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FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLET OF AZATHIOPRINE

Kadam Sagar*, Abnave Dattatray, Landge Dhananjay

Hon. Shri. Babanrao Pachpute Vichardhara Trust's, Group of Institutions, College of Pharmacy, Kashti, Ahmednagar, Maharashtra, India.

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ABSTRACT

The aim of the current work was to formulate as well as evaluate colon targeted matrix tablet using Azathioprine. Excipients include Eudragit S100, Microcrystalline cellulose, Lactose, Talc, Magnesium stearate. Quantities of the excipients were chosen by carrying out FT-IR method. Preformulation studies were performed so as to study the nature as well as compatibility of Active Pharmaceutical Ingredient with that of the excipients by physical observations along with FT-IR studies. The tablets were processed by direct compression method making use of the selected excipient quantities. Pre-compression parameters like tapped density, bulk density, Hauser's ratio, compressibility index, and compressibility index. The formulated Azathioprine matrix tablets were coated using pan coating method with enteric polymer Eudragit S 100. The final tablets were evaluated for weight variation, thickness, hardness, and drug content, friability and disintegration time and in-vitro dissolution studies. Cumulative percentage drug release found to be 64.24 % (lowest) for F1 to 97.66 (highest) for F9 up to 8 hr**.** as the sustained release is main aim, formulation F1 was selected a optimized formulation. Formulation F1 containing enteric coated matrix tablet of Azathioprine would be a promising formulation that will aid in achieving the purpose of treating inflammatory bowel diseases (ulcerative colitis) without any gastric irritation or ulcers, which is useful for patients having prehistory of ulcerative colitis.

Corresponding author
Kadam Sagar
Hon. Shri. Babanrao Pachpute Vichardhara Trust's,
Group of Institutions, College of Pharmacy,
Kashti- 414701, Ahmednagar,
Maharashtra, India
vsk.vision11@gmail.com
9422231111

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INTRODUCTION

The aim of a targeted drug delivery system is mainly to provide a desired drug concentration in the body by delivering to a target site, a specific therapeutic amount of drug. It is required for the drugs which have low solubility, instability, short half-life, poor absorption, a large volume of distribution, low specificity. Targeting might provide maximum therapeutic activity (which is done by preventing degradation or inactivation of drug). On the other hand, it will minimize adverse effects and also the toxicity of potent drugs by reducing dose [1]. From last few decades, there has been tremendous increased interest in area development of oral colon targeted drug delivery systems (CTDDS) also for treatment of local colonic disorders. CTDDS would be of great advantage in cases when a delay in absorption is required from a therapeutic point of view for e.g. for the treatment of diseases that are having major symptoms in the morning and that show circadian rhythm, like angina, nocturnal asthma, rheumatoid arthritis[2]. Colon targeted drug delivery can also be achieved by oral administration or rectal administration. In case for the manufacturing of dosage forms exhibiting controlled release, by including retardant material, direct compression of blend of drug, additives which would formulate a tablet. In this tablet the drug is inserted in matrix of the retardant, it is complex approach [3]. A drug along with retardant blend can be granulated before compression. There are numerous polymers that may be used in preparing matrix tablets which depends on the physicochemical properties of the drug to be incorporated in matrix system and also the required type of drug release. Example. Poly-hydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Polylactic acid (PLA), Polyethylene glycol (PEG), Polyglycolic acid (PGA), Sodium Carboxymethyl cellulose, Polyacrylic acid[4].

For drug diffusion the drug should be exposed to the bathing solution, and then dissolved in it. Interface existing between the drug (solid) and the bathing solution continuously moves toward the interior. It follows that for this system to be controlled by diffusion, the rate of dissolution of drug particles in the matrix should be much quicker than the diffusion rate of drug dissolution in the matrix. The objective of current study was to develop a colon targeted drug delivery system of Azathioprine used in the treatment of Ulcerative Colitis[5,6]. Azathioprine is pro-drug, its conversion takes place in the body into the active metabolite 6-mercaptopurine. It belongs to chemotherapy drug, but now it is rarely used for chemotherapy and more for immunosuppressant during organ transplantation, autoimune disease like rheumatoid arthritis, inflammatory bowel disease, Crohn's disease. It inhibit purine synthesis required for proliferation of cells, specially leukocytes and lymphocytes [7].

MATERIALS AND METHODS:

Azathioprine is a Gift Sample received from Glaxo Smithkline Pharmaceuticals ltd., Mumbai. Anhydrous lactose, Anhydrous lactose, Microcrystalline cellulose (Avicel pH 112), HPMC E-5 (Hypromellose E-5), Eudragit S-100, Magnesium stearate, Talc etc. this material are supplied from Thermocil Fine Chem ltd, Pune.

1.1 Preformulation Studies:

A) Physical Characterization

Pure drug was evaluated for physical properties such as appearance, odour, color, solubility, melting point.

