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A Study on Extended Drug Release Characteristics: Design, Development and Characterization of Metformin Hcl Loaded Gastroretentive Beads Using Ionic-Gelation Method

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KEYWORDS

Metformin, Beads, HPMC, Eudragit and Gastro Retentive Drug Delivery

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 & K100M are cellulose derivatives commonly used as matrix formers in sustained-release formulations. HPMC polymers provide controlled release of the drug by forming a gel layer upon contact with water, regulating drug diffusion. They offer versatility in controlling drug release kinetics by adjusting polymer concentration and viscosity. Eudragit polymers, including RL100, are acrylic-based polymers often employed in controlled-release formulations. Eudragit RL100 can enhance drug stability and prevent premature drug release in acidic environments, ensuring targeted delivery. Sodium alginate is strategically included to enable bead floatation, facilitating sustained drug release in a gastro retentive drug delivery system (GRDDS), is also known for its excellent biocompatibility and biodegradability. The beads undergo comprehensive in vitro evaluation, including buoyancy, drug content uniformity, and dissolution profiling. 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.

1. Introduction

Diabetes mellitus (DM) is a widespread endocrine disorder affecting more than 100 million individuals across the globe. For patients with type 1 DM, insulin replacement therapy forms the cornerstone of treatment, while type 2 DM management primarily revolves around dietary adjustments and lifestyle modifications. Additionally, various hypoglycaemic agents [1], including biguanides and sulfonylureas, are available for diabetes treatment. Recent estimates indicate that in 2010, approximately 285 million individuals aged 20–79 worldwide (6.6% of this age group) had diabetes. Projections suggest that by 2030, the number of adults with diabetes is expected to rise [2] to 438 million, constituting 7.8% of the adult population.

The manner in which a drug is administered can greatly impact its effectiveness [3]. According to Jorge et al., drug delivery systems serve the dual purpose of delivering a biologically active compound in a controlled manner and maintaining consistent drug levels in the body, minimizing fluctuations [4]. Controlled drug delivery systems aim to enhance the efficacy [5] of drug therapies. Sustained release drug delivery systems involve modifications to the formulation that prolong the therapeutic effects of the drug [6]. It is essential that the rate of drug absorption matches the rate of drug elimination from the body over

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the required duration to achieve the desired pharmacological response [7].

In combination with metformin or as a standalone treatment, several formulations of beads [8–12], containing pharmacologically active ingredients, have been investigated using analytical techniques [13, 14]. This study aims to develop metformin-loaded beads with controlled drug release by utilizing a blend of polymers, including sodium alginate, hydroxypropyl methylcellulose (HPMC) K4M, HPMC K100M, and Eudragit RL100. HPMC K4M and K100M, cellulose derivatives, are commonly employed as matrix formers in extended-release formulations. Sodium alginate contributes to the buoyancy of the beads in this formulation, promoting gastric retention. In the presence of calcium ions, it forms a gel, facilitating sustained drug release and prolonging the beads' residence time in the stomach. By carefully adjusting the ratios of these polymers, the kinetics of drug release are optimized to maximize medication efficacy.

2. Methods

Metformin HCl and Hydroxypropyl methylcellulose (HPMC K4M, and HPMC K100M) were obtained from Biocon biopharmaceutical company, India. Sodium alginate and calcium chloride analytical research grade was purchased from Sigma Aldrich and used as received. Eudragit RL-100 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 Ionıc-Gelatıon Method:

Beads containing Metformin HCl (formulation F1-F8) were prepared by ionotropic-gelation technique. Calculated number of polymers, say, 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 has been 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. Formulation F8 formulated without any polymer. Similarly, a constant amount of sodium alginate solution was prepared separately and mixed with the above prepared solutions and stirrer for 3 h until a clear homogeneous bubble free solution obtained. Further metformin was added to the polymeric solution and ultra-sonicated for 5-10min for debubbling. The resulting solution was added via a 21-gauge needle drop wise into 100 ml of 10% CaCl2 solution and retained as such for 15-25min to complete the reaction and harden the droplets. The wet beads were rinsed thrice with distilled water and dried at 60oC in hot air oven and put it in air tight container for further use.

