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Research Article

Formulation-Evaluation of Metformin Hydrochloride Sustained Release Matrix Tablet and Studying the Effect of Sintering Technique over the Drug Release *In-Vitro.*

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ABSTRACT
Diabetes has become a vastly spreading disorder taking millions of people under its wings every year, so is the ever expanding need of curing it. Many drugs are the choices for treatment and effective management of diabetes; Metformin Hydrochloride is one of them. Because of the gastrointestinal concern which makes its journey into the body difficult, a lot has to be done to make it a perfect choice. To achieve spatial as well as temporal control over the drug release, sustained release formulations are useful. Sustained release systems include any drug delivery system that achieves slow release of drug keeping plasma drug concentration consistently at desired level. In the present study, work has been done to formulate and evaluate sustained release matrix tablet containing Metformin Hydrochloride, a blend of polymers including Eudragit RL100, Eudragit RS100, and HPMC K4M. Wet granulation method is used for tablet formulation. A newer concept of sintering has also been tried to affect a better drug release performance. Evaluation studies were performed on the prepared tablets in relevance to various parameters. Study and test results as FTIR, DSC analysis proved compatibility of polymers with the drug; the blend of polymers help control the drug release over an extended time period. The release analysis revealed erosion mediated drug release.

KEYWORDS
Metformin Hydrochloride, Eudragit, HPMC, matrix tablet, sintering technique.

1. INTRODUCTION

Simple definition of sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug". [1,3]

Ideally a sustained release oral dosage form is designed to release rapidly some pre-determined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then released at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required. [1-3] The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms. Controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time.

Ideally two main objectives exist for these systems: 'Spatial' drug delivery, which is related to the control over the location of drug release. 'Temporal' drug delivery, in which the drug is delivered over an extended period of time during treatment.[4]

1.1. Sustained Release System

It includes any drug delivery system that achieves slow release of drug over an extended period of time.

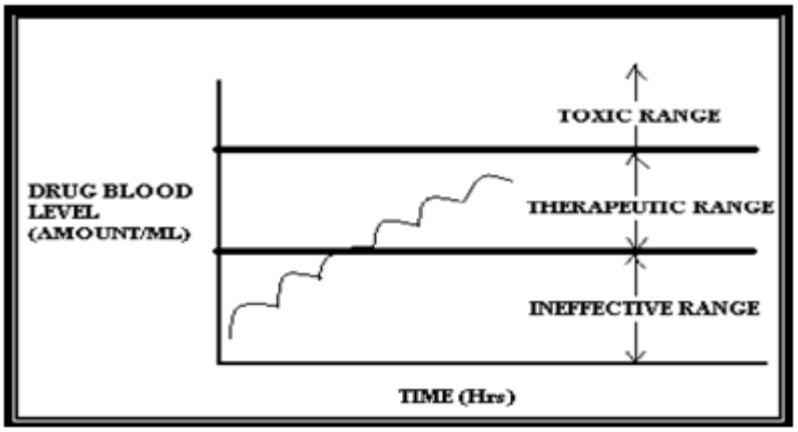
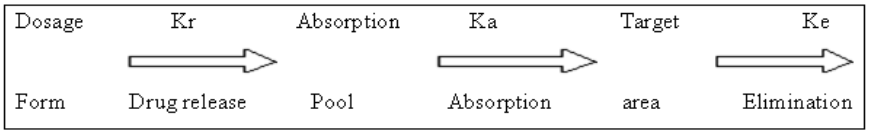


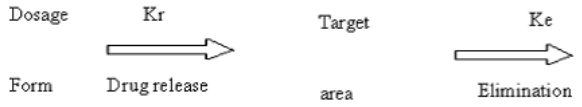
Fig. 1. Typical drug blood level time profiles for delayed release drug delivery by repeat action dosage form

1.2. Principle of Sustained Release Drug Delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.



The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non-immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This causes the above Kinetic scheme to reduce to the following.



Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release delivery system must be directed primarily at altering the release rate.

The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follow zero-order kinetics, as shown by the following equation:

K_r° = Rate In = Rate Out = $K_e C_d V_d$ ---Equation 1

Where,

K_r° : Zero-order rate constant for drug release-Amount/time.

K_e : First-order rate constant for overall drug elimination-time.

C_d : Desired drug level in the body – Amount/volume, and

V_d : Volume space in which the drug is distributed-Litres.

The value of K_e, C_d and V_d are obtained from appropriately designed single dose pharmacokinetic study. The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theoretically, non-zero order release may be equivalent clinically to constant release in many cases.

Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this being of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system. [4, 6,]

The rationale of this study is to investigate various blends of Eudragit RS100 and Eudragit RL100 and Hydroxy propyl methyl cellulose (HPMC) as a drug release modifier. Metformin HCl, which is highly soluble and poorly compressible used as a model drug.

In the last few years, diabetes has reached epidemic proportion and now becoming cause of premature mortality and morbidity. Some antidiabetic drug like Metformin HCl, having short half-life make them suitable candidate to be formulated as sustained-release drug delivery system to ensure safety and to improve efficacy of drugs as well as patient compliance, which can be achieved by better control of plasma levels and less frequent dosing.

