ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

DEVELOPMENT AND EVALUATION OF METFORMIN HYDROCHLORIDE TABLET IN DIABETIC TREATMENT

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ABSTRACT

This study's goal was to develop a gastroretentive system for metformin hydrochloride. The development and in vitro testing of gastro-retentive floating tablets of metformin are described in the current study. In order to create the formulations, cellulose derivatives like HPMC K4M and HPMC K15M were mixed in various ratios with gas-producing substances and other excipients. By using the direct compression method, floating tablets were created. Citric acid and sodium bicarbonate were utilised as a gas-generating agent. The formulations were evaluated in vitro using a variety of criteria, including hardness, friability, consistent drug content, in vitro floating experiments, in vitro dissolving studies, All of the formulations had nice visual appeal and better physical and mechanical characteristics. The formulation was tested for stability and IR spectroscopy, and it was discovered that it produced the greatest results for drug release and in vitro buoyancy time. The findings show that the formulation was stable and that the medication and polymer did not interact chemically.

Keywords: Metformin, buoyancy, and IR spectroscopy.

1. INTRODUCTION

Oral route for delivering drug is recognized for largely promising drug delivery system. There are many factors which affects the effective drug delivery. Maximum of drug products are generally administered by oral route.[1] There are many drugs which require locally delivery for the betterment of absorption. Factors like gastric emptying procedure, release pattern of drug from the dose, transit time from the gastrointestinal tract for the dose, are important for absorption in gastrointestinal tract.[2,3]

Gastro retentive drug delivery system is one kind of entry involves achieving a longer stomach residence time and then releasing the drug locally in the upper gastrointestinal tract to have a systemic impact. Floating drug delivery system (FDDS) is most commonly known as GRDDS.[4,5,6] This is a low-density system. There are numerous types of FDDS. FDDS is mainly of two types.[7] These systems are denoted as effervescent system and non-effervescent system. Effervescent drug delivery systems commonly comprise of mixture of effervescent substances, and swellable

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polymer.[8] This effervescent mixture generally comprises of carbonate or bicarbonate salts like sodium bicarbonate, and different kind of acids like citric and tartaric acid etc.[9]

Metformin hydrochloride is a medicine of biguanide class to treat hyperglycaemia. This is an AMP-dependent protein kinase activator. This medication ismainly used as the first line medication of choice for the management of type 2 diabetic condition. Also, this is used as a very preferable choice of drug in treatment of polycystic ovarian syndrome. It works by decreasing the Glucogenesis procedure by the liver. It also increases the secretion of Growth Differentiation Factor 15 and increases the insulin sensitivity to the body tissue.[10,11,12]

2. MATERIAL AND METHODS

2.1 Preparation of acidic buffer of pH 1.2 (N/10 HCl solution): To prepare this acidic solution, 8.4 ml of concentrated HCl have to be mixed in 1000 ml of distilled water. Then the pH is checked and adjusted with HCl or water or NaOH to get pH 1.2.

2.2 Preparation of Alkalline buffer of pH 6.8 (Phosphate Buffer): To prepare phosphate buffer, 11.45gm of potassium dihydrogen phosphate and 28.20 gm of disodium hydrogen phosphate have to be dissolved in adequate amount of distilled water. Then the level is to be made up to 1000ml. Then pH is to be checked and adjusted to 6.8.

2.3 Calibration curve for Metformin Hydrochloride in distilled water: Metformin Hydrochloride stock solution is made by accurately measuring 10 mg of the medication in an analytical balance and dissolving it in 100 ml of distilled water.

Then 1ml of the solution is to be further diluted to 100ml of distilled water. Thus 1µg/ml resulting solution is obtaining. Then serial dilution is to be done to obtain Metformin Hydrochloride solutions of concentration of 2 mcg/ml, 6 mcg/ml, 8µg/ml, 10 mcg/ml,12 mcg/ml. Absorbance of these specific solutions are to be checked at 233 nm in SHIMADZU UV-1900I UV/VIS spectrophotometer by using the distilled water as blank solution. The values of absorbance are noted and plotted against respective concentration to produce the calibration curve.

2.4 Calibration curve for Metformin Hydrochloride in acidic buffer: The stock solution of Metformin Hydrochloride is to be prepared by taking accurate amount of 10 mg of Metformin Hydrochloride in an analytical balance and dissolve it in 100ml of acidic buffer. Then 1ml of the solution is to be further diluted to 100ml of acidic buffer. Thus 1µg/ml resulting solution is obtaining. Then serial dilution is to be done to obtain Metformin Hydrochloride solutions of concentration of 2 mcg/ml, 4 mcg/ml, 6 mcg/ml, 8mcg/ml, 10 mcg/ml,12 mcg/ml. Absorbance of

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these all solutions are to be checked at 233 nm in SHIMADZU UV-1900I UV/VIS spectrophotometer by using the acidic buffer as blanksolution. The values of absorbance are noted and plotted against respective concentration to produce the calibration curve.

