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CONTROLLED DELIVERY OF METFORMIN: FORMULATION DEVELOPMENT AND *IN-VITRO* CHARACTERIZATION OF MATRIX TABLETS USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT: Diabetes Mellitus is a chronic metabolic disorder that has become increasingly evident, necessitating more stable and continuous therapeutic monitoring. Metformin Hydrochloride, being the primary treatment choice in type II Diabetes, presents certain limitations like improper GI absorption and the need for multiple dosing. Controlled drug delivery proves to be a better option in such conditions to provide an uninterrupted treatment. The present study is based on the development of oral controlled matrix tablets of Metformin. Plant-derived gums like Gum Okra, Gum Moringa, Gum Xanthan were extracted suitably and used as release controlling agents individually and in combination with Eudragit RL 100 in varying proportions. EC was employed to form a secondary backing layer. Thirteen formulations with polymers in different ratios were developed using the Wet granulation technique. The physicochemical properties of the prepared matrix tablets were found to be satisfactory. *In-vitro* release studies were performed in simulated media, 0.1 N HCl and Phosphate buffer, pH 6.8 and results have shown that formulation F11 containing Gum Moringa and Eudragit RL-100 (2:1 ratio) and EC layer exhibited the desired release of 99.46% ±0.75 throughout 24 h. Kinetic modelling of the dissolution data has shown that the drug release from the formulations followed Zero-order kinetics and shows the best fit to the Korsmeyer/Peppas model, representing the diffusion mechanism of drug release. The formulations were also found to be stable over the accelerated study period.

INTRODUCTION: Drug delivery can be hypothesized as the technology utilized to present the drug/ pharmaceutical agent to the desired body site for release and absorption or the subsequent transport of the active ingredients across the biological membranes in a safe, efficient, accurate, reproducible and convenient manner [1, 2].

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A drug delivery system (DDS) is an interface between a patient and drug [3, 4]. A drug's efficacy could be profoundly impacted by how it is delivered. A variety of drug delivery systems (DDSs) now facilitate to regulation of the pharmacokinetics, pharmacodynamics, toxicity, immunogenicity and efficacy of drugs [5].

The choice of delivery mechanism and route of administration for a specific drug molecule depends on the disease, the effect desired, and the product available and is essential to "optimize" the performance of that drug inside the body [6, 7]. Peroral administration is the universally accepted, most common, and patient compliant route and has

received much attention in the pharmaceutical field because of flexibility in designing dosage forms compared to other routes [8] and even small improvements in drug delivery can enhance patient compliance and drug bioavailability. Cost-effectiveness, ease of administration, better availability, and accessibility make oral delivery the most preferred route to date. Approximately 84% of the most-marketed pharmaceuticals are orally administered [9, 10]. Despite these features, certain factors like loss of drug stability, physiological and enzymatic barriers, the effect of physicochemical properties on absorption and other PK parameters delimitate the delivery of drugs by this route. In addition, though conventional dosage forms cause rapid effects, aspects of repetitive dosing, peak-trough profiling, duration of action, etc., restrict their formulation and use. To avoid this limitation, modified oral delivery products such as sustained/ controlled release formulations have recently increased interest in improving therapeutic advantages, patient compliance, and flexibility in formulation [11, 12].

The design of drugs as oral controlled release delivery systems (CRDDS) helps enhance efficacy and safety by precise release modulation and reduction in the dosing size and number. Controlled delivery can therefore consider a suitable option in the therapy of chronic disorders like Diabetes Mellitus, Hypertension, Renal dysfunction, Arthritis, Gastrointestinal disorders and so on. Matrix tablets forms one such class of controlled delivery systems enabling ease of formulation and administration [13]. Diabetes Mellitus is a complex, metabolic disorder defined by the level of hyperglycemia or rather termed a syndrome of multiple microvascular and macrovascular complications. It is one of the major accountable life expectancy threats for ~ 463 million populations in the global health scenario, necessitating continual medical supervision and strategies to mitigate multi-factorial risks [14, 15].

Metformin hydrochloride, chemically 1,1-dimethyl biguanide hydrochloride, is an orally administered biguanide and, if well tolerated, the preferred first-line choice for managing type 2 diabetes [16, 17]. Metformin acts by reducing hepatic glucose output and enhances glycemic control by improving insulin sensitivity in hepatic and peripheral tissues and decreasing intestinal absorption of glucose [18, 19]. It is a hydrophilic drug that shows incomplete absorption from the exhibiting an absolute bioavailability of 50 – 60 % [20]. Plasma half-life of the drug is relatively short, *i.e.,* 1.5-4.9 h [21] and it has proven incidence of severe gastrointestinal side effects like metabolic acidosis [22, 23]. Also, the drug is usually administered in larger doses of approximately 1.5-2.5g/day, the initial dose being 500 mg [24, 25]. Hence, despite being the primary option and a less complicated oral hypoglycemic agent, Metformin Hydrochloride necessarily requires an effective delivery system that facilitates controlled release of the drug, thereby enhancing bioavailability. In recent decades, natural phytochemicals like gums, polysaccharides, resins, mucilages etc., have emerged as excipients in pharmaceutical formulations. These have been extensively used as disintegrants, binders, release retardants, solubility enhancers, *etc*.

Less toxicity, sustainability, natural abundance, low cost, reproducibility, and compatibility with other excipients tend to be the major reasons for increased use of such plant-derived excipients. In the present study, natural polymers like Okra gum, Moringa gum and xanthan gum have been employed as rate-controlling agents. These, being high molecular weight, highly viscous, versatile gelling polymers, can modify the drug release rates and patterns in a required manner [26, 27, 28].

