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FORMULATION AND *IN-VITRO* EVALUATION OF METFORMIN SUSTAINED RELEASE MATRIX TABLETS

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Keywords:

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ABSTRACT: Sustained released dosage form having an advantage over immediately release drug delivery system by continuous release of medicaments for a specific period in a prolonged manner. Diabetes mellitus (DM) is a common test endocrine issue that influences in excess of 100 million individuals ls around the world. Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion. Metform in hydrochloride (Met) used in the treatment of type 2 diabetes, having a short half-life is a challenge for the researcher towards achieving sustained drug delivery systems. Met with higher dose shows high solubility and inherent compressibility. Towards the same, Met was formulated with different combinations of polymers such as chitosan, HPMCK 100 M and eudragit RL-100 by the wet granulation method. The formulated granules were subjected for a pre-compression study like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The formulated tablets possess for post-compression studies. Drug-polymer interactions were investigated by FTIR studies. *In-vitro* drug release kinetics is carried out at pH 6.8. Formulation F7 has been found to be the best formulation and sustains the drug release 99.8% at 12 h. Obtained results reveal that when the concentration of eudragit RL-100 is more could be a good matrix for controlling the release rate of Met better than all other combinations. *In-vitro* release kinetic study carried out for all the formulations and followed the kinetics, says non-fickian and diffusion release.

INTRODUCTION: AS of 2016, 422 million people have diabetes worldwide, up from an estimated 382 million people in 2013 and from 108 million in 1980. Accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.5% among adults, nearly double the rate of 4.7% in 1980. Type 2 makes up about 90% of the cases. Some data indicate rates are roughly equal in women and men. Still, male excess in diabetes has been found in many populations with higher type 2 incidence, possibly due to sex-related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking and alcohol intake.

All the pharmaceutical products formulated for systemic delivery *via* the oral route of admini-

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stration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Sustained-release sustained action, prolonged action controlled-release, extended-release, depot release are the various terms used to identify drug delivery systems designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of the drug.

The goal in designing sustained release delivery systems is to reduce the frequency of dosing or to increase the drug's effectiveness by localization at the site of the action, reducing the dose required, or providing uniform drug delivery. Towards this, a hydrophilic polymer is considered as an ideal drug carrier to arrive at a sustained release oral formulation [1, 4]. The ideal drug delivery systems have two things that would be required; first, it would be a single dose the duration of treatment, whether it is for days or week, as with infection, or for the patient's lifetime, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of the action, thereby minimizing side effects. Hydrophilic polymer like HPMC controls drug release by its rapid hydration, gelation, cross-linking, and swelling properties [5, 6]. HPMC matrix formulation imparts a steady rate of drug release due to several factors such as compression pressure, particle size and shape, and incorporation of binding agent [7]. Chitosan as a marine polymer obtained naturally widely used as drug carrier and shows the property of bioadhesive, mucoadhesive, hydrophilicity activity [8, 15]. These polymers have received special attention in the field of biomedical [16, 17,] and pharmaceutical industries as a component to control the release rate of active drugs [18, 20]. Similarly, research reports confirm that the eudragit RL-100 with the combinations of other hydrophilic polymers could be a good matrix for controlling the drug release rate of metformin compared to individual polymers. Metformin hydrochloride obtained from natural sources as a drug for the treatment of type II diabetes mellitus [21]. It shows low bioavailability and a shorter half-life [22, 23]. This current research focused on increasing the bioavailability and sustained the release rate of metformin tablets by incorporating different types of polymers and their combinations.

MATERIALS AND METHODS:

Materials: Analytical grade metformin hydrochloride, hydroxypropyl methylcellulose (HPMC K100M), and polyvinyl pyrrolidone were obtained from Nice and Oxford laboratory, India, respectively. Chitosan analytical research-grade, the low molecular weight was purchased from Sigma Aldrich and used as received. All other excipients were of analytical research-grade and used as received.

