Statistical evaluation of hydrophobic polymer based diclofenac sodium matrix tablet

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Abstract

The aim of the present study was to evaluate four hydrophobic polymers as a rate retarding agent. Eudragit L-100, kollidon-SR, ethyl Cellulose and Veegum were used as Hydrophobic polymers. The polymers and excipients were blended and tablets were prepared using hydraulic press tablet machine. It was found that the tablets which were blended with ethyl cellulose and veegum, failed to provide release retardation. But the tablets in which Eudragit L-100 and Kollidon-SR were present, provided better release retardation. The USP paddle method was selected to perform the dissolution test, carried out in 750 ml 0.1 HCl for first two hours and 1000 ml Phosphate buffer of pH 6.8 for six hours. It should be noted that the release of the drug was very low in the acidic medium. That's why, the dissolution data in the buffer stage (the very small amount of drug that was released in the acid stage included in the 1hour of the buffer stage) were only considered for the treating the data in various pharmacokinetic models. So, the original MDT value of each formulation would be the MDT value indicated (in bar diagram) plus 2 hours. It was found that, the MDT values of the formulations with the higher Eudragit L-100 content were the higher compared to the MDT values of the formulations with the higher Kollidon-SR content.

Keywords: Matrix tablets, eudragit, ethyl cellulose, veegum, kollidon SR.

Introduction

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs [2].
In the last two decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance [3]. Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives

is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing sustained release dosage forms because it makes such manufacturing easy [4]. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the release of drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodable and control the release of drug through pore diffusion and erosion [5]. An example of such water-insoluble plastic carrier is Eudragit, which is a group commercially available in anionic, cationic, and zwit-terionic forms [6]. Eudragit L l00-55 is an anionic co-polymer of methacrylic acid and methyl methacrylate. The ratio of free carboxyl group to the ester is approximately 1:1. It has a pH-dependent solubility and is readily soluble in neutral to weakly alkaline conditions and forms salts with alkalis [7]. This polymer is commonly used in tablet coating as an enteric coating polymer [8] Also, there have been some reports demonstrating that Eudragit L100-55 can be used as a sustained release carrier. Erosion is the main mechanism of release of drug dispersed in the polymer [9]. In addition, Eudragit L100-55 has been used as a colon-targeted drug delivery system [10] and to improve site-specific intestinal drug absorption [11]. Kollidon SR is one of the recently developed matrix forming agents with plastic behavior. Chemically, Kollidon SR is polyvinyl acetate and polyvinyl pyrrolidone based matrix retarding agent particularly suitable for the manufacture of pH independent sustained release matrix tablets. Polyvinyl acetate is a very plastic material that produces a coherent mass even under low compression force. When the tablets prepared with Kollidon SR are introduced into gastric or intestinal fluid, the water soluble polyvinyl pyrrolidone is leached out to form pores through which the active ingredients slowly diffuses outwards in a controlled and pre-determined fashion. Kollidon SR contains no ionic groups which render them inert to the drug molecule. Its high flowability, low reposition angle and excellent compressibility characteristics endow the tablets with desired hardness and low friability while simultaneously reducing the process variables and processing cost [12]. The present study was conducted to find out whether the four hydrophobic polymers can be used as a rate retarding agent.

Results and Discussion

To evaluate the flow properties of the ingredients used in those formulations (without adding glident), the bulk density, tapped density, Carr's Compressibility Index, Hausner ratio and angle of repose were determined. All the formulations showed Carr's Compressibility Index from 20.737 to 24.885%, Hausner Ratio from 1.262 to 1.331 and angle of repose in between 30.24 to 33.86^{O} (Table 2). If the CI (%) is 18 to 21%, it indicates the flow of the powder is poor to passable, whereas values between 23 to 25% indicate poor flow. Similarly, 1.25 to 1.5 indicates the flow of powder may be improved using glident. Angle of repose 30 to 34^{O} mean that the flow of powder is poor [13]. From all of the three parameters it can be concluded that the flow property of the powder mix of all formulations were poor to passable. To improve the flow property, glidents (talc and magnesium stearate) were added. Matrix tablets were prepared by using formula given in Table 1. The prepared tablets were evaluated for some physical parameters which were stated above. The results are given in Table 3.