MATERIALS AND METHODS:

Materials: Metformin Hydrochloride was obtained as a gift sample from Hetero Drugs Ltd., Hyderabad. Moringa gum and Okra gum were extracted in the laboratory using reported procedures. Xanthan gum was purchased from Himedia Laboratories Pvt Ltd., Nashik. Eudragit RL 100, Ethyl Cellulose, and other chemicals and reagents were of analytical grade purchased from Merck Laboratories.

Methods:

Extraction of Okra Gum: Okra gum was extracted from the fruits of *Abelmoschus esculentus*. Fresh okra fruits were collected from the local market, washed thoroughly, and sliced, followed by the removal of seeds. The pieces were soaked in distilled water for 5-6 h, boiled using a water bath at 60-80 °C for 1 h, and left undisturbed

for 2-3 h. The mixture was passed through layered muslin cloth and squeezed properly to completely extract mucilage and remove the unwanted pulp. The filtrate was then treated with an excess of acetone to precipitate the mucilage. After complete precipitation, the mucilage was isolated, dried in hot air oven at 40-50 °C, collected, pulverized, passed through sieve no.80 and stored in a desiccator for further uses [29, 30, 31, 32].

Extraction of Moringa Gum: Gum was extracted from the exudates of *Moringa olifera* tree stems by making incisions. It was then dried, milled and sifted through sieve no.80. The gum powder was then soaked in warm distilled water for 1 h. The mixture was homogenized for 4-5 h on a mechanical stirrer at room temperature and further subjected to centrifugation. The supernatant obtained was removed carefully and the process is repeated 4-5 times with a subsequent collection of the supernatants.

All the supernatants and residue wash portions were combined the volume made up to 500 ml and treated with twice the volume of ethanol by continuous agitation. The resultant precipitate was filtered, washed with distilled water, and further dried at 50-60 °C under vacuum. In the form of fine, creamish coloured powder, the processed and purified Moringa gum was stored in desiccators [26, 33, 34, 35].

Preformulation Study:

UV-Spectrometric Analysis:

Determination of Absorbance maxima: Stock solution of pure sample of Metformin was prepared by dissolving 50mg of drug in 50 ml of test media, *i.e.*, 0.1 N HCl and Phosphate buffer, pH 6.8. Aliquots from this stock solution were taken and diluted equivalent to 100µg/ml. This solution was scanned in the 200-400nm range to obtain absorption spectrum and λ_{max} in respective media using a double beam UV Visible Spectrophotometer (Analytical Technologies T60).

Construction of Standard Calibration Curve: Samples of different standards (5-30 µg/ml) were prepared from the stock solution by making suitable dilutions and analyzed spectrophotometrically at 233 nm and 228 nm against 0.1 N HCl and Phosphate buffer, pH 6.8 as blank solutions respectively. The obtained absorbance values were recorded and plotted into standard linear regression curves.

FTIR Study: A primary and essential concern in formulation development, drug-excipient compatibility can be rightly studied by Fourier transform Infrared Spectroscopy (FTIR) [36]. Samples of Pure drug Metformin Hydrochloride, Polymers (Gum Okra, Gum Moringa, Gum Xanthan, Eudragit RL 100, Ethylcellulose) and Physical mixtures corresponding to formulations were analyzed by KBr disc pellet technique using FTIR Spectrophotometer. The resultant spectra were interpreted to detect or study any possible interactions among drug and polymers.

Formulation Development of Metformin Controlled Release Matrix Tablets: Controlled release matrix tablets of Metformin Hydrochloride were prepared by wet granulation technique employing diverse natural gums (Gum Okra, Gum Moringa, Gum Xanthan) and synthetic polymer Eudragit RL 100 as rate-controlling agents. Ethylcellulose formed the backing layer of all the formulations.

TABLE 1: COMPOSITION OF METFORMIN HYDROCHLORIDE CONTROLLED RELEASE MATRIX TABLETS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500	500	500	500	500
Gum Okra	335	250	220	170	-	-	-	-	-	-	-	-	-
Gum Xanthan	-	-	-	-	335	250	220	170	-	-	-		-
Gum Moringa	-	-	-	-	-	-	-	-	335	250	220	170	-
Eudragit RL 100	-	85	115	165	-	85	115	165		85	115	165	335
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethyl cellulose 6 cps (backing layer)	20	20	20	20	20	20	20	20	20	20	20	20	20
Total Tablet weight	860	860	860	860	860	860	860	860	860	860	860	860	860

IPA: Iso propyl alcohol; q.s: quantity sufficient. All the ingredients mentioned are in mg.

Blends of drug along with polymers and other excipients were duly weighed sifted and required quantity of non-aqueous binder IPA was incorporated to prepare granules. The wet masses were primarily screened through sieve #12 and after drying through sieve #44 in order to achieve size uniformity. Magnesium stearate and talc were then added and the mixtures were subjected to compression on a rotary tablet compression machine (Saimach SMD-16 station, 16 mm oval, biconcave tooling) **Table 1.**

***In-vitro* Characterization of Tablets:**

Pre-Compression Parameters: The prepared blends of granules were preliminarily evaluated in terms of micromeritic properties such as bulk density, tapped density, Hausner's ratio, compressibility index, angle of repose before compression and the results were tabulated [37] **Table 2.**

Post Compression Parameters [37, 38]: The prepared tablets were characterized for the following physicochemical parameters and release patterns in the following manner.

