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DESIGN, EVALUATION AND OPTIMIZATION OF SULFASALAZINE MINI TABLETS - A COLON SPECIFIC TARGETED DRUG DELIVERY

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ABSTRACT

The aim of present study was to formulate the colon targeted matrix mini-tablet of Sulfasalazine and to evaluate the formulation for various parameter to release the active ingredient after predetermine time in a predetermine location with better pharmaceutical and therapeutic properties. Sulfasalazine has anti-inflammatory, immunosuppressive, and antibiotic actions, the pharmacological effects of which are mainly attributed to its breakdown products sulfapyridine and 5-aminosalicylic acid. Sulfasalazine is a medication used to treat rheumatoid arthritis, ulcerative colitis, and Crohn's disease. It is considered by some to be a first-line treatment in rheumatoid arthritis. Sulfasalazine is used to treat ulcerative colitis (a condition which causes swelling and sores in the lining of the colon [large intestine] and rectum) and also to maintain improvement of ulcerative colitis symptoms. It has been developed as colon-specific delivery systems for the treatment of inflammatory bowel disease (IBD).

Keywords: Sulfasalazine, Evaluation, Anti-inflammatory.

INTRODUCTION

Sulfasalazine is a sulfapyridine derivative and for its colon-specific prolonged release activity [1] and to optimize its effectiveness, the following objectives are envisaged to be achieved in this proposed research is to formulate Sulfasalazine matrix mini-tablets and to coat with enteric polymer, to evaluate the formulated tablets as per requirements of IHS standards [2], to evaluate the most satisfactory formulation, to select the best formulation based on *in-vitro* studies for colon targeting and to perform stability studies on the most satisfactory formulation [3].

METHODOLOGY

Preformulation Studies

Preformulation is the first step in the rational development of dosage form of a substance and is defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. This initial learning phase is known as pre-formulation. The basic purpose of the pre-formulation activity is to provide a rational basis for the formulation approaches, to increase the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance.

Evaluation of API

The Evaluation of Sulfasalazine was done according to IP. Following are some of the important parameters evaluated during pre-formulation studies.

Description

It is the initial evaluation during pre-formulation studies which assess the colour of the substance. This was only a descriptive test.

Solubility

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy.

Melting point

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle start to melt and last particle completely melts is regarded as melting range. Melting point of Sulfasalazine was conducted as per monograph.

Loss on drying

The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. Loss on drying of Sulfasalazine was measured by using moisture balance.

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Weigh approximately 2gm of Sulfasalazine and placed into a plate of moisture balance. Set the temperature to 45°C.

Flow Properties (Angle of Repose)

Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. The angle of repose of the powder or granules was determined by fixed funnel method. To assess the flow property of the powder granules, the height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder or granules above a paper that was placed on a flat horizontal surface. Accurately weighed powder blend was taken in a beaker. It was allowed to flow through the funnel freely on the surface of the paper to form a cone shaped pile. The diameter of the cone (d) and the height (h) of the pile was noted. From the diameter, radius (r) was calculated. The angle of repose (θ) was calculated using the following formula [4].

$$\Theta = \tan -1(h/r)$$

Bulk density

Bulk density is a characteristic of a powder rather than individual particles and is given by the mass M, of the powder occupying a known volume, Vo. It is expressed in g/ml. An accurately weighed quantity of granules was transferred into a 50 ml measuring cylinder with the aid of the funnel. The unsettled apparent volume, to the nearest graduated unit occupied by the granules was measured. Bulk density was determined using the formula [5].

$$\rho bulk = m/Vo$$

Where,

ρbulk = Bulk density; m = Mass of the blend

Vo = Untapped Volume

Tapped density

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed. The measuring cylinder containing a weighed quantity of granules (after measurement of bulk density) was subjected to 500 taps in tapped density tester (Electro Lab USP II). The tapped density was calculated by using the formula [6].

$$\rho t = m/Vt$$

Where,

ρt = Tapped density; m = Mass of the granules

Vt = Final tapped volume.