B) Micromeritic properties of core blend

a) Angle of repose:

It is determined by funnel method. The funnel is fixed at a particular height (2.5 cm) on a burette stand. The sample powder was allowed to pass through the funnel allowing it to form a pile. This area is encircled to measure radius. This similar procedure is repeated 3 times and the average value all 3 observation is taken. The angle of repose can be calculated by using equation.

$$\textbf{Angle of Repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where, h = height of pile, θ = angle of repose, r = radius of the base of the powder pile.

b) Bulk density determination:

Accurately weighed quantity of the powder (W) is taken in a measuring cylinder and volume (V0) is measured, Bulk density is calculated using the formula

Bulk density = Weight of the powder/ Volume of powder

c) Tapped density determination:

Accurately weighed quantity of powder (W) is taken in a measuring cylinder and the volume occupied by powder is measured. The cylinder is fixed in 'Tapped Densitometer' and is tapped for 500, 750 and 1250 times til the difference in the volume after successive tapping was less than 2%. The final reading was denoted by (Vf).

Tapped density = W/Vf g/ml

d) Carr's Index:

Carr's index is fast and popular method of predicting powder flow characteristics.

Carr's index was calculated using the formula:

$$Carr's\ index = \frac{(\text{Tapped Density} - \text{Bulk Density}))}{Tapped\ Density} \times 100$$

e) Hausner ratio:

Hausner ratio specifies the flow properties of the powder and measured by the ratio of tapped density to bulk density. Hausner ratio was calculated by using the formula.

$$\text{Hausner Ratio} = {}^{\text{Tapped density}}/_{\text{Bulk density}}$$

f) Compressibility Index (% Compressibility):

% compressibility specifies the flow property of powder and packing ability of tablet. It can be determined by measuring both the bulk and tapped density of a powder.

Compressibility Index can be calculated using equation:

$$\text{CI (\%)} = [(Dt - Db)/Dt] \times 100$$

Where, Db = bulk density, and Dt = tapped density.

g) Drug excipient interaction studies (FT-IR):

It provides accountable spectral data for any change in the functional group characteristics of a given drug molecule duing in the process of formulation.IR spectra of Azathioprine and its formulation were obtained by KBr pellet method using Perkin Elmer spectrum RX1 FT-IR spectrophotometer model.

1.2 Preparation of tablets:

a) Preparation of Tablets by direct compression:

Azathioprine, Microcrystalline cellulose, Lactose anhydrous, Sodium starch glycolate and HPMC were weighed and sifted individually through 40 # mesh. All the ingredients were transferred to poly bag and mixed for 10 min and blend was passed through 40 # mesh and mixed thoroughly. Magnesium stearate used as a lubricant was weighed, added and blended with the ingredients for 5 min. The mixture was compressed and film coated with coating solution.

Table No. I: Composition of core tablet.

Sr. No.	Ingredient Name	Quantity (mg)
1	Azathioprine	50
2	Cellulose Microcrystalline	15
3	HPMC E5	5
4	Talc	5
5	Magnesium stearate	5
6	Lactose anhydrous	20
Total Weight		**100**

1.3 Evaluation Parameters:

a) General Appearance and Organoleptic Properties

It includes evaluation of shape, size, taste, presence of an odor, physical flaws, color, consistency, surface texture, legibility of any recognizable markings are checked.

b) Shape, Thickness and Dimension

Six tablets from every batch were selected, measured for thickness as well as diameter using digital Vernier calipers.

c) Weight variation test:

Twenty tablets were weighed and then average weight and individual weight of each tablet was calculated. Standard deviation was calculated.

d) Hardness test:

To determine the hardness of tablet, scale of Monsanto tester was adjusted to 0 mark ; load was slowly increased til the tablet fractured.

e) Friability test:

20 tablets subjected to friability testing using Roche Friabilator and kept for 100 revolutions. After that tablets were removed, and de-dusted and weighed again. It is calculated by using formula:

$$\textbf{Friability (\%) = Initial weight } (W_0) \textbf{- Final weight} (W_1) \textbf{ / Initial weight } (W_0) \textbf{ x100}$$

f) Disintegration time:

The Disintegration test was done for six tablets using Tablet disintegration tester. Distilled water at temperature 37ºC ± 2ºC was employed as a disintegration medium for test and the time taken by tablet for complete disintegration of the formulated tablet in the apparatus was counted in seconds.

g) Dissolution Studies:

Drug release studies of the formulated Azathioprine tablets were performed in type- II USP Dissolution Tester Apparatus, (Paddle method) at 37 ± 0.5^0C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 ml of Deaerated water. Sample aliquots (10 ml) were taken from the dissolution apparatus at diverse time intervals. After sample withdrawal, equal amount of fresh medium was added into the dissolution flask.

h) Content Uniformity

The content uniformity test was used to ensure that each formulated tablet contains the acceptable amount of drug substance and posses very little variation among tablets within a batch.

