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Formulation and Evaluation of Sustained Release Tablets of Metformin Hydrochloride by Solid Dispersion Technique Using pH dependent and pH independent Eudragit Polymers

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ABSTRACT

Objectives: The purpose of the present investigation was to evaluate the influence of solid dispersion of pH dependent and pH independent Eudragit polymers on the sustained release metformin hydrochloride matrix tablets.

Materials and methods: Matrix formulations were prepared by direct compression techniques. The excipients used in this study did not alter physicochemical properties of the drug, as tested by FTIR and DSC. All the batches were evaluated various physical parameters. The in vitro drug dissolution and SEM studies were also carried out. Mean dissolution time is used to characterize drug release rate from a dosage form.

Results and discussion: Among the different examined polymer blends, Eudragit RLPO with S100 and Ll00 matrix tablets based on solid dispersion showed highly sustained release pattern. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type.

Conclusions: Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

KEY WORDS: Metformin hydrochloride, Sustained release, Matrix tablet, pH-independent polymers, pH-dependent polymers.

RESUMEN

Objetivos: El propósito de la presente investigación ha consistido en evaluar la influencia de la dispersión sólida de polímeros pH dependientes y pH independientes de Eudragit en los comprimidos de matriz de liberación prolongada de clorhidrato de metformina.

Métodos: Las formulaciones de matriz se han preparado a través de técnicas de compresión directa. Los excipientes utilizados en este estudio no han modificado las propiedades fisicoquímicas del fármaco, tal y como se ha probado mediante FTIR y DSC. Todos los lotes se han evaluado en varios parámetros físicos. También se ha llevado a cabo la disolución del fármaco in vitro y estudios de SEM (Microscopio electrónico de barrido). El tiempo medio de disolución se utiliza para describir el índice de liberación del fármaco de una forma farmacéutica.

Resultados y Discusión: Entre las distintas mezclas de polímeros examinadas, los comprimidos de matriz de Eudragit RLPO con S100 y Ll00 basados en una dispersión sólida han mostrado un patrón de liberación muy prolongado. El modelado cinético de los perfiles de la disolución in vitro ha revelado el margen de mecanismo de liberación del fármaco desde una difusión controlada hasta un tipo anómalo.

Conclusiones: La adecuación de los datos con la ecuación de Korsmeyer ha indicado que la difusión junto con la erosión podría ser el mecanismo de la liberación del fármaco.

PALABRAS CLAVE: clorhidrato de metformina, liberación prolongada, comprimido de matriz, polímeros pH dependientes, polímeros pH independientes.

INTRODUCTION

Sustained release (SR) drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance[1,2].

Amongst the available matrix forming polymers, methacrylic resins (Eudragit®) appear particularly attractive due to high chemical stability, compactability and variability in physicochemical characteristics[3]. Several experimental evidences revealed the release retarding ability of ammonio methacrylate (Eudragit® RL and RS) or methacrylic acid copolymers (Eudragit® L and S) in solid dosage forms[4-7]. In recent years, pH-dependent drug delivery systems are considered suitable for designing sustained-drug delivery system[8-11].

Incorporation of polymers with pH dependent solubility into controlled release matrix tablets seems to be an obvious approach that provides the desired release over an extended period of time. Hence, appropriate combinations of a pH-dependent polymer with a pH-independent one were suitable for adequately sustaining and controlling the release and assured more reproducible drug release behavior.

More recently, the concept of solid dispersion has been explored using insoluble carrier materials for sustained release action. The sustained solid dispersion offer various potential advantages for drugs having poor bioavailability and can be delivered efficiently there by maximizing their bioavailability and sustained action. The reduction of the dissolution rate is achieved by incorporating the drug in insoluble carriers which are considered as matrix system, help in prolonging the duration of time over which the drug is released and are considered suitable for formulations as sustained release dosage forms[12-15]. Previous reports have shown that by using solid dispersions containing a polymer blend it is possible to precisely control the rate of release of an extremely water soluble drug [16-19].

Metformin hydrochloride (MF HCL) is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h [20, 21]. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occur during the initial weeks of treatment. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for MF HCL to prolong its duration of action and to improve patient compliance .

The purpose of this research was to examine the controlled release of MF HCL from solid dispersion using different types of Eudragit®, i.e. RLPO and RSPO, insoluble but dispersible in water, and L-100, S-100, with pH-dependent solubility, were used, separately or in different (w/w) combinations.