Measurement of Powder Compressibility

Carr's compressibility index:

Compressibility index are a measure of the tendency for arch formation and the ease with which the arches will fail.

$$CI = \rho t - \rho bulk / \rho t \times 100$$

Where,

CI = Compressibility index; ρbulk = Bulk density

ρt = Tapped density

CARR'S COMPRESSIBILITY INDEX

Hausner's ratio

Hausner found that the ratio ρt / ρbulk was related to inter particle friction and, as such could be used to predict powder flow properties. He showed that powders with low inter particle friction, such as coarse spheres, had ratios of approximately 1.2; whereas more cohesive, less free flowing powders such as flakes have values greater than 1.6 [7].

$$\text{Hausner's Ratio} = \rho t / \rho bulk$$

Where,

ρbulk = Bulk density; ρt = Tapped density

Particle Size Analysis

Particle size distribution of the drug was estimated by sieving method. The sieves are stacked on top of one another in ascending degrees of coarseness. The test powder, for example 10gm, was placed on the top sieve. The nest of sieves was subjected to a standard period of agitation. The weight of material retained on each sieve was accurately determined.

Drug-Excipient Compatibility Studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the pre-formulation scientist must generate the needed information.

A. Physical observation

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a 2ml of cleaned and dried vial. This vial was kept for observation in stability chamber at 40oC ± 2oC / 75 ± 5% RH. Mixtures were also placed at 2- 8oC, 50oC and room temperature (Control). Physical observation has been carried out visually at the initial stage, after 15 days and after 1 month at 40oC ± 2oC / 75 ± 5% RH.

B. Chemical compatibility studies by FT- IR

Physical compatibility studies were assured by FT-IR studies. The pure drug sample, drug-excipient mixtures of the formulation were chosen for the study. The FT-IR spectra's of the above samples were studied after a period of 30 days from preparation of the mixtures, to facilitate prompt detection of incompatibility. The spectra's were obtained by preparing Potassium bromide pellets under dry

condition by using pellet press. The spectra of the pure drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems. If there are no changes in peaks of mixture when compared to pure drug, it indicates the absence of chemical interaction.

Evaluation of Powder Blend

The powder blends were evaluated for the following parameters before compression into tablets.

1. Angle of repose
2. Bulk density
3. Tapped density
4. Compressibility index and Hausner's ratio.
5. Moisture content.

Evaluation of Post-Compression Parameters

The compressed mini-tablets were evaluated for the following parameters.

General appearance

The mini-tablets should be free from cracks, depression, pinholes etc. the color and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth.

Hardness

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test81.Tablet hardness of all the formulations was measured using a Monsanto hardness tester.

Thickness

Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness, at constant compressive load, varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, whereas at constant die fill, thickness varies with variations in compressive load. Tablet thickness must be controlled within a ±5% variation of a standard value.

Friability

The laboratory friability tester is known as the Roche friabilator. This device subjects the tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that rotates at 25 rpm, dropping the tablets form a height of 6 inches with each revolution. Twenty tablets were weighed accurately and placed in the friabilator and was operated for 100 revolutions or 4 minutes. The tablets were then de dusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional uncoated tablets.

Disintegration Test

USP disintegration test specifies that one tablet is added to each of the six tubes in the USP disintegration apparatus. The apparatus is operated without disks, using simulated gastric fluid (pH 1.2) at 370C for 2 hrs. The tablets are then removed and must show no evidence of disintegration, cracking or softening. Disks are then added and the apparatus is operated using simulated intestinal fluid (pH 7.4) at 370C for a period of time limit specified in the monograph. The product passes the test if all tablets are disintegrated.

Weight Variation Test

Fifty mini-tablets were selected randomly and weighed individually. Calculate average weight and compare the individual mini-tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in and none deviate by more than twice the percentage.

