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FORMULATION AND EVALUATION OF BALSALAZIDE COLON TARGETED SUSTAINED RELEASE MATRIX TABLETS

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ABSTARCT

In the present research work sustained release matrix formulation of Balsalazide targeted to colon by using various polymers developed. To achieve pH-independent drug release of Balsalazide, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit RLPO and S100 were used as enteric coating polymers. The pre-compression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F6 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.45% drug release. It followed zero order kinetics mechanism.

KEYWORDS: Balsalazide, Colon targeteddrug delivery system, Ethyl cellulose, Eudragit RLPO, Eudragit S 100.

1. INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Nearly 50% of drug delivery systems available in the market are oral drug delivery systems and these systems have more advantages due to patient acceptance and ease of administration. In recent years, colon-specific drug delivery system[1] (CDDS) have been

developing as one of the site specific drug delivery system. Along with many application in local and systemic delivery of drugs. Balsalazide[2] is an anti-inflammatory drug. It is converted in the body to mesalamine also known as 5-Amino salicylic acid[3] and works by reducing bowel inflammation, diarrhoea, rectal bleeding, and stomach pain.also used in the treatment of mildly to moderately active ulcerative colitis Balsalazide itself is Poorly absorbed from the GI tract with an in-vivo bioavailability of <1% Although Balsalazide is less absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose.

1. Kruis, W.; Schreiber, I.; Theuer, D.; Brandes, J. W.; Schütz, E.; Howaldt, S.; Krakamp, B.; Hämling, J.; Mönnikes, H.; Koop, I.; Stolte, M.; Pallant, D.; Ewald, U. (2001). "Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0 g twice daily) was superior in preventing relapses". Gut. 49(6): 783–789. *doi*:*10.1136/gut.49.6.783*. *PMC 1728533*. *PMID 11709512*.

2. Aim and Objective of the study

The aim of the current research work is the designing and development of sustained release matrix formulation of Balsalazide specifically targeting colon region by using various polymers Ethyl cellulose[4], Eudragit RLPO and Eudragit S 100. The objective of this study was to prepare optimize the formulation of Balsalazide as a colon targeted tablet in order to extend the release of the drug to a desired period of time.

3. Plan of Work

1. Absorption maxima determination of Balsalazide.
2. Preparation of calibration curve in 1.2,6.8 and 7.4 P^H Buffer solutions.
3. Drug – Excipient compatibility studies- Fourier Transform Infrared (FTIR) spectroscopy.
4. Preformulation studies.[5]
5. Formulation of Tablets[5]
6. Formulation of core tablets
7. Formulation of compression coated tablets
8. Evaluation of post compression parameters for prepared Tablets
9. Application of Release Rate Kinetics To Dissolution Data

4. METHODOLOGY

Drug – Excipient compatibility studies: By FT-IR anlysis, the compatibility of the physical mixture was determined in relation with that of plain drug. FT-IR analysis of the plain drug and physical mixture of drug and excipients were conducted by KBr Plate method and spectrum was collected within the region 4,000–400 cm^{-1}. Resulted IR spectrum was observed for any new peaks at certain locations.

Formulation of Tablets: Preparation balsalazide colon specific tablets was accomplished in two step process in which initial step is the formulation of core tablet and the final step is compression coating. Before the compression coating, internal core tabletscomposed of active drug was formulated with super disintegrate. Then this formulation was coated according to compression coating method by including various compositions of polymers. Ethyl cellulose, Eudragit S100 and Eudragit RLPO were used as compression coating polymers.