Thickness: The thickness of the formulations was evaluated using vernier calipers by selecting 10 tablets from each batch at random.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling and shipping and is expressed in kg/cm^2. The hardness of 10 tablets from each batch was determined using Monsanto hardness tester.

Friability: The tablets' friability was determined using Roche Friabilator and expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by-

$$\% F = 100 (1-W_0 / W)$$

% Friability of tablets less than 1% were considered acceptable.

Uniformity of Weight: Twenty tablets were selected randomly from each batch and weighed individually. Average of such total weights was calculated and the % deviation was calculated using the equation-

% Weight variation = (Individual weight – average weight) / (Average weight) × 100

Check for weight variation. The percentage deviation in weight variation should fall within the USP limits (±5%).

Drug Content Uniformity: Five tablets from each batch were picked at a random, powdered, and samples equivalent to 500 mg of Metformin was taken into a 100 ml volumetric flasks containing respective media (0.1 N HCl & Phosphate buffer, pH 6.8).

The solutions were placed in a sonicator for 24 h, filtered through Whatman filter paper and the absorbances were measured [39].

***In-vitro* Dissolution Study:** *In-vitro* drug release from the controlled release matrix tablets was studied using USP type-II dissolution test apparatus (Electrolab TDT-08L) in 900ml of 0.1 N HCl for 2 hours and pH 6.8 buffer for remaining time span. The temperature of the medium was set at 37 ± 0.5 °C at 50 rpm.

An aliquot of 5 ml solution was drawn at pre-determined time intervals of 1, 2, 4, 6, 8, 10, 12, 16 and 24 h with subsequent replacement of same volume of fresh medium.

The samples were suitably filtered and analyzed spectro-photometrically against standard blank solutions at λ_{max} 233 nm for 0.1 N HCl and 228 nm for Phosphate buffer. The cumulative percent of drugs released was calculated and plotted against units of time to examine the release pattern.

Kinetic Modelling and Determination of Mechanism of Drug Release: The data obtained from the dissolution study was subjected to kinetic analysis by fitting into various models, namely Zero order, First order, Higuchi's square root, Hixson-Crowell, and Korsmeyer Peppas. This is essential to determine and evaluate the dissolution behavior, order, and mechanism of drug release.

Accelerated Stability Studies: To study the influences of handling and storage conditions such as temperature and humidity on the formulations,

accelerated stability testing was performed for the optimized formulation. This was performed by enclosing the matrix tablets in aluminum foil and exposed to 40 °C/75% RH (as per ICH guidelines) for 3 months.

The formulations were occasionally removed and analyzed for appearance, hardness, weight variation, percent drug content, and dissolution profile. The results were then compared to earlier ones [40].

RESULTS AND DISCUSSION: In the current research, controlled release matrix tablets of Metformin Hydrochloride were successfully formulated using schematic ratios of natural and synthetic polymers with a thin EC backing layer.

UV Spectrometric Analysis: The Standard solution of a pure sample of Metformin hydrochloride has shown absorbance maxima at 233 nm and 228 nm in 0.1 N HCl and Phosphate buffer, pH 6.8, respectively.

Calibration curves for a concentration range of 5-30 µg/ml were plotted, which exhibited regression co-efficient values of 0.999 (0.1 N HCl) and 0.998 (Buffer, 6.8) **Fig. 1, 2.**

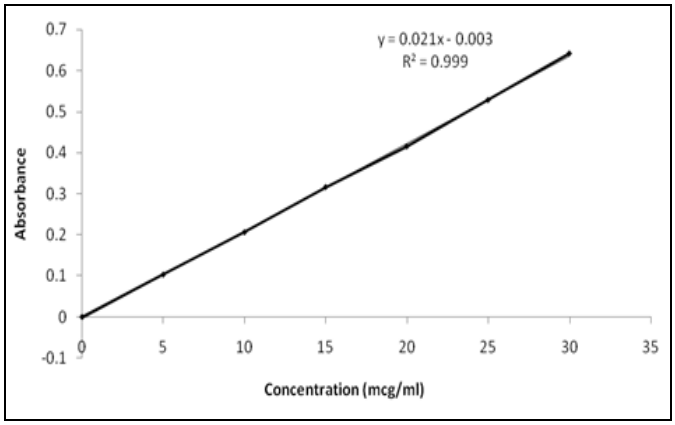

FIG. 1: CALIBRATION CURVE OF METFORMIN HYDROCHLORIDE IN 0.1 N HCL

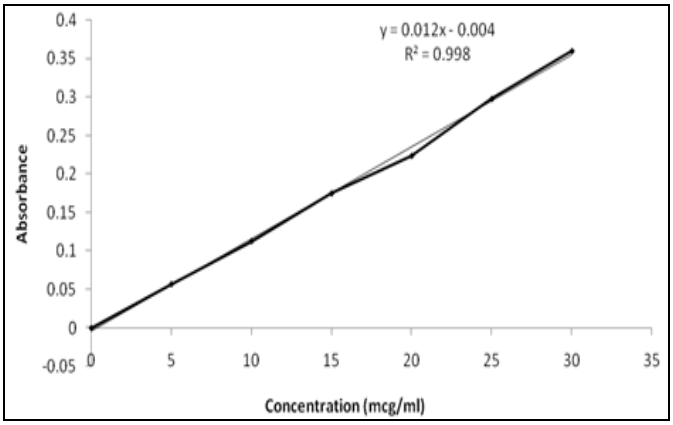

FIG. 2: CALIBRATION CURVE OF METFORMIN HYDROCHLORIDE IN PHOSPHATE BUFFER

Drug-Excipient Compatibility (FTIR) Study: The IR spectrum of Metformin hydrochloride and its mixtures with polymers containing were shown in **Fig. 3, 4, 5, 6,** and **7**.

