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FORMULATION AND EVALUATION OF COLON TARGETED CONTROLLED DRUG DELIVERY SYSTEM FOR BALSALAZIDE DISODIUM

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ABSTRACT

In the present research work controlled release matrix formulation of balsalazide disodium targeted to colon by using various polymers developed. Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction with pH-dependent solubility. To achieve pH independent drug release of Balsalazide Disodium, 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 L100 and S100 were used as enteric coating polymers. The precompression 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 F3 formulation was found to be optimized as it was retarded the drug release up to 24 hours and showed maximum of 99.25% drug release. It followed zero order kinetics mechanism.

KEYWORDS: Balsalazide disodium, Controlled Drug Delivery System, Eudragit L 100 and S 100.

INTRODUCTION

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). Targeted drug delivery into the

colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. 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 colo.[1-2] The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction.[3-4] It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.[5-6]

These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine.

Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a presolubilized form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug.

Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.[7]

Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5-aminosalicylic acid to the colon.

The aim of the present research work was to develop sustained release matrix formulation of Balsalazide Disodium targeted to colon by using various polymers. Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction with pH-dependent solubility. To achieve pH independent drug release of Balsalazide Disodium, pH modifying agents (buffering agents) were used. Balsalazide Disodium matrix tablets containing several retarding agents, were used in order to extend the release of drug over the desired period of time.

MATERIALS AND METHODS

Materials

Balsalazide Disodium was received as a gift sample from Caplin Point Research Laboratory. Ethyl Cellulose, Eudragit S100, Eudragit L100 and MCC pH-102 was gifted by FMC Bio-polymer (India). Croscarmellose sodium and Cross povidone was gifted by Chetan & Chetan (India). Purified Talc, Sodium starch glycolate and magnesium stearate was gifted by Cabot Sanmer (India).

Spectral Identification[8]

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by IR spectrometry.

The results are shown in Figure. No: 2-5.

Preformulation Studies[9-10]

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

Hence, the following preformulation studies were performed on the obtained sample of drug.

I. Organoleptic characters

II. Physical properties

1. Bulk Density (Db)
2. Tapped Density (Dt)
3. Angle of Repose (θ)
4. Hausner ratio
5. Carr's index (or) % compressibility
6. Hausner ratio

The results are shown in Table. no: 5

Formulation of core tablet

The core tablets are formulated by using 15mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in below table1.

Table. No: 1 Composition of core tablet.

Ingredient name	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ingredient	**mg/tablet**								
Balsalazide Disodium	793.30	793.30	793.30	793.30	793.30	793.30	793.30	793.30	793.30
Sodium starch glycolate	15	15	15	15	15	15	15	15	15
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
MCC pH-102	37.7	37.7	37.7	37.7	37.7	37.7	37.7	37.7	37.7
Total weight	850	850	850	850	850	850	850	850	850

Total weight of core tablet was fixed as 850 mg. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudrait L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below Table. No: 2

Table 2: Formulation of various batches of Balsalazide Disodium tablets.

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient	**mg/tablet**								
Ethyl cellulose	50	100	150	-	-	-	-	-	-
Eudragit S100	-	-	-	50	100	150	-	-	-
Eudragit L100	-	-	-	-	-	-	50	100	150
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC pH-102	194	144	94	194	144	94	194	144	94
Total weight	1100	1100	1100	1100	1100	1100	1100	1100	1100

Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed and prepared compression coated tablets are evaluated for various post comparameters.

Evaluation of post compression parameters for prepared Tablets[11-14]

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100.

Average weight of a tablet	Percentage deviation
130 mg or less	± 10
>130 mg and <324 mg	± 7.5
324mg or more	± 5

The results are shown in Table. No: 6.

b) Tablet Dimensions

Thickness and diameter were measured using calibrated Vernier calipers. Five tablets of each formulation were picked randomly and thickness and diameter was measured individually. The results are shown in Table. No: 6.

c) Thickness

The thickness of the tablets was determined by Vernier calipers. Five tablets from each batch were used and the average values were calculated. The results are shown in Table. No: 8.

d) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Five tablets were randomly picked and hardness of the tablets was determined. The results are shown in Table. No: 6.

e) Friability test

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Wt) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100revolutions. The tablets were weighed again (WF). The % friability was then calculated by-

$$\%F = \frac{W\ (initial) - W\ (final)}{W\ (initial)} \times 100$$

The results are shown in Table. No: 6.

f) Disintegration test

The disintegration time for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 20 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

The results are shown in Table. No: 6.

