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Development and Characterization of Metformin-Loaded Gastroretentive Beads for Controlled Drug Release

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Abstract: This study aims to develop metformin-loaded beads with controlled drug release by combining polymers such as Hydroxypropyl Methylcellulose (HPMC) K4M, HPMC K100M, Eudragit RL100, and sodium alginate. HPMC K4M and K100M are cellulose derivatives commonly used as matrix formers in sustained-release formulations. Eudragit polymers, including RL100, are acrylic-based polymers often employed in controlled-release formulations. Sodium alginate is strategically included to enable bead floatation, facilitating sustained drug release in a gastroretentive drug delivery system (GRDDS), is also known for its excellent biocompatibility and biodegradability. It forms a gel-like structure in the presence of calcium ions, aiding in sustained drug release and prolonging drug residence time in the stomach. The beads undergo comprehensive % yield, % drug content, pH, viscosity, swelling index, and *in vitro* dissolution profile. Findings suggest the potential of these beads for prolonged metformin delivery in the gastrointestinal tract, with sodium alginate enhancing both buoyancy and overall GRDDS effectiveness, promising benefits in diabetes management.

Keywords: Metformin, Hydroxypropyl Methylcellulose, Sodium alginate, Gastroretentive drug delivery system, Diabetes management, Diabetes mellitus

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Introduction

Diabetes mellitus (DM) as one of the endocrine diseases, with more than 100 million people are suffering from all over the world (Kharroubi and Darwish, 2015; Sandu *et al.*, 2016; Mukhtar *et al.*, 2020). It is a condition arising out of the failure of the body to adequately secrete insulin a glandular hormone (produced by the pancreas). Any scenario that results in inadequate insulin supply or site dysfunction is characterized by hyperglycemia; elevated blood glucose levels are an unambiguous sign of diabetes. By contrast, T2DM is mainly characterized by insulin resistance where tissues in the body fail to respond correctly to insulin (Muoio *et al.*, 2008; DeFronzo *et al.*, 2015; Zatterale *et al.*, 2020). T2DM is associated with many aspects of the life

styles including obesity, lack of physical activity and incorrect diet despite having hereditary component. It is ordered to harm many of body systems especially blood vessels, eyes, Kidney, heart and the nerves (Giri *et al.*, 2018; Amorrortu *et al.*, 2020). The condition accompanied by the presence of DM is a predictor of many complications that include retinopathy, blindness, cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, amputations etc. Diabetes atlas 2006 of "International diabetes federation" reveals that at present India has 40.9 million diabetics which will rise to 69.9 million by 2025 unless measures are taken to arrest it (Siddiqui *et al.*, 2013; Kawade *et al.*, 2020).

For most drugs conventional methods of drug administration are effective, but some drugs are unstable or produce toxicity and have narrow therapeutic ranges. Some drugs also possess solubility problems. In order to avoid such problems a continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies (Dika *et al.*, 2020). In Controlled drug delivery system the active drug is sustained to the targeted site as per the needs of body or disease state over a specified period of time (Hennessy *et al.*, 2005).

Gastroretentive delivery systems are one of the newest, promising approaches that aim at improving the pharmacokinetics and therapeutic effectiveness of drugs with a low fraction absorbed in the upper part of the GI tract (Lopes *et al.*, 2016; Ibrahim *et al.*, 2019). The concept of gastroretentive beads can be considered one of the most viable contemplating targeted drug release. Due to their small size and the use of appropriate polymers and excipients, these beads can either float on the stomach contents or remain within the stomach, allowing for a gradual release of the drug. This controlled release mechanism improves the drug's bioavailability by prolonging its presence in the stomach and ensuring a sustained therapeutic effect.

The beads are generally composed of polymers like naturally occurring polymers e.g. Sodium alginate, whereas synthetic polymers include Hydroxypropyl Methylcellulose (HPMC), and Eudragitetc, which assist in development of matrix to form stable structure with drug and helps in controlling drug release rate (Haque *et al.*, 2014; Patra *et al.*, 2015; Maskova *et al.*, 2020; Khiste *et al.*, 2021). The method used is ionotropic gelation where a polymer solution is treated with multivalent ions like calcium ions resulting in production of spherical beads. The addition of sodium alginate increases the buoyancy of beads so that it floads when the beads are in the gastric fluid. This characteristic is very important in GRDDS since it assist in maintaining the dosage form in the stomach where the release is controlled.

