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FORMULATION EVALUATION AND OPTIMIZATION OF METFROMIN HCL MATRIX TABLET USING NATURAL POLYMER

Ruhul Amin[1], Trideep Saikia[1] and Dr. Biswajit Das*[1]

Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam – 781017.

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***Corresponding Author**
Dr. Biswajit Das
Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam – 781017.

ABSTRACT

Objective: The overall objective of the present work was to develop an oral sustained release metformin HCL tablet using hydrophilic hydroxyl propyl methylcellulose and Xanthan gum polymer as rate controlling factor. **Method:** The excipients used in this study did not alter physicochemical properties of the drug, as tested by Fourier transform Infrared Spectroscopy and the thermal analysis using differential scanning calorimetry. Tablets were prepared by direct compression method using 10 mm punch. All the formulation was evaluated for thickness, weight variation, hardness, and drug content uniformity. Drug release kinetic models are evaluated to study the best release pattern. **Result:** Drug content was found to be 99%-101%. Hydrophilic matrix of HPMC alone could not control the Metformin release effectively for 12 h whereas when combined with Xanthan gum could slow down the release of drug and can be successfully employed for formulating sustained-release matrix tablets. The F8 formulation shows the drug release up to 97% Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release and having R2 values above 0.9. **Conclusion:** Thus, a stable, safe natural release retardant i.e.; xanthan gum, which can be effectively used in tablet formulation for sustain release of the drug.

KEYWORDS: HPMC, Xanthan gum, Matrix tablets, Release kinetics.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is

considered most natural, uncomplicated, convenient and safe [in respect to Parenteral route] due to its ease of administration, patient acceptance, and cost-effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1]

Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed. Controlled and Sustained Release, both has been used in consistent 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.[2]

Metformin hydrochloride has a half-life of 6.2 hours and the usual oral dosage regimen is 250 mg. HPMC, a semi synthetic derivative of cellulose, a swellable and hydrophilic polymer. It is very suitable to use a retardant material in sustained release matrix tablets, as it is nontoxic and easy to handle. Xanthan gum and Guar gum were used as sustained release carrier and regarded as a nontoxic and non-irritant material. The present study was designed to formulate matrix tablets using Xanthan gum and HPMC K100M Polymers.[3]

MATERIALS AND METHODS

Metformin hydrochloride was a purchase sample from Yarrow Chem Product, Mumbai, India. Hydroxy propyl methyl cellulose (HPMC K100M) and Xanthan gum were purchased from LOBA CHEMIE, Mumbai. All other chemicals used were of analytical grade.

Compatibility Studies

FTIR Studies

The pure drug, Metformin Hydrochloride and the physical mixture of pure drug with xanthan gum, HPMC K 100M in the ratio 1:1 were subjected to IR spectral studies using FTIR spectrophotometer (Bruker Alpha FTIR) at the scanning range of 4000-400 cm-1.[4]

DSC Studies

It is used to analyses thermal stress on drug and their mixture. Individual sample and 1:1 w/w physical mixture of drug were weighed and almost 5mg were taken in the DSC pan and scanned in the temperature range of 50 to 300°c in nitrogen environment. A heating rate of

10°c per minute was used and the thermograph were reviewed for evidence of any interaction.[4]

Preparation of sustained release tablets of Metformin hydrochloride

Various batches of tablets were prepared (table no. 1) by wet granulation technique. Tablets were prepared by adding PVP as a binder. All the ingredients were thoroughly mixed and granules are prepared by wet granulation technique. Then the granules are dried in a hot air oven. Finally, granules are passed through sieve mesh 20 to get uniform size of granules. Previously dried granules were lubricated by adding magnesium stearate and talc. The above granules were compressed with the help of 10 mm punch size, by keeping average weight 1000 mg.[5]

Micromeritic properties

The angle of repose was measured by using funnel method, which indicate the flow ability of the granules. Loose bulk density and tapped density was measured using the formula: LBD= weight of the powder/ volume of packing. TBD = weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD - LBD/TBD] X 100.[6]

Evaluation of Sustained Release Metformin HCL Matrix Tablet[7]

Weight Variation Test

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight more than 1000 mg should not be more than ±5%.

Friability Test

Weighed amount of 20 degusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets. Friability was calculated by the following formula.

F =100 (W0-W)/W

F = Friability, W0 = Initial weight, W = Final weight

Hardness Test

The hardness of tablets was carried out in Monsanto hardness tester. The result was complying with IP specification.