Evaluation of Prepared Tablets

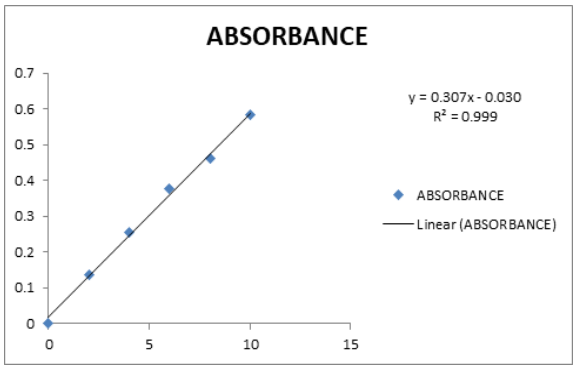
***In vitro* drug release studies:** Drug release studies of Balsalazide core tablets In pH 6.8 dissolution solution balsalzide core tablets of strength 325mg were tested in for the dissolution rates by using USP paddle type II apparatus. The drug concentration in sample was measured by UV- Visible Spectrophotometer at 270 nm. Balsalazide drug release studies were performed by using USP paddle-type dissolution[6] apparatus at 50 rpm, and a temperature of 37±0.5 °C.The drug release studies were conducted inSGF of pH 1.2 for the first 2 hours. Then, the studies were conducted in SGF of pH 7.4 and tested for drug release for 3 hours, and finally conducted in SGF of pH 6.8 upto 12 hours to mimic colonic pH conditions.

Compression coated[7] Balsalazide drug release conducted by adding 900ml of dissolution medium. Samples of dissolution[8] medium were drawn periodically in quantities of 5ml, and drug concentration was measured by UV-Visible spectrophotometer at 275 nm. The results were given with standard deviation.

Application of Release Rate Kinetics to Dissolution Data: The drug release rate kinetics mechanism of the designed dosage forms analysed by fitting the obtained data into first order, zero-order, Higuchi, and Korsmeyer-Peppas release model.

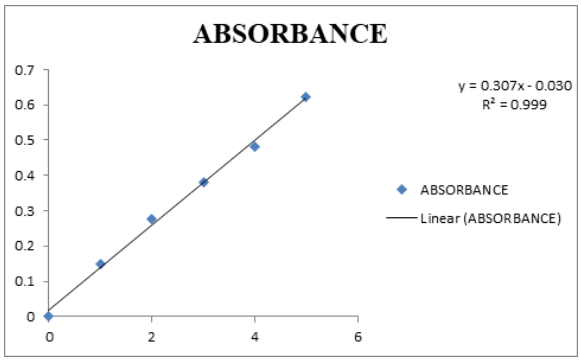
5. RESULTS AND DISCUSSIONS

No.	Conc [mg/l]	abs
1	0	0
2	2	0.138
3	4	0.256
4	6	0.376
5	8	0.461
6	10	0.582
7	12	0.824



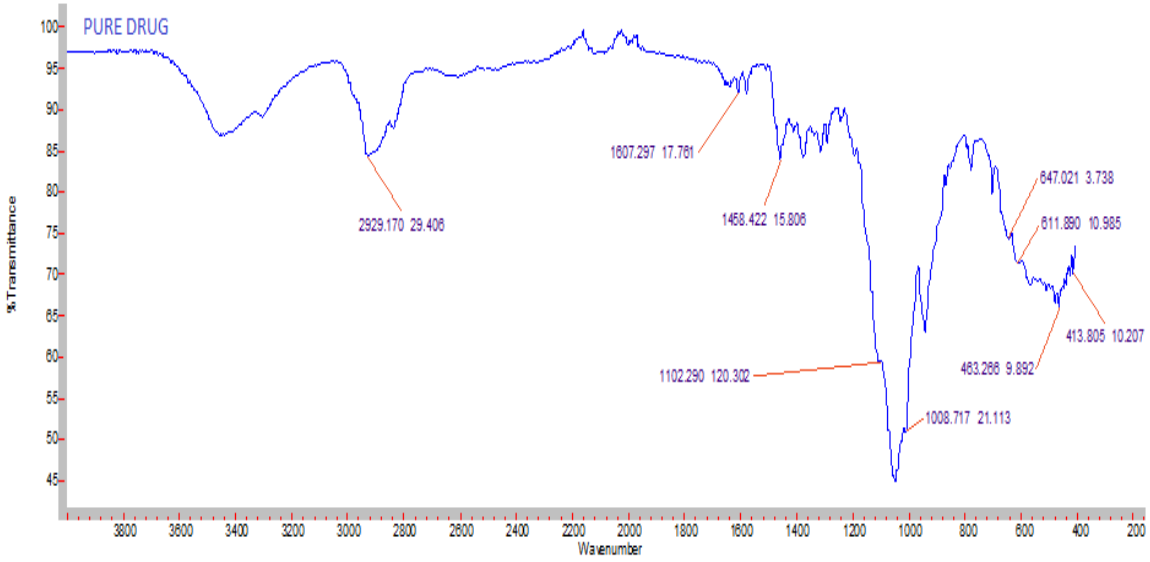
Standard Graph of Balsalazide in pH 1.2 buffer solution.