In the case of the release of controlled drugs, the beads have been developed to swell and release the drug at a predetermined time. This sustained release depends on the nature of polymer used, drug polymer ratio, and crosslink density. For example, with the help of HPMC K4M and K100M the methods work in tandem: in the gastric realm the polymer swells and forms a gel layer which regulates the drug diffusion rate. Moreover, Eudragit polymers aid in formulation of a pH sensitive system that have matte pKa of 5.45 and thus ensure slow and efficient drug release in the stomach acidic pH and not the small intestine.

The advantages of gastroretentive beads include long circulation of the drug in the stomach, increased assimilation, and reduced dosing, which has impact on drugs that are unstable or have low assimilation in lower part of the GIT (Gandhi *et al.*, 2012; Duttagupta *et al.*, 2015; Nareshkumar *et al.*, 2019). For example, metformin, which is an oral anti-diabetic drug, is

Table 1: Formulation of metformin HCl beads with different polymers in (mg)

Batch no.	Metformin (mg)	HPMC K4 (mg)	HPMC K100 (mg)	Eudragit RL-100 (mg)	Sodium alginate (mg)
F1	10	30	-	-	50
F2	10	-	30	-	50
F3	10	-	-	30	50
F4	10	10	10	10	50
F5	10	20	10	10	50
F6	10	10	20	10	50
F7	10	10	10	20	50
F8	10	-	-	-	50

well encapsulated in GAR by transforming it to gastroretentive beads to achieve sustained plasma level and to minimize GI intolerance. The fact that the beads float and sustain a controlled release profile provide better patient compliance and better therapeutic results.

In conclusion concerning the gastroretentive beads which are described in this study, one can state that such system is rather promising and effective in realizing the controlled drug release. Their slow gastric residency as well as the controlled/programmed release system make them a good choice for delivering drugs with a small absorption window; or drugs for which the action is desired primarily in the upper parts of the GI tract. Gastroretentive drug delivery can be considered to have a more stable and promising future in the future developments in polymers and drugs combination for better results of treatment and the patient.

This study aims to develop metformin-loaded beads with controlled drug release by combining polymers such as Hydroxypropyl Methylcellulose (HPMC) K4M, HPMC K100M, Eudragit RL100, and sodium alginate.

Materials and Methods

Metformin HCl and hydroxypropyl methyl-cellulose (HPMC K100M) were obtained from Biocon Biopharmaceutical Company, India. Eudragit RSPO was obtained from Nice Chemicals Private Limited, Cochin, India. All other excipients were of analytical research grade and used as received.

Preparation of beads by ionic-gelation method

Beads containing metformin HCl (formulation F1-F8) were prepared by ionotropic-gelation technique (Table 1). Calculated amount of polymers such as HPMC K4 and HPMC K100 and eudragit were used to prepare the solutions independently by using magnetic stirrer for 2 h until a clear solution was obtained. Formulation F1 to F3 has been prepared by individual polymers whereas formulation F4 to F7 is the composition of all three polymers at different ratios mentioned in Table 1. Formulation F8 was formulated without any polymer. Similarly a constant amount of sodium alginate solution was prepared separately and mixed with the above prepared solutions and stirred for 3 h until a clear homogeneous bubble free solution was obtained. Further metformin was added to the polymeric solution and ultra-sonicated for 5-10 min for debubbling. The resulting solution was added via a 21-gauge needle drop wise into 100 ml of 10% $CaCl_2$ solution and retained as such for 15-25 min to complete the reaction and harden the droplets. The wet beads were rinsed thrice with distilled

water and dried at 60°C in hot air oven and put it in air tight container for further use.

Results and Discussion

Drug polymers physical compatibility studies

Metformin HCl and polymers (HPMC K4M, HPMC K100M, Eudragit RL-100) mixtures were consider for the pre-compatibility study. The prepared mixtures showed no colour changes in their appearance. The physical compatibility was found to be optimum between drug and all polymers and considered as good formulation.