2.5 Calibration curve for Metformin Hydrochloride in phosphate buffer: The stock solution of Metformin Hydrochloride is to be prepared by taking accurate amount of 10 mg ofMetformin Hydrochloride in an analytical balance and dissolve it in 100ml of phosphate buffer. Then 1ml of the solution is to be further diluted to 100ml of phosphate buffer. Thus 1µg/ml resulting solution is obtaining. Then serial dilution is to be done to obtain Metformin Hydrochloride solutions of concentration of 2 mcg/ml, 4 mcg/ml, 6 mcg/ml, 8mcg/ml, 10 mcg/ml,12 mcg/ml. Absorbance of these all solutions are to be measured at 205 nm in SHIMADZU UV-1900I UV/VIS spectrophotometer by using the phosphate buffer as blank solution. The values of absorbance are noted and plotted against respective concentration to produce the calibration curve.

2.6 Preparation of Tablets

The floating patterned tablets of Metformin Hydrochloride were equipped via direct compression method. For this all the ingredients were weighed and mixed properly. Then the tablet compression goes on. After doing intermediate parameter check it is observed that formulation series F1 is not floating properly. So then required changes in formulations are done and formulation coded JUF series are punched. For tablet punching automated 8 station punching machine has been used.

2.7 Evaluation Studies

2.7.1 angle of repose

For this test to be performed at the first, the funnel is to be fixed at a specific height and a selected base is to be placed at specific space. Now the materials are to bepoured in the fixed funnel and it starts flowing on the base. After the whole material to be passed that forms a heap on the base. Now using this heap firstly, the measurement of the height of the heap is to be done. And then roughly a circle is to be drawn using the heap. A rough radius is to be measured from this circle. After getting the height and radius can

measured by inverse tangent rule.

$$\text{Angle of Repose } (\theta) = tan^{-1}(h/r)$$

2.7.2 Bulk volume and tapped volume

The mass of the sample divide with the bulk volume provides the bulk density or poured

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density. Thus, poured density is given by the equation.

$$\rho_p = M/V_p$$

tapped density is specified by the equation

$$\rho_t = M/V_t$$

2.7.3 Carr's Index

$$(CI) = \frac{(\rho_t) - (\rho_p)}{(\rho_t)}$$

2.7.4 Hausner Ratio

$$(HR) = \frac{(\rho_p)}{(\rho_t)}$$

2.8 Friability: Friability of the tablets were checked by using VEEGO digital friability apparatus. For performing the test 10 tablets of each formulation were taken and firstly weighed. Thereafter the tablets were then tumbled for 100 revolutions in friabilator. Those samples were the taken out from the friability apparatus and dedusted. Then the tablets were weighed then. The calculation was done as the percentage weight loss.

2.9 Hardness: Tablet hardness were checked via hardness tester by Monsanto. This instrument works depending upon the principle of application of diametrical force which results in breakage of the tablet. Maximum hardness of a tablet can be 20 kg/cm^2. For performing thistest randomly tablets are chosen and used. For testing the hardness of a specific tablet, the tablet is perfectly placed and the meter scale is fitted according to the size of the tablet. Then onwards force was applied and checked at which point the tablets gets broken. After that for being more sure VEEGO digital hardness tester being used to check hardness.

2.10 *In vitro* buoyancy study: To cheque the buoyancy time firstly 0.1 mole.lit-1 HCL or which can mimic the stomachic fluid and to be maintained at 37◦C. As the stomachic fluid is moreor less 900 ml, so this fluid needs to be the same amount. Then these dosage forms need to bedipped in the fluid. The time when it gets immerged in the fluid and takes the time to get floated is identified as floating lag time. Again, the time it remains floated on the facade ofthe fluid is denoted as total floating time.

2.11 *In Vitro* Dissolution: This study is done to check the drug release profile. To carry forward the test USP II VEEGO eight spindle dissolution apparatus was used. For this experiment 900ml of acidic buffer solution of pH 1.2 is to be used. At the time of the study 37±0.5º C vessel temperature

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is mandatory to maintain and motor rotation must be 50 rpm to mimic the in vivocondition. 5 ml of trial sample should be withdrawn at the time interval of 5 min, 10 min, 15 min, 30 min, 60 min, 90 min, 120 min, 150 min, 180 min, 210 min, 240 min, 270 min, 300 min and 5ml fresh dissolution medium was further added to the dissolution vessel after every withdrawal. Samples withdrawn are filtered and diluted and analyzed by using SHIMADZU UV-1900I UV/ VIS spectrophotometer. Thus, the absorbance of the diluted withdrawn samples is taken. The cumulative percentage of drug release was then calculated using the Higuchi diffusion, Korsmeyer-Peppas, zero order, first order, and Hixon Crowell plots.

2.12 Study using Fourier Transform Infrared Spectroscopy: FTIR is an analytical technique which is used for identification and characterization purpose for chemicals. This vibrational spectroscopic technique works by absorption or emission of infra-red ray. The fingerprint region for this spectroscopy is 4000 – 400 cm^{-1} and the scanning speed is 2mm/sec, and resolution is 4cm^{-1}. In case of pharmaceutical technology drug – excipients interaction study is done by FTIR. For FTIR spectrum pure drug, powdered sample of a tabletfrom the optimized batch and powdered sample of physical mixture of optimized batch is done. To check the interaction SHIMADZU, IR Prestige-21 is being used.