MATERIAL AND METHODS

Materials

Metformin HCl was obtained from Universal Medicament Nagpur, India. Microcrystalline cellulose (MCC, Avicel pH 101) was purchased from S. D. Fine Chem. Labs. (Mumbai, India), Eudragit RSPO, Eudragit RLPO, Eudragit S-100 and Eudragit L-100 were obtained as gift samples from Degussa India Ltd. (Mumbai, India). All other ingredients used throughout the study were of analytical grades and were used as received.

Study of physical interaction between drug and polymer

Fourier Transformed Infrared Spectroscopic Studies:

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm cm^{-1} using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

Differential Scanning Calorimetric Studies

DSC measurements were performed using a Mettler TA 4000 apparatus equipped with a DSC 25 cell in order to evaluate the drug-excipient compatibility and to verify the absence of solid-state interactions. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10^0C/min over a temperature range of 30–300^0C. Alumina was employed as the reference standard.

Preparation of Solid Dispersions

Solid dispersions of MF HCL were prepared with binary and ternary drug/polymer(s) mixtures of Eudragit RSPO,

RLPO, S-100 and L-100 with drug in different ratios by weight basis using solvent evaporation technique. Different ratio of polymers and drug were accurately weighed, mixed properly and solubilized in a common solvent ethanol (25 ml).The solvent was allowed to evaporate in hot air oven at 45±1^{0}C.The process of evaporation was opted until constant weight was obtained. Solid dispersion powder was then pulverized and passed through 20 mesh sieve.

Preparation of matrix tablets

The tablets containing solid dispersions systems of MF HCL were prepared by direct compression method as per the formula given in the Table 1. The tablets were compressed using a rotary tableting machine (Rimek Minipress I Ahmadabad, India) with 14-mm flat round punches. A constant compression force was obtained by using the same distance between the upper and lower punches. The binary mixtures were prepared at different drug to-polymer(s) w/w ratios (30%) , and ternary systems were all prepared by combining a pH-dependent polymer with a pH-independent one at different drug to polymer(s) ratio (1:0.7:0.3, 1:0.5:0.5, and 1:0.3:0.7) keeping the total polymer ratio 30% constant.. Just before compression, the surfaces of the die and punches were lubricated with magnesium stearate. All the tablets were stored in airtight containers for further study.

Evaluation of tablets

The prepared solid dispersion matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content[22, 23]. The prepared matrix tablets were evaluated as per standard procedure for hardness (n=6), weight variation (n=20), thickness (n=20), friability and drug content (Martin, 2001, Wells, 2002). Hardness of the tablets was tested using a Strong-Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test was conducted using Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by digital vernier caliper (For-bro Engineers, Mumbai, India). Drug content was analyzed by measuring the absorbance of standard and samples at λ = 233 nm using UV/Visible spectrophotometer (Shimadzu 1601, Kyoto, Japan).

In- vitro drug release studies

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5 ^{o}C. The dissolution media used were 900 mL of 0.1 mol/L HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of prewarmed (37±0.5 ^{o}C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Table 1. Composition of Various Trial Formulations for the metformin HCl tablet

Formulation code	Ingredients (mg.)						
	Metfor in HCL	Eudragit RSPO	Eudragit RLPO	Eudragit S100	Eudragit L100	MCC	Mg. Stearate
F1	500	300	-	-	-	190	10
F2	500	-	300	-	-	190	10
F3	500	-	-	300	-	190	10
F4	500	-	-	-	300	190	10
F5	500	210	-	90	-	190	10
F6	500	150	-	150	-	190	10
F7	500	90	-	210	-	190	10
F8	500	210	-	-	90	190	10
F9	500	150	-	-	150	190	10
F10	500	90	-	-	210	190	10
F11	500	-	210	90	-	190	10
F12	500	-	150	150	-	190	10
F13	500	-	90	210	-	190	10
F14	500	-	210	-	90	190	10
F15	500	-	150	-	150	190	10
F16	500	-	90	-	210	190	10

Analysis of release data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [24-26].

