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Research Article

PREPARATION AND EVALUATION OF KOLLIDON SR MATRIX TABLETS OF TINIDAZOLE FOR COLON SPECIFIC DRUG DELIVERY

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ABSTRACT

Amoebiasis is an infection of the large intestine caused by *Entamoeba histolytica*, and it is mainly present in the intra-intestinal lumen. The efficient treatment of amoebiasis and other colonic infections could be achieved by targeting the drug to the colon. Tinidazole is the drug of choice for intestinal amoebiasis and other colonic infections and the best approach for this drug is to target the drug to the colon which would make the drug effective with low dose and prevent the potential hazards observed in conventional dose. Moreover, addition of suitable polymers in the formulation could enhance the drug solubility. The aim of the present investigation was to formulate matrix formulations using different concentrations of Kollidon SR and PVP K-30, Eudragit S100 to prevent the premature drug release in the GI tract, the matrix formulations further taken for compression to test the suitability for targeted drug delivery to the colon. The release kinetics of the formulations was calculated. All the Matrix, compression coated formulations showed the desired physicochemical properties as per the official limits. Based on the drug release study in pH 1.2 (0.1N HCl), Phosphate buffer pH 6.8 and the results showed that among the 9 formulations FE2 and FL3 showed good dissolution profile to control the drug release respectively.

Keywords: Amoebiasis, Tinidazole, Koliidon SR , matrix tablets, release kinetics.

INTRODUCTION

A novel oral colon-specific drug delivery system (CDDS) has been developing as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. CDDS is convenient for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation *etc.*, CDDS, also selectively deliver drug to the colon, but not to the upper GI tract. Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon[1].

Matrix tablet has given new break through for novel drug delivery system in the field of pharmaceutical technology. In colon release matrix formulations the drug release from the dosage form is mainly controlled by type and proportion of polymers used in the preparation. Controlled release can be achieved by formulating drugs as matrix devices using Kollidon SR,(Polyvinylpyrolidine) PVP K-30, Eudragit S-100, (Polyethylene glycol)PEG 6000[2].

There are several ways in which colon-specific drug delivery has been attempted. Prodrugs coating with pH dependent polymers, design of timed-release dosage forms and the use of carriers that are degraded exclusively by colonic bacteria are an array of such attempts.

The targeting of orally administered drugs to the colon is accomplished by:

i) Coating with pH dependent polymers

ii) Timed release dosage forms

iii) Delivery systems based on the metabolic activity of colonic bacteria[3].

Amoebiasis is an acute or chronic inflammation that is caused by the parasitic amoeba, *Entamoeba Histolytica.* This is generally spreads by water and any prepared foods infected due to poor hygienic condition and that might cause contamination. It is featured by watery diarrhoea, bloody stools and feverish conditions.

Amoebiasis is an infection caused by *Entamoeba histolytica* and it spreads through infected fecal matter. The condition can also occur due to crowded living condition. Internal cause for amoebiasis is due to spread through the blood to the liver, brain or other vital internal organs[4].

MATERIALS AND METHODS

Materials:

Tinidazole was a gift sample from Rao's pharma (Hyderabad, India), Kollidon SR from Arrow chem. Products (Mumbai, India), PVP K-30, PEG 6000, Lactose from (S.D fine chem. Mumbai, India), Eudragit S 100 from Hi Media Laboratories (Mumbai, India).

Standard curve for Tinidazole:

100 mg of Tinidazole was weighed and dissolved in 100ml of pH-1.2 to prepare first stock solution. 1 ml of above solution was taken and diluted to 100ml with the same solvent to prepare StockII solution. The amount of stock II solution was further diluted with 0.1 N Hcl to get 5 µg, 10 µg, 15 µg, 29 µg, 25 µg,30 µg of drug per ml of the final solution . Then the absorbance was measured in a UV spectrophotometer at 310nm against PH 0.1N Hcl. The same procedure was repeated by using phosphate buffer PH 6.8

Methods:

Matrix tablets of Tinidazole were prepared by direct compresion method by using different concentrations of Kollidon SR with combination of various release retardant polymers. The polymers were PVP K-30, Eudragit S 100 and PEG 6000. All ingredients except magnesium stearate were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate was added and mixed for additional 2-3 minutes and finally, compressed by using tablet compression machine.

