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FORMULATION AND EVALUATION OF A COLON DRUG DELIVERY SYSTEM CONTAINING DIFLUNISAL

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Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for providing both systemic and local effects in various parts of the gastrointestinal tract. Recently, greater emphasis has been placed on controlling the site and/or rate of drug release from oral formulations to improve treatment efficacy and patient compliance. Many novel oral drug therapeutic systems have been invented like fast release, targeted release and colon specific drug delivery systems etc.. During the last decade there has been an interest in developing site specific formulations for targeting to the colon. The delivery of drugs to the colon has a number of therapeutic implications in the field of drug delivery. Localized delivery of the drugs in the colon is possible only when the drug is protected from the hostile environment of upper GIT. The various approaches that can be exploited to target the release of drug to colon include prodrugs, coating with pH sensitive polymers, coating with biodegradable, timed release systems, osmotic and bioadhesive polymers.

In the present study, solid dispersions of pH-dependent, time dependent and combined pH- and time-dependent systems were formulated using Eudragit RS100, Eudragit S100, Eudragit L100 and ethylcellulose, with different drug-to-polymer ratios. They were evaluated for their in-vitro release characteristics in an attempt to develop a colon-specific delivery system containing Diflunisal. Release studies of Diflunisal and Diflunisal solid dispersion systems with different polymers were employed using Release apparatus, USP (paddle type) (copley, England) showed that, the combination of pH- and time-dependent systems provided better results than the pH-dependent or the time dependent system alone. Using Eudragit S100 and Eudragit RS100 with Diflunisalin a ratio 2:3:1, respectively for preparing a solid dispersion used for developing a colon-specific delivery system of Diflunisal was the most successful formula. This formula released 0.22±0.03% of the drug included in it in the stomach pH and 26.29±0.91% of the drug in the intestine pH and 77.59±1.79% of the drug in the colon pH.

INTRODUCTION

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for improving product efficacy and safety, as well as patient convenience and compliance[1]. Most common routes of administration include the preferred non-invasive peroral, topical, nasal, buccal/sublingual, vaginal, ocular, rectal and inhalation routes[2].

The oral route is considered as the most convenient one for administration of drugs. Drug normally dissolves in gastric and intestinal fluids and then absorbed from these regions. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as these drugs need to be protected from the hostile environment of upper GIT[3].

Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer. In addition for using the column for local affect, it may be used also for systemic delivery of some drugs like insulin, calcitonin and vasopressin[4]. The colon may be also used for the delivery of drugs, which are polar and / or

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susceptible to chemical and enzymatic degradation in upper GIT[5] and for drugs which are highly affected by hepatic metabolism[6].

There are two approaches for colonic drug delivery. The first is by making covalent linkage of drug with carrier like azo bond, glycoside, glucuronide, cyclodextrin, dextran and amino-acid conjugates[7]. The second approache is by delivering the intact drug molecule to the colon by many ways like embedding in pH-sensitive matrices, time dependent delivery, bioadhesive systems, pressure controlled system, osmotic controlled drug delivery and polysaccharide based delivery systems[8].

One of the most effective approaches is by using the pH dependent polymers. This approach utilizes the existence of pH gradient in the gut that increases progressively from the stomach (pH 1.5-3.5) to the small intestine (5.5-6.8) and finally to the colon (6.4-7.0)[9].

The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. The problem with this approach is that the intestinal pH may vary because it is affected by diet, disease, presence of fatty acids and other fermentation products. Moreover, there is a considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine[10]. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose[11].

Using non steroidalanti inflammatory drugs for treating colon diseases is the best medical of choice. Diflunisal is a promising drug for treating colon ulcers but there are no studies confirm that[12]. Diflunisal acts by inhibiting the cyclo-oxygenase (COX)-mediated production of prostaglandins[13].

The aim of the present work is to prepare solid dispersions containing Diflunisal using different types of polymers, development of a suitable analytical technique for quantification of the drug and *in-vitro* evaluation of the prepared solid dispersions that would be used for developing a colonic drug delivery system for local delivery of Diflunisal.

MATERIALS AND METHODS

Materials

Diflunisal, Eudragit S100, Eudragit RS100, Eudragit L100 and ethylcellulose were obtained as a gift from Sigma-Aldrich (st. Louis, MO, USA). Disodium hydrogen phosphate, hydrochloric acid and sodium hydroxide pellets were obtained from Riedel-deHaen (Seelze, Germany). All other solvents and reagents were of analytical grade and used as received.

Preparation of solid dispersion

Solid dispersions containing Diflunisal were prepared by solvent evaporation technique[14], Eudragit S100, Eudragit RS100, Eudragit L100 and ethylcellulose were used and a mixture of ethanol and dichloromethane in 1:1 ratio was used as a common solvent for the drug and the polymer in the present study.

Method of preparation

Six hundred milligrams of Diflunisal were accurately weighed and dissolved in 100 ml of the solvent mixture. The calculated amounts of the polymer(s) according to the proposed formula were weighed and dissolved in 150 ml of the same solvent mixture at 40°C. The polymer solution was added gradually to the drug solution with continuous stirring using a magnetic stirrer (Maxi mix 11, Thermolyne Corporation, U.S.A.), then warmed over a water-bath at 40°C until the total volume was reduced to about 20 ml. The rest of the solvent was allowed to evaporate at room temperature in a porcelain dish till a dry film was obtained. The dry film formed was pulverized in a porcelain mortar and sieved through a sieve no. 450 in order to obtain granules with homogenous particle size. Each formulation was appropriately labeled and stored in a dessicator for release and further studies.

The composition of the prepared solid dispersions is illustrated in table 1.

Table 1: Composition of solid dispersions containing Diflunisal using different polymers.