Hydrophilic matrix tablets are a well-known type of sustained-release formulation for oral administration and being increasingly investigated for sustained release applications because of their good compatibility as well as they are easy and economical to formulate. Eudragit a hydrophilic polymer is structural component of methacrylic resins. The non-toxicity and low production costs make them great interest for the formulation of sustained release as it rapidly forms viscous solution and gels on contact with aqueous media. Matrices including Eudragit have been employed for the prolong-release of many drugs. Cellulose ether, which are commonly available as semisynthetic cellulose derivative, is a non-ionic polymer having properties to form viscous solutions and gels on contact with aqueous media can be used as hydrophilic matrix for sustained-release of oral dosage form.

Therefore this study is aimed to investigate the effect of various blends of Eudragit/HPMC on swelling and drug release from matrix tablets.

2. MATERIALS AND METHODS

Metformin HCl [9] obtained as a gift sample from Alkem Pharma, Panvel. Eudragit RS 100, Eudragit RL 100 was purchased from Evonic Degusa, Mumbai. HPMC K4M was obtained from Leben Laboratories Pvt. Ltd. Akola. MCC, Starch was obtained from Loba Chemie. Pvt., Ltd. Mumbai. Magnesium Stearate was obtained from Molychem, Mumbai. All the solvents used are of analytical grade and purchased from Qualigens, Mumbai.

2.1. Formulation of Metformin Matrix Tablets

Metformin matrix tablets were prepared by wet granulation method. Firstly all the ingredients were passed through 60 mesh sieve. Then accomplished by adding the starch paste to the powder mixture along with polymer (Eudragit RS 100 and Eudragit RL 100). Passing the wetted mass through a screen of the 44 mesh sieve. After drying the granulation mixture pass through 22 mesh sieves to reduce further the size of granules. Magnesium Stearate was used as a lubricant and microcrystalline cellulose was used as a diluent. Then appropriate amount of the mixture was weighed and then compressed using a multiple station rotary press at a constant compression force equipped with 17 mm capsule-shaped punches at a compression force required to produce tablets of 6-7 kg/cm^2 hardness.

Table 1. Formulations of Metformin HCl Matrix tablets.

FORMULATIONS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metformin HCl	500	500	500	500	500	500	500	500	500	500
Eudragit RS 100	100	150	-	-	60	100	150	-	-	60
Eudragit RL 100	-	-	100	150	60	-	-	100	150	60
HPMC K4M	-	-	-	-	60	-	-	-		60
Starch	q.s.	q.s	q.s	q.s	q.s	q.s.	q.s	q.s	q.s	q.s
MCC	130	80	130	80	50	130	80	130	80	50
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10
Total weight in mg	750	750	750	750	750	750	750	750	750	750

After sintering procedure[13] on F1, F2, F3, F4 and F5 Formulations up to 3 hours, so these formulations rearranged in F6, F7, F8, F9 and F10 respectively.

4. RESULTS AND DISCUSSION

3.1 Preformulation Data

3.1.1 Identification of Pure Drug

3.1.1.1 Melting Point Determination

The melting point of Metformin HCl was found to be 228°C to 230°C, which complied with standards thus indicating purity of the received drug sample.

FTIR spectral studies of Metformin HCl will be discussed in 3.1.1.2.

3.1.1.2 FTIR Spectral Studies

The FTIR spectrum of pure drug was found to be similar to the standard spectrum of Metformin HCl. The spectrum of Metformin HCl shows the following functional groups at their frequencies and is presented in Table 2 and Figure 2.

FTIR spectra of Drug with Eudragit RS 100 and Eudragit RL 100; mixture of drug with Eudragit RS 100, Eudragit RL 100, HPMC K4M and Optimized formulation are given in Figures 3,4 and 5 respectively.

Table 2. Characteristics of different functional groups of Metformin HCl.

Characteristic	**Energy (Cm^{-1})**
$-NH_2$ stretching	3371

-NH stretching	3293
N-H deformation and asymmetric NCN stretching	1623, 1559
CH_3 asymmetric and symmetric deformation	1474, 1446, 1417
C-N stretching and CH_3 rocking	1057, 934

