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TINIDAZOLE MATRIX TABLETS EMPOYING EUDRAGIT S 100 USING KOLLIDON SR FOR COLON SPECIFIC DELIVERY

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ABSTRACT

Colon specific drug delivery has gained increased delivery of drug in the treatment associated with the colon as a potential system for the systemic delivery of the therapeutic peptides and proteins. The absorption of the drug in the upper portion of the GI tract can be minimized until the drug reaches the proximal colon. The matrix tablets each can prepare by direct compression method. All the tablets were found to be non-disintegrating in acidic (pH1.2) and alkaline (pH7.4) fluids, the prepared tablets were of good quality with 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. From the drug release study it may be concluded that the (TK3) E3 formula of tinidazole 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. For the optimised formula (TK3) E3 having 25% kollidonSR with 10% of channelling agent (EudragitS100 to that of kollidon SR) showed minimal release in the lag period of 5 hours about 29.1% and 98.2% of the drug was released by the end of the 12h. The tinidazole matrix tablets formulated by employing kollidonSR and various channelling agents showed non-fickian diffusion mechanism and followed zero order kinetics. Matrix tablets (TK3) E3 formulated employing 25% kollidonSR and 10% eudragit S100 are best suited to be used for colon targeting of tinidazole.

KEYWORDS: Channelling agent, Eudragit S 100, Colon Target, KollidonSR, Tinidazole.

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. The release or 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.

Tinidazole is an anti- infective drug which is widely used in the treatment of colonic disorders like giardiasis, trichomoniasis and amoebiasis. The tinidazole is the drug of choice in the treatment of amoebiasis, an infection of the large intestine caused by Entamoeba histolytica, a single celled protozoan parasite.[3] Kollidon SR is a newly developed sustained release matrix excipient based on polyvinyl acetate and poly vinyl pyrrolidone. Due to its excellent flow and compression properties it is highly suitable for tablets made by direct compression.[4] The objectives of the present work is to design and evaluate colon specific matrix tablets of tinidazole using KollidonSR as a release retarding polymer. Channeling agents[5,6] are incorporated into KollidonSR matrix tablets to get the complete drug release within 12 hours. Kollidon SR is polyvinyl acetate and poly vinyl pyrrolidone based matrix retarding agent. It is particularly suitable for the manufacture of pH-independent sustained-release matrix tablets by direct compression. Kollidon SR matrix tablets were prepared and evaluated for their application in the design of colon targeted drug delivery systems of tinidazole. Among the various approaches, preparation of matrix tablets is one of the least complicated approaches. Hence formulation of matrix tablets is aimed in the present study for colon targeting. Matrix tablets of tinidazole containing various proportions of kollidon SR (8.3%, 16.6%, 25% and 33.3%) were prepared by using direct compression method. From the

results obtained, optimized formula was taken and to that, different types of channelling agents were added in the proportions of (5%, 10% and 15%) to the weight of the kollidon SR to get the complete release within 12 hour.

EXPERIMENTAL

MATERIALS AND METHODS

Tinidazole, A Gift sample from Aarey Drugs & Pharmaceutical Ltd**,** Mumbai.

KollidonSR, A Gift sample from BASF, Ltd, Mumbai.

Poly ethylene glycol 6000, A Gift sample from Loba Chemical.

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.

Hydochloride acid, A Gift sample from Finar Reagents.

Dihydrogen ortho phosphate, A Gift sample from Fishser Scientific.

Methanol, A Gift sample from Qualigens.

All other materials are procured commercial grade.

METHODS

Preparation of tablets

The Matrix tablets, each containing 300mg of tinidazole were prepared employing Kollidon SR in different percents as per the formula given in Table.1. The required quantities of medicaments, polymer kollidonSR, binder poly vinyl pyrrolidone (2.5% w/w) and diluent dicalcium phosphate were passed through the mesh no. 100 respectively. Then all the quantities were mixed thoroughly by using mortar and pestle. After thorough mixing, the lubricants 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 12mm round and flat punches.