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Balsalazide Disodium were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Drug release studies of Balsalazide Disodium core tablets

The core tablets containing 793.30 mg Balsalazide Disodium of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 344 nm.

Drug release studies of Compression coated

Balsalazide Disodium tablets

The release of Balsalazide Disodium from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5°C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated 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 (SIF, 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 (SIF, pH 6.8) was used upto 24 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Balsalazide Disodium tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 344 nm respectively. All dissolution runs were performed for six

batches. The results were given with deviation. The results are shown in Table. No: 7 and Figure. no: 6

Kinetic Modeling

Zero Order Kinetics[15-16]

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$$Q_t = Q_o + k_o t$$

Where, Q_t = amount of drug released in time't', Q_o = initial amount of drug in the solution, k_t = zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

First Order Kinetics[17-18]

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman. The following relation can express this model:

$$\text{Log } Q_t = \text{Log } Q_o + k_t t/2.303$$

Where, Q_t = amount of drug released in time't', Q_o = initial amount of drug in the solution, k_t = first order release constant.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amounts of drug released by unit of time diminish.

Higuchi Model[19]

Higuchi developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$f_t = k_H t^{1/2}$$

Where, k_H = Higuchi diffusion constant, f_t = fraction of drug dissolved in time't'.

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer-Peppas Model

Korsmeyer developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t);

$$f_t = at^n$$

Where, **a** = constant incorporating structural and geometric characteristics of the drug dosage form, **n** = release exponent, $f_t = M_t/M_\infty$ = fraction release of drug.

The results are shown in Table. No: 8.

Stability studies[20-22]

It is very essential that any product developed in the formulation department should be stable. The regulatory agencies in different countries try to ensure that the stability studies are carried out on the product. The formulation is subjected to accelerated stability conditions ($40^0C \pm 2^0C$/75% RH ±5%). The effects of temperature and time on the physical and chemical characteristics of the tablet were evaluated for assessing the stability of the formulated tablets. The results indicate that there wasn't any significant change in hardness & % drug content. There is a significant weight gain and increased wetting time. Disintegration and in vitro drug release was found to be increased a little more at 40^0C temperature. No significant change was observed in drug content.

The international Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements.

Table. No: 3: ICH guidelines for stability study.

Study	Storage condition	Time period
Long term	$25^0C \pm 2^0C$/60%RH±5RH (or) $30^0C \pm 2^0C$/65%RH±5%RH	12 month
Intermediate	$30^0C \pm 2^0C$/65%RH±5%RH	6 month
Accelerated	$40^0C \pm 2^0C$/75%RH±5%RH	6month

The results are shown in Table. No:9.

RESULT AND DISCUSSION

The present study was aimed to developing compression coated balsalazide disodium formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analysis of drug

Spectrophotometric analysis

λ max of drug was found to be 344nm.

Table. No 4: Standard curve of Balsalazide disodium.

Sr.No.	Conc. (µg/ml)	UV absorbance
1	0	0
2	1	0.105
3	2	0.210
4	3	0.302
5	4	0.420
6	5	0.511
7	6	0.602
8	7	0.721
9	8	0.811
10	9	0.902
11	10	1.050

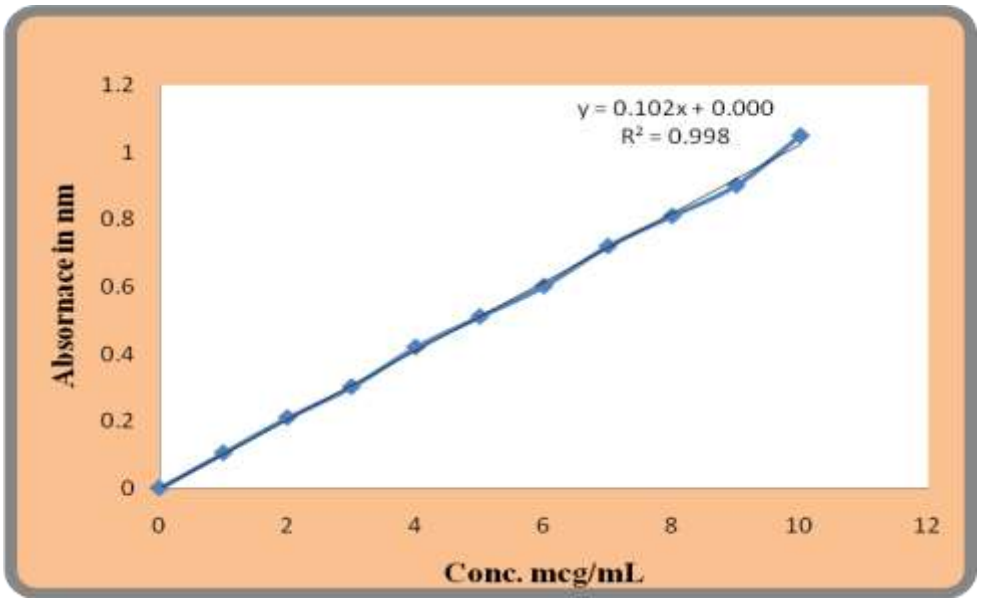

Fig no 1: Calibration curve of balsalazide disodium Infra-Red Spectrophotometric analysis.