3. RESULTS

3.1 Metformin HCl

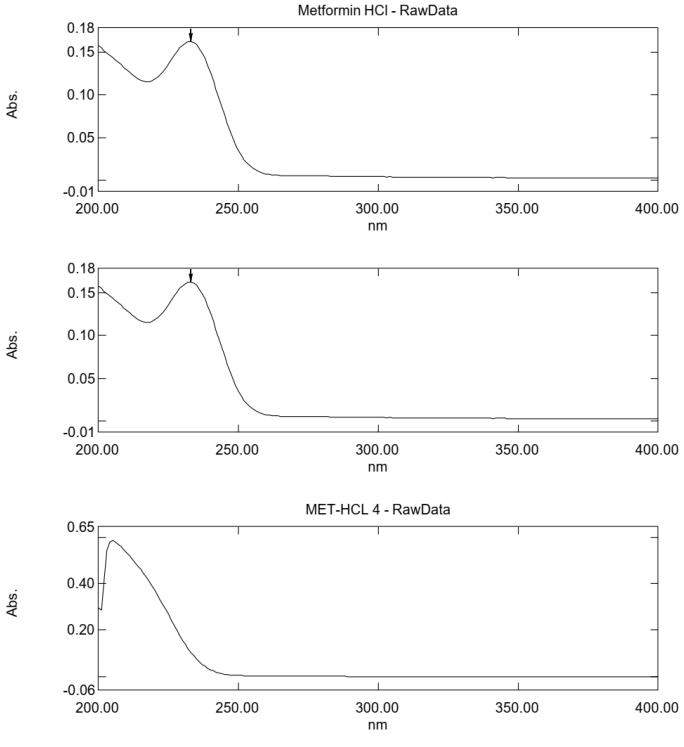

Figure 1. Calibration Curve

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3.2 FTIR study

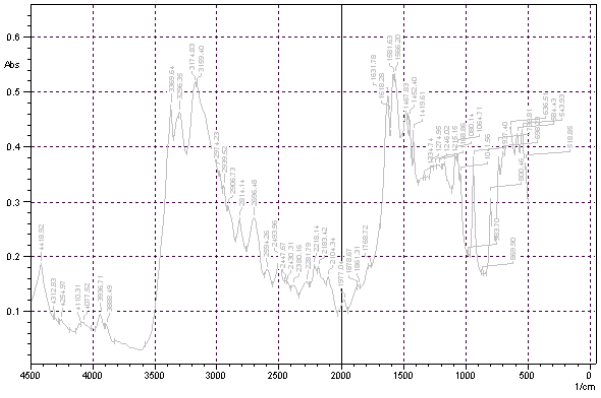

Figure 2. F.T.I.R. Study of pure drug (Abs Vs cm^{-1})

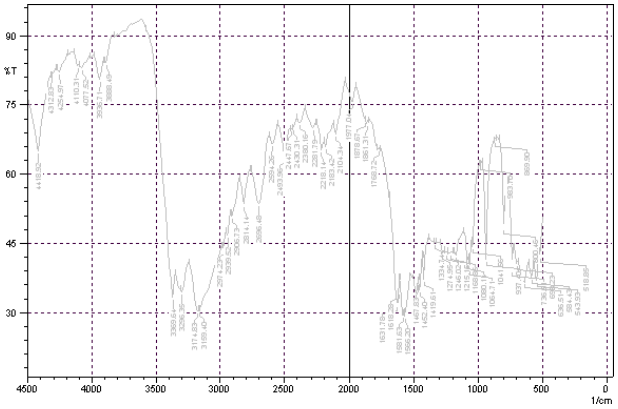

Figure 3. F.T.I.R. Study of pure drug (%T Vs cm^{-1})

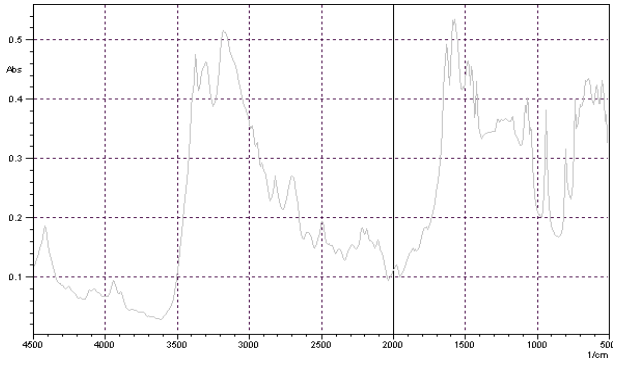

Figure 4. F.T.I.R. Study of pure drug (Abs Vs cm^{-1})

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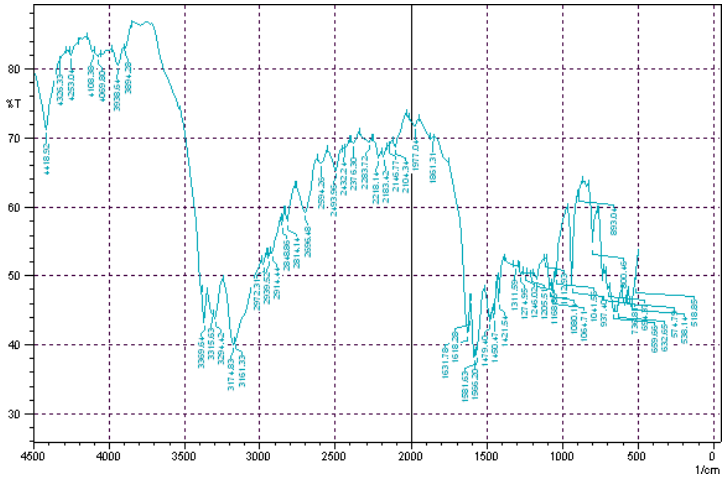