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

Pre-Compression Study:

Bulk density and tapped density mainly depend on the nature of the compound and its size. These properties of a compound may vary due to the crystallization, milling or in formulation. It also provides the true knowledge of the size of the final dosage Obtained results were within limits and observed excellent flow properties.

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 were not shown any 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. Obtained result reveals that there is no shifting or

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change in metformin spectra when it is in 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%.

Drug Content:

The drug content of formulated beads for all formulations. It provides the data that how much drug 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 that suits for oral route without producing irritation to the mucous membrane.

Viscosity:

The viscosity ranged between 399 and 999 cps for all formulations. Low viscosity was found for the formulation F3 and F8. Formulation F8 doesn't 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.

Drug Release Profile:

In-VıtroDissolution Study:

Drug release studies for all formulations were determined using multi bucket USP basket apparatus at 100rpm 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 used in calibration curve equation of metformin to further calculate the % of drug release at different interval of time.

Dissolution Apparatus (Multi basket type):

In- vitro dissolution time for formulations F1 to F8 beads shows variation in release period ranging from 5h to 18h. This may be attributed to the nature of polymer and their viscosity grades used in various proportions in formulations. The high viscosity grade of HPMC K100 forming complex matrix network and able to prolong release rate of metformin up to 10h in formulation F2. Low viscosity grade of HPMC K4M is unable to control the release rate of metformin and shows 97% release in 7h. Similarly, formulation F3 contain hydrophobic Eudragit polymer and observe that 99% release at 10h. An optimum release rate could not be 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 compare to individual polymers. Among all formulations formulation F7 has shown 98% drug release at 18h. Formulation F8 doesn't contain any polymers in the formulations and shows early release such as 99% at 5h. So, it confirms that polymers at different ratio shows better control on prolonging the release rate of metformin in oral dosage from.

3. Results

Drug-Polymers Compatibility Studies (FTIR):

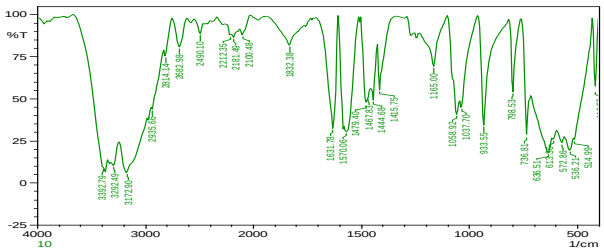

Figure 1: FTIR spectrum of Metformin HCl

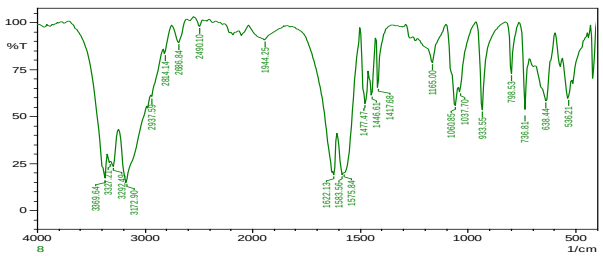

Figure 2: FTIR spectrum of HPMC K100M

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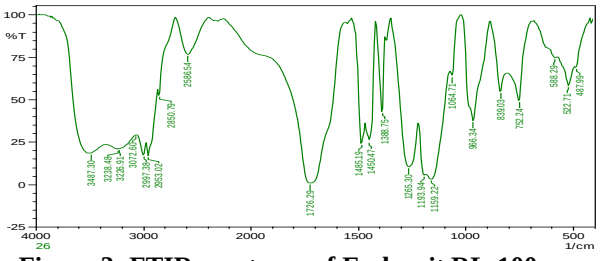