Drug compatibility study using FTIR

The FTIR spectrum of drug (Metformin hydrochloride), individual polymers (HPMC K4, K100 and Eudragit RL-100) and different composition of drug - polymers have shown in Figures 1 and 2. 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.

Percentage yield

It was observed that as the polymer viscosity increases in the formulation, the product yield also increases. The low percentage yield in some formulations may be due to adhesion of the polymeric solution to the container and magnetic bead during preparation. The percentage yield for all formulated beads was found to be in the range of 93 to 98% (Table 2).

Drug content

Table 2 shows the drug content of formulated beads for all formulations. It provides the data that how much drug is present in the prepared formulated metformin beads. It was found that the drug content for all the formulation lies between the ranges of 95% to 99%. The highest drug content was found in the optimized formulation F7.

pH

It was found that the pH of all the formulations was in the range of 5.98–6.82 (Table 2) that suits for oral route without producing irritation to the mucous membrane.

Viscosity

The viscosity ranged between 399 and 999 cps (Table 2) for all formulations. Low viscosity was found for the formulation F3 and F8. Formulation F8 does not contain any polymers but formulation F3 containing low viscosity grade of polymer at higher concentration. This could be the reason of low viscosity found in formulation F3 and F8.

Swelling index

The swelling index is a critical parameter associated with evaluating the fluid absorption or the capacity of making a material or a polymer swell. It is obtained by determining an increase in weight of the material being tested once the latter has been immersed in a liquid, preferably water, for some time. Swelling index is generally the measure of ability of a material to absorb liquid; higher swelling index is generally more desirable, especially for drug delivery systems, because it directly affects the release rate of the active drug. For example, in the gastroretentive delivery systems with high swelling index, beads enlarge and float on the stomach therefore provide longer retention period. The swelling index ranges from 68.82 to 86.88 (Table 2).

Drug release profile

In vitro dissolution study

Drug release studies for all formulations were determined using multi bucket USP basket apparatus at 100 rpm bearing 900 ml of pH 6.8 medium at 37 ± 0.5°C. At regular intervals of time, 5ml sample were withdrawn and replaced by fresh solution and the absorbance was measured at 232 nm after a suitable dilution. The obtained absorbance was used in calibration curve equation of metformin to further calculate the % of drug release at different interval of time.

In vitro Dissolution study

In vitro dissolution time for formulations F1 to F8

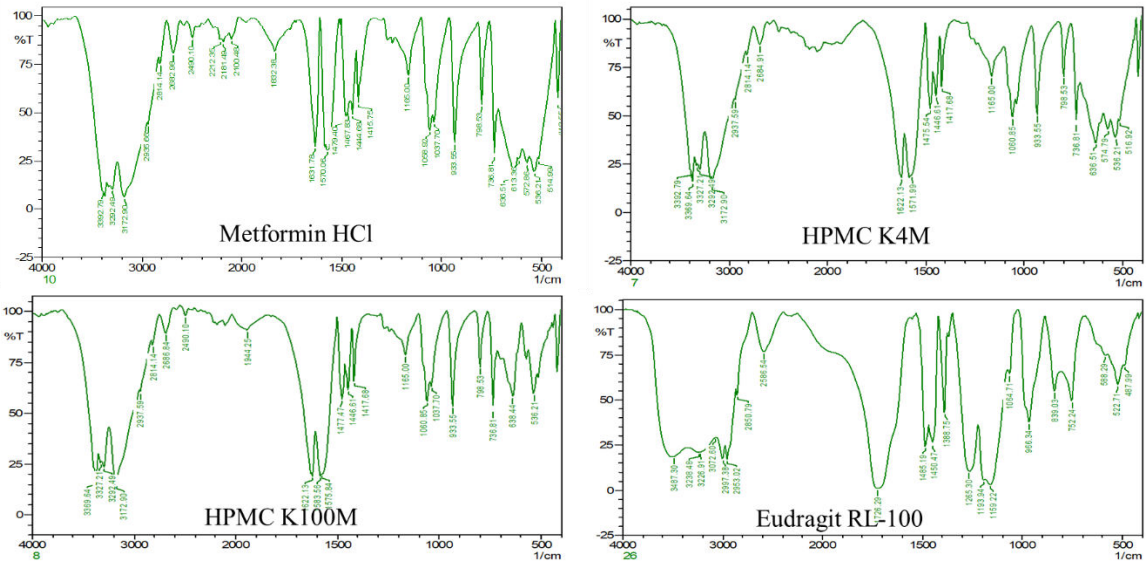

Fig. 1: FTIR spectra for pure metformin HCl, HPMC K4M, HPMC K100M and Eudragit RL-100.