INGREDIENTS	FP1	FP2	FP3	FL1	FL2	FL3	FE1	FE2	FE3
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
PEG-6000	7.5	15	22.5	--	--	--	--	--	--
Lactose	--	--	--	7.5	15	22.5	--	--	--
Eudragit S100	--	--	--	--	--	--	7.5	15	22.5
Talc	6	6	6	6	6	6	6	6	6
Magnesiumstearate	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

Table I: Formulations containing & various concentrations of excipients

Evaluation of physical properties:

The blended powder was evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, Hausner's Ratio and drug content etc. The prepared tablets were subjected to thickness, weight variation test, hardness, friability, drug content, in-vitro disintegration time, wetting time and water absorption ratio.

FT-IR spectra of the Tinidazole:

FT-IR spectra of prepared formulations were taken and compared with the spectrum of pure drug. The Characteristics peak of drug was checked in the best formulation spectra.

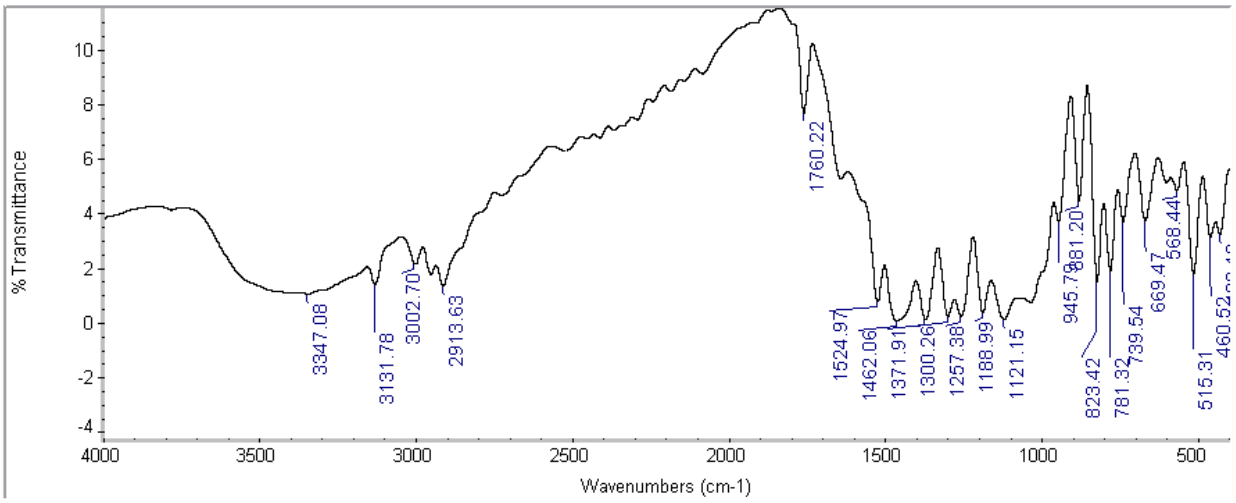

Figure 1: FT-IR of Tinidazole pure drug

In-vitro release study:

In-vitro release studies of Tinidazole matrix tablets were carried out in USP Type II (Paddle Type) apparatus by using 0.1N HCl and 6.8 pH phosphate buffer as a dissolution media. Rotated at 50 rpm and temperature maintained at 37 ± 0.5˚C. Sample was withdrawn up to 12 hrs and analyzed by UV-spectrophotometer at 310 nm.

RESULTS AND DISCUSSION

IR of the Tinidazole was determined by FTIR spectra as mentioned in the Physical mixture of drug and polymer was characterized by FTIR spectral analysis. From the results, it was concluded that there was no interference of the functional group as the principle peaks of Tinidazole were found to be unaltered in the drug- polymer physical mixtures, indicating they were compatible chemically for the best formulation.

