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FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE AND PIOGLITAZONE BILAYERED TABLETS USING NATURAL GUMS

K. Madhuri*[1], M. Prathap[1], A. M. S. Sudhakar babu[1], P. Venkateswararao[2], R. Sasidhar[3]

[1*]Department of Pharmaceutics, A. M. Reddy Memorial College of Pharmacy, Narasaraopet Guntur, Andhra Pradesh, India.

[2]Department of Pharmaceutical Chemistry, A. M. Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India.

[3]Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Duvvada Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Hyperglycemia is the technical term for high blood glucose (sugar). It happens when the body has too little or not enough insulin or when the body can‘t use insulin properly. The main objective of the present research work was to develop a bilayer tablet of immediate release Pioglitazone and controlled release Metformin Hydrochloride, which is used as an Anti-hyperglycemic agent. Metformin Hydrochloride has biological half-life nearly about 6 hours, so, an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. In controlled release layer natural gums like xanthum gum, gum tragacanth and guar gum were used as retarding materials and in immediate release layer croscarmellose sodium was used as a superdisintegrent to give the faster release of Pioglitazone. The tablets were prepared by wet granulation method and by direct compression. Granules were evaluated for precompression parameters and the tablets were evaluated for post compression parameters.

KEY WORDS

Bilayer tablets, Metformin Hydrochloride, Pioglitazone, Gum tragacanth and Crosscarmellose sodium.

Author for Correspondence:
K. Madhuri,
Department of Pharmaceutics,
A. M. Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India.
Email: kollu.madhuri7@gmail.com

INTRODUCTION[1]

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form. Ideally a drug to provide desired therapeutic action should arrive rapidly at the

site of action in optimum concentration, remain there for the desire time, be excluded from other site. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research. Once a day or at the most twice a day formulation is of most precious sorts for scientists working with oral dosage forms. A sustained release preparation that makes once or twice daily administration of drug possible might be an advantageous dosage form, especially in long-term therapy. This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream.

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. With advancement in technology and increase in awareness, towards modification in standard tablet is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient‘s perspective and utilize an approach that is unlikely to add complexity during regulatory approval process.

Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is controlled release part of single or multiple actives. They are also called as bilayer tablet, multi-layer matrix tablet.[2]

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site (s) of action is attainted immediately and is then maintained constant for the desired duration of the treatment[3]. Over the past 30 years as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantage of modified release per oral dosage forms, greater attention has been focused on development of sustained, controlled release and delayed release system. There are several reasons for the attractiveness of this dosage form. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting.

MATERIAL AND METHODS

Material

Pioglitazone hydrochloride and Metformin Hcl was obtained as a gift sample from Granules India ltd. Crosscarmellose sodium, Pvp-k30, Xanthum gum, Guar gum, Gum tragacanth, Micro crystalline cellulose, Lactose, Magnesium stearate, Talc and Sunset yellow were obtained from Yarrow Chem. Products, Mumbai. All the ingredients used were of analytical grade.

Methods

Formulation of bilayer tablet

Layer I –Metformin hydrochloride CR granulation

Metformin Hydrochloride, Xanthum gum/Guar gum/Gum tragacanth were sifted through 40 mesh sieve (stage 1). Then Povidone (K-30) was dissolved in purified water. The materials of stage 1 were loaded into the rapid mixer granulator and mixed for 15 Minutes at low speed. Granules were prepared by adding binder solution to powder mixture. The produced Metformin hydrochloride granules were dried in fluidized bed dryer at 500^{o}C till the loss on drying of 1.5-2.0% is achieved. Dried granules were passed through 20 mesh sieve. Sifted granules were

transferred to double cone blender. Colloidal Silicon dioxide was sifted through 40 mesh sieve and added to above step. Magnesium stearate and Talc were sifted through 60 mesh sieves and added to above step and mixed for 2 minutes.

Layer II– Pioglitazone IR (direct compression)

Pioglitazone was sifted through 30 mesh sieve. Lactose DCL 15, Microcrystalline cellulose, CCS, were sifted through 40 mesh sieve, sunset yellow lake was sifted through 100 meshes. Mix Pioglitazone with Lactose DCL 15 and Microcrystalline cellulose in geometrical mixing method. Then talc was sifted through 40 # mesh and added and mixed for 5 mins. Magnesium stearate was sifted through 60 mesh sieve and mix with above step for 2 minutes at fast speed.