***In-Vitro* Dissolution Studies**

The release rate of Sulfasalazine from capsule (mini-tablets) was determined using dissolution testing Apparatus I (basket method). The test was performed using 900ml of 0.1N HCl at 370 + 0.50C and 100 rpm for 2 hrs. Then replaced with 7.4 pH phosphate buffer and continued for 12 hrs. A liquot volume of 5ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. The drug release is determined from the absorbance of the sample and standard [8].

Stability Studies

Stability of a formulation can be defined as the time from the date of manufacture of the formulation until its chemical or biological activity is not less than a pre-determined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Formulation and the development of pharmaceutical products are not complete without proper stability analysis. It is carried out to assess the physical and chemical stability and safety use of the product. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with the time under the influence of a variety of environmental factors such as temperature, humidity, and light enabling recommended for storage conditions and shelf life. The ICH guideline recommends the following storage conditions for stability studies [9].

Accelerated stability studies

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. The International Conference of Harmonization (ICH) Guidelines titled "Stability testing for new drug substances and product" (Q1A) describes the stability test requirements for drug registration application in the European Union, and United States of America.

The accelerated stability was carry out by ICH guidelines.The formulation F6 was packed in high density polyethylene container and kept at 400C ± 20C and 75% ± 5% RH. Samples were analyzed for drug content and *in-vitro* dissolution studies in the intervals of 1, 2, 3 months.

RESULTS AND DISCUSSION

The present study was carried out to formulate colon targeted matrix mini-tablet of sulfasalazine using direct compression method. In this method, the powder blend was subjected to various evaluation studies such as bulk density, tapped density, compressibility index and Hausner's ratio and was compressed into mini-tablets. The compressed mini-tablets were evaluated such as thickness, hardness, friability, weight variation, assay, *in-vitro* dissolution studies, and accelerated stability studies. The tablets are coated using Enteric coating polymer (Eudragit FS30D) to target the release of pH 7.4. The uncoated and coated mini-tablets are evaluated for *in-vitro* dissolution studies and the mini-tablets were filled in capsule size "000" and sealed in HDPE (high density polyethylene) containers and were subjected to accelerated stability studies.

Table 1. Bulk Density and Tapped Density of Sulfasalazine

S. No	Raw material (API)	Bulk density (g/ml)	Average bulk density (g/ml)	Tapped density (g/ml)	Average tapped density (g/ml)
1	Sulfasalazine	0.459	0.453 ± 0.01	0.612	0.614± 0.003
2	Sulfasalazine	0.452		0.614	
3	Sulfasalazine	0.448		0.618	

Table 2. Particle Size Distribution of Sulfasalazine

Sieve no	Empty weight of sieve	Quantity retained (gm)	Mass retained (gm)	Cumulative mass retained (gm)	Cumulative % retained	Percentage passing %
#20	367.8	368.55	0.75	0.75	4.34	95.66
#30	417.65	417.85	0.2	0.95	5.5	94.50
#40	358.05	365.65	7.6	8.55	49.56	50.44
#60	343.45	343.65	0.2	8.75	50.72	49.28
#80	340.75	340.9	0.15	8.9	51.59	48.41
#100	332.5	332.85	0.35	9.25	53.62	46.38
Base	540.45	548.45	8	17.25	100	0

Table 3. FT-IR Spectral Values of Pure Sulfasalazine

S. No	Wave Number (cm^{-1})	Functional Group
1.	1720.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1321.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1068.0	C-O of carboxylic acid
6.	935.5	CH_2 bending vibration of alkane

Table 4. FT-IR Spectral Values of Sulfasalazine With Excipients

S. No	Wave Number (cm^{-1})	Functional Group
1.	1719.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1380.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1070.0	C-O of carboxylic acid
6.	936.3	CH_2 bending vibration of alkane

Table 5. Evaluation of Finished Product (Uncoated)

Parameters	F1	F2	F3	F4	F5	F6
Average weight (mg)	450±1.18	450±0.89	450±2.00	450±0.61	450±2.68	450±0.21