Method:

Select 30 tablets randomly. 10 of these tablets were assayed individually. Tablet passes the content uniformity test if nine of the ten tablets must contain not less than 85% and not more than 115% of the labeled drug content and the less content for 10th tablet should not be less than 75% and not more than 125% of the that of labeled content. If first set of tablet fails to meet these conditions, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

1.4 Release kinetics:

Zero order, Higuchi, first order, Korsmeyers-Peppas models were used to characterize drug dissolution / release profile.

a) Zero-order kinetics:

A zero-order release would be predicted by the following equation.

$$\textbf{At = Ao – Kot}$$

Where, At is Drug release at time t, Ao is Initial drug concentration, Ko is Zero-order rate constant (hr). When this obtained data is plotted as cumulative % drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to ko.

b)First-order kinetics:

A first order release would be predicted by the following equation.

$$\textbf{Log C = Log Co - Kt / 2.303 eq (2)}$$

Where C is Amount of drug remained at time t, Co is Initial amount of drug, K is First-order rate constant. When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values.

c) Higuchi model:

Drug release from the matrix devices by diffusion has been described by following Higuchis classical diffusion equation.

$$\textbf{Q = [DE/ } \tau \textbf{(2A- ECs) Cst] eq(3)}$$

Where, Q is Amount of drug release at time t, D is Diffusion coefficient of the drug in the matrix
A is Total amount of drug in unit volume of matrix, Cs is Solubility of the drug in the matrix
E is Porosity of the matrix, T is Time in hrs at which q is the amount of drug is release.

d) Korsmeyer Peppas model:

To understand the release pattern of drug from swellable matrices, the data were fitted to the following equation

$$Mt / M\acute{a} = Ktn \quad eq (5)$$

Where, Mt / Mά is Fraction of drug released at time't'
K is constant which incorporates the structural and geometrical Characteristics of the drug/polymer system.
n is Diffusion exponent related to the mechanism of release.
The above equation can be simplified by applying log on both sides we get

$$Log\ Mt / M\acute{a} = Log\ K + n\ Log\ t \quad eq (6)$$

1.5 Stability Study:

Stability study comprise storage of dosage form at very high temperature conditions, with the required extrapolations to make sure that the product will, over its designed shelf life, provide medication with same absorption rate as originally formulated one. The tablets of the optimized formulation are tested for stability for 3 months in accelerated and long term test conditions. The tablets are exposed to $40^0 \pm 2^0$C and 75±5% RH conditions for 3 months. The tablets are observed for change in physical appearance, moisture content, assay values, impurities and dissolution values at the end of first, second and third month. Stability was determined.

RESULTS AND DISCUSSION:

2.1 Preformulation study:

Table No II: Results of physical characterization of the drug.

Sr. No.	Description	Result
1	Appearance	Pale yellow crystals or yellowish powder.
2	Odour	Characteristic odor.
3	Solubility	Insoluble in water, Very slightly soluble in ethanol and chloroform; sparingly soluble in dilute mineral acids; soluble in dilute alkali solutions
4	Melting point	243.5 °C

Table No III: Flow Properties of API.

Sr. No	Flow Properties	Result
1	Bulk density (g/ml)	0.298gm/ml
2	Tapped density (g/ml)	0.506gm/ml
3	Compressibility index (%)	13.14
4	Hausner's ratio	1.13
5	Angle of repose	31˚45'

The experimental work started with the Preformulation of raw material analysis of Azathioprine. The results of physical characterization of the drug like appearance, odor and solubility are given in Table No.II. The results show that physical characterization of the drug candidate (API) complies with the USP specifications. The flow properties of API such as bulk density the tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted in the Table no. III and the results were found to be satisfactory.

2.2 Drug and excipients compatibility studies:

The physical compatibility studies between drug and excipient were carried out at 55^0C for 2 weeks and at 40 ± 2^0C/70 ± 5% RH for 4 weeks. The results show that there is no change from the initial white color after 2 and 4 weeks indicating that there is no physical incompatibility. The FTIR spectrum of pure Azathioprine showed bands at 2919 for O-H stretch, 1594 for C=O stretching Carboxylic acids, 1075 for C-C stretch in ring aromatics, 1018 for C-O stretch Esters , 760 for C-H aromatic, 473 for =C-H bend Alkenes. The FTIR spectrum of prepared formulation indicates the absence of any interactions between Azathioprine and excipients in the formulation.

