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FORMULATION AND *IN VITRO* EVALUATION OF METFORMIN HYDROCHLORIDE DIRECT COMPRESSIBLE TABLET USING BY HICEL™ MICROCRYSTALLINE CELLULOSE EXCIPIENT

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ABSTRACT

Metformin hydrochloride is generally used to regulate blood glucose level; It is mainly used for Insulin- dependent mellitus or Type II diabetes. Type II diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. Metformin hydrochloride is a very popular high dose pharmaceutical active. It is normally made by wet granulation method. Wet granulation is more time and man power consuming method. The overall objective of the present work was to develop Metformin hydrochloride tablets prepared by direct compression method, using HiCel™ 90M microcrystalline Cellulose. The tablets were evaluated for thickness, weight variation, hardness, friability and In vitro drug release. Mean dissolution time is used to characterize drug release rate of dosage from a dosage form. In this study, Metformin hydrochloride direct compressible tablet are made using HiCel™ 90M grade of microcrystalline cellulose. HiCel™ Microcrystalline Cellulose have good binding capacity with metformin hydrochloride, given good hardness with satisfactory dissolution profile of drug.

KEYWORDS: HiCel™ 90M microcrystalline Cellulose, Direct compression of metformin hydrochloride tablet, Hardness, friability, Dissolution profile.

INTRODUCTION

Diabetes mellitus is a worldwide public health challenge due to its high morbidity and mortality rate. It is one of the most prevailing and advancing disease in the world having affected 6.6% of the world population. It is estimation that by 2025 around 300 million people will be diagnosed with diabetes.[1] Metformin hydrochloride is the most widely used oral anti diabetic drug in the world. Metformin improves glucose tolerance by lowering both

basal and postprandial glucose by decreasing intestinal absorption of glucose, decreasing hepatic gluconeogenesis, increasing glycogenesis, lipgenesis and glucose uptake by adipocytes and muscle cell. Metformin is a highly water soluble drug. Metformin is an oral anti diabetic drug.[2] The oral route is considered to be one of the most acceptable routes used for the drug administration. Tablets are mostly preferred formulations by patients for the treatment of diseases, and it is beneficial particularly when the long term therapy is required[1,3]

Many types of Oral dosages forms are found such as tablets, capsules, syrup, and suspension etc. Out of these tablets are very easy to make and handle and its shelf life is also very good. Generally two types of method are use for making the tablets. First, is wet granulation and second is direct compression. Wet granulation method is time consuming and costly. Direct compression is an easier method for manufacture of tablets.[4] The pharmaceuticals API and all the excipients are blended as per the process and compressed into tablets. There are many excipients used in the pharmaceuticals field for manufacture of solid dosages forms.[5,6] Excipients are used for providing the bulk for pharmaceutical API. To improve the property of pharmaceutical API, different types and combinations of excipient are added. Excipients also used for drug manufacturing to achieve content and weight uniformity for the final dosage form. HiCel™ 90M Microcrystalline Cellulose is one of them.[7,8]

A pharmaceutical excipient HiCel™ MCC produced from the acid hydrolysis of alpha cellulose derived from purified wood pulp. It has excellent physical and chemical properties for direct compression formulation.[9] HiCel™ 90M microcrystalline cellulose powder has good flowability and compressibility. In tablet manufacturing process flowability play an important role in mixing and compaction, Powder flow in hopper is a crucial factor for direct compression formulation.[10] HiCel™ 90M MCC is a good binder and lubricant and disintegrates well. It helps to achieve satisfactory hardness and disintegration of tablet with less weight variation of tablet and uniform content uniformity.[9] In this study, HiCel™ 90M microcrystalline Cellulose is using to manufacture the metformin hydrochloride direct compressible tablets. All quality parameters i.e. Weight variation, hardness, thickness, disintegration, friability and dissolution test are evaluated.