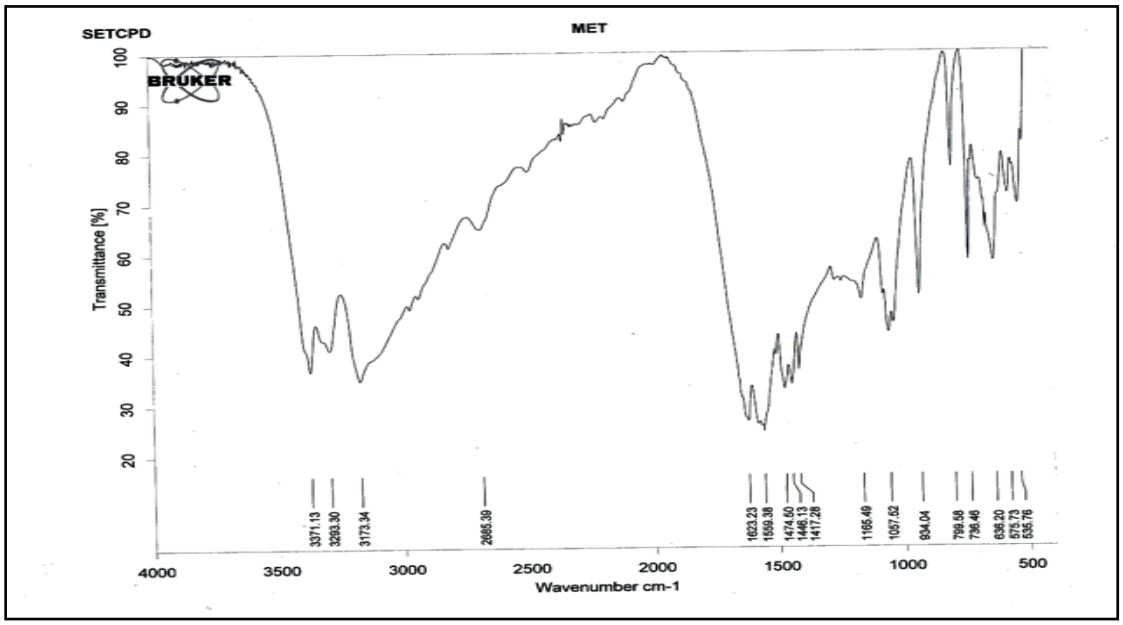


Fig. 2. FTIR spectrum of Metformin HCl.

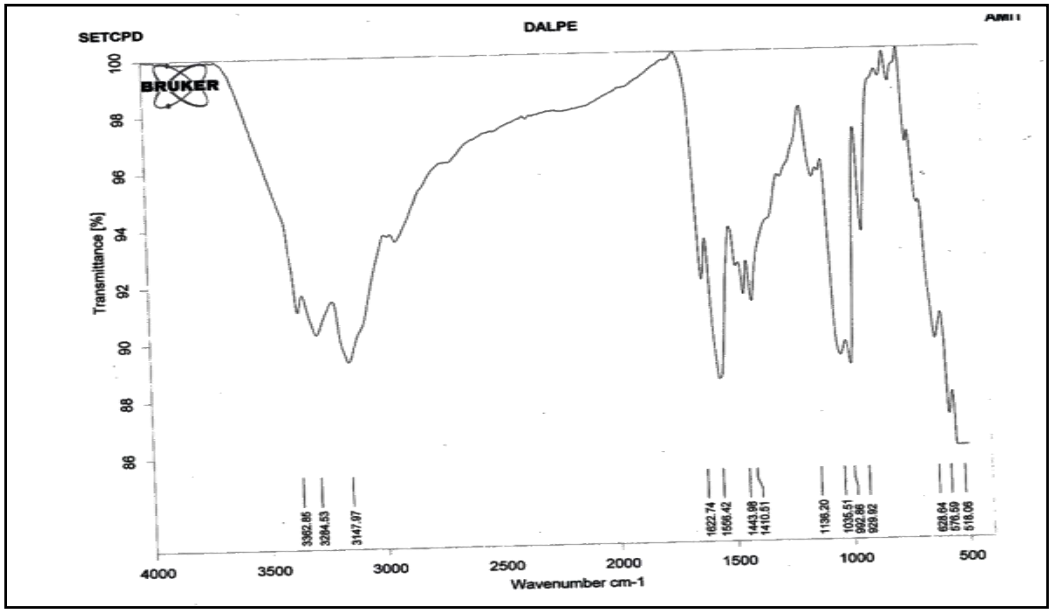


Fig. 3. FTIR spectrum of Drug, Eudragit RS100 and Eudragit RL 100 mixture.