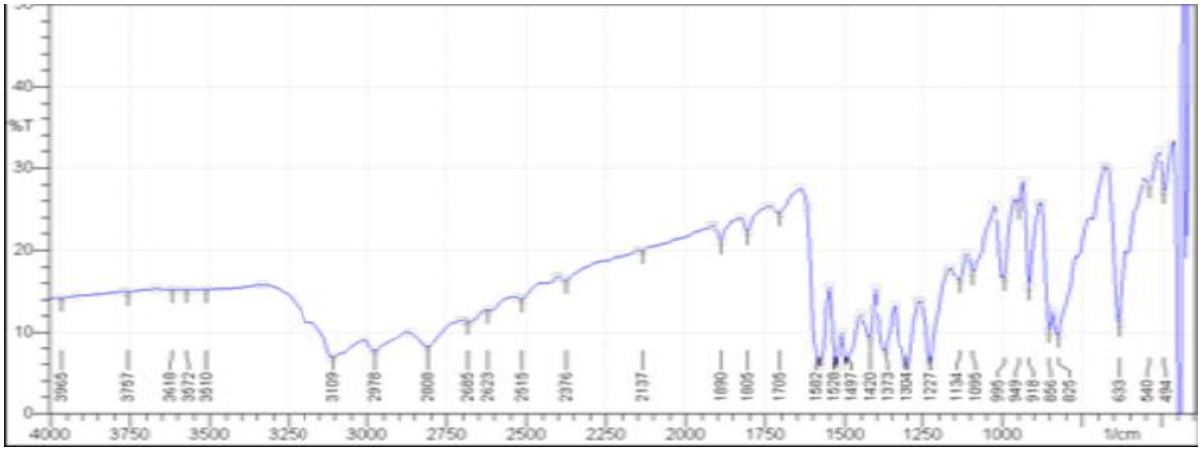

Figure No. 1: FTIR spectrum of Azathioprine.

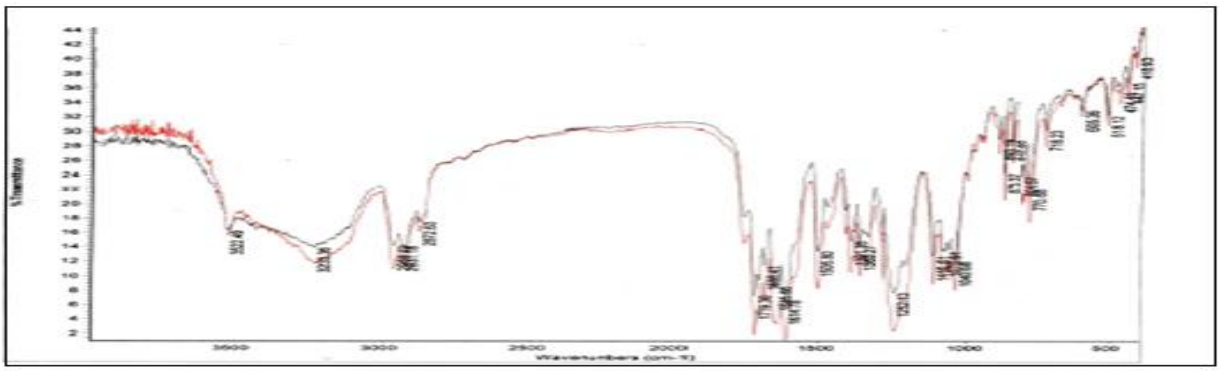

Figure No 2: FTIR spectrum of Azathioprine prepared formulation.

2.3 Flow properties of lubricated blend:

Table No. IV: Result for micromeritic study of core blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.12±0.03	0.564±0.01	0.666±0.03	15.31±0.01	0.846±0.06
F2	36.01±0.01	0.55±0.03	0.645±0.08	14.72±0.01	0.85±0.03
F3	32.74±0.08	0.53±0.06	0.606±0.06	14.19±0.03	0.858±0.06
F4	36.24±0.08	0.549±0.03	0.641±0.08	14.35±0.03	0.856±0.01
F5	34.8±0.03	0.57±0.01	0.66±0.03	13.63±0.06	0.86±0.04
F6	35.33±0.06	0.531±0.08	0.613±0.03	13.37±0.01	0.866±0.03
F7	37.08±0.04	0.581±0.03	0.671±0.01	13.41±0.08	0.865±0.07
F8	35.45±0.01	0.571±0.06	0.689±0.04	13.28±0.08	0.855±0.09
F9	35.12±0.03	0.567±0.01	0.654±0.08	13.12±0.06	0.845±0.08

The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. The results of angle of repose and compressibility index (%) ranged from 32.24±0.08 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. Carr's index (%) ranges from 13.12±0.06 to 15.31±0.01. Hausner's Ratio ranges from 0.845±0.08 to 0.866±0.03.

2.4 Preparation of tablets:

The tablets were prepared by direct compression. The tablets are prepared by using different excipients like diluents, binders and super disintegrants. Eudragit is used as release controlling polymer, while HPMC is used as binder. Cellulose microcrystalline is used as super disintegrants in the formulation.

2.5 Evaluation of tablets:

Table No V : Evaluation of Tablets.