MATERIALS AND METHODS

Material

Metformin Hydrochloride (USP) was obtained as a sample form IPCA Laboratories Limited (Aurangabad,India), Microcrystalline Cellulose (MCC HiCel^{TM} 90M), magnesium stearate was obtained as a gift sample from Prachin Chemical (Ahmedabad, Gujarat). Povidone K-30 was obtained as a sample from Ansul Life Science Mumbai (India). All other ingredients used were A.R.grade.

Method

Manufacturing process of HiCel^{TM} MCC[9]

Fibrous wood pulp cut into the pieces, charged in reactor with mineral acid and water, and hydrolyzed V/V at specific temperature, pressure, acid concentration and time. Mineral acid, temperature, pressure and time used as a catalyst for fast the reaction. After hydrolysis wood pulp breaks down into slurry. Thereafter it is washed and filtered with ammonia with the help of filter press for getting the conductivity below 75µs/cm, pH is neutral. Details mentioned in the figure no-1.

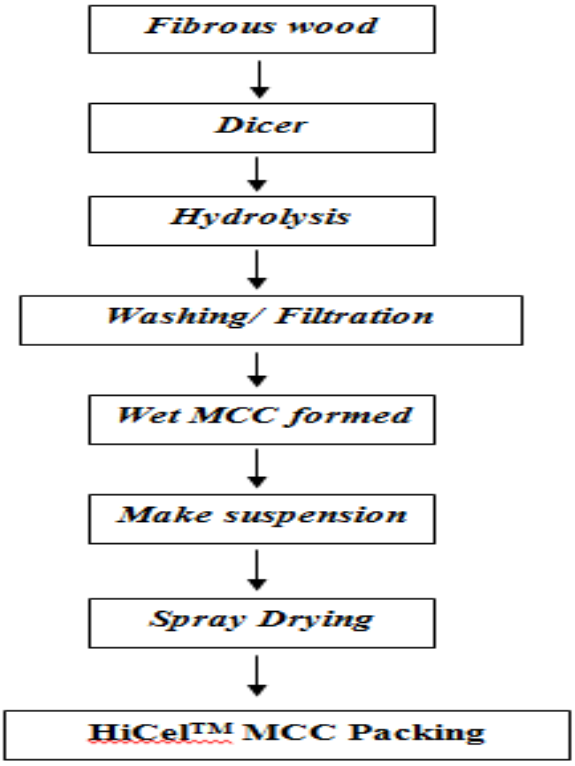

Fig. 1Manufacturing process of HiCel^{TM} microcrystalline Cellulose

Untapped Bulk density[10]

Untapped density is analyzed through graduated measuring cylinder class A. Take 20 gm of dry MCC powder pours into a graduated A grade 100 ml capacity cylinder slowly from the sidewall. Level the surface of sample in cylinder by slow movement and note down the occupied volume and calculate the untapped density of HiCel™ MCC by using following formula.

$$\text{Untapped density (BD)} = \frac{Weight\ of\ powder\ in\ gram}{Occupied\ volume\ in\ mL} \quad (1)$$

Angle of repose[10]

Pour 30gm of dry MCC through pour on powder flow tester (#10 mesh size), powder comes on the S.S cylinder surface until a pile build on the top of S.S cylinder. Measure the total height (S.S cylinder & pile) by scales. Using following formula find the calculated value this value check natural tangents chart for angle of repose and reported.

$$\text{Angle of Repose} = \frac{2h}{d} \quad (2)$$

Where

h = height of S.S cylinder

d = diameter of S.S cylinder

Particle size distribution (PSD)

Average particle size was analysised by Sieve shaker, PSD software (Retch-Japanese instrument). PSD software operate through computer. Take cleaned mesh sieve with bottom pan and top cover. Check sieve shaker and set mesh sieve with sample being analyzed on sieve jet. Take weight of all required mesh sieve with bottom. Arrange the sieve mesh sequence from top mesh +60, mesh +200 and bottom. Weight accurately 10 gm of MCC powder with the help of weight balance (Mettler Toledo, Model no. ML802/A01) and put into top of sieve. Fill the initial weight of mesh sieve and bottom into PSD table and start. After 5 minutes take out the sieves and again take weight with retain sample. Fill into the PSD software table, in graph shows the particles size.