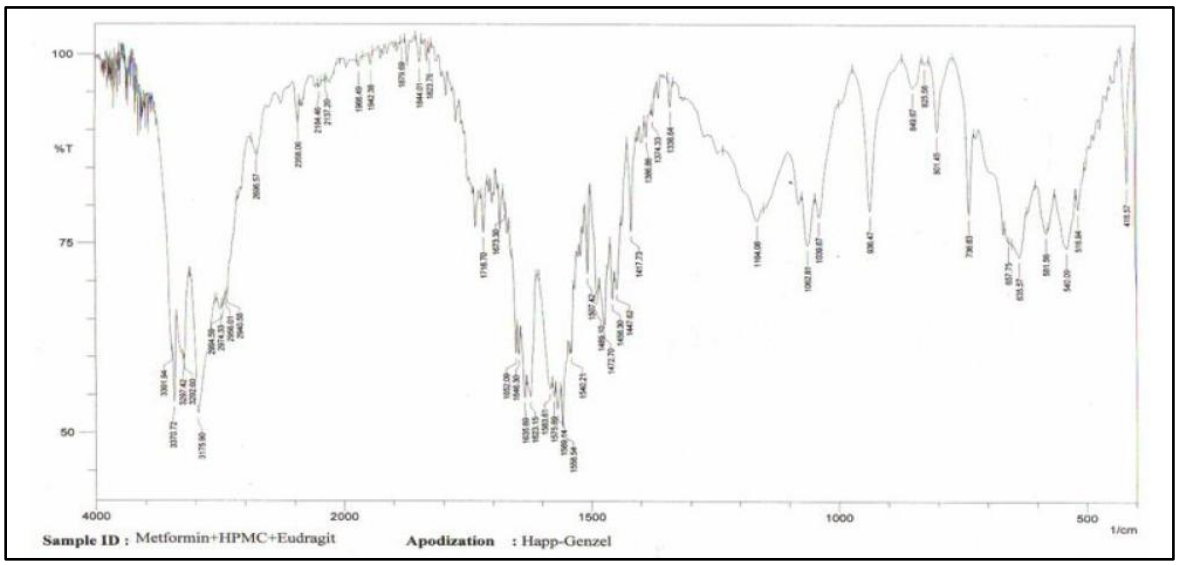


Fig. 4. FTIR spectrum of Drug, Eudragit RS100 and Eudragit RL 100 and HPMC K4M mixture.

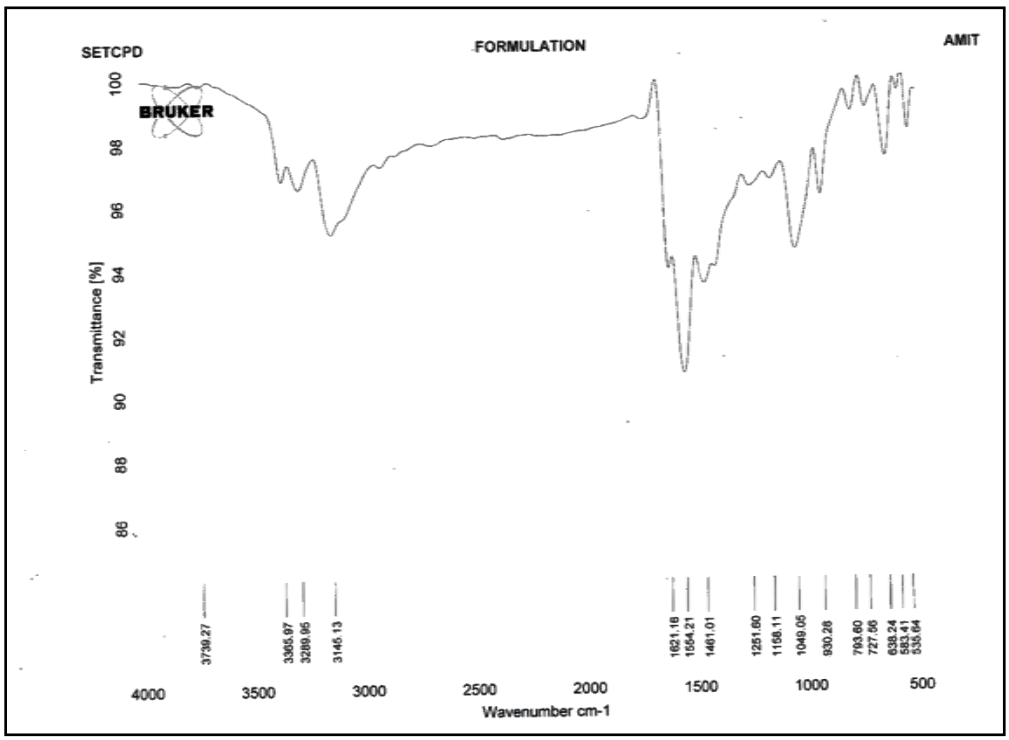


Fig. 5. FTIR spectrum of Optimized Formulation.

From FTIR spectrum of Metformin HCl, the characteristic peaks of different functional groups - NH_2 stretching(3371 Cm^{-1}), -NH stretching (3293 Cm^{-1}), N-H deformation and asymmetric NCN stretching(1623, 1559 Cm^{-1}), CH_3 asymmetric and symmetric deformation(1474, 1446, 1417 Cm^{-1}), C-N stretching and CH_3 rocking(1057, 934 Cm^{-1}) are present when compared with the standard spectrum of Metformin HCl, indicating the quality and purity of the drug sample.

3.1.1.3. Drug-Excipients Compatibility Study

Compatibility study of drug and polymer was conducted by employing FTIR Spectrum. The FTIR spectrum of Metformin HCl, Eudragit RS 100, Eudragit RL 100, its physical mixture and formulation are shown in Figure 2, 3, 4 and 5 respectively. Comparison of FTIR spectra of pure drug, polymer-drug mixture and formulation showed the presence of all the characteristic peaks of drug in the polymer-drug mixture and formulation indicating the chemical stability of drug in the polymer mixture. Thus, FTIR spectral studies indicated the absence of interactions between drug and polymers.

3.1.1.4. DSC (Differential Scanning Colorimetry) Studies

DSC thermograms of Metformin HCl, Mixture of Eudragit RS 100 and Eudragit RL 100 and Mixture of drug with Eudragit RS 100 and Eudragit RL 100 are given in Figure 6, 7 and 8 respectively.

