ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (5) 2013, 04-08

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF MIGLITOL USING HYDROPHOBIC POLYMERS

***Ashtamkar Joel[1], Chugh Naresh[1]**

[1] Department of Pharmacy, Vinayaka Missions University, Tamilnadu

ABSTRACT

In the present study, miglitol 25 mg controlled release matrices were prepared by direct compression and in vitro drug dissolution studies were performed to find out the drug release rate and patterns. Hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate (PVA) and their combination were used as rate controlling polymers. Effects of addition of hydroxypropyl methylcellulose phthalate and polyvinyl acetate on in-vitro drug dissolution were studied. Tablets were formulated using total polymer content as 20, 30 and 40 percent. In-vitro drug release was carried out using USP Type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, followed by 900 ml alkaline dissolution medium (pH 7.4) up to 12 hours. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. When hydroxypropyl methylcellulose phthalate and polyvinyl acetate were used alone as the only retarding polymer, retardation effect increased proportionately as the concentration of polymer increased; however lacked the desirable physical properties. Combination in the matrix gave both the retardation effect as well as desired physical properties to the formulation. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

KEYWORDS: Miglitol, Hydroxypropyl methylcellulose phthalate, Polyvinyl Acetate, Release Kinetics.

INTRODUCTION:

During the last two decades there has been remarkable increase in interest in controlled release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of controlled release is also being applied to veterinary products also. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration[1]. Hydroxypropyl methylcellulose phthalate and polyvinyl acetate can be used as matrix materials. The matrix may be tableted by direct compression.

Diabetes mellitus is a chronic disease that is characterized by disorders in carbohydrate, protein and lipid metabolism. Its central disturbance appears to involve an abnormality either in the secretion of or effects produced by insulin although other factors also may be involved. Diabetes mellitus is a metabolic disorder in which carbohydrate metabolism is reduced while that of proteins and lipids is increased.

Miglitol is an oral anti-diabetic drug that acts by inhibiting the ability of the patient to break down complex carbohydrates into glucose. It is primarily used in diabetes mellitus type 2 for establishing greater glycemic control by preventing the digestion of carbohydrates (such as disaccharides, oligosaccharides, and polysaccharides) into monosaccharides which can be absorbed by the body. Miglitol inhibits glycoside hydrolase enzymes called alpha-glucosidase. Since miglitol works by preventing digestion of carbohydrates, it lowers the degree of postprandial hyperglycemia.

Miglitol is systemically absorbed; however, it is not metabolized and is excreted by the kidneys. Also miglitol have a shorter half-life of 2 hours, it requires frequent dosing by oral route. Off various recent techniques for controlling drug release, matrix system offer various advantages of ease of formulation, better control on release profile of drug and better patient compliance.

MATERIALS AND METHOD:

MATERIALS:

Miglitol was obtained as gift sample from Meyer Organics Pvt. Ltd. Thane, Maharashtra. Hydroxypropyl methylcellulose phthalate (HPMCP) was obtained as gift sample from Pioma, Mumbai, Maharashtra. Polyvinyl acetate was obtained as gift sample from Signet, Mumbai,

*Corresponding author: Ashtamkar Joel Peres / Email: jashtamkar@gmail.com

Maharashtra. Other materials used were of analytical grade and procured from commercial sources.

METHODS:

PREPARATION OF SUSTAINED RELEASE MATRIX TABLETS OF MIGLITOL:

Controlled release tablets of miglitol[2, 3] were prepared by direct compression method[4] using microcrystalline cellulose as directly compressible vehicle. Hydroxypropyl methylcellulose phthalate (HPMCP) and polyvinyl acetate (PVA) were used as retardant material for preparation of tablets[5, 6]. Other excipients were magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. For preparation of controlled release tablets of miglitol, drug and polymer were weighed accurately, all the ingredients were sieved through 40 mesh screen and mixed with other ingredients and the powder mixture was compressed using 16 station rotary tablet compression machine using 5 mm punches. Tablet compression weight was adjusted to 50 mg. In total, 7 formulations containing different amounts of HPMCP (F1, F2, F3), PVA (F4, F5, F6) and combination of HPMCP & PVA (F7) were prepared. The formula for various formulations attempted have been given in **Table 1**: Composition of sustained release miglitol tablets

Table 1: Composition of sustained release miglitol tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7
Miglitol	25	25	25	25	25	25	25
HPMCP	10	15	20	-	-	-	10
PVA	-	-	-	10	15	20	10
MCC	14	9	4	14	9	4	4
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5

PHYSICAL CHARACTERIZATION OF FABRICATED TABLETS[7]:

The quality control tests for the tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used

Dial tablet hardness tester. Friability was determined b y Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the weight variation was calculated. Physical characters observed for various batches are given in **Table 2**: Evaluation of Physical characters of miglitol tablets.