Thickness (mm)	3.4± 0.16	4.2±0.09	4.7± 0.14	5.9± 0.12	5.7±0.01	5.9 ± 0.16
Hardness (kg/cm^2)	12.6 (± 0.15)	9.4 (± 0.22)	6.2 (± 0.30)	5.2 (± 0.32)	6.0 (± 0.30)	5.8 (± 0.11)
Friability (%)	0.36	0.41	0.39	0.31	0.35	0.33
Disintegration time (min)	-	24'46''	17'42''	14'45''	8'42''	7'18''
Assay (%)	99.34	99.2	98.51	99.85	99.53	100.21

All values are expressed as mean ± standard deviation, n=3

Table 6. Comparative Datas Of Uncoated And Enteric Coated Sulfasalazine Mini-Tablets

Trial	Mini-Tablet Thickness (mm)	Average Weight variation (mg)	Assay (%)	Drug release (%)
F6 Un coated	2.3 ± 0.16	690 ± 5	99.21 ± 0.12	99.69 at 8 hrs
F6 Enteric coated	2.4 ± 0.52	731 ± 5	99.99 ± 0.08	99.21 at 12 hrs

All values are expressed as mean ± standard deviation, n=3

Table 7. Stability studies for post compression parameters of (F-6) enteric coated tablets

Post compression Parameters	Storage condition: 40^{0}C± 2^{0}C /75±5%RH			
	Initial	**1st month**	**2nd month**	**3rd month**
Description	White coloured Enteric coated tablet	White coloured Enteric coated tablet	White coloured Enteric coated tablet	White coloured Enteric coated tablet
Average weight (mg)	477±0.21	477.38 ± 0.003	477.52 ± 0.006	477.67 ± 0.04
Disintegration time (minutes)	219'63''±0.03	219'13''±0.08	220' 38''±0.08	221' 7'' ±0.05

*All the values are expressed as mean's, n=3.

Table 8. *In-Vitro* Drug Release and Assay

Formulation	Time in hrs	Storage condition 40^{0}C±2^{0}C /75±5%RH					
		In-vitro drug release (%)				Assay (%)	
		Initial	1 month	2 month	3 month	Initial	After Stability
F6	24	98.51	98.31	97.42	97.28	100.21	100.1