Moisture Content(MC)[9]

Heat the shallow bottle in a hot air oven (Model no. PNX-14) at 105°C for 30 minutes after that cool it in desiccator at room temperature .Tare weight the Shallow bottle and take about

1 gm of HiCel™ MCC in shallow bottle, set oven at 105°C and kept for 3 hours. After 3 hours take out the shallow bottle allow to cool in desiccator at room temperature. When the shallow bottle is cool take weight again, Calculate moisture content by using the following formula.

$$MC = \frac{After\ drying\ weight\ of\ shallow\ bottle - empty\ \ weight\ of\ shallow\ bottle}{Sample\ weight\ in\ gram} \text{ X } 100 \quad (3)$$

XRD Analysis of MCC

This study carried out at Shah-Schulman Center for Surface Science and Nanotechnology Dharmsinh Desai University, using XRD instrument (model no- D8Advance,Bruker HiCel™ 90M microcrystalline cellulose scan at different angle of 2theta).

Preparation of metformin hydrochloride tablets[11]

Metformin hydrochloride tablets were prepared by direct compression method. Procedure is summarized in fig 2. Required quantity of materials are mentioned in tablet 1. All the ingredients are passed through 40-mesh sieve before use. Calculate the amount of drug, filler and lubricant on dry basis and mixed thoroughly. Magnesium stearate was added as lubricant, the mixture of all ingredients filled into the hopper of tablet machine than compressed using an ten station rotary press (Proton mini press, Ahmedabad, India) at a constant compression force equipped with a 12.5 mm concave faced punches at a compression force required to produced tablets of about 6-7 Kp(kgf) hardness.

Table no. 1 Tablet manufacture formula of Metformin Hydrochloride tablet for 100 tablets

Name of materials	*Quantity (mg)*	*Taken quantity (gm)*
Metformin Hydrochloride	*500*	*50*
HiCel Microcrystalline Cellulose 90M	*60*	*6*
HPMC-10 (Hydroxypropylmethyl cellulose)	*65.80*	*6.58*
Magnesium stearate	*5.20*	*0.52*

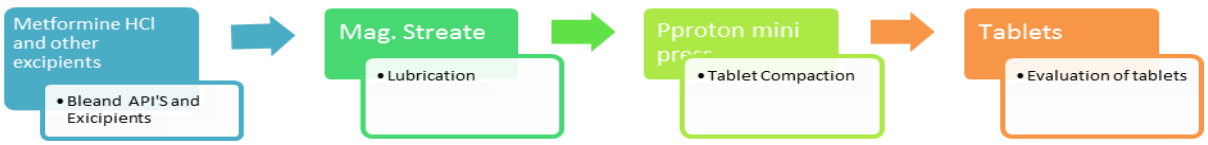

Fig.2 Direct compression manufacture process of Metformin Hydrochloride

Evaluation of tablets[9]

The prepared tablets were physical characterized immediately. Physical characters are sticking, Picking, mottling and double impression.

Weight Variation[11]

The weight variation of the tablets was evaluated by random 20 tablets were taken from each batch and each tablet was weighted individually using electronic digital balance (Mettler Toledo, Model No.-MS204S /A01) The average weight of all tablets was calculated following formula (equation 4) The Pharmacopoeial limit of weight variation is mentioned in (Table no.2) .

$$Average\ weight\ of\ tablet = \frac{Total\ weight\ of\ tablets}{Total\ no.of\ tablets} \quad (4)$$

Hardness of Tablet[12]

Random 10 tablets were taken from batch. Electronic digital hardness test machine (Labindia tablet hardness tester, Model No.-TH1050 M) was used for hardness test. Individually, a tablet was placed between two anvils, force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded. Finally the reading was taken in kp[kgf] on display of hardness machine.