Formula	Diflunisal	Eudragit L100	Eudragit S100	Eudragit RS100	Ethyl-cellulose
F1	1	1	-	-	-
F2	1	3	-	-	-
F3	1	5	-	-	-
F4	1	-	-	1	-
F5	1	-	-	2	-
F6	1	-	1	-	-
F7	1	-	3	-	-
F8	1	-	5	-	-
F9	1	-	3	-	0.5
F10	1	-	3	-	1
F11	1	-	3	2	-
F12	1	-	1	1	-
F13	1	-	1	2	-
F14	1	-	0.5	1.5	-
F15	1	-	1	1.5	-

Determination of diflunisal content in the prepared solid dispersions

An accurately weighed amount of each formulation equivalent to 25 mg Diflunisal was dissolved with 50 ml of a solvent mixture of ethanol and dicloro methane at 1:1 ratio. 1 ml from this stock solution was transferred to 50 ml volumetric flask, then the volume was completed to 50 ml with ethanol. Diflunisal content was determined spectrophotometrically at 255 nm (Shimadzu (UV- 160A) Japan). against ethanol as a blank with reference to standard curve.

The following equation was employed for calculation of drug entrapment efficiency[15]:

Entrapment efficiency=
(Drug entrapped/Theoretical drug content)*100.

Experiments were performed in triplicates and the average readings were reported (±SD).

In-vitro **drug release studies**

Release experiments were conducted on the binary and ternary formulations. The tests employed the USP XXIV method 2 (paddle type) release apparatus (Electro lab TDT-06P, India). The release medium was 500 ml 0.1 N HCl (pH 1.2) maintained at a temperature of 37±0.5°C with a stirring rate of 50 rpm.

5 ml Samples were withdrawn at pre-determined time intervals of 5, 15, 30, 60, 90 and 120 min., respectively. Fresh release medium was added to replenish for each sample. The samples were filtered through 0.45 µm filter (millipore filter) and the filtrate was analyzed for drug content using spectrophotometric method. After the last sample (2 hrs), the pH of the release medium was adjusted to 6.8 to simulate the intestinal pH (USP 24). This was achieved by addition of 200 ml of 0.3 M dibasic sodium phosphate and 25 ml of 1 N sodium hydroxide. Sampling was then continued for another 4 hrs at the end of which the medium was adjusted to 7.4 using 1 N sodium hydroxide and sampling was continued for another 4 hrs. The withdrawn samples were treated as above. Experiments were performed in triplicates and the average readings were reported (±SD).

RESULTS AND DISCUSSION

Diflunisal content

Drug content in the selected formula is illustrated in table 2.

From the table, it is clear that the percent of Diflunisal content in all prepared formulations ranged between 95% and 105%, which indicates that the selected method for preparation of solid dispersions was appropriate and convenient.

Table 2: Percentage of drug content in the selected formulations.

Formula	Diflunisal content% ±S.D.	Formula	Diflunisal content% ±S.D.
F1	99.102±4.211	F9	98.534±2.675
F2	99.204±2.361	F10	100.00±3.687
F3	102.678±1.928	F11	98.012±1.907
F4	99.428±3.519	F12	99.044±2.281
F5	96.911±4.030	F13	99.832±2.248
F6	101.165±2.237	F14	98.117±2.374
F7	99.133±1.349	F15	102.022±1.023
F8	99.945±4.841		

Release studies

Great attention has been devoted to the use of oral-delivery systems containing acrylic polymers, since these polymers are essentially insoluble in the gastric juice and may be used to impart enteric behavior to the encapsulated drug serving as a drug target device to the colon[16-18]. It is known that these polymers are sensitive to pH changes and are able to protect the drug from the release in the gastric fluid, which is very acid (pH = 1–2)[19&20].

Eudragit is a reversibly soluble polymer depending on pH[21] so it can promote a controlled delivery of drug in specific colonic diseases[22].In fact an enteric copolymer should have in its structure a hydrophilic monomeric unit, such as that of the methacrylic acid one, and another hydrophobic one, such as the methyl methacrylate. The behavior of this material is dependent on protonation state, at higher pH, the carboxylic groups became ionized, changing their conformations and expanding them due to the repulsion between the negative charges of the carboxylates. At lower pH the carboxylic groups are unionized. The conformations are so closed allowing that the copolymer can precipitate. This process is mimicking the pH change that accounts all over the gastro-intestinal tract[23].

In the present study Eudragit S100, Eudragit L100, Eudragit RS100 and ethylcellulose were used in order to delay the release of Diflunisal until reaching the colon.

Eudragit L100 is a pH dependent polymer which was used by Zahirul *et al*.[24] for colon-targeted delivery of mesalazine, but they found that eudragit L100 can't protect the drug until it reaches the colon. The authers found that addition Eudragit S100 to the solid dispersion of the drug and Eudragit L100 can solve this problem. Asghar and Chandran[25] found the same results with indomethacin. Solid dispersion of Eudragit L100 alone with the drug can't reach the colon. It released completely in the intestine.

The obtained results were in agreement with the previous studies, Eudragit L100 can't protect Diflunisal until it reaches the colon. The release results of the solid dispersions F1, F2 and F3 which have 1:1, 1:3 and 1:5 drug to polymer ratio respectively, are illustrated in table 3 and figure 1.

From table 3 and figure 1 it is clear that, at pH 1.2, the % of the amounts of the drug released after 120 min were 0.46±0.11, 0.42±0.02 and 0.42±0.08% from F1, F2 and F3 solid dispersions, respectively. It is clear that upon increasing the polymer ratio, the amount released was decreased. This may be due to the increase in the coat thickness. At pH 1.2, Eudragit L100 solid dispersions at different polymer ratios cause a significant reduction in the amount released of Diflunisal within 120 min. The release efficiencies (%DE) of F1, F2 and F3 solid dispersions were 0.35±0.01, 0.33±0.04 and 0.32±0.02% respectively.

Table 3: Cumulative amount of Diflunisal released from Diflunisal : Eudragit L100 solid dispersions at various pH values.

