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Research Article

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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METFORMIN HYDROCHLORIDE

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Abstract The aim of the current study is to design a sustained release matrix tablet of metformin HCl to maintain plasma level of drug for prolong period of time. Metformin HCl is antihyperglycemic agent used in the treatment of type II Non insulin dependent diabetes mellitus. Sustained release formulation of metformin HCl prolong drug absorption in the upper GI tract and permits once daily dosing in patient with type II diabetes mellitus. This newer formulation may enhance patient compliance compared to conventional immediate release metformin HCl. Metformin HCl present significant challenges due to its poor inherent compressibility, high dose and high water solubility. So matrix tablet of metformin HCl is formulated by different combination of matrix forming polymers such as hydroxypropyl methylcellulose and hydroxylpropyl cellulose by direct compression method. PVPK30 is used as a binder. Magnesium stearate and micro crystalline cellulose are used as a lubricant and filler respectively. Drug and polymer compatibility study is done by IR spectroscopy. The formulated powder mixture is evaluated for precompression parameters such as bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio for determining flow properties of mixture. Prepared tablets are subjected to post compression parameter such as hardness, thickness, weight variation, friability and drug content. All formulations showed compliance with pharmacopoeial standards. No physicochemical interaction is found between drug and polymers in IR spectrums. It would be desirable in dissolution study that formulation containing lower concentration of polymer will earlier drug release.

Keywords Metformin hydrochloride, sustained release matrix tablets, HPMC

Introduction

Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. Sustained releases products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion called loading dose and then sustain this level for a certain prolong time with the maintenance portion. The basic goal of sustained release is to provide promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body and increase patient compliance by reducing frequency of dose. Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect [1, 2].

Controlled and Sustained Release has both been used in inconsistent and confusing manner. Both represent separate delivery process. Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial

nature or both. Sustained release systems generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order [3, 4].

Sustained release usually tries to mimic zero order release by providing drug in slow first order fashion.

Advantages of sustained release dosage forms

Patient Compliance: Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen

Reduced 'see-saw' fluctuation: Administration of a drug in a conventional dosage form (except via intravenous infusion at a constant rate) often results in 'see-saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals.

Reduced total dose: Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition.

Improved therapy: Sustained blood level: The dosage form provides uniform drug availability blood levels unlike peaks and valley pattern obtained by intermittent administration.

Attenuation of adverse effects: The incidence and intensity of undesirable effect excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced [1, 3].

Matrix tablet

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown which includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, xanthan gum [5-7].

Materials and methods

Table 1.1: List of Material used

S. No.	Name	Supplier/Manufacturer
1.	Metformin Hydrochloride[8-11]	Torrent Pharmaceutical, Ahmadabad(Gujarat)
2.	HPMC [4,12-14]	HiMedia Laboratories Pvt. Ltd., Mumbai(India)
3.	Hydroxyrpropyl cellulose [4,12-14]	Chemdyes Corporation
4.	Starch [4]	Loba Chemie Pvt. Ltd., Mumbai(India)
5.	Microcrystalline cellulose [13]	Chemdyes Corporation
6.	Polyvinyl pyrolidone [4,12-14]	Loba Chemie Pvt. Ltd., Mumbai(India)
7.	Aerosil® [14]	HiMedia Laboratories Pvt. Ltd., Mumbai(India)
8.	Magnesium stearate [14]	HiMedia Laboratories Pvt. Ltd., Mumbai(India)

Preparation of matrix tablets by melt granulation

Melt granulation or thermoplastic granulation, is based on agglomeration carried out by means of a binder material, which is solid at room temperature and softens and melts at higher temperature (i.e., 50–90°C). When melted, the action of the binder liquid is similar to that in a wet-granulation process. Water-soluble binders used for melt granulation are macrogols (polyethylene glycols (PEG)). The binder is added either in a powder form to the starting

material at ambient temperature, followed by heating the binder above its melting point, or in a molten form to heated materials.

Hot melt granulation technique was used to prepare the drug-wax matrix formulations. First stearic acid was melted in a stainless steel vessel at 75°C. Metformin was sieved through 850µ aperture screen, and heated, spread on a metal tray in an oven at 75°C.

Granulation speed was 100 rpm for the impeller and 1500 rpm for the chopper while granulation time was 5 min. The granules were allowed to cool to room temperature by spreading them on metal trays and then sieved through 850µ aperture screen.