Thickness Test

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

Dissolution studies

The in-vitro release of Metformin HCL from formulated tablets was carried out in acid buffer pH 1.2 for 2 hours and then continued in phosphate buffer pH 7.4 for 10 hours. The studies were performed in USP dissolution apparatus II, (Dissolution Test Apparatus, Model DS 8000, LAB INDIA Pvt Ltd) at 37 ± 0.5° C and 100 rpm speed. Samples were taken at hourly interval and analysed for Metformin HCL content at 234.0 nm by using UV–visible spectrophotometer (Mode No. UV 3000+, LAB INDIA Pvt Ltd).[8]

Drug release kinetics

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model.[9][10]

RESULTS AND DISCUSSION

Compatibility study

Physical mixture of drug and polymer was characterized by FTIR and DSC spectral analysis for any physical as well as chemical alteration of drug characteristics. From results, it was concluded that there was no interference in the functional group as the principle peaks of Metformin Hydrochloride were found to be unaltered in the drug polymer physical mixture.

Micromeritic properties

Table indicates the powder characteristics of various batches of sustained release tablets. Various formulations show good flow properties. Results of Bulk density (0.471 – 0.494), Tapped density (0.532 – 0.559), Compressibility index (8.02 – 15.56), Angle of repose

(23.50^0 – 27.50^0) shows satisfactory results, which is required for better bioavailability. Results are mentioned in table no. 2.

Evaluation of physical parameters

From the physical parameters (Table no. 3) of each batch, it was concluded that the tablets of all batches had desirable physical characteristics. Results of Thickness of various batches of prepared formulations, (4.2-4.8 mm), Hardness (6-7 kg / sq. cm.) and Friability (0.9 – 0.26%) indicates that the tablets having sufficient strength to withstand physical abrasion. Tablets of all batches pass the weight variation test and uniformity in content was as per the limits prescribed in IP.

In Vitro Drug Release Study

Maximum % cumulative drug release was observed in F6. Minimum % cumulative drug release was observed in F1. The concentration of polymer varies, the release of the drug. The data of percentage drug release of all formulation are shown in Table 5.7 and the plots are shown in figure.

The in vitro dissolution studies were carried out for all the formulations from F1-F9 in USP apparatus type II using dissolution mediums phosphate buffer pH 6.8. The release data were noted for 12hrs for all the formulated batches. The result showed that with the varying concentration of polymer the release of drug showed sustained pattern. Formulation F1 containing 10% of polymer showed 4hrs to release 90% i.e. approximately 100% of Drug. Similarly, the formulations F2, F3, F4, F5 got released at 5,6,8,10hrs and F6, F7, F8, F9 showed sustained release pattern till 12hrs approximately 99%. Thus, with increase % of polymer, the release time was seen to be extended together with polymer. Results are mentioned in table no. 4 and 5 and fig no. 3,4,5,6 and 7.

Table 1- Formulation code.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCL	500	500	500	500	500	500	500	500
Xanthan Gum	100	150	200	250	300	350		-
HPMC K100	-	-	-	-	-	-	200	300
MCC	380	330	280	230	180	130	280	180
PVP K 30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**

Table 2- Pre compression Data.

Formulation code	Angle of repose (θ^0)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Carr's index (%)
F-1	23.50	0.475	0.533	1.12	10.88
F-2	23.61	0.478	0.532	1.11	10.15
F-3	25.34	0.493	0.536	1.08	8.02
F-4	24.78	0.486	0.545	1.12	10.82
F-5	24.04	0.478	0.553	1.16	13.56
F-6	25.30	0.472	0.559	1.18	15.56
F-7	25	0.471	0.556	1.81	15.28
F-8	26.05	0.474	0.536	1.13	11.57
F-9	27.50	0.494	0.544	1.10	9.19

Table 3- Post compression Data.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation	% of Drug content
F-1	4.5±0.03	6.5±0.3	0.12±0.03	1006±0.6	96.27±0.21
F-2	4.2±0.06	6.8±0.2	0.19±0.05	1007±0.5	96.59±0.24
F-3	4.5±0.03	6.5±0.8	0.9±0.01	1008±0.3	98.21±0.24
F-4	4.8±0.04	7±0.1	0.13±0.09	1009±0.01	97.62±0.12
F-5	4.3±0.07	6.5±0.8	0.23±0.02	1006±0.05	97.53±0.29
F-6	4.5±0.06	6.6±0.9	0.26±0.01	1006±0.04	96.19±0.32
F-7	4.6±0.07	6.9±0.5	0.19±0.04	1009±0.06	98.69±0.25
F-8	4.7±0.04	6.2±0.3	0.21±0.08	1008±0.04	97.56±0.23
F-9	4.2±0.05	6±0.9	0.25±0.01	1006±0.03	98.67±0.31

Table 4 – Dissolution Drug Release Data.