The following characteristic bands observed C=N-(stretching) 1629.55 cm^{-1} ,1655.59 cm^{-1}, 1669 cm^{-1}, C-N- (stretching) 1061.62 cm^{-1}, 1029.48 cm^{-1}, 1030.77 cm^{-1}, N-H- (stretching) 3397.96 cm^{-1}, 3378.67 cm^{-1}, 3394.1 cm^{-1}, in each case.

Hence, it can be noticed that no significant incompatibility could exist between Metformin hydrochloride and the used polymers like Eudragit-RL-100, Xanthan gum, Okra gum, and Moringa gum.

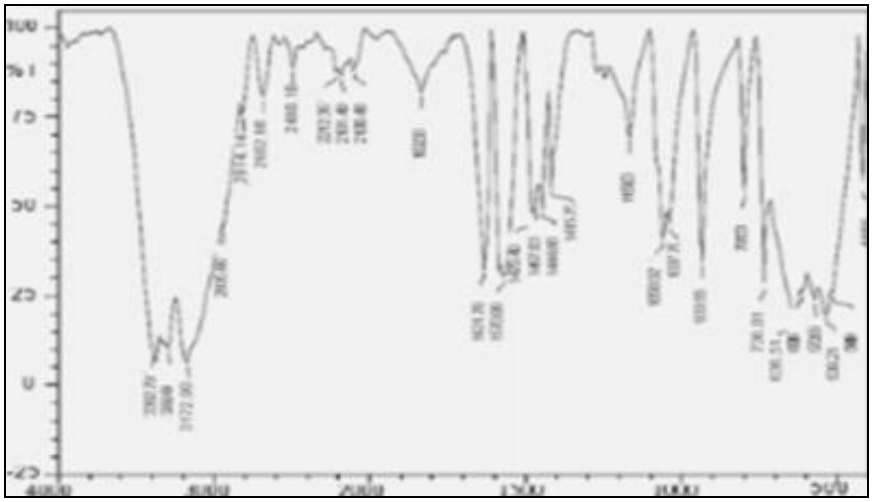

FIG. 3: FTIR GRAPH OF METFORMIN PURE DRUG

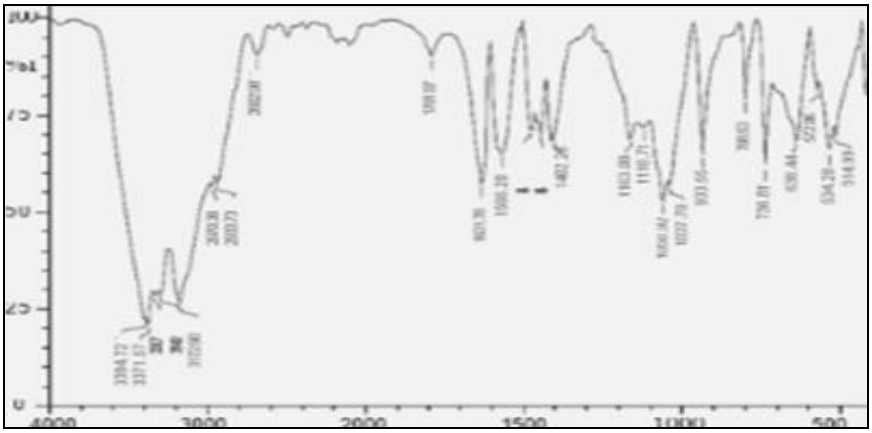

FIG. 4: FTIR GRAPH OF MIXTURE OF METFORMIN AND EUDRAGIT RL 100

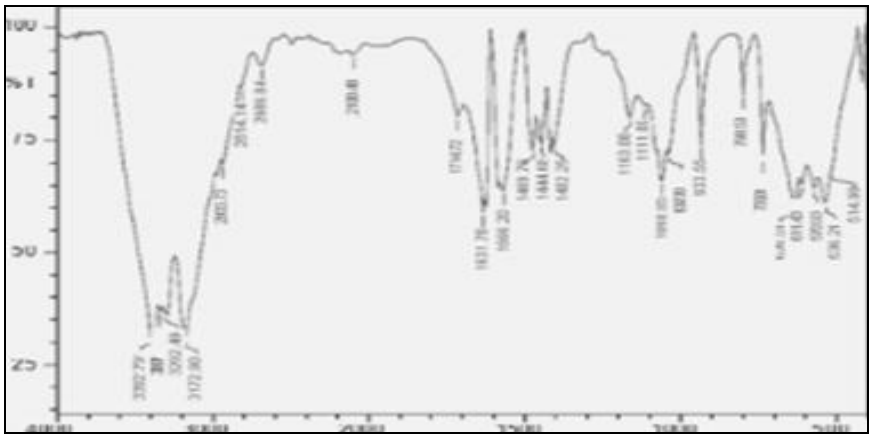

FIG. 5: FTIR GRAPH OF MIXTURE OF METFORMIN AND OKRA GUM

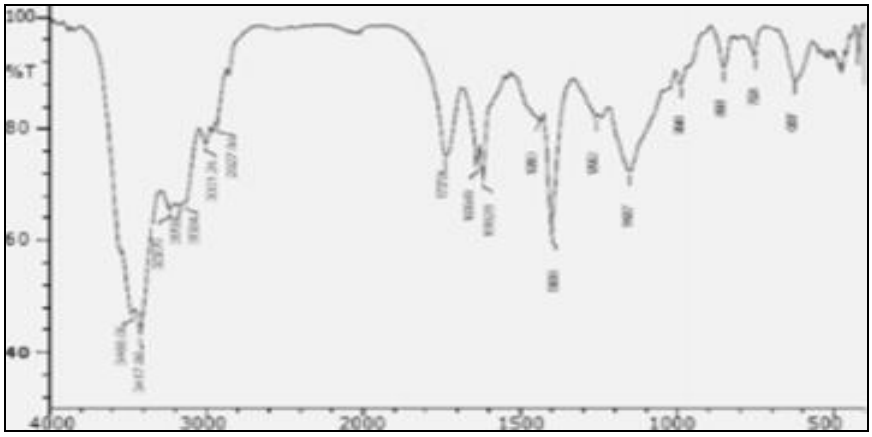

FIG. 6: FTIR GRAPH OF MIXTURE OF METFORMIN AND MORINGA GUM

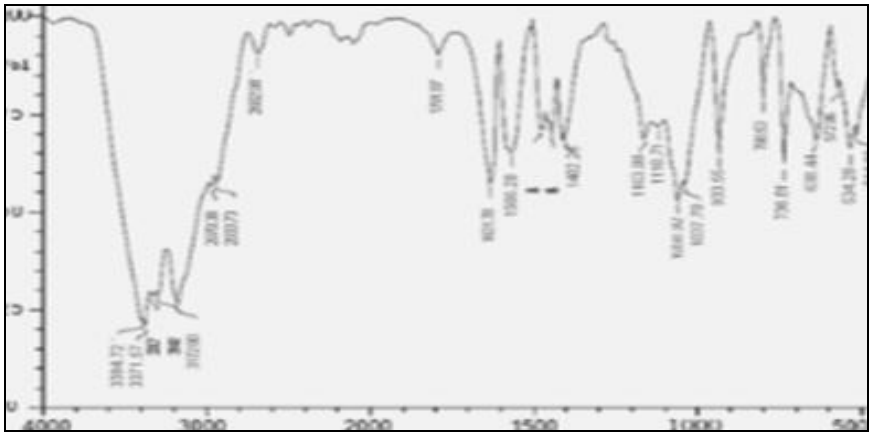

FIG. 7: FTIR GRAPH OF MIXTURE OF METFORMIN AND XANTHAN GUM

Precompression Parameters: Thirteen batches of formulations were prepared by wet granulation procedure and the granules were characterized. The results of the Pre-compression parameters are presented in **Table 2**. All the formulations have exhibited good to fair flow, enabling better compression and uniformity.

TABLE 2: PRE-COMPRESSION PARAMETERS OF THE GRANULES

Formulation	Angle of Repose (°)	%Compressibility	Hausner's Ratio
F1	31.02±0.15	16.33±0.12	1.2±0.03
F2	28.13±0.24	15.28±0.14	1.19±0.05
F3	26.5 ±0.06	15.03±0.18	1.16±0.06
F4	24.08±0.23	14.56±0.18	1.16±0.08