TABLE 1: FORMULATION OF MET HCL CONTAINING MATRIX TABLET (MG)

Batch No.	Drug	CH	HPMC K100M	EU-RL-100	PVP K-30	Lactose	Talc	Mg. Stearate
F1	500	300	-	-	35	5	5	5
F2	500		300	-	35	5	5	5
F3	500			300	35	5	5	5
F4	500	250	25	25	35	5	5	5
F5	500	50	200	50	35	5	5	5
F6	500	50	50	200	35	5	5	5
F7	500	25	25	250	35	5	5	5

Preparation of Sustained Release Matrix Tablet: Formulations F1-F7 were prepared by wet granulation technique. A weighed amount of all ingredients were passed through sieve no-44 and mixed uniformly.

PVPK 30 as a binder mixed with isopropyl alcohol were added to the ingredients to form a dough mass. The dough mass was then passed through sieve no.16. Prepared mass was dried at 50°-60 °C till loss on dry (LOD) is less than 1-2% w/w and then passed through sieve no.18.

The weighed Amount of granules were taken for compression of tablet in a cad mach single punching machine (CMB6 D-30, Cad mach Engg, Ahmedabad) using 12 mm round biconcave punch. Each 850 mg tablet contains 500 mg of metformin and other pharmaceutical excipients, as listed in **Table 1.**

Pre-formulation Study:

Bulk Density: Bulk density is the ratio of the mass by the volume of an untapped powder sample. The bulk density is measured in g/ml. The bulk density depends on both the density of the powder particles and the arrangement of the powder particles. The bulk density influences preparation, storage of the sample. The mathematical re-presentation is given below.

Bulk density = weight of the drug / Bulk volume

Tapped Density: In tapped density, the bulk powder is mechanically tapped in a graduated cylinder until the volume change is observed. Here the tapped density is calculated as mass divided by the final volume of the powder.

Tapped density = weight of the granules / tapped volume

Angle of Repose: It gives an idea of the flowability of granules or a bulk solid. There is some factor which responsible for the flowability of powders such as particle size, shape, surface area, etc. The flowability of the powder depends on the different environments and can be changed easily. The angle of repose was calculated by the following formula.

$$\theta = \tan^{-1} h/r$$

Where = θ = angle of repose, h = height of the formed cone, r = radius of the circular base

Carr's Index: It is one of the most important parameters to characterize the nature of granules.

Carr's index (%) = (Tapped density - Bulk density/ Tapped density) × 100Hausner's ratio

It is an important character to determine the flow property of granules in the presence of different compositions of polymers. The following formula can calculate this.

Hausner's ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow, and greater than 1.25 indicate poor flow.

Post-compression Study:

Weight Variation Test: Twenty tablets were selected randomly from each formulation and weighed individually using a digital balance (Shimadzu AUY 220, Uni Bloc, Germany). The average weights were calculated, and mean values were determined. It should not deviate more than ± 5% as per the Indian Pharmacopeia (IP).

Tablet Thickness Test: To determine the uniformity and physical dimension of tablet, thickness is measured by Vernier calipers for randomly selected 20 tablets from each formulation.

Hardness Test: Hardness is determined to measure the strength of a tablet for randomly selected 10 tablets from each formulation using Monsanto Hardness Tester [24].

Tablet Friability: Previously weighed 10 tablets were placed in Roche's friabilator for 15 min/ 100 rpm. The tablets were de-dusted and accurately weighed. The % loss was calculated as per IP. It is expected to be less than 1%.

Drug Content Uniformity: Ten tablets from each formulation were crushed and dissolved in water. The solution was filtered, and the drug content was determined by UV spectrophotometer (Jasco V-670, Japan) at 232 nm with a suitable dilution.

***In-vitro* Dissolution Test:** Drug release studies for all formulations were determined using USP type II dissolution. Secor India Lab) at 100rpm bearing 900 ml of pH 2 or pH 6.8 medium at 37 ± 0.5 °C. At regular intervals of time, 5 ml samples were withdrawn and replaced by fresh solution, and the absorbance was measured at 232 nm.

