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Original Article

DESIGN, DEVELOPMENT FORMULATION AND INVITRO DISSOLUTION STUDIES OF SUSTAINED MATRIX COATED TABLETS OF METFORMIN HYDROCHLORIDE

[1]KOPPULA TEJASWI*, [2]BRAHMAREDDY

[1,2]Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli-522438, Guntur (dt) Andhra Pradesh, India.
Email: gunukulavenkat@gmail.com

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ABSTRACT

The main objective of the present work was to develop sustained release matrix tablets of Metformin hydrochloride using different polymers viz. Hydroxypropyl methyl cellulose (HPMC) and natural gums like Guar gum and Eudragit.

The tablets were evaluated for Preformulation studies like the angle of repose [1] bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. In-vitro release of drug was performed in PBS pH 7.2 for twelve hours. All the physical characters of the fabricated tablet were within acceptable limits. The results of in vitro data of formulation F1 containing HPMC K4M as Matrix carrier and MCC as a diluent show prolonged release. But the release was slightly faster when compared to the innovator. The in vitro data of formulation F2, containing HPMC K15M as matrix carrier has shown prolonged release but at slightly faster rate when compared to the innovator. Formulation F3, containing Eudragit RLPO as matrix carrier, has shown prolonged release with 10% faster rate when compared to the innovator. F4 containing guar gum as a matrix carrier has shown prolonged release which was slightly slower when compared to the innovator. From the results above it could be understood that HPMC K4M & guar gum swell in the media and the drug entangled in its matrix is gradually leached by the media traveling the tortuous and viscous pathF8 formulation was found to be close to that of an innovator. Hence the "n" value was found to be 0.91 it shows that drug release follows super case 2 means of transport. It follows zero order release.

Keywords: Metformin hydrochloride, Hydroxypropyl methyl cellulose, Guar gum and Eudragit.

INTRODUCTION

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [1,2]. Many innovative methods have been developed for obtaining modified drug release. From the practical viewpoint, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form Hydroxypropyl methylcellulose (HPMC) is hydrophilic cellulose ether widely used as a pH-independent gelling agent in controlled release preparation, due to their release behavior of the drug [3]. Due to nontoxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials [4]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water are strongly time dependent. Upon contact with the gastrointestinal fluid hypoglycemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality [11]. Eudragit RSPO, which provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms. Guar Gum, either modified or unmodified is a very versatile and efficient natural polymer covering a number of applications in various industries like food, beverages, pharmaceuticals, cosmetics, paper, textile, construction, oil & gas well drilling, mining etc, due to its cost effective emulsifying and thickening properties. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with a relatively short plasma half-life of 1.5 - 4.5 h [12, 13]. An obstacle to the more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment [14].Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance. The overall objective of this study was to develop matrix sustained release tablets of metformin using natural gums (xanthan gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (hydroxypropyl methylcellulose) with respect to in vitro drug release rate.

MATERIALS AND METHODS

Metformin hydrochloride was obtained from Cipla pharmaceuticals Ltd (Hyderabad, India). Hydroxypropyl methylcellulose K4M, Guar gum, Eudragit, Magnesium Stearate, Citric acid were obtained from Hyderabad Chemicals, India, and the remaining were from SD. All other ingredients used were of laboratory reagents and used as such without further testing. All other ingredients used throughout the study were of analytical grade and were used as received.

Preparation of metformin hydrochloride matrix tablets

All the ingredients sufficient for a batch of 20 tablets according to formula was passed through sieve in order to enhance the flow and compaction properties and drug was triturated with polymer in a glass mortar and pestle to achieve a homogenous blend and geometrically mixing was done with effervescent agent, filler and other excipients sufficient for a batch of 20 tablets according to the formulae were passed through the mesh and thoroughly the blend was mixed to ensure complete mixing. Then Tablets (750mg) were compressed by using 10.0mm diameter, spherical tablet punches on a 16 station rotary compression machine.

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content [19]. The hardness of the tablets was tested using a Monsanto hardness tester.

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 [20]. Drug content was analyzed by measuring the absorbance of standard and samples at λ=236 nm using UV/Vis spectrophotometer (Lab India UV/VIS 3000+).