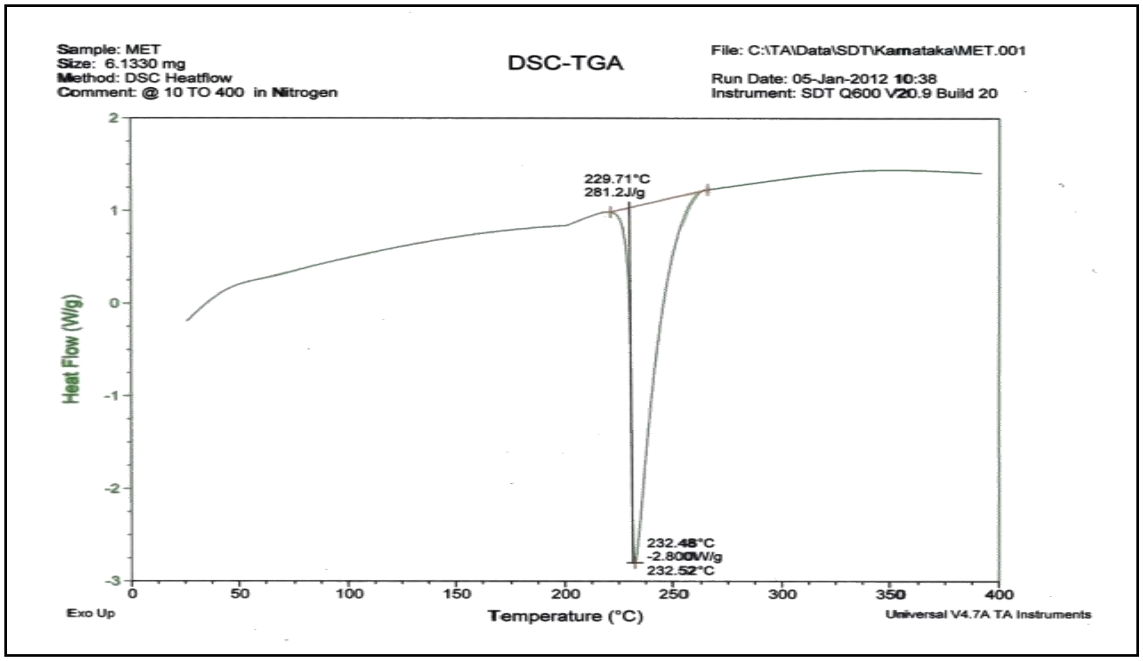


Fig. 6. DSC Thermogram of Metformin HCl.

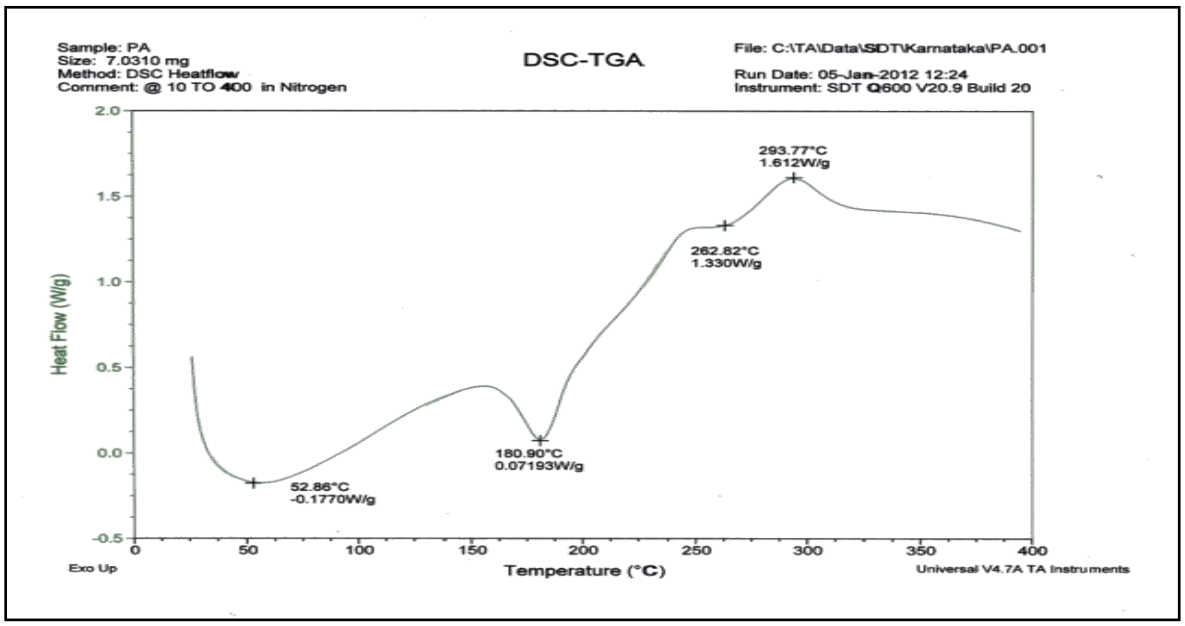


Fig. 7. DSC Thermogram of Eudragit RS 100, Eudragit RL 100 mixture.