Pre- compression parameter:

Flow properties of the granules were evaluated by determining the bulk density 0.389±0.07 to 0.404±0.04, tapped density 0.350±0.081 to 0.473±0.098, angle of repose 25.10^0±0.38^0 to 30.01^0±0.27^0 and compressibility index 8.88±0.030 to 15.43±0.124.

Formulation	Bulk density g/cc	Tapped density g/cc	Compressibility index%	Angle of repose(ɵ)
FP_1	0.404±0.04	0.461±0.120	12.36±0.020	25.64^0±0.34^0
FP_2	0.397±0.01	0.393±0.090	15.43±0.124	27.33^0±0.23^0
FP_3	0.400±0.08	0.439±0.133	8.88±0.030	25.20^0±0.42^0
FL_1	0.390±0.03	0.451±0.124	13.23±0.047	27.51^0±0.34^0
FL_2	0.395±0.06	0.350±0.081	9.10±0.097	29.40^0±0.22^0
FL_3	0.401±0.02	0.361±0.142	13.23±0.110	27.50^0±0.41^0
FE_1	0.389±0.07	0.430±0.123	10.22±0.119	30.01^0±0.27^0
FE_2	0.409±0.09	0.461±0.093	11.27±0.114	25.10^0±0.38^0
FE_3	0.399±0.02	0.473±0.098	13.50±0.122	26.80^0±0.18^0

Table II: Pre-Compression Parameter results

Post- compression parameter:

The % weight variation was within pharmacopoeia limits of ±5% of weight. The weights variations range from 595.9±0.44 to 600.3±0.23. Hence all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of each batch ranged between 6.0±0.05 and 6.5±0.06 Kg/cm^2. This ensures good handling characteristics of all batches. The values of friability test were tabulated in table. The friability was in the range 0.210±0.005 to 0.447±0.005, So, less than 1% in all formulations ensuring that the tablets were mechanically stable.

The present study reveals to control the drug release by increasing the concentration of Kollidon SR as a retarding agent with different polymers like PVP K-30, Eudragit S 100, PEG 6000. The combination of different ratios of Lactose and Eudragit S 100 with Kollidon SR showed better release profile 98.54% and 98.22% respectively rather than other combinations.

Formulation	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
FP1	3.9±0.09	599.5±0.12	6.0±0.04	0.210±0.005	98.25±0.044
FP2	4.0±0.02	599.8±0.62	6.5±0.03	0.223±0.0012	99.31±0.037
FP3	4.0±0.01	600.1±0.54	6.0±0.07	0.284±0.003	90.54±0.07
FL1	3.9±0.07	598.8±0.13	6.5±0.04	0.323±0.006	98.67±0.087
FL2	4.0±0.04	600.5±0.32	6.4±0.08	0.254±0.003	99.37±0.058
FL3	3.8±0.09	595.9±0.44	6.3±0.03	0.294±0.001	97.96±0.073
FE1	4.0±0.01	599.6±0.67	6.0±0.05	0.447±0.005	92.62±0.08
FE2	4.0±0.03	600.3±0.23	6.1±0.08	0.363±0.001	99.73±0.056
FE3	4.0±0.02	599.9±0.14	6.5±0.06	0.244±0.004	96.51±0.061