Table 2: Flow properties of different formulations of DS loaded hydrophobic polymer based matrix tablets

Formula	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (%)	Hausner Ratio	Angle of Repose (Degree)
F-1	0.536	0.713	24.885	1.331	33.57
F-2	0.556	0.740	24.904	1.332	33.86
F-3	0.562	0.748	24.816	1.330	33.49
F-4	0.530	0.668	20.737	1.262	30.24
F-5	0.565	0.737	23.376	1.305	32.54
F-6	0.588	0.779	24.550	1.325	33.12
F-7	0.498	0.640	22.203	1.285	32.89
F-8	0.484	0.620	21.913	1.281	31.24

Table 3: Physical parameters of DS loaded hydrophobic polymer based matrix tablets

Formula	Avg. Wt. (mg.)	Avg. Diameter (mm.)	Avg. Thickness (mm.)	Friability (%)	Hardness (Kg)
F-1	399.56	12.96	2.41	0.56	8.80
F-2	399.12	12.98	2.93	0.88	10.70
F-3	400.06	12.88	2.47	0.22	4.40
F-4	399.47	12.87	2.70	0.25	4.9
F-5	399.25	12.89	2.22	0.26	7.00
F-6	399.58	12.92	2.10	0.39	7.00
F-7	399.26	12.86	2.62	0.47	8.40
F-8	399.56	12.86	2.65	0.49	9.10

The average weight of the prepared tablets were found between 39912 to 400.06 mg, average diameter were 12.86 to 12.96 mm, average thickness were 2.10 to 2.93 mm, average friability were 0.22 to 0.88% and hardness were 4.40 to 10.70 kg. From the results it was evident that, the variation of average weight, diameter and thickness were minimal. The results of hardness of tablets might be described to the better binding property of the polymer. The friability values were less than 1%. The European and US Pharmacopoeia state that a loss up to 1% is acceptable [15]. It was indicated that the tablet surfaces are strong enough to withstand mechanical shock and attrition during storage and transportation and until they are consumed [25]. The relationship of the axial and radial tensile strength of all the formulations was presented in Figure 1.

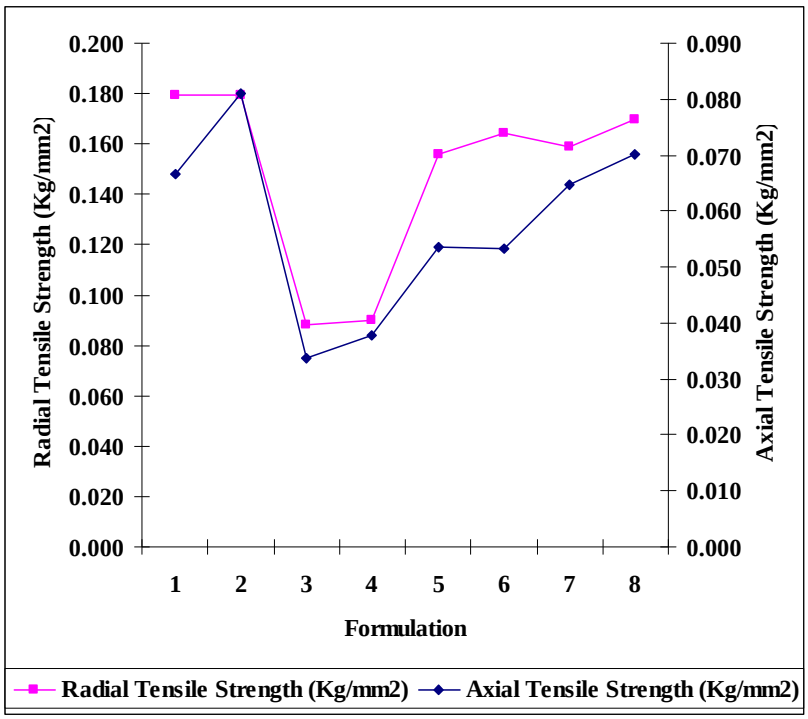

Figure 1: Relationship between axial and radial tensile strength of DS loaded hydrophobic polymer based matrix tablets.