Sr. No.	Batch code	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay %w/v	Disintegration (min)
1	F1	104±0.38	1.45±0.06	6.9±0.24	0.107±0.16	99.9	25 min4sec
2	F2	104.3±0.38	1.46±0.06	6.9±0.24	0.107±0.16	101.1	18min1sec
3	F3	104.7±0.25	1.48±0.025	6.8±0.18	0.173±0.04	99.9	17min38sec
4	F4	103.5±0.19	1.45±0.020	6.9±0.34	0.123±0.37	99.6	16min17sec
5	F5	103.6±0.17	1.45±0.12	6.8±0.15	0.18±0.43	100.1	15min 46sec
6	F6	103.8±0.42	1.46±0.036	6.8±0.16	0.14±0.016	99.8	15min13sec
7	F7	102.8±0.13	1.42±0.054	6.9±0.39	0.183±0.03	102.9	12 min55sec
8	F8	103.1±0.02	1.43±0.017	7.0±0.45	0.19±0.02	100.5	12min 53sec
9	F9	103.4±0.06	1.43±0.12	7.0±0.42	0.19±0.06	100.5	12min 23 sec

The film coated tablets are evaluated for weight variation, thickness, hardness, friability, disintegration time and assay values. The results were shown in Table No. V. The values are in the range of 102 to 104 mg for weight variation for formulations F1 to F9.Thickness and hardness values range from 1.42 to 1.48 mm and 6.8 to 7 kg/cm^2 respectively. Results are in the range of 0.10 to 0.19 for friability and 12 to 25 minutes for disintegration of tablets. Assay values are in the range of 99% to 101%.

2.6 In vitro dissolution studies:

Table No. VI: % Drug Release of Azathioprine from Formulations.

Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	0.26	0.34	1.51	4.37	2.39	2.61	4.37	5.72	8.06
2	0.44	0.54	5.67	18.68	17.88	21.71	10.5	15.84	20.94
3	4.65	1.26	25.6	26.46	30.45	30.41	31.33	24.37	30.26
4	17.87	22.22	38.7	31.55	40.59	46.7	48.8	46.84	45.44
5	29.18	34.05	43.74	40.82	55.01	52.37	60.8	68.9	63.86
6	35.45	48.41	51.8	47.6	73.85	71.64	74.23	73.84	72.93
7	61.04	50.05	59.4	50.73	83.34	80.73	87.15	89.95	90.23
8	64.24	70.97	65.9	69.65	91.92	91.4	92.8	95.96	97.66

From In –vitro dissolution study, Cumulative % drug release found to be 64.24 % (lowest) for F1 to 97.66 (highest) for F9 up to 8 hr**.**

2.7 Determination of release kinetics:

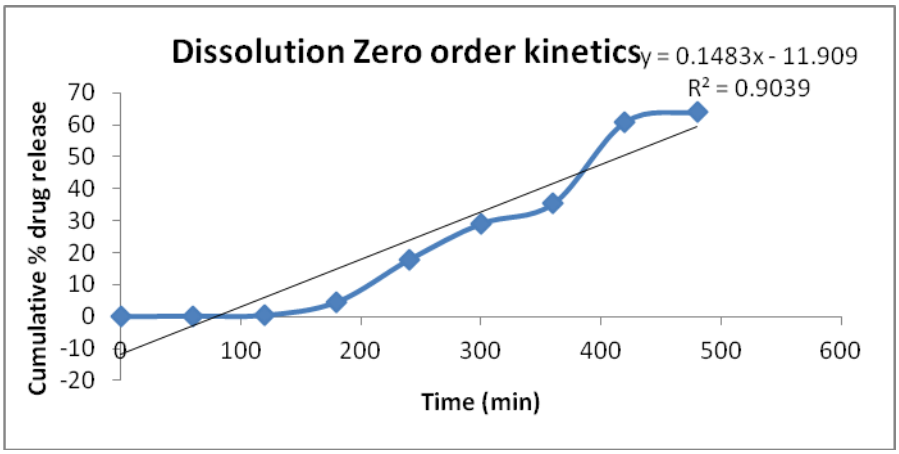

Figure No. 3: Formulation F1- Zero order kinetics.

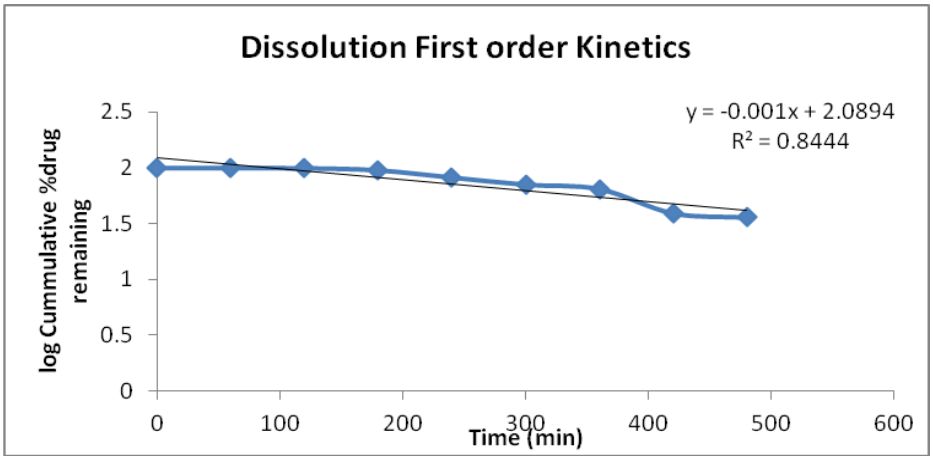

Figure No. 4: Formulation F1-First order kinetics.