ESTIMATION OF DRUG CONTENT[8]:

An UV/Vis spectrophotometric method based on the measurement of absorbance at 625 nm in phosphate buffer of pH 7.4 and 0.1 N alkaline potassium permanganate was used as coloring agent for estimation of miglitol. From each batch of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 150 mg was transferred into a 100 ml volumetric flask, 100 ml phosphate buffer pH 7.4 was added and the solution was sonication for about 30 min. The solution was made up to 100 ml with alkaline potassium permanganate and phosphate buffer pH 7.4. Same concentration of the standard solution was also prepared by taking 100 mg of drug in a 100ml volumetric flask made up to volume with coloring agent and phosphate buffer pH 7.4.The drug content was estimated by measuring the absorbance of both standard and sample solutions at 625 nm using UV/Vis spectrophotometer (Systronic 2201). Results are tabulated in **Table 3**: Drug content In-vitro drug release studies of miglitol tablets.

***IN-VITRO* RELEASE STUDIES:**

The *in-vitro* dissolution studies were performed using USP type 2 dissolution apparatus (paddle) at 50 rpm. The dissolution medium consisted of 1.2 pH medium for first 2 hours and for subsequent 22 hours in phosphate buffer pH 7.4 (900 ml), maintained at 37±0.5 ^{o}C. The release studies were conducted in triplicate. Aliquot of samples (5ml) were withdrawn at specific time intervals and drug content was determined spectrophotometrically at 625 nm. Results are tabulated in **Table 3**: Drug content In-vitro drug release studies of miglitol tablets.
Results of *in-vitro* dissolution studies are shown graphically in **Figure 1:** Plot of Cumulative % drug released v/s Time for different formulation (F1-F7).

KINETICS OF *IN-VITRO* DRUG RELEASE[8]:

In-vitro release data obtained was treated to zero order rate equation, Higuchi's equation and Korsmeyer-Peppas equation to know precisely the mechanism of drug release from matrix tablet.

Release data obtained is treated with following modes of data treatment.

Zero order equation - Cumulative percentage drug release vs. Time in hours.

First order equation – Log cumulative percentage drug remained vs. Time in hours.

Higuchi's Diffusion equation - Cumulative percentage drug release vs. Square root time. Korsmeyer- Peppas equation - Log cumulative percentage of drug release vs. Log time.

Results are tabulated in **Table 4**: Different kinetic models for miglitol tablets.

RESULT AND DISCUSSION:

In present work an attempt has been made to formulate controlled release matrix tablets of miglitol using hydrophobic polymers namely hydroxypropyl methylcellulose phthalate and polyvinyl acetate as rate controlling polymer and effect on in vitro drug dissolution were studied by addition of these polymers at concentrations of 20%, 30% and 40%. Also one formulation was prepared using combination of hydroxypropyl methylcellulose phthalate and polyvinyl acetate at 20% each.

PHYSICAL CHARACTERIZATION OF TABLETS:

The formulation of tablets was done by using direct compression technique which was found acceptable. All the formulations were prepared according to the formula given in T**able 1**. The prepared matrix tablets were evaluated for various physical properties as indicated in T**able 2**.

Table 2: Evaluation of Physical characters of miglitol tablets

Formulation code	Thickness (mm)**	Weight variation (%)	Hardness (N)**	Friability (%)*
F1	2.51 ± 0.01	0.76 ± 0.09	29.47 ± 1.39	0.69 ± 0.04
F2	2.54 ± 0.06	1.32 ± 0.12	30.63 ± 2.47	0.68 ± 0.03
F3	2.46 ± 0.02	0.94 ± 0.05	31.28 ± 2.83	0.65 ± 0.01
F4	2.49± 0.05	1.24 ± 0.14	28.72 ± 1.57	0.46 ± 0.03
F5	2.51 ± 0.04	0.69 ± 0.11	30.96 ± 1.69	0.43 ± 0.02
F6	2.54 ± 0.03	1.23 ± 0.13	32.17 ± 2.74	0.42 ± 0.04
F7	2.51 ± 0.03	0.95 ± 0.08	33.61 ± 1.69	0.22 ± 0.03

*****All the values are expressed as a mean ± SD., n = 3

****** All the values are expressed as a mean ± SD., n = 6

The results of evaluation studies can be summarized as follows:

The thickness of the formulations was found to be in the range of 2.46 ± 0.02mm to 2.54 ± 0.06 mm. The crushing strength of tablets was in the range of 28.72 ± 1.57 N to 33.61 ± 1.69 N. The loss in total weight of the tablets due to friability was less than 0.5% for formulations F4, F5, F6 & F7 and was greater 0.5% for formulations F1, F2 & F3. The high value of crushing strength and low friability indicated that the compressibility of miglitol and adjuvant was good for formulations F4, F5, F6 & F7; however compressibility was not good for formulations F1, F2 & F3.

