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KOLLIDON SR AND EUDRAGIT S100 EMPLOYING FOR DICLOFENAC SODIUM SUSTAINED RELEASE TABLETS IN COLON SPECIFIC DELIVERY

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ABSTRACT

The Matrix Tablets each containing 50 mg of diclofenac sodium are prepared employing kollidonSR by direct compression method. All the tablets were found to be non-disintegrating in acidic (pH1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with respect to drug content, hardness and friability. As the tablets formulated were non- disintegrating in acidic fluids, they are considered suitable for colon targeting. The drug release study it may be concluded that the (DK2) E2 formula of diclofenac sodium matrix tablets have given the desired release profile by showing a minimal release during the lag period of 5 hrs and complete release at the end of 12 hrs. The tablets having the optimised formula (DK2) E2, having 25% kollidonSR with 5% of channelling agent (Eudragit S 100) showed minimal release of 27.4% in the lag period of 5 hours and 99.3% of the drug was released the end of 12hours. The diclofenac sodium matrix tablets formulated by employing kollidonSR and channelling agent showed non-fickian diffusion mechanism and following zero order kinetics. The optimized formula (DK2) E2 follows Supercase II transport as mechanism for drug release and it follows zero order kinetics. Matrix tablets (DK2) E2 formulated employing 25% kollidonSR and 5% Eudragit S 100 are best suited to be used for colon targeting of diclofenac sodium.

KEYWORDS: Colon target, Eudragit S 100, Diclofenac sodium, PVP, Channeling agent.

1. INTRODUCTION

Colon targeted drug delivery has the potential to deliver bioactive agents for the treatment of various colonic diseases including inflammatory bowel disease (IBD) and rheumatoid arthritis and can be effectively treated by the local delivery of drugs to the large intestine. The other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction.[1] Colon specific drug delivery has gained increased importance not just for the delivery of drug in the treatment associated with the colon, but also as a potential system for the systemic delivery of the therapeutic peptides and proteins.

By this technique, release and absorption of the drug in the upper portion of the GI tract can be minimized until the drug reaches the proximal colon. Precise colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological condition particular to the colon. Hence, continuous effort has been made on designing colon-specific delivery system with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs.[2] The formulation should be such that when taken orally minimum amount of drug should be release up to 5 hours and the complete release up to 12 hours. Oral delivery of the drug to the colon is very valuable in the treatment of the colon diseases like ulcerative colitis, carcinomas, amoebiasis, inflammatory bowel disease (IBD) and rheumatoid arthritis and can be effectively treated by the local delivery of drugs to the large intestine whereby high local concentration of the drug can be achieved while minimizing the side effects that occurs due to the release of drug in upper GIT (Gastro Intestinal Tract) or systemic absorption.

Diclofenac sodium[3,4,5] is frequently used for treating rheumatoid arthritis. Rheumatoid arthritis shows peak symptoms in the early morning but diclofenac sodium can't be taken early in the morning as it cause gastric disturbance. A formulation which does not release diclofenac in the stomach but releases it in colon and releases the drug in a slow and controlled manner will very useful in the treatment of rheumatoid arthritis. The objective of the research work to prepare matrix tablets of diclofenac sodium employing kollidonSR for colon Specific drug delivery. To evaluate the prepared kollidonSR matrix tablets of diclofenac sodium. The optimized release formulae for the kollidonSR was procured and various channeling agents were incorporated to enhance the dissolution rate. To evaluate kollidonSR matrix tablets channeling agent (PEG 6000) of diclofenac sodium. To develop a

optimized formula of kollidon SR matrix tablets channeling agent of diclofenac sodium. As the tablets should release minimum amount of drug in first 5 hours and complete release upto 12 hours.

2. EXPERIMENTAL

2.1 MATERIALS AND METHOD

Diclofenac sodium, A Gift sample from Sekasaria labs KollidonSR, A Gift sample from BASF, Ltd, Mumbai Poly ethylene glycol 6000, A Gift sample from Loba Chemicals Lactose monohydrate, A Gift sample from Finar Reagents Eudragit S100, A Gift sample from Archids Labs. Magnessium stearate, A Gift sample from Moly Chem Talc, A Gift sample from Moly Chem Dicalcium phosphate, A Gift sample from Rhone- Poulenc Basic chemical Co Hydochloride acid, A Gift sample from Finar Reagents Dihydrogen ortho phosphate, A Gift sample from Fishser Scientific Methanol, A Gift sample from Qualigens