Time (hrs.)	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0.5	19.34± 0.42	14.52± 0.21	15.85± 0.19	12.72± 0.16	9.05±0 .23	8.02±0. 13	10.66±0 .23	5.31±0 .17	10.55± 0.35
1	43.70±. 36	38.12± 0.46	27.76± 0.23	25.88± 0.20	17.27± 0.08	19.09±0 .36	30.71±0 .18	18.44± 0.26	20.89± 22
1.5	59.99± 0.31	57.56± 0.47	39.89± 0.19	37.23± 0.22	33.66± 0.17	40.41±0 .31	59.65±0 .24	42.07± 0.29	38.06± 0.17
2	75.86± 0.58	64.75± 0.82	55.92± 0.15	45.13± 0.19	59±0.1 3	54.68±0 .25	62.35±0 .28	52.99± 41	53.45± 0.35
3	82.2±2 0.91	78.06± 0.22	62.59± 0.21	47.18± 0.08	66.06± 0.17	56.72±0 .27	66.88±0 .19	66.17± 0.33	57.53± 0.41
4	90±0.1 1	87.19± 0.45	65.84± 0.25	53.71± 0.10	71.30± 0.25	62.64±0 .19	71.32±0 .36	71.78± 0.15	64.83± 0.39
5		96.16± 0.15	72.60± 0.29	70.41± 0.18	76.01± 0.16	71.61±0 .26	77.80±0 .51	77.74± 0.31	66.85± 0.26
6			94.61± 0.67	83.61± 0.18	82.07± 0.11	76.01±0 .19	80.11±0 .28	80.36± 0.17	72.42± 0.23
8				92.36± 008	89.16± 0.42	81.19±0 .23	85.16±0 .31	83.22± 0.22	78.03± 0.77
10					96.06± 0.17	86.01±0 .12	89.25±0 .16	86.45± 0.27	87.95± 0.22
12						91.12 ±0.32	96.16±0 .19	94.15± 0.14	99.68± 0.11

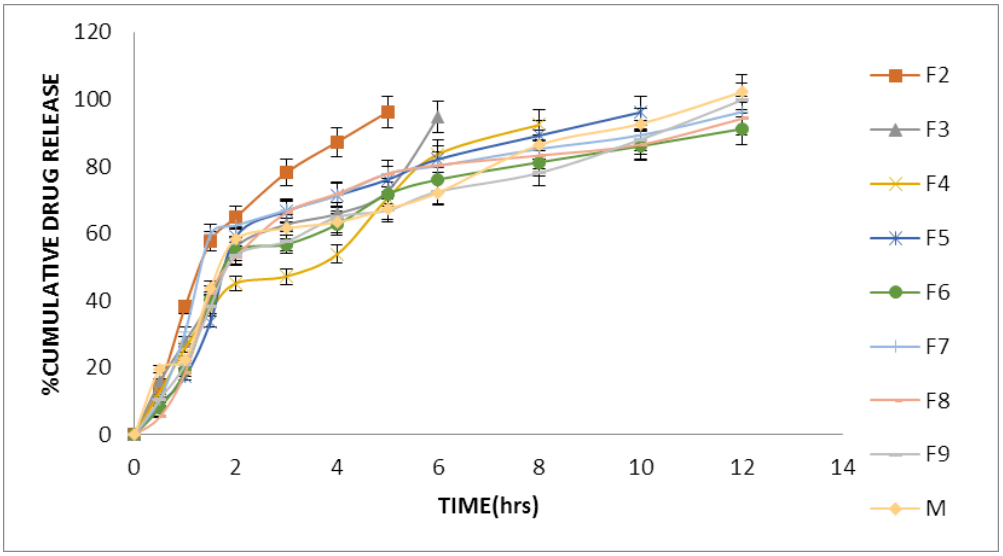

Fig 3 – Drug release curve.