No.	Conc [mg/l]	Abs
1	0	0
2	1	0.148
3	2	0.275
4	3	0.379
5	4	0.481
6	5	0.621
7	6	0.859

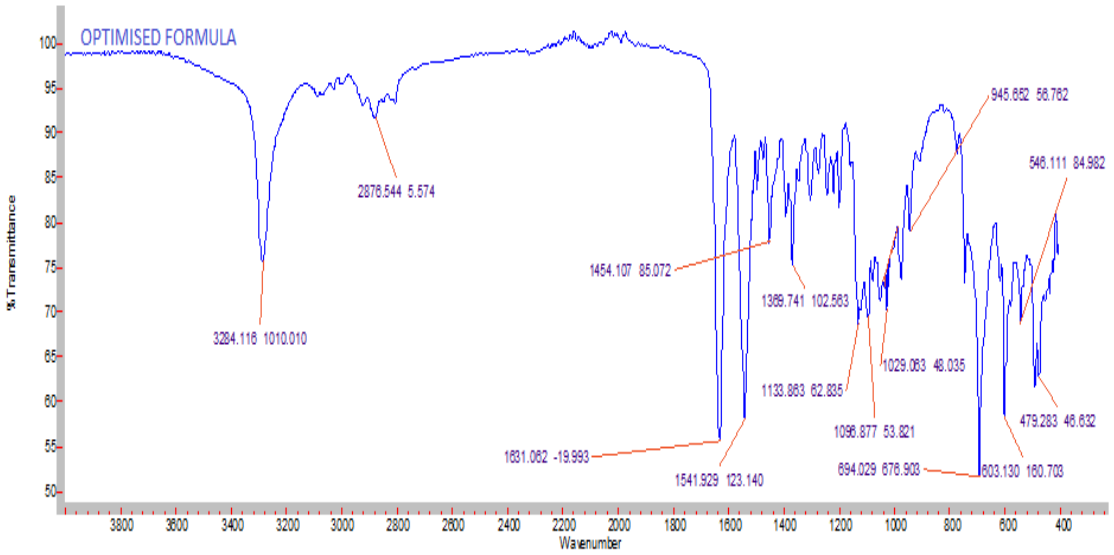


Standard Graph of Balsalazide in pH 6.8 buffer solution.

compatability studies



FT-IR spectrum of pure drug



FT-IR spectrum of optimized formulation

Preformulation parameters of core material

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01	0.55	0.645	14.72	0.85
F2	34.8	0.57	0.66	13.63	0.86
F3	36.05	0.53	0.606	14.19	0.838
F4	34.19	0.531	0.613	13.37	0.866
F5	36.24	0.549	0.641	14.35	0.856
F6	33.25	0.564	0.666	15.31	0.854
F7	37.08	0.581	0.671	13.41	0.865
F8	35.12	0.567	0.654	13.12	0.845
F9	35.45	0.571	0.689	13.28	0.855

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.52	4.8	99.76
F2	305.4	4.2	0.54	4.9	99.45
F3	298.6	4.4	0.51	4.9	99.34
F4	310.6	4.5	0.55	4.9	99.87
F5	309.4	4.4	0.56	4.7	99.14
F6	310.7	4.2	0.45	4.5	98.56
F7	302.3	4.1	0.51	4.4	98.42
F8	301.2	4.3	0.49	4.7	99.65
F9	398.3	4.5	0.55	4.6	99.12

Formulation of core tablet

The core tablets having 325mg of the active drug were formulated. The composition of core tablet formulation containing drug and excipients[9] was given in below table.