***In-vitro* Release Kinetic Study:** To examine the release mechanism of drugs from the tablets, the *In-vitro* drug release data of metformin was carried out for all the formulations with the following release models mentioned below.

Where Mt = Amount of drug dissolved at time t, Mo = Initial amount of drug, K1 = First order release constant, K0 = Zero-order release constant, KH = Higuchi rate constant, Kk = Korsmeyer–Peppas model release

- Zero-order: Mt = Mo+ Kot
- First-order: ln Mt = ln Mo+ K1t
- Higuchi model: Mt = KH √t
- Korsmeyer-Peppas model: Mt/Mo = Kktn

apparatus (Secor India Lab) at 100 rpm bearing 900 ml of pH 2 or pH 6.8 medium at 37 ± 0.5 °C Kk = Korsmeyer-Peppas model release.

RESULTS: Fig. 1-7: shows the FTIR spectra of metformin HCl, chitosan, HPMC K100M, eudragit RL-100 and their compositions. A high intense stretching frequency occurring at 3392.79 and 1631.78 cm^{-1} correspond to -OH and –NH3+ groups present in Metformin HCl. On the other hand, CH shows 1622.13 cm^{-1} corresponds to–NH3+ groups, HPMC shows a peak at 3469 cm^{-1} assigned to -OH groups, and eudragit RL-100 has shown 3487.30 cm^{-1} correspond to -OH groups. In case of drug and polymer compositions, the broadening of bands appears at the range of 3392.79, 3394.72, 3466 cm^{-1} can be inferred due to intermolecular H-bonding between drug and polymers. **Table 2**. listed the comparative study for pre-compression of all the formulations F1-F7. All parameters such as bulk density, tapped density, angle of repose, carr's index and Hauser's ratio values lie between 0.247 to 0.453 gm/ml, 0.21 to 0.48 gm/ml, 26.49 to 31.07, 16.37 to 25.39, and 1.11 to 1 [21]. respectively. The result concluded that obtained results were within limits and show excellent flow properties for the prepared granules. Similarly, **Table 3** lists all the post-evaluation data and compares physicochemical properties of all the formulations (F1-F7). The obtained result reveals that prepared tablets were mechanically stable for further study. All formulations are subjected to dissolution test, and formulation F7 shows 97.88% of drug release with 12 h represents in figure 8. Formulation F7 has been considered as the best formulation depending on their controlling the release rate of metformin due to the high concentration of eudragit present in polymeric matrixes. Further, the study carried out for disintegration test for all formulations. The in-vitro release kinetic study was carried out for all formulations F1-F7 and follows both the kinetics, say non fickian and diffusion release.