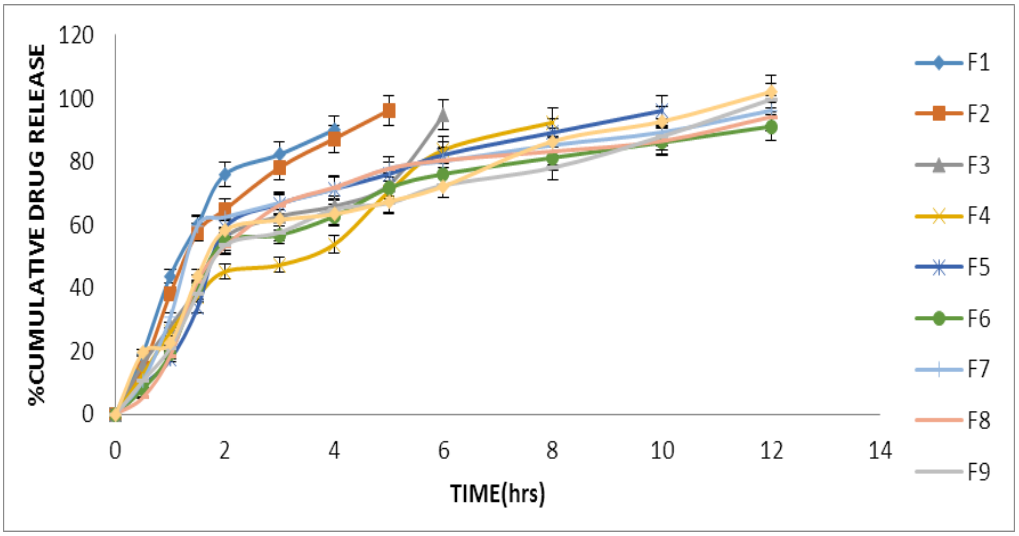

Fig 4 – Zero order drug release.

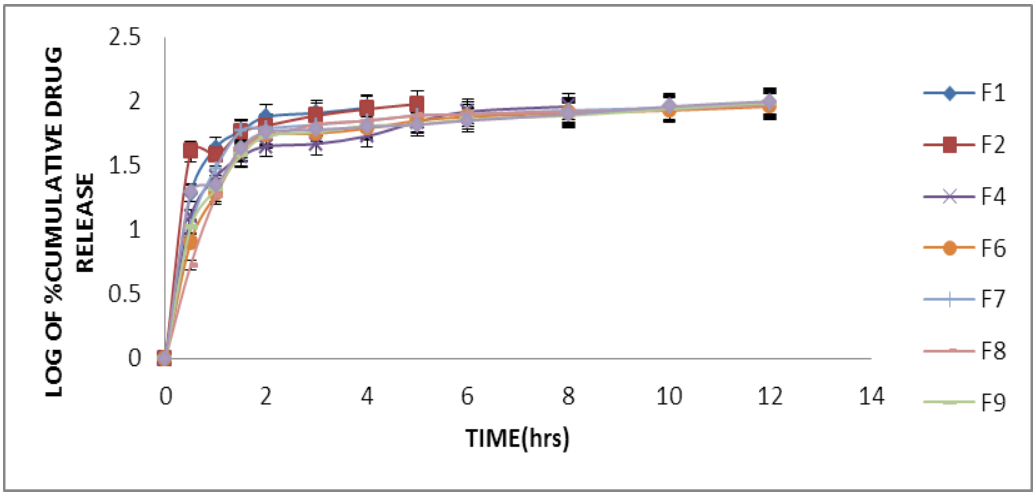

Fig 5- 1ST Order drug release.

