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Research Article

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Design of Tinidazole Matrix Tablets of for Colon Specific Drug Delivery Employing Eudragit S 100, PEG 6000 and Lactose

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ABSTRACT

The 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. The hardness of the tablets was in the range of 6-7 kg/sq.cm. The weight loss in friability test was less than 0.3% in all the cases. All the matrix tablets prepared contained 100 ± 2.5% of the labelled claim. All the tablets were found to be non-disintegrating in acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with the drug content, hardness and friability. 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 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. 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: Tinidazole; Kollidon; Eudragit s100; Lactose; Colon target

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INTRODUCTION

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The Drugs which are meant to be incorporated into a colonspecific delivery system should fulfill one or more of the following physico-chemical/therapeutic criteria [1-4]. First, these drugs should exhibit local effects in the colon to treat intestinal diseases. Peptide drugs like amylin and non-peptide drugs such as oxyprenolol are some examples of agents with these effects. Secondly, these drugs may demonstrate a suboptimal absorption in the upper gastrointestinal tract. This physiological factor that affects colonic drug delivery and bioavailability is the variation in pH of the GIT [5-7]. 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 channeling 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.

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:

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 medicament, 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 12 mm round and flat punches.

Table 1: Formulae of tinidazole matrix tablets

Formulation	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

Estimation of tinidazole content in tablets:

Five tablets were accurately weighed and powdered. The tablets 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 ± 0.5ºC. 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. 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 310 nm for tinidazole using an Elico SL 210 double beam UV spectrophotometer. The drug release experiments were conducted in triplicate.

Data analysis:

The drug release data were analysed as per zero order, first order, Higuchi and Peppas equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared [8,9].

RESULTS AND DISCUSSION

Matrix tablets each containing 300 mg of tinidazole are prepared employing KollidonSR in different percents (8.3%, 16.6%, 25% and 33.3%) by direct compression method. Hardness of the tablets was in the range of 6-7 kg/sq.cm. Weight loss in friability test was less than 0.3% in all the cases. All the matrix tablets prepared contained 100 ± 2.5% of the labelled claim. All the tablets were found to be non-disintegrating in acidic (pH 1.2) and alkaline (pH 7.4) 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 0.1 N hydrochloric acid for the first two hours followed by phosphate buffer of pH 7.4 for the next 10 hours. The drug release profiles of tinidazole matrix tablets and the release profile of the optimized formulae was given in Tables 2 and 3 shown in Figures 1-4. The drug release parameters are summarized in Figures 5-7.

Table 2: Drug release profile of tinidazole matrix tablets prepared employing KollidonSR

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

Table 3: Formulae of tinidazole matrix tablets using various channelling agents

Formulation	(TK3)P2	(TK3)P3	(TK3)P4	(TK3)L2	(TK3)L3	(TK3)L4	(TK3)E2	(TK3)E3	(TK3)E4
Tinidazole	300	300	300	300	300	300	300	300	300
Kollidon SR	150	150	150	150	150	150	150	150	150
PVP K-30	15	15	15	15	15	15	15	15	15
PEG6000	7.5	15	22.5	--	--	--	--	--	--
Lactose	--	--	--	7.5	15	22.5	--	--	--
Eudragit S 100	--	--	--	--	--	--	7.5	15	22.5
Talc	6	6	6	6	6	6	6	6	6
Mg. Stearate	6	6	6	6	6	6	6	6	6
Dicalcium Phosphate	115.5	108	100.5	115.5	108	100.5	115.5	108	100.5
Total Weight(mg)	600	600	600	600	600	600	600	600	600

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 5hours, 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 PEG 6000, lactose monohydrate and 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.

