated thrice. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (hours) 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) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models.

RESULTS AND DISCUSSION

The results for angle of repose and compressibility index ranged from 29.06±0.13 to 32.97±0.11 and 20.86±0.11 to 22.92±0.09 respectively (Table II). An angle of repose of less than 30 degrees indicates good flow properties (Aultron, 1998). This was further supported by the lower compressibility index. Granules with Carr's index values around 21% and below are considered to have fair and excellent flow properties (Aultron, 1998). Table III gives the physical parameters (hardness, and thickness, friability) and weight uniformity of all the fabricated tablets. Table III also shows the drug content of these tablets. The tablet formulations in all the batches prepared contained metformin HCl within $100 \pm 5\%$ of labeled content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications for weight variation and friability (less than 0.7%).

In the trial study to determine the optimum concentration of hydrophobic wax material (s) to release drug with predetermined level, a range of 75 to 85 mg combined materials consisting of bees wax and other hydrophobic material per tablet with 4% w/v ethyl cellulose as granulating agent showed good consistency, with desired sustained release. The attempt to increase amount of cetyl alcohol and reduce bees wax in F-IV and F-V, resulted improved drug release. This is due to the better matrix erosion by the cetyl alcohol resulting from higher water penetration in the matrix. Stearic acid or cetyl alcohol in combination with bees wax provides the necessary physical characteristics to form an easily compressible matrix tablet.

TABLE IV - *In vitro* release kinetic values of metformin from selected formulations

Formulation	First order[1]	Higuchi[2]	Zero order[3]	Korsmeyer-Peppas[4]	
	R^2	R^2	R^2	R^2	n
F-I	0.7496	0.7923	0.6817	0.8800	0.296
F-II	0.8494	0.8933	0.8027	0.9413	0.272
F-III	0.9653	0.9835	0.9747	0.9804	0.332
F-V	0.9792	0.9925	0.9661	0.9634	0.361
F-VI	0.9643	0.9941	0.9497	0.9686	0.382

[1]First order equation, $\log Q = \log Q_0 - kt/2.303$, [2]Higuchi equation, $Q = k \, t^{1/2}$, [3]Zero order equation, $Q = Q + k \, t$, [4]Korsmeyer-Peppas equation, $Q_t/Q_\mu = kt^n$

The results of dissolution studies of formulations F-I and F-II are shown in Figure 1. Tablets F-I, and F-II released 59.70±1.03% and 54.2±2.26% respectively, of their metformin HCl content at the end of 2 hours. Each data point in the dissolution profile represents the mean of three determinations. Both the two values of percentage release at 2 hours in the different batches differed significantly (single factor ANOVA) at $P < 0.01$ (DF=2, F=14.71). Formulations F-I and F-II, containing bees wax in combination of glycerin monostearate or stearic acid, failed to sustain release beyond 72% at the end of 8 hours. These formulations remained impermeable, probably due to less water penetration in the matrix. Figure 2 indicates that F-III, F-IV and F-V released 45.70±0.50%, 51.3±1.20%, and 57.6±1.32% of metformin HCl at the end of 2 h and 78.0±0.61%, 85.33±1.50%, and 92.1±1.4 % at the end of 8 hours, respectively. Formulation III failed the drug release requirements at the end of 8 hours by just 2%. The differences between 2 hours release values for F-III, F-IV and F-V were significant at $P< 0.001$ (DF=2, F= 92). Significant differences were observed between 8 hours release values ($P<0.001$, DF=2 and F=88).

Incorporation of higher amount of cetyl alcohol in F-IV and F-V was found to be more suitable to give good drug release characteristics.

The dissolution data (from the values of 1 to 8 hours drug release) of all batches were fitted to first-order, Higuchi, zero-order and Korsemeyer-Peppas models. As clearly indicated in figure 1 and figure 2, the formulations didn't follow zero-order release kinetics. The model that best fitted the release data was evaluated by correlation coefficient (R^2). R^2 values for all formulations in various models are given in Table IV. When the data were plotted according to a first-order equation, the formulations F-III, F-IV and F-V showed a fair linearity, with regression
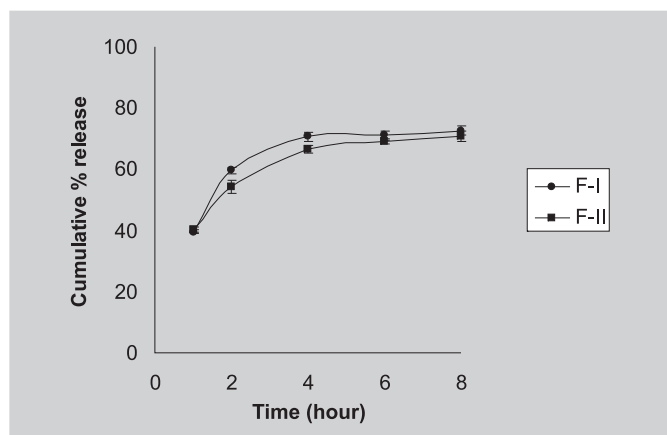