Ingredient Name	Quantity (mg)
Balsalazide	325
Cross carmellose sodium	81.25
Talc	5
Magnesium stearate	5
MCC pH102	QS
Total weight	500

500mg of weight was fixed as total weight of core tablet. The tablets are prepared by using 9mm flat punch is utilized for tablet punching and the resulted tablets were subjected to compression coating.

Formulation of compression coated tablets: Ethyl cellulose, Eudragit RLPO 100 and Eudragit S 100 polymers were employed for the compression coating of core tablets in different ratios. The composition of coating materials for each formulation is given in below table.

Ingridient Name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	40	81.25					40		40
Eudragit RLPO (mg)			40	81.25			40	40	
Eudragit S100 (mg)					40	81.25		40	40
Magnesium Stearate(mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	250	250	250	250	250	250	250	250	250

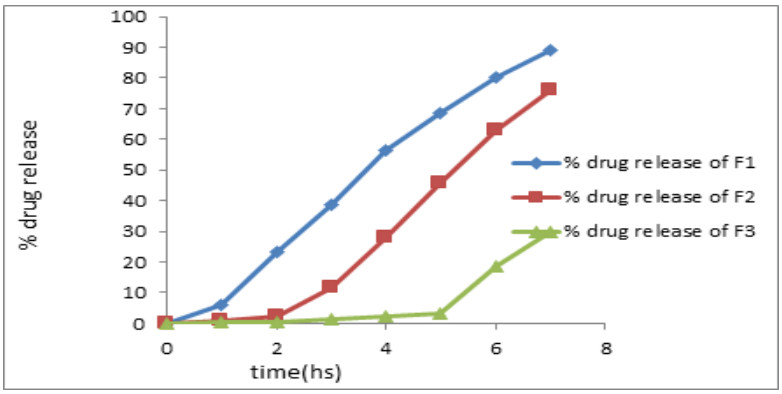
***In-Vitro* Drug Release Studies**

The dissolution rate of compression coated100mg Balsalazide tablets were tested in pH 6.8 phosphate buffer by employing USP paddle-type dissolution apparatus at 50 rpm, and a temperature of 37±0.5°C. Thus, drug release studies were conducted insimulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SGF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme-free simulated intestinal fluid (SGF, pH 6.8) was used upto 12 hours to mimic colonicpH conditions.

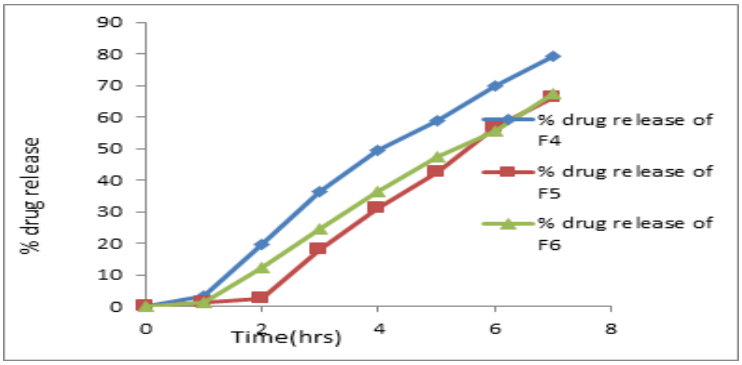
Drug release was measured from compression coated Balsalazide tablets, added to 900 ml of dissolution medium. The concentration of drug in samples withdrawn in each interval was analyzed UV-Visible spectrophotometer at 320 nm, 319 and 275 nm respectively. All dissolution runs were performed for six batches.