2.2 METHODS

2.2.1 Preparation of tablets

Matrix tablets each containing 50mg of diclofenac sodium were prepared employing Kollidon SR in different ratios as per the formula given in Table.1. The required quantities of medicaments, polymer Kollidon SR, binder Poly vinyl pyrrolidone(1.25%w/w) and diluent dicalcium phosphate were passed through the mesh no. 100 respectively and added in the case of optimized formulation using Eudragit S 100 (5%, 10% and 15% as channeling agent). Then all the quantities were mixed thoroughly by using mortar and pestle. After thorough mixing the lubricants such as Talc (1%) and Magnesium stearate (1%) were passed through mesh no. 100 into the blended powder. Once again these are also blended in a mortar and pestle. The tablet blend was compressed into tablets on a rotary multi- station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm. Using 8 mm round and flat punches.

2.2.2 Estimation of diclofenac sodium content in tablets

Five tablets were accurately weighed and powdered. The tablet powder equivalent to 50 mg of medicament was taken into 25 ml volumetric flask and 20ml of methanol was added. The mixture was shaken thoroughly for about 30 min. while warming in hot water bath to dissolve the diclofenac sodium. The solution was then made upto volume with methanol. The methonolic solution was subsequently diluted suitably with phosphate buffer of pH 7.4 and assayed for diclofenac sodium at 276 nm.[3,4]

2.2.3 Hardness

Hardness of matrix tablets prepared was tested using Monsanto Hardness Tester.

2.2.4 Friability

Friability of matrix tablets prepared was determined in a Roche Friabilator.

2.2.5 Disintegration time

Disintegration time was determined in Thermonic Tablet Disintegration Test Machine using 0.1 N Hcl and phosphate buffer of pH 7.4 as fluids.

2.2.6 In-vitro Drug Release Study

Diclofenac sodium release from matrix tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, DS 8000) employing a paddle stirrer with a dissolution fluid volume of 900 ml at 100 rpm and at 37 ± 0.5^{0}c. The dissolution was carried out in 0.1 N hydrochloric acid in the first 2 hrs and in pH 7.4 phosphate buffer for the remaining 10 hrs. The samples of 5 ml each were withdrawn at different time intervals over a period of 12 hrs. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 276 nm for diclofenac sodium using an Elico SL 210 double beam UV spectrometer. The drug release experiments were conducted in triplicate.

2.2.7 Data analysis

Release data were analysed as per zero order, first order, Higuchi & Peppas equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

3. RESULTS AND DISCUSSION

Matrix Tablets each containing 50 mg of diclofenac sodium are prepared employing kollidonSR in different percents (12.5%, 25%, 37.5% and 50%) by direct compression method. Hardness of the tablets was in the range of 6-7kg/sq.cm. Weight loss in friability test was less than 0.3% in all the cases. All the matrix tablets prepared contained $100\pm2.3\%$ of the labelled claim. All the tablets were found to be non-disintegrating in acidic (pH1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with respect to drug content, hardness and friability. As the tablets formulated were non- disintegrating in acidic and alkaline fluids, they are considered suitable for colon targeting.

Diclofenac sodium release from the matrix tablets prepared was studied in 0.1N HCl for the first two hours followed by phosphate buffer of pH 7.4 for the next 10 hours. Drug release profiles of diclofenac sodium matrix tablets and the release profile of the optimized formulae are given in Table.2 and shown in Fig.1. The drug release parameters are summarized in Table.5. Diclofenac sodium release was relatively rapid in the case of matrix tablets (DK1) prepared employing 12.5% kollidonSR and by the end of the lag time of 5hours, 39.5% of release was observed. When 25% of kollidonSR was used in the formula (DK2), the release by the end of the lag period was about 28.5%. The matrix tablets (DK3) containing 37.5% kollidonSR, released 18.5% by end of the lag period while the matrix tablets(DK4) having 50% kollidonSR, released 14.8% by the end of the lag time but released only 37.2% by 12 hours. From the formulation DK1, 100% drug release was achieved within 10 hours and for the formulation DK2, 83.5% drug was release in 12 hours but the remaining formulations, DK3,DK4, released below 50% of the drug by 12 hours. It was next planned to incorporate channelling agents like Eudragit S100 in the optimised formulae from the above experiments, to get the 100% drug release within 12 hours by keeping the minimum amount of drug release in the first 5 hours. DK2 was selected for further studies as its drug release was considered as optimum.