Thickness of tablet[9]

Random 10 tablets were taken from each sample. Vernier caliper (M&W Precision tools serial no-11071909) was used for thickness test. Individually, a tablet was placed between two external jaws and take reading in millimeter (mm).

Friability of Tablet[9]

Random 10 tablets were taken. The tablets were carefully dusted prior to testing, then the 10 tablets were weighted electronic digital balance (Mettler Toledo,Model no. ML802/A01). This was considered as the initial reading. After weight the tablets, all the tablets were placed in the drum of friability tester and rotate 100 times at 25 rpm. After 100 revolutions the 10 tablets were removed and re-weighted. This was the final reading. The percentage was calculated by following formula (equation 5). According to USP the tablets should not lose more than 1% of their total weight.

$$\%\ Friability = \frac{Tablet\ weight\ before\ friability - Tablet\ weight\ After\ friability}{Tablet\ weight\ beforefriability} \times 100 \quad (5)$$

Dissolution of tablet[13]

The drug release studies were conducted as per USP method and using USP dissolution apparatus type 2, (Paddle type) (Labindia, Serial no.-DT14480429) at a rotational speed of 50 rpm per minute in 1000 ml of pH 6.8 phosphate buffer (Potassium di-hydrogen ortho phosphate) solution at 37±2 °C at in for 30 minutes. Check absorbance of sample using by UV VIS-Spectrophotometer (Simadzu model no-1800). Each sample (n=6) was spectrophotometerically determined at 233 nm.

RESULT AND DISCUSSION

Manufacture process of HiCel™ 90M MCC

Microcrystalline Cellulose is white crystalline, free flowing powder.

Untapped bulk density

Untapped bulk density of microcrystalline cellulose of HiCel™ 90M grade is 0.30 g/CC.

Angle of Repose

Microcrystalline crystalline cellulose has excellent flow properties. Angle of repose of HiCel™ 90M was 39°.

PSD

Particle size of HiCel™ 90M microcrystalline cellulose is 100 µm. Particle size shown in fig no-3.

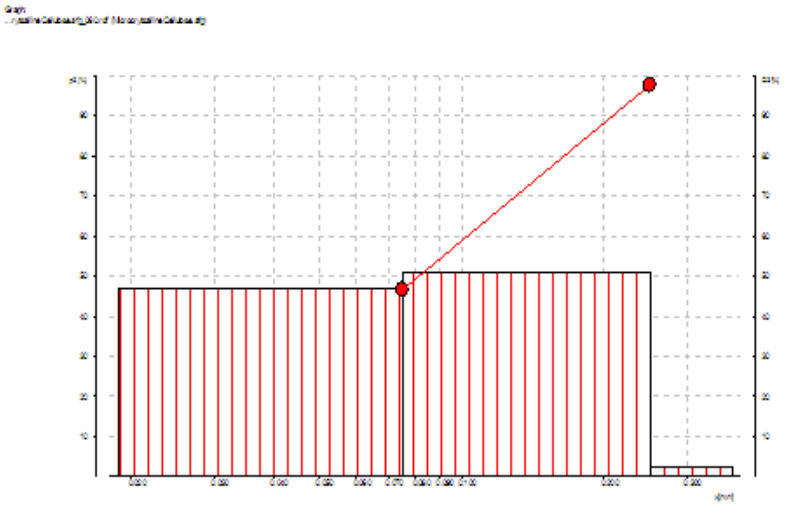

Fig. 3 Particle size distribution of HiCel™ 90M microcrystalline cellulose

Moisture content

Moisture content of HiCel™ 90M is 4.65 %.