Fig. 1. FT-IR Spectra Of Pure Sulfasalazine

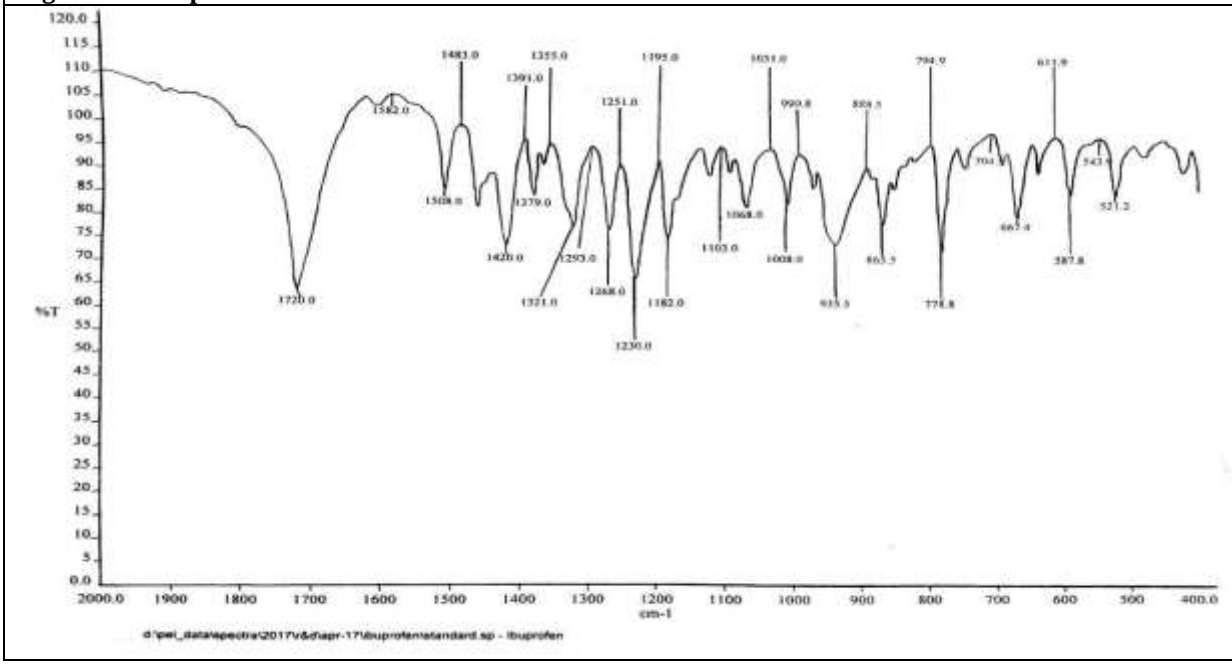


Fig. 2. FT-IR Spectra Of Sulfasalazine With Excipients

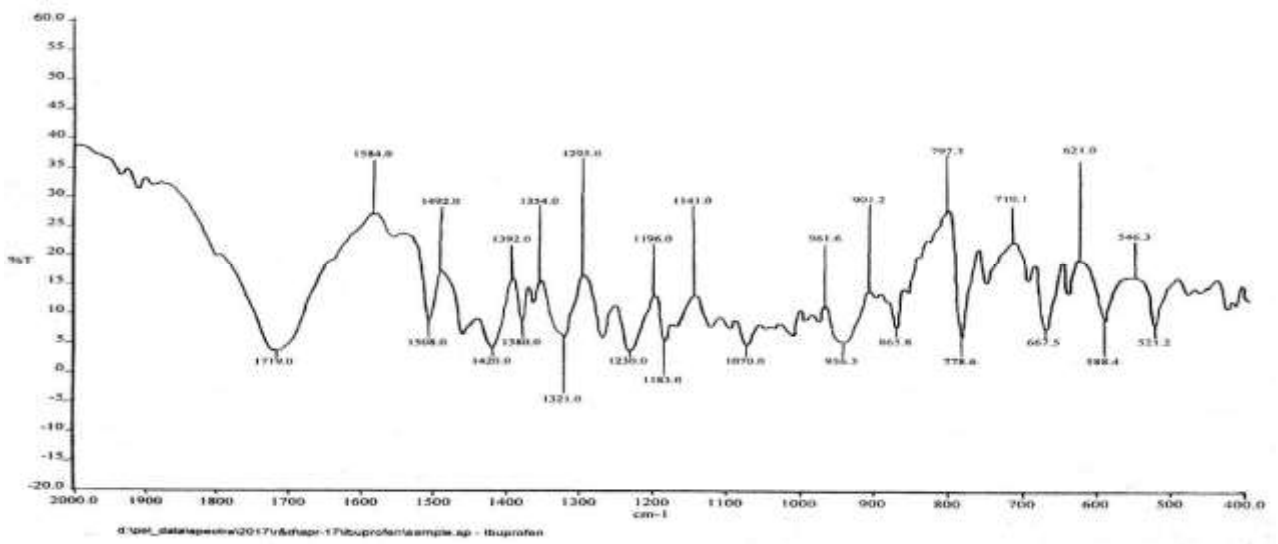
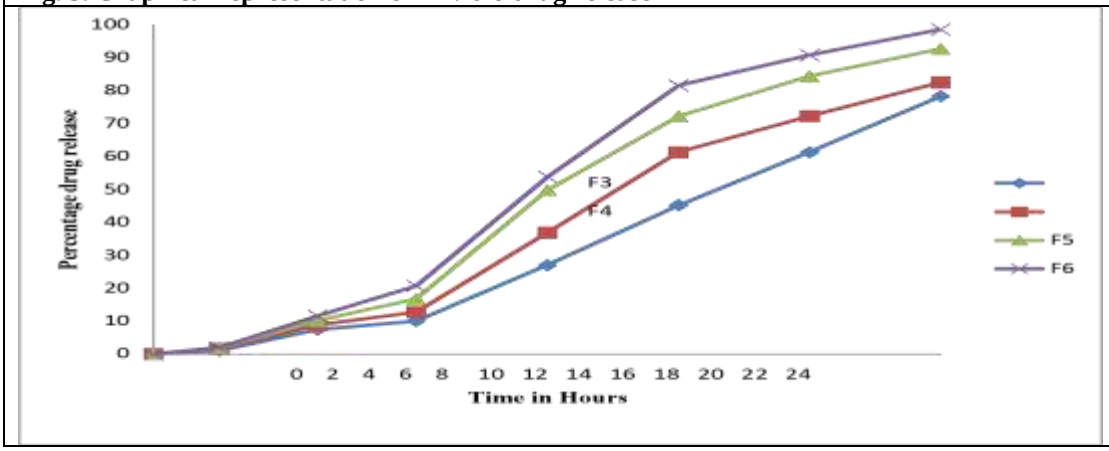