DRUG CONTENT AND *IN-VITRO* DRUG RELEASE OF TABLETS:

Drug content and in-vitro drug release studies are indicated in **Table 3**. Drug content was found to be uniform among different formulation of tablets and ranged from 98.35 ± 0.90% to 101.21 ± 1.12 %. In-vitro drug release studies revealed that formulations F1, F2 and F3 containing hydroxypropyl methylcellulose phthalate as retarding polymer showed maximum $t_{50\%}$ at 7.27 ± 0.08 hours and maximum $t_{80\%}$ at 12.81 ± 0.13hours. In-vitro drug release studies revealed that formulations F4, F5 and F6 containing polyvinyl acetate as retarding polymer showed maximum $t_{50\%}$ at 4.08 ± 0.11 hours and maximum $t_{80\%}$ at 16.22 ± 0.07 hours. For formulation F7 containing combination of hydroxypropyl methylcellulose phthalate and polyvinyl acetate $t_{50\%}$ was observed at 4.85 ± 0.16hours and maximum $t_{80\%}$ at 12.32 ± 0.15hours. Time at $t_{50\%}$ and $t_{80\%}$ increased as the concentration of polymer increased. Though promising results are observed for $t_{50\%}$ and $t_{80\%}$ for formulations containing hydroxypropyl methylcellulose phthalate as retarding polymer, physical characters are not good. Though promising results are observed for physical characters for formulations containing polyvinyl acetate as retarding polymer, $t_{50\%}$ and $t_{80\%}$ are not good. Formulation F7 containing combination of hydroxypropyl methylcellulose phthalate and polyvinyl acetate each at 20% (total polymer concentration 40% in formulation) showed good results for physical characters as well as $t_{50\%}$ and $t_{80\%}$. Combination worked in synergy giving desirable results.

Table 3: Drug content and in-vitro drug release studies of miglitol tablets

Formulation code	Drug content (%)	Time required to release 50% of drug ($t_{50\%}$) (hrs.)	Time required to release 80% of drug ($t_{80\%}$) (hrs.)
F1	100.72 ± 1.41	4.54 ± 0.13	7.53 ± 0.07
F2	99.82 ± 0.67	5.36 ± 0.05	8.16 ± 0.14
F3	100.84 ± 0.59	7.27 ± 0.08	12.81 ± 0.13
F4	101.21 ± 1.12	3.57 ± 0.14	12.06 ± 0.09
F5	99.43 ± 1.34	3.85 ± 0.07	13.91 ± 0.05
F6	99.71 ± 0.91	4.08 ± 0.11	16.22 ± 0.07
F7	98.35 ± 0.90	4.85 ± 0.16	12.32 ± 0.15