Release Kinetics

In model-dependent approaches, release data were fitted to five kinetic models including the zero-order (Eq. 1), first order (Eq. 2), Higuchi matrix (Eq. 3), Peppas–Korsmeyer (Eq. 4), and Hixson–Crowell (Eq. 5) release equations to find the equation with the best fit.

$$R = k_1 t \quad \text{(Eq. 1)}$$

$$\log UR = k_2 t / 2{:}303 \quad \text{(Eq. 2)}$$

$$R = k_3 \sqrt{t} \quad \text{(Eq. 3)}$$

$$\log R = \log k_4 + n \log t \quad \text{(Eq. 4)}$$

$$(UR)^{1/3} = K_5 t \quad \text{(Eq. 5)}$$

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{t} Wt(R_t-T_t)^2\right]^{-0.5} x\ 100\right\}$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixon–Crowell model, respectively. To describe the kinetics of drug release from matrix tablets, release data was analyzed according to Kosmeyer et al's equation as

$$M_t/M_\infty = Kt^n$$

Where,

M_t/M_∞ = fraction solute release

t = release time

K= kinetic constant characteristic of the drug/ polymer system

n = exponent that characterizes the mechanism of release of traces.

Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were n=0.5 (indicates a classical Fickian diffusion-controlled drug release) and n=1 (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of n between 0.5 and 1 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport [27].

In order to compare the release profile of different formulas with possible difference in release mechanisms (n values), a mean dissolution time [28] (MDT) was calculated using the following equation.

$$MDT = (n/n+1).\ K^{-1/n}$$

Where n = release exponent and k = release rate constant

Similarity Factor (f2) Analysis

To evaluate and compare dissolution data, the dissolution profile was statistically analyzed using dissolution similarity factor f_2. The equation for calculating f_2 is given below.

Where, n = numbers of dissolution time point

W_t = Optional weight factor

R_t = Reference dissolution point at time t

T_t = Test dissolution point at time t

In vitro release profile of the marketed MF HCl sustained release (SR) tablets, (Obimet SR, Abbot) was performed under similar conditions as used for in vitro release testing of the test product for the release of MF HCl. The similarity factor between the 2 formulations was determined using the data obtained from the drug release studies [29]. The f_2 value between 50 and 100 suggest that the dissolution is similar. The f_2 values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

Scanning electron microscopy

Electron micrographs MF HCl hydrochloride matrix tablets before and after dissolution was obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to observation. The scanning electron microscope was operated at an acceleration voltage of 30kV.

Statistical Analysis

The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA) and in all the cases $p < 0.001$ was considered as significant.

RESULTS AND DISCUSSION

Study of physical interaction between drug and polymer

Fourier Transformed Infrared Spectroscopic Studies

FTIR studies revealed that MF HCl hydrochloride showed two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching, and characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching. No significant

Figure 1. In vitro cumulative release of Metformin HCL from batches F1 to F4. Each point represents mean ± SD, n=3

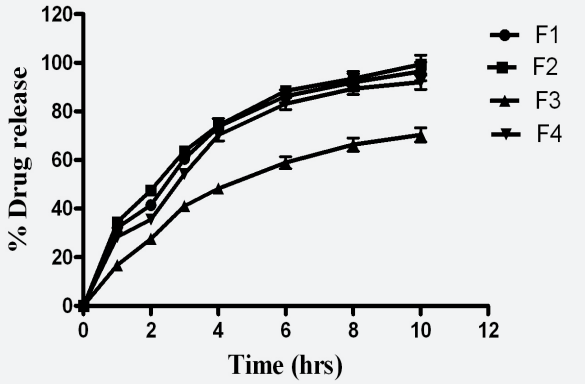
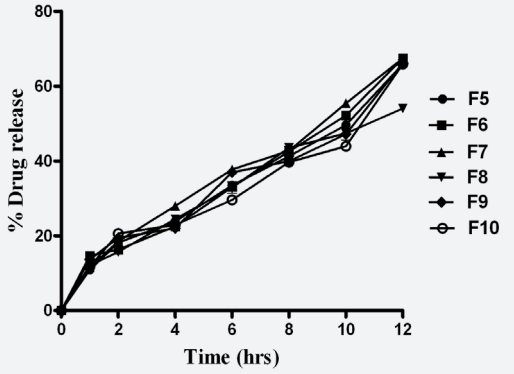


Figure 2. In vitro cumulative release of Metformin HCL from batches F5 to F10. Each point represents mean ± SD, n=3



shifts of reduction in intensity of the FTIR bands of MF HCl hydrochloride were observed.