Table III: Post- compression parameter results

Time in Hrs	FP1	FP2	FP3	FL1	FL2	FL3	FE1	FE2	FE3
0	0	0	0	0	0	0	0	0	0
0.5	8.532± 0.04	9.802± 0.09	13.212 ±0.06	7.275± 0.03	9.209±0. 08	10.546± 0.04	5.404± 0.04	5.928± 0.03	6.183±0.0 3
1	13.588± 0.02	19.311 ±0.04	25.412 ±0.07	10.576 ±0.07	16.745± 0.01	20.686± 0.01	8.263± 0.01	8.974± 0.06	9.285±0.0 1
2	19.342± 0.06	21.404 ±0.06	37.477 ±0.03	14.832 ±0.06	23.486± 0.06	25.819± 0.09	9.408± 0.04	10.374 ±0.07	10.976±0. 05
3	26.404± 0.03	29.543 ±0.07	49.532 ±0.04	19.286 ±0.04	25.385± 0.04	28.874± 0.03	16.363 ±0.06	17.837 ±0.05	22.597±0. 07
4	30.411± 0.02	38.775 ±0.01	63.458 ±0.08	24.911 ±0.03	26.974± 0.02	32.764± 0.04	17.574 ±0.04	19.537 ±0.06	29.812±0. 02
5	39.712± 0.05	51.792 ±0.04	78.112 ±0.04	33.225 ±0.08	36.990± 0.07	46.332± 0.04	25.683 ±0.04	29.137 ±0.01	37.135±0. 09
6	44.732± 0.01	69.837 ±0.05	91.232 ±0.05	39.512 ±0.03	42.284± 0.05	63.684± 0.01	36.438 ±0.01	41.238 ±0.08	49.686±0. 07
8	52.300± 0.04	87.319 ±0.03	--	47.398 ±0.01	55.890± 0.04	72.594± 0.03	49.628 ±0.06	58.687 ±0.04	64.945±0. 03
10	62.413± 0.02	98.591 ±0.08	--	53.221 ±0.01	73.991± 0.05	89.694± 0.07	55.346 ±0.04	75.346 ±0.01	82.637±0. 05
12	84.510± 0.07	--	--	59.354 ±0.07	92.683± 0.01	98.546± 0.01	62.313 ±0.05	98.223 ±0.07	--