The melt granules were mixed with PEO and microcrystalline cellulose (pre-sieved through a 600µ screen), mixed with colloidal silicon dioxide (pre-sieved through a 425µ screen) and magnesium stearate [5, 6].

Table 1.2: Trial Formulations

S. No.	Ingredients(mg)	F1	F2	F3	F4	F5	F6
1.	Metformin(mg.)	500	500	500	500	500	500
2.	HPMC K100	20	32	52	85	97	13
3.	HPMC K4M	-	-	-	-	-	7
4.	Avicel	90	78	58	25	13	90
5.	PVP K30	25	25	25	25	25	25
6.	Starch	-	-	-	-	-	-
7.	HPC	-	-	-	-	-	-
8.	Mg Stearate	7.5	7.5	7.5	7.5	7.5	7.5
9	Aerosil	7.5	7.5	7.5	7.5	7.5	7.5
10	Total	650	650	650	650	650	650

Results and Discussion

Compatibility Study between Drug and Excipients

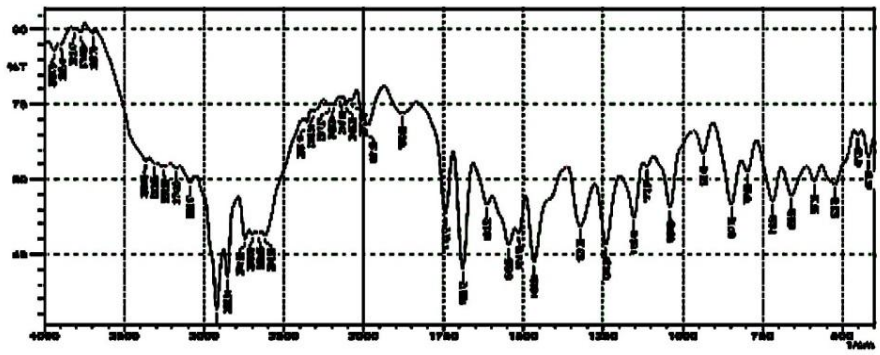

Figure 1.1: FTIR Spectra of Drug and HPMC

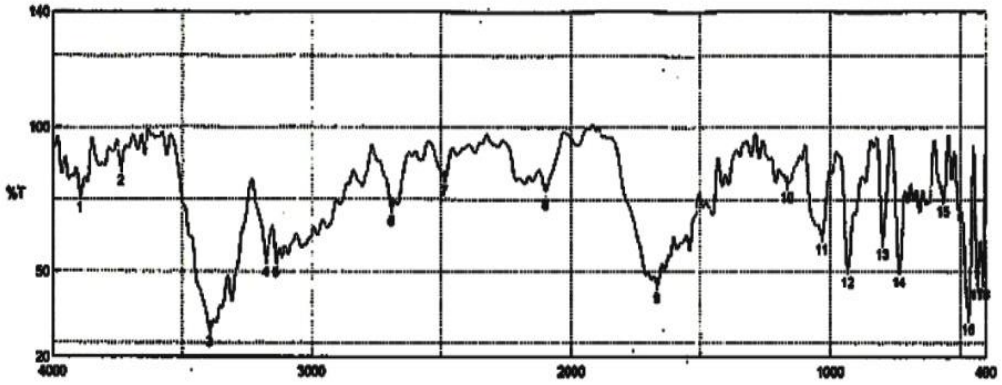

Figure 1.2: FTIR Spectra of Drug and HPC

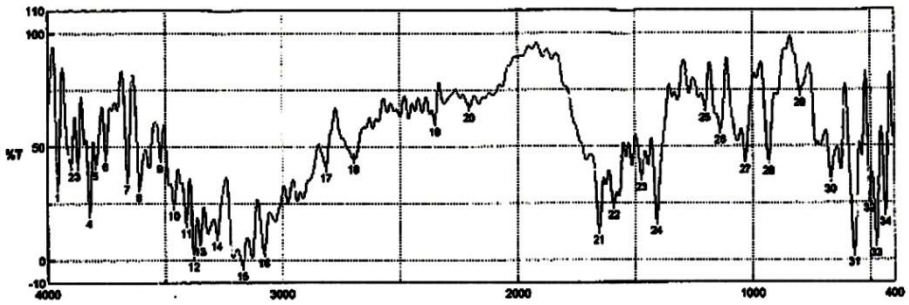

Figure 1.3: FTIR Spectra of Drug and MCC

Calibration curve of metformin hydrochloride

The calibration curve of metformin was prepared in distilled water. The slope of the calibration curve is as follows and the solution follows Beer's law in the range of 1-6µg/ml.