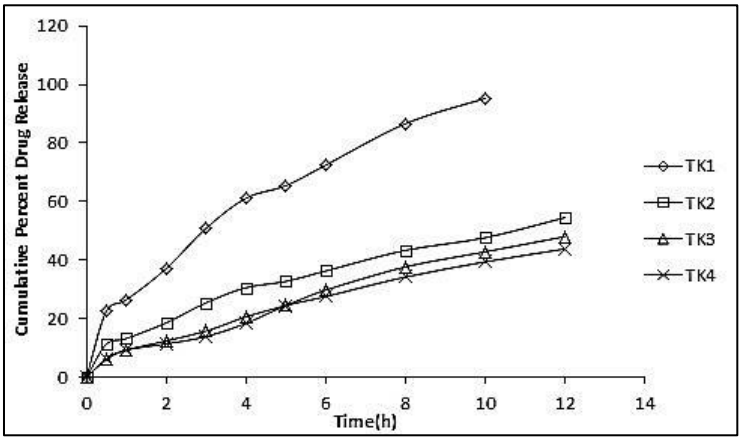

Figure 1: Drug release profile of tinidazole matrix tablets prepared employing different ratios of KollidonSR

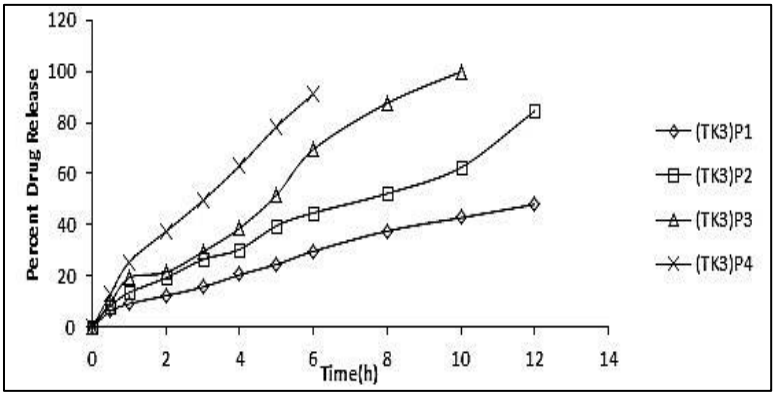

Figure 2: Drug release profile of tinidazole matrix tablets of prepared employing KollidonSR with PEG 6000 as channelling agents

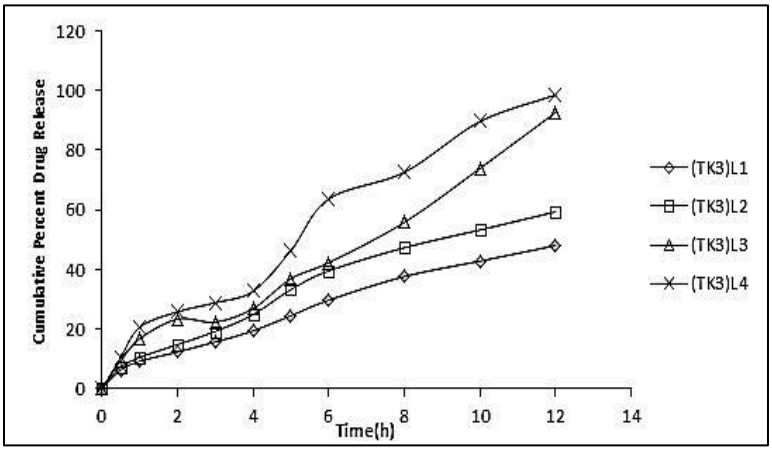

Figure 3: Drug release profile of tinidazole matrix tablets prepared using KollidonSR with lactose as channelling agents

PEG 6000 was incorporated at 5% (TK3)P2, 10% (TK3)P3, and 15%(TK3)P4 in the matrix tablets employing kollidon SR at the percentage of 25%(TK3). The drug released from the formulations (TK3)P2, (TK3)P3 and (TK3)P4 was 39.7%, 51.7% and 78.3% in 5 hours and 84.5%, 100% and 100% in 12 hours. From the above results, it was found that the minimum amount of drug released (39.7%) in 5 hours was from the formulation (TK3) P2, whereas more amount of the drug was released from the other formulations.

