



Designing of Sustained-Release Metformin Hydrochloride Tablets for the Treatment of Type-II Diabetes Mellitus

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Abstract

The aim of the current study was to design sustained release-based drug delivery system for Metformin hydrochloride (MS). The objective of the present work was to develop an oral sustained release Metformin hydrochloride tablet prepared by wet granulation method using hydrophilic hydroxyl propyl methylcellulose and Xanthan gum polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Hydrophilic matrix of HPMC alone could not control the Metformin release effectively for 12 hr 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 dosage regimen of Metformin hydrochloride is 500mg tablet twice in a day. The drug eliminated in urine (about 90%) is in 24hrs with plasma elimination half life of 6.2 hrs. Hence Metformin hydrochloride was chosen as a model drug with an aim to develop a sustained release system for a period of 12 hrs. The sustained release tablet was prepared by wet granulation technique using controlled release polymer hydroxyl propyl methyl cellulose (HPMC) and using xanthum gum combindly for controlling release rate. The tablet formulation (MS5) containing 150mg of HPMCK100M and 25mg of Xanthum gum considered as overall best formulation (with an in vitro release of 97.86%). This sustained release system was found to deliver MS at a zero-order rate for 12 hrs. Short term stability study (at 40±2°C/ 75±5% RH for three months) on the best formulation indicated that there no significant changes in drug content. IR spectroscopic study indicated that there are no drug excipient interactions.

Keywords: Sustained release, Metformin hydrochloride (MS), Xanthum gum, Zero order, IR

Introduction

In therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than one or twice daily, greatly reduces patient compliance. So in recent year considerable attention has been focused on the development of novel drug delivery system and the main reason for this paradigm shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity. In the form of novel drug delivery system, an existing drug molecule can get a new life there by increasing its market value competitiveness and patent life among the various novel drug delivery system available in the market, per oral sustained release system hold the major market share because of their obvious advantages of ease of administration and better patient compliance. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule. Hence oral sustained release systems continue to be the most popular amongst all the drug delivery systems¹. 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 compliance².

Many innovative methods have been developed for obtaining modified drug release. Hydroxypropylmethylcellulose (HPMC) is hydrophilic controlled release polymer widely used as a pH-independent gelling agent in controlled release preparation, due to their release behavior of the drug. Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is used as release retarding materials³. The mechanism involved in the drug release from hydrophilic matrices is complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution. The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. Xanthan gum is a high-molecular-weight extracellular polysaccharide produced by fermentation process of gram negative bacterium *Xanthomonas campestris*. Xanthan gum is biodegradable and biocompatible and forms gel in water hence, appears to be gaining appreciation for the fabrication of matrices with controlled drug release characteristics⁴. The gel forming properties of HPMC and Xanthum gum has been used to develop sustained release dosage forms. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion of matrix. Metformin hydrochloride is used as the treatment of Type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality⁵. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 hr. An obstacle to 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 treatment⁶. 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 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

Materials

Metformin hydrochloride was obtained from Dr Reddy's pvt Ltd, India. Microcrystalline cellulose (MCC, Avicel pH 101) was purchased from S. D. Fine Chem. Labs, (Mumbai, India). Hydroxypropyl methylcellulose K100M were obtained as a gift sample from Hetero Drugs Pvt Ltd, Hyderabad. Xanthan gum was obtained as gift samples from Zydus Healthcare Pvt. Ltd. Ahmedabad.. All other ingredients used were of laboratory reagents and used as such without further testing. All other solvents and reagents used were of analytical grade.

Drug excipient studies

The IR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the IR study it can be concluded that the major peaks of drug remains intact and no interaction was found between the drug and polymer.

Preparation of sustained release tablets

The tablets were prepared by wet granulation technique. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through sieve No. 30 and lubricant and glidant were passed through sieve No. 80. All the ingredients except lubricant (magnesium stearate), glidant (talc) were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution and granulated through sieve No.30 and dried in a hot air oven at 60°C for sufficient (3-4 hrs). So that the moisture content granules reached to 2-4%. The dried granules were passed through sieve No.30 and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets (800 mg each) with standard concave punches (diameter 10 mm) using 27 station rotary compression machine (CMB4D-27 Cadmach, Engg, Ahmedabad, India).