Differential Scanning Calorimetric Studies

DSC analyses were performed in order to evaluate possible solid-state interactions between the components and, consequently, to assess the actual drug-excipient compatibility in all the examined formulations. The thermal curves of pure components and those of some representative ternary systems. The DSC curve of pure MF HCl exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 °C (Tonset = 231.2, Tpeak = 233.33 and ΔHfusion = -313.51 J/g). The DSC curves of both Eudragit RLPO and RSPO exhibited a flat thermal profile. The thermal profile of Eudragit L-100 and S-100 showed a broad endothermic band ranged between 50 and 100°C, due to the polymer dehydration, followed by a second endothermic effect at higher temperature, attributable to the melting of its crystalline portion, as shown in Figure 2. The DSC curves of both Eudragit RLPO and RSPO exhibited a flat thermal profile, indicative of the completely amorphous nature of these two polymers. The thermal curves of both binary and ternary drug–polymer(s) mixtures, obtained by solid dispersion corresponded to the superimposition of those of the single components, indicating the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. As a further confirmation of the absence of any incompatibility problem, no variations in the thermal behavior of samples of binary and ternary combinations were observed after their tableting and subsequent powdering. Thus no definite solid-solid interaction could be concluded Examination of all the DSC thermograms.

Tablet characteristics

In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits. A plain punch with the same radius each time was used for all formulations in tablet pressing, and the differences in tablet radius was not significant ($P < 0.05$).

Friability value of all formulations and commercial tablets less than 1% indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed [30]. The average percentage deviation of all tablet formulations was found to be within the limit. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%.

Drug release studies

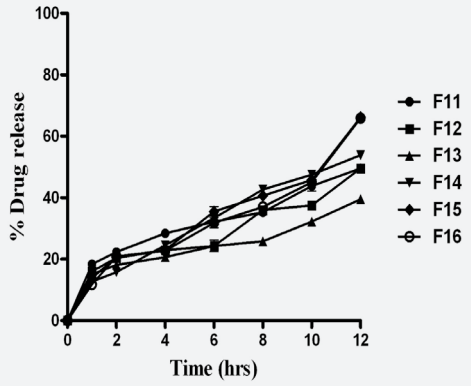
The results of dissolution studies of formulations F1 and F2 composed of binary solid dispersion of drug and Eudragit RSPO and RLPO (30%) respectively, exhibited typical diffusion profiles characterized by an initial faster release phase followed by a more or less marked decrease in release rate as shown in Figure 1. The entire drug content (41.58 and 47.56% respectively) was released within 2 h and a sustained drug release pattern was not observed. This might be due to the higher number of quaternary ammonium groups and greater permeability of Eudragit RLPO. When exposed to the dissolution medium, the solvent penetrates into the free spaces between macromolecular chains of Eudragit RLPO. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to polymer relaxation by the stress of the penetrated solvent. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core.

Release profile of formulations F3 and F4 composed of binary mixtures of drug and pH-dependent Eudragit L-100 and S-100 (30%) respectively are shown in Figure

1. Eudragit S-100 (F3) showed the lowest drug release rate (only 70 % delivered after 10 h), being the polymer with the least swelling properties and becoming soluble only at pH 7. Eudragit L-100 matrix tablets (F4) showed a rather linear release profile (92% delivered after 10 h). Evidently, in this case the progressive lengthening of the drug diffusion path way was almost counterbalanced by the increase in polymeric matrix solubility at intestinal pH. However, unfortunately, the release behavior from these matrices was not well reproducible, as shown by the error bars, probably due to the irregular erosion process of the matrix.

Matrix tablets were then prepared by solid dispersion using combinations of a pH-dependent Eudragit with a pH independent one in the different (0.7:0.3, 0.5:0.5 and 0.3:0.7 w: w) polymer/polymer ratio (while keeping the total polymer ratio 30%), with the aim of obtaining more regular and reproducible release profiles. The release profile of formulations F5, F6, F7 and F8, F9, F10 containing the combination of S-100 and L-100 with Eudragit RSPO (30:70, 50:50 and 70:30 respectively) are shown in Figure 2; whereas Figure 3 shows the release profile of Formulations F11, F12, F13 and F14, F15, F16 containing the combination of S-100 and L-100 with Eudragit RLPO (30:70, 50:50 and 70:30 respectively). Among the different examined polymer blends, matrix tablets based on S-100/RLPO solid dispersion gave the more sustained release pattern, while the combination of L-100/RLPO and L-100/RSPO tablets displaying the highest percent of MF HCl release, but more reproducible results. Tablets with higher content of pH-independent polymer still exhibited a diffusional release profile, being the diffusion process prevailing over the erosion one. On the contrary, tablets with a higher content of the pH-dependent polymer gave the highest percent of final drug released and exhibited more linear release profiles, indicating that the erosion mechanism becomes predominant at intestinal pH. As for the influence of the kind of pH-independent polymer, RLPO confirmed its better permeability properties than RSPO, as previously observed in tablets prepared using single polymers (Figure 1). Moreover, the use of such blends of polymers as matrices for tablets allowed the obtainment of more regular release profiles, with the best equilibrium between the values of % drug released, respectively, at gastric and intestinal pH. This was made possible by the combination of the good erodible properties of S-100 and L-100 with the swelling ones of RLPO and RSPO polymers. Dissolution profile of optimized best formulations (F9 and F15) were compared with the marketed tablet of MF HCl (Obimet SR™) and the release of drug from Obimet SR™ was found to be 72.15% at the end of 10 h.