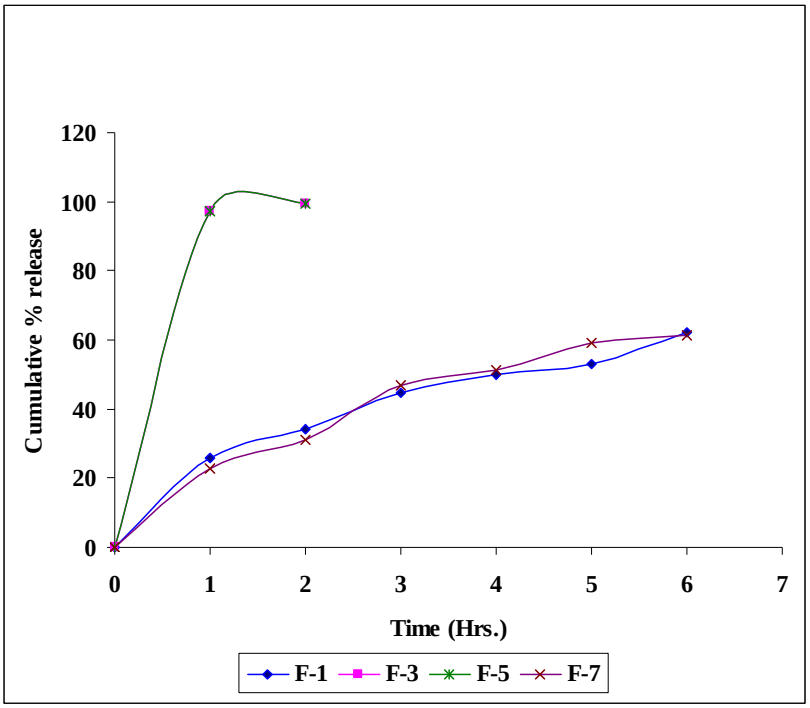

Figure 2: Comparison of release profiles of F-1, F-3, F-5 and F-7 (containing 40% hydrophobic polymers)

After in vitro dissolution studies, the cumulative percent release versus time curve of 40% hydrophobic polymer based matrix tablets were shown in Figure 2 and that of 60% polymer containing shown in Figure 3. It should be noted that the release of the drug was very low in the acidic medium. That's why, the dissolution data in the buffer stage (the very small amount of drug that was released in the acid stage included in the 1hr. of the buffer stage) were only considered for the treating the data in various pharmacokinetic models. From those figures it was observed that, F-3, F-5, F-4 and F-6 showed about 100% release of DS within 3 hours. F-3 and F-4 contained 40 and 60%ethyl cellulose respectively and F-4 and F-5 contained 40 and 60% veegum. So, here it can be concluded that the ethylcellulose and veegum have not any sustaining action at 40 and 60% concentration level. Eudragit L100 and Kollidon SR based matrix tablets (both 40 and 60% concentration level) showed sustaining action up to 6 hours.