X-ray diffraction

X-ray diffraction spectra scan image of HiCel™ MCC 90M is shown in fig. 4. During scanning, a graph is obtained between intensity and 2-theta. In graph three clear peaks are observed. That proves that no impurities are present in HiCel^{TM} microcrystalline cellulose, and scanning of MCC at different- different 2theta angles. The clear Peaks of 2theta angle observed at 15.0 °, 22.0° and 35.0°. The highest peak of 2- theta angle is 22.0°.

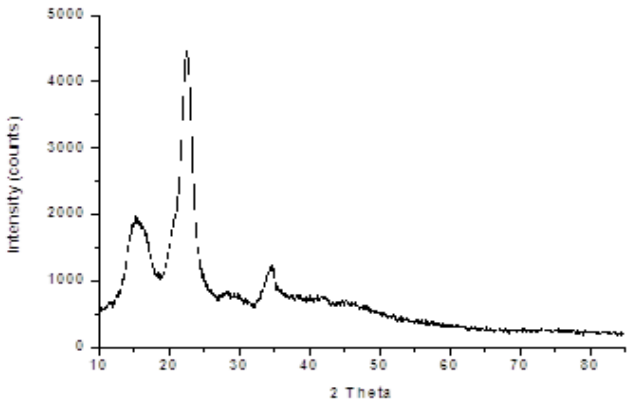

Fig. 4 X-ray diffraction of HiCel™ microcrystalline cellulose

Preparation of Metformin HCl tablet

650mg total weight of metformin hydrochloride tablet compress on 350 KN compression force. Tablets are free from all defects, white color and elongated shaped shown in the fig 5.

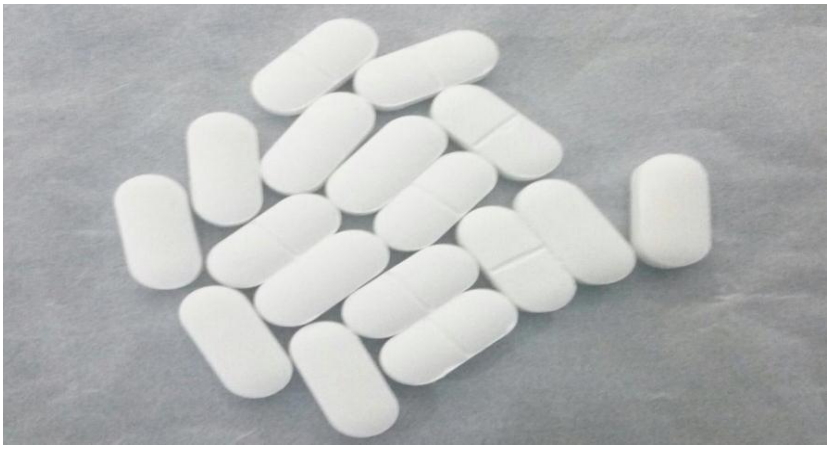

Fig.5 Metformin Hydrochloride DC tablets

Weight variation

Individual tablet weight mark in the table no-2 and fig 6. Average weight of tablets is 650.2 mg.

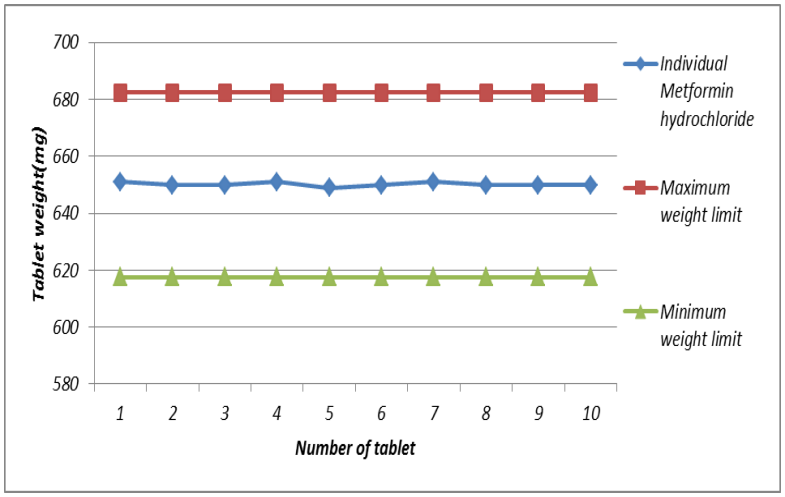

Fig-6 Weight variation of Metformin Hydrochloride tablet with acceptable maximum and minimum pharnacopoiea limit.

