IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2017 Vol.:11, Issue:1

Formulation and Evaluation of Metformin Hydrochloride Immediate Release Tablets by Using Low-Density Excipients

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

SHAZIYA TASNEEM*, Dr. K. V. RATNAMALA

R.B.V.R.R. Women's College of Pharmacy, Barkatpura, Hyderabad, Telangana, India.

Submission: 20 November 2017
Accepted: 30 November 2017
Published: 30 December 2017

Keywords: Metformin hydrochloride, Preformulation studies, Immediate-release tablets, Wet granulation and Direct compression method.

ABSTRACT

The purpose of this research is to prepare and evaluate Metformin hydrochloride immediate-release tablets with lower weight by wet granulation technique and direct compression method. In this study, low-density polymers were used such as Microcrystalline cellulose, dibasic calcium phosphate, Cross povidone, Croscarmellose sodium and magnesium stearate. The polymers were selected by conducting preformulation studies. The prepared formulations are compared with innovator product **(Glycomet-850)**. Drug-Excipient compatibility studies were performed and the dibasic calcium phosphate, Cross povidone, Croscarmellose sodium and magnesium stearate were chosen as there was no interaction with drug and excipients during the study period. The formulations F1-F4 were formulated using wet granulation method and direct compression method and the tablets were evaluated for Weight variation, Hardness, Friability, in-vitro drug release, and disintegration. *In-vitro* release studies show that the formulation F3& F4 of wet granulation method and direct compression method shows 99.3% & 100.1%, 98.4% & 99.9%. The innovator product shows 96.5% drug release in 45 minutes. Hence it has been concluded that the formulation containing the high concentration of polymer had earlier drug release.

INTRODUCTION:

Preformulation is a group of studies that focus on the physicochemical properties of a new drug substance that could affect the drug performance and the development of a dosage form. This could provide important information about formulation design or support that need for molecular modification[1,3,7]. Every drug has intrinsic chemical and physical properties which have been considering before the development of pharmaceutical formulation. An objective of the preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physicochemical parameter of new drug substances[4,5].

A tablet is a pharmaceutical dosage form. Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable excipients and prepared either by molding or by compression. The excipients can include diluents, binders, granulating agents, glidants and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract[5,12].

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption[7,5,12].

Metformin hydrochloride is freely soluble in water & partially soluble in acetone, ether, chloroform, with 50-60% of Bioavailability,4-8.7 hours of biological half-life hours. Metformin is an anti-hyperglycemic agent which improves glucose tolerance in the patient with type 2 diabetes, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production & intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization[23].

A dose of Metformin Hydrochloride: 500mg tablet taken daily 3 times in a day, the 850mg tablet taken daily twice in a day750mg, 1000mgtablets once in a day.

MATERIALS AND METHODS:

MATERIALS: Materials were selected by conducting the preformulation studies. And the selected excipients are microcrystalline cellulose, dibasic calcium phosphate, cross povidone, croscarmellose sodium, magnesium stearate.

METHODS: Metformin hydrochloride immediate-release tablets were prepared by Wet granulation and direct compression method. For Wet granulation method, Drug is added to the granulator and grounded Suitable, then adjuvant is added and mixed in blender, Granulating liquid is added to form a damp mass of the powdered material which resembles agglomerates The mass is screened to form pellets or granules, These pellets or granules are dried to remove excess liquid, Dry screening of granules results in size reduction then Lubricating agent is added and the mixture is thoroughly mixed in a blender, The resultant granules by machine tooling of tablet press.

For Direct compression method, all the ingredient is weighed. The required quantity of drug and excipients are added in a blender mixed thoroughly. Then blended powder material is compressed in a tablet. The compositions of different methods and different formulations shown in the **Table:1& 2**

Table 1: Composition of tablets formulation by wet granulation method

Sr. No.	Powders	F1(mg)	F2(mg)	F3(mg)	F4(mg)
1	Metformin hydrochloride	500	500	500	500
2	MCC	50	-	75	-
3	Dibasic calcium phosphate	-	75	-	100
4	Croscarmellose sodium	52	47	47	32
5	Crospovidone	50	30	30	20
6	Magnesium stearate	8	8	8	8
7	Water	QS	QS	QS	QS
	Total	660	660	660	660

Table 2: Composition of tablets formulation by direct compression method

Sr. No.	Powders	F1(mg)	F2(mg)	F3(mg)	F4(mg)
1	Metformin hydrochloride	500	500	500	500
2	MCC	50	-	75	-
3	Dibasic calcium phosphate	-	75	-	100
4	Croscarmellose sodium	52	47	47	32
5	Crospovidone	50	30	30	20
6	Magnesium stearate	8	8	8	8
	Total	660	660	660	660

EVALUATION OF METFORMIN HYDROCHLORIDE IMMEDIATE RELEASE TABLETS:

Weight variation Test: This test is performed by taking, 10 tablets of each formulation and were weighed using an electronic balance and the test was performed according to the official method.The weight variation test would be satisfactory method of determining the drug uniformity the percentage deviation was calculated by using formula

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Hardness Test: Tablets requires a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks handling in the manufacture, packing, and shipping. The most widely used apparatus to measure tablet hardness is the Monsanto hardness tester.It was recorded in Kg/cm^2 and in Newtons (N) respectively.

Friability: Friability of a tablet is defined as its resistance to shock and abrasion encountered during manufacture, packing, transport, and usage. The friability of tablets was usually determined by using Roche friabilator. It consists of a transparent drum containing an arm-shaped blade.The drum has a diameter of 300mm and a depth of 3.5mm.This drum can be rotated at a speed of 25rpm.

Method:10 Tablets were accurately weighed in a digital balance (W_1) and then placed in a friabilator, allow it to rotate for 4mins i.e, 100 revolutions.The tablets are then removed from the drum, dusted and weighed again (W_2). The difference between the initial weight of tablets and final weight gives the friability of the tablets.