***In-vitro* Drug Release profile for coated formulations (F1-F9)**

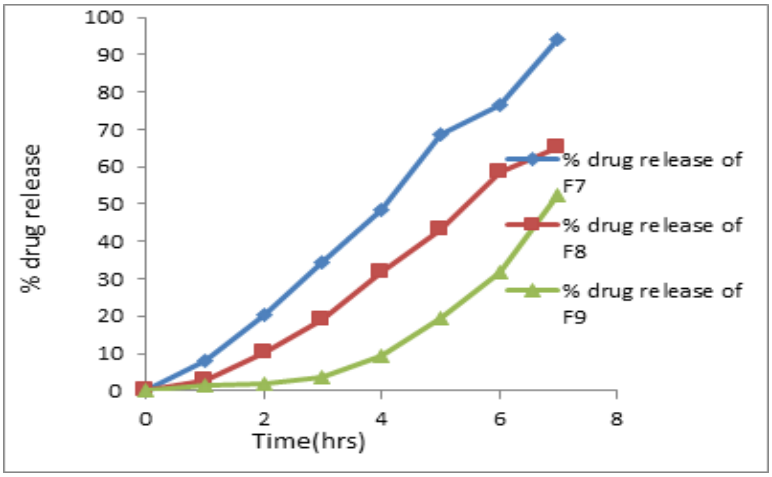
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.19	0.73	0.34	3.39	1.11	1.44	8.06	2.65	1.32
2	23.16	2.46	0.54	19.88	2.49	12.30	20.46	10.23	1.74
3	38.49	11.46	1.26	36.45	18.19	24.44	34.46	19.19	3.67
4	56.34	28.19	2.22	49.59	31.19	36.61	48.41	31.57	9.57
5	68.44	45.79	3.05	59.01	42.46	47.30	68.76	43.08	19.48
6	80.16	62.87	18.41	69.85	56.78	55.68	76.73	58.74	31.88
7	89.16	76.19	30.05	79.46	66.19	67.53	94.23	65.13	52.47
8	98.14	85.16	48.69	86.19	79.46	78.72		78.45	62.46
9		92.78	55.38	99.14	91.46	83.34		85.67	73.47
10		97.73	72.34		96.19	90.67		98.45	83.44
11			87.56			96.12		98.12	92.47
12			93.69			98.45			96.44



Dissolution of formulations F1-F3



Dissolution of formulations F4-F6



Dissolution of formulations F7-F9

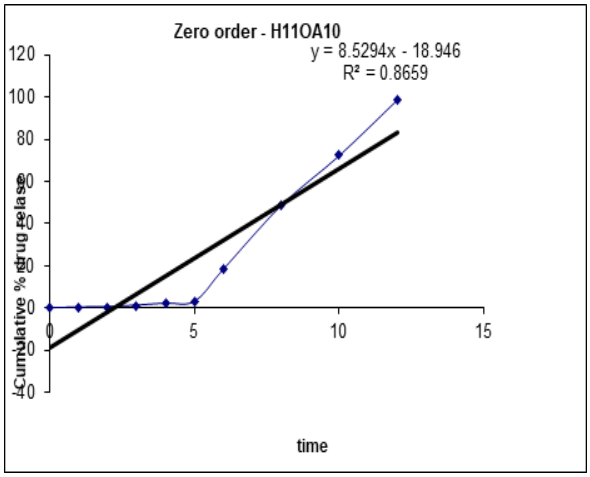
From the dissolution studies it was clear that F3,F6 & F9 formulations were delayed the release of drug up to 12 hours, with drug release of 93.69%,98.45% and 96.44 % respectively. F1 –F2 are ethyl cellulose alone formulations and increase in ethyl cellulose concentration increase the delayed nature of formulations. F3 –F4 are Eutragit RLPO alone formulations and increase in Eudragit RLPO concentration increase the delayed nature of formulations.F5-F6 are Eudragit S100 The formulation decelerated the drug release up to 12 hours and disclosed maximum release in 12 hours that is in colon region. F6 declared as optimized one.

Application of Release Rate Kinetics to Dissolution Data

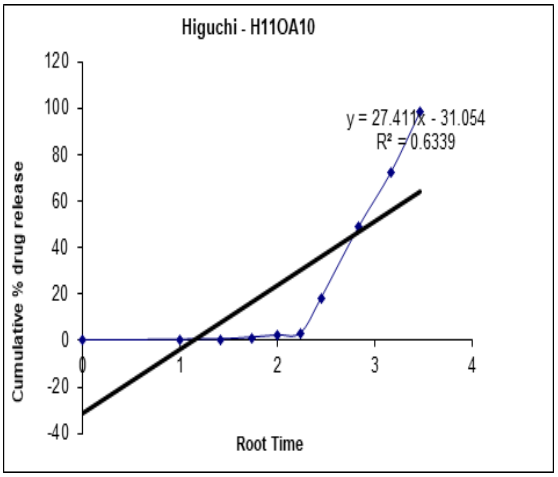
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Release kinetics data for optimised formulation