EVALUATION PARAMETERS

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMENMB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

PH of the solution

The pH studies were done for both Metformin Hydrochloride and Pioglitazone by dissolving them in their suitable solvents and determining the pH with the help of pH potentiometer.

Pre-compression studies of granules

Angle of repose

The angle of repose was determined by the funnel method (Repos gram). The accurately weighed drug or tablet blend was taken in a funnel. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\tan \theta = h / r$$

Where h = height of the pile.

r = radius of the pile.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined by passed through a #18 sieve to break the clumps, if any. Accurately weighed 50 g of the drug was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 $\pm$ 2 mm. The tapped volume (V_a) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tap volume was measured to the nearest graduated unit. The same thing was done for powder blend of the tablet. The LBD and TBD were calculated in g per ml using following formulae,

$$\text{Bulk density} = M / V_0$$

Where M = Mass of the sample.

V_0 = Bulk volume of the powder.

Tapped density (Td)

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. The cylinder was placed in the tapped density apparatus and allowed to fall under its own weight on to a hard surface (USP-II), that provides fixed a drop of 3mm(±10%) at a nominal rate of 250 drops per minute is used. Tapping was continued until no further change in volume was noted. Td was calculated using the following equation;

$$D_t = m / V_i$$

Where, m = Mass of the powder.

V_i = Tapped Volume of the powder.

Compressibility index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30 % is defined as the free flowing material.

$$C_I = (1-V_i/V_0) \times 100$$

Where V_i = Tapped Volume of the powder.

V_0 = Bulk volume

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausners ratio = D_t/D_b

Where, Dt = the tapped density,

Db = the bulk density.

Post compression studies of bilayer tablet

Physical appearance

The general appearance of tablets its visual identity and over all elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color presence or absence of odour, taste, surface texture and consistency of any identification marks.

Tablet size and thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter .Tablet thickness should be controlled within a + or -5%. In addition thickness must be controlled to facilitate packaging.

Average weight of tablets

Take randomly 20 tablets and weigh accurately 20 tablets and calculate the average weight.

Average weight =weight of 20 tablets/20

Hardness test

This is the force required to break a tablet in diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel fractures the tablet. Hardness of 5 kg considered as suitable for handling the tablet.

Weight variation test

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets of Average weight was calculated.

$$\% \text{ Deviation} = \frac{\text{(Individual weight – average weight)}}{\text{Average weight}} \times 100$$

Friability test (As per USP)

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. After 100 rotations (4 minutes), the tablets were taken out from the friabilator. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = Weight of the tablet before test.

W_2 = Weight of the tablets after test.

Drug content uniformity

The tablets were assayed for the drug content using methanol as the extracting solvent. Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml methanol. The solution was diluted appropriately using pH 6.8 phosphate buffer and Metformin Hcl was estimated spectrophotometrically at 232 nm using pH 6.8 phosphate buffer as blank.

The same procedure should be done for Pioglitazone using 0.1N Hcl at 270nm

Content of active ingredients (assay)

The amount of active ingredient(s) was determined and compared with standards stated in the monograph. Twenty tablets were used for assay. All the batches should fall within the limit of 95–105 %.

***In vitro* dissolution studies**

In vitro release of the drug[5] was determined by estimating the dissolution profile. Dissolution test for Pioglitazone and Metformin Hcl. *In vitro* drug release study was carried out using USP apparatus II at 37ºC ± 0.5ºC, at 100rpm. 0.1N Hcl (pH 1.2) was used as dissolution medium for the first hr followed by pH 6.8 phosphate buffer for further 12hrs. 5 ml of sample was withdrawn after every hour and was replaced with an equal volume of fresh dissolution medium to maintain the equilibrium. Collected samples are analyzed by UV spectrophotometer at 270nm and 232nm respectively for Pioglitazone and Metformin Hcl.

Data Analysis (Curve Fitting Analysis)

To analyze the mechanism of the drug release rate kinetics of the dosage form, the Data obtained were plotted as:

1. Cumulative percentage drug released Vs time (Zero order plots)
2. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3. Log cumulative percentage drug remaining Vs time (First order plots)
4. Log cumulative percentage drug release (Peppas plots).

Stability studies

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists deterioration. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

RESLTS AND DISCUSSION

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Pioglitazone and Metformin Hcl were found to be unaltered in the spectra of the drug-polymer physical mixture (Figure No.1 and 2).

