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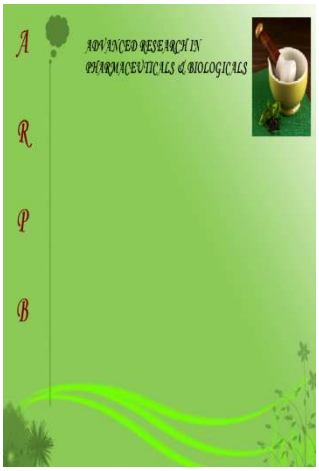

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FORMULATION DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLET OF METFORMIN HYDROCHLORIDE

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ABSTRACT:

The objective of the present study was to develop once-daily sustained-release matrix tablets of metformin HCl, anti-diabetic agent which is prescribed for the treatment of non-insulin dependent diabetes mellitus. The tablets were prepared by the non-aqueous wet granulation method. Isopropyl alcohol solution of polyvinylpyrrolidone (PVPK30) was used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC) and locust bean gum (LBG). The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, and *in vitro* release studies. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated that formulation M5 (HPMC: LBG, 200:30 mg) could extend the drug release up to 8 hours. The successful formulation of the study, exhibited satisfactory drug release (M5) was compared with the marketed formulation (Obimet SR™) and showed very close to release profile which suggests sustained release profile.

Keywords: Metformin HCl, HPMC K15, Locust bean gum, t30, t50.

(Research Article)

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. Metformin HCl (MTH) is an anti-diabetic agent which is prescribed for the treatment of non-insulin dependent diabetes mellitus[1]. In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with MTH suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (60%), high incidence of gastro intestine tract side effects (30% cases) and decreased absorption of the drug with food that delays tmax by half-an-hour. The rationality, therefore, exists for formulation of MTH as a sustained release formulation. The primary benefit of sustained release preparations of MTH compared to an immediate release formulation is that a more uniform maintenance of blood plasma active concentration is achieved. Thus, potentially avoiding undesirable peaks and troughs associated with multiple immediate release preparations. Hydroxypropyl methyl cellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery system[2]. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly[3]. 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[4,5]. As reported by Ford *et al*,[6] as the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix. Narasimhan and Peppas[7] showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC[8]. Additionally a useful natural polysaccharide, locust bean gum (LBG), also called carob gum, as it is derived from carob (Ceratonia siliqua) seeds. LBG has an irregularly shaped molecule, composed of a 1-4-linked β-*D*-mannan backbone with 1-6-linked α-*D* galactose side groups. This neutral polymer is only

slightly soluble in cold water; it requires heat to achieve full hydration and maximum viscosity. Thus, it could be used as carrier for sustained release formulation being working as thickener for a wide range of pHvalues[9,10].

Thus, in present investigation the matrix tablet dosage form of MTH was prepared by taking an advantage of naturally occurring LBG and extensively used synthetic polymer, HPMC K15, for sustained release of the drug. The study involves preparation of matrix tablet by nonaqueous granulation method using various combinations of the polymers and evaluation of prepared tablets for their physicochemical properties.

MATERIALS AND METHODS

All materials (active and expedients) are obtained from Pharma Impex Lab, Kolkata and Curex Pharma Pvt Ltd, Nepal.

Preparation of matrix tablets: Matrix tablets were prepared by non-aqueous wet granulation method reported earlier with slight modofication[11]. The composition of various formulations is given in **Table 1**. HPMC K15, LBG and microcrystalline cellulose were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using a solution of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through mesh No 16. Thereafter, the drug Metformin hydrochloride was added to the wet granules and mixed thoroughly in a plastic bag. The granules were then dried at 50ºC for about 2 h with residual moisture content of 2 to 3% w/w. The dried granules were then mixed with 1% magnesium stearate and 1% talc for 2 min. Tablets were compressed at 700 mg weight on a 10-station mini rotary tableting machine (General Machinery Co, Mumbai, India) with 12-mm punches at a constant rotational speed of 72 rpm.