Figure 5. F.T.I.R. Study of excipients (Abs Vs cm^{-1})

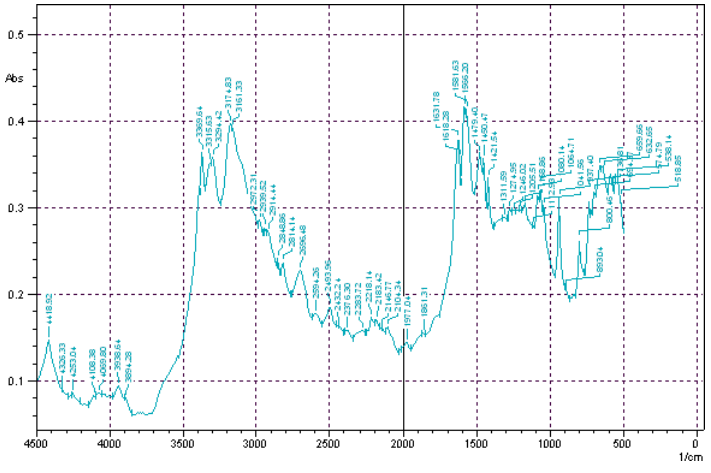

Figure 6. F.T.I.R. Study of excipients (Abs Vs cm^{-1})

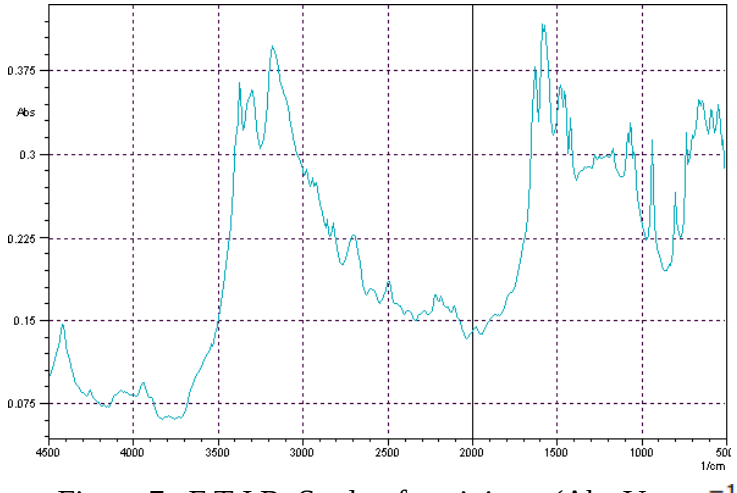

Figure 7. F.T.I.R. Study of excipients (Abs Vs cm^{-1})

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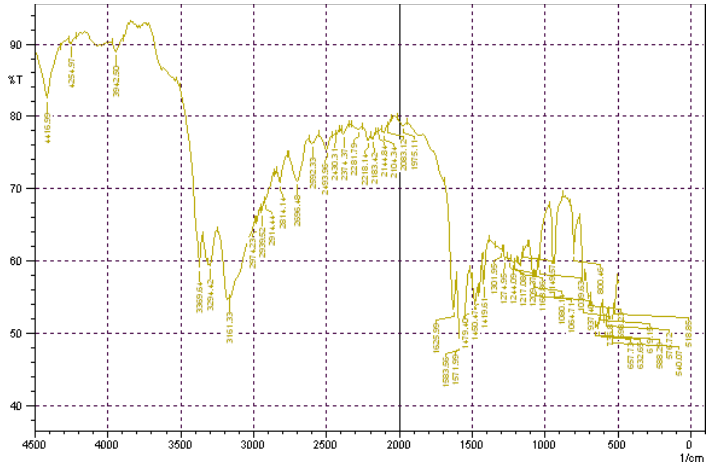

Figure 8. F.T.I.R. Study of Formulation (%T Vs cm^{-1})

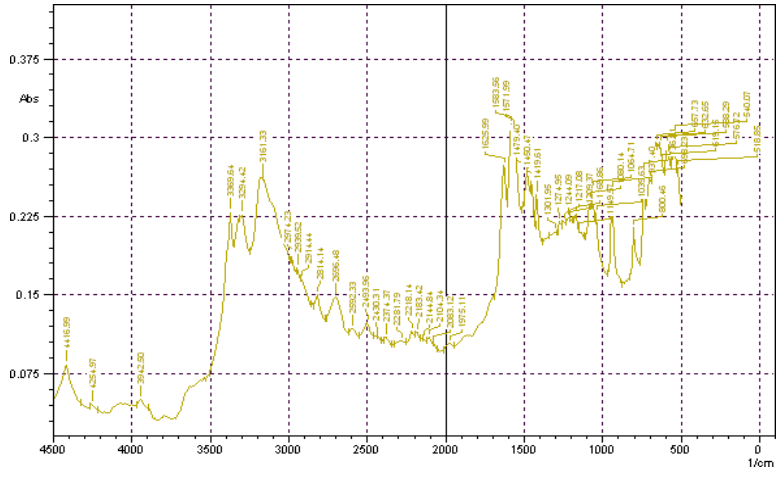

Figure 9. F.T.I.R. Study of Formulation (Abs Vs cm^{-1})

