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Original Article

DEVELOPMENT AND EVALUATION OF BILAYER TABLETS FOR IMMEDIATE AND CONTROLLED RELEASE OF METFORMIN HYDROCHLORIDE

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ABSTRACT

Objective: The purpose of this study was to develop and evaluate bi-layer tablets for the immediate and controlled release of Metformin Hydrochloride for effective treatment of type 2 Diabetes mellitus.

Methods: The immediate release layer was prepared by using super disintegrants like cross carmellose sodium, sodium starch glycolate and sustained release layer was prepared by using hydrophilic polymer like HPMC K 100 and PVP. Various proportions of super disintegrants and polymer were used to select the best formulation composition. Bilayer tablet of metformin was prepared by wet granulation method and was evaluated for physical characteristics like hardness, weight variation, and friability. *In vitro* release of drug was performed in USP type II dissolution test apparatus using phosphate buffer (pH 6.8) as dissolution media and dissolution was continued for 9 h for the sustained release layer. For immediate release layer, readings were recorded in each 10 min time interval for the first 1h.

Results: From the obtained result it was found that all the formulations were within the limit of the standard. The hardness was found to be in the ranges from 5.1 to 5.5 kg/cm^2, weight variation was in the range 0.53% to 0.83%, friability of all the formulations was within the range (<1%)and percentage of drug content was more than 97%. The drug release of the tablet was in the range of 85%-91% in 9 h.

Conclusion: From the result obtained, it is found that the formulation F6 satisfies all the criteria as sustained release tablet for the effective treatment of type 2Diabetes mellitus.

Keywords: Bilayer tablet, Metformin Hydrochloride, Type II diabetes mellitus, super disintegrants, Hydrophilic polymers, Wet granulation

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INTRODUCTION

Bilayer 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 layer as initial dose and the second layer as a maintenance dose. Bi-layer tablets are prepared with one layer of the drug for immediate release when maximum relief needs to be achieved quickly with second layer design to release drug later as the second dose or in an extended release or for both immediate releases. It also avoids repeated administration of drug [1].

Diabetes is one of the most prevailing and advancing diseases in the world have affected 6.6% of the world population. Metformin hydrochloride is the most widely used oral Anti Diabetic drug in the world. Metformin shows high aqueous solubility and low cell membrane permeability. The usual dosage for Metformin is 250–500 mg 3-4 times daily, up to a maximal of 2.5 g/day. The absolute bioavailability of Metformin hydrochloride is 50–60% and is having a short biological half-life of 6.2 h. The use of Metformin therapy has the high incidence of gastrointestinal side effects. Frequent dosing schedule leading to high GI side effects and high daily dose makes its use unsuccessful, thus it is reasonable to formulate sustained release Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects, thus improving the patient compliance [2, 3]. In the present study, immediate release and sustained release bi-layer tablet (homogeneous type) of Metformin Hydrochloride were formulated to achieve better therapeutic profile by using sodium starch glycolate, cross carmellose sodium as a super disintegrant and HPMC K100, PVP as the hydrophilic polymer.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was purchased from Yarrow Chem Product, Mumbai and dicalcium phosphate, microcrystalline cellulose, xanthum gum, sodium starch glycolate, cross carmellose sodium, HPMC K 100, PVP, magnesium stearate, talc, eosin yellow, amaranth blue, potassium dihydrogen phosphate, sodium hydroxide were obtained from college laboratory at Girijananda Chowdhury Institute of Pharmaceutical Science.

Methods

The bilayer tablets of for immediate and controlled release of Metformin Hydrochloride were developed in two stages. Blends of the immediate release layer and sustained release layer of Metformin Hydrochloride were prepared separately.

Preparation of immediate release layer

For immediate release layer drug (125 mg), super disintegrants, diluents were weighed according to the formula and transferred to mortar and pestle and mixed thoroughly. Then in a beaker 10 ml of water was taken and mixed with a binder (xanthum gum), which was used as a granulating liquid. Then the solution was added to the mixture, kneaded to form a wet mass. The wet mass was passed through sieve no. 20; wet granules were allowed to dry at 50 °C, then again passed through sieve no. 40 to form dry granules. To the coarse, 5% fine, lubricants (magnesium stearate), glidants (talc) were added [4].

