Formulation and Evaluation of Sustained Release Matrix Tablets by Using Different Polymers

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ABSTRACT

The current paper was an attempt to design a sustained release dosage form using various grades of hydrophilic polymers. Metformin hydrochloride is an oral anti-hyperglycaemic drug belongs to BCS class III. Its short biological half life is 3 hrs hence it is an ideal candidate for sustained release formulation. The present investigation was aimed to formulate and evaluate sustained release matrix tablets of metformin hydrochloride using hydrophilic rate retarding polymers Hydroxy propyl methyl cellouse K100M and xanthan by direct compression. magnesium carbonate is used as a binders. From the in-vitro release studies it was found that the optimized formula containing Hydroxy propyl methyl cellouse K100M and 1.29% xanthan gum as retarding polymers showed a desired release of 97.09% for 12 hrs when compared to that of marketed product. From the results it was found that HPMC K100M and xanthan alone could not control the release effectively for 12 hrs. optimized concentration retarded the drug release effectively for 12 hrs. The dissolution data obtained from all the developed formulations were fitted in release kinetics.

Keywords: Metformin hydrochloride, HPMC K100M, Matrix tablet, Sustained release direct compression.

INTRODUCTION:

Oral route is the most frequently used route of drug administration. Oral dosage forms are intended usually for systemic effects. In most of the orally administered drugs, targeting is not a primary concern, and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety.1In general, the goal of sustained release dosage form is to maintain therapeutic blood
or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form . alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval.2 These are designed to complement the pharmaceutical activity of the medicaments in order to achieve better selectivity and longer duration of action.3The development of sustained release dosage forms has become the subject of interest to many pharmaceutical scientists in recent years. The development of these dosage forms depend on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in-vivo environment. Developing oral sustained release formulations for highly water soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologies.4 Its relative low bioavailability is 50-60% together with its short half-life 3hrs require repeated administrations of high doses to maintain effective plasma concentrations, thus

reducing patient compliance and/ or enhancing the incidence of side effects.

Certain considerations for the formation of sustained release formulation,
1. If the active compound has a long half-life (over 6 hours), it is sustained on its own.
2. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
3. If the absorption of the active compound involves an active transport, the development of a time release product may be problematic.
4. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

MATERIALS AND METHODOLOGY:

Metformin Hydrochloride was obtained as gift sample from AurbindoPharma Ltd, Hyderabad, A.P, and India. xanthum gum, sodium carboxy methyl cellulose, microcrystalline cellulose, and magnesium carbonate,was supplied from S.D. Fine Chem. Ltd, Mumbai, India. HPMC K100M was procured from StridesArcolabs, Pvt. Ltd, Bangalore, India.

Preparation of sustained release matrix tablets:
Sustained release matrix tablets of metformin HCL were prepared by direct compression method. HPMC K100M and xanthum gum were used as rate controlling polymers. The concentrations of the above ingredients were optimized on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers andexcipients such as magnesium carbonate, The powder mix was blended for 20 minutes to have uniform distribution of drug in the formulation. Then, magnesium carbonate,was added and mixed for not more than 1 minute (to ensure good lubrication.) About 850 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 19×8 mm flat-surface punches. The hardness of the tablets was adjusted at 4-5.5 kg/cm^2 using monsanto hardness tester.

Evaluation parameters:
Pre compression parameters:
Angle of Repose: The angle of repose is the constant, three dimensional angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.
Bulk Density: The bulk density was determined by transferring the accurately weighed sampleof powder to the graduated cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculatedby using the following formula.

Bulk Density = Mass/BulkVolume:
Tapped Density: Weighed powder sample was transferred to a graduated cylinder and was placedon the tap density apparatus, was operated for fixed number of taps (100). The tapped density was determined by the following formula.
Tapped Density = Mass/Tapped Volume.
Percentage Compressibility: Based on the apparent bulk density and the tappeddensity, the percentage compressibilityof the bulk drug was determined by the following formula.
% Compressibility = Tapped density – Bulk density × 100/ Tapped density
Hauser's Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.
Hauser's ratio = Tapped density/ Bulk density
Drug to Polymer compatibility Study:The IR spectrums of metformin HCL &dosage forms containing polymers (HPMC K100M, xanthum gum and excipient MCC) were recorded using FTIR spectrophotometry.

Post compression parameters:
Hardness: The hardness of ten tablets was found using monsanto hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.
Friability: The friability of the tablets was determined using Roche friabilator(Remi Electronics, Mumbai, India).

It is expressed in percentage.10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. The tablets were then taken, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Weight variation: Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

Thickness: The thickness of the tablets was determined using screw gauge. Five tablets from each batch were used.