Eudragit S 100 was incorporated at 5%(DK2)E2, 10%(DK2)E3,15%(DK2)E3 in the matrix tablets employing kollidon SR at the percentage of 25%(DK2). The drug released from the formulations (DK2)E2, (DK2)E3 and (DK2)E4 was 28.5%, 49.8% and 68.3% in 5. From the above results it was found that minimum amount of drug released (28.5%) in 5 hours from the formulation (DK2) E2, whereas more amount of the drug released from the other formulations.

The formulations containing channelling agents showed increase in drug release than matrix tablets without channelling agents. The Eudragit S 100 is insoluble in 0.1N HCl and soluble in alkaline fluids. The formulation (DK2) E2 was optimized because of the less amount of drug (28.5%) release in first five hours and 100% release in 12 hours. The formulations containing 10% and 15% Eudragit S 100 were not optimized because they released 49.8% and 68.3% of the drug in the first five hours and they released 100% of the drug in less than 12 hours. The final formulation containing diclofenac sodium optimized was (DK2) E2.

The drug release data were analyzed as per Zero order, First order, Higuchi and Peppas equation models. The correlation coefficient (r) values in the analysis of the release data as

per different kinetic models are given in Table.4. The Analysis of release data as per zero order and first order kinetic models indicated that the diclofenac sodium release from matrix tablets followed zero order kinetics. The correlation coefficient (r) values were higher in the zero order models than in the first order model. In the case of drug release study of the optimised formula (DK2) E2 the release followed zero order kinetics. Plots of √time vs percent drug released were found to be linear. So it is obeying Higuchi's[6] mechanism that is diffusion mechanism. When the release data were analysed as per Peppas[7] equation, the release exponent 'n' was in the range 0.6-0.9 for all formulated matrix tablets of diclofenac sodium employing kollidonSR and polymer with various channelling agents, indicating non-Fickian (anamalous) diffusion as the release mechanism. But in the case for optimized matrix tablets prepared, the release exponent 'n' value was 1.08 which indicates supercase II transport. As such, these matrix tablets (DK2) E2 formulated employing 25% kollidonSR using 5% eudragit S 100 may be considered suitable for colon targeting of diclofenac sodium for 12 hours adminstration.

Table.1 Formulae of Diclofenac sodium Matrix Tablets

Formulation	DK1	DK2	DK3	DK4
Diclofenac sodium	50	50	50	50
Kollidon SR	25	50	75	100
PVP K-30 (1.25%w/w)	2.5	2.5	2.5	2.5
Talc (1%)	2	2	2	2
Mg. Stearate (1%)	2	2	2	2
Dicalcium Phosphate	118.5	93.5	68.5	43.5
Total Weight (mg)	200	200	200	200

Table.2 Drug Release Profile of Diclofenac Sodium Matrix Tablets Prepared Employing Kollidon SR

Time (hrs)	Mean Percent of Diclofenac Sodium Released employing kollidonSR ($\bar{x}$±s.d) (n=3)			
	DKI	DK2	DK3	DK4
0	0	0	0	0
0.5	5.6±0.37	4.2±0.23	3.3±0.34	2.7±0.47
1	7.3±0.52	6.1±0.5	4.7±0.37	4.0±0.26
2	10.5±0.26	8.3±0.16	6.2±0.29	5.6±0.25
3	20.9±0.4	17.4±0.19	11.8±0.2	10.4±0.13
4	26.9±0.27	22.2±0.21	14.9±0.48	12.1±0.45
5	39.5±0.26	28.5±0.5	18.5±0.23	14.8±0.24
6	52.3±0.38	38.0±0.42	25.0±0.29	18.6±0.31
8	85.2±0.37	52.2±0.33	30.6±0.53	24.1±0.39
10	99.9±0.44	65.2±0.14	39.0±0.27	31.4±0.42
12	—	83.5±0.11	51.9±0.5	37.2±0.51

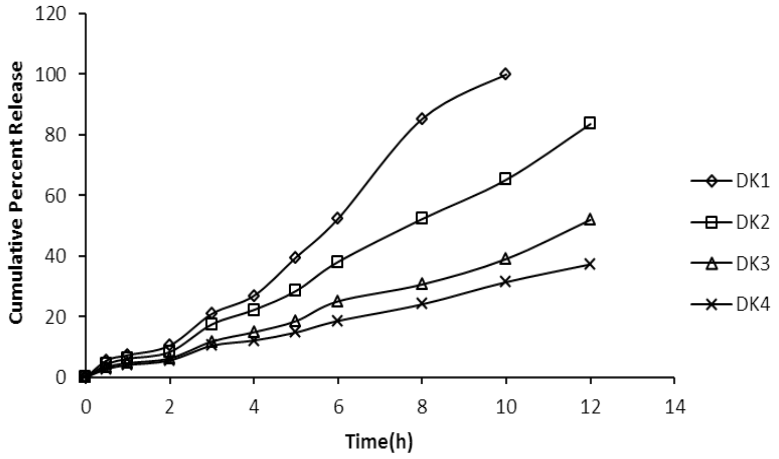

Fig.1 Drug Release Profile of Diclofenac sodium Matrix Tablets Prepared Employing Different Ratios of KollidonSR