Acceptance limits value is **0.5%-1%.**

Percentage friability = Initial weight – Final weight x 100
Final weight

Disintegration Time: The disintegration time of the tablet was determined using disintegration test apparatus in distilled water as the medium which was maintained at 37.0º ± 0.5ºC.The time taken for disintegration of individual tablets were noted.(n=3).

Method: A tablet was placed in each glass tube and the basket containing these glass tubes is positioned in a beaker containing the required fluid such that all the tablets dip properly.The apparatus was then operated for a specified time.The tablet passes the disintegration test when none of the drug particles remain on the mesh screen, the tablet must disintegrate completely and all particles must pass through the mesh.

***In vitro* Dissolution study of tablets:** The in-vitro dissolution of Metformin hydrochloride was studied using USP dissolution apparatus type 2(Paddle type) Electro lab model no.14L, Basic, Mumbai.900ml of 0.1N HCl buffer media was taken and transferred into dissolution vessel.The medium was maintained at the temperature of 37.0º±0.5ºC and paddles were operated at 75rpm at 232nm. The tablets were placed into each dissolution basket.A sample of the 5ml solution was withdrawn from each vessel at regular intervals of time i.e, 5, 10, 15, 25, 30, 45, 55 and 60 minutes and replaced immediately with the fresh medium order to maintain sink condition.The collected samples were analyzed for drug release by maintaining sink conditions. The collected samples were analyzed for drug release by UV-Visible spectrophotometer.

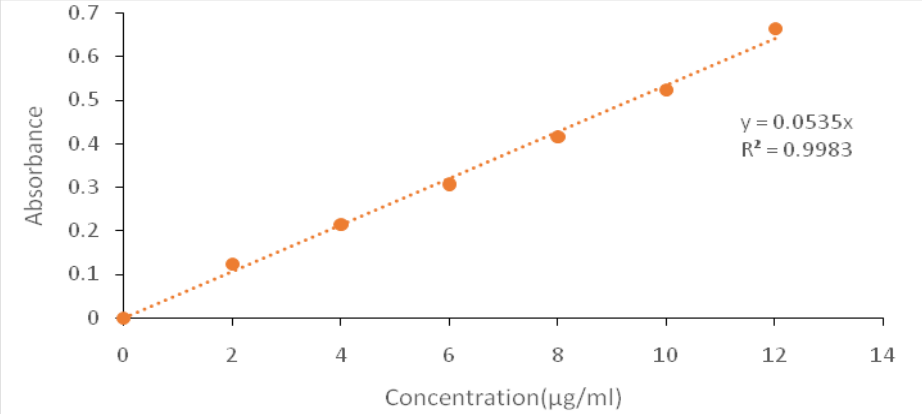
RESULTS AND DISCUSSION:

Analytical method developed for the estimation of Metformin Hydrochloride:

The standard curve was constructed as given in the table and the figure.The standard graph was found to be linear with r^2 value of 0.998 as shown in the figure.The method obeyed Beer's law in the concentration range of 2-12µg\ml.

Table 3: Standard graph of Metformin Hydrochloride

Concentration(µg/ml)	Absorbance(n=3)	% CV
2	0.123±0.5	4.06
4	0.214±0.9	4.20
6	0..307±1.2	3.90
8	0.416±1.7	4.08
10	0.523±2.1	4.01
12	0.663±2.6	3.92



(Figure:1)The standard curve of Metformin Hydrochloride.

Table 4: Preformulation studies of various excipients

Sr. No.	Powders	Bulk density(gm /ml)	True density	Angle of repose	Compressibility index	Hausner ratio
1	Potato starch	0.8	1.14	33.4	25.7	1.3
2	Maize Starch	0.3	1.25	41.6	41	1.7
3	Lactose	0.5	1.34	43.01	50	1.3
4	Mannitol	0.3	1.3	43.7	38.8	1.6
5	Sucrose	0.8	1.12	22.29	13.3	0.88
6	Microcrystalline cellulose	0.3	1.53	45.5	47.2	1.8
7	Ethyl cellulose	0.2	0.34	28.8	26.6	1.3
8	Polyvinylpyrrolidone	0.3	0.9	39.8	37.7	1.6
9	Boric acid	0.7	1.2	20.2	15.2	1.1
10	Sodium chloride	1.1	2.06	15.5	25.9	1.3
11	Magnesium stearate	0.4	0.4	29.4	43.3	0.1
12	Sodium starch glycolate	0.8	1.1	34.1	30.6	1.4
13	Croscarmellose sodium	0.4	0.9	41.1	44.2	1.7
14	Crosspovidone	0.2	0.7	36.9	37.5	1.6
15	Dibasic calcium phosphate	0.5	1.9	24.4	37.5	1.6
16	Sodium acetate	0.7	1.63	20.3	11.39	1.12
17	Sodium benzoate	0.3	1.56	27.47	30	1.43
18	Sodium lauryl sulphate	0.2	0.39	22.7	16.07	1.19

Preformulation studies of Drug and Selected excipients: The pure drug was evaluated for Bulk density, True density, Angle of repose, Compressibility index, Hausner ratio and results were given in the below table and the angle of repose was found to be 54.8 showing the drug to be fairly free-flowing properties.

Table 5: precompression parameters of drug and excipients

Sr. No.	Powders	Bulk density	True density	Angle of repose	Compressibility index	Hausner ratio
1	Metformin hydrochloride	0.4	1.05	54.8	35.7	1.5
2	Microcrystalline cellulose	0.3	1.5	45.5	47.2	1.8
3	Dibasic calcium phosphate	0.5	1.9	24.4	37.5	1.6
4	Croscarmellose sodium	0.4	0.9	41.1	44.2	1.7
5	Crospovidone	0.2	0.7	36.9	37.5	1.6
6	Magnesium stearate	0.4	0.4	29.4	43.3	0.1

DRUG EXCIPIENTS COMPATABILITY STUDIES: Various excipients like Microcrystalline cellulose, Dibasic calcium phosphate, Croscarmellose Sodium, Crospovidone, Magnesium stearate have been evaluated for compatibility with the drug as it binary mixtures in the ratio of 1:1 and sealed with the rubber closure. And the drug excipient methodology and results are given in the below table.