Drug content: For determination of drug content three tablets from each formulation were weighed individually, crushed and a quantity of powder equivalent to 100mg weighed and is dissolved in 100 ml of 6.8 pH buffer to give a solution of 1mg/ml. 1.0 ml of this solution was further diluted up to 10.0 ml with 6.8 pH bufferto give a solution of concentration 100 µg/ml.Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 232 nm against blank.

In-vitro dissolution study:

The *in-vitro* drug release studies from the prepared matrix tablets were performed according to the USP paddle method (Apparatus 2) using 900ml of 0.1 N HCl, simulating the gastric fluid or phosphate buffer pH 6.8, simulating the jejunal fluid thermo stated at 37 ± 0.5° C and stirred at 50 rpm. SGF and SJF were used in sequence to simulate the tablet transit from stomach to jejunum. Samples were taken at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12 hrs and diluted to suitable concentration and analyzed for metformin hydrochloride content at 232 nm by using UV–Visible spectrophotometer.(Figure no 2)

Kinetic modeling

In order to understand the kinetic and mechanism of drug release. The result of in vitro drug release study of matrix tablets were fitted with different kinetic equation likeIn zero order(cumulative amount of drug released vs time), First order (log cumulative % of drug remaining vs time),Higuchi's model(cumulative % of drug released vs square root of time) Korsmeyer peppase equation(log cumulative % of drug released vs log time), and the exponent *n* was calculated through the slope of the straight line curve obtained by the analysis of above plots(Table No 3)

RESULTS AND DISCUSSION:

Sustained release matrix tablets were prepared by direct compression method. Sustained release can be achieved by formulating drug as matrix devices using HPMC K100M and guar gum as polymers. The hydration rate of HPMC K100M increases with an increase in the hydroxyl propyl content. The results of % compressibility and Hausner's ratio were <20 and <1.25 and results of angle of repose, bulk density and tapped density were also found to be within the limits.(Table no1) From the results it was shown that all the formulations met good flow properties, hence satisfactory. The interaction study in between the drug and polymer was evaluated using FT-IR spectrophotometer.(Figure no1) All the developed formulations were evaluated for thickness, hardness, friability, weight variation, drug content and *in-vitro* drug release study. The average hardness for the formulations DF1-DF4 containing HPMC K100M (4.0 to 4.1 Kg/cm$^{2)}$ and for the formulations DF5-DF8 containing xanthan(3.5 to 3.6) and for the formulations DF9-DF12 containing combination of HPMC K100M and xanthan(5.4 to 5.5).The average weight variation(5%),friability(0.8%), Drug content(95to105%) for all the developed formulations were found to be within the specified IP limits(Table no-2). Among all the developed formulations DF12 showed maximum drug release for 12 hrs. The dissolution study of best formulation (DF12) when compared to that of marketed product, showed a desired release of 97.09% for 12 hrs. The release of M was found to be zero order indicated by higher R^2 value than the first order and the dissolution data when fitted in korsmeyer- peppas equation n value was found in the range of 1.303 which indicates super case II transport. The optimized best formulation DF12 was found to exhibit zero order release indicated by higher R^2 value than the first order, The dissolution data when fitted in higuchi model it describes that the drug release follows diffusion process and when fitted in korsmeyer-peppas equation n value was found in the range of 1.339 which indicates super case II transport diffusion owing to swelling and erosion of polymers. then it is non-Fickian or anomalous diffusion.

Table No.1 Data for pre-compression parameters of tablet formulations (DF1-DF12)

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's Ratio	Angle of repose (Ɵ)
DF1	0.520±0.003	0.625±0.005	16.8	1.20	26.773±0.002
DF2	0.531±0.001	0.627±0.005	15.3	1.15	27.743±0.005
DF3	0.543±0.001	0.641±0.005	15.2	1.18	27.170±0.045
DF4	0.520±0.005	0.625±0.003	16.8	1.20	25.656±0.015
DF5	0.520±0.001	0.625±0.001	16.8	1.20	28.006±0.108
DF6	0.510±0.001	0.641±0.005	20.4	1.25	25.630±0.017
DF7	0.520±0.005	0.641±0.003	18.8	1.24	26.426±0.025
DF8	0.510±0.003	0.625±0.001	18.4	1.22	25.113±0.004
DF9	0.581±0.005	0.643±0.001	11.5	1.13	28.933±0.008
DF10	0.555±0.001	0.641±0.001	13.4	1.15	29.063±0.028
DF11	0.585±0.005	0.641±0.003	13.4	1.15	27.02±0.206
DF12	0.595±0.003	0.642±0.002	9.3	1.10	27.936±0.075

Table 2: Data for post compression parameters of tablet formulations (DF1-DF12)