Preparation of sustained release layer

For sustained release layer drug (375 mg), a hydrophilic polymer (HPMC K 100, PVP), diluents were weighed according to the formula and transferred to mortar and pestle and mixed thoroughly and wet granulation technique was followed as same as immediate release tablet. Here, in granulating liquid colour was also added. Finally, lubricants and talc are added to the granules and blended. The lubricated granules are manually fed into the die over the immediate release layer [4].

Evaluation of the granules

Preformulation

Preformulation studies were conducted for drug Metformin Hydrochloride. Preformulation characteristics like organoleptic properties, solubility, the melting point were determined [5].

Table 1: Formulation table of immediate release layer

S. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Metformin hydrochloride	125	125	125	125	125	125
2	Sodium Starch Glycolate	20 (10%)	20 (10%)	20 (10%)	10 (5%)	20 (10%)	20 (10%)
3	Cross Carmellose Sodium	-	-	-	10 (5%)	20 (10%)	-
4	Xanthum Gum	12	12	12	12	12	12
5	Dicalcium Phosphate	17.5	17.5	17.5	17.5	8	17.5
6	Microcrystalline Cellulose	17.5	17.5	17.5	17.5	7	17.5
7	Talc	4	4	4	4	4	4
8	Magnesium Stearate	4	4	4	4	4	4
9	Total weight	200	200	200	200	200	200

Table 2: Formulation table of sustained release layer

S. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Metformin hydrochloride	375	375	375	375	375	375
2	HPMC K100	25 (5%)	50 (10%)	25 (5%)	25 (5%)	25 (5%)	50 (10%)
3	PVP	-	-	25 (5%)	25 (5%)	25 (5%)	50 (10%)
4	Xanthum Gum	30	30	30	30	30	30
5	Dicalcium Phosphate	25	12.5	12.5	12.5	12.5	-
6	Microcrystalline Cellulose	25	12.5	12.5	12.5	12.5	-
7	Talc	10	10	10	10	10	10
8	Magnesium Stearate	10	10	10	10	10	10
9	Eosin Yellow	q. s	q. s	q. s	q. s	q. s	q. s
10	Amaranth Blue	q. s	q. s	q. s	q. s	q. s	q. s
11	Total weight	500	500	500	500	500	525

Pre compression characteristics

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, Carr's index and Hausner's ratio [6].

Post compression parameters

Weight variation test

20 tablets were selected randomly from each batch, their weight was individual, collectively and the average weight was determined. The individual weight of the tablets was then compared to the average weight. The test requirements are met if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10% [6].

Friability

The friability of tablets was determined using Roche fribilator to measure the mechanical strength of tablets. It is expressed in percentage (%). 10 tablets from each batch were weighed separately (W initial) and placed in the fribilator. The fribilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablet was reweighed (Wfinal) and the % friability (F) was then calculated for each batch by using the formula [6].

$$F= [\{(Winitial)–(Wfinal)\}/(Winitial)] * 100$$

Hardness

Five tablets were randomly picked and hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2.

Dissolution studies

Drug release studies were done in phosphate buffer pH 6.8 as dissolution media by using USP type II dissolution apparatus (paddle type). The assembly is kept in a jacket vessel of water maintained at 37±0.5 °C and 50 rpm speed. The dissolution studied was carried out for 9 h. For immediate release layer, 10 ml of samples were collected at 10 min time interval for the first 1h and for the sustained release layer, 10 ml of samples were collected at 1 h time interval for rest 8hs and then filtered. It was replaced immediately with an equal amount of fresh buffer. The samples were then analyzed spectrophotometrically after suitable dilution at a wavelength of 230 nm, taking phosphate buffer as blank [6].

Drug content

10 tablets of each formulation were powdered. Powder equivalent to 500 mg of Metformin hydrochloride was weighed and transferred to 100 ml volumetric flask, initially about 50 ml of phosphate buffer 6.8 was added and the flask was shaken thoroughly and the volume was made up to 100 ml with the buffer solution. The resulting solution was filtered. From this 1 ml was taken and diluted to 100 ml with buffer solution. From this 10 ml was taken and diluted to 10 ml. From the resulting solution, drug content was estimated at 230 nm using UV spectrophotometer taking phosphate buffer as blank [6].