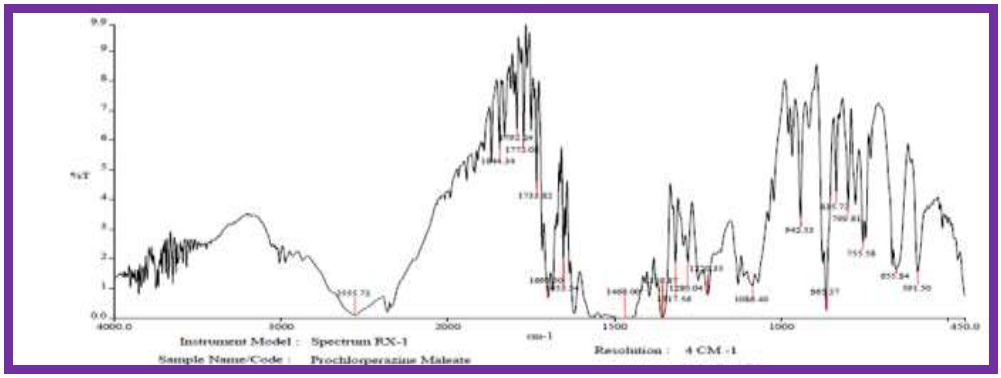

Fig no 2: IR Spectra of drug (balsalazide disodium).

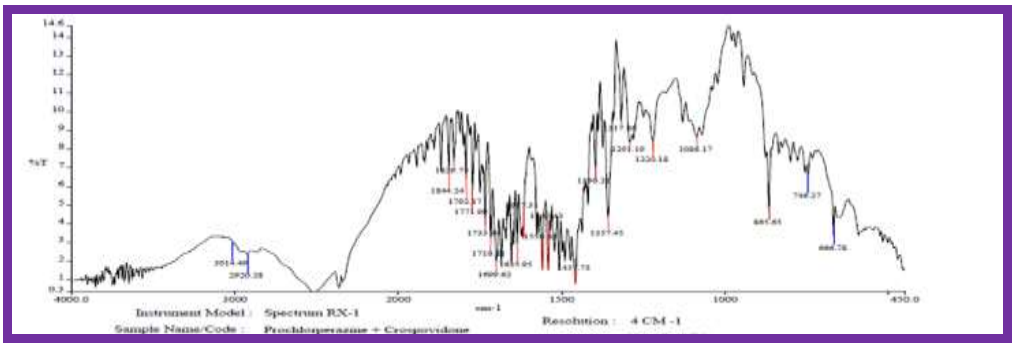

Fig no 3: IR Spectra of drug (balsalazide disodium +Ethyl Cellulose).

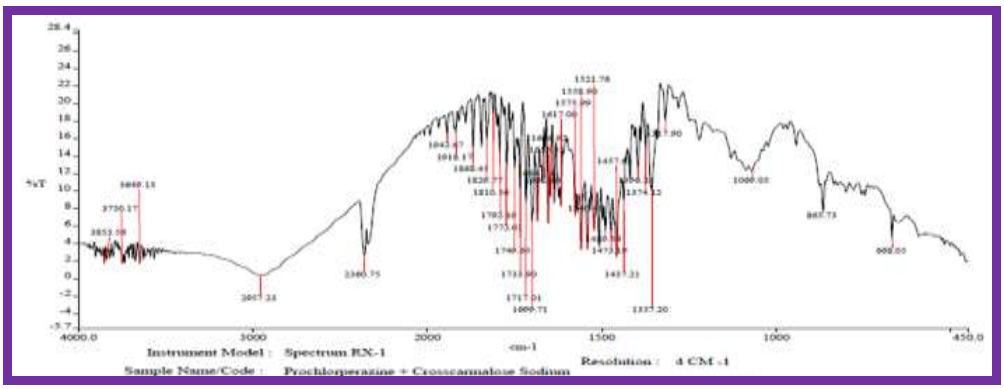

Fig no 4: IR Spectra of drug (balsalazide disodium +Eudragit S 100).