Formulation code	Bulkdensity (g/cc)	Tapped Density g/cc	Carr's Index %	Hausr's Ratio	Angle of repose(Ɵ)
DF1	6.0±0.01	4.0±0.11	0.48	849±1.15	102.12
DF2	6.0±0.02	4.1±0.15	0.46	850±1.21	98.60
DF3	5.9±0.02	4.2±0.21	0.53	851±1.52	96.24
DF4	6.0±0.01	4.0±0.13	0.51	848±2.88	99.20
DF5	6.0±0.01	3.5±0.13	0.36	850±0.16	103.96
DF6	5.9±0.01	3.6±0.09	0.32	850±0.02	95.25
DF7	6.0±0.02	3.6±0.06	0.38	849±1.15	96.26
DF8	6.0±0.03	3.5±0.2	0.34	845±1.24	97.37
DF9	6.0±0.03	5.5±0.28	0.54	848±2.32	99.58
DF10	5.9±0.01	5.4±0.15	0.63	846±1.14	98.63
DF11	6.0±0.04	5.5±0.23	0.57	849±1.73	97.28
DF12	6.0±0.03	5.4±0.25	0.58	850±0.15	104.96

Table No 3: Treatment of dissolution data of the formulations DF1, DF2, DF3, DF4, DF5, DF6, DF7, DF8, DF9, DF10, DF11, DF12 and M

formulation code	zero order	first order	higuchi	korsmeyer-peppas	
	R^2	R^2	R^2	n	R^2
DF1	0.977	0.975	0.967	1.441	0.991
DF2	0.996	0.971	0.975	1.374	0.992
DF3	0.997	0.941	0.968	1.367	0.994
DF4	0.990	0.947	0.971	1.294	0.994
DF5	0.992	0.975	0.957	1.340	0.980
DF6	0.992	0.970	0.953	1.277	0.996
DF7	0.994	0.951	0.959	1.198	0.992
DF8	0.996	0.937	0.964	1.130	0.988
DF9	0.980	0.948	0.978	1.426	0.985
DF10	0.992	0.948	0.982	1.417	0.981
DF11	0.998	0.877	0.972	1.348	0.989
DF12	0.991	0.868	0.985	1.336	0.976
M	0.990	0.865	0.985	1.303	0.995