Release kinetic

The dissolution data obtained were fitted to various kinetic models like Zero order, First order, Higuchi, Korsemeyer Peppas to determine the release mechanism of prepared tablets [7].

Drug excipient compatibility

Studies of drug excipient compatibility represent an important phase in the pre-formulation stage of new dosage form development as it is most desirable for consistent efficacy, safety, and stability of drug product. The successful formulation of solid dosage form depends on careful selection of excipients which are added to facilitate administration, to promote consistent release and bioavailability of drug and protect it from degradation. Bruker FT-IR and Perkin Elmer DSC was used for thermal analysis of pure drug, excipients and formulations.

RESULTS AND DISCUSSION

Pre-compression parameters

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, Carr's index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules are shown in table 3 and table 4. The bulk density and tapped density of granules of both the layer were found to be in the range of 0.334 to 0.590 gm/ml and 0.423 to 0.702 gm/ml. The angle of repose varied from 23.32 to 38.3 which indicate good flow properties of the powder. While Compressibility index and Hausner's ratio were found in the range of 16.5 to 21.8 and 1.17 to 1.29 respectively. These values indicate that the powder mixture of all batches of formulation exhibited good flow properties.

Post compression parameters

The results of physical evaluation of tablets are given in table 5. The tablets of different batches were found uniform with respect to a hardness within the range of 5.1 to 5.5 kg/cm^2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also found within the limit. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is±5% and all the formulations were found to comply with the specifications given in I. P. for weight variation test. Weight variation of all tablets was found to be in the range of 0.53% to 0.83%. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 97%.

Dissolution studies

***In vitro* drug dissolution study of immediate release layer**

The *in vitro* drug release data is shown in table 6. The formulations F1-F3 and F6 having a composition of 10% Sodium starch glycolate showed 24% drug release. Formulation F4 showed 26.63% (131 mg) drug release and Formulation F5 showed maximum drug release, showing up to 28% (140 mg) of the total drug in first one h. This may be due to the presence of 10% Sodium starch glycolate and 10%Cross carmellose sodium as a super disintegrant in F5. All the batches disintegrate within first one h.

***In vitro* drug dissolution study of sustained release layer**

For the sustained release layer of Metformin hydrochloride, the dissolution was carried up to 9 h. The results showed that as the concentration of polymer increases the drug release is more controlled. F1 (5%HPMC) and F2 (10% HPMC) required 8hr to release 91% and 88% of its total drug respectively. F3, F4 and F5 (5%HPMC and 5%PVP) required 9 h for 87 % drug release. And F6 (10%HPMC and 10%PVP) required 9 h to release 85% of its total drug from the tablet. The result of *in vitro* dissolution study showed that drug from all the batches was released in a controlled way.

Kinetics and mechanism of release analysis

After fitting into a different model, it was observed that all the formulations follow the First order and Higuchi release kinetics. And from the "n" value of Krosemeyer Peppas of prepared formulations, shown in table 7 which was found to be in the range of 0.63 to 0.77 indicating erosion and diffusion controlled the release of the drug.

Table 3: Precompression evaluation of immediate release granules

Formulation	Bulk density (kg/m^3)	Tapped density (kg/m^3)	Angle of repose(θ °)	Carr's index (%)	Hausner's Ratio
F1 (10%SSG)	0.402	0.482	38.3	16.5	1.20
F4 (5% SSG+5%CCS)	0.478	0.578	26.71	16.53	1.27
F5 (10% SSG+10% CCS)	0.590	0.702	23.32	15.69	1.17

Table 4: Precompression evaluation of sustained release granules

Formulation	Bulk density (kg/m^3)	Tapped density (kg/m^3)	Angle of repose(θ °)	Carr's index (%)	Hausner's Ratio
F1 (5% HPMC)	0.472	0.604	26.42	21.8	1.28
F2 (10% HPMC)	0.487	0.584	28.2	16.61	1.19
F3 (5% HPMC+5% PVP)	0.449	0.579	36.87	22.4	1.29
F6 (10% HPMC+10% PVP)	0.33 4	0.42 3	25. 17	20.80	1.25