Time (min)	pH	Cumulative amount of Diflunisal released (%) ±S.D.			
		F1	F2	F3	Free drug
		D:P 1:1	D:P 1:3	D:P 1:5	
15	1.2	0.27±0.07	0.24±0.03	0.23±0.01	2.45±0.002
30	1.2	0.31±0.01	0.29±0.02	0.27±0.03	2.71±0.001
60	1.2	0.33±0.02	0.31±0.05	0.29±0.07	3.04±0.004
90	1.2	0.40±0.09	0.38±0.02	0.37±0.04	3.61±0.007
120	1.2	0.46±0.11	0.42±0.02	0.42±0.08	4.34±0.004
135	6.8	44.79±1.13	38.95±0.91	26.65±0.75	91.51±0.71
150	6.8	83.69±1.02	89.97±0.95	55. 32±1.18	100.00±0.52
180	6.8	100.00±0.73	99.18±0.45	87.22±1.76	
210	6.8		100.00±0.57	100.00±0.78	

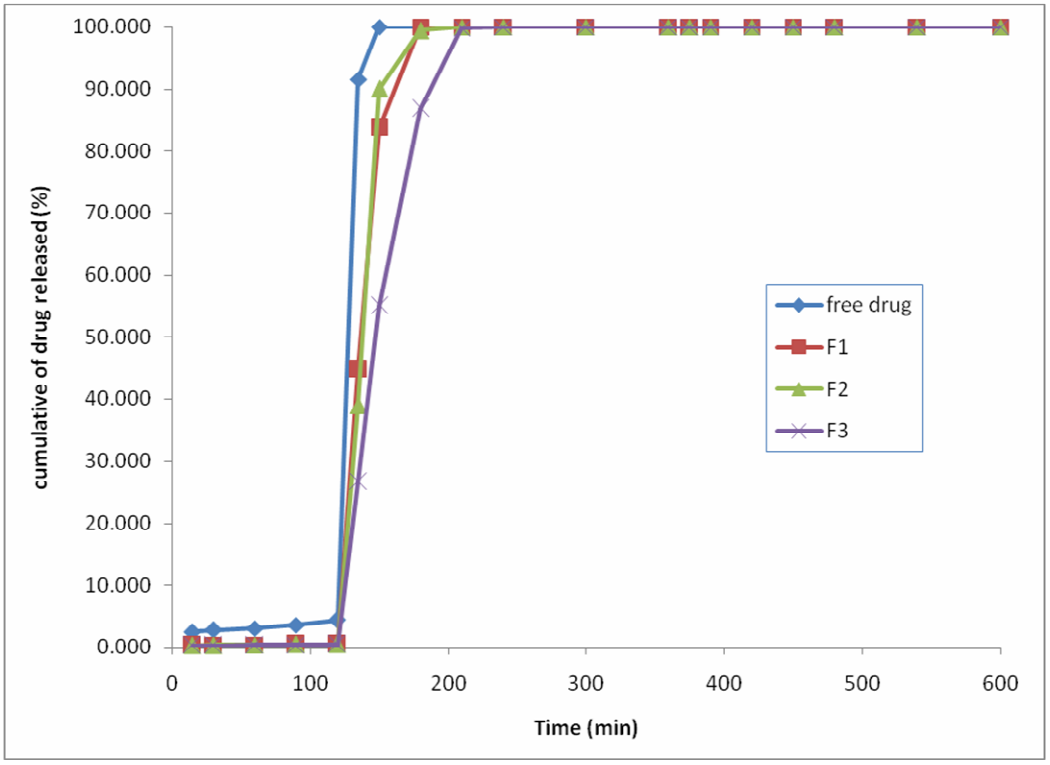

Fig. 1: Cumulative amount of Diflunisal released from Diflunisal : Eudragit L100 solid dispersions at various pH values.

At pH 6.8, the % of the amounts of the drug released after 210 min were 100% for F1, F2 and F3 solid dispersions, so that Eudragit L100 can't protect the drug in its matrix until it reaches the colon as it dissolves completely at pH 6.8 which is lower than that of the colon[26]. The release efficiencies (%DE) of F1, F2 and F3 solid dispersions were 94.86±0.27, 94.96±0.11 and 89.24±0.09% respectively.

Eudragit RS100 is a time dependent polymer which was used by Pignatello *et al*.[27] and Pignatello *et al*.[28] in a solid dispersion with Diflunisal in order to get a sustained release formula.

The findings of the present study complied with the previous studies. Formula 4 and F5 solid dispersions contained 1:1 and 1:2 drug to polymer ratio. Formula 4 can't protect the drug until it reach the colon. All the drug was released in the intestine. Formula 5 can protect the drug until it reaches the colon but it can't release all the drug in the colon. Drug release results from F4 and F5 are illustrated in table 4 and figure 2.

From table 4 and figure 2 it is clear that, at pH 1.2, the % of the amounts of the drug released after 120 min were 0.36±0.03 and 0.26±0.02 from F4 and F5 solid dispersions, respectively. It is clear that upon increasing the polymer ratio in the formula, the percentage released decreased, this may be due to the increase in coating efficiency. All Eudragit RS100 solid dispersions at different polymer ratios cause a significant reduction in the percentage of Diflunisal released after 120 min as compared to the free drug. The release efficiencies of F4 and F5 solid dispersions were 0.25±0.05 and 0.17±0.07% respectively.

Table 4: Cumulative amount of Diflunisal released from Diflunisal : Eudragit RS100 solid dispersions at various pH values.