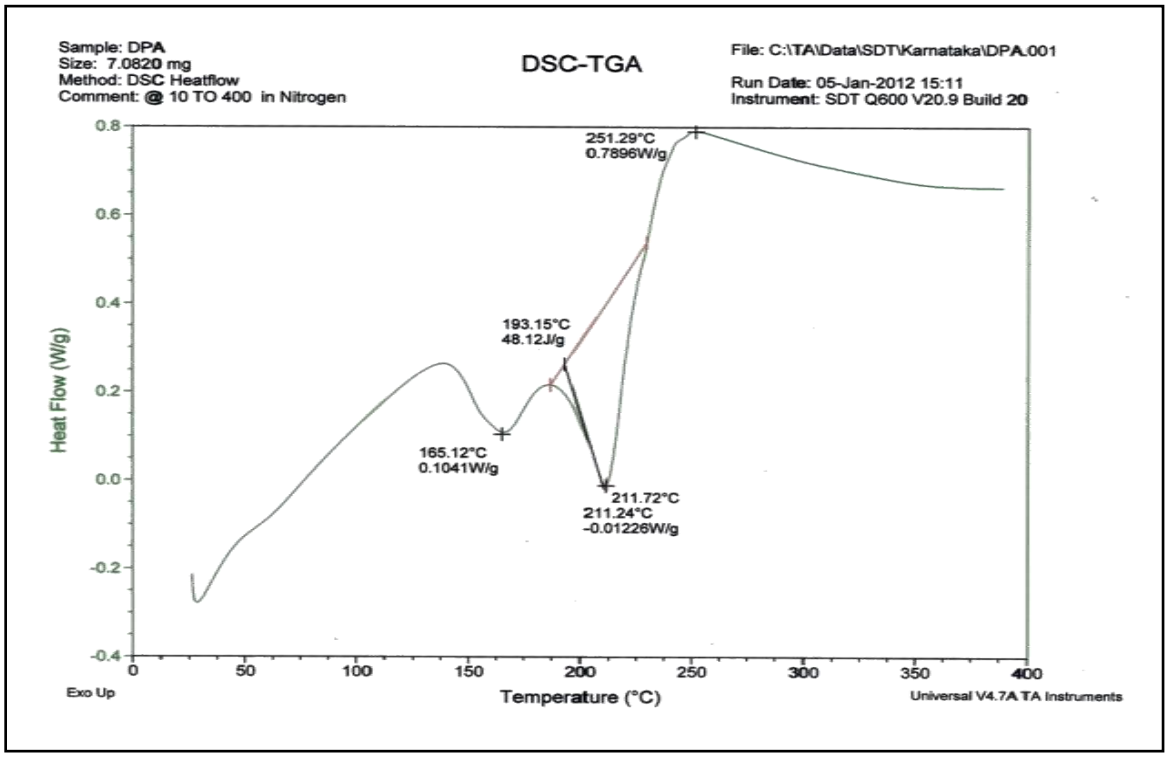


Fig. 8. DSC Thermogram of Metformin HCl, Eudragit RS 100 and Eudragit RL 100 mixture.

DSC was performed to investigate the crystallinity of drug in the matrix as well as thermal compatibility of drug with polymers. DSC thermograms of Metformin HCl, Eudragit RS 100 and Eudragit RL 100 mixture and Drug polymer mixture were taken. For polymer mixture Figure 7

two endothermic peaks at 180.90˚C due to Eudragit RS 100 and Eudragit RL 100 because melting point of both polymers are found to be nearer and another peak at 262.82˚C and exothermic peak observed at 293.77˚C due to polymer degradation. Thermogram of Metformin HCl Figure 6 showed a sharp endothermic peak at 232.48˚C indicating melting of the drug. In case of drug polymer mixture Figure 8 shows three peaks, two endothermic and one exothermic. First endothermic peak at 165.12˚C indicating melting of Eudragit RS 100 and Eudragit RL 100, second endothermic peak at 211.72˚C indicating melting of Metformin HCl and exothermic peak at 251.29˚C indicates degradation of polymers, as peak corresponding to Metformin HCl is observed, indicating the crystalline dispersion of Metformin HCl particles into the polymer matrix. The thermal data shows that drug is thermally compatible with the polymers. In preformulation studies, it was found that, the estimation of Metformin HCl by spectrophotometric method at 233 nm in pH 1.2 acidic buffer, pH 6.8 phosphate buffer and distilled water had good reproducibility, at the concentration between 2-12 µg/ml. Correlation between concentration and absorbance was found to be closer to 1.0.

3.1.2. Pre compression Data

Table 3. Pre compression data.

Formulations	Angle of repose (Degrees)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	33.24±0.002	0.56±0.027	0.67±0.002	16.41±1.13	1.19±0.08
F2	32.05±0.003	0.54±0.003	0.68±0.028	20.48±0.97	1.25±0.13
F3	31.36±0.004	0.59±0.002	0.72±0.035	18.05±0.13	1.22±0.11
F4	34.44±0.021	0.56±0.031	0.75±0.023	25.33±0.87	1.33±0.07
F5	33.16±0.002	0.55±0.004	0.64±0.003	14.06±0.69	1.16±0.21

Total weight taken 10 gm. for tests, No of strokes 100 for tapped density

Table 3 shows pre compression data of the formulations. Angle of repose was found between 31.36 to 34.44 degrees, bulk density was found between 0.54 to 0.59 (gm/ml), Tapped density was found between 0.64 to 0.75 (gm/ml), Carr's index was found between 13.63 to 25.33% and Hausner's ratio was found between 1.15 to 1.33.