Table 5: Postcompression evaluation of tablets

Formulation code	Hardness (kg/cm^{-2})	Friability (%)	Weight variation %	Drug content %
F1	5.4	0.25	0.83	97.971
F2	5.2	0.39	0.69	99.628
F3	5.1	0.42	0.53	99.915
F4	5.5	0.75	0.63	99.239
F5	5.3	0.26	0.69	97.920
F6	5.3	0.58	0.68	99.526

Table 6: *In vitro* drug release data

Time (min)	F1	F2	F3	F4	F5	F6
10	11.572	12.185	11.887	15.759	14.059	11.035
20	15.255	16.657	15.255	18.468	16.323	16.637
30	20.918	18.788	20.918	21.067	18.149	19.107
40	21.536	20.598	21.536	21.259	22.960	20.960
50	23.089	22.450	23.089	24.389	25.663	22.706
60	25.368	24.112	25.537	26.262	28.667	24.794
120	32.054	28.501	32.631	30.501	33.841	27.435
180	42.405	38.002	38.842	38.002	37.121	32.247
240	52.482	48.823	47.857	45.033	46.766	40.926
300	68.588	64.127	59.900	57.315	56.946	54.031
360	76.197	75.183	70.932	68.364	66.427	65.376
420	85.218	82.885	76.453	77.357	74.953	72.698
480	91.711	88.558	85.849	84.378	82.849	80.571
540			88.409	87.378	89.849	85.281

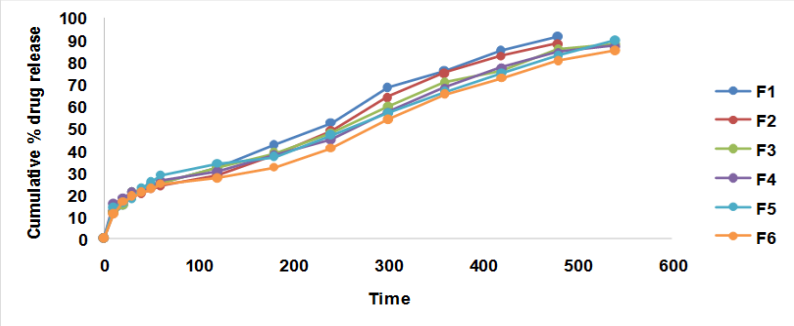

Fig. 1: Drug release study for bilayer metformin hydrochloride tablets in phosphate buffer pH 6.8

Table 7: Release kinetics parameter

Model	Parameter	F1	F2	F3	F4	F5	F6
Zero Order	R^2	0.9519	0.9626	0.8860	0.8952	0.8836	0.9215
	K_o	0.209	0.201	0.177	0.174	0.173	0.165
First Order	R^2	0.9671	0.9623	0.9735	0.9654	0.9592	0.9584
	K_1	0.004	0.003	0.003	0.003	0.003	0.003
Higuchi	R^2	0.9507	0.9354	0.9641	0.9543	0.9637	0.9345
	KH	3.851	3.689	3.556	3.482	3.483	3.290
Hixson Croswel	R^2	0.9821	0.9789	0.9783	0.9723	0.9626	0.9690
	KHC	0.001	0.001	0.001	0.001	0.001	0.001
Korsemayer Peppas	R^2	0.9920	0.9890	0.9840	0.9788	0.9817	0.9744
	n	0.730	0.772	0.638	0.658	0.633	0.713
	KKP	1.024	0.766	1.575	1.374	1.590	0.935