In vitro drug release studies

In-vitro drug release from the sustained tablets was carried out in triplicate at 37°C±0.1°C in a USP type II rotating basket dissolution apparatus (Lab India, Hyd) at a rotation speed of 50rpm. Drug release from the sustained tablets was studied in 900ml of phosphate buffer pH 6.8 for 12 hrs. At regular time intervals i.e., at every one hour, samples were withdrawn and analyzed for the drug using a UV-visible spectrophotometer. Drug release from the sustained tablets was determined at 236 nm. The release data obtained were fitted to various mathematical models to know which mathematical model was best to fit the obtained release profile. The parameters; the time exponent (n), the release rate constant (k), the regression coefficient (R^2), were determined for Korsmeyer- Peppas equation to know the release mechanism[21].

Kinetic Analysis of release data

The release data obtained were treated according to zero-order (R=k1 t), first-order (R=k1 t), Higuchi (R=k3 √t)[22], Peppas model. Time (t); k1, k2, k3, k4, and k5 are the rate constants of zero-order, first-order, Higuchi matrix,& Peppas-Korsmeyer, respectively. In order to compare the release profile of different formulas with a possible difference in release mechanisms (n values), a mean dissolution time (MDT)[14] was calculated using Eq. MDT=(n/ n+1).K-1/n, Where n = release exponent and K= release rate constant[22].

Statistical Analysis

The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software GraphPad Prism (San Diego, CA) and in all the cases P < 0.001 was considered as significant.

RESULTS AND DISCUSSION

STANDARD GRAPH OF METFORMIN

Table 1:Standard graph of Metformin.

S. No	Concentration	Absorbance at 236
1	0	0
2	50	0.2335
3	75	0.3488
4	100	0.4678
5	125	0.5582
6	150	0.6507

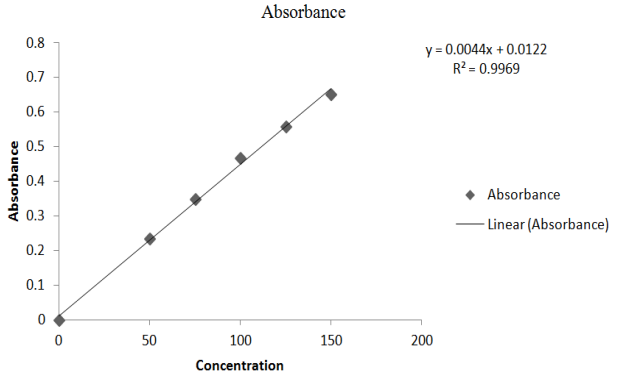

Fig.1: Standard curve of Metformin.

FT- IR Studies

FTIR studies revealed that metformin HCl showed two typical bands at 3647 and 3565 cm^{-1} due to N-H primary stretching vibration and characteristics bands at 1696 and 1514 cm^{-1} assigned to C=N stretching. No significant change in the appearance of characteristic peaks of pure drug spectra was observed (fig-2). This indicates that the drug is compatible with the polymers used in the investigation.

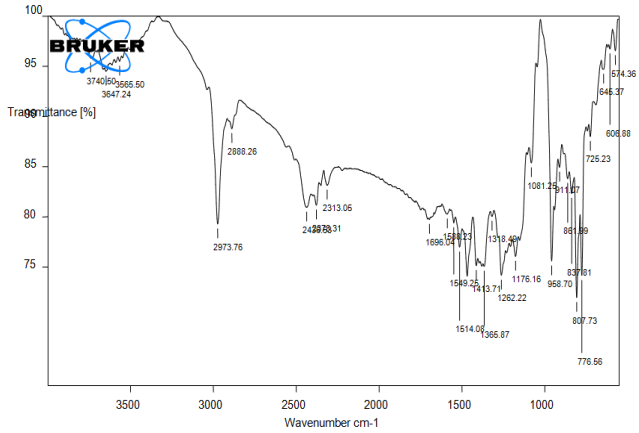

Fig.2: Pure Metformin.

Physical properties of the Drug

Pre-Compression Characterization of Metformin Hydrochloride Matrix Tablet:

The angle of repose for the formulated blend was carried out and the results were shown in table 2 It concludes all the formulations blend was found to be in the range from 21-26 its indicate well to the passable flow of granules. Compressibility index was found in the range from 9.14 % -22.21 % indicating the powder blend has the excellent to good flow property for compression

Table 2: Pre-Compression Studies.