Time (min)	pH	Cumulative amount of Diflunisal released (%) ±S.D.	
		F4	F5
		D:P 1:1	D:p 1:2
15	1.2	0.18±0.01	0.09±0.00
30	1.2	0.21±0.03	0.12±0.02
60	1.2	0.24±0.01	0.14±0.02
90	1.2	0.27±0.02	0.22±0.01
120	1.2	0.36±0.03	0.26±0.02
135	6.8	60.08±0.98	8.35±0. 71
150	6.8	71.76±1.16	10.42±0.88
180	6.8	82.02±1.68	15.01±0.96
210	6.8	92.22±1.94	22.11±1.03
240	6.8	100.00±0.42	26.04±1.08
300	6.8		30.12±1.14
360	6.8		32.00±1.09
375	7.4		38.13±1.11
390	7.4		39.17±1.07
420	7.4		39.25±0.75
450	7.4		41.04±0.22
480	7.4		42.00±0.56
540	7.4		44.12±1.17
600	7.4		46.23±1.23

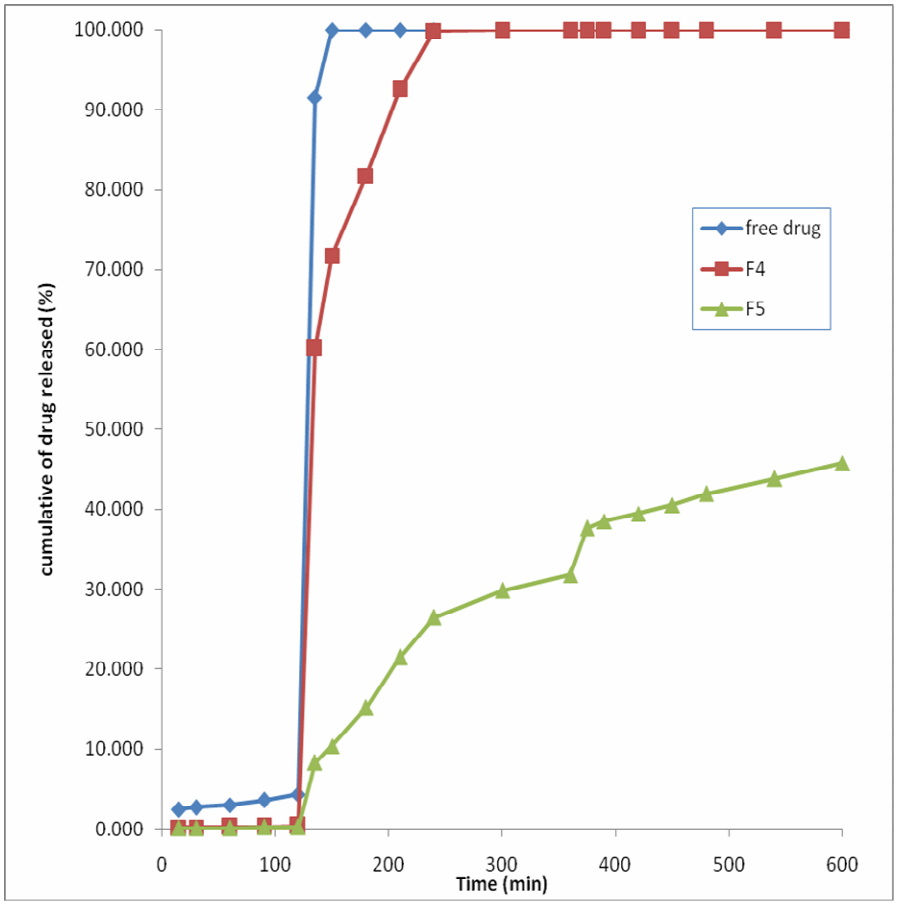

Fig. 2: Cumulative amount of Diflunisal released from Diflunisal : Eudragit RS100 solid dispersions at various pH values.

At pH 6.8 the % of the amounts of the drug released after 240 min were 100 and 32±1.09% from F4 and F5 solid dispersions, respectively. The release efficiencies of F4 and F5 solid dispersions were 91.34±0.24 and 23.22±0.14% respectively.

At pH 7.4 the % of the amount of the drug released after 240 min was 46.23±1.23% from F5. The release efficiencies of F4 and F5 solid dispersions were 100.00±0.17 and 41.97±0.26% respectively.

Eudragit S100 is a pH dependent polymer which was used for many purposes. Khan *et. al*.[29], used Eudragit S100 solid dispersion with mesalazine for delaying its release until it reaches the colon but combining it with Eudragit L100-55 might give much better results. Kadam and Gattani[30] used Eudragit S100 with theophylline for developing tablets for pulsatile drug delivery system but also it couldn't give good results until it was combined with Eudragit RL100.

Similar results were noticed in the present study. Eudragit S100 solid dispersions with a certain ratios (1:3 and 1:5 drug to polymer ratio respectively) could delay release of Diflunisal until it reaches the colon, but it couldn't give the required results when it was alone. The release results of the solid dispersions F4, F5 and F6 which contain 1:1, 1:3 and 1:5 drug to polymer ratio respectively which are illustrated in table 5 and figure 3.

From table 5 and figure 3 it is clear that, at pH 1.2, the % of the amounts of the drug released after 120 min were 0.39±0.03, 0.29±0.01and 0.231±0.02% from F6, F7 and F8 solid dispersion, respectively. It is clear that upon increasing the polymer ratio at pH 1.2, different types of Eudragit S100 solid dispersions at different polymer ratios cause a

significant reduction in the percentage released of Diflunisal after 120 min. The release efficiencies of F6, F7 and F8 solid dispersions were 0.15±0.03, 0.19±0.06 and 0.15±0.04% respectively.

At pH 6.8, the % of the amounts of the drug released after 240 min were 100.00±0.54, 63.12±0.63 and 27.22±0.45% from F6, F7 and F8 solid dispersions, respectively. Presence of Diflunisal with Eudragit S100 in a solid dispersion form caused a significant decrease in the percentage released after 240 min as compared with the free drug. The release efficiencies of F6, F7 and F8 solid dispersions were 73.67±0.08, 48.56±0.15 and 16.86±0.31% respectively.

At pH 7.4, the % of the amounts released after 240 min were 94.19±0.53and 53.42±0.59% from F7 and F8, respectively. In case of F7 and F8, not all the drug included in the two solid dispersions was released after 10 hrs of release at different pH values from 1.2 to 7.4. This may be due to the fact that the release of the drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases[31]. The release efficiencies of F6, F7 and F8 solid dispersions were 100.00±0.13, 84.26±0.25 and 45.00±0.22 % respectively.