Pre-compression Studies

All the formulations (granules) prepared by both the methods showed the angle of repose less than 30ºC, which reveals good flow property (Table No.3). The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.40 gm/cm^3 to 0.782 gm/cm^3 and 0.51 gm/cm^3 to 0.869 gm/cm^3 respectively (Table No.3). The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 11.0 to 17.9%.

Post-compression Studies

The mean thickness was almost uniform in all the formulations and values ranged from 6.2 mm to 6.84 mm. The standard deviation values indicated that all the formulations were within the range (Table No.4).

The hardness values ranged from 3.12 to 3.60 kg/cm^2 for formulations were almost uniform. Tablet hardness is not as absolute strength (Table No.4).

All the tablets passed weight variation test as the average percentage weight variation was within the pharmacopoeia limits of 7.5%. It was found to be 1049 mg to 1053mg. The weight of all the tablets was found to be uniform with low standard deviation (Table No.4).

The drug content (Table No.5) of the tablets was found to be between 97.14 to 99.53 %. The results were within the range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the average drug content

present in the tablet.

Layer 1 - Metformin Hydrochloride

In formulation F1 the controlled layer consists of 11%, F2 consists 14%, and F3 consists 16% of Guar gum respectively. *In vitro* release studies of F1, F2, and F3 incorporated with 11%, 14%, and 16% Guar gum were carried out in 6.8 phosphate buffer. All the tablet formulations showed acceptable properties but the result of dissolution studies indicating that F1, F2, F3 released the entire drug at the end of 8hours. This might be due to slow hydration of matrix and property of thick gel layer.

F4, F5, F6 incorporated with 11%, 14%, and 16% of Gum tragacanth also failed to meet the needed theoretical dissolution release. This may be due to chance of bacterial contamination that retards the swelling nature of tragacanth. So it could not sustain the release more than 8hours.

In formulation F7, F8, F9 containing Xanthum gum in 11%, 14%, 16% proportions respectively extended the drug release more than 8hours. F7 formulation with 11% of Xanthum gum extends up to 9hours with maximum release of 99.38%. F8 formulation with 14% of Xanthum gum extends up to 10hours with maximum release of 98.26%. F9 formulation with 16% of Xanthum gum extends up to 12hours with maximum release of 99.48%. Increasing the percentage of polymer increase retardation of drug. This may be due to increase of diffusion path length of the drug and strong interactions of Xanthum gum molecules with drug that leads to formation of tough complex. These results suggest that formulation F9 with 16% Xanthum gum extended up to 12hours with maximum release of 99.48%.

Layer -2 Pioglitazone

In the formulation (P), immediate release layer of Pioglitazone was prepared by dry granulation method with CCS, Microcrystalline cellulose, Magnesium stearate, Sunset yellow lake. The immediate release layer consists of CCS in the concentration of 10%, where the weight of the tablet was adjusted with Microcrystalline cellulose. The release profile of Pioglitazone P was found to be within the limits and assay was more than 95%. Hence no further formulation was formulated and the formulation P Was finalized as optimized formula for the preparation of immediate release layer.

Release Kinetics

F-9 shows the higher R^2 value for zero order plots. This indicates that the drug releases is concentration independent and following 'Zero' order kinetics. It is also expressed by Higuchi equation and showed high linearity. To confirm the diffusion mechanism the data were fitted in korsemayer equation with slope (n) and R^2 value is 0.987. This indicates the release of drug follows non-fickian transport. It means the release of drug from tablet is both diffusion and dissolution mechanism (Table No.5).

Stability Studies

The tablets from trials F9 was charged for stability at 30 ^oC/ 65%RH and 40^oC/75% for two months and the 2 months results was found to be satisfactory.