Figure 3. In vitro cumulative release of Metformin HCL from batches F11 to F16. Each point represents mean ± SD, n=3



Release Kinetics

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient values (r2) of all batches were shown in Table 2. On analyzing regression coefficient values of all batches, it was found that Batch F1 and F4 exhibited almost first order kinetics. Formulation F5, F7, F8, F9, F10, F14, F15, F16 and Obimet SR™ followed Kosermeyr –peppas model. Batch F6 followed Hixon crowell kinetics whereas remaining all the formulations showed Higuchi's release kinetics.

The in vitro release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (r^2=0.98to 0.99) [24]. To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation (26). The values of n for tablets made from solid dispersion systems indicated that different mechanisms of release were observed for drug according to the polymer content. The formulations showed good linearity (r^2 = 0.97 to 0.98) with slope (n) between 0.431- 0.868, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. This was attributed to changes in drug release mechanism from erosion to diffusion due to encapsulation of drug particles by polymer in matrices prepared from solid dispersion system.

The time taken to release 25% (t_{25}), 50% (t_{50}), and 75% (t_{75}) of drug from different formulations was determined (Table 3). Mean dissolution time (MDT) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. The MDT was significantly higher when the combination of pH dependent polymers with the pH dependent polymers was carried out than the plain polymers, which clearly

Table 2. In vitro release kinetics parameters of metformin HCl matrix tablet.

Formulation code	Zero order		First order		Higuchi		Hixon-crowell		Korsmeyer-peppas		
	r^2	k	r^2	K	r^2	k	r^2	k	N	r^2	K
F1	0.804	12.22	0.998	-0.322	0.987	32.95	0.976	-0.072	0.511	0.979	32.53
F2	0.773	12.54	0.982	-0.388	0.989	33.95	0.988	-0.080	0.471	0.987	35.99
F3	0.897	8.57	0.982	-0.135	0.991	22.79	0.963	-0.038	0.639	0.988	17.99
F4	0.842	11.62	0.995	-0.269	0.985	31.18	0.972	-0.064	0.558	0.975	28.28
F5	0.982	6.762	0.986	-0.097	0.962	17.47	0.991	-0.028	0.763	0.996	10.78
F6	0.983	6.925	0.986	-0.101	0.956	17.86	0.991	-0.026	0.701	0.974	12.07
F7	0.976	7.200	0.993	-0.106	0.969	18.70	0.993	-0.035	0.763	0.993	11.62
F8	0.948	6.221	0.984	-0.084	0.978	16.28	0.975	-0.025	0.699	0.987	11.36
F9	0.962	6.712	0.970	-0.096	0.959	17.43	0.975	-0.024	0.669	0.977	12.63
F10	0.969	6.464	0.964	-0.091	0.953	16.75	0.973	-0.027	0.690	0.987	11.68
F11	0.802	5.798	0.917	-0.076	0.994	15.59	0.890	-0.023	0.431	0.990	17.54
F12	0.894	5.364	0.950	-0.068	0.984	14.23	0.936	-0.021	0.474	0.969	14.65
F13	0.814	4.421	0.890	-0.054	0.985	11.88	0.869	-0.017	0.868	0.974	14.04
F14	0.945	6.197	0.994	-0.083	0.981	16.27	0.974	-0.025	0.679	0.985	11.76
F15	0.957	6.688	0.967	-0.096	0.962	17.42	0.972	-0.025	0.648	0.982	13.12
F16	0.967	6.476	0.964	-0.092	0.954	16.77	0.972	-0.027	0.685	0.985	11.81
Obimet SR	0.955	8.09	0.987	-0.127	0.974	21.16	0.985	-0.036	0.989	0.706	14.99