Table 5: Cumulative amount of Diflunisal released from Diflunisal : Eudragit S100 solid dispersions at various pH values.

Time (min)	pH	Cumulative amount of Diflunisal released (%) ±S.D.		
		F6	F7	F8
		D:P 1:1	D:P 1:3	D:P 1:5
15	1.2	0.20±0.02	0.12±0.01	0.075±0.04
30	1.2	0.26±0.00	0.14±0.02	0.112±0.01
60	1.2	0.27±0.04	0.18±0.01	0.127±0.03
90	1.2	0.30±0.01	0.23±0.03	0.195±0.01
120	1.2	0.39±0.03	0.29±0.01	0.231±0.02
135	6.8	15.75±0.37	23.47±0.25	6.259±0.11
150	6.8	28.11±0.12	27.52±0.16	6.753±0.13
180	6.8	59.05±0.34	44.03±0.29	10±0.24
210	6.8	70.00±0.39	51.05±0.13	14±0.36
240	6.8	82.31±0.18	52.00±0.47	17±0.46
300	6.8	95.06±0.27	54.23±0.32	23±0.39
360	6.8	100.00±0.54	63.12±0.63	27.22±0.45
375	7.4		70.37±0.57	38±0.31
390	7.4		74.51±0.46	39±0.29
420	7.4		78.21±0.25	41±0.52
450	7.4		83.54±0.72	43±0.37
480	7.4		85.81±0.54	45±0.17
540	7.4		90.07±0.61	48±0.22
600	7.4		94.19±0.53	53.42±0.59

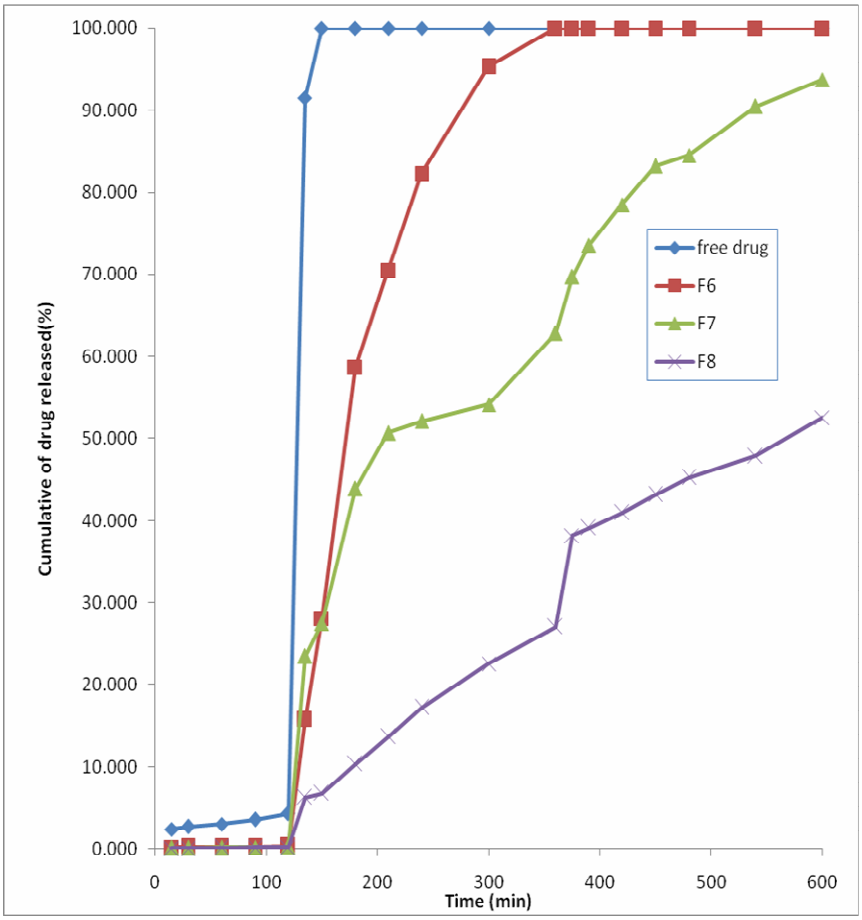

Fig. 3: Cumulative amount of Diflunisal released from Diflunisal : Eudragit S100 solid dispersions at various pH values.

Combining two systems like pH dependent system and time dependent system for controlling the release of a drug was found to be more efficient than using one of the polymers alone. Gowda *et al.*[32] used a solid dispersion containing ethylcellulose as a time dependent polymer and Eudragit S100 as a pH dependent polymer for minimizing the unwanted toxic effects of anti-anginal ranolazine by kinetic control of drug release. The same combination was used with Diflunisal in the present study for delivering it to the colon.

The release results of the solid dispersions F6, F7 and F8, which contain 1:3:0.5 and 1:3:1 drug to Eudragit S100 to ethylcellulose ratio respectively, are illustrated in table 6 and figure 4.

From table 6 and figure 4 it is clear that, at pH 1.2, the % of the amound of drug released after 120 min were 0.319±0.002 and 0.352±0.004 % from F9 and F10, respectively. It is clear that, upon increasing the ratio of ethylcellulose, the percentage released after 120 min at pH 1.2 was more than the that released from solid dispersions of Eudragit S100 only. The release efficiencies of F9 and F10 solid dispersions were 0.21±0.05 and 0.23±0.10% respectively.

At pH 6.8, the % of the amounts of the drug released after 240 min were 65.270±0.27and 71.870±0.42% from F9 and F10, respectively. The release efficiencies of F9 and F10 solid dispersions were 46.46±0.16 and 55.78±0.28% respectively.

At pH 7.4, all the % of the amount of Diflunisal that was still included in the solid dispersion, was released completely from both F9 and F10. The release efficiencies of F9 and F10 solid dispersions were 95.34±0.34 and 97.37±0.12% respectively.