Table No.1: Composition of immediate release Pioglitazone layer

S.No	Ingredients	Quantity(mg)
1	Pioglitazone	30
2	Micro crystalline cellulose	85
3	Crosscarmellose sodium	15
4	Magnesium state	2
5	Talc	2
6	Sunset yellow	1

Table No.2: Composition of controlled release Metformin hydrochloride layer

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin Hcl(mg)	500	500	500	500	500	500	500	500	500
2	PVP k 30(mg)	30	30	30	30	30	30	30	30	30
3	Tragacanth gum(mg)	100	120	140	_	_	_	_	_	_
4	Guar gum(mg)	_	_	_	100	120	140	_	_	_
5	Xanthan gum(mg)	_	_	_	_	_	_	100	120	140
5	Microcrystalline cellulose(mg)	100	100	100	100	100	100	100	100	100
6	Lactose(mg)	120	100	80	120	100	80	120	100	80
7	Magnesium stearate(mg)	10	10	10	10	10	10	10	10	10
8	Talc(mg)	10	10	10	10	10	10	10	10	10
9	Isopropyl alcohol	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table No.3: Results of flow properties of Metformin Hcl and Pioglitazone layers

Formulation code	Bulk density(g/ml)	Tapped Density	Angle of repose^{o}	Carr's Index (%)	Hausner's Ratio
F1	0.526	0.612	26.76	14.0	1.16
F2	0.662	0.763	27.54	13.23	1.15
F3	0.695	0.823	24.65	15.5	1.18
F4	0.782	0.869	28.68	11.0	1.11
F5	0.560	0.631	24.68	11.25	1.12
F6	0.628	0.714	25.16	14.27	1.17
F7	0.650	0.754	26.15	15.20	1.15
F8	0.566	0.789	24.12	14.40	1.12
F9	0.737	0.754	24.15	13.25	1.19
P(IR)	0.40	0.51	28.41	17.9	1.24

Table No.4: Uniformity of Thickness, Hardness, Friability, and Weight variation of Pioglitazone and Metformin Hcl bilayer tablets

S.No	Formulation code	Weight Variation (mg)	Uniformity of Thickness (mm)	Hardness (kg/cm^3)	Friability %	Drug content uniformity %
1	F1	1051	6.85	3.58	0.24	98.14
2	F2	1053	6.59	3.42	0.39	99.14
3	F3	1049	6.77	3.28	0.57	97.45
4	F4	1050	6.73	3.12	0.75	99.53
5	F5	1051	6.84	3.44	0.89	97.14
6	F6	1049	6.74	3.46	0.86	98.97
7	F7	1050	6.78	3.60	0.9	98.26
8	F8	1045	6.84	3.57	0.86	99.45
9	F9	1050	6.59	3.54	0.73	98.6
10	P(IR)	-	-	-	-	98.0

Table No.5: *In vitro* release study of immediate release layer

S.No	Time(min)	Cumulative% drug release(p)
1	5	22.705
2	10	42.1486
3	15	56.2486
4	30	65.1248
5	45	83.2497
6	60	98.854

Table No.6: *In vitro* release study of Metformin hydrochloride controlled release layer

Cumulative % drug release										
S.No	**Time in hours**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	1	24.07	23.29	22.71	23.68	22.33	20.39	21.36	19.43	18.46
2	2	35.80	35.22	33.09	34.44	34.05	32.49	31.14	29.78	27.65
3	3	49.01	46.69	45.90	46.88	47.46	46.67	38.35	37.57	36.40
4	4	59.33	55.84	58.93	58.93	58.34	57.00	48.64	47.09	45.73
5	5	71.38	68.65	69.65	70.60	69.44	68.27	58.94	57.00	54.09
6	6	80.34	78.58	77.23	79.75	78.20	75.49	70.60	68.08	66.57
7	7	91.99	90.62	91.97	90.82	89.46	87.51	81.11	79.54	77.41
8	8	99.20	98.81	98.24	98.23	97.26	97.05	88.12	86.95	86.17
9	9	-	-	-	-	-	-	99.38	97.82	96.46
10	10	-	-	-	-	-	-	-	98.26	97.05
11	12	-	-	-	-	-	-	-	-	99.48

Table No.7: Stability studies of Pioglitazone and Metformin Hcl for 3 months

S.No	Storage condition	Description	Dissolution		Assay	
			Pioglitazone	Metformin Hcl	Pioglitazone	Metformin Hcl
1	Label Claim	_	30mg/tab	500mg /tab	30mg/tab	500mg/tab
2	Initial	Complies	98.5	97.7	98.7	99.5
3	1stmnth	Complies	97.8	97.5	98.5	99.3
4	2ndmnth	Complies	96.8	96.4	97.3	98.5
5	3rdmnth	Complies	95.4	95.7	96.5	97.4

Table No.8: Kinetic models of optimized batch (F9)

S.No	Release kinetics	Correlation coefficient(R^2)
1	Zero order equation	0.96
2	First order equation	0.601
3	Higuchi(diffusion)co-efficient	0.955
4	Korsmeyer Peppas equation	0.987