3.2 Evaluation of Matrix Tablets

3.2.1 Post compression Data

Table 4. Post compression Data.

Form.	Diameter (mm)	Thickness (cm), n=3	Hardness (kg/cm^2), n=3	Weight (mg), n=20	Friability (%)	Drug Content (%), n=3
F1	17	0.578±0.004	5.46±0.11	769.35±5.97	0.73	99.35±1.13
F2	17	0.625±0.002	4.86±0.13	745.30±7.42	0.87	98.95±0.97
F3	17	0.668±0.001	4.73±0.08	746.35±6.19	0.78	98.47±0.13
F4	17	0.594±0.002	5.66±0.14	755.60±5.18	0.65	99.27±0.83
F5	17	0.624±0.004	5.26±0.12	757.45±7.52	0.64	99.11±0.69

Thickness, hardness, weight and drug content are mean of n determinations values are given in Mean ± Standard deviation (S.D.). Post compression studies were carried out and the data are given in Table 4. Weight, friability and drug contents of the tablets are found to be complied with the standards.

3.2.2. In Vitro Drug Release

Table 5. In vitro Drug release of formulation F1, F2, F3, F4, F5.

Sr. No.	Time (hr)	% Cumulative drug release				
		F1	**F2**	**F3**	**F4**	**F5**
1	0	0	0	0	0	0
2	1	20.67	18.44	23.20	21.86	18.29
3	2	28.11	26.18	30.94	28.11	26.62
4	3	38.08	34.21	41.80	37.63	33.61
5	4	56.80	53.10	49.68	47.15	49.38
6	5	65.90	64.11	73.33	68.87	68.13
7	6	76.79	72.74	82.85	80.47	78.24
8	7	91.33	88.66	91.48	90.44	90.59
9	8	98.77	97.73	99.22	98.17	96.24

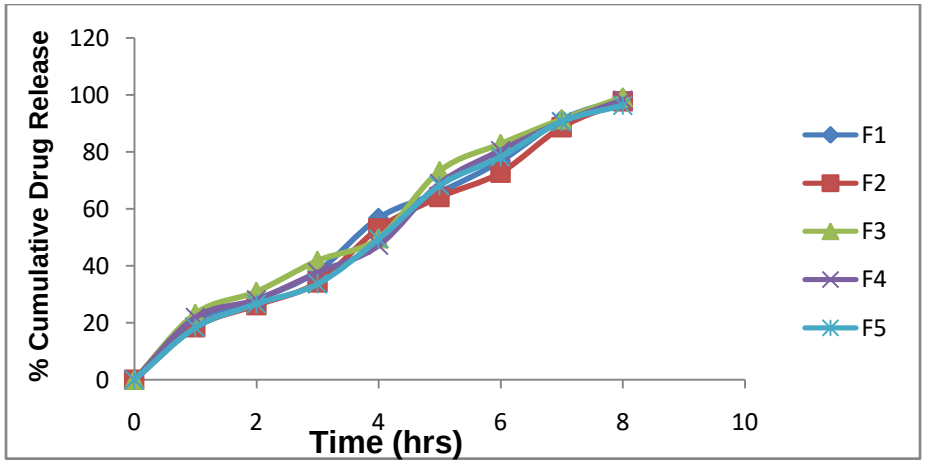


Fig. 9. *In vitro* Drug releases of Formulation F1, F2, F3, F4, F5.

Table 6. *In vitro* Drug release of formulation F6, F7, F8, F9, F10.

Sr. No.	Time (hr)	% Cumulative drug release				
		F6	F7	F8	F9	F10
1	0	0	0	0	0	0
2	1	15.61	12.79	8.33	6.39	6.99
3	2	23.50	21.27	21.86	9.96	11.30
4	3	27.81	26.47	26.92	21.71	22.76
5	4	36.14	33.76	33.32	32.42	34.36
6	5	43.88	41.95	40.01	39.42	39.81
7	6	57.57	52.51	52.51	42.26	46.71
8	7	64.41	62.33	62.18	54.15	54.74
9	8	73.48	70.66	70.80	61.88	64.26
10	9	77.65	76.76	75.12	68.13	70.36
11	10	86.72	84.94	82.71	78.69	80.03
12	11	94.01	91.63	91.78	88.80	90.44
13	12	99.81	98.77	99.37	95.20	96.84