Fig. 2: Plot showing zero order kinetics of F1-F6

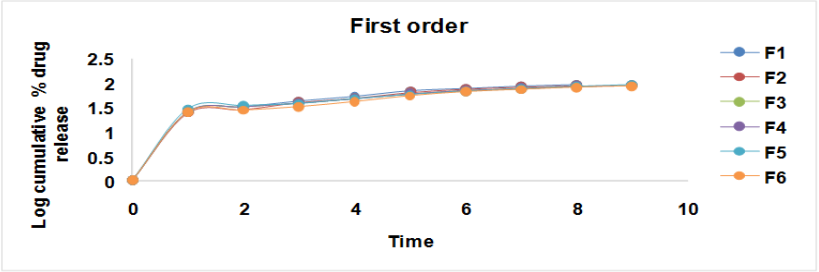

Fig. 3: Plot showing first order kinetic model of F1-F6

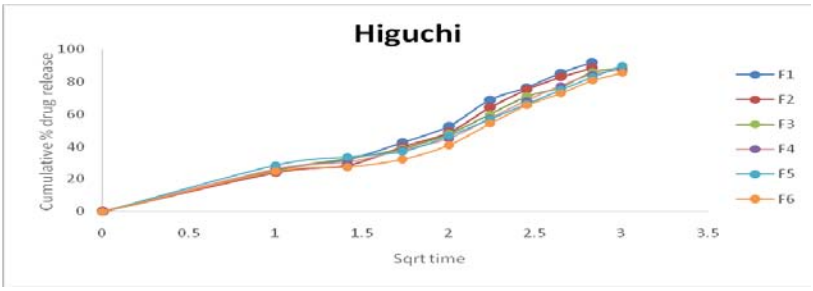

Fig. 4: Plot showing higuchi model of F1-F6

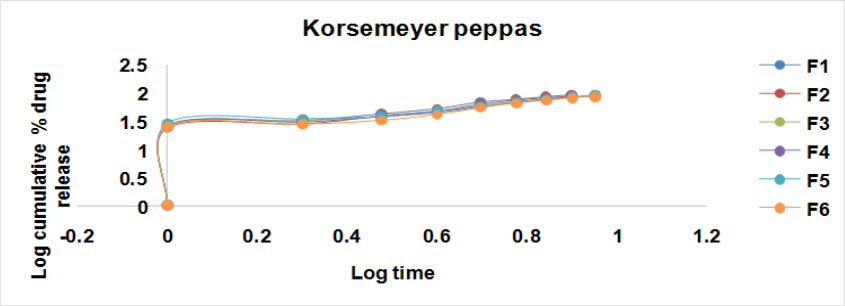

Fig. 5: Plot showing Korsmeyer-peppas model of F1-F6