F5	28.16±0.15	15.65±0.1	1.18±0.76
F6	27.3±0.4	15.4±0.45	1.18±0.04
F7	25.11±0.25	14.7±0.21	1.17±0.03
F8	25.09±0.16	14.03±0.16	1.15±0.02
F9	29.15±0.14	16.21±0.13	1.18±0.05
F10	26.01±0.07	15.7±0.1	1.16±0.08
F11	25.1± 0.22	14.12±0.13	1.14±0.01
F12	24.8±0.1	13.25±0.15	1.13±0.08
F13	22.05±0.72	12.59±0.15	1.12±0.02

The values are indicative of mean± S.D (n=3)

Post Compression Parameters: The organoleptic appearance of the formulations was examined to be good and satisfactory. As shown in **Table 3** infer that all the formulations exhibited sufficient mechanical strength and uniformity in weight and drug content. Results were found to be within the compendial limits.

TABLE 3: POST COMPRESSION PARAMETERS OF CONTROLLED RELEASE MATRIX TABLETS

Formulation	Average Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	856.25±3.15	6.03±0.15	5.34±0.23	0.65±0.03	96.22±0.42
F2	862.11±1.23	6.26±0.14	5.14±0.45	0.61 ±0.05	92.45±0.58
F3	852.2 ±4.14	6.82±0.17	5.08±0.31	0.58±0.06	99.12±0.2
F4	860.54±1.05	7.05±0.13	5.26±0.22	0.78±0.01	101.3±0.05
F5	861.56±2.10	6.43±0.15	5.02±0.74	0.70±0.02	100.0±0.82
F6	857.48±4.21	7.15±0.44	5.35±0.03	0.56±0.04	97.64±0.36
F7	855.72±3.36	7.53±0.29	5.7±0.34	0.88±0.03	93.4±0.19
F8	858.82±2.08	7.31.±0.11	5.21±0.64	0.63±0.07	101.55±0.76
F9	862.43±0.64	7.92±0.12	5.14±0.14	0.35±0.08	98.51±0.09
F10	859.5±1.05	8.25±0.15	5.24±0.14	0.45±0.01	100.3±0.25
F11	860.07±0.75	8.72±0.12	5.05±0.08	0.38±0.01	99.82±0.15
F12	857.23±2.33	8.2±0.31	5.44±0.16	0.33±0.03	100.61±0.33
F13	855.30±1.15	6.32±0.31	5.12±0.35	0.87±0.06	99.4±0.52