Fig. 3. Graphical representation of in-vitro drug release



The color, solubility, melting point and moisture content of the API were evaluated. It was found to be within the range of the monograph. The angle of repose of API was found to be $38^0.56' \pm 0.69$. Hence the drug belongs to fair flow and requires glidant to improve the flow property. The average bulk density and tapped density was found to be 0.453 ± 0.01 and 0.614 ± 0.003 g/ml respectively. Based on Compressibility index and Hausner's ratio, it indicates the Sulfasalazine (API) belongs to poor flow property. From the particle size analysis it was concluded that the particles size of the API was found to be moderately coarse powder. From the drug excipients compatibility study, it was observed that there was no characteristic change or interaction between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Sulfasalazine.

The bulk density and tapped density of all formulations were measured by using graduated measuring cylinder. The bulk density was found in the range of 0.31-0.41gm/cm^3. The 3 acceptable limits - tapped density was between 0.35-0.46 gm/cm.

If the compressibility index of the powder is between 11 and 15, it shows good flow character, here all the formulations exist in the range between 11.73-13.63. It indicates that the granules showed good flow character. The result showed that the Hausner ratio of all the formulations was between 1.12-1.14, if the Hausner ratio lies between 1.12-1.18, it shows good flow behavior of the granules or powder. The result indicates good flow property of the granules. If the angle of repose is within 35^0, it indicates good flow property of the granules. The result showed that the angle of repose of all the formulations was between 29^0-33^0.It proved that the flow properties of all formulations are good. The thickness of the tablets was in the range of 3.4 to 5.9 mm. This is due to the upper and lower punch adjustments during compression process. The prepared tablets in all the trials possessed good mechanical strength with sufficient hardness in the range of 12.6 to 5.2 kg/cm^2. The friability of the tablets was found to be within 1%. All the above trail formulations have passed the friability test.

The average weight of all the formulations was found to be 450mg. It is within the permissible range. The percentage of drug content was found among different batches of the tablets and ranged from 98.5 to 100.21 which were within the acceptable limits.

Sulfasalazine mini-tablet of the above trial (F6) was satisfied of all the parameters. It was coated by using enteric coating method. The coated tablets were evaluated for the following parameters including thickness, disintegration test, weight variation, assay and *in-vitro* studies. Sulfasalazine enteric coated mini-tablets were compared with the same trial of uncoated Sulfasalazine mini-tablets. The thickness of enteric coated mini-tablets was found to be more than uncoated mini-tablets. Weight variation was increased in enteric coated mini-tablets than the uncoated mini-tablets. This is due to the coating of core tablet.