Formulation code	Bulk Density	Tap Density	Compressibility Index	Hausner's Ratio	Angle of repose
F1	0.512	0.610	16.06	1.19	24.2
F2	0.520	0.612	15.03	1.17	24.2
F3	0.50	0.60	16.66	1.2	25.7
F4	0.51	0.612	16.66	1.2	24.3
F5	0.50	0.61	18.03	1.22	25.1
F6	0.52	0.63	17.46	1.21	24.2

Post Compression Studies

The following tables give the physical parameters such as hardness, thickness, friability and weight uniformity of all the fabricated tablets. All the tablets of different formulations showed acceptable results with respect to weight variation, drug content uniformity, friability. All formulations showed less than 1% (w/w) friability, which was within the prescribed limits [23]. According to the Pharmacopoeia recommendation for tablets weighing more than 324 mg, ±5% deviation from the mean weight is acceptable [24]. 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%

Table 3: Post Compression Studies.

S.No	Formulations	Hardness Test(kg/cm)	Thickness Test (mm)	Friability Test (%)	% of Weight variation test
1	F1	12.20	5.1	0.576	99.5
2	F2	13.10	5.09	0.579	100.0
3	F3	13.12	5.1	0.605	99.8
4	F4	12.25	5.1	0.612	99.7
5	F5	12.52	5.11	0.610	100.0
6	F6	12.61	5.1	0.617	99.9

IN VITRO RELEASE KINETICS

In vitro drug release profiles of the prepared Metformin Hydrochloride tablets were studied. The release data obtained from all the formulations F-1, F-2, F-3, F-4, F-5, and F6 were mentioned in table 4. The release of drug from the Tablet exhibited a sustained & controlled pattern over an extended time period. The tablet formulation F-1 was found to release the drug of about 99% after 12 hrs, The tablet formulation F-5 was found to release the drug of about 95% after 12 hrs, thus concluded to have sustained drug release for longer period of time in sustained and controlled pattern.

Table 4: In vitro Dissolution Studies

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	12.12	15.67	16.11	15.64	14.38	19.75
2	16.47	25.49	24.24	22.40	25.34	27.93
3	38.49	30.56	30.11	29.16	30.80	38.53
4	45.56	32.44	35.64	34.89	38.50	42.76
5	56.44	38.36	40.51	40.65	45.37	46.99
6	59.76	45.36	46.0	44.12	50.28	49.28
7	61.43	51.10	52.14	56.31	59.45	56.12
8	64.36	58.74	60.63	62.54	65.82	60.5
9	64.36	64.53	67.84	64.38	69.37	68.53
10	89.1	72.26	73.04	79.12	79.37	70.15
11	97.74	78.15	73.04	84.40	86.74	75.38
12	98.51	92.26	90.26	93.31	94.53	91.41

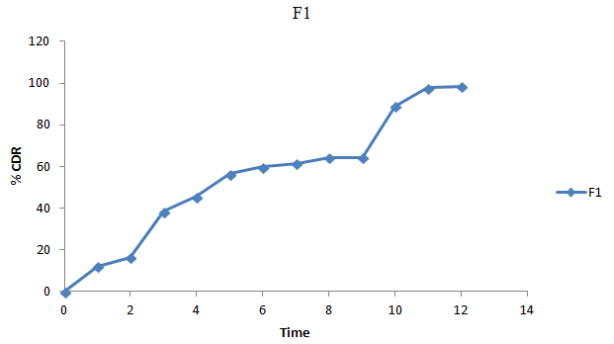

Fig 3: In vitro drug release from formulation F1.