The values are indicative of mean± S.D (n=3)

***In-vitro* Dissolution Study:** Dissolution studies were performed to study the release of Metformin Hydrochloride from the formulations (F1-F13) in 0.1 N HCl and Phosphate buffer, pH 6.8 for 24 hours. The dissolution profiles, as represented by the cumulative percentage of drug released at each sampling interval, were recorded and summarized in **Table 4**. All the formulations were prepared using the varying drug: polymer ratios using rate modifying natural polymers like Gum Okra, Gum Moringa, Xanthan gum, and synthetic Eudragit RL-100, alone and in combination. Ethyl Cellulose was used to form a thin, constant backing layer to the matrix tablets to provide uni-directional movement, which is a primary concern for controlling the drug release. Metformin Hydrochloride, being a hydrophilic drug, essentially requires high mol. wt or hydrophobic rate retarding polymers in order to achieve prolonged release. Hence, in the present study, natural and synthetic polymers were used in combinations and different proportions, utilizing the beneficial properties of both. Natural polymers were able to retard the drug release upto 10-12 hour only, and their compression properties were slightly poor and, hence, exhibited faster erosion (F1, F5 and F9).

Combination of gums with Eudragit in different proportions has enhanced their stability, aesthetic appearance, compression strength and thereby, release pattern, *i.e.*, matrix formation and gelling, facilitating slower diffusion of drug. It can be seen from the results for formulations composed of Okra gum, Eudragit RL-100 (F1-F4) that maximum release of the drug has occurred much earlier than the total study period, *i.e.*, F1-98.53±3.13 after 10 hrs to F4- 97.6±2.86 after 16 hours **Table 4, Fig. 8**. Formulations F5-F8 composed of Xanthan gum and Eudragit RL-100 also released the drug before the total sampling interval as shown to be F5 99.18±2.09 at the end of 10 h to F8- 97.8±1.44 after 16 h **Table 4, Fig. 9.** The results for formulations composed of Gum Moringa and Eudragit RL-100 (F9-F12) show that the dissociation was rather slow with these formulations in comparison to other formulations, *i.e.*, F9- 99.57 ±2.65 at the end of 12 h to F12- 90.53 ±2.71 after 24 h, which relatively indicates greater controlling and gelling effect of Gum Moringa compared to other natural gums employed in the study **Table 4, Fig. 10**. Hence, Formulation F11 (2:1 ratio of Gum Moringa and Eudragit RL-100) exhibited a cumulative release of 99.46 ±0.75 after 24 h and has also satisfied all aspects of physicochemical, organoleptic properties. Mechanical strength has been considered as the best formulation. Formulations containing Eudragit-RL-100 alone (F13) have conferred a release of 82.53±1.53 over 24 h, which could cause drug deposition in the body and might result in overdosage on subsequent dosing. This could be due to the hydrophobic nature of Eudragit, which formed a matrix with the hydrophilic drug and prevented its rapid release from the formulation.

TABLE 4: *IN-VITRO* DRUG RELEASE DATA OF MATRIX TABLET FORMULATIONS (F1-F13)

Time (H)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	19.82 ±4.09	13.34 ±2.26	10.91 ±2.16	9.70 ±4.31	25.08 ±2.14	20.34 ±1.50	16.3 ±3.03	12.6 ± 3.31	16.82 ±4.09	11.58 ±3.06	6.42 ±2.16	4.18 ±4.31	3.61 ±1.24
2	33.40 ±6.08	27.82 ±4.09	21.5 ±3.64	17.5 ±2.46	38.31 ±5.3	35.24 ±3.7	28.45 ±2.44	23.9 ±2.26	31.40 ±6.08	21.25 ±3.67	12.5 ±1.45	7.71 ±3.46	6.20 ±2.23
4	52.83 ±4.53	39.45 ±3.24	30.61 ±5.72	28.18 ±2.82	52.35 ±3.11	49.67 ±2.96	45.17 ±3.81	34.17± 4.08	45.38 ±4.53	32.5 ±2.00	23.53 ±3.7	14.43 ±2.82	11.43 ±3.56
6	76.06 ±4.21	53.76 ±3.01	44.85 ±6.26	41.85 ±3.4	79.52 ±2.01	63.17 ±4.06	60.62 ±3.07	56.57± 3.28	68.09 ±3.55	45.16 ±3.01	34.06 ±2.07	21.63 ±3.4	17.35 ±2.05
8	89.50 ±5.32	71.02 ±3.46	57.18 ±3.24	55.54 ±3.75	91.86 ±5.27	79.02 ±3.52	77.16 ±3.24	78.4 ±2.55	85.50 ±5.32	62.21 ±2.55	46.50 ±3.63	29.42 ±3.31	23.55 ±1.64
10	98.53 ±3.13	83.68 ±2.72	72.52 ±4.12	68.77 ±5.01	99.18 ±2.09	90.68 ±3.24	89.52 ±4.12	86.3 ±4.73	92.68 ±3.13	78.68 ±2.72	57.14 ±2.12	37.48 ±3.01	29.04 ±4.12
12	---	97.87 ±5.66	86.4 ±4.98	83.09 ±2.64	---	98.7 ±4.16	96.29 ±3.83	91.95± 2.68	99.57 ±2.65	91.87 ±5.66	69.08 ±1.45	43.43 ±2.16	35.48 ±2.9
16	---	---	99.53 ±3.51	97.6 ±2.86	---	---	---	97.8±1. 44	---	98.61 ±2.04	81.3 ±2.92	58.74 ±2.11	47.08 ±3.08
20	---	---	---	---	---	---	---	---	---	---	90.68 ±1.57	75.85 ±1.46	68.21 ±2.07
24	---	---	---	---	---	---	---	---	---	---	99.46 ±0.75	90.53 ±2.71	82.53 ±1.53

