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Development and Characterization of Miglitol As Immediate Release and Metformin HCL As Sustained Release Bilayered Tablets

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ABSTRACT

The purpose of this research work was to formulate an anti-diabetic in a single dosage form i.e. Metformin HCl in sustained release layer and Miglitol in immediate release layer of the bilayer tablet. The tablets were prepared using Hydroxypropyl methylcellulose (HPMC K4M & HPMC K15M, sodium alginate and xantham gum) an as release retarding polymers in various combination and concentrations. The effect of different super disintegrants on immediate release in various concentrations was also studied. Eight formulations of immediate release layer were prepared using SSG and CCS super disintegrants with different proportions and were evaluated for different parameters. Among the eight formulations M4 containing CCS as disintegrant showed a better release of 95.50±0.15% for 30 mins was selected. Using this MT4 formulation eight formulations of sustained release layer of Metformin. HCL was prepared with HPMC k15M polymer and evaluated. Among nine formulations of bilayered tablets MM4 was showed 98.66±0.65% at the end of 8 hrs. was selected as optimized formulation. This optimized formulation was evaluated for parameters like, thickness, hardness, friability, weight variation, drug content, in vitro drug release and stability and results were found to be with in USP limits.

Keywords: Bilayer Tablets, SSG, Croscarmellose sodium, Hydroxypropyl methylcellulose, Metformin, Miglitol, in vitro drug release studies.

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INTRODUCTION

The development of the sustained release drug delivery system is to release the drug in a sustained manner for longer period of time to avoid the side effects and adverse effects. The advantages of the sustained therapy involves the improvement of the patient acceptance criteria. To reduce the dosing frequency. To avoiding the dose dumping. To release the drug over longer period without any side effects [1]. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices [2]. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity. For the administration of fixed dose combinations of different APIs, prolong the drug product lifecycle, vocal mucoadhesive transmission systems, fabricates novel active ingredient transmission systems such as masticate device and floating tablets for gastro-retentive drug delivery[3]. Controlling the transmission rate of either single or two various active API'S. To release the drug in two forms the drugs are sandwiching each other in one layer in order to discharge the drugs in two forms. In order to accomplish swellable (or) erodible barriers for sustained release. The incompatible drugs are isolate from the each other to separate in compatible Active pharmaceutical ingredient (APIs) from each other, to regulate the discharge of active ingredient from one layer by promote the functional property of the other layer[4].

MATERIALS AND METHOD

Metformin and Miglitol were received gift samples from Hetero labs, Hyderabad. HPMC K15, HPMC K4M, Ethyl cellulose, Sodium starch Glycolate, Cross carmellose, Microcrystalline cellulose, Magnesium stearate, Talc and Yellow Iron oxide all the chemicals of Laboratory grade we obtained from A.R Chemicals, Hyderabad.

Method

Compatibility studies:[5]

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. So before producing the actual formulation, compatibility of Metformin and Miglitol with polymers and other excipients were tested using the Fourier Transform Infrared Spectroscopy(FT-IR).

FORMULATION DEVELOPMENT:

Preparation of bilayer tablets:

Preparation of Immediate Layer of Miglitol by Direct Compression Method

Weigh all the ingredients in required quantity. Transfer all ingredients into a mortar, triturate for 10minutes until to get fine powder and sieve the material. (#60). Then transfer the material into blender for proper distribution of drug in blend for 10minutes. Then addition of lubricant, mix well. Compression using tablet compression machine.