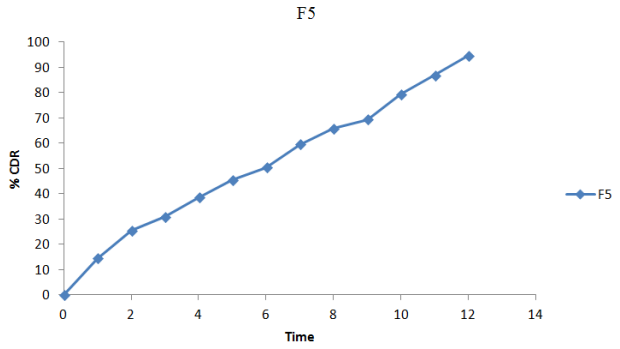

Fig. 4: In vitro drug release from formulation F5

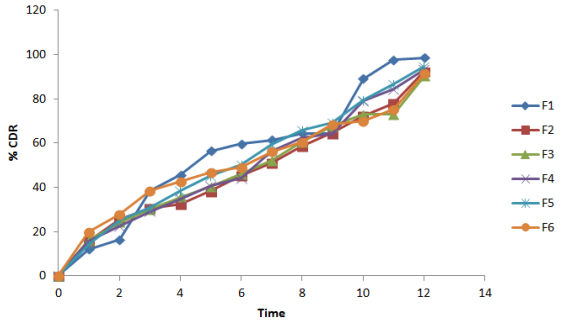

Fig.5: Cumulative % drug release studies of all formulations

RATE ORDER KINETICS

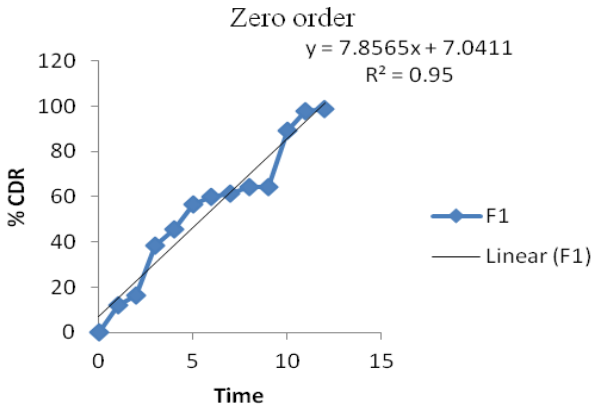

Fig.6: Zero order Kinetics.

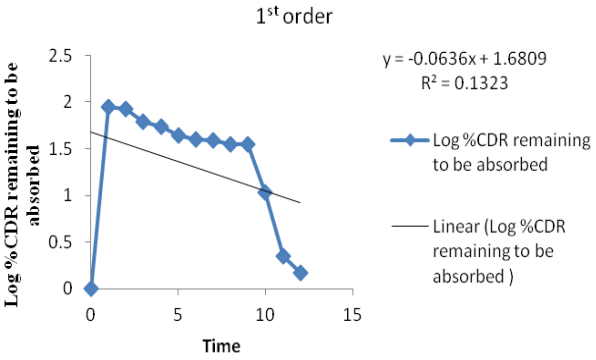

Fig.7: First order Kinetics.

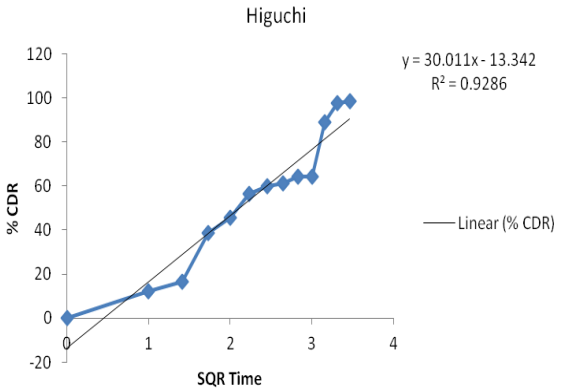

Fig.8: Higuchi Kinetics.

Korsmeyer–Peppas Model

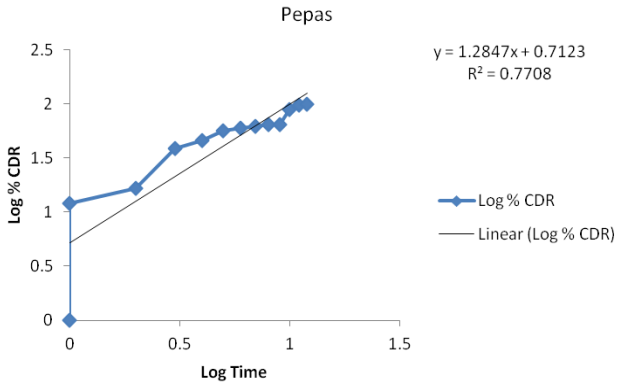

Fig.9: Pepas Kinetics.

CONCLUSION

The findings of the present study demonstrate that the drug release rate increased when the concentration of hydrophilic polymer was increased. The cumulative percentage drug release for all formulations was found. The formulation, F1 is considered as the best formulation, since it shows maximum in vitro drug release as 98.51 in 12hrs. The best formulation (F1) follows Zero order kinetics and follows Higuchi mechanism in the drug release.

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