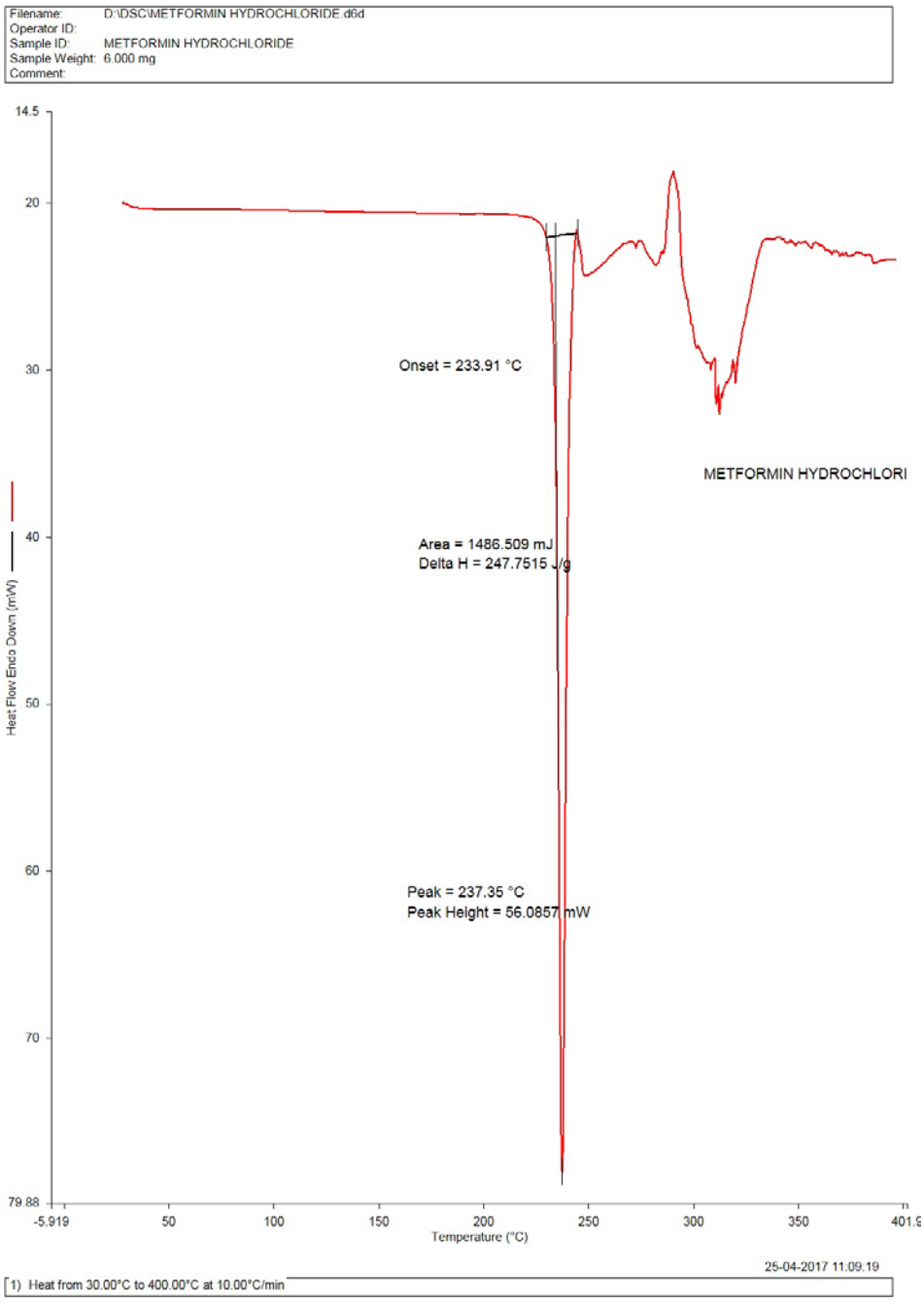

Fig. 6: DSC thermo gram of metformin hydrochloride

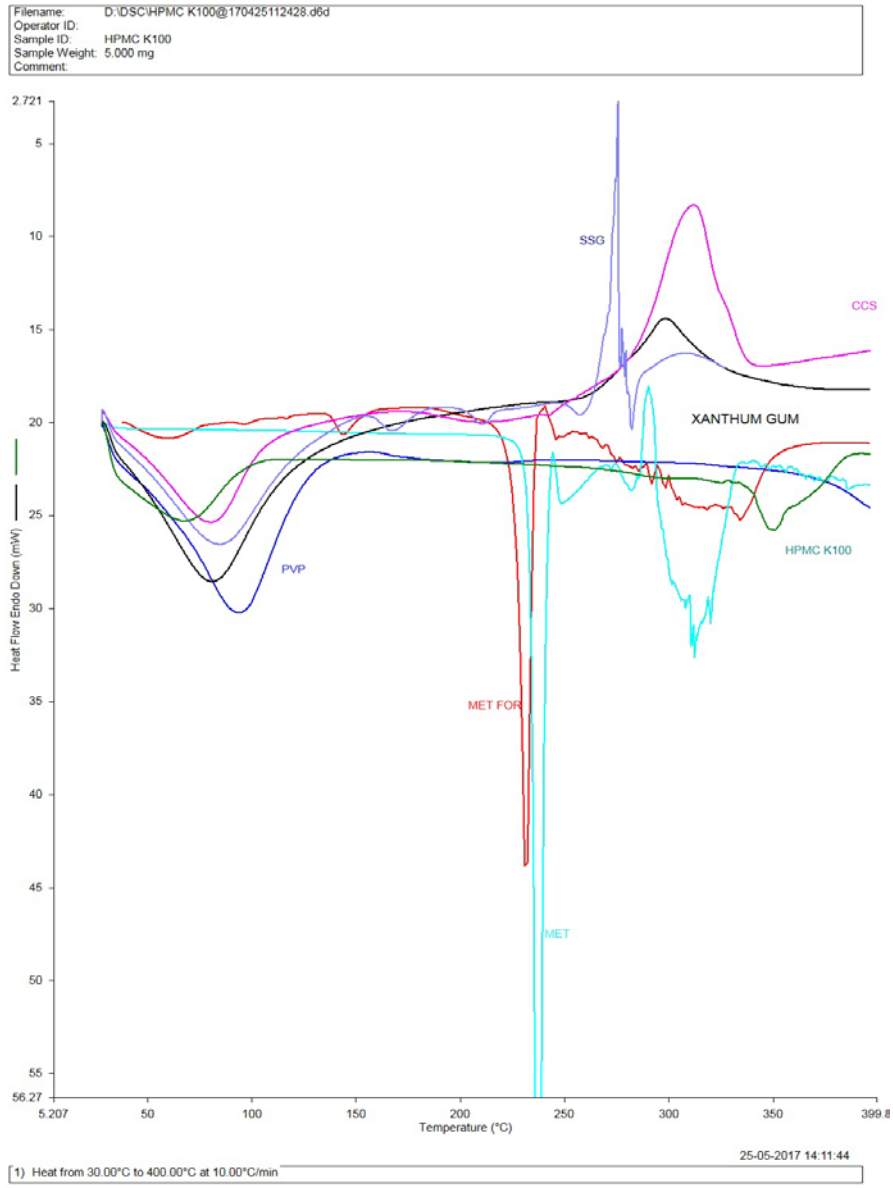

Fig. 7: DSC thermogram of Overlap (SSG-Sodium starch glycolate, CCS-Cross carmellose sodium, MET-metformin hydrochloride, MET FOR-metformin hydrochloride formulation)