F9 and F10 solid dispersions didn't match with the requirements of the colonic delivery as they released 65.270±0.27 and 71.870±0.42% respectively of the drug in the intestine. Few amount of the drug could reach the colon.

Another combination of time dependent and pH dependent systems was studied by Akhgari *et al.*[13]. They evaluate the combination of pH-dependent and time-dependent polymers for design of colon delivery system of indomethacin pellets. Eudragit S100 and Eudragit L100 were used as pH-dependent polymers and Eudragit RS100 was used as a time-dependent polymer.

In the present study combining Eudragit S100 and Eudragit RS100 was sufficient to obtain a successful colon drug delivery system. Many preparations with different drug to polymer ratios were studied in order to obtain a suitable formula.

Table 6: Cumulative amount of Diflunisal released from Diflunisal : Eudragit S100 : Ethylcellulose dispersions at various pH values.

Time (min)	pH	Cumulative amount of Diflunisal released (%) ±S.D.	
		F9	F10
		Drug : Eud S100 : E.C. 1:3:0.5	Drug : Eud S100 : E.C. 1:3:1
15	1.2	0.12±0.01	0.17±0.02
30	1.2	0.17±0.03	0.19±0.01
60	1.2	0.21±0.01	0.22±0.05
90	1.2	0.24±0.04	0.26±0. 03
120	1.2	0.32±0.02	0.35±0. 04
135	6.8	20.11±0.22	33.68±0.11
150	6.8	24.18±0.27	37.02±0.23
180	6.8	36.26±0.56	40.48±0.33
210	6.8	42.09±0.32	43.97±0.27
240	6.8	50.57±0.39	59.59±0.51
300	6.8	56.19±0.61	70.98±0.38
360	6.8	65.27±0.27	71.87±0.42
375	7.4	77.75±0.38	79.50±0.67
390	7.4	81.18±0.47	88.37±0.75
420	7.4	89.65±0.42	98.61±0.23
450	7.4	99.50±0.31	100.000±0.46
480	7.4	100.000±0.53	

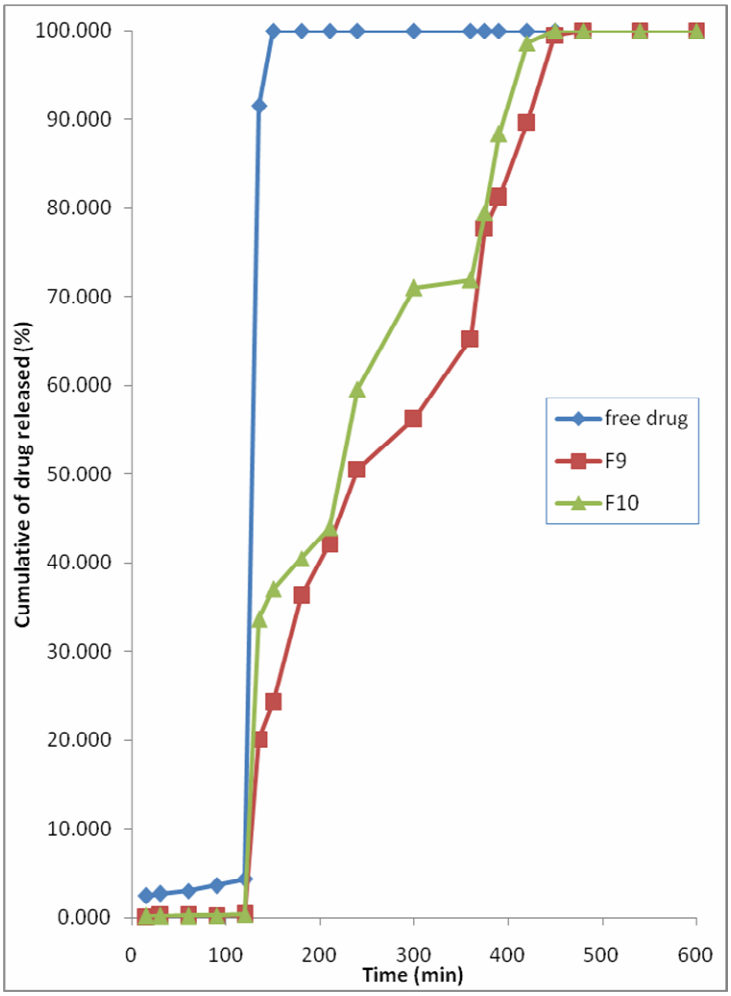

Fig. 4: Cumulative release of Diflunisal results from Diflunisal : Eudragit S100 solid : Ethylcellulose solid dispersions and the free drug at various pH values.

The release results of the solid dispersions F11, F12, F13, F14 and F15 which contain 1:3:2, 1:1:1, 1:1:2, 1:0.5:1.5 and 1:1:1.5 drug to Eudragit S100 to Eudragit RS100 ratio respectively are illustrated in table 7 and figure 5. These results indicate that at pH 1.2, the % of the amounts of the drug released were 0.217±0.03, 0.29±0.00, 0.20±0.03, 0.27±0.01 and 0.32±00.03% from F11, F12, F13, F14, and F15 respectively. The release efficiencies (%DE) of F11, F12, F13, F14 and F15 solid dispersions were 0.14±0.09, 0.18±0.04, 0.18±0.04, 0.17±0.06 and 0.22±0.11% respectively.

At pH 6.8 the % of the amounts of the drug released after 240 min were 26.29±0.91, 60.52±0.67, 22.59±0.38, 50.36±0.46 and 71.72±0.62% from F11, F12, F13, F14, and F15, respectively. At this pH value, all combined pH- and time-dependent solid dispersion provided a significant reduction in the cumulative percentage released after 240 min. The release efficiencies (%DE) of F11, F12, F13, F14 and F15 solid dispersions were 17.47±0.23, 49.36±0.19, 17.46±0.35, 41.26±0.22 and 62.66±0.38% respectively.