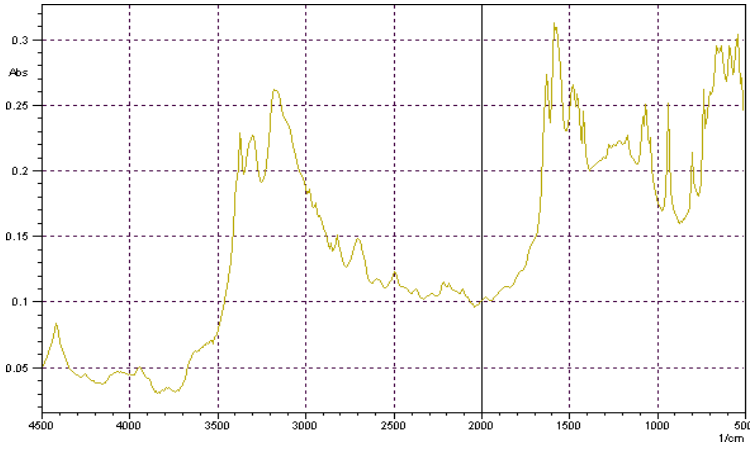

Figure 10. F.T.I.R. Study of Formulation (Abs Vs cm^{-1})

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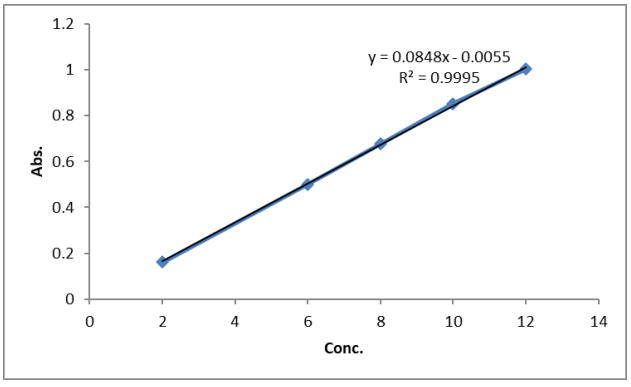

Figure 11. Metformin Hydrochloride Calibration Curve in Distilled Water at 233nm

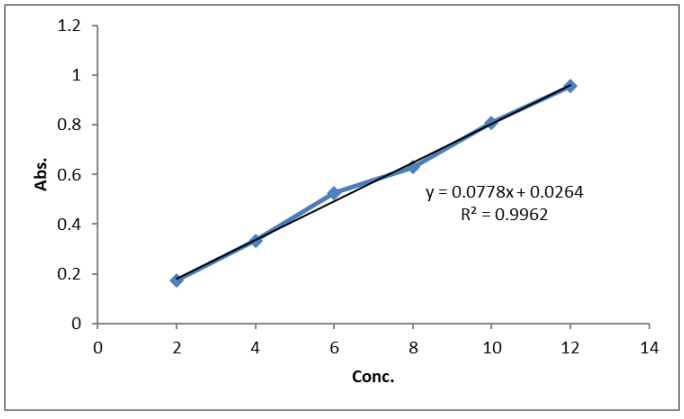

Figure 12. Calibration Curve of Metformin Hydrochloride in Phosphate Buffer (pH 6.8) at 233nm

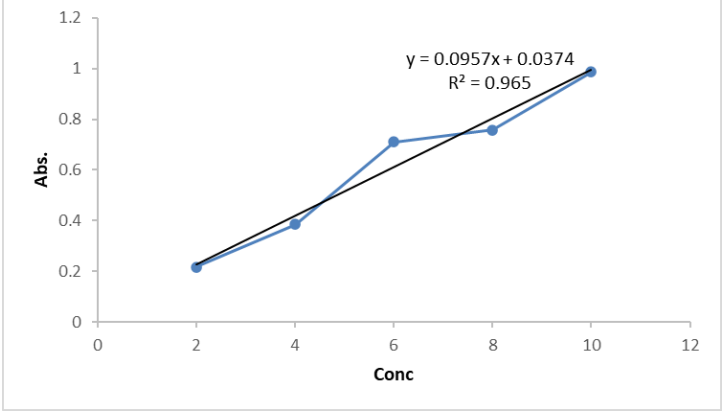

Figure 13. Metformin Hydrochloride Calibration Curve in Acidic Buffer (pH 61.2) at 205nm

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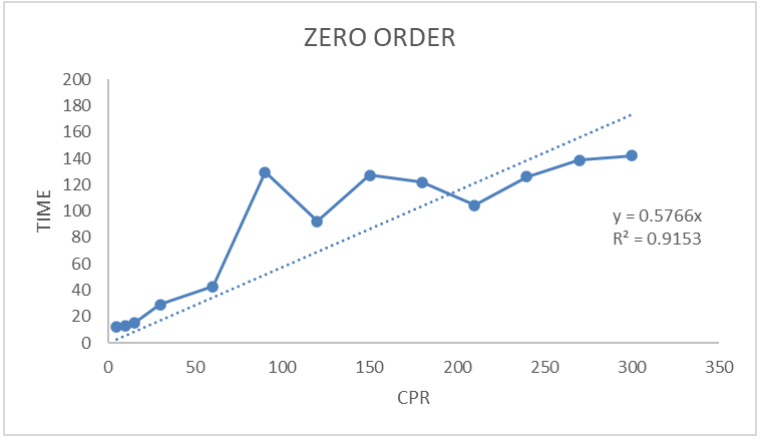