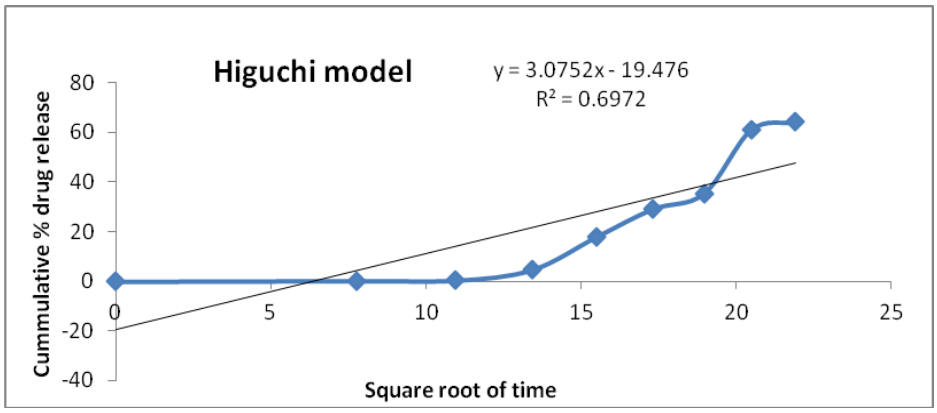

Figure No. 5: Formulation F1-Higuchi model.

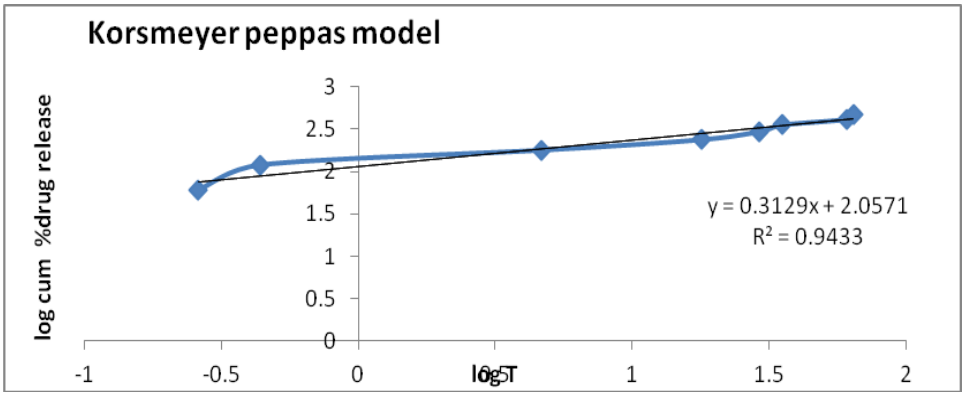

Figure No.6: Formulation F1-Korse Meyer Peppas mode.

Table No.VII: Dissolution model summary.

Model	Equation	R^2 value
Zero order kinetic	y = 0.1483x - 11.909	0.9039
First order kinetic	y = -0.001x + 2.0894	0.8444
Higuchi	y = 3.0752x - 19.476	0.6972
Korsmeyer Peppas	y = 0.3129x + 2.0571	0.9433

From the above summary, Formulation F1 shows highest R^2 value for Korsmeyer Peppas model, which indicate possible release mechanism of drug through matrix tablet**.**

2.8 Stability studies:

Stability studies were performed for the formulation F8. The stability study was performed at 40±2^{0}C /75±5 % RH for 1 to 3 months. These tablets were then analyzed for appearance, moisture content, drug content, impurities and in vitro drug release. The overall results showed that the formulation is stable by the end of 1st, 2nd and 3rd months.

Table No. VIII: Stability Study data (Accelerated) of Trial F – 08.

Sr. No.	Parameters	Specifications	Test Condition			
			40 ± 20C & 75 ± 5% RH(Accelerated)			
			Day-0	Month-1	Month-2	Month-3
1	Description	Light yellow colored, oblong shaped tablets	Complies	Complies	Complies	Complies
2	Moisture content	-	1.315	1.325	1.34	1.35
3	Assay	90-110	100.9	100.3	99.7	98.6
	Related substances by HPLC					
4	I. Unknown impurity	NMT 0.5	0.175	0.013	0.036	0.024
	II. Total impurity	NMT 2.0	0.188	0.503	0.577	0.781
5	Dissolution	NLT than 75% At 8 hr	63.3	61.7	60.3	59.8

2.9 Comparison between optimized batch and Innovator product:

The optimized batch F1 is compared with Immuring. The drug release profile of optimized batch and marketed product was observed to be 98.7% and 97.2% at the end of 45 minutes. Formulation F-1 has similar release profile to the Immuring release. The dissolution efficiency of all the formulations and innovator product are determined. The Dissolution Efficiency of optimized formulation is 64.24 % and that of the innovator is 79.97%.