At pH 7.4 the % of the amounts of the drug released after 240 min were 77.59±1.79, 100.00±0.71, 30.97±0.31, 80.77±0.44 and 100.00±0.54% from F11, F12, F13, F14, and F15, respectively. The release efficiencies (%DE) of F11, F12, F13, F14 and F15 solid dispersions were 60.73±0.09, 80.49±0.16, 27.34±0.11, 65.75±0.24 and 87.16±0.10% respectively.

It is clear that the addition of time dependent polymer in combined pH- and time-

dependent system could control drug release at pH 7.4 and as a result, the delivery of much more drug to the colon would be guaranteed as compared to pH-dependent system (Akhgari *et al.*[33].

From the obtained results, it could be concluded that F11 and F14 showed good results as colonic drug delivery systems but F11 is better than F14 as it protect about 75% of the from being released in the intestine. F14 protect only 50% of the drug until it reaches the colon.

Table 7: Cumulative Diflunisal released from Diflunisal : Eudragit S100 : Eudragit RS100 solid dispersions at various pH values.

Time (min)	pH	Cumulative amount of Diflunisal (%) ±S.D.				
		F11	F12	F13	F14	F15
		Drug : Eudragit S100 : Eudragit RS100				
		1:3:2	1:1:1	1:1:2	1:0.5:1.5	1:1:1.5
15	1.2	0.06±0.01	0.11±0.01	0.05±0.01	0.09±0.01	0.14±0.03
30	1.2	0.11±0.04	0.14±0.02	0.09±0.05	0.13±0.01	0.18±0.01
60	1.2	0.11±0.02	0.15±0.01	0.10±0.02	0.15±0.03	0.21±0.05
90	1.2	0.17±0.07	0.22±0.03	0.16±0.02	0.22±0.06	0.25±0.02
120	1.2	0.22±0.03	0.29±0.00	0.20±0.03	0.27±0.01	0.32±00.03
135	6.8	1.29±0.12	19.28±0.13	10.34±0.13	26.54±0.21	43.76±0.12
150	6.8	9.48±0.44	31.43±0.64	11.50±0.25	30.23±0.19	49.72±0.23
180	6.8	13.21±0.23	42.83±0.25	14.25±0.15	33.66±0.28	54.89±0.38
210	6.8	15.64±0.68	47.91±0.78	16.91±0.41	38.06±0.12	60.59±0.26
240	6.8	17.76±0.73	54.97±0.51	18.14±0.17	43.24±0.17	65.25±0.51
300	6.8	22.95±0.52	57.80±0.34	20.28±0.22	48.42±0.34	70.68±0.33
360	6.8	26.29±0.91	60.52±0.67	22.59±0.38	50.36±0.46	71.72±0.62
375	7.4	33.73±1.07	63.98±0.41	24.03±0.14	53.49±0.27	75.08±0.28
390	7.4	40.37±0.84	65.33±0.27	24.82±0.27	55.88±0.22	77.06±0.31
420	7.4	45.87±1.29	68.39±0.64	25.66±0.16	58.26±0.41	79.98±0.44
450	7.4	54.71±1.36	75.59±0.82	26.51±0.23	60.38±0.34	83.95±0.82
480	7.4	67.22±1.24	79.66±0.73	27.09±0.19	63.56±0.23	87.92±0.98
540	7.4	72.25±1.62	89.69±0.95	28.74±0.22	73.09±0.53	92.16±0.72
600	7.4	77.59±1.79	100.00±0.71	30.97±0.31	80.77±0.44	100.00±0.54

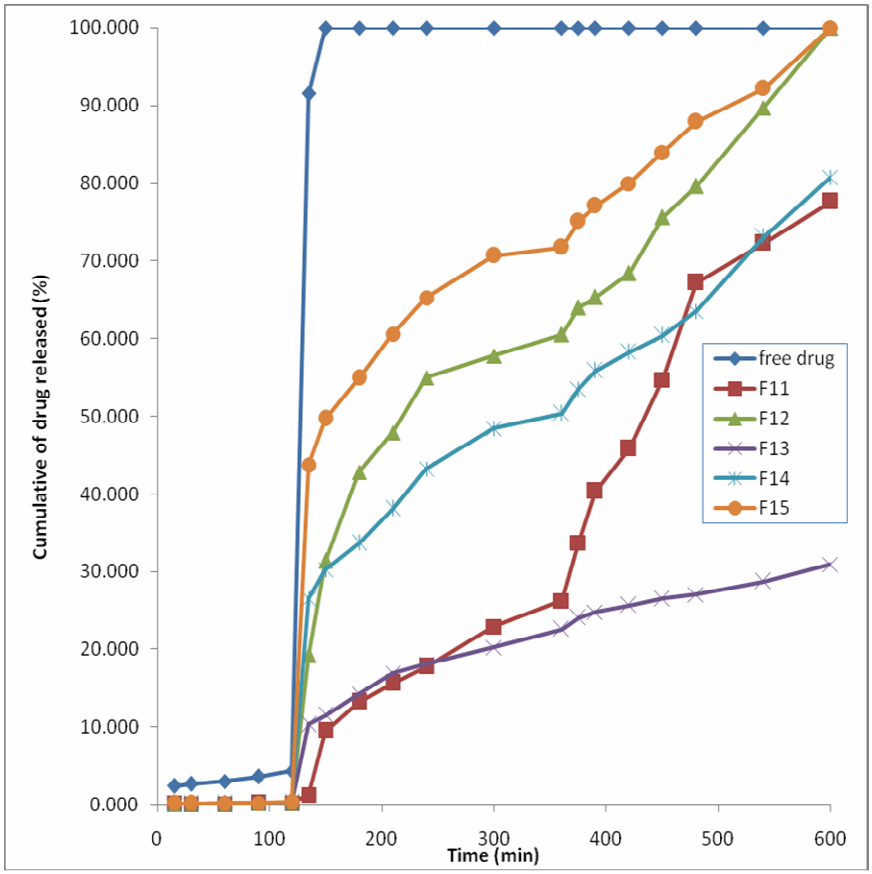

Fig. 5: Cumulative release results of Diflunisal from Diflunisal : Eudragit S100 : Eudragit RS100 solid dispersions and the free drug at various pH values.