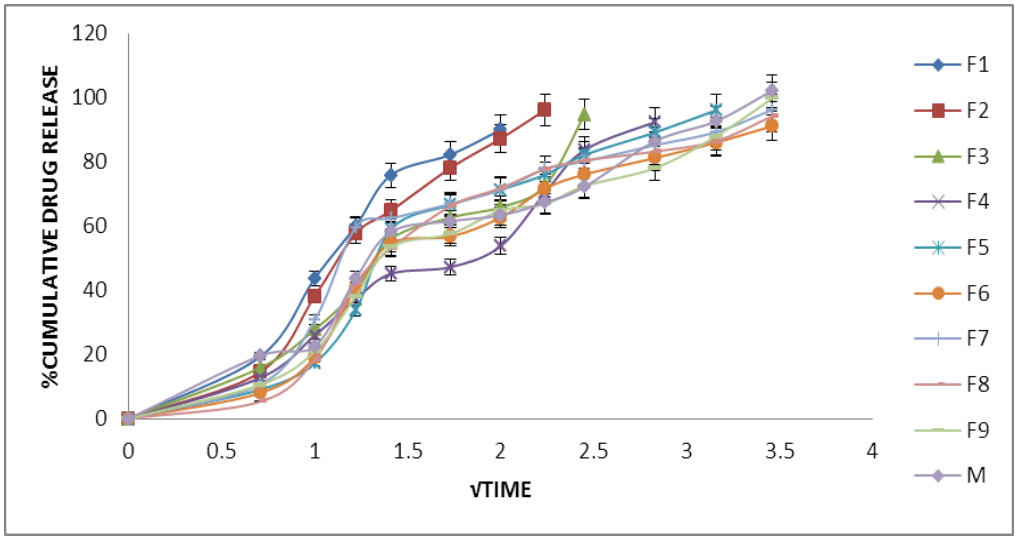

Fig 6 – Higuchi model drug release.

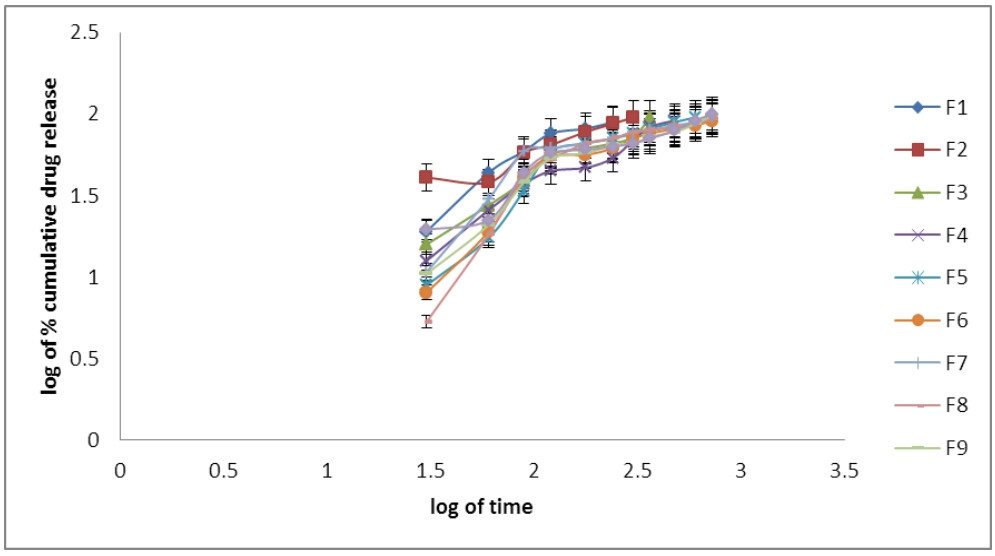

Fig 7 – Korsmayer Peppas model drug release.

Table 5 - Kinetic Release Data.

FA Code	Zero order		First Order		Higuchi Model		Korsemeyer-Peppas Model	
	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2
F1	18.766	0.8448	0.3643	0.5448	49.422	0.9568	0.7367	0.9292
F2	16.358	0.8835	0.2463	0.4368	46.535	0.9661	0.4228	0.9078
F3	12.36	0.9182	0.2141	0.5377	37.535	0.9624	0.6734	0.9601
F4	12.144	0.9518	0.1641	0.5281	33.878	0.9714	0.6693	0.9621
F5	8.5112	0.7915	0.1314	0.4949	34.324	0.929	0.7762	0.8881
F6	6.2352	0.7808	0.0986	0.4429	28.65	0.9313	0.6844	0.8534
F7	5.5837	0.6962	0.0896	0.3711	28.04	0.8811	0.5637	0.7846
F8	6.4099	0.7175	0.1039	0.4439	30.00	0.9002	0.7818	0.8098
F9	6.5539	0.848	0.0965	0.4444	29.244	0.9564	0.6329	0.8947
Marketed	7.2864	0.8397	0.0892	0.4027	29.269	0.9598	0.5025	0.9099

CONCLUSION

After the completion of the work it was found that with increase with polymer drug release takes more time so with increase in the concentration of polymer drug release increase.

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