Figure 14. Zero Order Release (JUF1)

Figure 15. Zero Order Release (JUF2)

Figure 16. Zero Order Release (JUF3)

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Figure 17. First Order Release (JUF1)

Figure 18. First Order Release (JUF2)

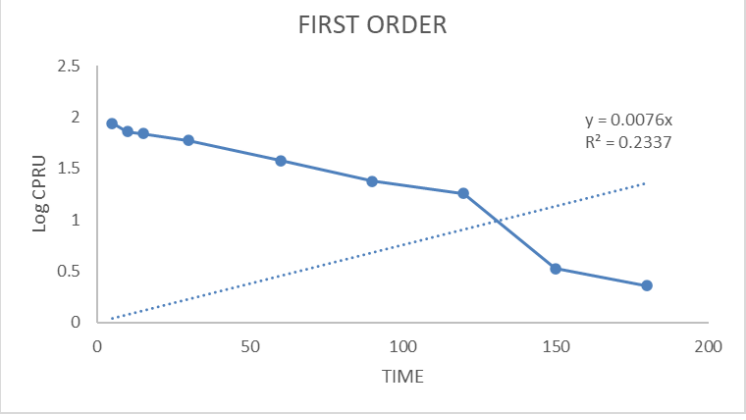

Figure 19. First Order Release (JUF3)

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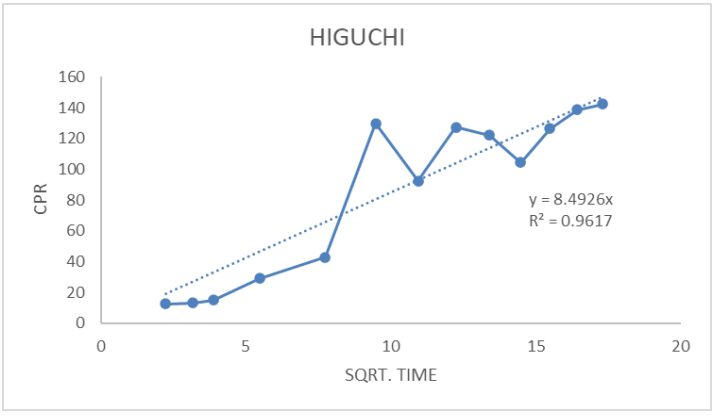

Figure 20. Higuchi plot (JUF1)

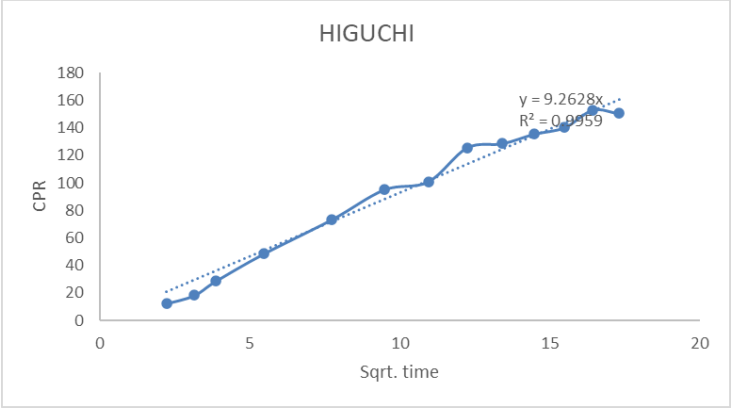

Figure 21. Higuchi plot (JUF2)

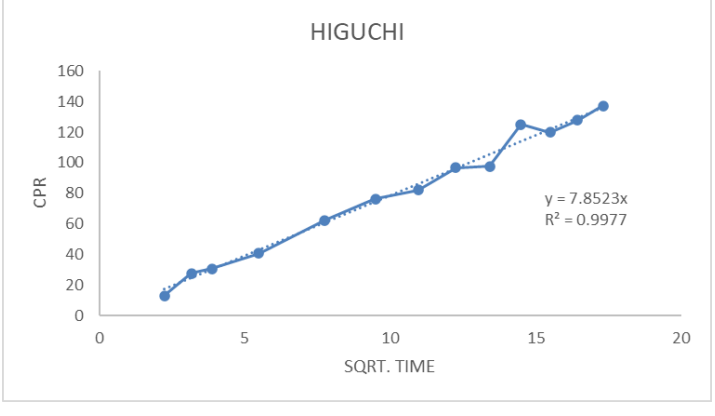

Figure 22. Higuchi plot (JUF3)