Table-1 Composition of Metformin hydrochloride (MS) tablets

INGREDIENTS(mg)	MS1	MS2	MS3	MS4	MS5
API(Metformin HCL)	500	500	500	500	500
HPMCK100M	0	200	50	100	150
Xanthum Gum	200	0	150	100	50
MCC(Microcrystalline cellulose)	90	90	90	90	90
Mgnesium Stearate	5	5	5	5	5
Talc	5	5	5	5	5
Total	800	800	800	800	800

Evaluation of Granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \Theta = h/r$$

$$\text{Therefore, } \Theta = \tan^{-1}(h/r)$$

Where Θ = angle of repose.

h = height of the cone in cm.

r = radius of the cone base in cm.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas

Bulk density = weight of the powder/bulk volume of the powder

Compressibility index

The compressibility index of the granules was determined

By Carr's compressibility index.

$$\text{Carr's index \%} = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density of the granules.

D_b is the bulk density of the granules

Evaluation of Tablets

Thickness

The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from $\pm 5\%$ of the standard value was determined.

Hardness

Monsanto hardness tester determined hardness of the tablets. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded

Friability

Friability of tablets was performed in a Roche friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed.

Weight variation test

Uniformity of weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation.

Uniformity of drug content

Drug content for MS tablet was done by the assay method. First the prepared tablet (500mg API) was crushed and added to 100ml of phosphate buffer pH 6.8. After 30 minutes the solution was filtered and from 100ml solution 2ml was withdrawn diluted upto 100ml with phosphate buffer pH 6.8 which was the stock solution. From the stock solution 4ml was withdrawn and diluted upto 50ml getting desired concentration 8 μ g/ml. From the desired concentration, the drug content of formulations were calculated using calibrated standard curve equation $y=0.075x+0.088$.

In vitro dissolution studies

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at $37 \pm 0.5^\circ\text{C}$. The dissolution media used were 900 mL of 0.1 mol/L HCl for first 2 hr followed by pH 6.8 phosphate buffer solutions for 12hr. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of prewarmed ($37 \pm 0.5^\circ\text{C}$) 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 UV spectrophotometer (ELICO SL 164)) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (hr) curve.

Statistical analysis

Except dissolution all evaluation parameters were expressed as mean \pm standard deviation.

Stability studies

Short term stability studies on the above promising formulation (at $40\pm 2^\circ\text{C}/75\pm 5\%$ RH for 3 months) have shown no significance changes in physical appearance and drug content.

Result and Discussions

All the compressible excipient by wet granulation method was prepared using xanthum gum along with HPMC. This excipient was evaluated for bulk density, tapped density and Carr's index. Sustained release tablets of MS were prepared by using the above excipient and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index and angle of repose (Table-2) and for post compression parameters such as hardness, weight variation, friability, thickness and drug content uniformity (Table-3).

Table-2 Precompression parameters of MS formulation

Formulation code	Bulk density (gm/cc) \pm S.D	Tapped density (gm/cc) \pm S.D	Angle of repose (degree) \pm S.D	Carr's Index (%) \pm S.D
MS1	0.57 \pm 0.06	0.64 \pm 0.05	26.27 \pm 0.98	12.28 \pm 0.01
MS2	0.58 \pm 0.05	0.66 \pm 0.01	28.36 \pm 0.89	12.12 \pm 0.03
MS3	0.58 \pm 0.03	0.67 \pm 0.03	28.42 \pm 1.06	13.43 \pm 0.02
MS4	0.59 \pm 0.04	0.69 \pm 0.03	25.42 \pm 1.03	14.49 \pm 0.01
MS5	0.63 \pm 0.02	0.71 \pm 0.02	24.97 \pm 0.93	11.26 \pm 0.03

The bulk density of pre-compression blends was found to be in the range of 0.57 to 0.63 gm/cc, tapped density in the range of 0.64 to 0.71 gm/cc, the Carr's index values were in the range of 11.26 to 14.49% and angle of repose in the range of 24.97 to 28.42. The hardness of the tablet formulations was found to be in the range of 6.8 to 7.1 kg/cm². The friability values were found to be in the range of 0.52 to 0.94%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits. The percent drug content of all the tablets was found to be in the range of 97.60 to 99.9% of the expected MS content, which was within the acceptable limits. The results are shown in Table-4. The thickness values were found to be in range of 5.49-5.50mm.

