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Research Article

PREPARATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE TABLET FORMULATIONS OF METFORMIN HCL

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ABSTRACT

An attempt was to formulate the oral sustained release metformin hydrochloride matrix tablets by using hydroxypropyl methylcellulose of different viscosity grades (HPMC K4M, HPMC K15M, and HPMC K100M). The tablets were prepared by wet granulation technique. The granules were evaluated for angle of repose, loose bulk density, tapped and bulk density. It shows satisfactory results. The tablets were subjected to thickness, weight variation, drug content, hardness, friability, and *in vitro* release studies. The *in vitro* dissolution study was carried out for 8 h using USP dissolution apparatus II (paddle) in 900mL 0.1 N HCl as dissolution media. The release mechanisms were explored and explained with zero order, first order, Higuchi, Kromayer's and Hixon-Croweel equations. The optimized formulation was found to be buoyant for 8 h in stomach. It is cleared that the drug release from matrix tablets prepared by HPMC K100M provides a better result in preparation of SR formulation of metformin hydrochloride.

Key words: metformin HCl, sustained release, hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, dissolution.

INTRODUCTION

Introduction of matrix tablet as sustained release has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating sustained release dosage form [1-3]. Hydroxypropyl methyl cellulose (HPMC) is the widely used hydrophilic polymer to prolong drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability and very low toxicity. It regulates the release of drug by controlling the swelling and cross linking [4, 5].

Type-2 diabetes mellitus is a chronic progressive disorder characterized by defective insulin secretion and increased insulin resistance. It is widely accepted that it required intense and tight glycemic control to prevent several cardiovascular complications. Metformin hydrochloride is an orally administered biguanide, widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action [6]. It is a hydrophilic drug which slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability is reported to be of 50 - 60% has relatively short biological half life of 1.5 - 4.5 h [7, 8]. However, frequent dosing schedule and risk of gastrointestinal symptoms make its dose optimization complicated. Thus, it is reasonable to assume the requirement of sustained release metformin formulation to prolong its duration of action and to improve patient compliance.

Recently several studies have been carried out to investigate the pharmacokinetic of oral controlled release products of metformin HCl. Fiona *et al* [9], of Colorcon Ltd., has described the method for preparation of metformin HCl 500 mg extended release tablet, by direct compression method. In commercial scale it creates the problem of poor powder flow ability from hoper to compression machine followed by weight variation, content uniformity, hardness and friability due to poor inherent compressibility of metformin HCl.

SR micro capsules of metformin by ethyl cellulose had been described by Balan *et al* [10] Where metformin gave *in vitro* release for up to 22 h. But preparation of microcapsules in commercial scale and optimization of drug release rate is troublesome. The objective of this study was to prepare sustained release metformin HCl tablets using hydrophilic materials, HPMC and PVP K30, to evaluate the *in-vitro* release characteristics and to predict and correlate the release behavior of metformin HCl from the matrix. The commonly adopted models for understanding the release of drugs from matrices are Zero-order. Zero order, first order, Higuchi's kinetics and Korsmeyer's equation to evaluate the drug release mechanism and kinetics.

MATERIALS AND METHODS

Materials

HPMC K4M, HPMC K15M HPMC K100M was purchased from Dow Chemicals (Midland, MI, USA); metformin HCl, PVP K30, Talc and magnesium stearate obtained as gift samples from M/s Inga Laboratories Private Ltd. India. All other solvents and reagents were purchased from Merck chemicals, India, and were of analytical grade.

Formulation of Metformin HCl Sustained Release (SR) Tablets

Preparation of Tablets

Different tablet formulations were prepared by wet granulation technique Table 1. All the powders except magnesium stearate and talc were passed through 60 mesh sieve. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent (alcoholic solution of PVP) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 14 mesh sieve. The granules were dried at 50°C for 2 h in a tray drier. Once dry, the granules were passed through 20 mesh sieve. Talc and magnesium stearate were finally added as glidant and lubricant. Granules thus obtained were compressed at the average hardness of 5 – 7 kg/sq.cm on a twenty station rotary tablet press (Cad mach, India).