The values are indicative of mean± S.D (n=3)

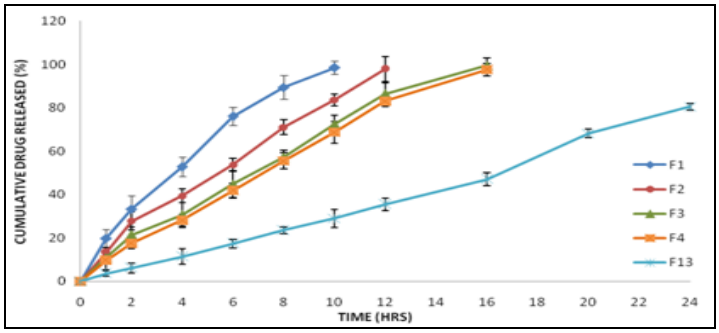

FIG. 8: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATIONS F1-F4

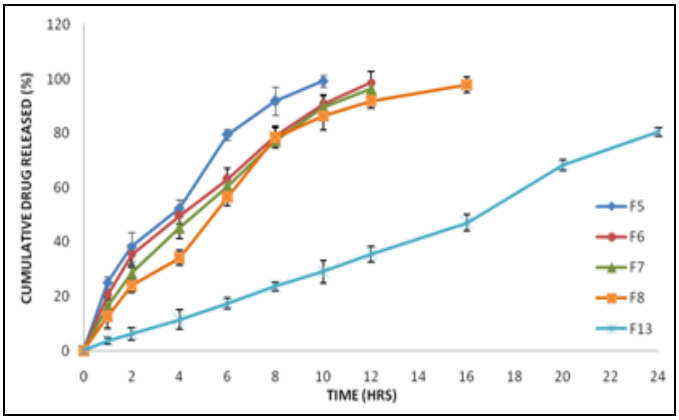

FIG. 9: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATIONS F5-F8

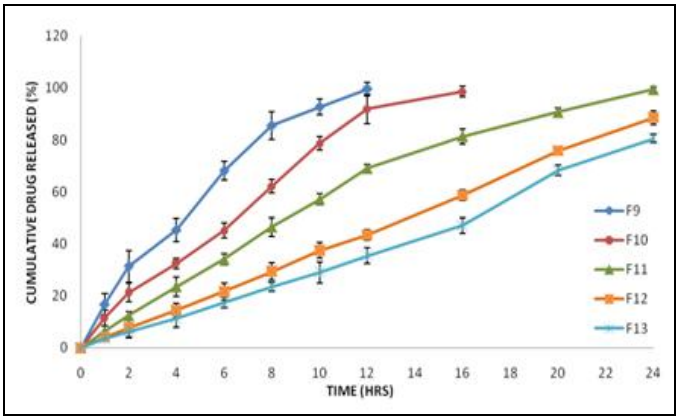

FIG. 10: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATIONS F9-F12

Kinetic Modelling and Determination of Mechanism of Drug Release: The data obtained from drug release studies were analyzed for order and mechanism of release by best-fit method.

Values of the regression coefficient (R^2) were considered important for interpreting and determining release kinetics. Results of kinetic analysis of optimized formulation F11 are represented in **Table 5.**

In a comparison of the order of release, it was found that almost all the formulations exhibited zero-order release (R^2- 0.965 for F11), which indicates that the drug release from the matrix tablets is independent of the initial drug load.

Such a phenomenon ensures a consistent and stable dosage regimen. EC backing layer, which causes uni-directional release, can play a crucial role in this process. The linearity and R^2 values of Higuchi plots (0.953) state that the mechanism of release of Metformin from the matrix tablets was diffusion controlled.

This can be due to natural gums polymers' high viscosity and swelling index.

But due to these gums' lesser stability and higher hydrophilicity, synthetic Eudragit was added, resulting in better formulations.

Korsmeyer-Peppas equations were plotted, and the value of diffusion exponent 'n', 0.786 indicates that the diffusion was 'non-fickian.

Hence, by considering the dissolution data and results of kinetic analysis, F11 was selected to be the optimized formulation.

TABLE 5: KINETIC MODELLING DATA OF OPTIMIZED F11 FORMULATION

S. no.	Kinetic Model	R^2	n
1	Zero order	0.965	4.313
2	First order	0.829	-0.076
3	Higuchi	0.953	22.68
4	Korsmeyer-Peppas	0.991	0.786
5	Hixson-Crowell	0.911	0.147