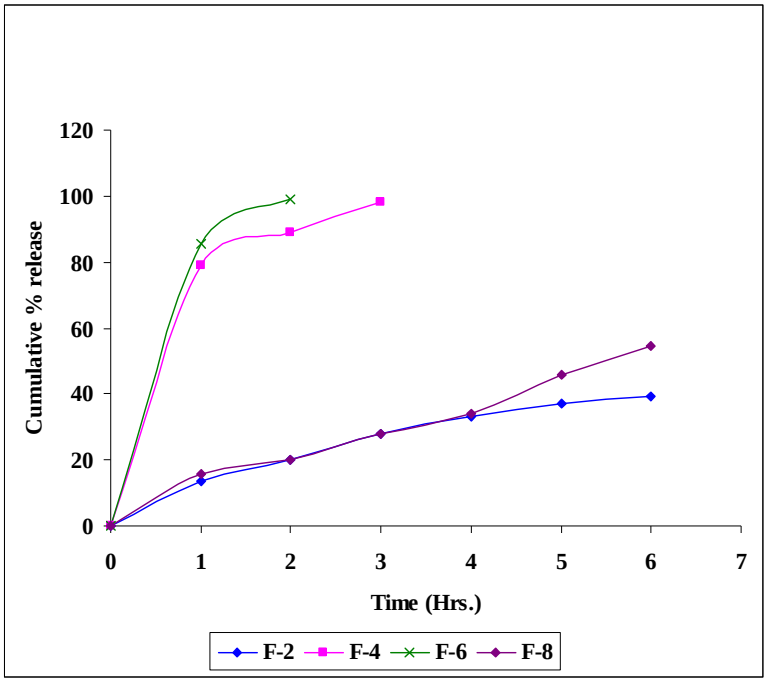

Figure 3: Comparison of release profiles of F-2, F-4, F-6 and F-8 (containing 60% hydrophobic polymers)

From the output of one way repeated measures ANOVA and post hoc test for release pattern of DS from F-1 to F-8, the within subject effect showed calculated F is greater than 1 for all methods (p value = 0.000). So, time is highly significant at any reasonable level of significance. Thus it can be concluded that the percent release on time differed significantly. The multiple comparisons (Bonferroni and Dunnett) were also carried out. The paired comparison of the eight groups with the control group give p value = 0.001, whereas the comparison between F-1 to F-7 gives p value = 1.0, meaning the release profile between F-1 and F-7 measured at different time points are very much similar to that of the control group. Finally it can be stated that there was significant difference (except F-1 and F-7) between the release patterns of DS from matrix tablets ($p< 0.05$). Bonferroni test also provides no difference between F-1 and F-8. The dissolution data were treated to zero order, first order, Higuchi and Korsmeyer release pattern. The kinetic constants (k_o, k_H and k_1), the regression coefficients (R^2) and release exponent (n) were presented in Table 4. From Table 4, it was evident that, F-1, F-2, F-7 and F-8 were best fitted to four different release models. F-1 and F-7 were fitted to Higuchi model (R^2 = 0.995 and 0.985 respectively), indicating the release of drug from the matrix was occurred mainly through pore formation followed by dissolution of the surface drug. F-2 fitted to Korsmeyer model (R^2 = 0.992) with n value of 0.618, meant that the release of DS from the matrix was governed by a diffusion-erosion coupled process. F-8 was fitted to zero order model with R^2 value of 0.975. As F-8 sustained up to 6 hours and it was fitted to zero order model, it was taken as the reference standard to determine the similarity factor of the release profiles of the other formulations. Among the other formulations only F-2 had a f_2 value of 56.829 which was greater than 50, indicating that F-2 is more similar to F-8. F-1 and F-7 were nearly similar to F-8.

Table 4: Kinetic constants, Regression coefficients (R^2), release exponents (n) and similarity factor (f_2) of different formulations of DS loaded hydrophobic polymer based matrix tablets

Formula	Zero-order		Higucchi		First-order		Korsmeyer		f_2
	R^2	K_0	R^2	K_H	R^2	K_1	R^2	n	
F-1	0.802	11.694	**0.995**	24.827	0.965	0.146	0.989	0.481	45.303
F-2	0.888	7.606	0.987	16.012	0.968	0.083	**0.992**	0.618	56.829
F-3	0.718	59.132	**0.924**	79.177	0.932	2.434	1.000	0.030	11.949
F-4	0.660	39.408	0.939	46.734	**0.975**	1.260	0.994	0.196	11.963
F-5	0.720	59.286	0.925	79.376	**0.959**	2.681	1.000	0.032	11.909
F-6	0.823	56.769	0.973	75.239	**0.986**	0.685	0.842	0.217	12.969
F-7	0.864	12.030	**0.985**	62.505	0.974	0.163	0.979	0.591	44.039
F-8	**0.975**	9.168	0.924	19.116	0.973	0.123	0.956	0.707	Ref

Swelling and erosion index of the tablets are presented in Table 5. Swelling index were highest for F-1 (180.159% at 4 hours), then for F-7 (177.143% at 4 hours) and erosion index were highest for F-7 (63.158% at 4 hours) and F-1 (36.188 % at 4 hours). Eudragit L100 based polymer showed little more swelling action than kollidon SR based tablets.