Table 1: Composition of Immediate Layer Containing Miglitol

S.No.	Ingredients	M1 (mg)	M2 (mg)	M3 (mg)	M4 (mg)	M5 (mg)	M6 (mg)	M7 (mg)	M8 (mg)
1	Miglitol	10	10	10	10	10	10	10	10
2	Sodium starch glycolate	4	6	8	-	-	-	2	-
3	Crosscaramellose sodium	-	-	-	4	6	8	-	2
4	Microcrystalline Cellulose	5	5	5	5	5	5	5	5
5	yellow iron oxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
6	Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
7	Magnesium stearate	5	3	1	5	3	1	7	7
	Total wt	25	25	25	25	25	25	25	25

Table 2: Composition of sustained Layer Containing Metformin

S.No.	Ingredients	MT1	MT2	MT3	MT4	MT5	MT6	MT7	MT8
1	Metformin	300	300	300	300	300	300	300	300
2	Methocel k4M	50	100	-	-	-	-	-	-
3	Methocel k15m	-	-	50	100	-	-	-	-
4	Sodium alginate	-	-	-	-	50	100	-	-
5	Xanthamgum	-	-	-	-	-	-	50	100
6	Microcrystalline Cellulose	148	98	148	98	148	98	148	98
7	Talc	2	2	2	2	2	2	2	2
	Total Wt	500	500	500	500	500	500	500	500

Formulation of bilayer tablets:

Optimized batch of Immediate Layer (F4) and different formulations of Bilayer tablets (MM1 to MM 8) used to formulate Bilayer tablets of Metformin. HCL and Miglitol. The powder Sustain layer granules were blended for 20 min. to obtain uniform distribution of the drug in formulation. 500 mg of the powder mix was accurately weighed and fed into the die of single punch tablet press and compressed at 1.5 N compression force using 10-mm concave punches. The Immediate layer mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 25 mg of the powder mix was accurately weighed and manually fed into the die on controlled release layer and compressed at a compression pressure of 3 N using 10-mmconcave punches.

Table 3: Formulation of sustained release layer with optimized Miglitol formulation

S.No.	Ingredients	MM1	MM2	MM 3	MM 4	MM 5	MM 6	MM 7	MM 8
1	Miglitol (mg)	10	10	10	10	10	10	10	10
2	Sodium starch glycolate	4	6	8	-	-	-	2	-
3	Crosscaramellose sodium	-	-	-	4	6	8	-	2
4	Microcrystalline Cellulose	5	5	5	5	5	5	5	5
5	yellow iron oxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
6	Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
7	Magnesium stearate	5	3	1	5	3	1	7	7
Total wt (mg)		25	25	25	25	25	25	25	25
8	Metformin	300	300	300	300	300	300	300	300
9	Methocel k4M	50	100	-	-	-	-	-	-
10	Methocel k15m	-	-	50	100	-	-	-	-
11	Sodium alginate	-	-	-	-	50	100	-	-
12	Xantham gum	-	-	-	-	-	-	50	100
13	Microcrystalline Cellulose	148	148	148	148	148	148	148	148
14	Talc	2	2	2	2	2	2	2	2

Evaluation of tablet:

Weight variation [6]

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness[6]

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness [7]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability [7]

Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

$$\% F = \{1-(Wo/W)\} \times 100$$

Drug Content Uniformity [8]

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg bilayered tablet. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask, to it 1 ml of 5% Ninhydrin solution was added and boil this solution for 3 min, cool it and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at Suitable wavelength using reagent blank.

***In- Vitro* Release study** [9]

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 7.4 for remaining period of time. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, to it add 1 ml of 5 % Ninhydrin solution and 1 ml of 0.1 N NaOH solution, boil for 3 min at water bath, cool it at room temperature and make the volume with distilled water. The diluted samples were assayed at Suitable wavelength.

Stability studies [10]

The success of an effective formulation can be evaluated only through stability studies. The prepared bilayered tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 90 days.