Table 3. Dissolution Parameter of Sustained Metformin HCl Matrix Tablets

Formulation code	t25 %(h)	t50 %(h)	t 75 %(h)	MDT(h)
F1	0.9	2.1	4.3	2.74
F2	0.5	2.2	4.9	2.72
F3	1.2	4.8	10.8	3.28
F4	1.1	2.6	5.1	2.90
F5	3.0	7.5	12.7	4.68
F6	3.1	7.0	12.6	4.66
F7	2.7	6.8	11.5	4.39
F8	3.1	8.3	14.9	3.76
F9	2.8	7.8	14.3	4.70
F10	3.0	8.2	14.8	4.95
F11	2.6	10.3	23.1	3.44
F12	3.1	12.3	27.8	4.10
F13	4.4	17.7	39.8	3.77
F14	3.0	8.4	15.3	3.74
F15	2.7	7.9	14.7	4.72
F16	3.0	8.2	14.8	4.94
Obimet SR	1.4	5.6	12.6	4.10

indicated sustained release nature of the combination of both Eudragits.

Similarity Factor (f2) Analysis

Similarity factor analysis between the prepared tablets (F9, F15) and Obimet SR tablet for the release of MF HCl, showed *f*2 factor greater than 50 which confirms that the release of drug from the prepared tablets was similar to that of the marketed tablet.

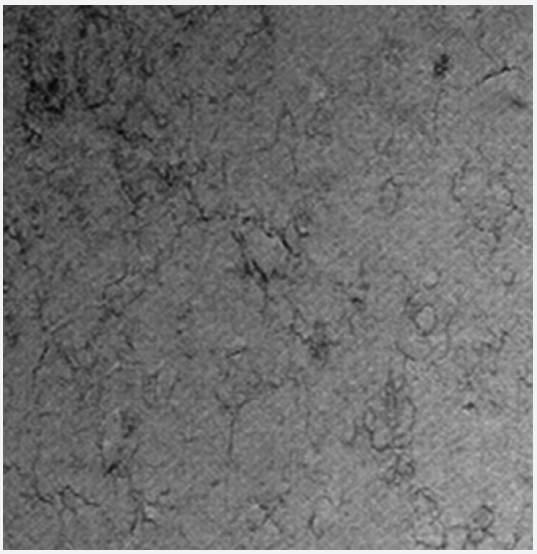
Scanning electron microscopy

The SEM images of the tablet were taken before and after dissolution as shown in Figure 4. The SEM images of the tablet before dissolution showed intact surface without

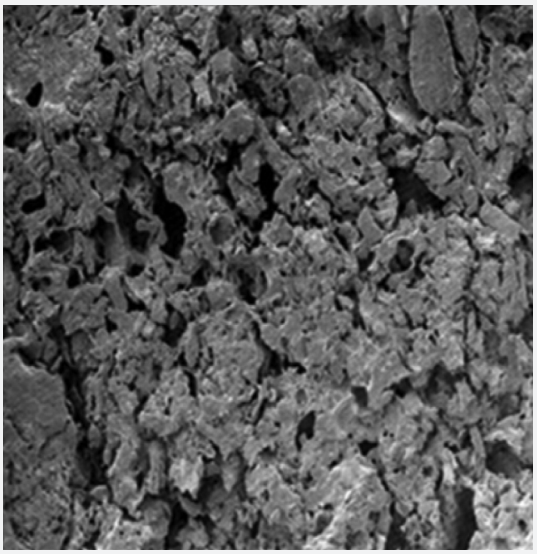
any perforations, channels, or troughs. After dissolution, revealed many pores with increasing diameter. The solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium, which clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of MF HCl from formulated matrix tablets.

Figure 4. Scanning electron microscopy (SEM) image of tablet before and after dissolution

Before dissolution



After dissolution



CONCLUSION:

The use of solid dispersion technique for preparation of drug and polymer mixtures affected matrix characteristics. The drug release behavior was markedly influenced by the kind of Eudragit used, and, when utilized in mixtures, by their relative w/w ratio. When eudragit RSPO and RLPO were used as the only retarding polymer for MF HCl tablet a sustained drug release pattern was not observed. It was found that, appropriate combinations of a pH-dependent polymer with a pH-independent one were suitable for adequately sustaining and controlling MF HCl release and assured more reproducible drug release behavior. Among the different examined polymer blends, matrix tablets based on S-100/RLPO solid dispersion gave the more sustained release pattern. In particular, the use of a mixture of EudragitS-100 and L-100 (pH-dependent) and Eudragit RLPO (pH-independent) in the 0.3:0.7 w/w ratios enabled a highly reproducible drug release profile to be achieved. The formulations showed good linearity which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion.

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