Characterization of matrix formulations

Weight Variation

For the determination of weight variation of each batch, tablets were randomly sampled and individual weight of 20 tablets was taken in analytical balance. Mean ± standard deviation (s.d) was calculated.

Thickness

From randomly sampled tablets, thickness of 10 tablets was measured individually using digital vernier caliper. Then mean ± s.d was calculated. Diameter Variation: Diameters of 10 tablets from each batch were checked using digital vernier caliper. Then mean ± SD was calculated.

Hardness

Hardness of 10 tablets was measured individually using pre-calibrated digital hardness tester. Then mean ± SD was calculated.

Friability

Twenty tablets were weighed in a balance having readability of one mg. These tablets were transformed into a friabilator set 100 revolutions. After the completion of revolution dust was removed completely, weighed again in the same balance and percentage loss was calculated.

Drug content

Twenty tablets were weighed and its average weight was taken which was crushed in motor and pestle. The powder weight equivalent to single tablets i.e. 500 mg was dissolved in 10 mL water in a 100 mL volumetric flask and allowed to stand for 10 min. To that 75 mL of methanol was added initially followed by addition of sufficient methanol to produce 100 mL which was then filtered through whatmann filter paper. 5 mL of this resulting solution was further diluted to 50 mL with 7.2 pH phosphate buffer: methanol (1 : 1). Again 5 mL was diluted to 50 mL by the same solvent. The absorbance of each of the standard and sample solution were taken in UV-visible spectrophotometer at 320 nm using equal volumes of 7.2 pH phosphate buffer and methanol as blank.

***In-vitro* Release Studies**

InVitro dissolution study of all the formulated tablets and market sample was carried out for 8 h in USP dissolution apparatus II (paddle) at 37 ± 2°C and 100 rpm in 900 mL 0.1 N HCl. Sample of 10 mL was withdrawn at pre determined time intervals and replaced with the same volume of dissolution media (37 ± 2°C) to maintain the constant volume. Solution samples were analyzed by high performance liquid chromatography (HPLC). The percentage of drug dissolved was calculated based on the concentrations of drugs. The target profile design parameters of an SR product for metformin HCl were as follows:

- After 1 h: 35 ± 15, %
- After 4 h: 65 ± 15, %
- After 8 h: 100 ± 15. %

Effect of Different Viscosity Grades of HPMC

Different HPMC viscosity grades, (K4M, K15M and K100M), were used. The influence of these viscosity grades, on the matrix porosity and on metformin HCl release rate, was investigated according to the formula presented in the Table 1.

Effect of Different Tooling on the Matrix Tablets

Drug release from HPMC matrix tablets from batch F3 was compressed round- concave 14 mm punch and analyzed to know the effect of surface area on the drug release

Mathematical Modeling of Drug Release Profile

Release drug data modeling

The suitability of several equations, which are reported in the literature to identify the mechanism for the release of metformin HCl, was tested with respect to the release data. Some diffusion models Korsmeyer–Peppas are expected to be valid only up to approximately 60% cumulative drug released.

The datas were evaluated according to the following equations:

Zero Order Kinetic

It describes the system in which the drug release rate is independent of its concentration.

$$M_t = M_o + K_o\, t \quad (1)$$

First Order Kinetic

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\log M_t = \log M_o + kt/2.303 \quad (2)$$

Higuchi Model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$Mt = M_{o+}\, k_H t^{1/2} \quad (3)$$

Korsmeyer-Peppas model

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$$Mt = M_{o+}\, k_k t^n \quad (4)$$

Where Mt is the amount of drug dissolved in time t, M_0 the initial amount of drug, K_0 the zero-order release constant, K the first order release constant. K_H the Higuchi rate constant, K_K the release constant and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent n indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport.