RESULTS AND DISCUSSION

Drug compatibility studies:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

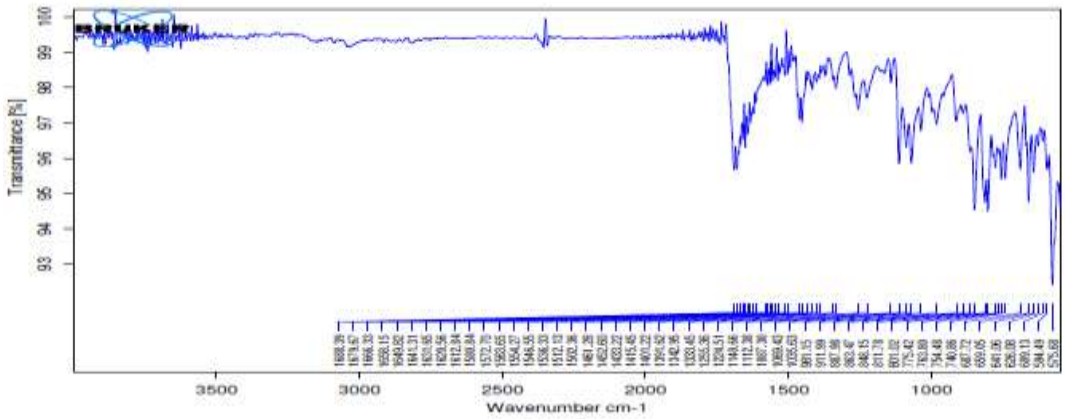

Figure 1: FTIR Studies of Pure drug of Miglitol

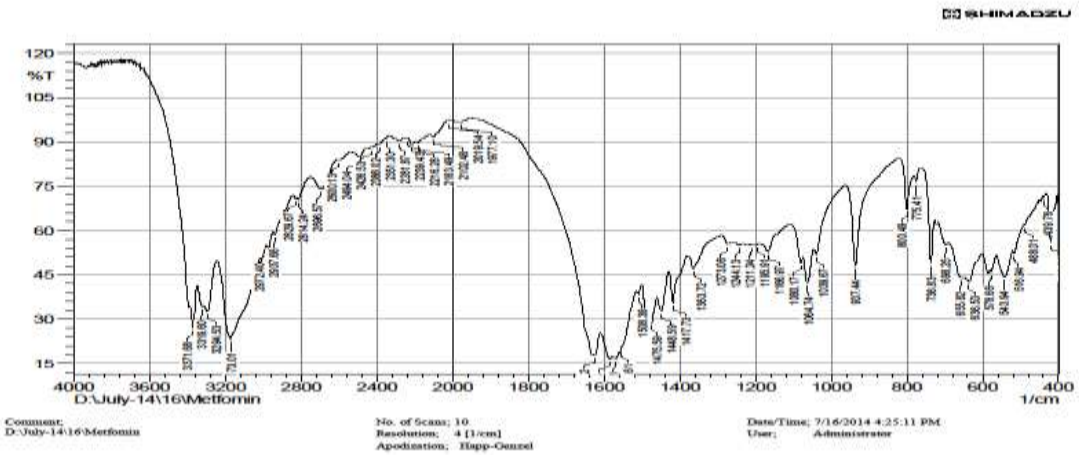

Figure 2: FT-IR graph for Metformin HCL Pure Drug

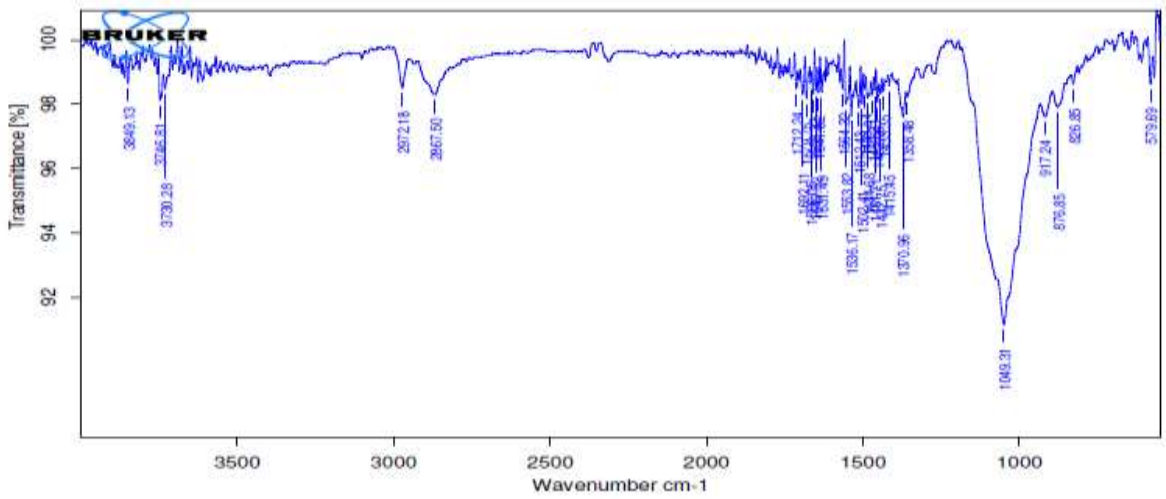