Hardness

Metformin hydrochloride individual tablet hardness reported in the table no2 and fig no7 Average hardness of ten tablets is 6.17 kp(kgf).

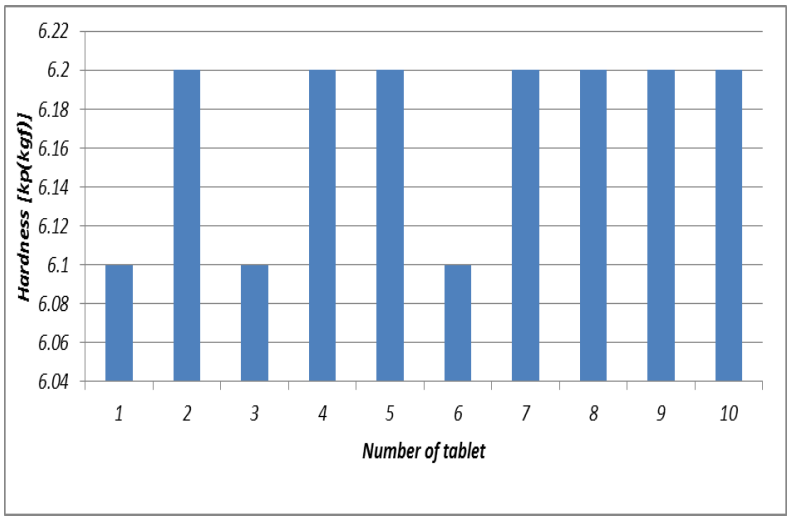

Fig.7 Individual tablet hardness of Metformin hydrochloride DC tablet

Thickness

Thickness variation of tablets is very less, individual tablet thickness mentioned the table no-2 and fig 8 average thickness is 5.26mm.

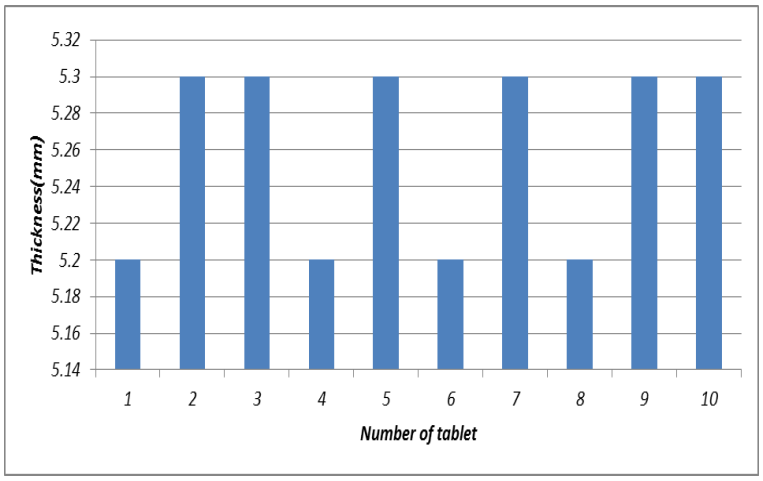

Fig.8 Thickness variation of Metformin hydrochloride tablet

Friability

Percentage friability of Metformin hydrochloride tablet reported in the fig 9. Average friability of tablets is under limit. Percentage of friability limit in pharmacopeia not more than 1%. Average friability is 0.1274%.