Table.3 Drug Release Profile of Diclofenac sodium Matrix Tablets using Eudragit S100

Time (hrs)	Mean Percent of Diclofenac sodium Released employing kollidonSR with eudragit S100 (x̄±s.d) (n=3)			
	(DK2)E1	(DK2)E2	(DK2)E3	(DK2)E4
0	0	0	0	0
0.5	4.2±0.23	3.9±0.14	7.1±0. 37	16.3±0.34
1	6.1±0.5	5.3±0.29	9.5±0.33	18.1±0.41
2	8.3±0.16	6.8±0.16	13.7±0.26	21.5±0.18
3	17.4±0.19	14.5±0.53	33.3±0.28	42.2±0.13
4	22.2±0.21	20.3±0.35	40.6±0.39	51.5±0.53
5	28.5±0.5	27.4±0.51	49.8±0.16	68.3±0.37
6	38.0±0.42	41.5±0.39	62.0±0.46	85.6±0.56
8	52.2±0.33	56.2±0.21	76.5±0.22	97.4±0.16
10	65.2±0.14	76.0±0.27	98.5±0.4	—
12	83.5±0.11	99.3±0.49	—	—

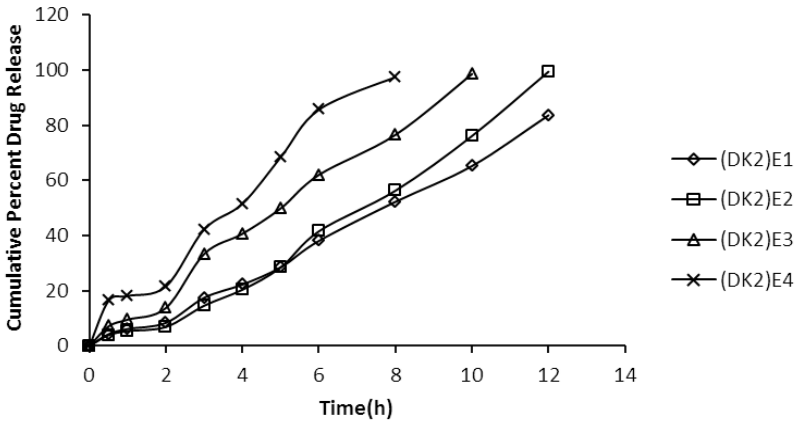

Fig.2 Drug Release Profile of Diclofenac sodium Matrix Tablets Prepared Employing of KollidonSR with Eudragit S100

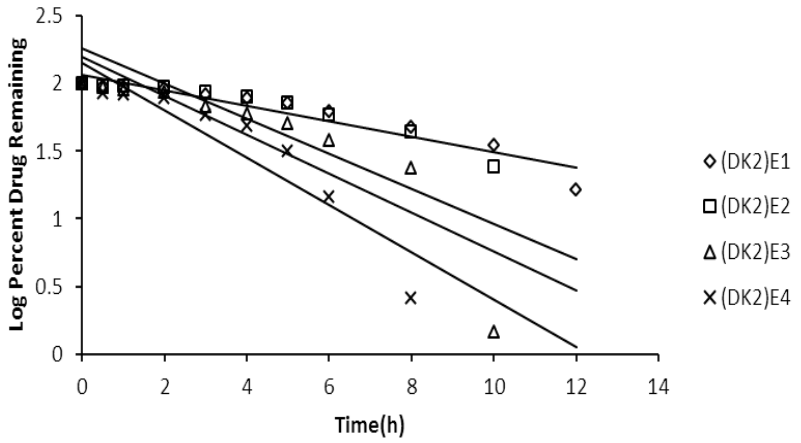

Fig.3 First Order Plots of Diclofenac sodium Matrix Tablets Employing KollidonSR using Eudragit S100