Figure 3: FT-IR Spectra of mixture of Miglitol, Metformin and all the excipients

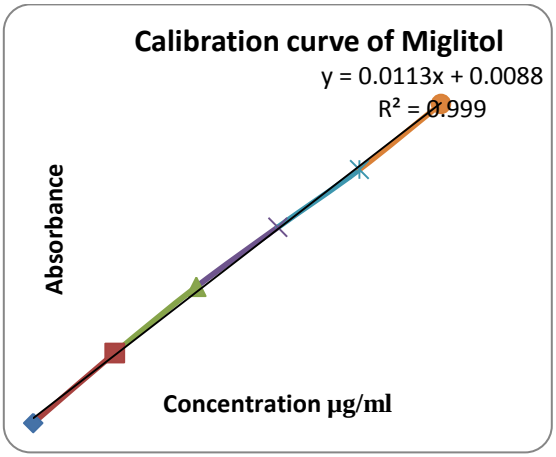

Figure 4: Calibration curve for Miglitol in 0.1N HCl (1.2 pH buffer)

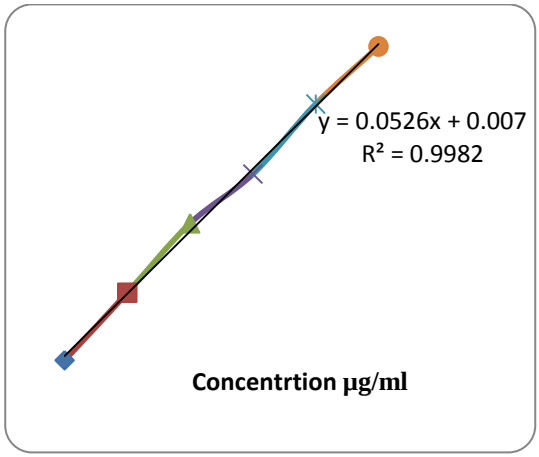

Figure 5: Standard graph of Metformin in 0.1N HCl (1.2 pH buffer):