Table 1 Formulation summary of matrix tablets (700 mg tablet)

Formulation code	Drug (mg)	HPMC K15M (mg)	Locust bean gum (mg)	PVPK30 (mg)	MCC (mg)	Mg stearate (mg)	Talc (mg)
M1	300	100	170	60	80	5	5
M2	300	130	140	60	80	5	5
M3	300	140	130	60	80	5	5
M4	300	170	120	60	80	5	5
M5	300	200	70	60	80	5	5

Differential Scanning Calorimetry: Sustained release matrix tablets of

Metformin Hydrochloride was also characterized by means of DSC (Perkin Elmer Instrument Pyris 1 at a heating rate 100^0C /min and in the heating range of 550^0C to 3000^0C) and FTIR Perkin Elmer GX Spectrophotometer Instrument using KBr pellets in the heating range of 400 cm—1 to 4000 cm—1) spectral technique for the polymer and the drug compatibility.

Physicochemical properties of tablets[12-14]

Thickness: The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado), and the test was performed according to the official method.

Hardness and Friability: For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cad-mach, Ahmedabad, India) and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively.

Drug content: To determine drug content, 20 tablets were taken and crushed to powder with mortar and pestle. 300 mg of powder was taken and dissolved with appropriate amount of solvent with the aid of sonicator. After which the solution was filtered through whatman filter paper (90 mm diameter). The total amount of the drugs within the tablets was analyzed after appropriate dilution of test solution by using UV spectrophotometer (Systronics UV-VIS Spectrophotometer 118) against the reference solution with suitable Dilution at 274 nm.

In vitro drug release: *In vitro* drug release study from 6 tablets of each formulation, in triplicate, was determined using the USP I (basket) apparatus (DBK Instrument, Mumbai-60) where 900 ml of 0.1N HCl and phosphate buffer saline of pH 7.4 were used as dissolution media maintained at 370C (±0.50C) at 100 rpm. The release rates from the tablets were conducted in a dissolution medium of 0.1 N HCl for 2 h and thereafter in phosphate buffer saline of pH 7.4 for 6 h, 5 ml of aliquot were withdrawn at 1, 2, 3, 4, 5, 6, 7 and 8 h with replacement of fresh media. Then the solution samples were analyzed in UV–VIS double beam spectrophotometer, while keeping the dissolution media as a blank at 274 nm.

Drug release profiles were drawn using MS-Excel software and the values of t30 and t50 were obtained by interpolation from Excel graph.

RESULTS AND DISCUSSION

DSC study was carried to study the incompatibility between the formulation ingredients. The typical DSC thermogram data obtained from DSC scans. Examination of all the DSC thermograms reveals that there is no interaction between drug and polymers used for the drug formulation. The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, weight variation, drug content, hardness, friability, and *in vitro* dissolution. The thickness of the tablets ranged from 5.23 ± 0.03 to 5.23 ± 0.05 mm. The average percentage deviation of 20 tablets of each formula was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 97.78 ± 4.5 to 99.71 ± 3.4. The hardness and percentage friability of the tablets of all batches ranged from 4.50 ± 0.21 to 4.75 ± 0.21 kg/cm 2 and 0.39 to 0.65%, respectively (**Table 2**). All the formulations showed uniform thickness. In weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is ±5 %. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 95%. The formulation M5 showed a comparatively high hardness value of 4.75 kg/cm 2. This could be due to the presence of more HPMC K15, which is generally responsible for more hardness of the tablet. The low hardness value observed with formulation M1 may be due to the presence of more of LBG which generally decreases the hardness of tablets being a natural gum. Tablet hardness is not an absolute indicator of strength[15]. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability. The

results of dissolution studies of formulations M1, M2, M3, M4 and M5, composed of varying concentration of HPMCK15 and LBG, and prepared using PVPK30 as granulating agent, are shown in **Fig. 1**. Tablets M1, M2, M3, M4 and M5 released 12.55%, 14.75%, 15.46%, 17.42% and 20.55% of MTH at the end of 2 hours; and 41.53%, 43.12%, 43.21%, 46.14% and 51.42% of drug at the end of 8 hours, respectively.