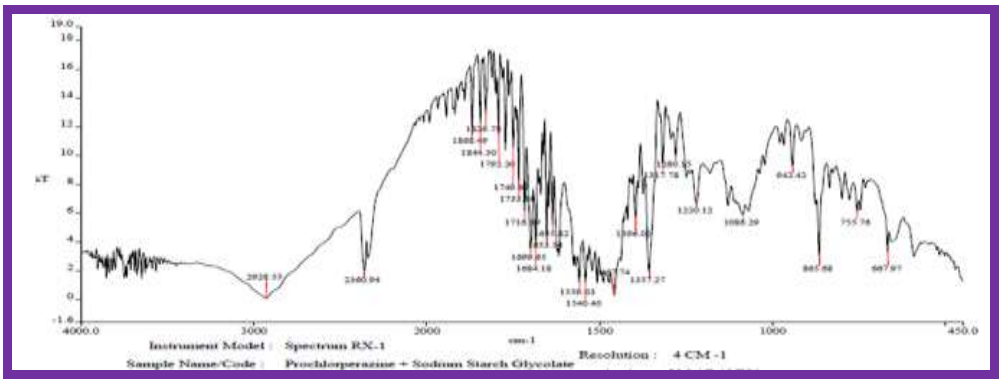

Fig no 5: IR Spectra of drug (balsalazide disodium +Eudragit L 100).

Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR studies revealed that was compatible with all the excipients used in the formulation F3. There were no changes in the functional groups present in the drug and it indicated that all the polymers, diluents and lubricants used in the formulation are compatible with balsalazide disodium.

Evaluation of Blend

Table. No 5: Evaluation of Blend.

Batch Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose(ɵ)	Carr's index(%)	Hausner ratio
F1	0.581	0.672	29°.77'	13.431	1.155
F2	0.410	0.472	29°. 21'	15.122	1.151
F3	0.396	0.459	32°. 11'	13.725	1.159
F4	0.393	0.462	33°. 29'	14.935	1.176
F5	0.382	0.458	32°. 18'	16.594	1.199
F6	0.388	0.471	31°. 34'	17.622	1.214
F7	0.410	0.492	33°. 38'	16.667	1.200
F8	0.391	0.479	31°. 49'	18.372	1.225
F9	0.421	0.477	29°. 17'	11.740	1.133

*Average of three determinations.

Evaluation of Physical Parameters of the FDT Formulations

Table. No: 6:-Evaluation Parameters of Batch F1 TO F9.

Formulations	Weight Variation (mg)*	Thickness (mm)*	Friability (%)*	Hardness (N)	Drug Content*
F1	1108±3	6.7±0.2	0.2	160±9	101.12 ± 1.6
F2	1120.5±2	7.0±0.2	0.04	150±5	101.89 ± 2.1
F3	1102.7±3	7.0±0.3	0.05	130± 8	100.56 ± 1.8
F4	1114.2±5	7.0±0.3	0.03	100± 10	99.13 ± 2.2
F5	1098±3	7.0-7.10	0.028	150± 10	102.14 ± 1.9
F6	1110±5	6.9±0.3	0.028	130± 9	98.38 ± 2.6
F7	1106±3	6.9±0.2	0.01	120± 8	97.08 ± 2.9
F8	1103±3	6.7±0.2	0.02	160± 9	97.67 ± 2.5
F9	1101±5	6.9±0.1	0.06	130± 5	99.14 ± 1.8

*Average of three determinations.

Table. no: 7 The *in vitro* drug release profile for coated formulation (F1-F9).

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	1.5	1.02	0.34	2.5	2.12	1.23	9.56	5.62	3.65
2	7.54	6.54	0.56	12.25	10.12	7.64	15.26	9.54	6.58

3	12.25	10.25	0.78	17.25	15.65	12.36	19.56	11.25	8.78
4	15.36	12.24	1.89	25.23	22.23	18.26	34.54	29.58	15.56
5	17.25	15.65	3.15	49.56	45.26	37.46	48.56	39.56	39.36
6	25.23	21.26	19.52	60.26	51.26	41.57	68.51	57.48	48.56
8	69.63	56.25	54.3	79.23	69.65	63.25	88.78	64.56	59.36
12	92.53	89.56	84.65	98.65	91.25	76.52	99.54	87.54	68.65
18	99.50	98.89	90.56	-	92.32	87.56	-	92.25	78.41
24	-	-	99.25	-	94.56	91.56	-	93.25	82.25

*Mean ± SD, n=3.