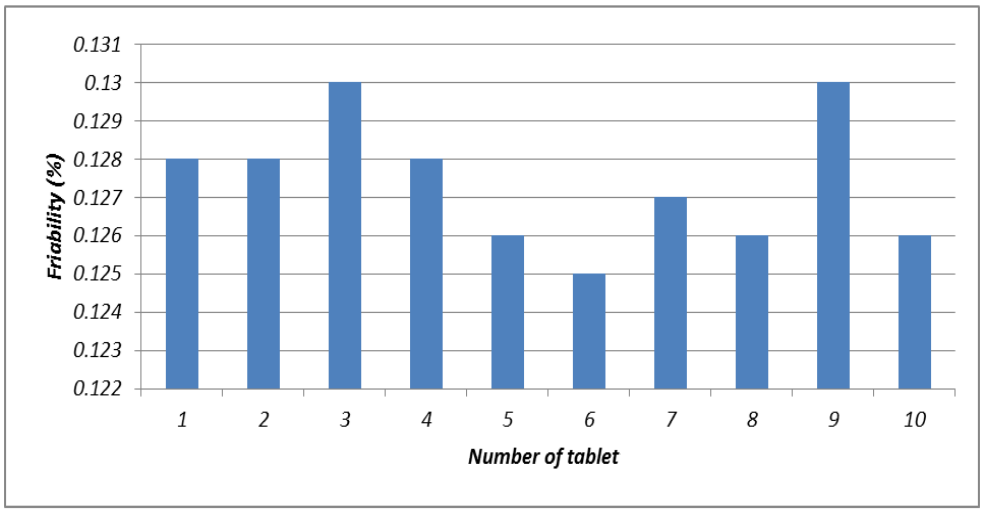

Fig. 9 percentage friability of individual ten tablet of Metformin hydrochloride

Table no- 2 Individual tablet result of Weight variation, hardness, thickness, and friability

No. of Tablet	Weight Variation(mg)	Hardness [kp(kgf)]	Thickness (mm)	Percentage Friability(%)
1	*651*	*6.1*	*5.2*	*0.128*
2	*650*	*6.2*	*5.3*	*0.128*
3	*650*	*6.1*	*5.3*	*0.13*
4	*651*	*6.2*	*5.2*	*0.128*
5	*649*	*6.2*	*5.3*	*0.126*

6	*650*	*6.1*	*5.2*	*0.125*
7	*651*	*6.2*	*5.3*	*0.127*
8	*650*	*6.2*	*5.2*	*0.126*
9	*650*	*6.2*	*5.3*	*0.13*
10	*650*	*6.2*	*5.3*	*0.126*
Average	*650.2*	*6.17*	*5.26*	*0.1274*

DISSOLUTION

Drug release percentage in particular time interval reported in fig.10.

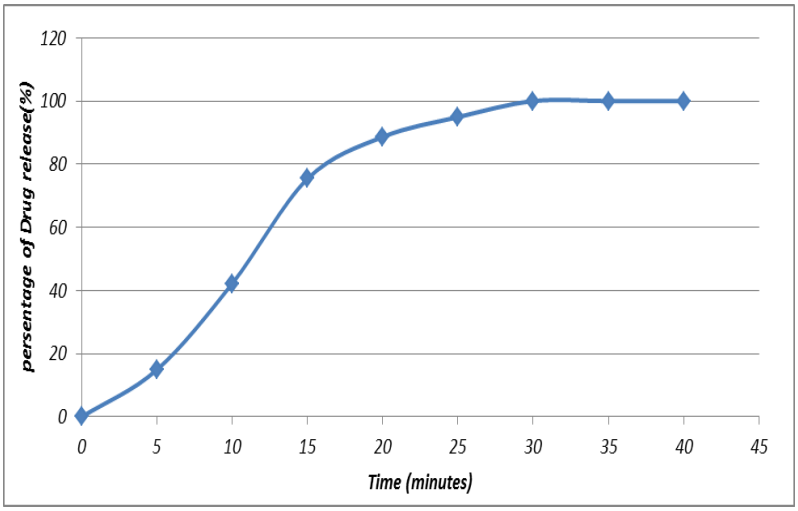

Fig.10 Percentage release of metformin hydrochloride tablet at different time intervals