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نشرة العلوم الصيدلية
جامعة أسيوط

صياغة وتقييم أنظمة دوائية للإنطلاق إلي القولون تحتوي علي عقار دفلونيزال

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يعد توصيل الدواء عن طريق الفم من أهم أنظمة التوصيل الدوائي وأوسعها انتشارا وذلك لسهولة الإستخدام ، ومن الطبيعي بعد تناول الجرعة الدوائية عن طريق الفم أن يتم ذوبانها فى المعدة وامتصاصها فى الأمعاء الدقيقة والذي يعتبر أمر غير مرغوب فيه عند تصنيع نظام دوائي يستهدف علاج الأمراض الموضعية فى القولون لذا كان من الضروري إبتكار نظام دوائي يستهدف توصيل الجرعة الدوائية إلى القولون دون فقدانها عن طريق الامتصاص فى المعدة أو الأمعاء الدقيقة. ويعد هذا النظام من أهم أنظمة التوصيل الدوائي حيث إنه يساعد فى العلاج الموضعي للكثير من الأمراض مثل إلتهاب القولون التقرحي ومرض كراون والزحار الأميبي. كما أن هناك مميزات عديده لهذا النوع من أنظمة التوصيل الدوائي وهو أن القولون يعتبر مكاناً جيداً لامتصاص بعض البيبتيدات والأدوية البروتينيه وذلك لاحتوائه علي نسبه قليله من الإنزيمات الهاضمه للبروتين. ومن الواضح أن القولون يستجيب إلى محسنات الامتصاص بشكل أفضل من المعدة والأمعاء حيث أن الدواء يستقر به لفترة زمنيه أطول عند المقارنة بالفترة التى يقضيها الدواء بالمعدة والأمعاء ويعد هذا سببا أيضا فى زيادة نسبة الإتاحة الحيوية للدواء مما يتيح إستعمال كمية أقل من الدواء فى الجرعة الواحدة مما له أعظم الأثر فى تقليل الأعراض الجانبيه للدواء. يحتوى القولون على وسط ذي أس هيدروجيني متعادل مما يحمي الأدوية القابلة للتفاعل مع الأوساط الحمضية أو القلوية الشديدة.

توجد استراتيجيات عديدة مقترحة لتوصيل الأدوية المعطاه عن طريق الفم خاصة إلى القولون والتي تشمل إما تكوين رابطه تساهميه بين الدواء والحامل الذى يحمله حتى وصوله إلي القولون حيث يتم كسرها أو توصيل مركب الدواء كما هو دون ما أية روابط كيميائيه بينه وبين الحامل وذلك عن طريق نوع آخر من أنظمة التوصيل الدوائي كالأنظمه التى يتم تفعيلها عن طريق الميكروفلورا وأيضا أنظمه تعتمد على الزمن وأخرى تعتمد على الأس الهيدروجيني وأنظمه تجمع بين الأس الهيدروجيني والزمن معا وأنظمه تعتمد على الضغط.

إن نظام التوصيل الدوائي المخصص للقولون لابد وأن يحتوي على بعض المتطلبات الأساسية حتى يتسنى له توصيل الدواء للقولون بشكل فعال وذلك نظراً لبعد موقع القولون وما يقابله الدواء من سوائل مذيبه له بالمعدة والأمعاء الدقيقه في طريقه حتى القولون. تتمثل هذه المتطلبات فى أن النظام الدوائي المخصص لتوصيل الدواء للقولون لابد ألا يتحلل أو يتفتت فى القناه الهضمية العلوية وألا يطلق الدواء المحمل فيه كما أنه ينبغي أن يكون النظام الدوائي سهل الصياغه فى شكل مناسب لتحميل الدواء.

إن عقار الديفلونيزال هو دواء مضاد للإلتهابات غير إستيرويدي طويل المدي يستخدم عادة لعلاج الآلام الحاده بعد العمليات الجراحية والألم المصاحب للإلتهاب المزمن فى المفاصل نتيجة خشونة المفاصل أو الروماتويد وهو أحد مشتقات حمض السالسيليك والذى يظهر نشاطا مضاد للإلتهابات ومسكنا للألم وخافضا للحرارة عن طريق تثبيط إنزيم السيكلوأوكسيجيناز، أما بالنسبه لتأثيره على

الصفائح الدموية فإن الديفلونيزال ليس كالأسبرين تماما فى تأثيره على معدلات النزيف وخصائص الصفائح الدمويه. إن الديفلونيزال حتى مع أعلى جرعاته وهى جرعة ١٠٠٠ مج مرتين يوميا لا يحقق فرقا ملحوظا فى قياسات زمن النزيف والذى يعد ميزة عظيمة بالنسه للمرضى ذوى معدلات النزيف العالية.

وإعتمادا على الخصائص المضاده للإلتهابات لدى عقار الديفلونيزال فإن تطوير نظام دوائي مخصص للقولون من الممكن ان يكون ذا فائدة عظيمة فى علاج بعض الأمراض الموضعية فى القولون مثل مرض كراون وإلتهاب القولون التقرحى والزحار الأميبي.

في الدراسة الحالية تم صياغة خمسة أنظمة تشتت صلب تحتوى على ثلاثة أنواع من أنظمة التوصيل الدوائي المخصص للقولون هى النظام المعتمد على الأس الهيدروجيني والنظام المعتمد على الزمن كذا النظام الجامع بين الإعتماد على الأس الهيدروجيني والإعتماد على الزمن معا بإستخدام أنواع ونسب مختلفه من البوليمرات وكذا نسب مختلفه من عقار الديفلونيزال وتم تقييم هذه الأنظمه من حيث خصائصها المعملية وأدائها الحيوى فى محاولة لتطوير نظام توصيل دوائي مخصص للقولون لعقار الديفلونيزال.