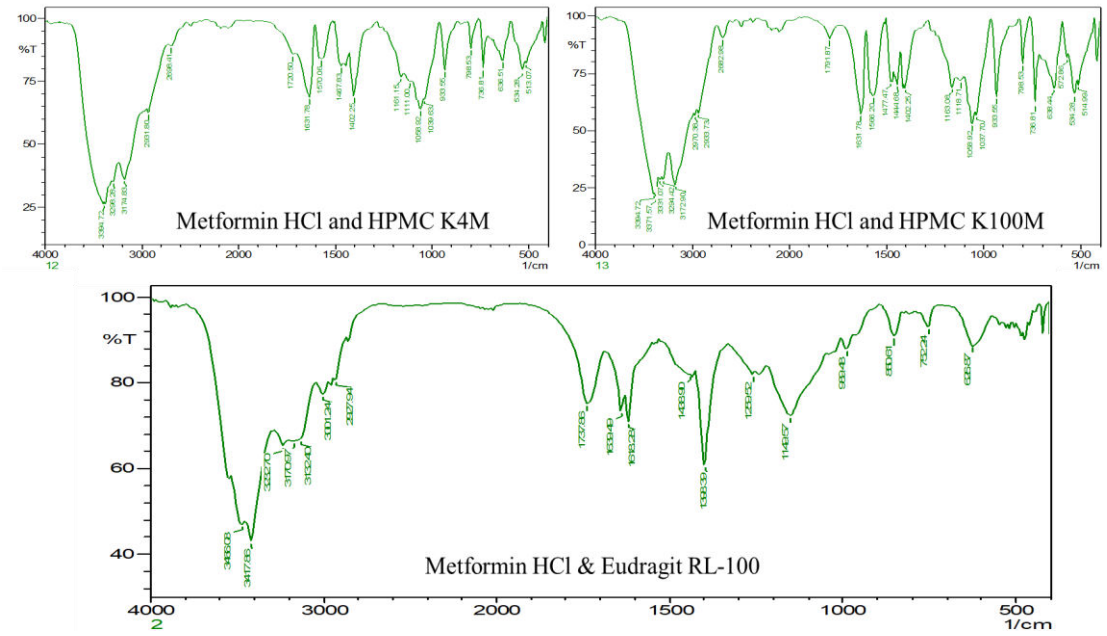

Fig. 2: FTIR spectra for the mixture of metformin HCl, with HPMC K4M, HPMC K100M and Eudragit RL-100.

beads shows variation in release period ranging from 5 h to 18 h (Fig. 3). This may be attributed to the nature of polymer and their viscosity grades used in various proportions in formulations. Low viscosity grade of HPMC K4M in formulation F1 is unable to control the release rate of metformin and shows 97% release in 7 h. The high viscosity grade of HPMC K100 forming complex matrix network and able to prolong release rate of metformin 96% at 10h in formulation F2. Similarly formulation F3 contains hydrophobic eudragit polymer and shows 99% release at 10 h. An optimum release rate could not obtained by individual polymers. Formulation F4 to F7 contain different ratio of polymers in formulations. Obtained results confirm that different compositions of polymers provide better control of metformin release as compared to individual

Table 2: Evaluation study of metformin HCl beads

Formulation	Percentage yield (%)	Drug content (%)	pH	Viscosity (cps)	Swelling index
F1	97.84±0.59	97.47±1.66	5.98±0.78	490.99±1.89	86.88
F2	98.32±0.21	99.11±0.33	6.13±0.98	999.34±11.04	72.87
F3	95.95±1.09	96.11±0.72	6.82±0.72	428.68±17.77	68.82
F4	96.77±0.32	96.99±0.43	6.43±0.11	490.77±15.42	77.22
F5	96.91±0.14	96.11±0.34	6.11±1.32	452.75±13.82	84.32
F6	97.81±0.12	97.59±0.23	6.7±0.83	966.96±10.21	78.91
F7	96.98±0.93	98.56±1.99	6.82±0.01	459.72±13.26	68.11
F8	93.53±0.11	95.15±0.37	5.99±0.87	399.99±13.32	73.19