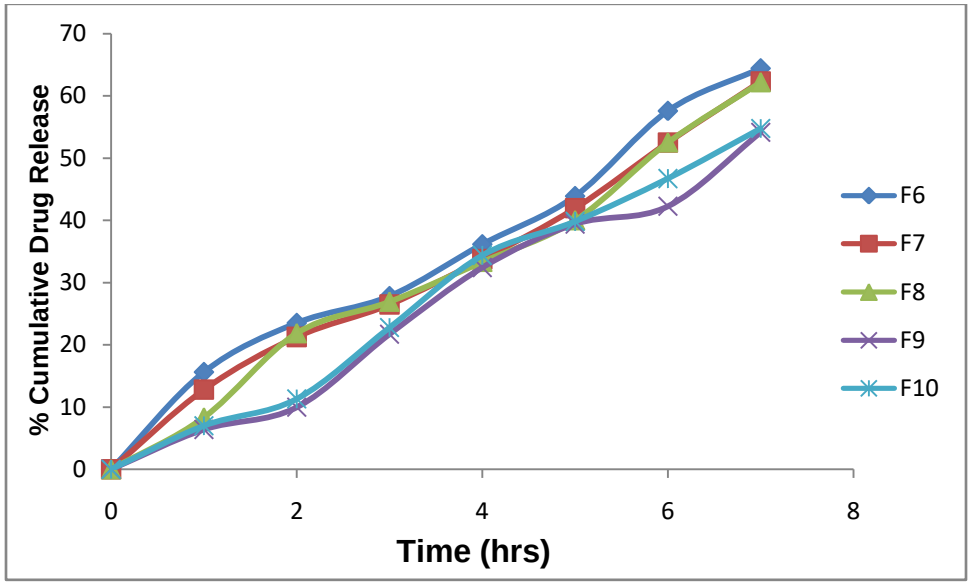


Fig. 10. *In vitro* Drug release of formulation F6, F7, F8, F9, F10.

The release data obtained from the formulations are mentioned in Table 5, 6 and Figures 9 and 10.

It was observed that the drug release from the formulations decreased with increase in the amount of polymer added in each formulation. The release showed a biphasic release with an initial burst effect. In the first hour drug release was 20.67%, 18.44%, 23.20%, 21.86%, 18.29%, 15.61%, 12.79%, 8.33%, 6.39% and 6.99 for F1, F2, F3, F4, F5, F6, F7, F8, F9 and

F10formulations respectively. The mechanism for the burst release can be attributed to initial wetting of the polymers cause swelling of outer layer of the tablets.

The overall cumulative % drug release for F1, F2, F3, F4 and F5 were 98.77%, 97.73%, 99.22%, 98.47% and 96.24% respectively at the end of 8 hour. And for F6, F7, F8, F9, F10 were 99.81%, 98.77%, 99.37%, 95.20% and 96.84% at the end of '12 hours.'

In the formulations the drug: polymer (Eudragit RS100) ratio 2:1(F1) shows better drug release as compared to(F2). From Eudragit RL100 formulations drug polymer: ratio with (F3) shows a better release than (F4). In the formulations where mixture of both polymers is used with HPMC K4M shows increase in sustained time.

In the formulations F6, F7, F8, F9, F10 using after sintering procedure. This type of system provides a significant and convenient method for achieving sustained release in oral dosage forms. Among all these formulations F6 and F8 shows better drug release and increase in sustained time.

4. CONCLUSION

The aim of this study was to formulate and evaluate Eudragit RS 100, Eudragit RL 100, HPMC K4M based matrix tablets of Metformin HCl. Matrix tablets of different drug polymer ratios were prepared by wet granulation method and evaluated.

From the experimental results, it was concluded that:

Matrix tablets of Metformin HCl were prepared by wet granulation method using Eudragit RS 100, Eudragit RL 100, and HPMC K4M as a drug release modifier by using different drug polymer ratio. FTIR studies confirmed absence of chemical interactions between drug and polymers. DSC studies showed crystalline dispersion of Metformin HCl particles into the polymer matrix and the drug is thermally compatible with the polymers. The blends were evaluated for pre compression studies and prepared matrix tablets were evaluated for thickness, hardness, weight variation, % friability and Drug content.

In vitro drug release showed that the drug release decreases with increase in the amount of polymer added in each formulation. Release studies also showed that the swelling of matrix tablets influenced the drug release and a biphasic release with an initial burst effect due to initial wetting of the polymers cause swelling of outer layer of the tablets. Swelling data shows that the matrix tablets appeared to swell almost from the beginning. The matrix tablets swelled or eroded while in contact with the aqueous medium and formed a continuous gel layer or underwent combination of swelling and erosion.

This research work deals with the objective of developing oral sustained release formulations through matrix tablets containing Metformin hydrochloride using plastic polymers such as Eudragit RS 100 and Eudragit RL 100 by sintering technique in varying concentration and comparative evaluation of their controlled release potential were also investigated.

In conclusion, among the different strategies employed for the design of a controlled release dosage form, sintering technique for the preparation of polymer matrices for controlled release metformin hydrochloride appears to be an alternative technique. This new method for controlling

the release rate of metformin hydrochloride has been developed using Eudragit and HPMC polymer and was tested. At room temperature when exposed to acetone vapors, Eudragit RS100, Eudragit RL 100 and HPMC K4M powder particles fused or welded to each other due to coming in contact with other particles were the particles. The extent of fusion depends on concentration of polymer. This type of system provides a significant and convenient method for achieving sustained release in oral dosage forms. The release of the drug form un-sintered matrix tablets containing F1, F2, F3, F4, F5 formulations was 100% within 8 hours, and the release of the drug form sintered matrix tablets containing F6, F7, F8, F9, F10 formulations was 100% within 12 hours. This clearly shows that Eudragit RS 100, Eudragit RL 100, HPMC K4M polymers increased sustained time of tablets when employed as sintering procedure on matrix tablets.

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