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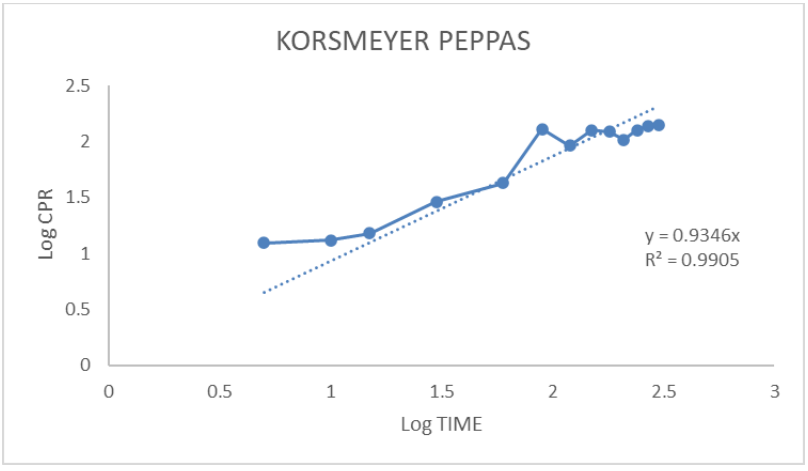

Figure 23. Korsmeyer Peppas plot (JUF1)

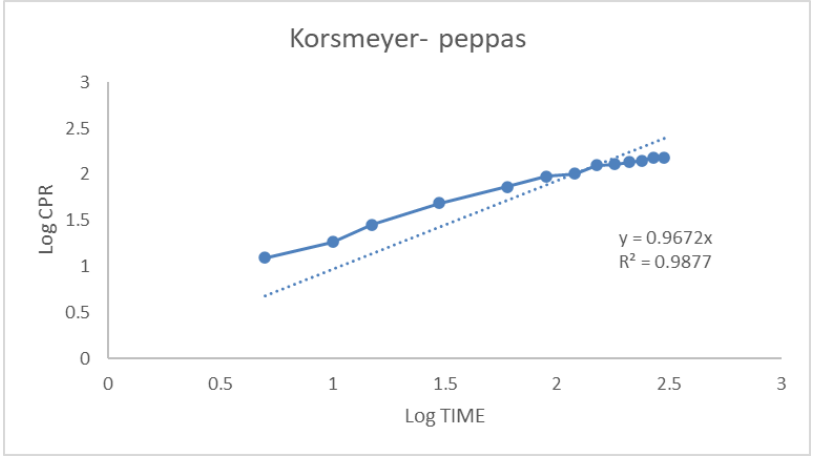

Figure 24. Korsmeyer Peppas plot (JUF2)

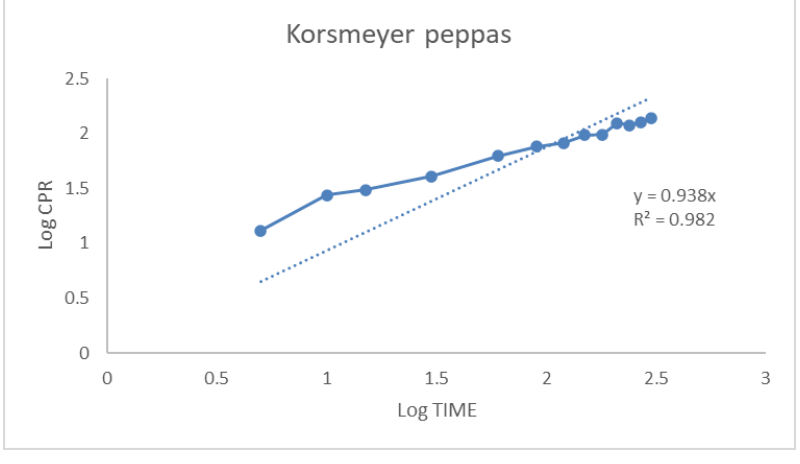

Figure 25. Korsmeyer Peppas plot (JUF3)

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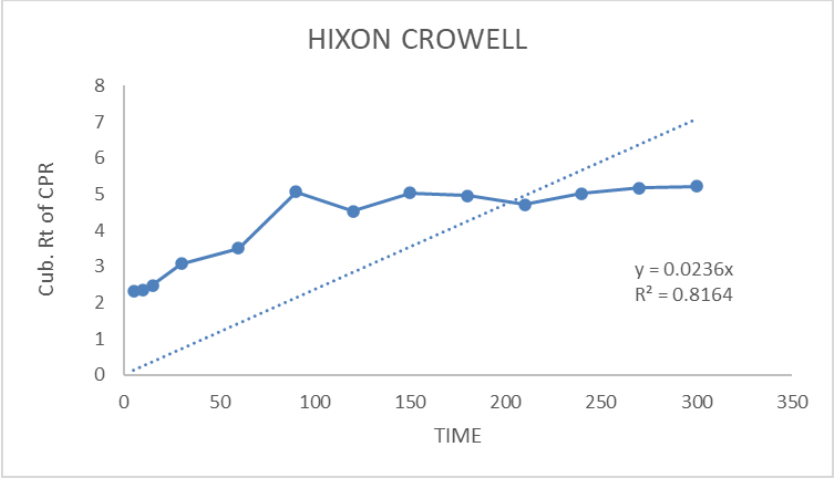