The dissolution profiles of formulations were studied in terms of t30 and t50 (time to release 30 % and 50 % of the drug, respectively) and the results are depicted in **Table 2**. It was found that as the concentration of HPMC K15 increases the values of t30 and t50 increased. This polymer has been well known to retard the drug release by swelling in aqueous media[16]. Thus, a polymer's ability to retard the drug release rate is related to its viscosity. The high dissolution rate observed with formulations with higher amount of LBG could be due to its low swellability. However, processing factors including wetting on granulation, particle size, and hardness also affect the release rate of drug from tablets. Among the polymers tested, HPMC could retard the release only up to 8 hours. HPMC is mixed with alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituent's. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent[17]. In the present study, HPMC K15 was used because it forms a strong viscous gel on contact with aqueous media, which may be useful in controlled delivery of highly water-soluble drugs. The dissolution profile of the best formulation (M5) was compared with the marketed tablets of MTH (Obimet SR™) and is shown in **Fig 2**. It was found that the prepared formulation showed similar drug release pattern as compared to marketed formulation. Thus, the prepared formulation might be used clinically for the treatment of diabetes being a sustained release dosage form.

Table 2 Physical properties of sustained release matrix tablets of Metformin HCl

Batch code	Tablet weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)	T30 (min)	T50 (min)
M1	700 ± 2.45	5.23 ± 0.04	4.50 ± 0.21	0.63	99.71 ± 3.4	4.53	7.56
M2	700 ± 4.15	5.23 ± 0.05	4.50 ± 0.23	0.65	99.64 ± 2.4	4.76	8.05

M3	700 ± 3.14	5.23 ± 0.03	4.75 ± 0.12	0.41	98.98 ± 3.4	4.83	7.94
M4	700 ± 3.45	5.23 ± 0.04	4.75 ± 0.13	0.41	97.45 ± 4.2	4.87	8.11
M5	700 ± 4.15	5.23 ± 0.05	4.75 ± 0.21	0.39	97.78 ± 4.5	4.89	8.16

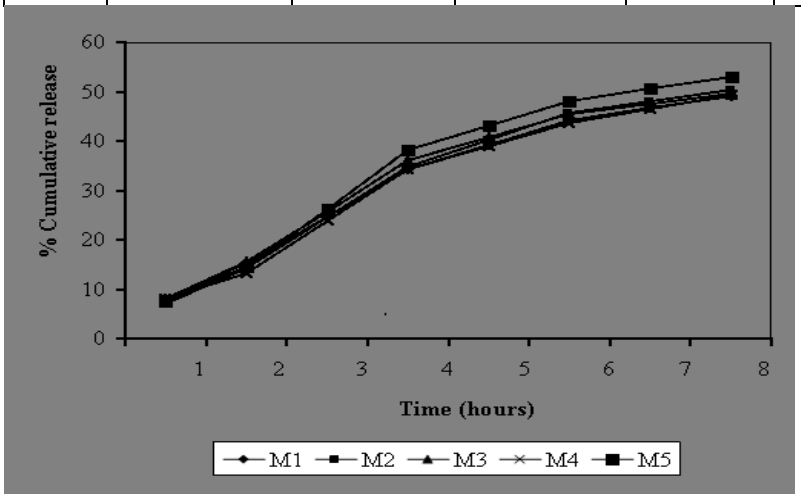

Fig 1 *In vitro* percentage drug release profile for the sample M1 to M5

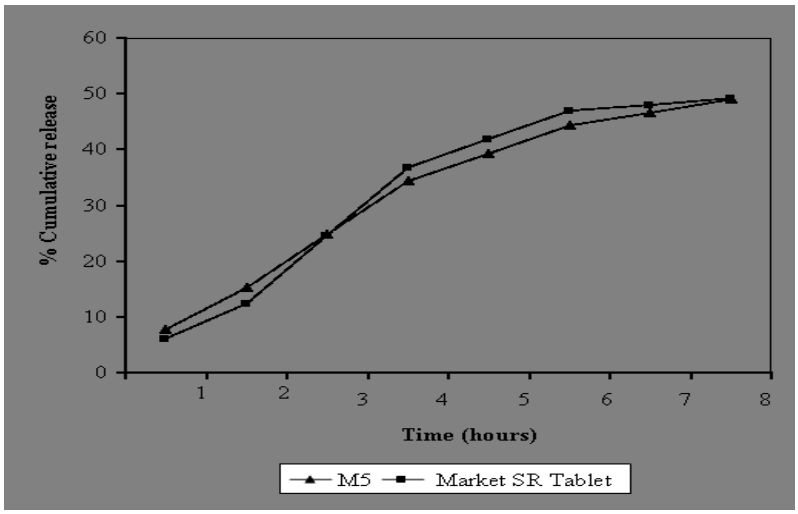

Fig 2 Comparative release profile of sample M5 and market SR formulation

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