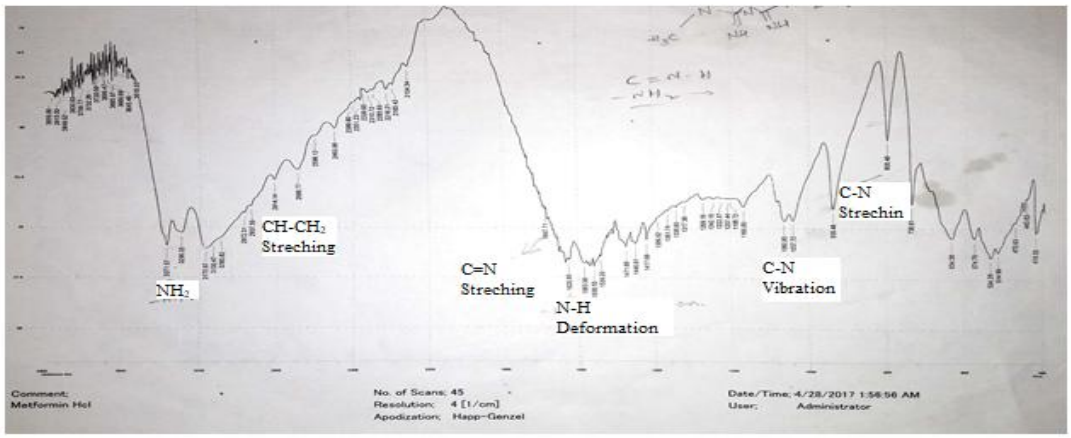


Figure 2: FTIR spectra of Pure Metformin Hydrochloride

Group	**Range cm^{-1}**
NH_2	3371
N-H Deformation	1625
C=N Stretching	1687
C-N Stretching	800
$CH-CH_2$Streching	2816
C-N Vibration	1060

The FTIR spectra of pure drug compare with the official and all the peaks corresponding to the pure drug were retain in the FTIR spectrum that was generated as indicated in the above table.