Figure 26. Hixon Crowell plot of Formulation Coded JUF1

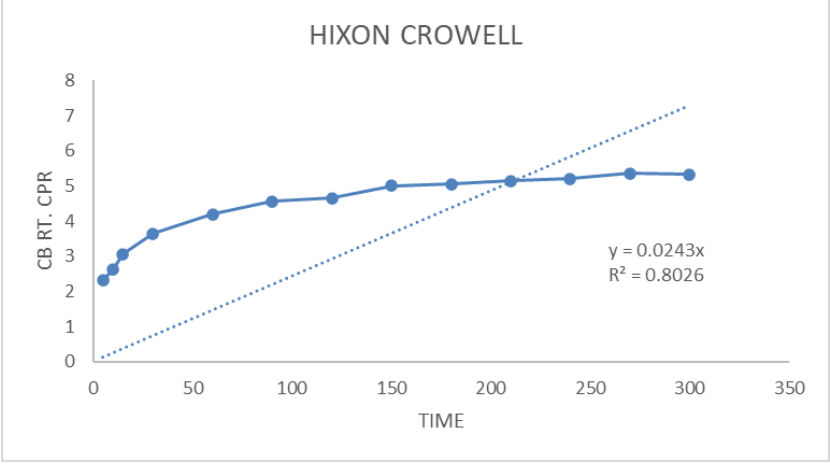

Figure 27. Hixon Crowell plot of Formulation Coded JUF2

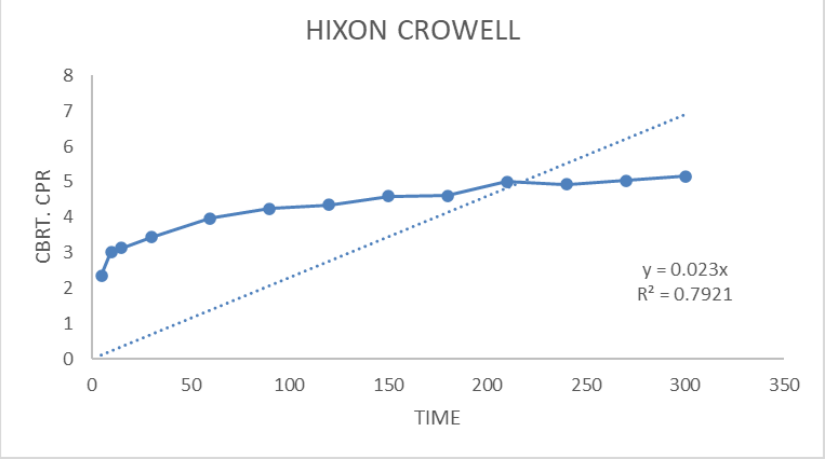

Figure 28. Hixon Crowell plot of Formulation Coded JUF3

Hardness: The hardness of all prepared batches of metformin tablets was tested. It was found that the hardness varies from the range of 5-8 kg/ cm^2 which helps the tablets in floating and drug release.

Friability Test: As the hardness test of the tablets are not the indicator of absolute strength so the

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friability of all the prepared tablets were checked. In this case of friability testing, loss % weight varies from the range of 0.015 -0.22 %. So, it can be concluded that the report does not cross the maximum limit.

Buoyancy Study: After checking in vitro buoyancy study it can be concluded that tablet coded JUF1 floated for more than 6 hours and other two formulations coded JUF2 and JUF3 are floated for more than 8 hours. This is suitable for sustained release.

F.T.I.R.: Through F.T.I.R. study many peaks are found in all the graphs. After doing a comparison of those graphs it can be stated that there is no major shift in the peak values seen. So it can be concluded like that there are no major interaction of excipients seen with the model drug Metformin Hydrochloride.

Drug Release Study: For the series tablets coded JUF all shows Higuchi pattern of drug release. According to Higuchi, drug release is a diffusion process based on the square root time-dependent Fick's law. This relationship can be used to explain how drugs dissolve from different kinds of pharmaceutical dose forms with modified release.

4. SUMMARY & CONCLUSION

Metformin Hydrochloride is widely used to treat non-insulin dependent diabetic condition. It also shows promising activity in poly cystic ovarian syndrome. But the main problem of the drug is narrow absorption window and moderate biological activity. Also, there is a urgent need of having a good sustained release formulation by taking250 mg drug as not available. So, to overcome these problems floating tablet of Metformin Hydrochloride is formulated. Tosupport the system and to give it a proper buoyancy many polymers are used in the formulations. Mixture of citric acid and sodium bicarbonate is used as effervescent mixture to offer the buoyancy. Here the natural polymer psyllium husk forms a hydrogel after getting the contact with the gastric content and helps in maintaining buoyancy. From F.T.I.R. analysis it can be stated that there are no significant interaction between drug and excipients. From drug release study we concluded that the tablets are following Higuchi drug release pattern which is diffusion mechanism and follows Fick’s law.

From the obtained data, we can conclude that;

- In order to prolong the anti-hyperglycemic medicine Metformin Hydrochloride's time in the stomach and hence enhance bioavailability, floating tablets of the drug can be created.
- The formulated tablets of series coded JUF shows pleasing results for different physicochemical evaluations like hardness, friability, in vitro buoyancy study and in vitro drug release study.
- These formulations took more or less 4 minutes to get buoyant which is okay to

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prevent those tablets from disintegrating.

- There is no drug excipient interaction seen. So, it can be stated that the actual activity of the model drug Metformin Hydrochloride can be achieved.
- Prepared floating tablets are best fitted to diffusion mechanism for drug release.

As a result, the findings of the current comprehensive investigation strongly suggest that the floating tablet of metformin hydrochloride has great potential to replace traditional dose forms. However, more clinical research is necessary to determine the effectiveness of these formulations for patients with Type II diabetes and polycystic ovary syndrome.

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