Estimation of tinidazole content in tablets

Five tablets were accurately weighed and powdered. The tablet powder equivalent to 300 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 tinidazole. 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 tinidazole at 310 nm. Four samples of tablet powder were analysed in each case.

Hardness

Hardness of matrix tablets prepared was tested using Monsanto hardness tester.

Friability

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

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.

***In-vitro* Drug Release Study**

Tinidazole 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 75 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 and replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 310 nm for tinidazole using an Elico SL 210 double beam UV spectrophotometer.

Data analysis

The drug 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.

RESULTS AND DISCUSSIONS

Matrix tablets each containing 300 mg of tinidazole are prepared employing Kollidon SR in different percents (8.3%, 16.6%, 25% and 33.3%) 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 $100\pm2.5\%$ of the labelled claim. All the tablets were found to be non-disintegrating in acidic (pH1.2) and alkaline (pH7.4) fluids.

As such, the prepared tablets were of good quality with 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. Tinidazole release from the matrix tablets prepared was studied in 0.1N hydrochloric acid for the first two hours followed by phosphate buffer of pH 7.4 for the next 10 hours. Drug release profiles of tinidazole matrix tablets and the release profile of the optimized formulae was shown in Figs.1, Fig.2. The drug release parameters are summarized in Tables.5. Tinidazole release was relatively rapid in the case of matrix tablets (TK1) prepared employing 8.3% kollidonSR and by the end of a lag time of 5 hours, 65.5% of release was observed. When 16.6% of kollidonSR was used in the formula (TK2), The release at the end of lag period was about 32.7%.The matrix tablets(TK3) containing 25% kollidonSR released 24.5% at the end of the lag period while the matrix tablets(TK4) having 33.3% kollidonSR released 27.1% at the end of lag time but released only 43.8% by 12 hours. From the formulation TK1, 100% drug release was achieved within 10 hours but in the remaining formulations TK2, TK3, TK4 50% drug was released upto 12 hours. Channelling agents like Eudragit S100 were tried to get the 100% drug release within 12 hours by keeping the minimum amount of drug release for first 5 hours .TK3 was selected for further studies.

Eudragit S 100 was incorporated at 5% (TK3)E2, 10% (TK3)E3,and 15% (TK3)E4 in the matrix tablets employing kollidon SR at the percentage of 25% (TK3). Drug released from the formulations (TK3) E2, (TK3) E3 and (TK3) E4 was 25.6%, 29.1%, and 37.1% in 5 hours and 62.3%, 100% and 100% in 12 hours. From the above results it was found that the minimum amount of drug released (25.6%) in 5 hours was from the formulation (TK3) E2, whereas more amount of the drug was 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 hydrochloric acid and soluble in alkaline fluids. The formulation (TK3) E3 was considered as having the optimized formula, because of the less amount of drug release in the first five hours (29.1%). The formulations containing 5% and 15% eudragit S 100 were not optimized. The formulations containing 5% eudragit S 100 released 25.6% of drug in the first five hours but it failed to release the 100% release in 12 hours. The formulation containing 15% eudragit S 100 released more amounts (37.1%) of drug in the first five hours compared with the formulation containing 10% eudragit S 100. The optimized formulation containing tinidazole was (TK3) E3.

The drug release data were analyzed as per Zero order, First order, Higuchi and Peppas equation models.[7,8] The correlation coefficient (r) values in the analysis of the release data as per different kinetic models are given in Tables.3, Table.4 and Table.5 shown in Fig.3, Fig.4 and Fig.5. The Analysis of the release data as per zero order and first order kinetic models indicated that the tinidazole release from matrix tablets followed zero order kinetics.[9-16] 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 (TK3) E3 the release also followed zero order kinetics. Plots of √Time vs. percent drug released were found to be linear. So it is obeying Higuchi's drug release mechanism that is diffusion mechanism.