Table 5: Swelling and erosion index (%) of DS loaded hydrophobic polymer based matrix tablets

Time (Hrs)	Swelling Index (%)				Erosion Index (%)			
	F-1	F-2	F-7	F-8	F-1	F-2	F-7	F-8
1	146.535	136.311	134.276	131.593	21.094	12.152	26.873	2.413
2	157.895	153.271	139.623	136.096	30.000	17.054	44.063	3.593
4	180.519	169.686	177.143	159.490	36.188	26.786	63.158	6.366

The release rate of DS was very small in acidic media for 2 hours, that's why the dissolution data in the buffer stage (the very small amount of drug that was released in the acid stage included in the 1hour of the buffer stage) were only considered for the treating the data in various pharmacokinetic models. So, the original MDT value of each formulation would be the MDT value indicated (in bar diagram) plus 2 hours. Figure 4 shows the MDT value of the eight formulations. Highest MDT value was observed for F-5 (9.63 hours), then for F-8 (6.75 hours). The MDT value is the indicator of sustaining action of polymer. F-2 and F-3 showed least MDT values as it showed immediate release of DS. Swelling and erosion index of eudragit L100 based and kollidon SR based tablets were given in table 5, indicating that the polymer when swelled more, they were also eroded more.

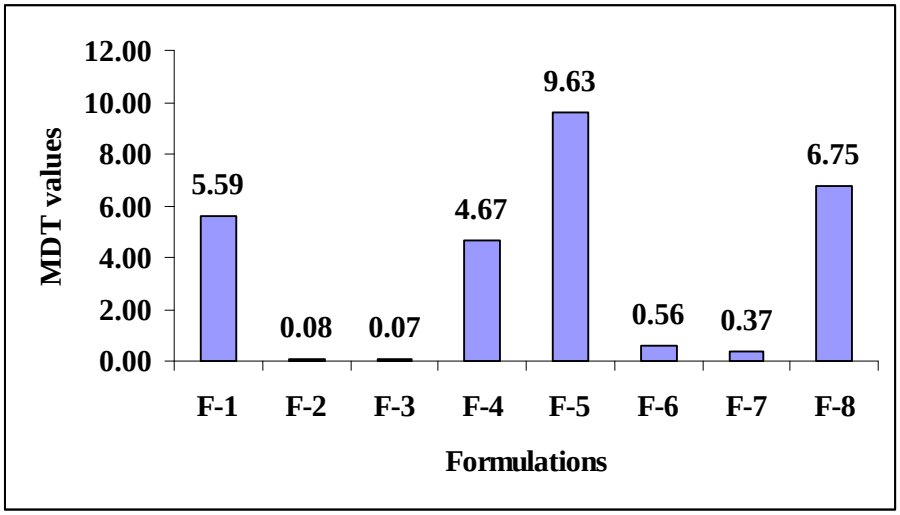

Figure 4: MDT values of all formulations of DS loaded hydrophobic polymer based matrix tablets.

Materials and Methods

Diclofenac sodium (DS) was a gift sample of Square Pharmaceuticals Ltd. Eudragit L100, ethylcellulose, veegum and Starch 1500 were purchased from Techno Pharma (Bangladesh). Kollidon SR and kollidon K30 were from BASF (Bangladesh). Magnesium stearate and talc were purchased from Wilfrid, UK. Among the reagents, tribasic sodium phosphate, 37% (w/v) hydrochloric acid and sodium hydroxide were from Merck, Germany.

Preparation of matrix tablets

Matrix tablets of diclofenac were prepared by simple direct compression method. All the ingredients were weighed accurately, mixed thoroughly to produce a homogenous mixture and were taken in a Perkin-Elmer hydraulic press (USA), equipped with 13 mm diameter die. It was previously lubricated with talc. Now using 8 tones pressure it was compressed into tablet (according to the formulation given in Table 1).