***In-Vitro* drug release**

F1: The method used in this trial is direct compression. The concentration of Eudragit S 100 used was 80 mg/unit, Ethyl cellulose concentration was 60mg/unit. Lactose 30GR was 50mg/unit. And the concentration of Talc and magnesium stearate used was 5mg/unit. The hardness of the tablet were crossed the specification limit.

F2: Same as procedure of F1. But in this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 60 mg/unit and 55mg/unit. And diluent concentration increased to 75mg/unit. The hardness of this formulation were better than the above formulation but the time required to disintegrate tablets were crossed the specification limit.

F3: The hardness were achieved. But the time required to disintegrate tablets were crossed the specification limit. In this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 50 mg/unit and 40 mg/unit to reduce the hardness of the tablets. And the diluent concentration increased to 100mg/unit. This formulation was selected for coating. And the tablets were subjected to *in-vitro* dissolution study. The release was found to be 78.22±0.78 at 24 hrs.

F4: In trial 4 the concentration of Eudragit S100 and Ethyl cellulose was further decreased to35mg/unit and 25mg/unit and increased the Lactose 30GR concentration to 130mg/unit. The disintegration time of tablet was better than the above formulations but crossed the limits. The tablets were subjected to *in-vitro* dissolution study.

F5: The concentration of Eudragit S100 and Ethyl cellulose was further decreased to 20mg/unit and 15mg/unit and increased the Lactose 30GR concentration to 154mg/unit. The concentration of Magnesium stearate was increased to 6mg/unit to improve the lubrication of granules. The disintegration time of tablet was found to be within the limit. The triethyl citrate was used in the enteric coating part, to give better flexibility to the polymer. The tablets are subjected to *in-vitro* dissolution study. The percentages of drug release were found to be 92.65±0.95 at 24 hrs. It was better than the earlier trials.

F6: The concentration of Eudragit S 100 and Ethyl cellulose was further decreased to 14mg/unit and 10mg/unit and increased the Lactose 30GR concentration to 165mg/unit. The tablets of this trial are subjected to *in-vitro* dissolution study. The percentage of drug release showed 98.51±0.78 at 24 hrs. This trial was taken as confirmatory trial and subjected as stability studies.

The F-6 formulation of enteric coated tablets was carried out for the stability study. It was kept at 40^0C± 2^0C /75±5%RH. It revealed that there were no significant changes in color but slight increase in average weight and disintegration time. The sample was tested at one month interval.

The F6 formulation of enteric coated tablets was carried out for the stability study, it was kept in 40^0C± 2^0C /75±5% RH for the period of three months. Percentage of drug release and assay was determined. The data's does not showed much variation during stability studies. The results revealed that the product was stable.

CONCLUSION

Preformulation studies were performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between API and all the excipients selected. The Sulfasalazine matrix mini-tablets were successfully formulated by direct compression method using the selected excipients quantities. The formulated mini-tablets were evaluated for both pre-compression and post-compression parameters as per requirements of standards. And the results were complied with the pharmacopoeia specification. The formulated Sulfasalazine matrix mini-tablets were coated with enteric polymer Eudragit FS30D by pan coating method. From among the entire batches, formulation F6 showed 98.79% drug release at 24 hrs. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the trial F6 was considered as best formulation. From the results obtained, it can be concluded that formulation F6 containing enteric coated matrix tablet of Sulfasalazine would be a promising formulation to achieve the purpose which treat inflammatory bowel diseases (ulcerativecolitis) without any gastric irritation or ulcers, which is useful for patients having pre-history of ulcerativecolitis. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the trial F6 was considered as best formulation. From the results obtained, it can be concluded that formulation F6 containing enteric coated matrix tablet of Sulfasalazine would be a promising formulation to achieve the purpose which treat inflammatory bowel diseases (ulcerativecolitis) without any gastric irritation or ulcers, which is useful for patients having pre-history of ulcerativecolitis.

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