Figure 3: FTIR spectrum of Eudragit RL-100rum of HPMC K4M

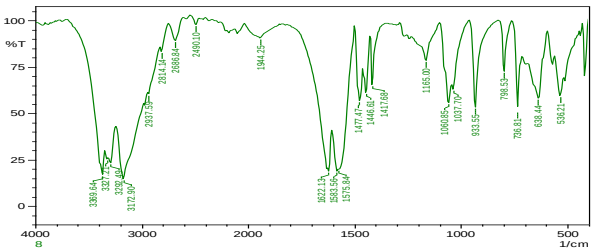

Figure 4: FTIR spectrum of HPMC K100M

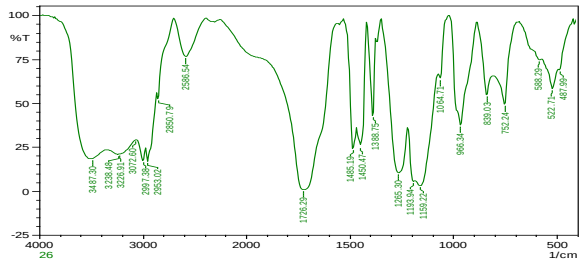

Figure 5: FTIR spectrum of Eudragit RL-100

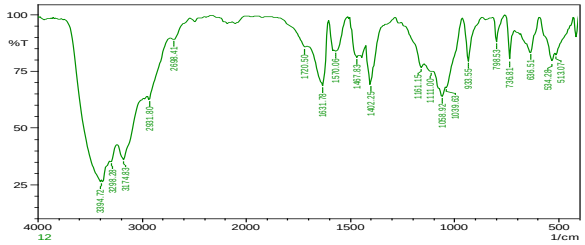

Figure 6: FTIR spectrum of Metformin HCl and HPMC K4M

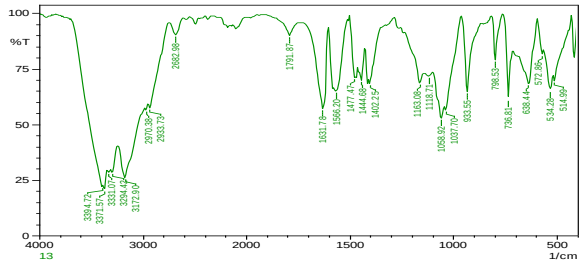

Figure 7: FTIR spectrum of Metformin HCl and HPMC K100M

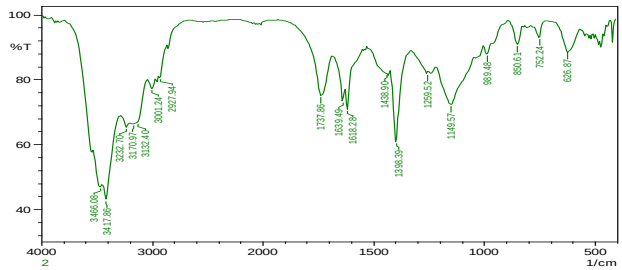

Figure 8: FTIR spectrum of Metformin HCl and Eudragit RL-100

Table 2: Pre-Compression Study of Metformin HCl API

S. No.	Pre-Compression Parameters	Metformin HCl
1	Bulk density (g/mL)	0.24 ± 0.91
2	Tap density (g/mL)	0.25 ± 0.25
3	Angle of repose (0)	22.84 ± 0.41
4	Carr's index	9.83 ±0.61
5	Hausner's ratio	1.03 ± 0.14

Table 3: Evaluation study of Metformin HCl beads

Formulation Code	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

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Table 4: *In vitro* dissolution profile for Metformin Hydrochloride Beads (F1 - F8) (All Values in %)

F. Code	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	9hr	10hr	11hr	12hr	13hr	14hr	15hr	16hr	17hr	18hr
F1	27.58	43.80	55.98	64.37	78.10	86.68	97.35	-	-	-	-	-	-	-	-	-	-	-
F2	15.85	27.46	39.28	43.96	47.44	54.91	59.78	78.47	87.33	96.83	-	-	-	-	-	-	-	-
F3	29.35	44.22	58.87	64.91	72.39	79.78	84.11	92.19	96.35	99.28	-	-	-	-	-	-	-	-
F4	30.31	45.76	59.22	67.11	73.28	78.71	82.31	87.22	91.91	95.67	99.21	-	-	-	-	-	-	-
F5	19.62	33.90	48.84	55.83	60.81	64.96	68.82	73.71	79.52	85.22	92.11	98.78	-	-	-	-	-	-
F6	11.96	26.40	34.03	38.13	47.94	50.26	53.7	67.39	71.7	79.81	85.18	93.13	97.32	99.91	-	-	-	-
F7	5.21	15.63	25.51	30.87	41.66	49.81	55.71	60.41	64.39	68.85	75.49	79.62	82.51	86.15	89.46	92.71	96.79	98.71
F8	45.59	71.76	82.72	94.32	99.18	-	-	-	-	-	-	-	-	-	-	-	-	-