All the values are expressed as a mean ± SD., n = 3

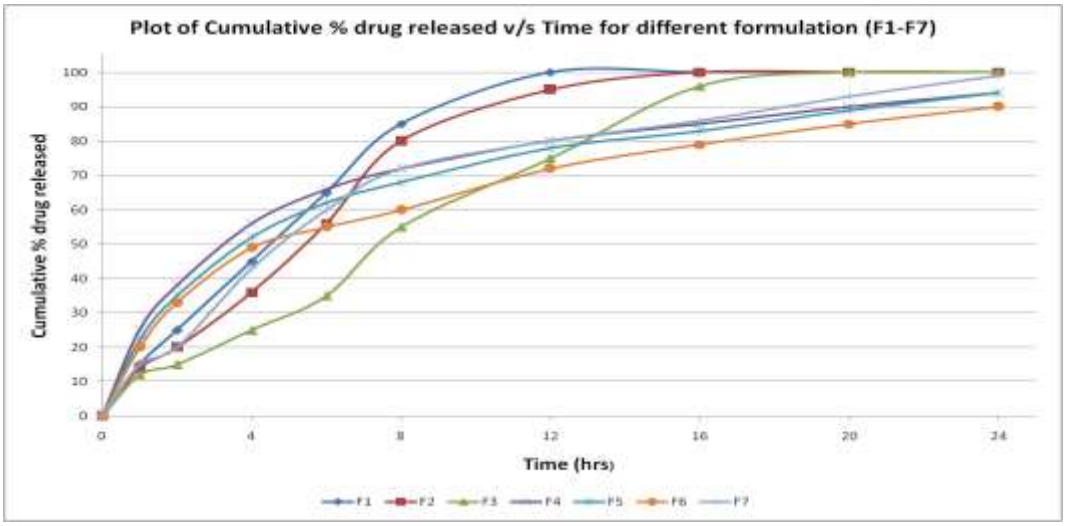

Figure 1: Plot of Cumulative % drug released v/s Time for different formulation (F1-F7)

KINETICS OF DRUG RELEASE:

There are various applied mathematical models for dissolution data of miglitol controlled release tablet are shown in T**able 4**. Formulations F1, F2, F3 and F7 have Korsmeyer - Peppas as best fit kinetic model for drug release. These formulations followed anomalous mechanism for drug transport i.e. non-Fickian kinetics indicating deviation of drug release from Fick's law and where drug release is combination of pure diffusion controlled coupled with dissolution controlled drug release. Formulations F4, F5 and F6 have First Order as best fit kinetic model for drug release indicating the percentage of drug dissolved at a certain time point may be equivalent to the percentage surface area at that time point.

Table 4: Different kinetic models for miglitol tablets

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer - Peppas			Best fit model
				R^2	n	k	
F1	0.747	0.847	0.877	0.933	0.629	1.246	Korsmeyer - Peppas
F2	0.800	0.930	0.907	0.949	0.684	1.163	Korsmeyer - Peppas
F3	0.931	0.940	0.963	0.973	0.579	1.007	Korsmeyer - Peppas
F4	0.825	0.986	0.937	0.959	0.403	1.457	First Order
F5	0.856	0.988	0.956	0.966	0.440	1.404	First Order
F6	0.893	0.993	0.975	0.973	0.450	1.362	First Order
F7	0.848	0.922	0.947	0.949	0.623	1.204	Korsmeyer - Peppas

CONCLUSION:

Results of present research work demonstrate that the combination of hydrophobic polymers was successfully employed for formulation of miglitol controlled release tablets. It is observed that combination of polymers produce a more linear release from matrix tablets as well as proper physical characters with low standard deviation. Hydroxypropyl methylcellulose phthalate and polyvinyl acetate in the concentration of 40% to the total polymer concentration is promising concentration for oral controlled release tablets of miglitol and that can be further give release above 24 hours. In all the formulations, drug release rate is inversely proportional to the concentration of polymer. From this study, it is possible to design promising oral controlled release matrix tablets containing miglitol for the treatment of type 2 diabetes mellitus diseases with more efficacy and better patient compliance.

ACKNOWLEDGEMENT:

The authors are sincerely thankful to Meyer Organics Pvt. Limited (Thane, India) for providing infrastructure facilities to carry out this research work.

REFERENCES:

1. Yie WC, Senshang L. Drug Delivery: Controlled Release. In: Swarbik J eds. Encyclopedia of Pharmaceutical Technology. Vol 2. 3rd ed. New York, USA: Informa Healthcare; 2007:1082-1103.

2. Kumar G, Juyal V and Badoni PP. Formulation and evaluation of matrix tablets of acarbose. Drug Invention Today. 2010; 2(5):264-267.

3. Patel H Dhrupesh R, Panchal, et al. Matrix type drug delivery system: a review. J Pharm Sci Bioscientific Res. 2011; 1(3):143-151.

4. Robinson JR, Lee VHL. Controlled Drug Delivery. 2nd ed. New York: Marcel Dekker Inc; 1987:29-30.

5. Ruchatz F, Kolter K, Wittemer S, et al. Kollidon SR - a new excipient for sustained release matrices, USA: BASF; 2000.

6. Steenpa T, Rock TC, Kolter K. Kollidon SR – sustained release formulations of different drugs, USA: BASF; 2003.

7. Pena R, Verain. Analysis of different parameters of an optimized prolonged release formulation obtained by five processes. In: Pharmaceutical Technology – Controlled Drug Release. Vol 2. London: Ellis Horwood; 2005:57-70.

8. Ibrahim FA, Ali FA, Ahmed SM. Kinetic Determination of acarbose and miglitol in bulk and pharmaceutical formulation using alkaline potassium permanganate. Int J Biomed Sci. 2007; 3: 20-30.

9. Costa P, Manuel J, Lobo S. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001; 13:123-133.