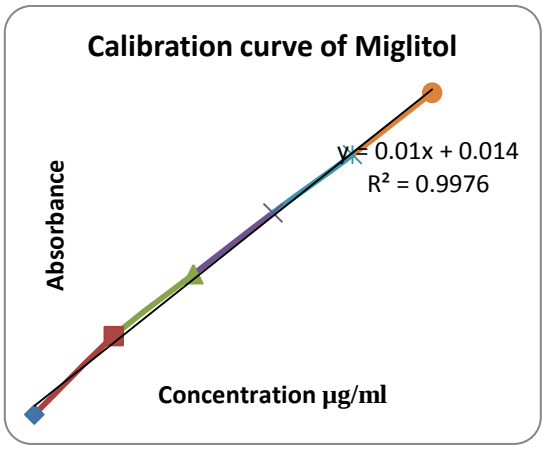

Figure 6: Calibration curve of Miglitol in 6.8 pH phosphate buffer

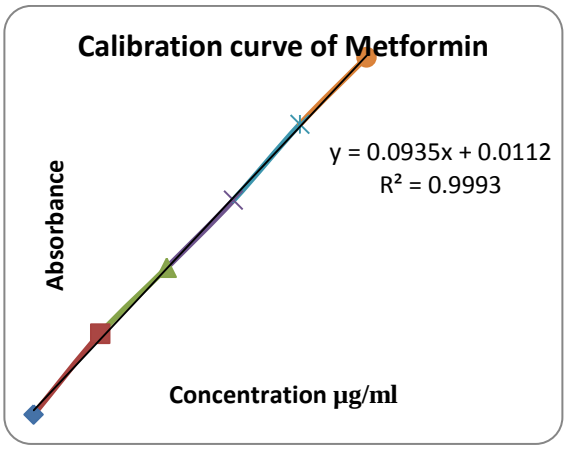

Figure 7: Calibration curve of Metformin in 6.8 pH phosphate buffer

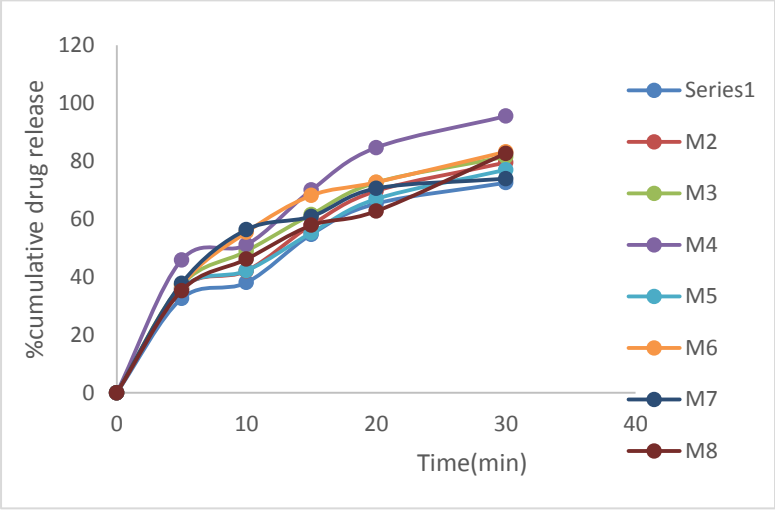

Figure 8: In-vitro dissolution profiles for Miglitol immediate layer

Table 4: In-vitro dissolution Profiles for Miglitol Immediate layer at 226 nm in 0.1N HCl

Time (Mins)	M1	M2	M3	M4	M5	M6	M7	M8
0	0	0	0	0	0	0	0	0
5	32.52±0.19	35.95±0.19	37.26±0.16	45.85±0.19	35.95±0.21	37.20±0.19	37.80±0.17	35.25±0.16
10	38.05±0.16	42.10±0.20	48.90±0.21	51.10±0.17	42.16±0.19	55.41±0.20	56.32±0.19	46.15±0.20
15	54.69±0.21	57.90±0.22	61.55±0.23	69.96±0.21	55.20±0.20	68.10±0.22	60.89±0.16	57.80±0.21
20	65.30±0.18	69.66±0.18	72.60±0.18	84.64±0.23	66.90±0.15	72.67±0.18	70.55±0.14	62.70±0.17
30	72.50±0.16	79.50±0.21	81.50±0.19	95.50±0.15	76.98±0.16	83.20±0.21	73.92±0.18	82.65±0.22

Table 5: Evaluation of post compression parameters for Bilayered tablets

Parameter	MM 1	MM 2	MM 3	MM 4	MM 5	MM 6	MM7	MM 8
Weight variation	525±0.20	525±0.31	550±0.28	525±0.27	550±0.25	525±0.30	550±0.29	525±0.28
Thickness (mm)	2.5±0.56	2.6±0.50	2.3±0.52	2.6±0.54	2.5±0.49	2.5±0.53	2.5±0.54	2.5±0.57
Hardness(kg/cm^2)	6.1±0.18	6.6±0.20	6.7±0.19	6.6±0.22	6.5±0.23	6.4±0.25	6.3±0.21	6.4±0.23
Friability (%)	0.15±0.15	0.18±0.18	0.15±0.17	0.18±0.16	0.15±0.19	0.18±0.14	0.15±0.13	0.16±0.16
Drug content	91.28±0.96	92.50±0.89	93.56±0.85	98.60±0.85	95.63±0.88	94.85±0.87	93.69±0.85	91.28±0.90