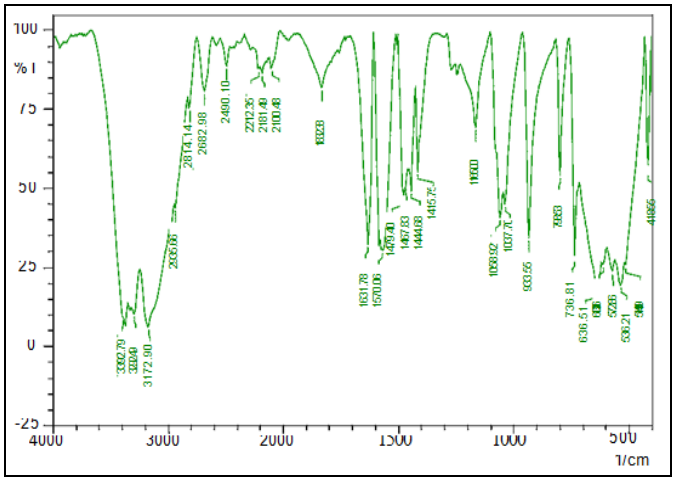

FIG. 1: FTIR SPECTRUM OF METFORMIN HCL

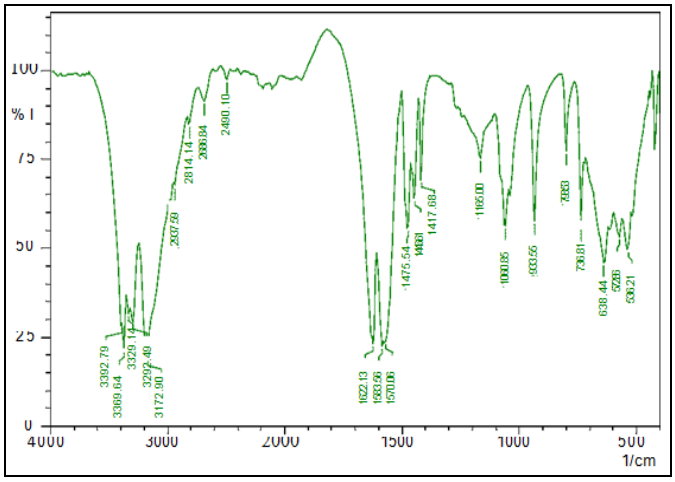

FIG. 2: FTIR SPECTRUM OF CHITOSAN

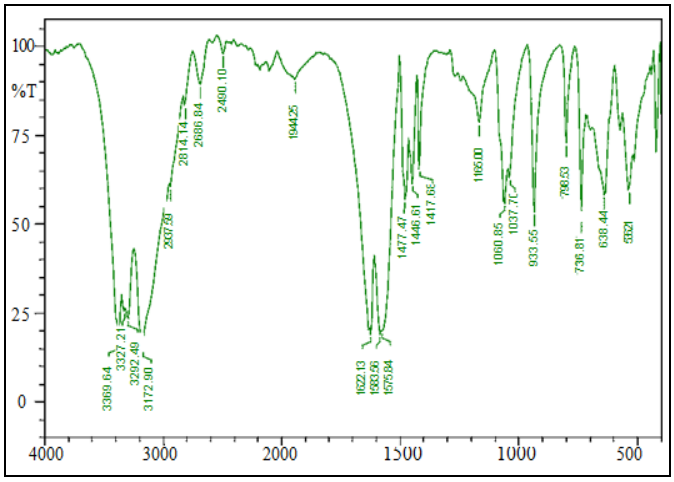

FIG. 3: FTIR SPECTRUM OF HPMC K100M

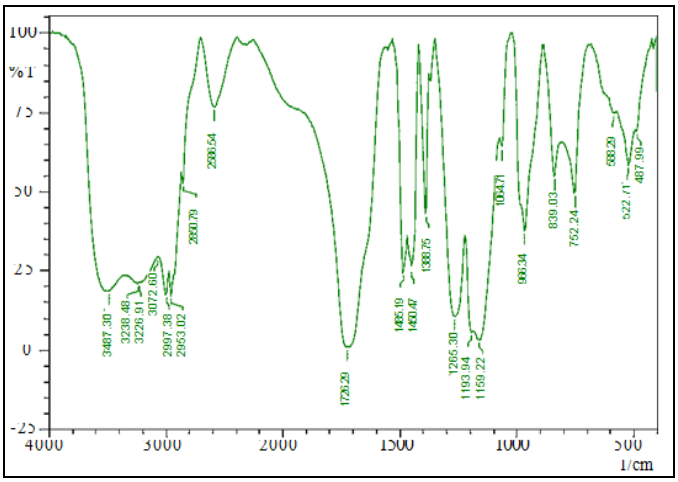

FIG. 4: FTIR SPECTRUM OF EUDRAGIT RL-100

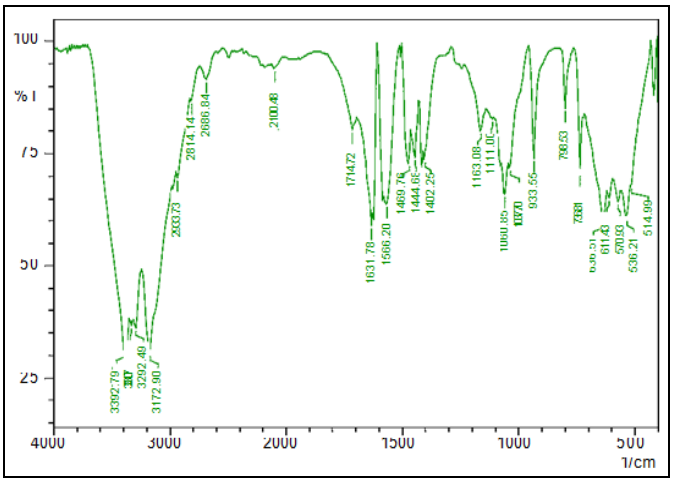

FIG. 5: FTIR SPECTRUM OF METFORMIN HCL AND CHITOSA

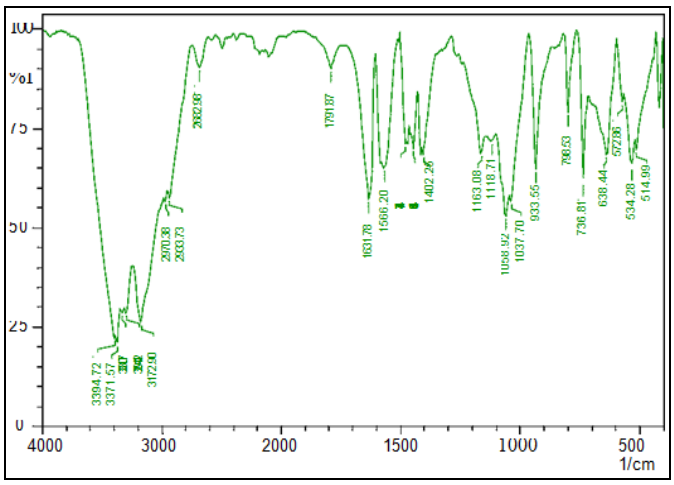

FIG. 6: FTIR SPECTRUM OF METFORMIN HCL AND EUDRAGIT RL-100