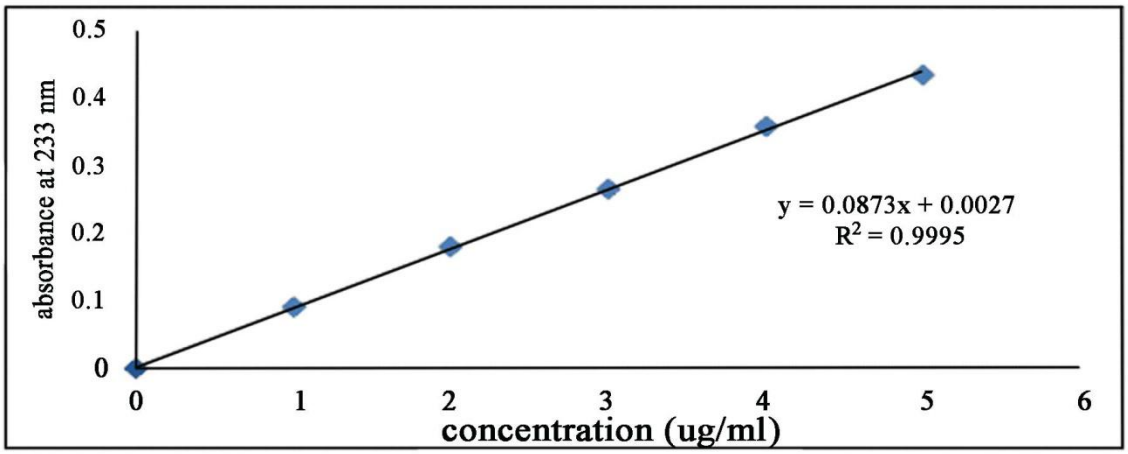

Figure 1.4: Calibration Curve of Metformin HCl

Table 1.3: Statistical parameters related to standard curve

Parameter	Values
Correlation coefficient	0.999
Equation of line	0.0873X+0.0027

Table 1.4: Evaluation of Precompression parameters

S. No.	Formulation Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	F1	0.422	0.492	37.85	14.28	1.16
2	F2	0.418	0.500	36.11	16.32	1.21
3	F3	0.413	0.493	34.11	16.32	1.19
4	F4	0.423	0.483	34.83	12.5	1.14
5	F5	0.418	0.513	33.71	14.28	1.24
6	F6	0.417	0.499	36.56	16.32	1.19

Table 1.5: Evaluation of prepared matrix tablets

Batch No	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability	Drug Content (%)
1	622 ± 2.68	5.30± 0.04	5	0.61%	96.03
2	633± 3.42	5.32± 0.02	6	0.69%	99.36
3	644 ±2.71	5.30± 0.02	4	0.64%	96.93
4	641± 2.41	5.32± 0.02	5	0.67%	99.81
5	638± 3.32	5.34± 0.04	7	0.55%	96.21
6	647± 3.21	5.38± 0.02	6	0.49%	99.91

***In vitro* dissolution study**

Release rate of drug from tablet is determined using USP dissolution apparatus type II at 37±0.5°C. The dissolution test is carried out using 900 ml of 0.1 N HCl dissolution medium at 100 rpm for the required period of time. At an appropriate interval, specific volume of aliquots were withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions were filtered through Whatman filter paper and solutions are analyzed using UV spectrophotometer.