For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release

(VIII) Stability Studies

Stability studies were conducted on metformin HCl sustained release matrix tablets to assess drug stability with respect to drug content and drug release characteristics. Tablets are packed in strip, blister and bulk and stored in the drug stability testing chambers (Campbell Electronics, Mumbai, India) for up to 6 months. Typical stress condition of 40 ± 2°C at 75 ± 5% RH to represent accelerated stability condition. Drug stability testing chambers containing a saturated aqueous solution in contact with an excess of a definite solid phase at a given temperature to maintain constant humidity in an enclosed space were used.

RESULTS AND DISCUSSION

Physical Characterization of the Designed Tablets

The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 2. Tablet hardness was found to be good (between 6 to 8 kg/cm2) depending on the compression force applied, and friability was less than 0.5% (wt/wt). The manufactured tablets showed low weight variation and a high degree of drug content uniformity, indicating that wet granulation is an acceptable method for preparing good-quality matrix tablets of metformin HCl.

In Vitro Release Studies

The results of dissolution studies indicated that F-I, F-II, and F-III released 40.61%, 39.5%, and 36.11% of metformin HCl at the end of 1 h; and 98.51%, 101.3%, and 93.44% of drug at the end of 8 h respectively (Figure 1). Among these formulations, the release rate was decreased in the following polymer order: HPMC K4M < K15M < K100M. These polymers have been well known to retard the drug release by swelling in aqueous media. HPMC K4M and K15M released the drug at a faster rate than HPMC 100M at the same drug: polymer ratio. A polymer's ability to retard the drug release rate is related to its viscosity. HPMC K4M, K15M and K100M exhibited viscosity values of 4000, 15000, and 100000 cps respectively. These results are in accordance with the earlier reported viscosity values for these polymers. The high dissolution rate observed with HPMC K4M could be due to its low swell ability, indicated by lower viscosity values compared to other two polymers. However, processing factors including wetting on granulation, particle size, and hardness also affect the release rate of drug from tablets.

Initially, tablets were prepared with HPMC K4M (F1) released 40.61% and 81.23% of metformin HCl within 1 and 4 h respectively. And the tablets with HPMC K15M (F2) shows 81.01% drug released within 4 h. The tablets prepared with K100M (F3), drug-to-polymer

ratios of 5: 2 and isopropyl alcohol as granulating agent retard the release oh metformin HCl 36.11%, 73.65% and 93.44 at 1h, 4 h and 8 h respectively. F3 formulation has showed an optimal formulation due to its closest profile to the target in terms of release.

F-I to F-II showed burst release of metformin HCl in the initial hours, which is probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules. A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release. These formulations also showed a high release in the initial hours. However, among these formulations, F3 was selected for further development because they showed comparatively less deviation from the theoretical release profile. Result of the dissolution of metformin HCl from matrix tablets are shown in (Figure 1).

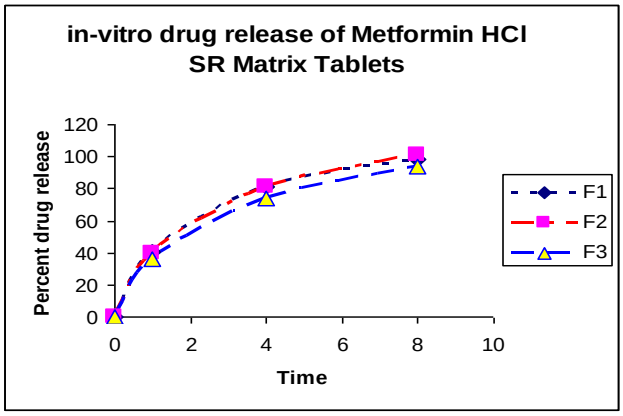

Figure 1: Result of the dissolution of Metformin HCL

Drug Release Kinetics

The zero-order rate Equation 1 describes the systems where the drug release rate is independent of its concentration. The first order Equation 2, describes the release from systems where the release rate is concentration dependent. Higuchi's model Equation 3 describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r2) was determined (Table 3). It was found that the *in vitro* drug release of metformin HCl SR (formulation F3) was best explained by Higuchi's equation, as the plots showed the highest linearity (r2 = 0.996399), followed by first order (r2 = 0.99896) and zero order (r2 = 0.936517). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics). However, drug release was also found to be very close to first-order kinetics, indicating that the concentration plays a major role in the drug release of highly water soluble drug. Figure 1 also verifies the correlation of the metformin HCl SR release profile with the theoretical profile.