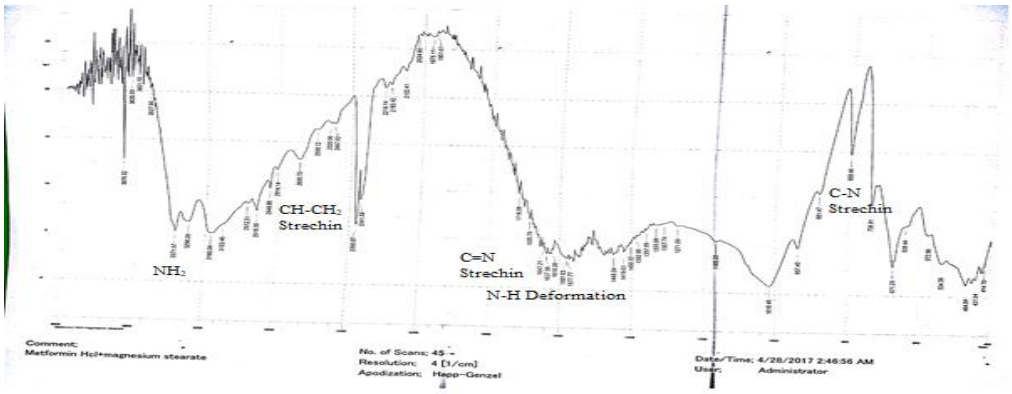


Figure 3: FTIR spectra of Pure Metformin Hydrochloride & Magnesium stearate

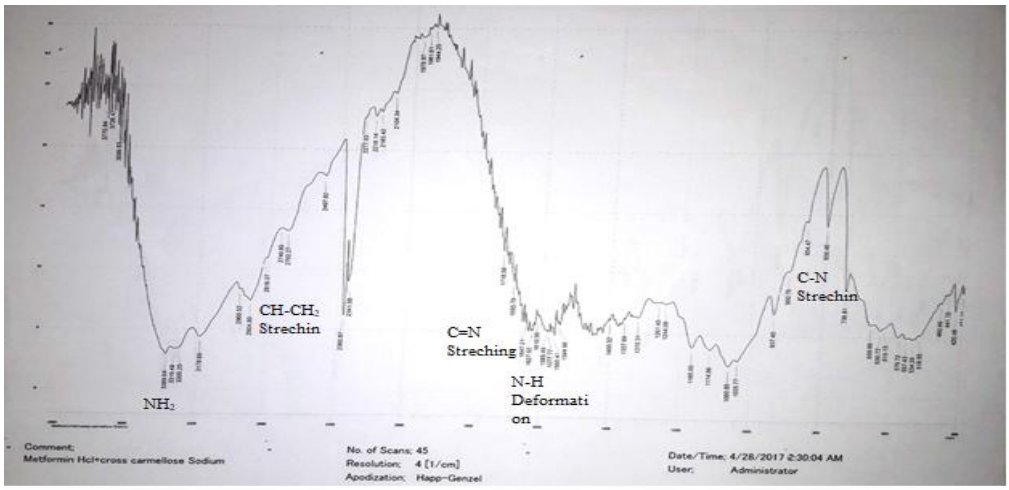


Figure 4: FTIR spectra of Pure Metformin Hydrochloride and Croscarmellose sodium

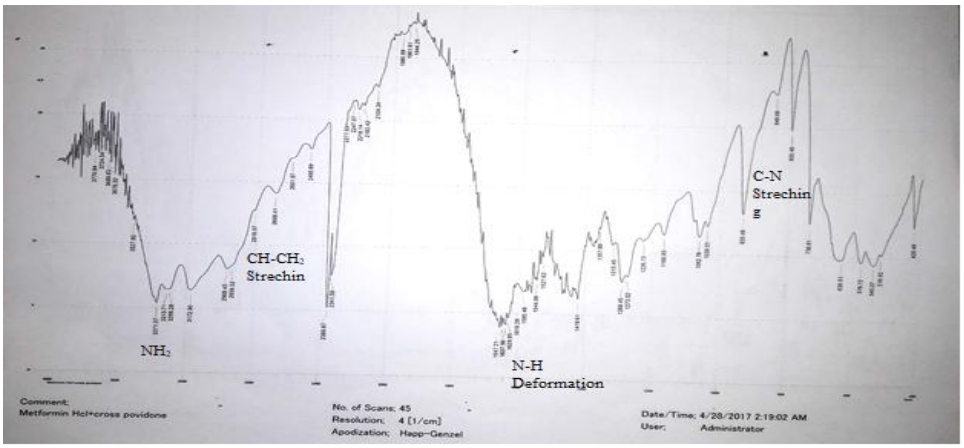


Figure 5: FTIR spectra of Pure Metformin Hydrochloride and Crospovidone

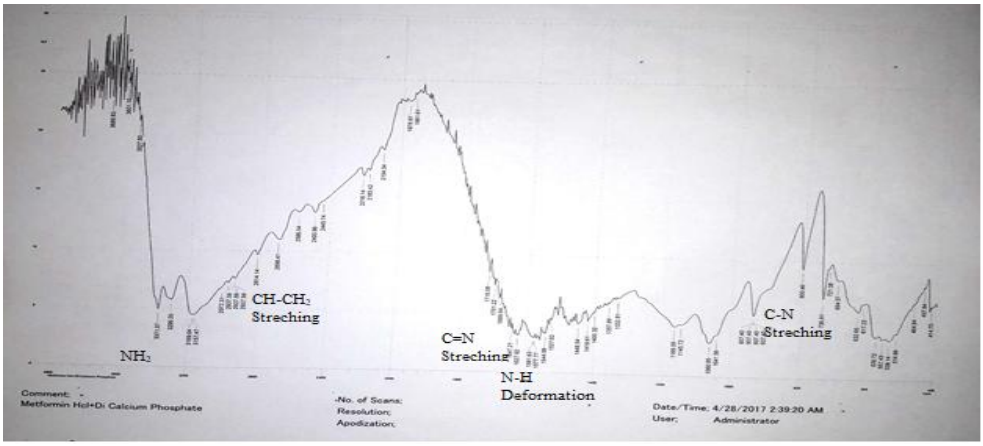


Figure 6: FTIR spectra of Pure Metformin Hydrochloride &Dibasic Calcium phosphate

Figure:2,3,4,5,6 are the FTIR spectra's of various excipients like Magnesium Stearate, Croscarmellose Sodium, Crospovidone, Dibasic Calcium phosphate retained all the characteristic peaks of Metformin Hydrochloride and hence these excipients were employed in the formulation of Metformin Hydrochloride immediate-release tablets.

Table 6: Compression parameters of prepared formulations by wet granulation method (n=3)

Formulation	Weight variation(mg)	Hardness(N)	Friability(%)	Disintegration Time(min)
F1	660±0.09	3.0±0.1	0.14±0.01	31±0.47
F2	660±0.08	3.1±0.2	0.14±0.01	29±0.47
F3	660±0.08	3.2±0.2	0.12±0.08	23±0.47
F4	660±0.09	3.2±0.01	0.11±0.08	20±0.47

(Table:7) Compression parameters of prepared formulations by direct compression method (n=3):

Formulation	Weight variation(mg)	Hardness(N)	Friability(%)	Disintegration Time(min)
F1	660±0.08	3±0.08	0.32±0.06	23±0.04
F2	660±0.07	3.2±0.1	0.37±0.03	21±0.04
F3	660±0.07	3.3±0.04	0.52±0.05	18±0.09
F4	660±0.08	3.2±0.01	0.57±0.03	19±0.09

Drug release profile of prepared formulations by Wet granulation method and Direct compression method: Metformin hydrochloride immediate-release tablets were prepared by using Microcrystalline cellulose 50mg and 75mg in F1 and F3 formulation, Dibasic calcium

phosphate 75mg and 100mg in F2 and F4 formulation, Croscarmellose Sodium, Crospovidone, Magnesium stearate and the percentage drug release was estimated by UV Visible spectrophotometer and the results were given in the below table.

Table 8: *In vitro* drug release profiles of prepared formulations by wet granulation method (n=3)

Time	F1	F2	F3	F4
5	14.7±0.1	17.6±0.2	31.3±0.2	29.5±0.2
10	23.2±0.2	24.5±0.2	37.9±0.2	38.7±0.2
15	31.3±0.2	30.9±0.3	49.3±0.2	48.6±0.2
25	39.4±0.1	43.6±0.1	59.5±0.2	58.5±0.2
30	48.2±0.1	48.8±0.2	66.6±0.2	65.1±0.1
45	54.1±0.3	57.1±0.2	87.8±0.3	82.8±0.1
55	62.4±0.2	66.8±0.2	95.2±0.1	94.1±0.2
60	70.9±0.2	74.6±0.2	99.3±0.2	100.1±0.2