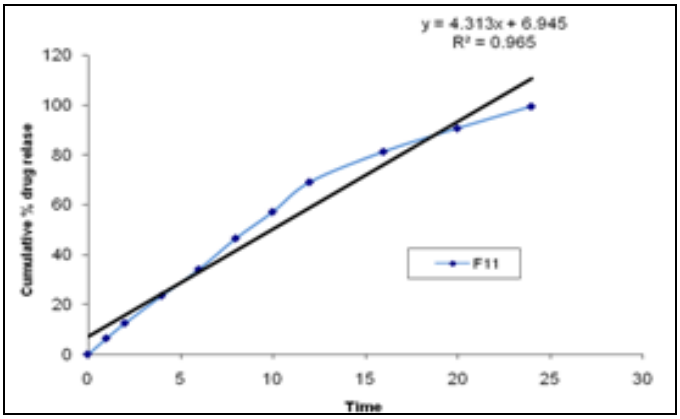

FIG. 11: ZERO ORDER PLOT OF F11

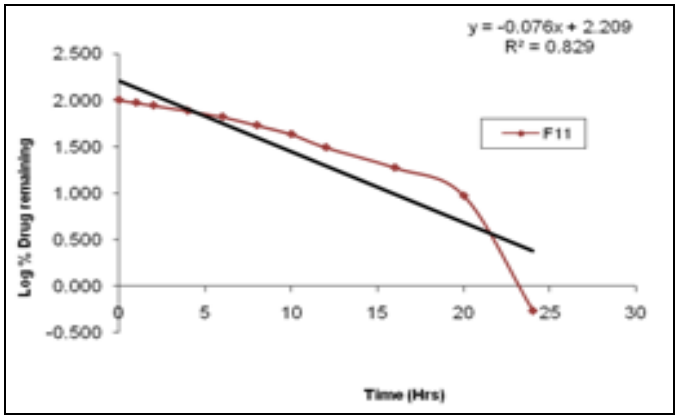

FIG. 12: FIRST ORDER PLOT OF F11

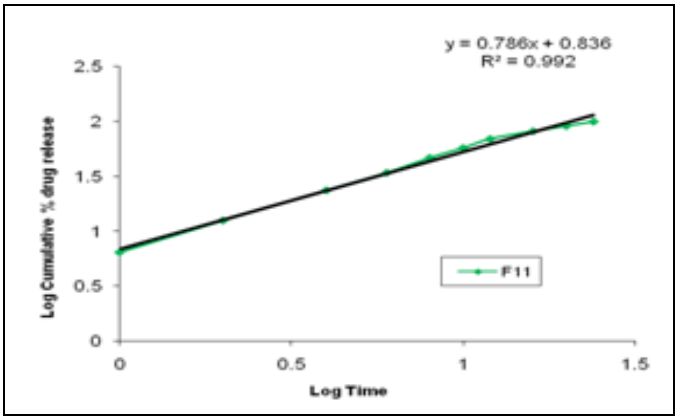

FIG. 13. KORSMEYER-PEPPAS PLOT OF F11

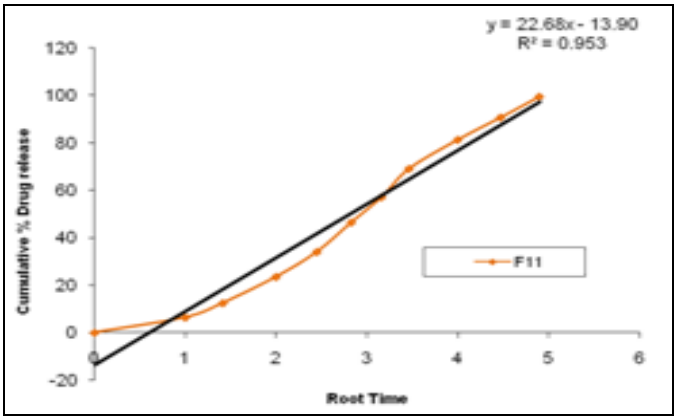

FIG. 14. HIGUCHI PLOT OF F11

Accelerated Stability Study: Accelerated stability study for the optimized formulation F11 was carried out for a period of 3 months at specified conditions of temperature and RH (40 °C and 75%RH). It was observed that no significant changes could be noticed in the physicochemical properties and release characteristics. Hence, it can be inferred that the developed formulations exhibited better stability **Table 6.**

TABLE 6: RESULTS OF ACCELERATED STABILITY STUDY OF F11

Formulation	Parameter	Initial	After 1 month	After 2 months	After 3 months
F11	% Drug Release	99.46 ±0.75	98.65 ±1.28	98.07 ±1.12	97.75 ±0.56
F11	% Drug Content	99.82±0.15	99.52 ±1.21	100.08 ±0.22	99.71 ±1.18

CONCLUSIONS: The main objective of any therapy would be to provide the required amount of a drug to the target site and achieve and maintain desired plasma concentration over a prolonged period of time, and reduced side effects. Controlled matrix formulations can be presumed to be suitable in optimizing drug therapy by maintaining effective drug concentrations and improving patient compliance. In the present study, thirteen batches of matrix tablets of Metformin hydrochloride (F1-F13) were formulated using natural polymers like Okra gum, Xanthan gum, Moringa gum, and the synthetic polymers such has Eudragit RL100 in combinations. EC was used to form a backing laminate to establish controlled release of the drug by causing the uni-directional release. The formulations were characterized for all the possible parameters, and the results were found to be satisfactory. Among all the formulations, F11 (Moringa gum and Eudragit RL 100 2:1 ratio) has shown good physical properties, mechanical strength, uniform content, and better release over 24 hours (99.46% ±0.75). It was also evident from the kinetic modelling and accelerated stability study that F11 exhibited zero-order kinetics, following non-Fickian diffusion and stable profiles over 3 months. Also, the designed formulations can offer convenient administration (single dosing/day), enhanced patient compliance with 24 hour glycemic control, and reduced adverse effects. Hence, from the above study, it can be concluded that there is ample scope for the use of natural gums as release modifiers in the formulation development of oral controlled release dosage forms of Metformin hydrochloride.

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