Table-6: In-vitro dissolution data of bilayer tablets

Time (Hrs)	MM1	MM 2	MM 3	MM 4	MM 5	MM 6	MM 7	MM 8
0	0	0	0	0	0	0	0	0
1	18.78±0.65	18.65±0.62	17.98±0.59	15.56±0.58	21.24±0.62	19.66±0.65	18.57±0.63	13.49±0.59
2	37.94±0.60	34.92±0.59	26.91±0.58	23.68±0.61	35.78±0.57	29.73±0.67	25.68±0.58	25.78±0.62
3	44.68±0.58	47.93±0.59	41.24±0.62	56.98±0.63	46.48±0.57	39.48±0.54	45.90±0.53	39.48±0.52
4	57.98±0.54	59.72±0.61	53.90±0.60	69.97±0.56	53.18±0.58	47.18±0.53	57.89±0.50	53.18±0.49
5	64.59±0.59	65.92±0.57	68.92±0.56	76.15±0.55	67.94±0.50	56.94±0.49	67.96±0.51	69.94±0.50
6	79.85±0.56	78.83±0.57	72.13±0.52	88.99±0.53	78.56±0.49	69.16±0.58	79.34±0.59	72.50±0.61
7	82.36±0.62	82.36±0.59	80.25±0.61	91.25±0.58	89.25±0.49	80.25±0.56	82.65±0.58	82.30±0.59
8	90.23±0.61	93.25±0.63	90.25±0.64	98.66±0.65	96.25±0.66	90.32±0.68	90.30±0.70	94.85±0.65

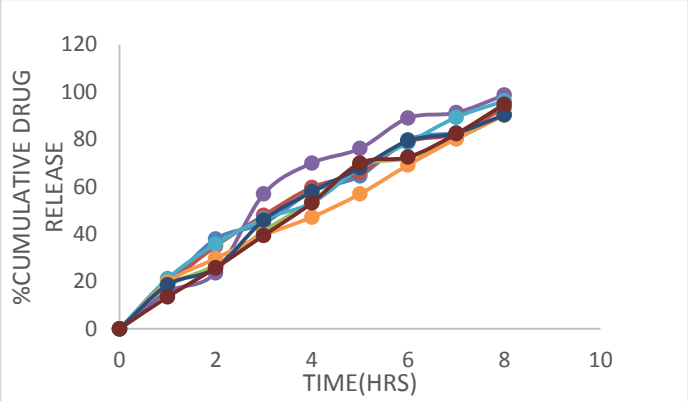

Figure 9: % Cumulative drug release graph of bilayered tablets of Metformin and Miglitol

All the Eight formulations of bilayered tablets were subjected to dissolution studies. Dissolution was carried out in USP type II apparatus at 50 rpm in the volume of 900ml dissolution media of 0.1NHCL for initial 2 hours then in 6.8 pH phosphate buffer for next 6 hours. Among all formulations, MM4 shows better drug release of (98.66±0.65 %) at the end of 8hrs, when compared with all other formulations. So formulation MM4 selected as optimized formula. In the dissolution studies the combination of HPMC k15 M polymer were showing better drug release up to 8 hrs.