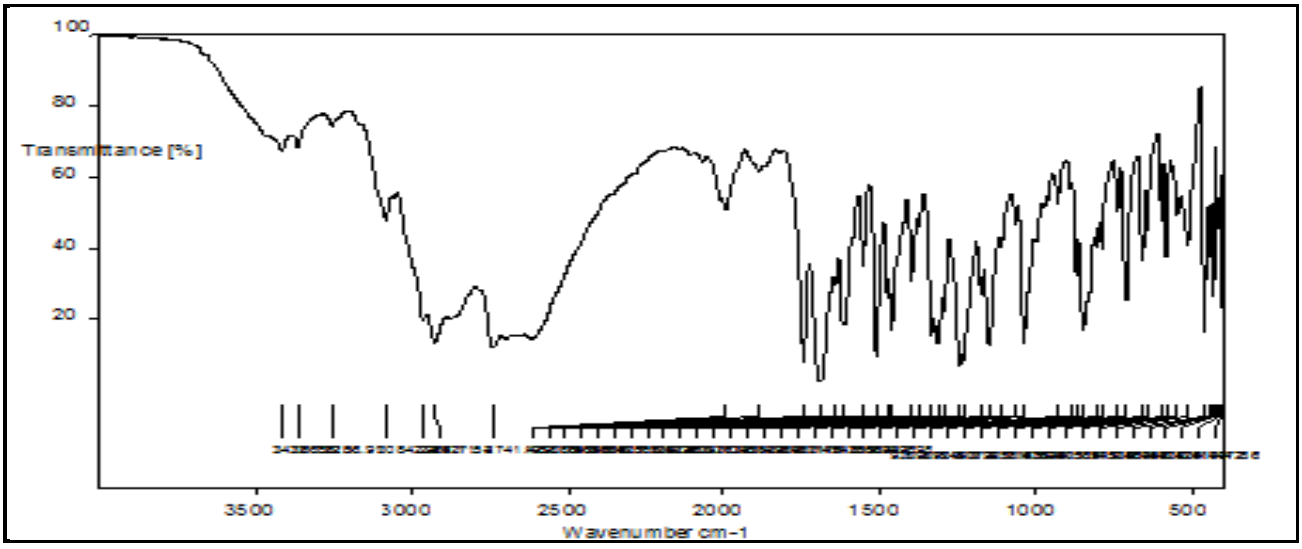

Figure No.1: FT-IR spectrum of pure Pioglitazone

Figure No.2: FT-IR spectrum of pure Metformin Hcl

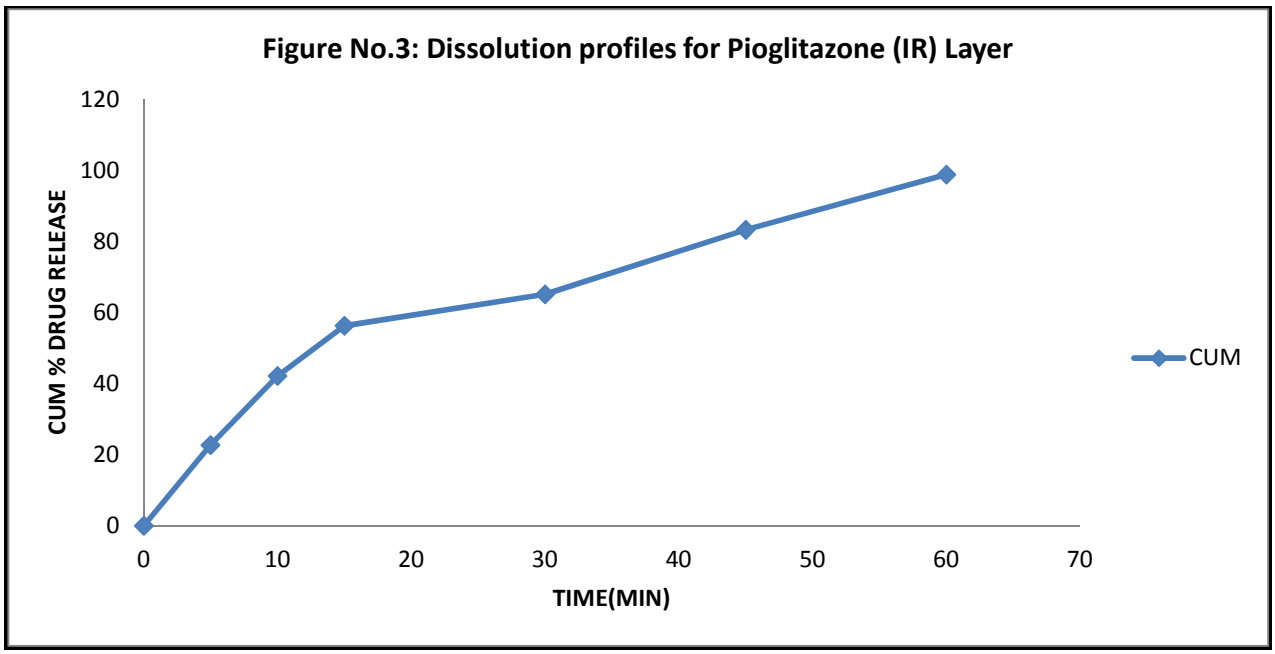

Figure No.3: Dissolution profiles for Pioglitazone (IR) Layer

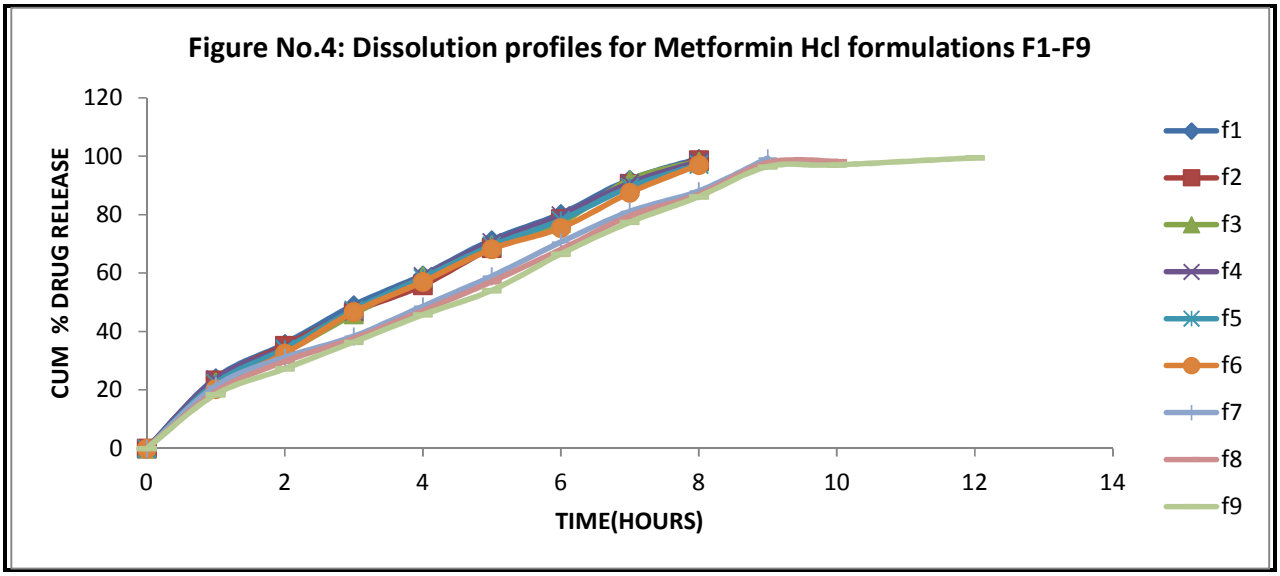

Figure No.4: Dissolution profiles for Metformin Hcl formulations F1-F9

CONCLUSION

Success of the *In vitro* drug release studies recommends the product for further *in vivo* studies, this may improve patient compliance. From the literature Metformin Hcl and Pioglitazone, individual dosage form was used in the management of diabetes mellitus. Combination of Pioglitazone as immediate release layer and Metformin Hcl as controlled release layer improves the patient compliance and it gives additive effect. From the results formulation F9 has been selected as best formulation among all the other formulations. Formulation F9 provides better *in vitro* release from layer 2. The data obtained from in vitro release study were fitted to various mathematical model like Zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion for optimized formulation (F9). Thus the release of the drug from the dosage form was found to be diffusion and non-fickian release. The formula optimized and it was selected for stability studies as per ICH guidelines.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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