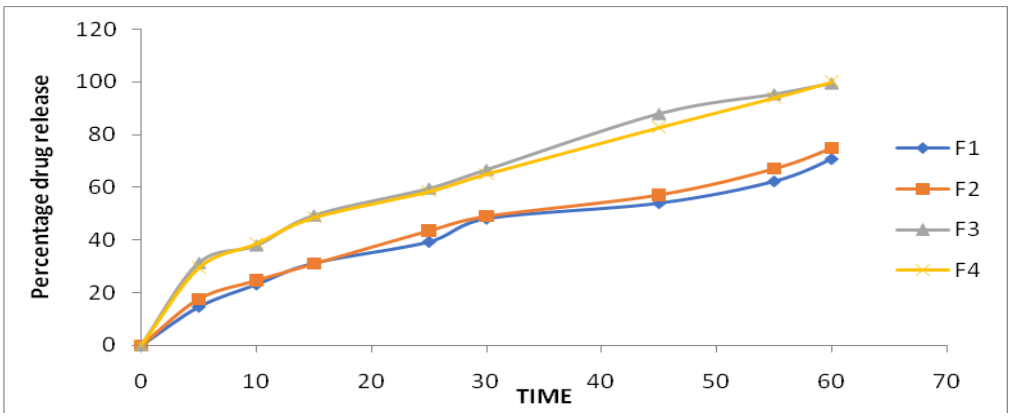


Figure 7: Drug release profiles of Metformin hydrochloride tablets by Wet granulation method

Table 9: *In vitro* drug release profiles of prepared formulation by direct compression method (n=3)

Time	F1	F2	F3	F4
5	15.4±0.2	16.9±0.1	28.8±0.3	30.3±0.2
10	24.3±0.4	23.9±0.1	39.4±0.3	40.1±0.4
15	30.2±0.7	31.6±0.3	48.2±0.2	50.7±0.2
25	41.9±0.3	42.3±0.3	55.9±0.2	57.7±0.1
30	49.3±0.1	52.8±0.2	64.8±0.1	66±0.3
45	55.9±0.5	57.6±0.1	83.1±0.2	86±0.3
55	63.3±0.1	66.6±0.08	93.7±0.2	94.5±0.1
60	72.6±0.5	73.6±0.2	98.4±0.2	99.9±0.08

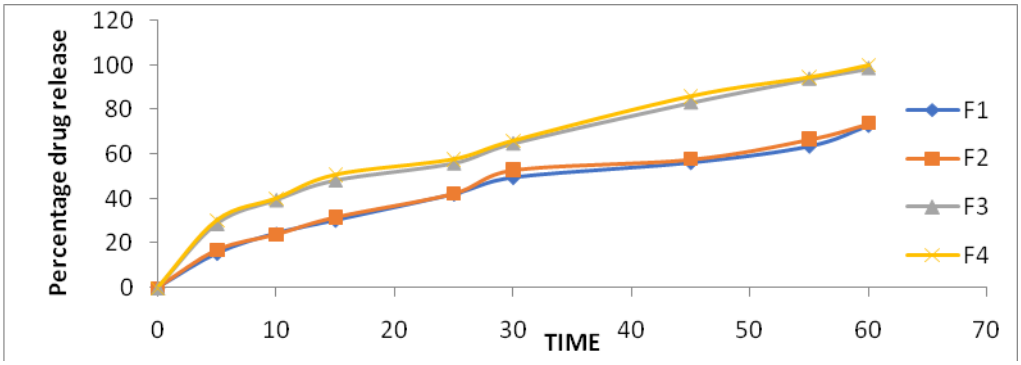


Figure 8: Drug release profile of Metformin hydrochloride by Direct compression method

***In-vitro* Drug release profile of Marketed GLYCOMET-850 formulation:**

GLYCOMET-850 is a Metformin hydrochloride immediate release tablet dissolution was performed as per the SOP and the percentage drug release was estimated by UV-Visible spectrophotometer.

Table 10: *In vitro* drug release of marketed formulation

Time (mins)	Percentage drug release
5	18.1
10	29.8
15	53.7
25	55.6
30	60.1
45	96.5

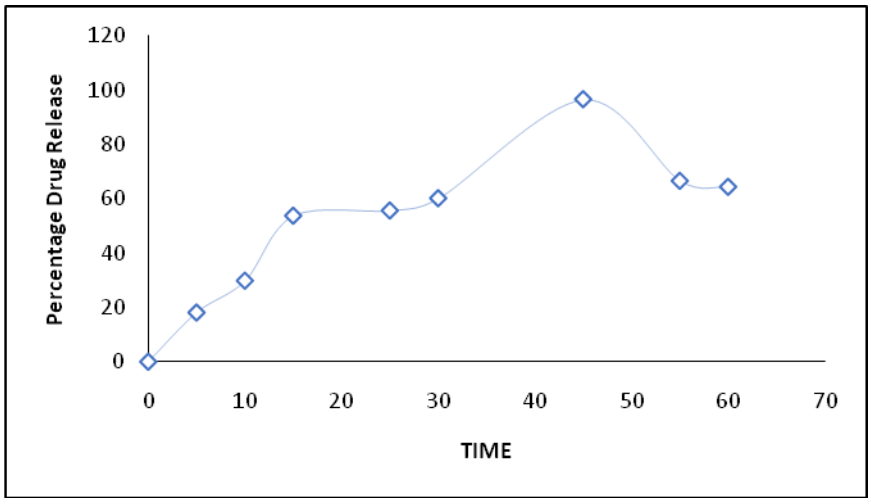


Figure 9: Drug release profile of Glycomet-850

From the table, it has been shown that the graph was plotted between percentage drug release on Y-axis and time on X-axis.Hence the drug was completely released at 45 minutes.