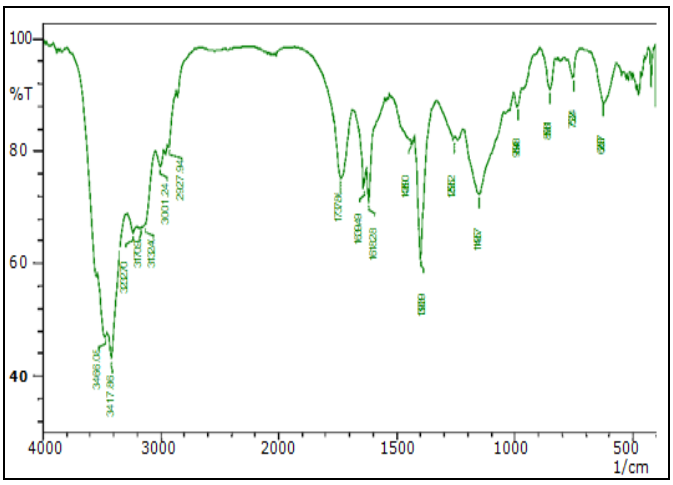

FIG. 7: FTIR SPECTRUM OF METFORMIN HCL AND HPMC K100M

DISCUSSION: Fig. 1 to **7.** shows the FTIR spectra of metformin HCl and polymers (such as chitosan, HPMC K100M, eudragit RL-100) and their compositions. The obtained result reveals that there is no shifting or change in metformin spectra when it is combined with pure polymers. This proves that individual polymers and their different weight ratios are compatible with the drug metformin hydrochloride.