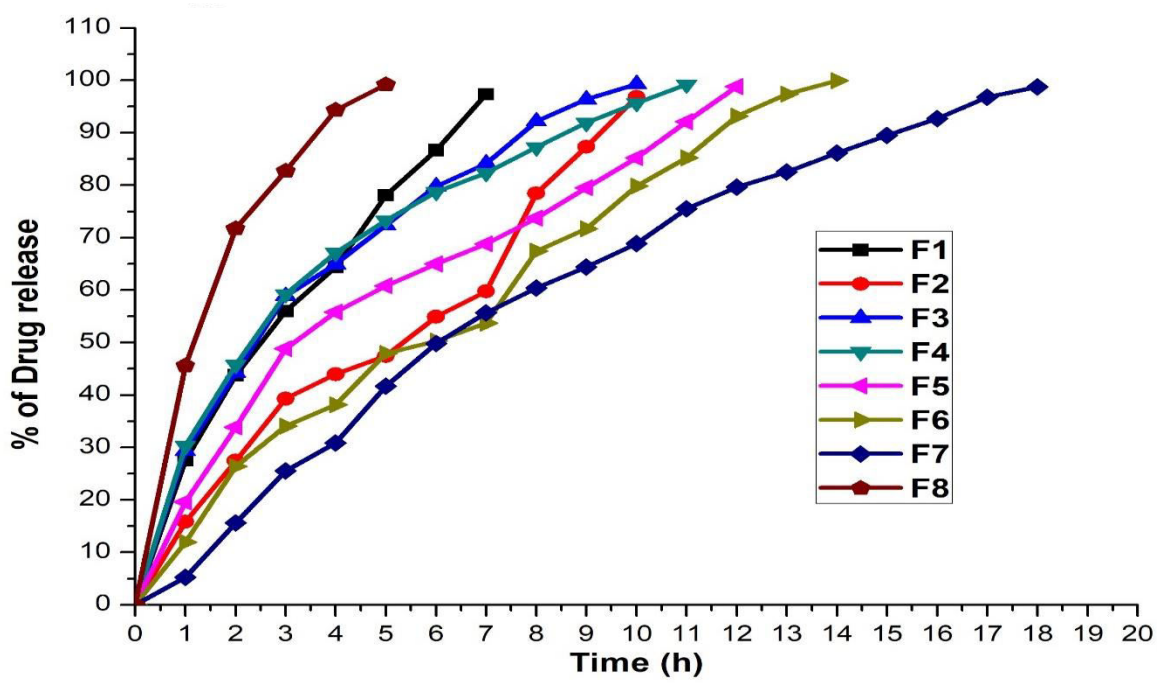

Fig. 3: *In vitro* dissolution profile of metformin hydrochloride beads formulation F1-F8.

Table 3: Release kinetics of metformin hydrochloride beads formulation F1-F8

Formulation	R^2 Values					Order of release
	Zero order plots	First order plots	Higuchi plots	Korsmeyer-peppas plots		
				R^2	Diffusional exponent (n)	
F1	0.965	0.847	0.985	0.997	0.887	Diffusion & Erosion
F2	0.976	0.77	0.927	0.995	0.978	Diffusion & Erosion
F3	0.907	0.86	0.976	0.987	0.992	Diffusion & Erosion
F4	0.872	0.857	0.961	0.98	0.986	Diffusion & Erosion
F5	0.932	0.765	0.989	0.993	0.979	Diffusion & Erosion
F6	0.984	0.666	0.962	0.994	0.987	Diffusion & Erosion
F7	0.963	0.879	0.975	0.976	0.963	Diffusion & Erosion
F8	0.871	0.923	0.991	0.986	0.974	Diffusion & Erosion