When the release data were analysed as per Peppas equation, the release exponent 'n' was in the range 0.6-0.9 for all formulated matrix tablets of tinidazole employing kollidonSR polymer with various channelling agents, indicating non-Fickian (anamalous) diffusion as the release mechanism. As such, these matrix tablets (TK3) E3 formulated employing 25% kollidonSR using 10% eudragit S 100 are considered suitable for colon targeting of tinidazole for 12 hours adminstration.

Table: 1 Formulae of Tinidazole Matrix Tablets

Name of Ingredients	TK1	TK2	TK3	TK4
Tinidazole	300	300	300	300
Kollidon SR	50	100	150	200
PVP K-30	15	15	15	15
Talc	6	6	6	6
Mg. Stearate	6	6	6	6
Dicalcium Phosphate	223	173	123	73
Total Weight (mg)	600	600	600	600

Table: 2 Drug Release Profile of Tinidazole Matrix Tablets Prepared Employing Kollidon SR

Time (hrs)	Mean Percent of Tinidazole Released employing kollidon SR (x±s.d) (n=3)			
	TKI	TK2	TK3	TK4
0	0	0	0	0
0.5	22.5±0.23	11.2±0.54	6.3±0.15	5.9±0.53
1	26.4±0.42	13.2±0.39	9.2±0.26	9.2±0.29
2	37.0±0.12	18.5±0.22	12.3±0.47	11.3±0.18
3	50.8±0.36	25.4±0.3	15.7±0.43	13.8±0.53
4	61.1±0.14	30.5±0.41	20.6±0.28	18.3±0.23
5	65.4±0.27	32.7±.0.38	24.5±0.17	24.3±0.13

6	72.4±0.34	36.2±0.19	29.7±0.16	27.5±0.4
8	86.6±0.11	43.3±0.24	37.6±0.38	34.2±0.51
10	95.2±0.32	47.6±0.51	42.8±0.4	39.4±0.34
12	—	54.5±0.25	48.0±0.33	43.8±0.16

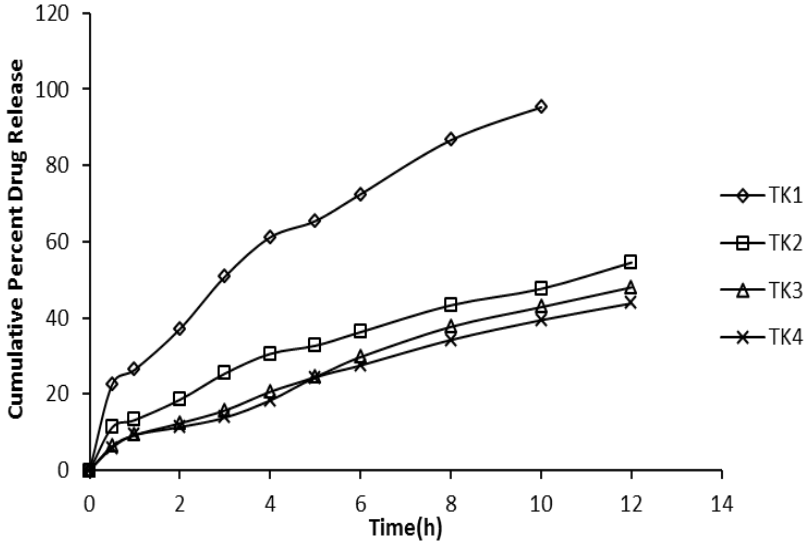

Fig: 1 Drug Release Profile of Tinidazole Matrix Tablets Prepared Employing Different Ratios of KollidonSR

Table: 3. Drug Release Profile of Tinidazole Matrix Tablets using Eudragit S100 Channelling Agents