TABLE 2: PRE-FORMULATION STUDY FOR MET HCL GRANULES (F1 TO F7)

Formulation	Bulk density	Tapped Density	Angle of Repose	Carr's index	Hausner's ratio
F1	453.01 + 0.01	0.48 + 0.02	30.02 + 0.97	25.39 + 2.04	1.18 + 0.02
F2	268.1 + 0.03	0.32 + 0.09	29.12 + 0.19	21.52 + 1.08	1.14 + 0.06
F3	247.0 3+ 0.9	0.23 + 0.09	27.61 + 0.05	19.72 + 1.54	1.11 + 0.01
F4	448.1 + 0.3	0.47 + 0.05	31.07 + 0.73	24.37 + 1.92	1.21 + 0.07
F5	349.03 + 0.06	0.39 + 0.04	27.33 + 0.93	20.13 +1.13	1.15 + 0.04
F6	350.01 + 0.09	0.27 + 0.08	28.51 + 0.03	18.45 + 2.07	1.16 + 0.02
F7	249.07 + 0.31	0.21 + 0.05	26.49 + 0.01	16.37 + 1.38	1.15 + 0.01

Metformin contained granules were evaluated for their pre-formulation properties that play an important role in granules flowability and compression of granules. The comparative study for pre-compression of all the formulations is listed in **Table 2.** Obtained results were within limits and showed excellent flow properties. All parameters such as bulk density, tapped density, angle of

repose, carr's index and Hauser's ratio values lies between 0.247 to 0.453 gm/ml, 0.21 to 0.48 gm/ml, 26.49 to 31.07, 16.37 to 25.39 and 1.11 to 1.21, respectively.

Evaluation of Metformin Hcl Tablets (F1-F7): Physicochemical properties play a vital role in the drug delivery system. So a comparison of physicochemical properties of all the formulations (F1-F7) is listed in **Table 3.** The weight variation was found to be within the limit of ± 5%. The average weight for all formulations was found to be in the range of 851.09 to 848.13 mg. The uniform thickness was obtained throughout all the formulations and found in the range of 4.89 ± 0.39 to 5.29 ± 0.31 mm.

The formulated tablets passed through the hardness and friability tests as per the standard limits, the hardness ranging from 6.54 ± 0.83 to 7.03 ± 0.04 and the percentage of friability obtained below 1%.

The drug content for different formulations was found to be within the standard limit of 97.89 ± 1.99% to 99.97 ± 0.09%. The prepared tablets are thus mechanically stable for further study.

TABLE 3: EVALUATION OF MET HCL TABLETS (F1-F7)

Formulation	Tablet Weight variation (mg)	Tablet Thickness (mm)	Tablet Hardness (kg/cm^2)	Tablet Friability (%)	Drug content (%)
F1	848.13 + 1.08	5.29 + 0.31	7.02 + 0.32	0.58 + 0.01	99.49 + 1.99
F2	849.17 + 1.72	5.16 + 0.36	6.81 + 0.51	0.26 + 0.41	98.96 + 0.22
F3	848.24 + 1.13	5.23 + 0.07	7.03 + 0.04	0.42 + 0.11	99.15 + 0.21
F4	849.25 + 1.07	4.89 + 0.39	6.72 + 0.05	0.66 + 0.39	97.89 + 1.99
F5	848.17 + 1.83	5.09 + 0.02	6.91 + 0.87	0.37 + 0.45	97.99 + 0.93
F6	850.31 + 1.8	5.17 + 0.71	6.54 + 0.83	0.56 + 0.13	98.76 + 0.08
F7	851.09 + 1.02	4.91 + 0.05	6.99 + 0.87	0.34 + 0.26	99.97 + 0.09

Metformin is a hydrophilic drug, maintains the body sugar level by slowdown the sugar absorption in the small intestine reduces glucose production in the liver, and utilizes insulin present in the body. The sustained release drug delivery is ideal for prolonging its activity; patient Compliance 25 facilitates complete drug release in the small intestine by using different types and grades of polymers. In- vitro dissolution time for formulation F1 to F7 tablets show variations in release due to the different types of polymers incorporate in the formulations.