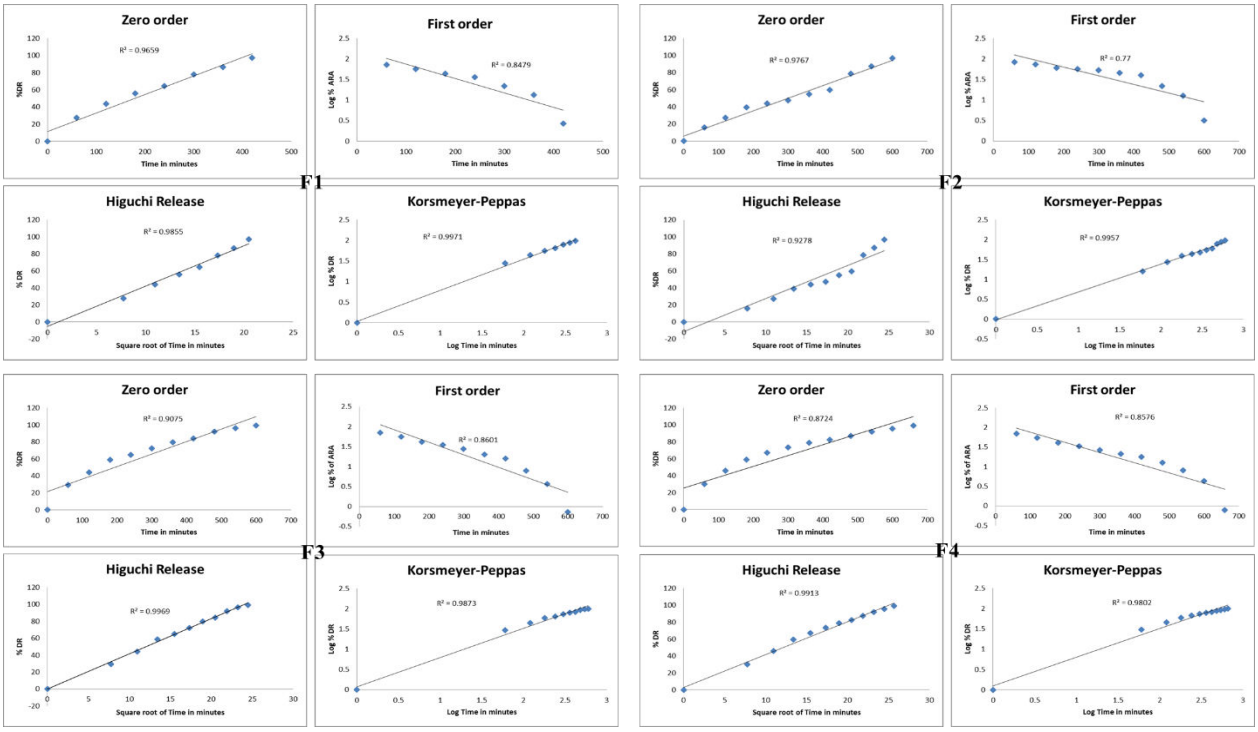

Fig.4: Release kinetics of metformin hydrochloride beads formulation F1-F4.