Table 1: Formulation of diclofenac sodium loaded hydrophobic polymer based matrix tablets

Formula	Drug (Diclofenac Na)	Eudragit l-100	Ethyl cellulose	Vegum	Kollidon SR	Starch 1500	Kollidon-30	Magnesium Stearate	Talc	TOTAL
1	100	160	-	-	-	110	20	5	5	400
2	100	240	-	-	-	30	20	5	5	400
3	100	-	160	-	-	110	20	5	5	400
4	100	-	240	-	-	30	20	5	5	400
5	100	-	-	160	-	110	20	5	5	400
6	100	-	-	240	-	30	20	5	5	400
7	100	-	-	-	160	110	20	5	5	400
8	100	-	-	-	240	30	20	5	5	400

Evaluation of powder characteristics

Carr's Index and Hausner Ratio

Both poured density (PD) and tapped density (TD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a Pharmatest densitometer (Veego, India) with 100 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. A useful empirical guide is given by Carr's Compressibility Index (equation 1). Tapped and poured densities of the powder mix of all formulations (without adding glident) were measured. A similar index (equation 2) has been defined by Hausner (1967) [13].

$CI\ (\%) = (TD\text{-}PD) \times 100 \div TD$…… (1)
$\text{Hausner Ratio} = TD \div PD$…….. (2)

Where, TD = Tapped Density, PD = Poured Density, CI = Carr's Index.

Angle of Repose

Angle of repose of the powder mix of all formulations (without adding glident) was determined according to the fixed funnel and freestanding cone method [14]. A glass funnel (75 mm) was secured with its tip at a given height (H) above a graph paper placed on a horizontal surface. Powder (2.5 g) was poured through the funnel until the apex of conical pile touched the tip of the funnel and then the angle of repose (θ) was calculated using the following formula (equation 3),

$\tan\theta = H \div R$……. (3)

Where R is the radius of conical pile [15].

Evaluation of tablets

Hardness and tensile strength

Five tablets of each of the formulations were taken and hardness was measured by hardness tester (Veego, India). The average value was calculated and the testing unit was kg. Measurement of tensile strength was conducted in the axial and radial directions with the intact matrix discs according to Fell and Newton (equation 4 and 5) [16]:

$T_{axial} = 4F \div (\pi \times D^2)$…….. (4)
$T_{radial} = 2F \div (\pi \times D \times H)$…….(5)

Where F, D and H are the crushing force (kg/mm^2), diameter (mm) and thickness (mm) of the NAP-RAN tablets.

Thickness Measurement

Six tablets of each of the formulations were taken and thickness was measured by Vernier Caliper. The values were reported in millimeter (mm). Mean was calculated.

Diameter Measurement
Six tablets of each of the formulations were taken and diameter was measured by digital Vernier Caliper (SDK, China). The values were reported in millimeter (mm). Mean was calculated.

Friability Test
Six tablets of each of the formulations were taken and friability was measured by Friability tester (Veego, India). Weights of six tablets were taken. The tablets were introduced into the rotating disk and it was allowed to rotate at 25 rpm for 4 minutes. At the end of the rotation, tablets were collected, dedusted and reweighed.The friability was calculated as the percent of weight loss. Tablet integrity is determined by calculating the percent of friability by using the following formula:

Percent of friability = $(M_1 - M_2) \div M_1 \times 100\%$..... (6)

Where, $M_1$and M_2 are average weight of the tablets before the rotation and after rotation respectively.