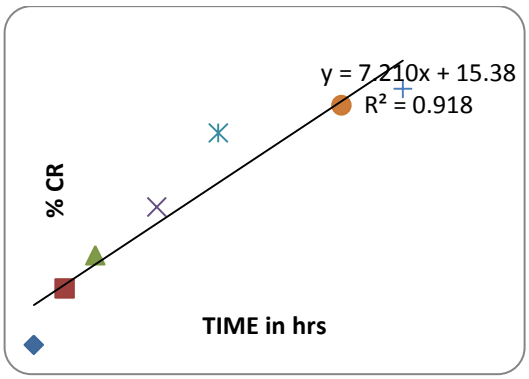

Figure 10: Zero order plot of optimized formulation

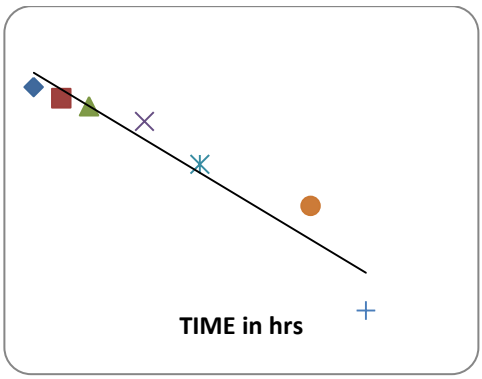

Figure 11: First order plot of optimized formulation

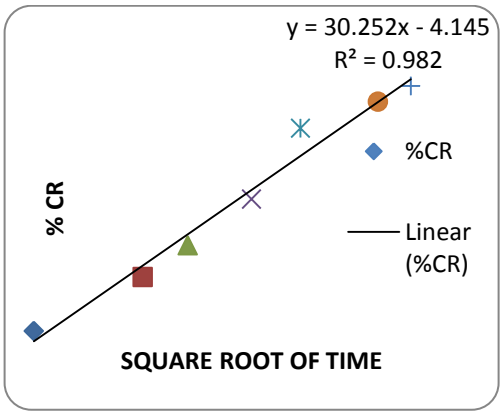

Figure 12: Higuchi plot of optimized formulation

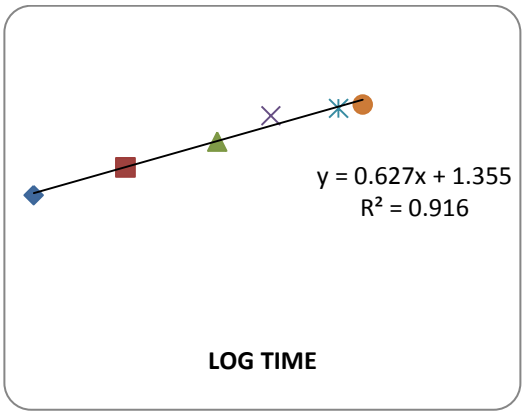

Figure 13: Kores Mayer Peppas plot of optimized formulation

The *in-vitro* drug release was fitted to the various kinetic models. The regression coefficient (R^2) value for zero order, first order, higuchi's and Peppas were plotted for formulation F6 and (R^2) was found to be 0.918, 0.915, 0.982, and 0.916 respectively. The drug release kinetics followed the zero order kinetics.

Table 7: Stability data of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug release ± SD Optimized formulation		
			25^0C/60%	**30^0C/75%**	**40^0C/75%**
1	01	No Change	98.66±0.65	98.66±0.65	98.66±0.65
2	30	No Change	98.64±0.58	98.62±0.61	98.54±0.60
3	60	No Change	98.61±0.54	98.61±0.55	98.59±0.61
4	90	No Change	98.59±0.60	98.59±0.58	98.54±0.62

There was no significant change in physical and chemical properties of the tablets of formulation MM4 after 3 Months, for parameters like % drug release and assay values at various conditions (at 40^0C/ 75% RH) was observed as per ICH guidelines .

CONCLUSION:

The prepared powders yielded the desired flow properties. The selected formulation complied with the pharmacopoeial standards. The release rate followed Zero order kinetics. The drug release was found to be dependent on the polymer employed in the preparation of sustained release layer. The formulation MM4 has shown higher R^2 value and better in-vitro dissolution release, hence it was considered as better formation. Thus, the major objectives of the investigation were fulfilled.

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