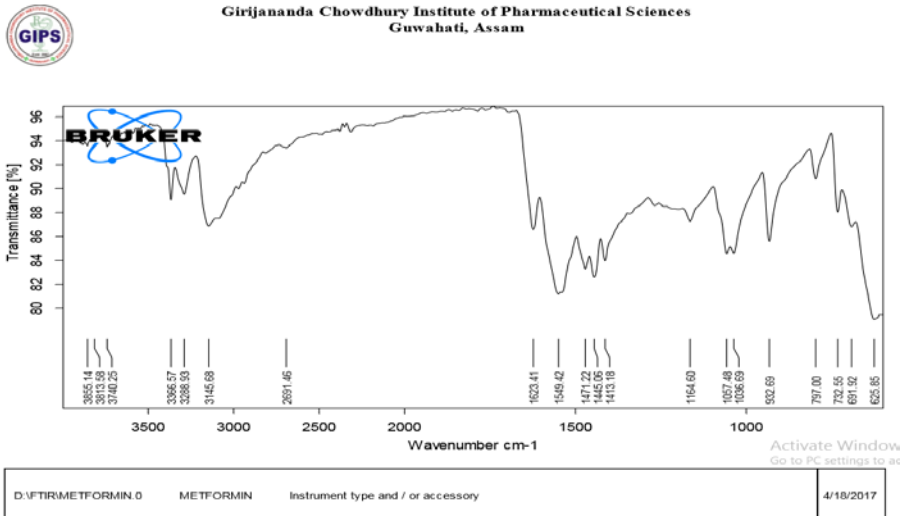

Fig. 8: IR spectrum of metformin hydrochloride

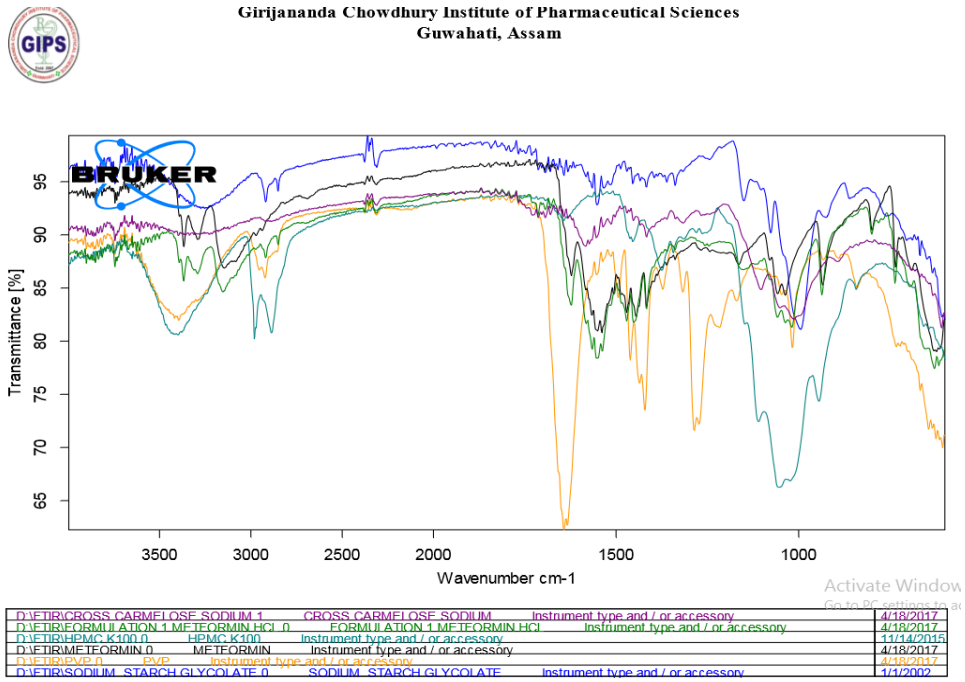

Fig. 9: IR spectrum of overlap

CONCLUSION

The present work involved formulation of bilayer tablets for the immediate and controlled release of Metformin hydrochloride using sodium starch glycolate and cross carmellose sodium as super disintegrant and HPMC K100, PVP as a retardant polymer.

The pre compression parameters and post compression parameters were obtained for all the formulations and were found to be within the acceptable limits. The drug-excipient compatibility studies confirmed that the both drugs are compatible with selected disintegrants sodium starch glycolate, cross carmellose sodium and polymer HPMC K100, PVP.

The drug release study from Metformin hydrochloride sustained release layer showed that as the concentration of the polymer increase the drug release decreases. The release of drug in the first h varies between 24% to 28% of total drug and the second layer drug release varies 85% to 91% of total drug contained in a controlled manner for 9 h. The results reveal that with increase concentration of HPMC K100 and PVP retardation of drug release takes place. From the kinetic study, the drug release from drug layer follows the First order and Higuchi model. The “n” values of Korsemeyer Peppas of the prepared formulation were found to in the range of 0.63 to 0.77 indicating erosion and diffusion controlled the release of the drug.

