ORIGINAL ARTICLE

Formulation and evaluation of matrix tablets of miglitol using different grades of HPMC

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Miglitol is a second-generation -glycosidase inhibitor with a chemical structure of 1-desoxynojiromycin. It acts as a potent competitive inhibitor of the alfa glycosidase in the microvilli of the intestinal brush border. Miglitol has a short biological half-life (2 h) and its bioavailability is >90%. Moreover, the site of absorption of miglitol is in the intestine. Therefore, the objective of the present work is to develop a sustained release matrix drug delivery systemfor the drug miglitol for the better management of the disease, to minimize side-effects as well as to improve patient compliance using different grades of HPMC K-4, HPMC K-15 and HPMC K-100 in different proportions and combinations by the direct compression technique.

Key words: *Bioavailability, controlled release, direct compression technique, hydrophilic polymer, miglitol*

INTRODUCTION

Miglitol is a second-generation -glycosidase inhibitor with a chemical structure of 1-desoxynojiromycin. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal α-glucoside hydrolase enzymes. Membrane-bound intestinal α-glucosidase hydrolyzes oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in delayed glucose absorption and lowering of post-prandialhyperglycemia.[1]

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 insulin oreffects 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.[1,2]

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 that can be absorbed by the body. Miglitol inhibits glycoside hydrolase enzymes called alfa-glucosidase. Becausemiglitolworks by preventing the digestion of carbohydrates, it lowers the degree of post-prandial hyperglycemia.[3]

The matrix tablets can be prepared by the direct compression method. Among manypolymers used in theformulation of matrix-based controlled release drug delivery systems, the hydrophilicpolymer matrix systems arewidely used because of their flexibility to obtain a desirable drugrelease profile, cost-effectivenessand broad regulatory acceptance.[4] Hydroxypropylmethylcellulose (HPMC) is the first choice for the formulation of a hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, non-ionic nature, consistent reproducible release profile, cost-effectiveness and utilization of existing conventional equipmentand methods.[5] Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from the dosage form is

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controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses.[6,7]

MATERIALS AND METHODS

Materials

Miglitol was obtained as gift sample from Glenmark Pharmaceuticals Pvt. Ltd., Nasik, Maharashtra.

HPMC of different grade was obtained as a gift sample from Signet, Mumbai, Maharashtra.Other materials used were of analytical grade and procured from commercial sources.

Preparation of sustained release matrix tablets of miglitol

Controlled release tablets of miglitol were prepared by the direct compression methodusing microcrystalline cellulose as the directly compressible vehicle. HPMC-K-4, HPMC-K-15 andHPMC-K-100 were used as the retardant material forpreparation of the tablets. Other excipients were magnesium stearate as a lubricant and talcas a glidant. For preparation of the controlled release tablets, miglitol and polymer were weighed accurately, all the ingredients were sieved through a 40-mesh screen and mixed with other ingredients and the powder mixture was compressed using a 16 station rotary tablet compression machine using 5-mm punches. Tablet compression weight was adjusted to 50 mg. In total, 10 formulations in which six formulationscontained different concentrationsofHPMC grades (F1, F2, F3, F4, F5, F6) and fourformulations of combinations of different grade of HPMC (F7, F8, F9, F10) were prepared.

The formula for various formulations attempted has been given in Table 1.

Physical characterization of the fabricated tablets

The quality control tests for the tablets, such as hardness, friability, weight variation, etc., were determined using the reported procedure. The tablet crushing strength was tested using acommonly used dial tablet hardness tester. Friability was determined by a Roche® friabilator (Electro Lab Pvt. Ltd. Mumbai, 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 and the average weight was recorded. Physical characters observed for various batches are given in Table 2.

Estimation of drug content

A UV spectrophotometric method based on the measurement of absorbance at 228 nm was used for the estimation of miglitol. Five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred into a 250 mL flask containing 100mLof 0.1N HCl (pH 1.2) andphosphate buffer (pH 3.4, 4.6, 6.0 and 7.4). The flask was then shaken on a flask shaker for 24 h and kept for 12 h for the sedimentation of the undissolved materials. The solution was filtered through a Whatman filter paper (0.45 μm). Tenmilliliters of this filtrate was taken and an appropriate dilution was made. The samples were analyzed at 228 nm using a UV visible spectrophotometer. The drug content was determined from the standard curve prepared at λ_{max} of 228 nm. The results are shown in Table 2.