CONCLUSION

HiCel^{TM} 90M microcrystalline cellulose has good flowability and compressibility. It has good binding and disintegration properties. It easily Binds with metformin hydrochloride and gives good Hardness at lower compression force. Weight variation and friability of tablet is under satisfactory limits. This study proved that HiCel^{TM} Microcrystalline cellulose is good excipient for direct compressible tablet formulation.

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Conflicts of interests

The authors state and confirm no conflict of interests. No direct funding was received for this study.

REFERENCES

1. Kumar Hemanth G., Jaganathan J.,Kumar SambathR., Parumal.P.(Formulation and *in-vitro* evalution of bilayer floating tablets of metformin hydrochloride and sitagliptin phosphate).Int J of Advanced Pharmaceutics, 2012; 2(2): 64-81.
2. Rojas J., Gonzalez Cesar, Rico Carolina, Saez Oswaldo.(Formulation of a modified release metformin. HCl matrix tablet: Influence of some hydrophilic polmers on release rate and *in-vitro* evalution).Brazillian J of Pharmaceutical Sciences, 2011; 47(3): 483-494.
3. Motaher Mohammed, Chowdhury Hassain, Nawreen, Rana S.Md.(Formulation development and *InVitro* evaluation of combination product of glyuride and metformin hydrochloride tablet).Bangladesh Pharmaceutical J, 2013; 16(2): 195-203.
4. Alam Kamran, Zafar Farya, Shareef Huma.(Development and evalution of metformin hydrochloride 500mg sustained release tablets).J of Pharmaceutical and Biomedical Sciences, 2013; 36(36): 1844-1852.
5. Narasimharao R, Reddy M.A, Reddy N.S., Divyasagar P and K. Keerthana.(Design and evaluation of metformin hydrochloride extended release tablets by direct compression.Int J of Res in phar and biomedical sciences, 2011; 2(3): 1113-1118.
6. Wadher J.Kamlesh, Kakde B.R, Umekar J.Milind. (Formulation of sustained release metformin hydrochloride matrixtablet:Influence of hydrophilic polymers on releas rate and evalution.Int J of Res in Controlled release, 2011; 1(1): 9-16.
7. Nanjwade K.B, Mhase R.S and Manvi FV. (Formultaion of extended release metformin hydrochloride matrix tablet).Tropical J of Phar Res., 2011; 10(4): 375-383.
8. Shashidhar R. and Sagar Vidya G.(Formulation and development of ploating drug delivery system of metformin hydrochloride extended release and glimepiride immediate release into bilayered tablet dosage form:*In vitro* evaluation). Int J of Pharmacy, 2013; 3(1): 217-227.
9. Tomar Monika, Singh Ajay Kumar, Sinha Amit Raj.(Powder and Tablet profile of microcrystalline cellulose(MCC) of different with degrees of polymerization).Int. J of Recent Scientific Res, 2016; 7(6): 12044-12047.
10. Tomar Monika, Singh Ajay Kumar, Sinha Amit Raj. (Physicochemical parameter of microcrystalline cellulose and the most acceptability in pharmaceutical industries).J of Innovations in phar and biological Sciences, 2015; 2(4): 570-578.

11. Babu S.G, Kumar D.V, Rakesh M,Sandeepthi B. Malthy PS.(Formulation development and invitro evalution of bilayer tablets of ramipril and metformin using nature and synthetic polymers). Int J of pharmacy and biological Sciences, 2014; 4(3): 83-95.
12. Kumar Vijay,US006117451A;2000
13. USP30-NF25. (Pharmacopieal forum). 27(3): 2495.