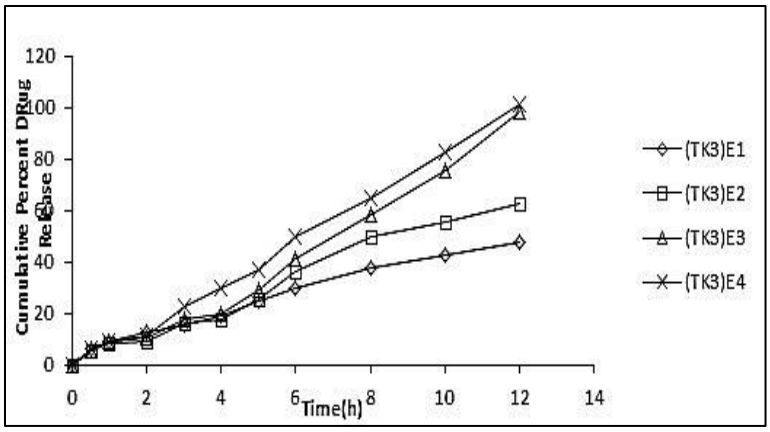

Figure 4: Drug release profile of tinidazole matrix tablets prepared employing of KollidonSR with eudragit S100 as channelling agents

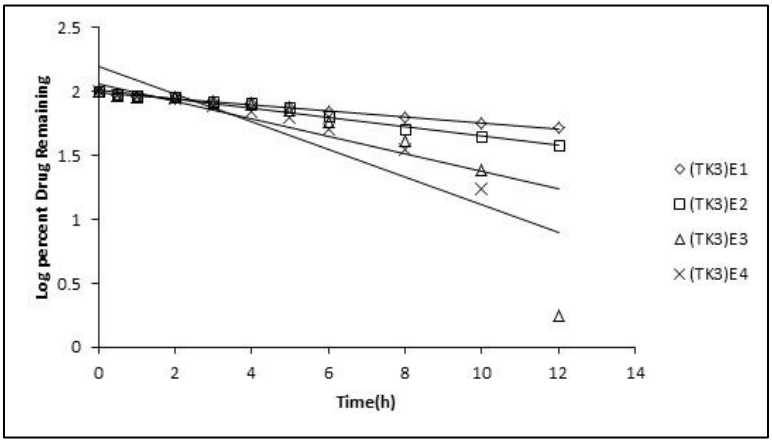

Figure 5: First order plots of tinidazole matrix tablets employing KollidonSR using eudragit S100 as channelling agents

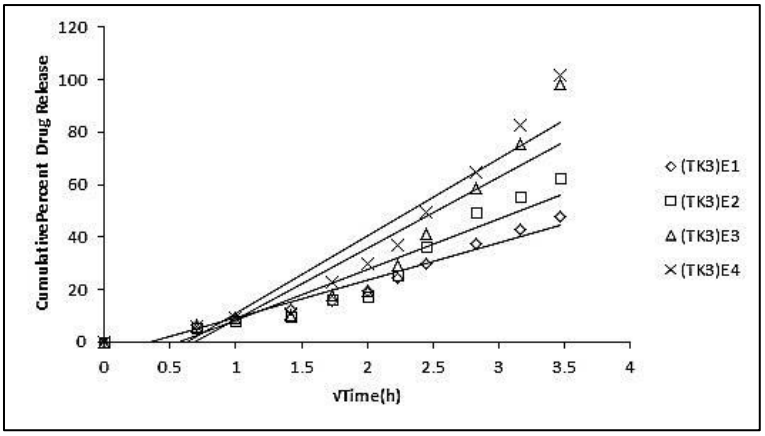

Figure 6: Percent release vs. square root time plots of tinidazole matrix tablets prepared employing KollidonSR using Eudragit S100 as channelling agents

Lactose was incorporated at 5%(TK3)L2, 10%(TK3)L3, 15%(TK3)L4 in the matrix tablets employing kollidon SR at the percentage of 25%(TK3). The drug released from the formulations (TK3) L2, (TK3) L3 and (TK3) L4 was 33.2%, 36.9%, and 46.38% in 5 hours and 59.3%, 100% and 100% in 12 hours. From the above results it was found that the minimum amount of drug released (33.2%) in 5 hours was from the formulation (TK3) L2, whereas more amount of the drug was released from the other formulations.