Swelling index

The swelling index of the tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the

Table 1: Composition of the matrix tablet formulations of miglitol

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Miglitol	25	25	25	25	25	25	25	25	25	25
HPMC K-4	15	30	-	-	-	-	15	-	15	10
HPMC K-15	-	-	15	30	-	-	15	15	-	10
HPMC K-100	-	-	-	-	15	30	-	15	15	10
Microcrystalline cellulose	47	32	47	32	47	32	32	32	32	32
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Starch	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5

Weight of one tablet is 100 mg

Table 2: Results of thickness, weight variation, hardness, friability and drug content

Parameter batch	Weight variation (mg)	Hardness (kg/cm²)*	Friability (%)	Thickness (mm)*	Drug content (%)
F1	Pass	4.06	0.38	2.066	99.50
F2	Pass	4.10	0.39	2.100	92.89
F3	Pass	4.13	0.59	2.133	91.69
F4	Pass	4.06	0.58	2.066	99.59
F5	Pass	4.10	0.58	2.100	99.38
F6	Pass	4.20	0.59	2.200	97.05
F7	Pass	4.16	0.59	2.166	99.60
F8	Pass	4.26	0.39	2.133	100.02
F9	Pass	4.13	0.30	2.166	95.62
F10	Pass	4.16	0.33	2.125	99.50

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

Table 3: Swelling index of the tablets of batch F1 to F10 (%)

Batch	Time (h)						
	0	1	2	3	4	5	6
F1	0	32.23	41.38	54.32	63.78	74.12	81.2
F2	0	49.25	61.54	72.90	82.37	92.54	100.22
F3	0	29.09	39.45	51.32	61.12	71.97	80.35
F4	0	39.21	51.92	63.76	72.52	84.2	96.56
F5	0	45.65	53.35	64.32	75.45	80.09	94.58
F6	0	56.73	66.76	77.72	82.26	94.60	101.25
F7	0	26.76	40.98	49.54	59.06	69.78	75.99
F8	0	35.45	45.78	59.87	69.58	81.02	90.36
F9	0	39.06	47.96	55.32	65.34	76.09	87.11
F10	0	25.87	36.54	47.86	57.98	69.96	72.44

tablets was determined at pre-defined time intervals. The swelling index was calculated using the following equation:

Swelling index WU $=(W_1-W_0) \times 100$

W_0

Where,

W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

The results are shown in Table 3 and graphically in Figure 1.

***In vitro* release studies**

An *in vitro* dissolution study was carried out using a USP I apparatus (basket apparatus) in 900 mL of 0.1N HCl (pH 1.2) and phosphate buffer of pH 7.4 for 12 h. The temperature of the dissolution medium was kept at 37 ± 0.5°C and the basket was set at 50 rpm. One milliliter of the sample solution was withdrawn at a specified interval of time. The absorbance of the withdrawn samples was measured at λ_{max} 228 nm using a UV visible spectrophotometer. The concentration was determined from the standard curve of miglitol prepared in distilled waterat λ_{max} 228 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve. Results are tabulated in Table 4. Results of *in vitro* dissolution studies are shown graphically in Figure 2.

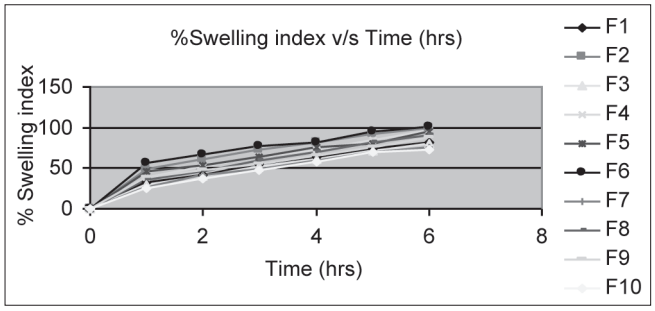

Figure 1: Comparison of % swelling index of various formulations

Kinetics of *in vitro* drug release

The release rate kinetic data for all the formulations areshown in Tables 5 and 6.

RESULTS AND DISCUSSION

Results of *in vitro* release profile indicated that formulation F8 was the most promising formulation as the extent of drug release from this formulation was high compared with theother formulations. Results of the *invitro* swelling study indicate that the formulation F8 hasa considerable swelling index.

A stability study was conducted on tablets of batch F8 stored at 0°C and 40°C for 1 month. Tablets were evaluated for hardness, friability, *in vitro* release profile and drug content. After 1 month, no significant changes were observed in any of the studied parameters during the study period. Thus, it could be concluded that the formulation was stable. It was concluded that the tablets of batch F8 had considerable swelling behaviors and *in vitro* drug release. It was observed that tablets of batch F8 followed the Zero orderrelease profiles.