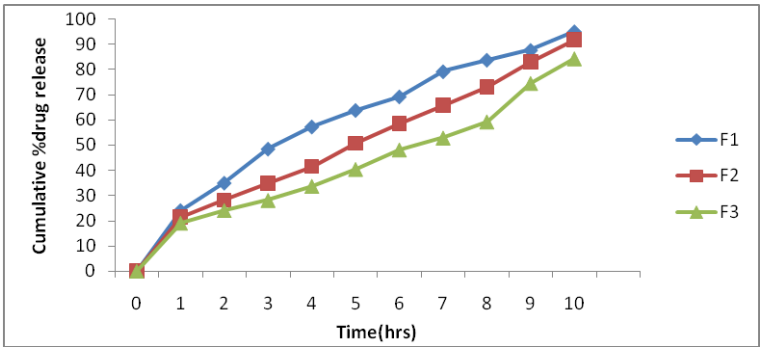

Figure1.5: Zero order plot for formulation F1, F2, F3

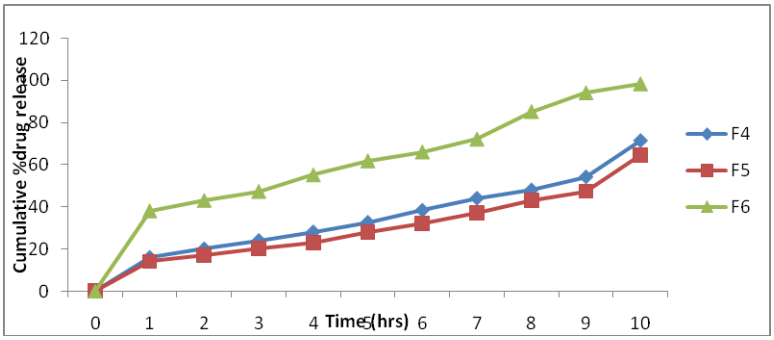

Figure 1.6: Zero order plot for formulation F4, F5, F6

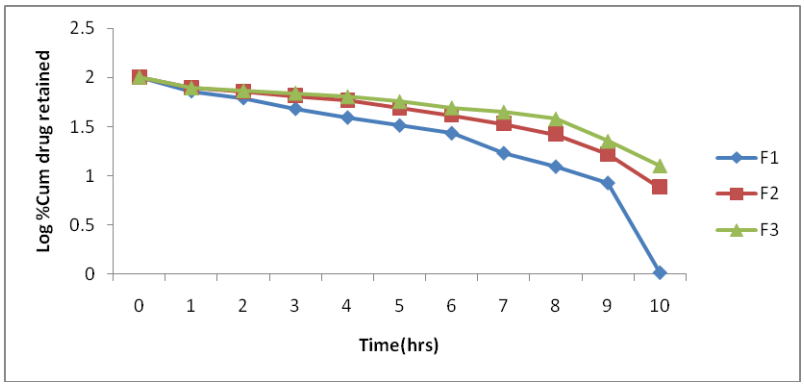

Figure 1.7: First order plot for formulations F1, F2, F3

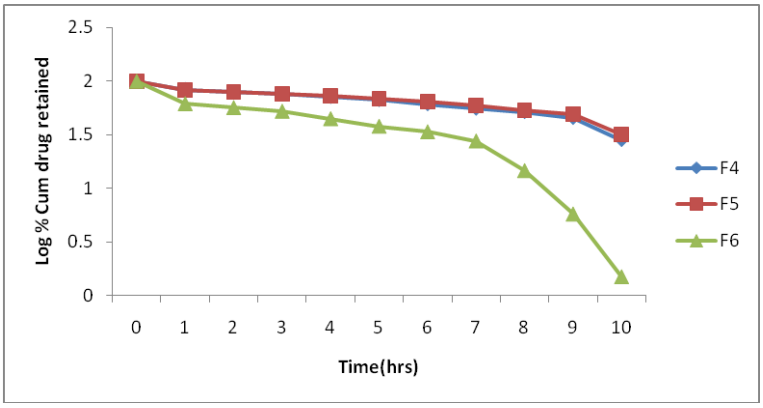

Figure 1.8: First order plot for formulations F4, F5, F6

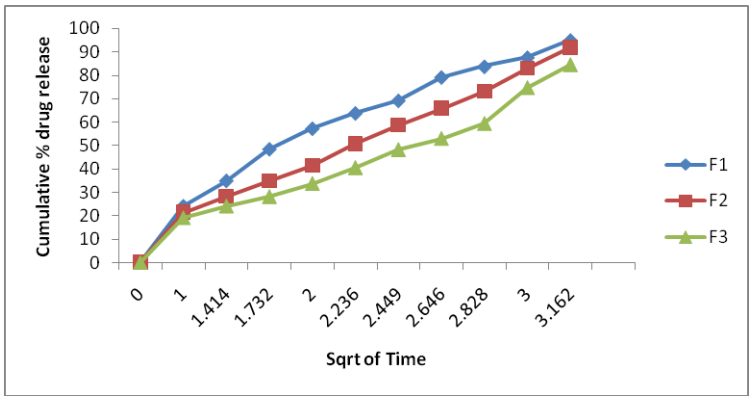

Figure 1.9: Higuchi plot for formulations F1, F2, F3

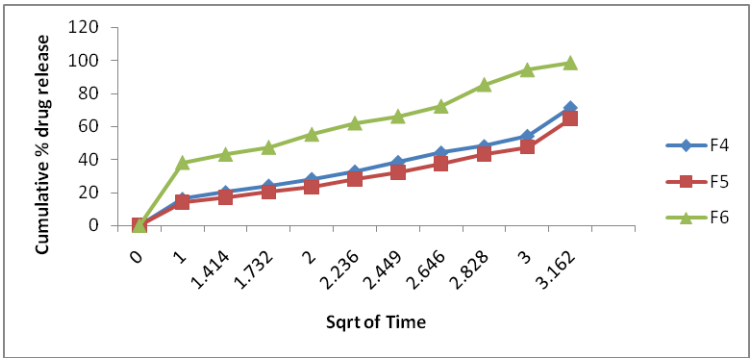

Figure1.10: Highuchi plot for formulations F4, F5, F6

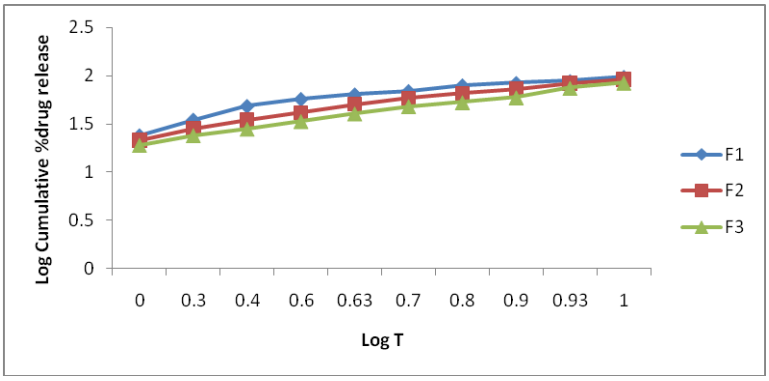

Figure1.11: Korsmeyer Peppas plot for formulations F1, F2, F3

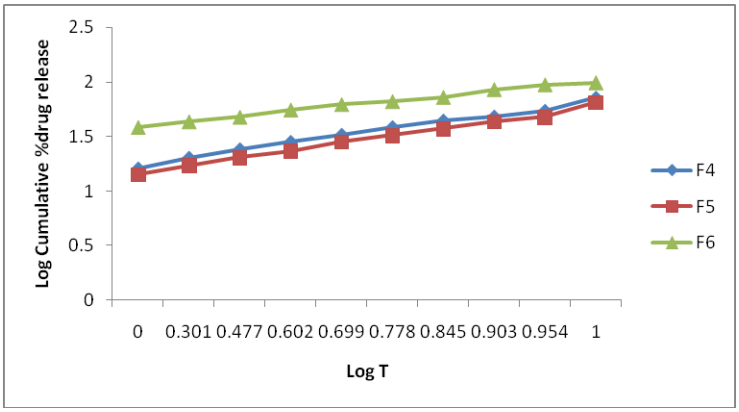

Figure1.12: Korsmeyer Peppas plot for formulations F4, F5, F6

Table 1.6: Kinetic values obtained from different plots of *in vitro* study

Code	Zero order		First order		Highuchi model		Peppas's model		
	R^2	K	R^2	K	R^2	K	'n'	R^2	K
F1	0.785	14.98	0.962	-0.387	0.982	36.25	0.479	0.972	37.67
F2	0.822	14.52	0.977	-0.340	0.986	34.99	0.516	0.976	34.23
F3	0.764	15.58	0.970	-0.461	0.983	37.78	0.466	0.976	40.18
F4	0.805	14.68	0.964	-0.358	0.985	35.45	0.492	0.978	36.08
F5	0.656	9.748	0.878	-0.166	0.965	26.66	0.420	0.963	30.93
F6	0.863	8.725	0.965	-0.138	0.988	23.32	0.592	0.983	19.99

Conclusion

IR spectra did not show any additional peak for new functional group indicating no chemical interaction between drug and polymer. They both are compatible. Flow properties of granules are also within the satisfactory range. The kinetic treatment of the drug release data of the prepared formulations indicated that drug release was diffusion controlled and directly proportional to square root of time. Drug release mechanism is clearly defined by Higuchi model kinetics and drug release follows the Fickian diffusion mechanism. The viscosity of the polymer was found to affect the drug release and inverse relationship appeared to exit between polymer viscosity and drug release thus, higher the viscosity of the polymer, lower the drug release [15-19].

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