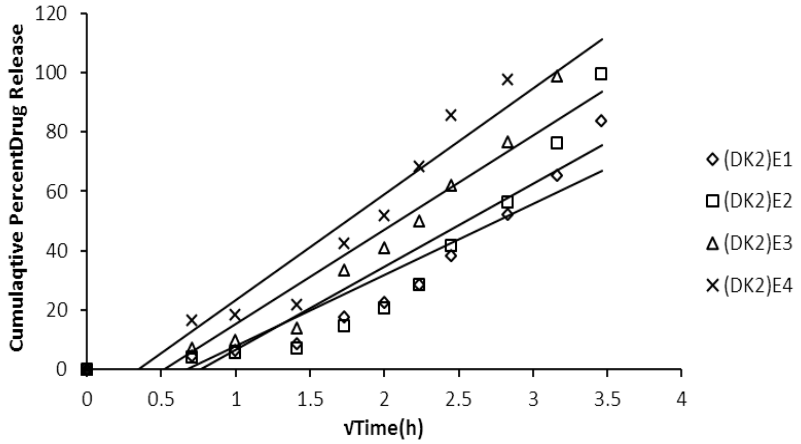

Fig.4 Percent Release Vs Square Root Time Plots of Diclofenac sodium Matrix Tablets Prepared Employing Kollidon SR Using Eudragit S100

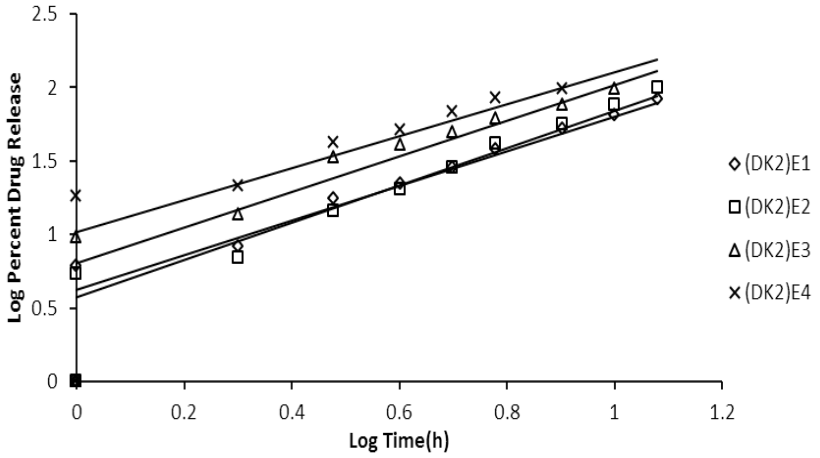

Fig.5 Log Percent Released Vs Log Time Plot of Diclofenac sodium Matrix Tablets employing Kollidon SR using Eudragit S100

Table.4 Correlation Coefficient (r) Values in the Analysis of Release Data as per Zero, First Order and Higuchi plot

Formulation	Correlation coefficient ('r'value)		
	Zero order plot	First order plot	Higuchi plot
(DK2)E1	0.995	0.949	0.936
(DK2)E2	0.987	0.801	0.910
(DK2)E3	0.996	0.869	0.955
(DK2)E4	0.986	0.926	0.965

Table. 5 Diclofenac sodium Release Characteristics of Matrix Tablets with Eudragit S100

Formulation	Eudragit S100 Concentration (%)	T_{50} (h)	T_{90} (h)	K_0 (mg/ml)	K_1 (h^{-1})	'n' in Peppas equation
(DK2)E1	0	7.8	--	6.850	0.132	0.981
(DK2)E2	5	7.1	11.6	8.151	0.299	1.082
(DK2)E3	10	5	9.8	9.839	0.332	0.940
(DK2)E4	15	4	7.6	12.002	0.404	0.714

4. CONCLUSIONS

1. The drug release study it may be concluded that the (DK2) E2 formula of diclofenac sodium matrix tablets have given the desired release profile by showing a minimal release during the lag period of 5 hrs and complete release at the end of 12 hrs.
2. The Diclofenac sodium tablets having the optimised formula (DK2)E2, having 25% kollidonSR with 5% of channelling agent (EudragitS100 to that of kollidonSR) showed minimal release of 27.4% in the lag period of 5 hours and 99.3% of the drug was released y the end of 12hours.
3. The diclofenac sodium matrix tablets formulated by employing kollidon SR and various channelling agents showed non-fickian diffusion mechanism and following zero order kinetics.
4. The optimized formula (DK2) E2 follows Supercase II transport as mechanism for drug release and it follows zero order kinetics.
5. Matrix tablets (DK2) E2 formulated employing 25% kollidonSR and 5% eudragit S100 are best suited to be used for colon targeting of diclofenac sodium.

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