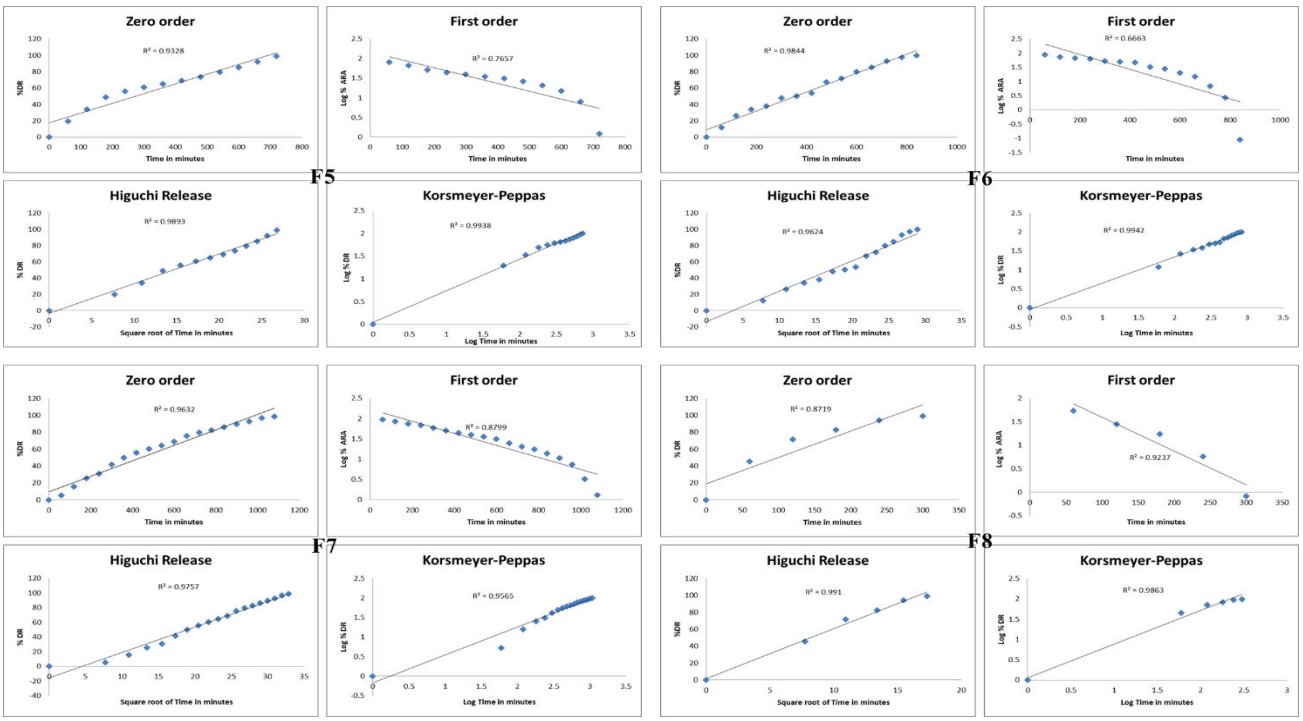

Fig. 5: Release kinetics of metformin hydrochloride beads formulation F5-F8.

polymers. Among all formulations formulation F4, F5, F6 and F7 have shown 99%, 98%, 99% and 98% drug release at 11 h, 12 h, 14 h and 18 h, respectively. Formulation F8 does not contain any polymers in the formulations and shows early release such as 99% at 5 h. So it confirms that

polymers at different ratio show better control on prolonging the release rate of metformin in oral dosage from.

Pharmacokinetic modeling of drug dissolution profile

Keeping in mind the end goal to decide the correct system of medication discharge from the formulation, the *in vitro* dissolution studies were assessed by zero order, first order, Higuchi, and Peppa's equations. The standard of picking the most proper model was in accordance with highest R^2 value as the best fit. The results are shown in Table 3 and Figures 4 and 5. Drug release is both diffusion and erosion-controlled mechanism observed in all formulations F1 to F8.

Conclusion

Hydrophobic polymer Eudragit RL-100 is blended into the hydrophilic polymer solution containing HPMC K and K100, considered to be effective matrices to control the release rate of metformin. Among the two hydrophilic polymers, HPMC K100 shows high viscosity grade in comparison to HPMC K4. Formulation F1, F2 and F3 are prepared by individual polymers HPMC K4, K100 and eudragit RL-100. Formulation F4 to F7 based on the composition of HPMC K4, K100 and eudragit RL-100 at different ratios. From the study it was found that individual polymer HPMC K4 which is low viscosity grade polymer is unable to sustain the release of metformin up to 97% at 7 h, whereas HPMC K100 which is high viscosity grade of hydrophilic polymer, can able to sustained the release of metformin up to 96% at 10 h. Similarly formulations F3 has shown 99% drug release at 10 h. Formulation F4 to F7 which is the combination of HPMC K4, K100 and eudragit RL-100 at different ratio have shows better controlling of metformin release up to 99% at 11h, 98% at 12 h, 99% at 14 h and 98% at 18 h, respectively. Formulation F8 is unable to control the release rate of metformin due to the absence of polymers in the formulation 99% at 5 h. Among all formulations formulation F7 has shown 98% drug release at 18 h. It revealed that high viscosity grade of polymer at higher concentration could be a good barrier for highly water soluble drug. Release kinetic study for all formulations confirm that all formulation have followed diffusion and erosion mechanism as per the R^2 value calculation.

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Conflict of Interest

The authors declare no conflicts of interest.

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