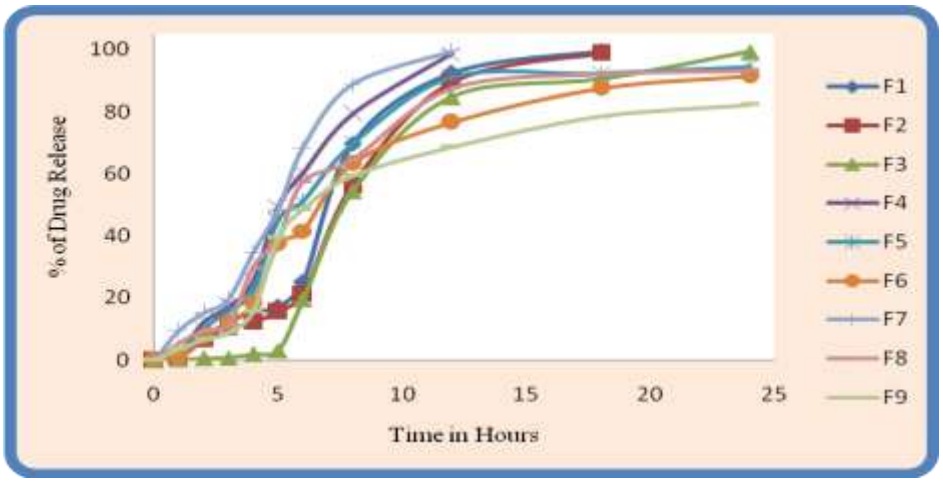

Fig.no: 6 The *In Vitro* drug release profile for coated formulation (F1-F9).

Table. No: 8. Values of R^2, k and n for formulations.

Formulation	Higuchi		Korsmeyer–Peppas		Mechanism of drug release
	R 2	k (h -1/2)	R 2	n	
F1	0.8345	19.362	0.1633	0.1151	Predominantly Higuchi
F2	0.867	20.225	0.1803	0.1455	Predominantly Higuchi
F3	0.9924	20.405	0.1494	0.1947	Predominantly Higuchi
F4	0.9696	20.155	0.1548	0.1589	Predominantly Higuchi
F5	0.9242	19.450	0.1456	0.1455	Predominantly Higuchi
F6	0.9406	18.945	0.1327	0.155	Predominantly Higuchi
F7	0.8615	16.626	0.0928	0.1563	Predominantly Higuchi
F8	0.7836	12.895	0.0029	0.0128	Predominantly Higuchi
F9	0.951	20.417	0.1691	0.1586	Predominantly Higuchi

The R2, k and n values are given in Table 8. All Formulations provided good fit to the Higuchi model. According to this model, the drug release from these tablets may be controlled by diffusion. From the above result it was evident that the formulation F3 followed zero order kinetics.

Table. no: 9. Stability data's of optimized formulation F3.

S. No	Parameter	Initial	First month	Second month	Third month
1	Appearance	No changes	No changes	No changes	No changes
2	Weight Variation (mg)*	1102.7±3	1102.5±3	1102.1±3	1101±3
3	Thickness (mm)*	7.0±0.3	7.0±0.3	7.0±0.3	6.9±0.3
4	Friability (%)*	0.05	0.14	0.11	0.10
5	Hardness (N)	130± 8	129± 8	128±7	128.12±7
6	Drug Content*	100.56 ± 1.8	100.24 ± 1.7	100.19 ± 1.4	100.10 ± 1.1

*Average of three determinations.

CONCLUSION

As per flow ability scale, the drug has good characteristics to flow. The excipients did not make any effect on the flow of blend. Thus it was decided to use direct compression method.

CONCLUSION

Systematic study was carried involving preparation and evaluation of Colon targeted oral drug delivery system for balsalazide disodium using release retarding polymers, such as Ethyl cellolose, Eudragit L-100 and Eudragit S-100. Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule and 4-aminobenzoyl-β-alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5-aminosalicylic acid to the colon. Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction with pH-dependent solubility. To achieve pH independent drug release of Balsalazide Disodium, pH modifying 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 L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were found to be in limits, which indicates free flow. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques, which were found to be in limits. Among all the formulations, F3 formulation was found to be optimized as it retarded the drug release up to 24 hours and showed maximum of 99.25% drug release. From the above investigation it was observed that formulation F3 was found to be best among the prepared formulations which may be used for prolong drug release in colon for, thereby improving patient compliance and bioavailability.

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