From the above results and discussion, it is concluded that the formulation of sustained release matrix tablet of

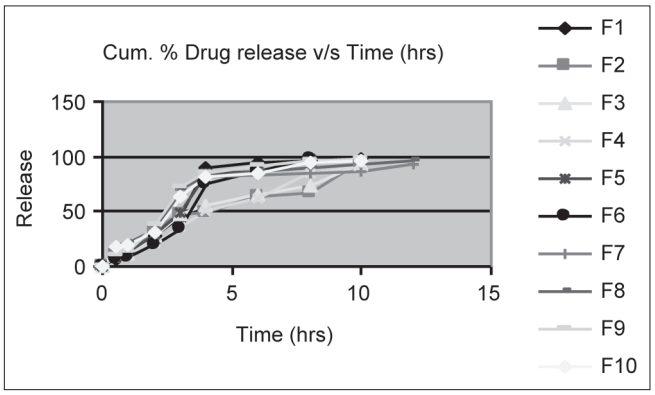

Figure 2: Plot of cumulative % drug released versus time for different formulations (F1-F10)

Table 4: Cumulative % release of drug of the various formulations

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
0.5	6.1	9.88	9.39	8.78	7.56	7.3	17.8	18.42	10.1	17.45
1	11.84	10.59	11.48	11.96	12.32	7.56	20.13	20.5	13.2	18.76
2	28.07	34.63	27.46	21.23	29.52	18.92	33.41	32.82	37.2	30.23
3	46.07	46.95	47.1	36.27	49.16	34.88	69.65	69.55	71.1	62.93
4	90.35	49.51	55.76	50.02	85.52	75.49	81.33	82.24	84.7	81.11
6	94.86	64.27	64.76	61.36	86.49	86.96	83.01	86.14	90.9	85.25
8	96.57	66.24	72.97	84.81	98.45	98.18	84.57	89.8	96	94.41
10	98.04	94.92	92.78	90.95			86.73	93.35	97.6	95.89
12							92.81	96.78		

Table 5: Kinetic values obtained from *in vitro* released data of different miglitol matrix tablets formulations

Formulation	Plot of log cum. % drug retained v/s time (first order plot)			Plot of cum. % release v/s time (zero order plot)		
	Slope	First order rate constant K= −slope×2.303	Regression coefficient	Slope	Rate constant K= −slope	Regression coefficient
F1	−0.218	0.5020	0.9078	11.984	−11.984	0.8086
F2	−0.1194	0.274	0.8207	9.2056	−9.2056	0.9434
F3	−0.1134	0.261	0.9166	9.5763	−9.5763	0.9571
F4	−0.1191	0.274	0.9486	10.273	−10.273	0.9739
F5	−0.2544	0.585	0.9028	14.997	−14.997	0.919
F6	−0.2459	0.566	0.8789	15.467	−15.467	0.9169
F7	−0.1016	0.233	0.8347	8.6611	−8.6611	0.752
F8	−0.1354	0.311	0.9334	9.457	−9.457	0.9973
F9	−0.197	0.453	0.9737	10.855	−10.855	0.8007
F10	−0.1663	0.382	0.9631	10.161	−10.161	0.8418

Table 6: Kinetic values obtained from *in vitro* released data of different miglitol matrix tablets formulation

Formulation	Plot of cum. % drug released v/s time in sq. root (Higuch matrix)		Plot of log cum. % drug released v/s log time (log T) (Peppas)		Plot of (% retained)$^{1/3}$ v/s time (Hixson-Crowell)	
	Slope	Regression coefficient	Slope	Regression coefficient	Slope	Regression coefficient
F1	52.09	0.8666	1.374	0.9303	−0.4343	0.8692
F2	39.073	0.9498	1.0634	0.9111	−0.2773	0.9035
F3	40.78	0.9699	1.1025	0.9418	−0.276	0.9655
F4	43.118	0.9587	1.1447	0.9656	−0.2941	0.9719
F5	57.992	0.9236	1.4035	0.954	−0.5165	0.9475
F6	58.667	0.8865	1.494	0.8972	−0.5125	0.9283
F7	38.569	0.8333	0.837	0.8687	−0.2531	0.8059
F8	41.688	0.8658	0.8557	0.8792	−0.3095	0.8899
F9	48.153	0.8805	1.1557	0.8901	−0.3975	0.9297
F10	44.304	0.8943	0.9074	0.8886	−0.3563	0.9374

miglitolcontaining HPMC K-15 (15%) and HPMC K-100 (15%), batch F8, can be taken as an ideal or optimized formulation of sustained release matrix tablets for 12-h release as it fulfills all the requirements for a sustained release matrix tablet.

CONCLUSION

Results of the present research work demonstrate that the combination of hydrophilic polymers was successfully employed for the formulation of miglitol controlled release tablets. It is observed that a combination of polymers produce a more linear release from matrix tablets with low standard deviation. HPMC and hydroxypropyl cellulose in the concentration of 40% to the total polymer concentration is a promising concentration for oral controlled release tablets of miglitol that can further give release above 12 h. In all the formulations, the 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.

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