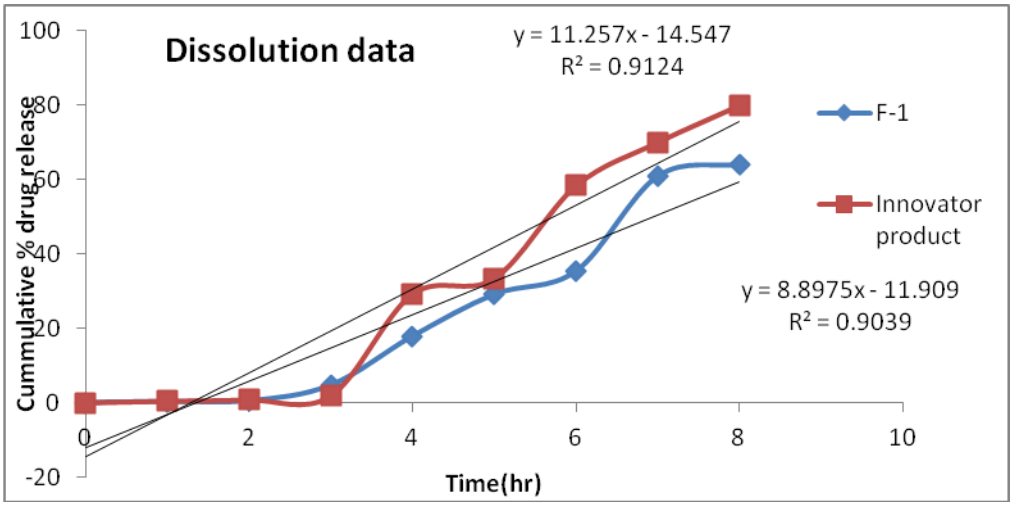

Figure No. 7 : Comparison of Dissolution data for F1 and Innovator product.

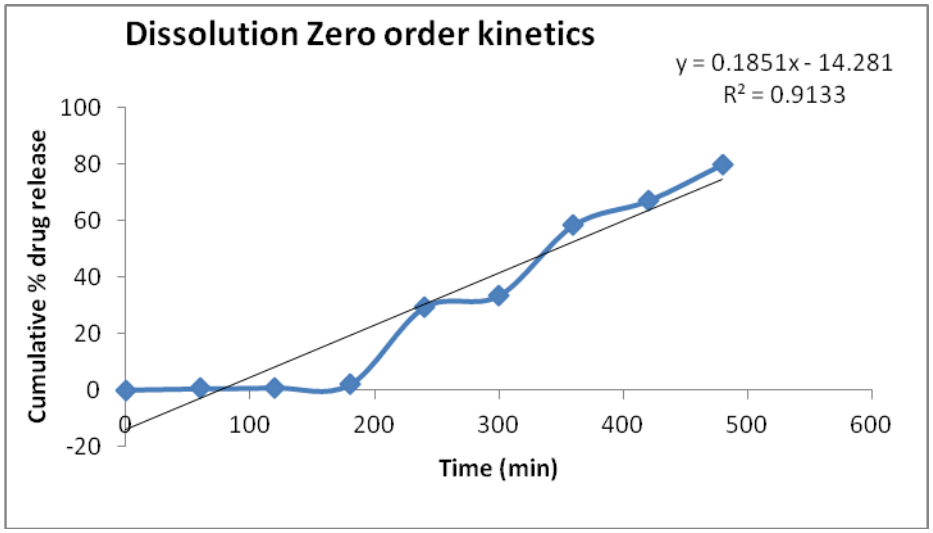

Figure No. 8: Dissolution zero order kinetics for innovator product.

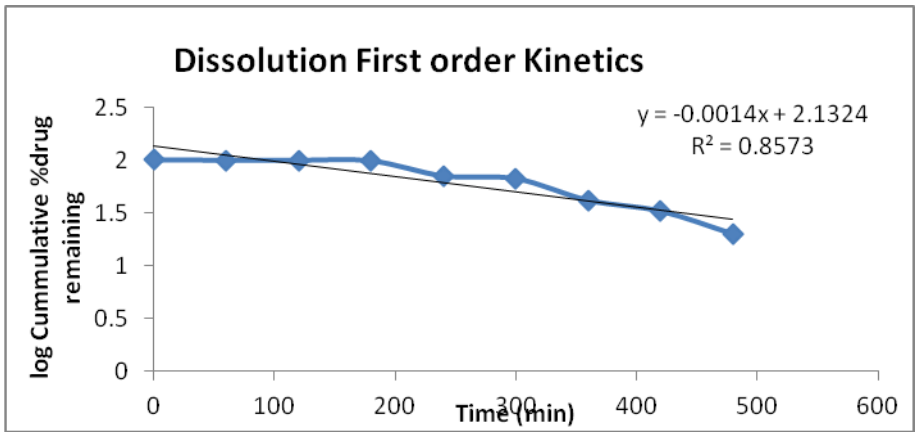

Figure No. 9: Dissolution first order kinetics for innovator product.