Table 11: Comparative dissolution study of optimized formulations prepared by wet granulation method with glycomet-850

Time (min)	F3	Glycomet-850	F4
5	31.3	18.1	29.5
10	37.9	29.8	38.7
15	49.3	53.7	48.6
25	59.5	55.6	58.5
30	66.6	60.1	65.1
45	87.8	96.5	82.8
55	95.2	-	94.1
60	99.3	-	100.1

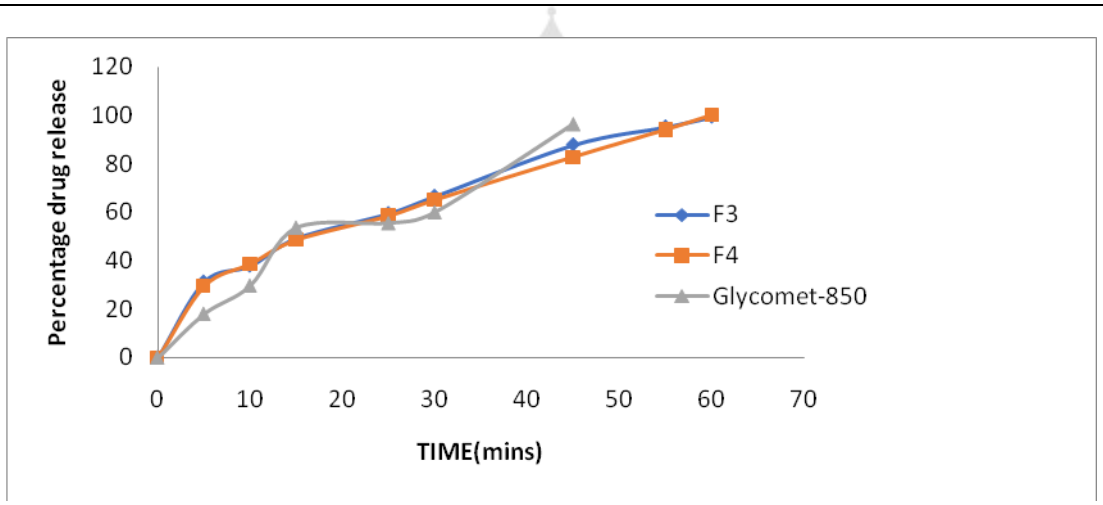


Figure 10: Comparative dissolution study of optimized formulations prepared by Wet granulation method with Glycomet-850.

From the above figure, it was observed that the optimized formulations F3& F4 prepared by wet granulation method shows 99.3% and 100.1% drug release in 1 hour whereas Glycomet-850 shows 96.5% drug release in 45 minutes.

Table 11: Comparative dissolution study of optimized formulations prepared by direct compression method with glycomet-850

Time (min)	F3	F4	Glycomet-850
5	28.8	30.3	18.1
10	39.4	40.1	29.8
15	48.2	50.7	53.7
25	55.9	57.7	55.6
30	64.8	66	60.1
45	83.1	86	96.5
55	93.7	94.5	-
60	98.4	99.9	-

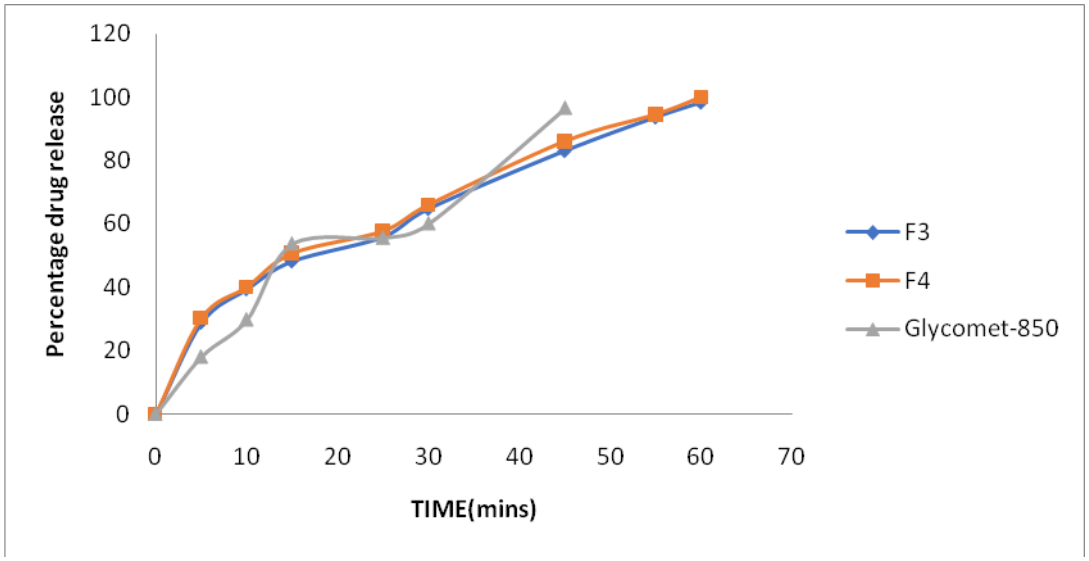


Figure 11: Comparative dissolution study of optimized formulations prepared by Direct compression method with Glycomet-850

From the above figure, it was observed that the optimized formulations F3& F4 prepared by direct compression method shows 98.4% and 99.9% drug release in 1 hour whereas Glycomet-850 shows 96.5% drug release in 45 minutes.

Table 12: Tablet weights of different brands of metformin hydrochloride

Sr. No.	Brands of Metformin hydrochloride	Tablet weight (mg)
1	Cipla	540
2	Glycomet	590
3	Glyciphage-500	550
4	Metgem-500	690
5	Metatime-500	590
6	Glycomet-850	1gm
7	Glyciphage-850	940
8	Prepared formulation	660

From the above table, it was clear that different brands of Metformin hydrochloride tablets are available in the market with a tablet weight 540mg-1gm.Hence from this, it was clear that there were no tablets available in the market with a tablet weight range between 540mg & 690mg.