In vitro release studies
The release rates of DS from the matrix tablets were determined by using US Pharmacopoeia-XXII dissolution apparatus 2 (Veego, India). The dissolution test was performed using 750 ml 0.1N HCl solution at 37°C± 0.5°C using 50 rpm for first 2 hours. At the end of the 2 hours, the medium was removed from the vessels and the tablet was subjected to the buffer stage. 20 ml of 5 N sodium hydroxide was added to the medium and stirred for 5 minutes. Then the amount of DS in the sample solution was determined by UV absorbance at the wavelength of maximum absorbance at about 276 nm (Shimadzu, Japan) of filtered portions of the solution under test with a standard curve (according to USP 27). After 2 hours, the acid stage was changed into buffer stage followed by addition of 250 ml 0.2 M trisodium phosphate in the 750 ml 0.1N HCl and if necessary, adjust with 2 N hydrochloric acid or 2N sodium hydroxide to a pH of 6.8± 0.05. Now the release rate of DS in buffer was measured for next 6 hours, withdrawing 10 ml of sample at 1 hour interval and replacing with 10 ml of the fresh medium to maintain the volume constant. The samples were filtered through a Whatmaan filter paper (0.45μm) and diluted to a suitable concentration with required media.

Release kinetics
The suitability of several equations that are reported in the literature to identify the mechanisms for the release of NAP from SR portion was tested with respect to the release data. The data were evaluated according to the following equations:
Zero-order model [17]:

$M_t = M_0 + K_0 t$ …… (7)

Higuchi model [18, 19]:

$M_t = M_0 + K_H t^{0.5}$ …….. (8)
Korsmeyer-Peppas model [20, 21]:

$M_t = M_0 + K\, t^n$ ……... (9)

Where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug, K_0 is the zero-order release constant, K_H is the Higuchi rate constant, K is a release constant and n is the release exponent that characterizes the mechanism of drug release.
First order model [22]:

$LogC = LogCo - kt/2.303$……. (10)

Where, C = cumulative percent of drug release, Co = the initial concentration of drug and k = first order rate constant.

The magnitude of the exponent n indicates that the release mechanism is Fickian diffusion, case II transport or anomalous transport. In the present study (cylindrical shape) the limits considered were n = 0.45 (indicates a classical Fickian diffusion-controlled drug release) and n = 0.89 (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of n between 0.45 and 0.89 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation), commonly called anomalous non-Fickian transport. Values of n greater than 0.89 indicates super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport [23].
Due to the differences in drug release kinetics, the constant k, though one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rates in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution according to Mockel and Lippold [24] using the following equation:

$MDT = n \times (K^{-1/n}) \div (n+1)$……. (11)

Where n is the release exponent and K is the kinetic constant calculated from Equation 9. The similarity factor was used to compare the difference of dissolution profiles of the test matrix tablets is given below:

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad \textbf{……. (12)}$$

where R_t and T_t are the percentage of drug dissolved at each time point for the test and reference products, respectively and n is the number of dissolution samples taken The US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products have suggested that 2 dissolution profiles can be considered similar if f_2 is between 50 and 100 [25].

Statistics
To compare the means of all release data and to assess statistical significance between them, one way repeated measures analysis of variance (ANOVA) performed at the 5% significance level, using SPSS software Version 16.0.

Determination of Swelling (Eroding Behavior)
The swelling-eroding behavior of matrix tablets was determined by the method reported by Al-Taani and Tashoush [26]. Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of *in vitro* drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were placed in a vacuum oven at 40°C and after 48 hours tablets were removed and weighed. Swelling (%) and erosion (%) was calculated according to the following formula, where S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix

% Swelling = (S × 100) ÷R …… (13)

% Erosion = (T – R) × 100 ÷T …….. (14)

Conclusion

Among the four hydrophobic polymer used in the matrix tablets, ethyl cellulose and veegum were not proved to be a sustaining polymer, whereas eudragit L100 and kollidon SR showed sustained action up to 6 hours at 40% and 60% concentration. The release pattern of F-1 and F-7 were found to be similar by one way repeated measures ANOVA (Dunnett test) and that of F-1 and F-2 were found to be similar by measuring similarity factor, f2. F-1 and F-7 fitted to Higuchi model. Finally MDT values were found to be increasing with increased concentration of hydrophobic polymers. Swelling index was highest for F-1 (180.159% at 4 hours) and erosion index were for F-7 (63.158% at 4 hours). Eudragit L-100 based polymer showed little more swelling action than kollidon SR based tablets.

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