Time (hrs)	Mean Percent of Tinidazole Relased employing kollidonSR with eudragit S100 (x±s.d) (n=3)			
	(TK3)E1	(TK3)E2	(TK3)E3	(TK3)E4
0	0	0	0	0
0.5	6.3±0.15	5.4±0.12	5.9±0.23	6.1±0.4
1	9.2±0.26	8.2±0.19	8.9±0.29	9.2±016
2	12.3±0.47	9.4±0.34	10.3±0.16	10.9±0.19
3	15.7±0.43	16.3±0.29	17.8±0.21	22.5±0.23
4	19.4±0.28	17.5±0.15	19.5±0.46	29.8±0.36
5	24.5±0.17	25.6±0.43	29.1±0.38	37.1±0.55
6	29.7±0.16	36.4±0.11	41.2±0.25	49.6±0.27
8	37.6±0.38	49.6±0.3	58.6±0.16	64.9±0.1
10	42.8±0.4	55.3±0.57	75.3±0.19	82.6±0.2
12	48.0±0.33	62.3±0.34	100±0.47	100±0.2

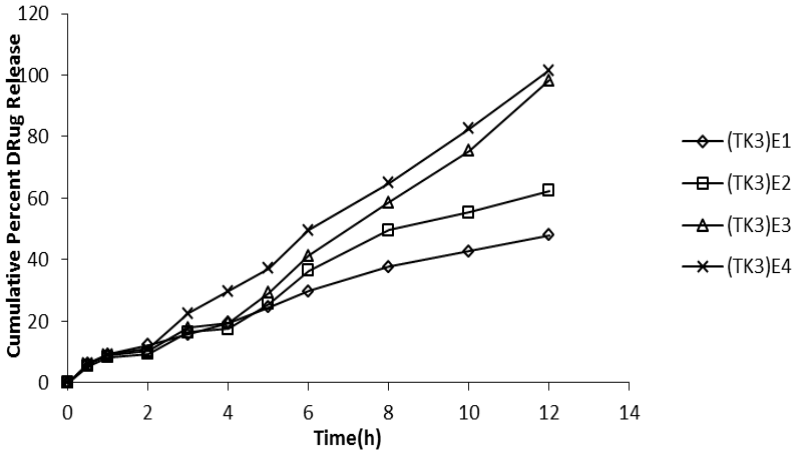

Fig.2 Drug Release Profile of Tinidazole Matrix Tablets Prepared Employing of KollidonSR with Eudragit S100 as Channelling Agents

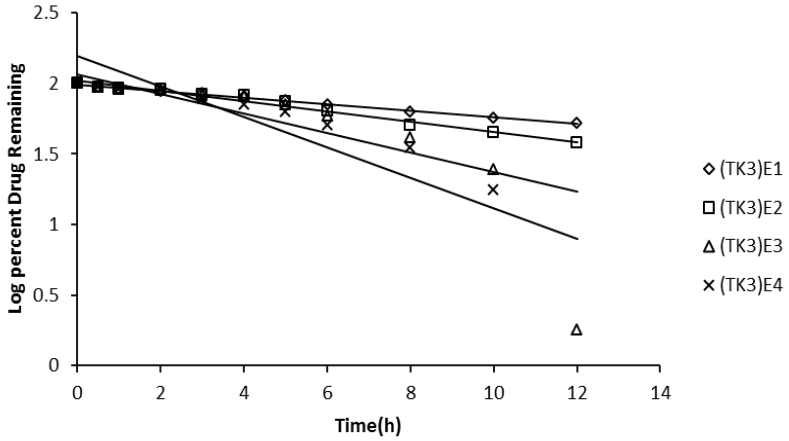

Fig.3 First Order Plots of Tinidazole Matrix Tablets Employing KollidonSR using Eudragit S100 as Channelling Agents.