Mechanism of Drug Release

The corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas (Equation 4) indicated a good linearity (r2 = 0.9959). The release exponent n was 0.4653, which appears to indicate a coupling of the diffusion and erosion mechanism—so-called non-Fickian or anomalous diffusion—and may indicate that the drug release is controlled by more than one process. Reddy *et al* observed similar results with a matrix tablet of nicorandil with an n value of 0.71, 23 and Fassihi and Ritschel with a matrix tablet of theophylline with an n value of 0.724 Both these groups of researchers also considered the corresponding n values to indicate an anomalous release mechanism.

Effect of HPMC Viscosity

It is suggested that the hydrophilic polymer such as HPMC when comes in contact with the water, it absorbs water and swells to form an gel layer which serves as a barrier to drug diffusion. The drug release process from a HPMC matrix involves water penetration into the dry matrix,

hydration and gelation of the polymer, dissolution of the drug and diffusion of the dissolved drug

through the resultant gel layer. Since the movement of the drug through the matrix system is predominantly diffusion controlled, it may be expected from Stokes-Einstein equation, which states that the process will be slower in the more viscous layer regarding drug release profiles of the formulated tablets. It was observed that there was a gradual decrease in the rate of release of the drug from the polymer HPMC with increase in the viscosity as shown in (Figure 1).

Effect of different Tooling on the Matrix Tablets

Different shaped tablets, the release of metformin HCl from the hypromellose matrices resulted slight increase in drug release profiles. It may be due to higher surface area of round tablets.

CONCLUSIONS

In our study, to reach an intended target release profile, SR formulation of metformin HCl tablets were developed with polymer substance such as HPMC K100M. It has been revealed that excipient such as HPMC K100M with polyvinyl pyrrolidone can be used with wet granulation method. This application has shown similar results with other studies in the literature in terms of SR formulation preparations. However, in developing SR formulations containing metformin HCl, it has been shown that HPMC K100M provides a better result in preparation of SR formulation prepared by wet granulation method. F3 formulation (5: 2 ratio) has showed an optimal formulation due to its closest profile to the target in terms of release.

Table 1: Composition of 500mg Metformin HCl

Ingredient			F1	F2	F3
Metformin HCl			50 0	50 0	50 0
Hydroxypropylmethyl K4M	cellulose		20 0		
Hydroxypropylmethyl K15M	cellulose			20 0	
Hydroxypropylmethyl cellulose K100M			200		
Polyvinyl pyrrolidone K30	50	50	70		
Magnesium stearate	5	5	5		
Talc	5	5	5		
Isopropyl alcohol	q.s.	q.s.	q.s.		
Total	76 0	76 0	780		

Table 2 :

Formulations	Hardness (kg/cm^2}	Thickness (mm) ± s.d (n=10)	Weight variation (mg) ± s.d (n=10)	Friability (%)	Assay (%) ± s.d (n=3)
F1	6-7	6.48±	760±	0.1	96.74 ±
F2	7-8	6.52±	760±	0.1	99.4±
F3	6-7	6.51±	780±	0.1	99.5±

Table 3: Release Kinetics of Metformin HCL SR.

	Zero Order		First Order		Higuchi		Korsmeyer and Peppas	
	K_o	R^2	kt	R^2	k_H	R^2	n	R^2
F1	11.28	0.9217	-0.24	0.9354	35.635	0.9231	0.436723	0.9922
F2	11.69	0.9330	-0.95	0.9771	36.053	0.9939	0.455242	0.9929
F3	10.78	0.9365	-0.44	0.9896	33.636	0.9963	0.465375	0.9959

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