Table-3: Postcompression parameters of formulation

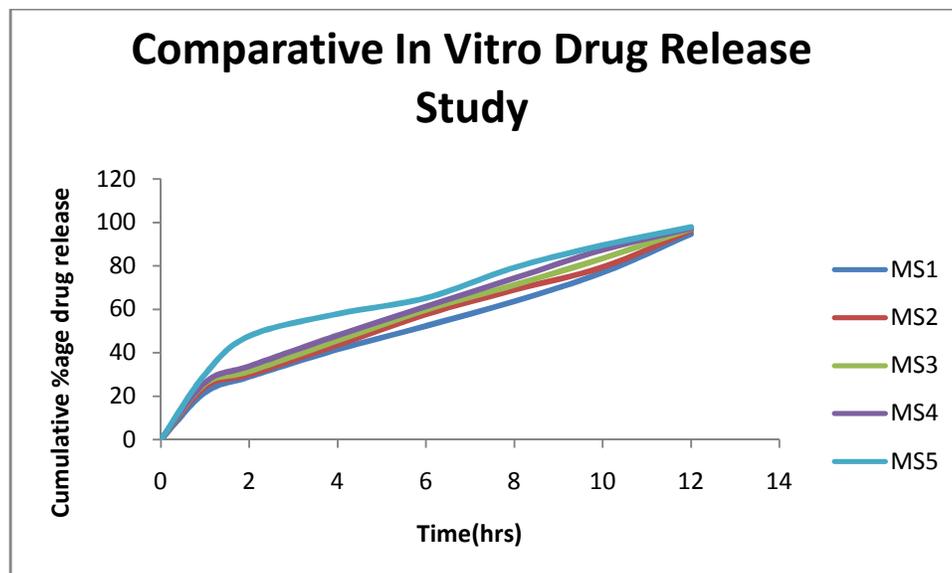
Formulation code	Hardness (kg/cm ²) \pm S.D	%Friability \pm S.D	%Drug content \pm S.D	Average wt. of 1tablet \pm S.D	Thickness (mm \pm S.D)
MS1	6.9 \pm 0.114	0.58 \pm 0.01	98.85 \pm 0.01	800.2 \pm 0.01	5.50 \pm 0.28
MS2	6.8 \pm 0.118	0.88 \pm 0.03	97.73 \pm 0.42	800.5 \pm 0.13	5.50 \pm 0.11
MS3	6.8 \pm 0.152	0.94 \pm 0.08	97.60 \pm 0.13	800.3 \pm 0.21	5.50 \pm 0.07
MS4	7.1 \pm 0.155	0.52 \pm 0.01	99.3 \pm 0.12	800.3 \pm 0.14	5.50 \pm 0.12
MS5	6.9 \pm 0.153	0.67 \pm 0.02	99.9 \pm 0.25	801.3 \pm 0.01	5.49 \pm 0.14

Content uniformity

From the content uniformity test by assay method it was found that the percentage of drug content (%D.C) was maximum in MS5 formulation (99.3 \pm 0.12). Hence it was the best formulation among the various formulations like MS1, MS2, MS3 and MS4.

In vitro dissolution studies

From the in vitro drug release study it was found that the percentage of drug release (%D.R) was maximum in MS5 formulation giving 97.86 of drug release. Hence it was the best formulation among the various formulations like MS1, MS2, MS3 and MS5 (Figure-1)

Figure-1: Comparison in vitro drug release study of various batches of MS formulations

Conclusion

A sustained release based drug delivery system can be designed for Metformin hydrochloride using HPMC as controlled release polymer and xanthum gum as gum that helped in controlling the drug release from matrix. From the findings of the present study states that the hydrophilic matrix of HPMC alone could not control the Metformin HCL release effectively for 12 hr whereas when combined with xanthan gum could slow down the release of drug from their matrices and can be successfully employed for formulating sustained-release matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Metformin HCL tablets. It was evident from the results that rate of drug release can be controlled through HPMC and xanthum gum. From the developed formulations the release of Metformin hydrochloride was best in MS5 formulation i.e. (in-vitro study). From the FTIR study, it was confirmed that the drug & excipients in the formulations were compatible with each other.

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