Table IV: Cumulative percentage of drug release of FP1 to FE3

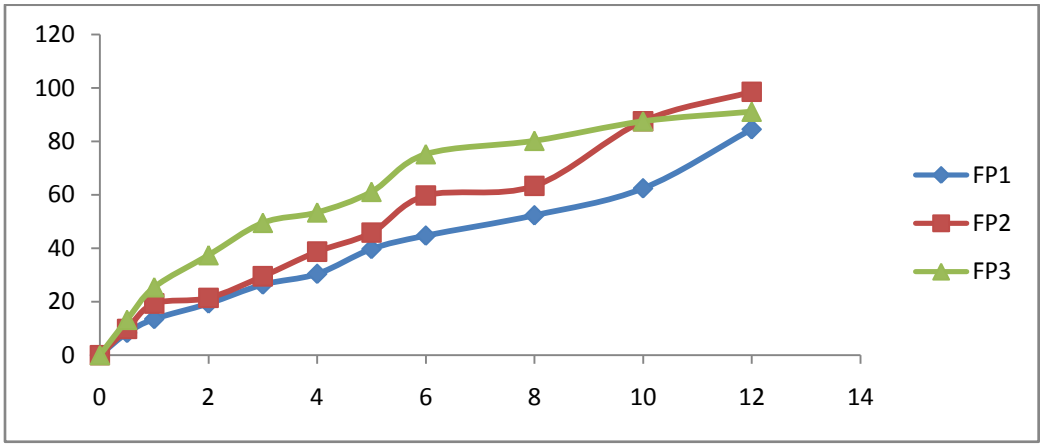

Figure 2: Cumulative percentage release Vs Time profile of FP1 and FP2, FP3

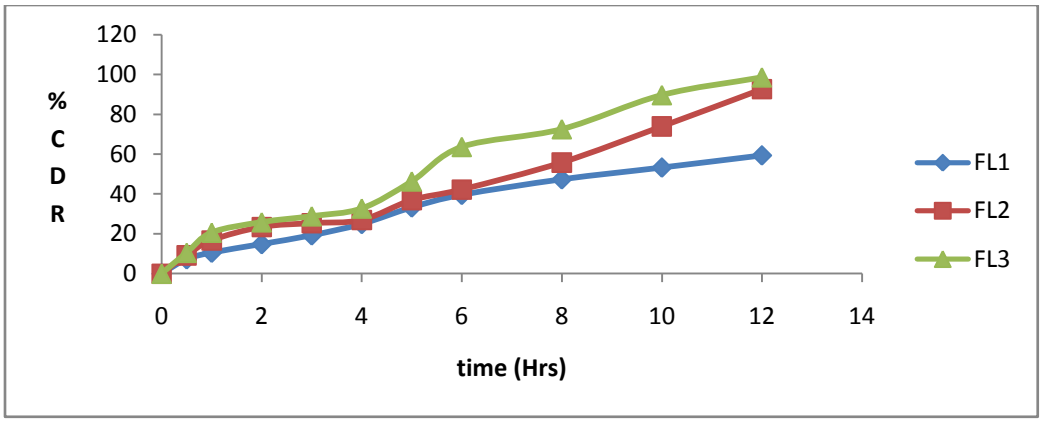

Figure 3: Cumulative percentage release Vs Time profile of FL1 and FL2, FL3

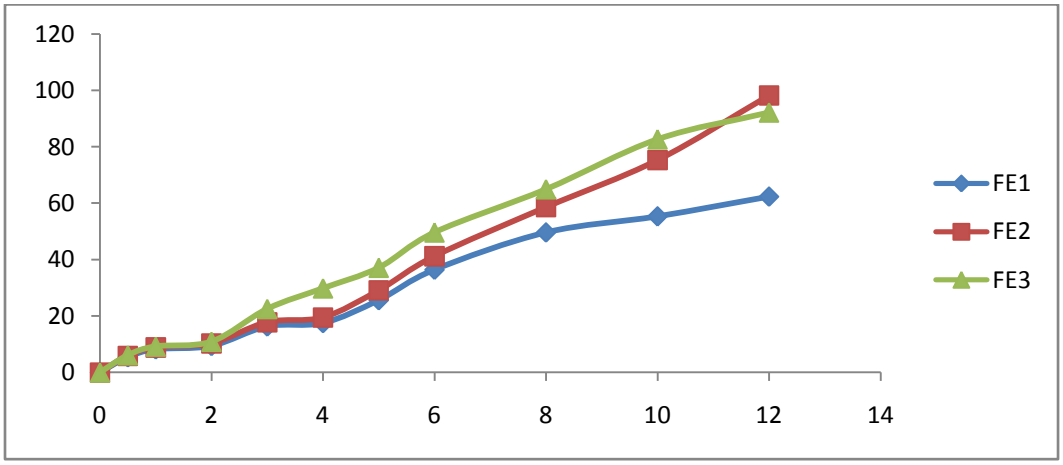

Figure 4: Cumulative percentage release Vs Time profile of FE1 and FE2, FE3

Stability study:

The selected formulation FL3 and FE2 were subjected to stability studies for 90 days at 25ºC in 60% RH, 30ºC in 65% RH, 40ºC in 75% RH, *in- vitro* permeation study was performed on every 15 days and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content.

CONCLUSION

From the drug release study it was concluded that the FE2 formula of Tinidazole matrix tablets was given the desired release profile by showing a minimal release during the lag period of 5 hours and complete release by the end of 12 hrs. For the optimized formula FE2 having 25% Kollidon SR with 5% of channeling agent (Eudradit S100 to that of Kollidon SR) showed minimal release in the lag period of 5 hrs about 29.1% and 98.2% of the drug was released at the end of the 12hrs. Matrix tablets formulated by employing 25% Kollidon SR and 10% Eudrgit S100 are the best used for colon targeting of Tinidazole. The results of *in- vitro*

dissolution study indicated that the drug release was in controlled fashion. To analyze the mechanism of drug release from the matrices, the *in-vitro* drug release data were fitted to Zero order, First order. It was observed that the release of drug followed non-Fickian diffusion mechanism and followed zero order kinetics.

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