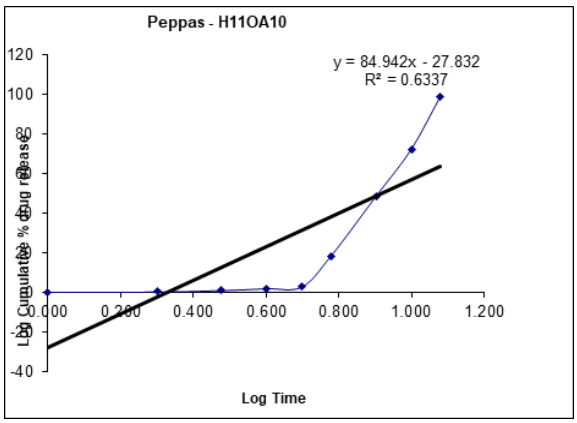
CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0	0		2.000	0	0	0	100	4.642	4.642	0.000
0.34	1	1.000	-0.469	0.000	1.999	0.340	2.9412	-2.469	99.66	4.642	4.636	0.005
0.54	2	1.414	-0.268	0.301	1.998	0.270	1.8519	-2.268	99.46	4.642	4.633	0.008
1.26	3	1.732	0.100	0.477	1.994	0.420	0.7937	-1.900	98.74	4.642	4.622	0.020
2.22	4	2.000	0.346	0.602	1.990	0.555	0.4505	-1.654	97.78	4.642	4.607	0.035
3.05	5	2.236	0.484	0.699	1.987	0.610	0.3279	-1.516	96.95	4.642	4.594	0.048
18.41	6	2.449	1.265	0.778	1.912	3.068	0.0543	-0.735	81.59	4.642	4.337	0.304
48.69	8	2.828	1.687	0.903	1.710	6.086	0.0205	-0.313	51.31	4.642	3.716	0.926
72.34	10	3.162	1.859	1.000	1.442	7.234	0.0138	-0.141	27.66	4.642	3.024	1.617
98.69	12	3.464	1.994	1.079	0.117	8.224	0.0101	-0.006	1.31	4.642	1.094	3.547



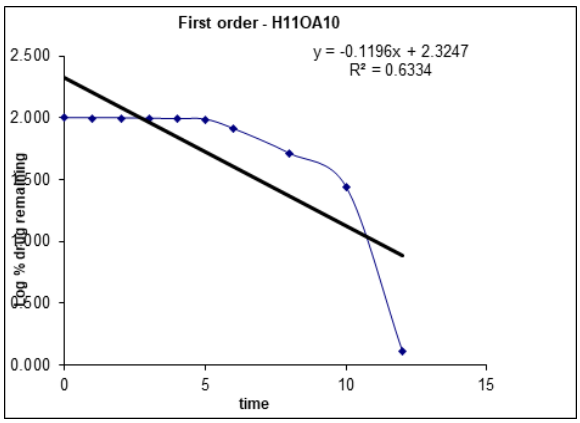
Zero order release kinetics graph



Higuchi release kinetics graph



Kars mayer peppas graph



First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed zero order kinetics.

6. CONCLUSION

In the present research work colon specific, basalazide sustained release matrix formulations were developed with various polymers.pH-independent drug release of Balsalazide was accomplished by the inclusion of pH modifying agents in formulations. A two step process was utilized to prepare the Colon targeted tablets. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers like Eudragit RLPO and S100 and Ethyl cellulose. The physical blend of all formulations were assessed for various flow properties and all the formulations were in accepted limits. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests.F6 formulation was found to be optimized among all the developed formulations as it decelerted the drug release up to 12 hours and disclosed a maximum of 98.45% drug release. It followed zero order kinetics mechanism.

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