The formulation containing a higher proportion of eudragit (F7) is found to have better control in drug release rate than other polymers. This can be attributed to the matrix network with HPMC, which is also considered as a rate-controlling polymer. The combination of eudragit and HPMC act as a gel-forming barrier and retarding the rate of diffusion of the drug molecule. Formulation F1 showed immediate release of metformin 99.76% within 30 min as it disintegrates rapidly and act as an immediate-release tablet. Formulations F2 and F3 have shown a relatively slower rate of drug release of 99.77% and 95.31% within 5 h and 7 h, respectively attributed to the presence of higher viscosity grade and gelling nature of polymers. Formulations F4 has shown 98.63% of drug release within 6 h due to the composition of a higher Amount of chitosan with eudragit and HPMC. Formulation F5 and F6 have shown 98.91% and 96.51% within 8h and 10h, respectively. Formulation F7 shows 97.88% of drug release with 12 h due to the gradually increasing concentration of eudragit in the formulation. Figure 8 has shown the drug release pattern for different formulations (F1- F7).

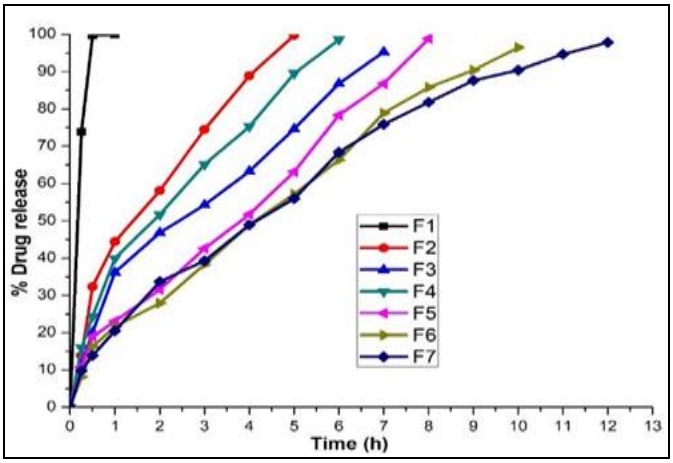

FIG. 8: *IN-VITRO* DRUG RELEASE OF METFORMIN FROM DIFFERENT POLYMER MATRICES FORMULATION F1-F7

Release Kinetic Study: The release kinetic parameters for all mathematical models of drug release are obtained from the dissolution study and shown in **Table 4.** Kinetic release studies are evaluated by zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas model. The release kinetics follows both the kinetics, say non-fickian and diffusion release for the formulation F1 to F7.

TABLE 4: RELEASE KINETICS OF MET FROM THE PREPARED FORMULATIONS (F1-F9)

Batch No	R2 Values						
	Zero order plots	First order plots	Hixson-crowell plots	Higuchi plots	Korsmeyer-peppas plots R2	Diffusional exponent (n)	Order of release
F1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
F2	0.9808	0.9143	0.8484	0.9292	0.9862	0.9508	non fickian
F3	0.9525	0.9315	0.9907	0.9796	0.9836	0.9736	Diffusion
F4	0.9773	0.9161	0.9648	0.9377	0.9867	0.9417	non fickian
F5	0.9911	0.9178	0.9786	0.9638	0.9927	0.9563	non fickian
F6	0.976	0.7949	0.9514	0.9657	0.9798	0.9533	non fickian
F7	0.9672	0.9428	0.984	0.9595	0.9679	0.9258	Diffusion

CONCLUSION: In this study, we have successfully designed a biocompatible matrix as a drug carrier for highly water-soluble metformin drugs in order to prolong the release rate for an optimum time period. So here, different types of polymers have been taken in different compositions to achieve the target. Chitosan polymer could not sustain metformin release for more than 30 min., but in combination with other polymers, the release rate is extended up to 6 h in F4. Matrices prepared with a high concentration of eudragit polymer with a combination of HPMC and chitosan proved to be a useful drug carrier to retard the metformin release up to 12 h in F7. The high viscosity grade and higher concentration eudragit with HPMC and chitosan are highly advantageous towards the formation of a complex network matrix to prolong the release pattern in a sustained manner.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest.

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