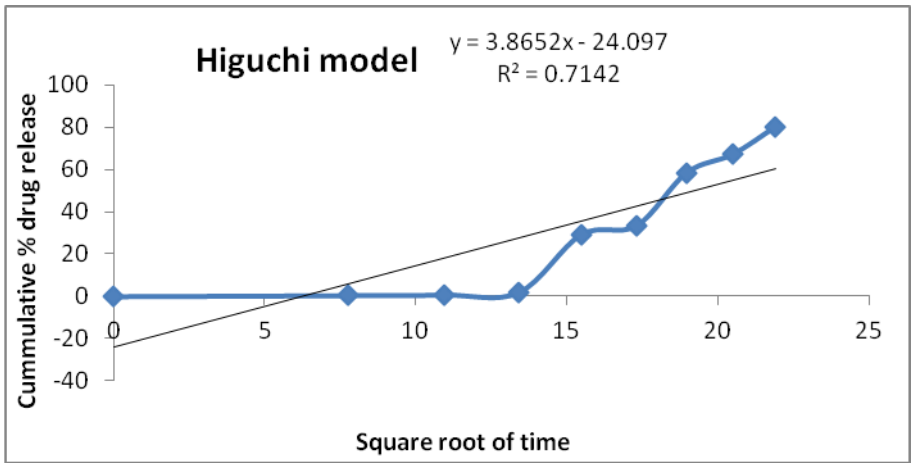

Figure No. 10: Dissolution Higuchi model for innovator product.

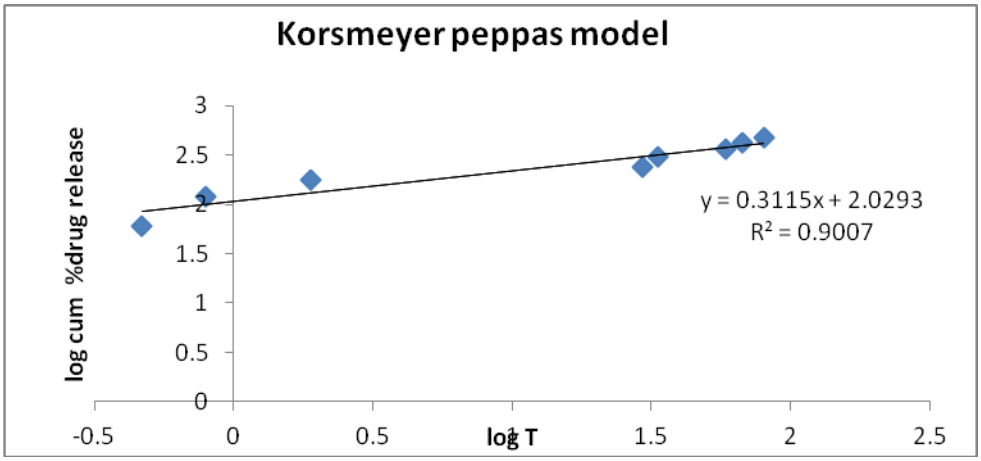

Figure No. 11: Dissolution Korsmeyer Peppas model for product.

Table No. IX: Comparison of release kinetics for Innovator product.

Model	R^2 value	
	Formulation F1	Marketed product
Zero order kinetic	0.9039	0.9133
First order kinetic	0.8444	0.8573
Higuchi	0.6972	0.7142
Korsmeyer Peppas	0.9433	0.9007

From the above table, it can be observed that innovator product follows zero order drug release, while optimized formulation F1 follows Korsmeyer-Peppas model.

CONCLUSION

The Azathioprine matrix tablets were formulated successfully by direct compression method making use of the selected excipient quantities. The final formulated tablets were evaluated for pre-compression and post-compression parameters as given in the requirements of standards and the results were complied with the pharmacopoeia specification. The formulated Azathioprine matrix tablets were coated with enteric polymer Eudragit S100 by pan coating method. From the entire batches, formulation F1 showed 64.24% drug release at 8 hrs. So the trial F1 was considered as best formulation as it provides sustained release. From the results obtained, it can be concluded that formulation F1which contained enteric coated matrix tablet of Azathioprine will be a promising formulation in order to achieve the purpose which treat inflammatory bowel diseases (ulcerative colitis) without any gastric irritation or ulcers, that is useful for patients having prehistory of ulcerative colitis.

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CONFLICT OF INTEREST

The authors declared that they have no any conflict of interest.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

LIST OF ABBREVIATIONS:

CTDDS : Colon targeted drug delivery system
PHEMA: Poly-hydroxyethylemethylacrylate
PVA : polyvinyl alcohol
PEG : Polyethylene glycol
PLA : Polylactic acid
PGA : Polyglycolic acid

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