Table 13: Dissolution profile of optimized formulations of metformin hydrochloride immediate release tablets by wet granulation method before and after 3 months stability (n=3)

Formulation code	Before stability			After stability		
	Physical appearance	Hardness (N)	% drug release (n=3)	Hardness (N)	% drug release (n=3)	Physical appearance
F3	White	3-3.2	99.3±0.2	3-3.2	99.4±0.1	White
F4	White	3-3.2	100±0.2	3.-3.2	99.9±0.1	White

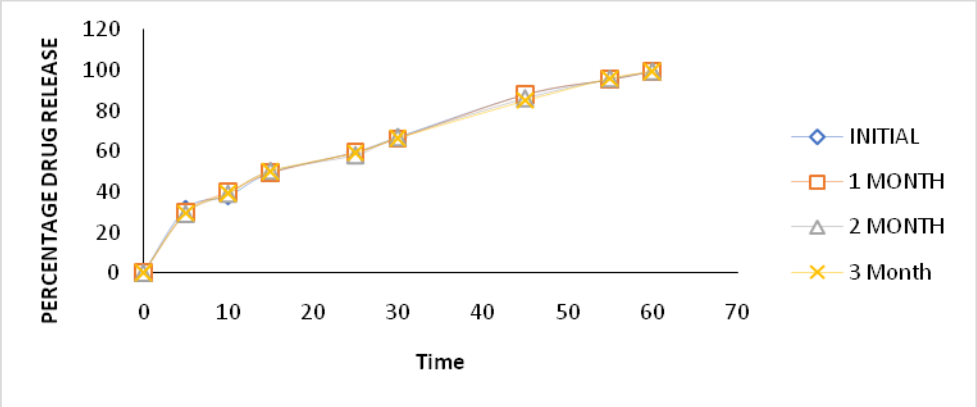


Figure 12: Percent Drug Release Profile of optimized formulation F-3 of Metformin hydrochloride after Stability studies

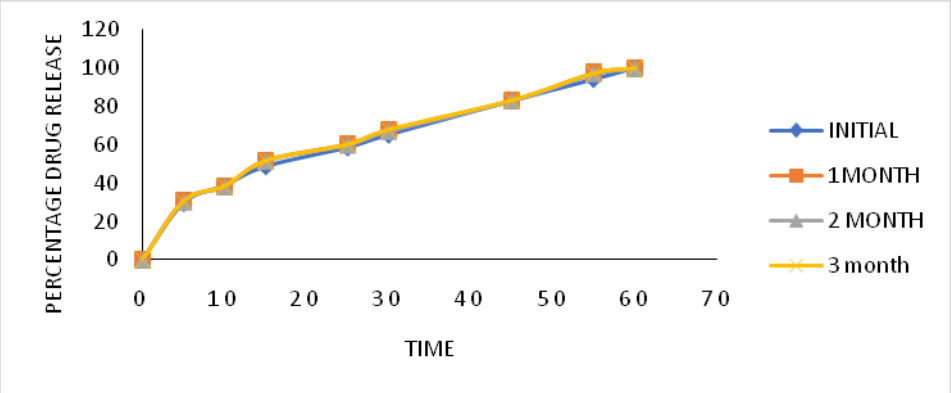


Figure 13: Percent Drug Release Profile of optimized formulation F-4 of Metformin hydrochloride after Stability studies

Table 14: Dissolution profile of optimized formulations of metformin hydrochloride immediate release tablets by direct compression method before and after 3 months stability (n=3)

Formulation code	Before stability			After stability		
	Physical appearance	Hardness (N)	% drug release (n=3)	Hardness (N)	% drug release (n=3)	Physical appearance
F3	White	3-3.3	98.4±0.2	3-3.3	98.6±0.2	White
F4	White	3-3.3	99.9±0.08	3-3.3	99.7±0.06	White

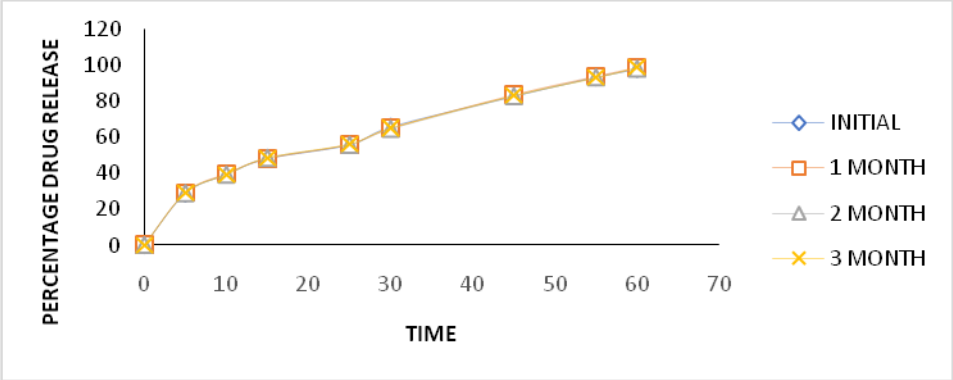


Figure 14: Percent Drug Release Profile of optimized formulation F-3 of Metformin hydrochloride after Stability studies

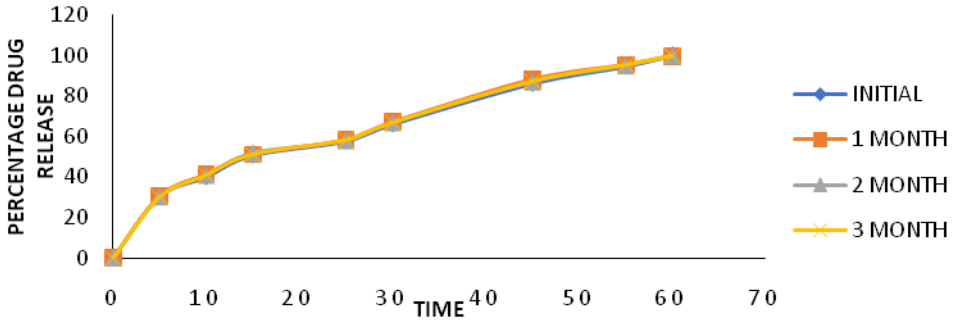


Figure 15: Percent Drug Release Profile of optimized formulation F-3 of Metformin hydrochloride after Stability studies