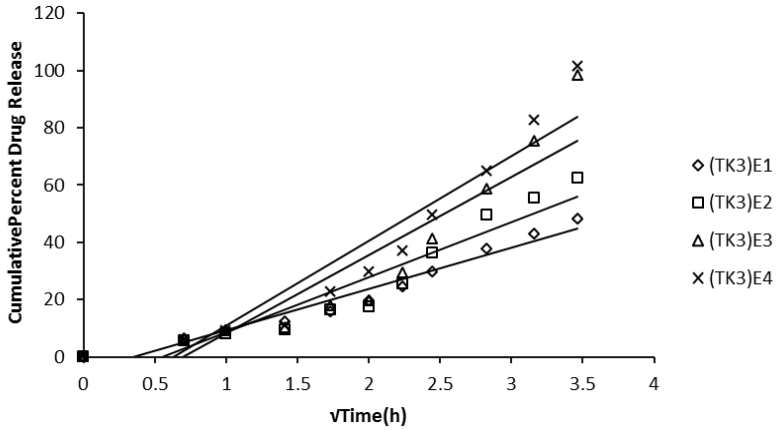

Fig.4 Percent Release Vs Square Root Time Plots of TInidazole Matrix Tablets Prepared Employing KollidonSR Using Eudragit S100 as Channelling Agents

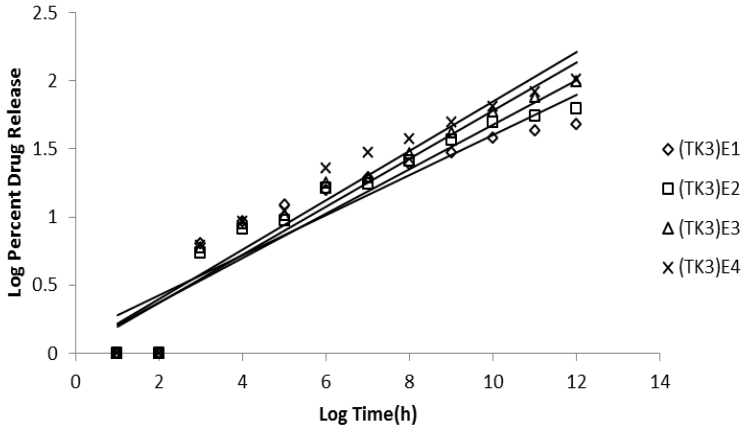

Fig.5 Log Percent Released Vs Log Time Plot of Tinidazole Matrix Tablets employing Kollidon SR using Eudragit S100 as Channelling Agents

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
(TK3)E1	0.992	0.997	0.979
(TK3)E2	0989	0.987	0.949
(TK3)E3	0.987	0.839	0.915
(TK3)E4	0.996	0.958	0.941

Table: 5 Tinidazole Release Characteristics of Matrix Tablets

Formulation	Eudragit S100 Concentration(%)	T_{50} (h)	T_{90} (h)	K_0 (mg/ml)	K_1 (h^{-1})	'n' in Peppas equation
(TK3)E1	0	----	----	3.900	0.053	0.657
(TK3)E2	5	8	----	5.397	0.083	0.815
(TK3)E3	10	7.2	11.4	7.895	0.248	0.898
(TK3)E4	15	6	10.5	8.203	0.158	0.904

CONCLUSIONS

1. The matrix tablets each can prepare by direct compression method.
2. All the tablets were found to be non-disintegrating in acidic (pH1.2) and alkaline (pH7.4) fluids, the prepared tablets were of good quality with 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.
3. From the drug release study it may be concluded that the (TK3) E3 formula of tinidazole 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.

4. For the optimised formula (TK3)E3 having 25% kollidonSR with 10% of channelling agent (EudragitS100 to that of kollidonSR) showed minimal release in the lag period of 5 hours about 29.1% and 98.2% of the drug was released by the end of the 12h.
5. The tinidazole matrix tablets formulated by employing kollidonSR and various channelling agents showed non-fickian diffusion mechanism and followed zero order kinetics.
6. Matrix tablets (TK3) E3 formulated employing 25% kollidonSR and 10% eudragit S100 are best suited to be used for colon targeting of tinidazole.

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