FIGURE 1- *In vitro* release profiles of metformin from batches F-I and F-II matrix tablets. *In vitro* cumulative release of metformin from formulation F-I (–●–), F-II (–■–). Each point represents mean ± SD, n=3
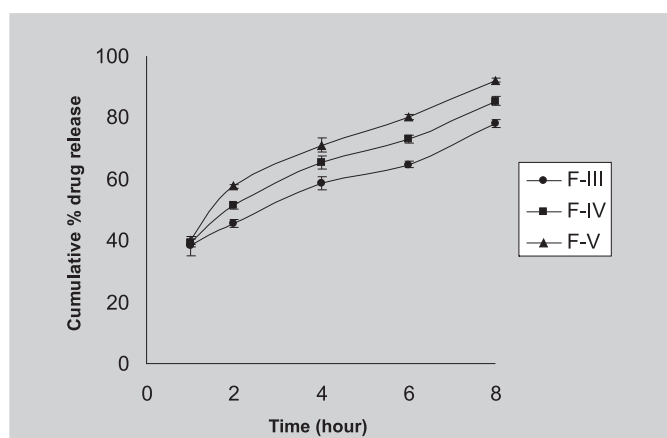

FIGURE 2- *In vitro* release profiles of metformin from batches F-III, F-IV and F-V matrix tablets. *In vitro* cumulative release of metformin from formulation F-III (–●–), F-IV (–■–) and F-V (–▲–). Each point represents mean ± SD, n=3

values 0.9653, 0.9792 and 0.9643. The best fit with higher correlation ($R^2 > 0.98$) was found with the Higuchi's equation for F-III, F-IV and F-V formulations. Release of a drug from a hydrophobic matrix tablet generally involves both pore diffusion and matrix erosion. Dissolution yielded incomplete drug release, probably due to coating of certain fraction of drug by waxy material, no clear inference could be made regarding the kinetics of the drug release from formulations F-I and F-II. The release profiles of F-III, F-IV and F-V could be best explained by Higuchi model, as the plots showed high linearity, with correlation coefficient (R^2) values 0.9835, 0.9925 and 0.9841 respectively. The diffusion mechanism of drug release was further confirmed by Korsmeyer-Peppas plots that showed fair linearity (R^2 values between 0.96 and 0.98), with slope values less than 0.5, indicating that drug release mechanism from the selected tablets was diffusion controlled. This finding was in accordance with other reported works (Goodhart *et al.,* 1974; Peterlin, 1980; Reza *et al.,* 2002).

CONCLUSION

The approach of the present study was to make an evaluation of wax materials as sustained release matrix for water soluble drug, metformin HCl and to assess the kinetics of drug release mechanism. Bees wax and cetyl alcohol can be used for sustained release of metformin HCl. The mechanism of drug release from wax matrices has been a matter of controversy since wax matrices tend to be more heterogeneous than other matrices (Dakkuri A *et al.* 1978). The study reveals that, the release of water soluble drug, metformin HCl exhibited diffusion dominated mechanism. The wax and cetyl alcohol ratio plays an important role in overall release of the drug. The hydrophobic wax matrix tablet is a promising approach to achieve appropriate sustained release dosage.

RESUMO

Planejamento e características de liberação de comprimidos de liberação controlada de cloridrato de metformina

O cloridrato de metformina (metformina.HCl) foi formulado como comprimido de liberação controlada, empregando materiais cerosos como matriz hidrofóbica, e o comportamento dessa formulação foi investigado. Comprimidos com matriz de liberação controlada contendo 500 mg de metformina.HCl foram desenvolvidos usando diferentes combinações de cera de abelha. Os comprimidos foram preparados pela técnica de granulação por via úmida. A

formulação foi otimizada com base nas propriedades aceitáveis do comprimido e na liberação in vitro. *A formulação resultante produziu comprimidos monolíticos, com dureza ótima, uniformidade de espessura, uniformidade de peso e baixa friabilidade. Encontraram-se diferenças significativas no perfil de liberação do fármaco de diferentes combinações de cera de abelha. Os resultados dos estudos de dissolução indicaram que as formulações F-III, F-IV e F-V (matrizes de combinações de cera de abelha e álcool cetílico) exibiram padrão de liberação de fármaco muito próxima do perfil teórico. Aplicando modelos de equações cinéticas, o mecanismo de liberação de fármacos das três formulações seguiu o modelo de Higuchi, uma vez que se observou alta linearidade, com coeficiente de correlação (R²) de 0,98 ou maior. As matrizes dos comprimidos contendo álcool cetílico permitiram melhor liberação do fármaco do que aqueles dos outros materiais estudados. Entretanto, a velocidade de liberação variou com a quantidade de álcool cetílico na matriz. O valor "n" ficou abaixo de 0,5 (modelo de Korsmeyer-Peppa), demonstrando que o mecanismo que controla a liberação foi quase Fickiano. Assim, os resultados do estudo cinético permitiram concluir que os comprimidos fabricados com matriz hidrofóbica, nesse caso, liberam o fármaco por meio de mecanismo de difusão.*

UNITERMOS: Metformina.HCl. Matrizes hidrofóbicas. Fármaco/liberação controlada. Modelo cinético. Equação de Higuchi.

ACKNOWLEDGEMENTS

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