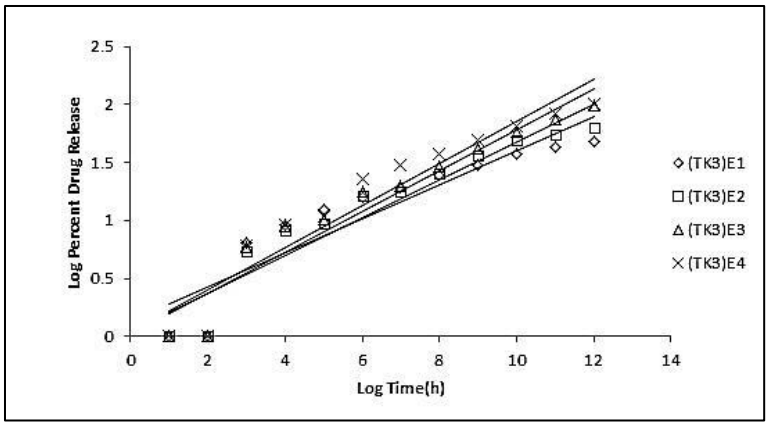

Figure 7: Log percent released vs. log time plot of tinidazole matrix tablets employing KollidonSR using eudragit S100 as channelling agents

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). The 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. Lactose and PEG 6000 released the drug in higher amounts than eudragit S 100 because of hydrophilic nature. The Eudragit S 100 is insoluble in 0.1 N hydrochloric acid and soluble in alkaline fluids. So, it released lower amounts when compared with other channelling agents like lactose and PEG 6000. 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, and 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 Tables 4 and 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 [10-17]. The correlation coefficient (r) values were higher in the zero order model 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 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 administration (Tables 4 and 5).

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	989	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	----	----	3.9	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

CONCLUSION

- The 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.
- The hardness of the tablets was in the range of 6-7 kg/sq.cm. The weight loss in friability test was less than 0.3% in all the cases.
- All the matrix tablets prepared contained 100 ± 2.5% 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 the drug content, hardness and friability.
- 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 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.
- 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.

REFERENCES

[1] S Das; R Deshmukh; A Jha. *Syst Rev Pharm*. **2010**, 1(1), 79-85.
[2] VR Leuva; BG Patel; DJ Chaudhary; JN Patel; MMK Modasiya. *J Pharm Res*. **2012**, 5(4), 2293-2297.
[3] M Kumar; A Ali; P Kaldhone; A Shirode; VJ Kadam. *J Pharm Res*. **2010**, 3, 3.
[4] AK Philip; B Philip. *Oman Med J*. **2010**, 25(2), 79-87.
[5] M Halsas; T Penttinen; P Veski; H Jürjenson; M Marvola. *Die Pharmazie*. **2001**, 56(9), 718-723.
[6] SN Makhija; PR Vavia. *J Control Release*. **2003**, 89(1), 5-18.
[7] SO Gupta; PM Bedi; NE Bedi. *Int J Appl Pharm*. **2010**, 2(1), 1-6.
[8] TJ Higuchi. *Pharm Sci*. **1963**, 52, 1145.
[9] PL Ritger; NA Peppas. *J Control Release*. **1987**, 5, 37.
[10] KPR Chowdary; RK Prakasa. *Asian J Pharm Clin Res*. **2012**, 5(1), 161-164.
[11] KPR Chowdary; KSP Rao; D Madhuri. *Int J Appl Biol Pharm Technol*. **2011**, 2. 4.
[12] KP Chowdary; KSP Rao. *Int J Pharm Res Dev*. **2011**, 3, 125-130.
[13] PT Sundari; KS Rao. *Asian J Chem*. **2009**, 21(8), 5847.
[14] KP Chowdary; PT Sundari; KS Rao. *Int J Chem Sci*. **2008**, 6, 3.
[15] KP Chowdary; K Rao; S Prakasa. *Asian J Chem*. **2011**, 23(10), 4520-4524.
[16] KP Chowdary; RK Prakasa. *Asian J Pharm Clin Res*. **2012**, 5(1), 161-164.
[17] KP Chowdary; KSP Rao. *Der Pharmacia Lettre*. **2011**, 3(5), 146.