The drug release study tablet showed desired release profile for both layers. The first layer shows sufficient drug release within one h and the second layered showed controlled drug release for 9 h. Hence the formulated Bilayer tablet can be used for effective and prolong management of Blood glucose level and it use for the treatment of Diabetes Mellitus 2. The study also reveals that sodium starch glycolate and cross carmellose sodium can be effectively used for the formulation of immediate release tablets and HPMC K100, PVP can be used as effective polymers for controlled release of the drug.

CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Dandare MS, Sarage RD, Bhaskara S. Bilayer tablet: A Novel Approach for Immediate Release of Telmisartan and Hydrochlorothiazide Combination; 2012;4:3970-83.
2. Brito SR. Design and evaluation of sustained release bilayer tablet of metformin hydrochloride with metoprolol tartrate. Int J Novel Trends Pharm Sci 2011;1:10-7.
3. Rendle RD, Rutledge F, Hughes KJ, Heller J, Durham AE. Effects of metformin hydrochloride on blood glucose and insulin responses to oral dextrose in horses. Equine Veterinary J 2013;45:751-4.
4. Chandira RM, Arafath AAMY, Bhowmik D, Jayakar B, Kumar KPS. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. Pharma Innovation 2012;1:26-39.
5. Shah RB, Tawakkul AK, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. Am Assoc Pharm Sci PharmSciTech 2008;9:250-8.
6. Hadi MA, Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on a combination of hydrophilic and hydrophobic polymers. J Appl Pharm Sci 2012;2:101-7.
7. Shoaib MH. Evaluation of drug release kinetics from ibuprofen matrix tablets. Pakistan J Pharm Sci 2006;19:119-24.

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