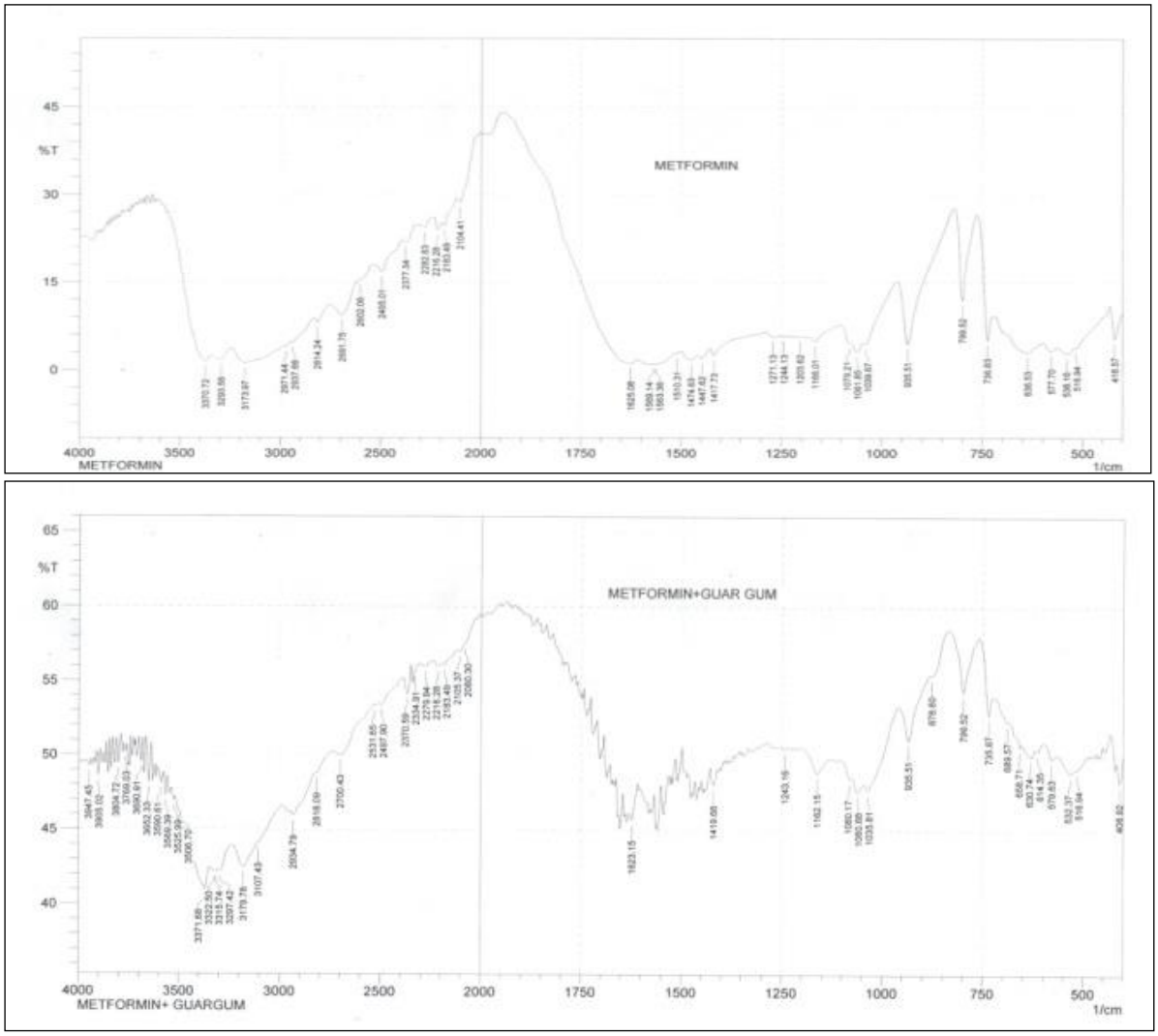

Figure No 1:FT-IR spectra of (A) pure metformin HCL, (B) metformin HCL and xanthum gum (1:1 molar ratio) physical mixtures.

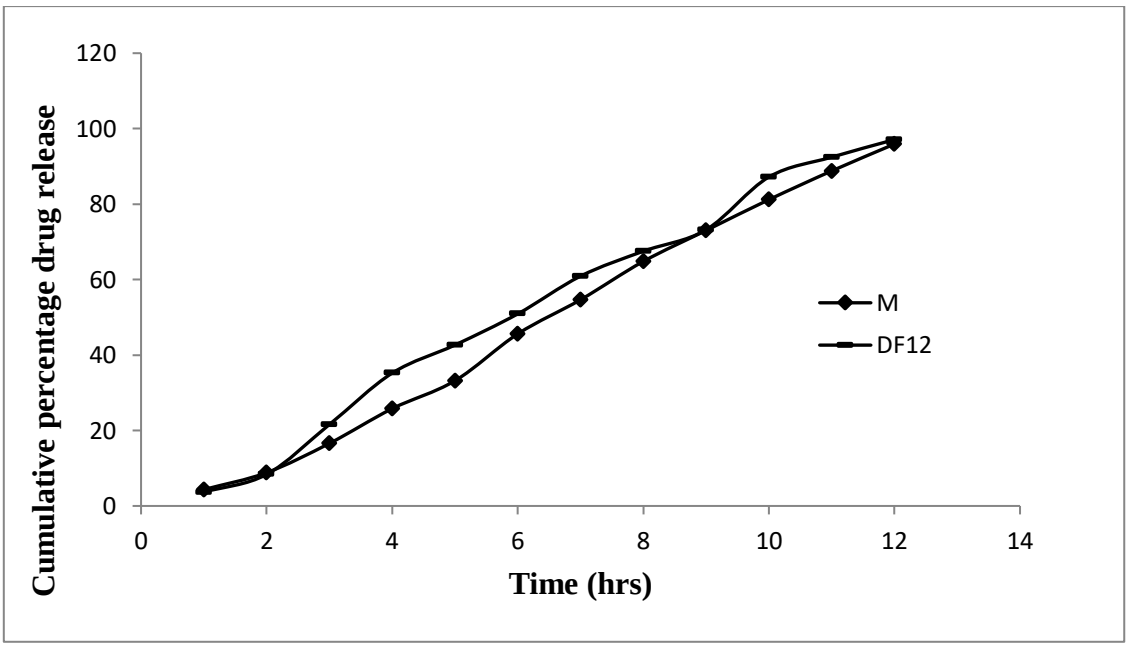

Figure No 2: % cumulative drug release profile of M and DF12

CONCLUSION:

Sustained release matrix tablets were prepared by direct compression technique using HPMC K100M and xanthum gum as polymers in optimized concentrations. From the results it was concluded that formulation DF12 was the best optimized formulation. The optimized best formulation DF12 followed zero order release indicated by higher R^2 than the first order.

ACKNOWLEDGEMENT:

The authors wish to express their sincere gratitude of department of pharmaceutics, R R College of pharmacy, Chikkabanavara, Bangalore, Karnataka, India for providing necessary facilities to carry out this research work.

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