CONCLUSION:

From all the parameters studied, it has been concluded that optimized formulations of wet granulation method and direct compression method were found to be best regarding all the properties evaluated. The drug release was found to be within the limit as per USP at the end of 1 hour. The stability study indicated that the optimized formulation was stable even after storing at 40±20C/75±5% RH for 3 months. Thus, the results of the present study clearly indicated a promising potential of Immediate Release Metformin HCl tablets containing Microcrystalline cellulose, Dibasic calcium phosphate, Cross povidone, Croscarmellose Sodium, Magnesium stearate shows the better release when compared with other formulations and could be used for effectively treating diabetes mellitus.

ACKNOWLEDGEMENT: The author would like to express their gratitude to Dr.M. Sumakanth, Principal R.B.V.R.R Women's College of Pharmacy for providing the sufficient facilities to carry out the research work.

REFERENCES:

1. Herbet A.Liberman, Leon Lachman, and Joseph B. Schwart, *Pharmaceutical dosage forms: Tablets* USA: Marcel Dekker,1989; Volume 1(2).
2. Martin, A., Swarbrick.J., and Cammarata, A. *Physical Pharmacy: Physical Chemical Principles in the pharmaceutical sciences.*3rd. Lea and Febiger, Philadelphia, 1983.
3. Allen LV, Popovich NG, and Ansel H.C: Ansels*Pharmaceutical Dosage Forms and Drug Delivery Systems*. Lippincott Williams and Wilkins, Wolters Kluwer, New York, Edition 9, 2005: 431-492.
4. Vilegave K, Vidyasagar G, and Chandankar P: *Preformulation studies of pharmaceutical new drug molecule and products*: An Overview. American journal of pharmacy and health research 2013; 1(3): 1-20.
5. Gaud RS, Yeole PG, Yadav AV and Gokhale S.B: Textbook of pharmaceutics. Nirali Prakashan, Pune, Edition 12, 2011: 71-74.
6. Chein YW: *Novel drug delivery systems*. North Carolina, Edition 2, revised and expanded, vol. 50: 381-528.
7. Gopinath R, Naidu RAS: *Pharmaceutical preformulation studies- current review*. International journal of pharmaceutical and biological archives 2011; 2(5): 1391-1400.
8. Sarfaraz K. Niazi, Handbook of Preformulation, Pharmaceutical Scientist Inc.
9. Kalinkova, G.N. *Studies of beneficial interactions between active medicaments and excipients in pharmaceutical formulations.* International Journal of Pharmaceutics 1999,187, 1–15.
10. Pharmaceutical dosage form and design by David Jones pharmaceutical press 2008 edition pg.no-203-210.
11. Bentley's Textbook of Pharmaceutics, E.A. Rawlins. Eighth Edition ELBS
12. Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig. The theory and Practice of Industrial Pharmacy, Third Indian Edition, Varghese Publishing House Hind Rajasthan Building, Dadar Bombay 400014, 1987
13. N.K. Jain, S.N. Sharma. Vallabh Prakashan Textbook of professional pharmacy,
14. Morris, K.R. Structural aspects of hydrates and solvates. In Polymorphism in Pharmaceutical Sciences, Drugs and the Pharmaceutical Sciences; Brittain, H., Ed., Marcel Dekker: New York, NY, USA, 1999; Volume 95, pp. 125–181.
15. Abdullah, E.C., Geldart, D. The use of bulk density measurements as flowability indicators, Powder Technol. 1999, 102, 151–165.
16. Banker GS and Rhodes CT: Modern Pharmaceutics. Revised and expanded, Marcel Dekker, Inc. Newyork, Edition 4, vol.121, 2008:167-185.
17. Vincent HK Li, Vincent HK Lee and Robinson JR: Influence of drug properties and drug administration on the design of sustained and controlled release system. Controlled drug delivery fundamental and applications. Marcel Dekker, New York, Edition 2, 1987: 3-61.
18. Kulkarni G T, Gowthamarajan B and Suresh B: *Stability testing of pharmaceutical products-An overview.* Indian Journal of Pharmaceutical Education 2004; 38(4): 194-198.
19. Jain NK and Sharma SN: A Textbook of professional pharmacy. Vallabh Prakashan, Pitampura Delhi, 2004: 317-333.
20. M. Gibson, Pharmaceutical Preformulation, and Formulation, HIS Health Group, Englewood, CO, 2001.
21. Gilbert S, Banker, Christopher TR. Preformulation. In: Modern Pharmaceutics. IVth ed. New yark Marcel D. Inc. Basel;2005. p.167-185.
22. Gerry S. *Pharmaceutical Pre-formulation and Formulation. In*: Mark Gibson. (Ed). Florida: Boca Rotan. Interpharm/CRC;2004. p.21-22.
23. Kamlesh J. Wadher, *Formulation of Sustained Release Metformin Hydrochloride Matrix Tablets: Influence of Hydrophilic Polymers on the Release Rate and In-vitro Evaluation.*
24. Kotta Kranthi Kumar et al *Design, development and characterization of sustained release of metformin and gliclazide bilayered tablets*. International Journal of Biopharmaceutics. 2010; 1(2): 67-71.
25. RangasamyManivannan. et al, *Formulation, and evaluation of metformin hydrochloride sustained-release tablets.* International Journal of Biopharmaceutics. 2013; 4(2): 73-79,
26. R. Deveswaran, *Development of sustained release metformin hydrochloride tablets using a natural polysaccharide* International Journal of Applied Pharmaceutics Vol 4, Issue 2, 2012.