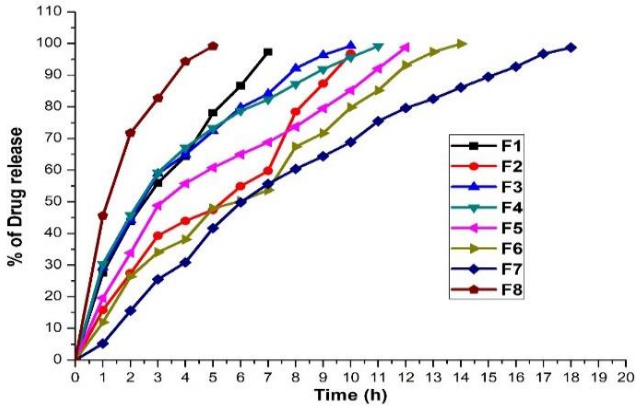

Figure 9: In vitro dissolution profile of Metformin hydrochloride beads (F1-F8)

4. Discussion

Pre-Compression Study:

Bulk density and tapped density mainly depend on the nature of the compound and its size. These properties of a compound may vary due to the crystallization, milling or in formulation. It also provides the true knowledge of the size of the final dosage form. The density of the solid also affects their compression and flow property after final production. Pre compression results of Metformin HCl have been reported in Table 2. Obtained results were within limits and observed excellent flow properties.

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 were not shown any colour changes in their appearance. The physical compatibility was found to be optimum between drug and all polymers and considered as good formulation.

Drug Polymer 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 has shown in Figure 1 to 8. Obtained result reveals that there is no shifting or change in metformin spectra when it is in 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% shown in Table 3.

Drug Content:

Table 3 shows the drug content of formulated beads for all formulations. It provides the data that how much drug present in the prepared formulated metformin

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beads. It was found that the drug content for all the formulation lies between the ranges of95% 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 that suits for oral route without producing irritation to the mucous membrane. All the results are reported in Table 3.

Viscosity:

The viscosity ranged between 399 and 999 cps shown in Table 3 for all formulations. Low viscosity was found for the formulation F3 and F8. Formulation F8 doesn't 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.

Drug Release Profile:
***In-Vitro* Dissolution Study:**

Drug release studies for all formulations were determined using multi bucket USP basket apparatus at 100rpm 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 used in calibration curve equation of metformin to further calculate the % of drug release at different interval of time.

Dissolution Apparatus (Multi basket type):

In- vitro dissolution time for formulations F1 to F8 beads shows variation in release period ranging from 5h to 18h shown in Table 4 and figure 9. This may be attributed to the nature of polymer and their viscosity grades used in various proportions in formulations. The high viscosity grade of HPMC K100 forming complex matrix network and able to prolong release rate of metformin up to 10h in formulation F2. Low viscosity grade of HPMC K4M is unable to control the release rate of metformin and shows 97% release in 7h. Similarly, formulation F3 contain hydrophobic Eudragit polymer and observe that 99% release at 10h. An optimum release rate could not be 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 compare to individual polymers. Among all formulations formulation F7 has shown 98% drug release at 18h. Formulation F8 doesn't contain any polymers in the formulations and shows early release such as 99% at 5h. So, it confirms that polymers at different ratio shows better control on prolonging the release rate of metformin in oral dosage from.

5. 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 is 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 unable to sustain the release of metformin up to 97% at 7h. Whereas HPMC K100 which is high viscosity grade of hydrophilic polymer, can able to sustained the release of Metformin up to 96% at 10h. Similarly, formulations F3 has shown 99% drug release at 10h. Formulation F4 to F7 which is the combination of HPMC K4, K100 and Eudragit RL-100 at different ratio have shown better controlling of metformin release up to 99% at 11h, 98% at 12h, 99% at 14h and 98% at 18h respectively. Formulation F8 is unable to control the release rate of metformin due to the absence of polymers in the formulation 99% at 5h. Among all formulations formulation F7 has shown 98% drug release at 18h. It reveals that high viscosity grade of polymer at higher concentration could be a good barrier for highly water-soluble drug.

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