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BOX BEHNKEN EXPERIMENTAL DESIGN IN THE DEVELOPMENT OF MESALAMINE TABLETS FOR COLON DELIVERY

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ABSTRACT

Mesalamine tablets were formulated by the direct compression method. The in vitro experimental work consists of two major parts, including screening of the formulation variables and optimizing the formulation with central composite, Box-Behnken design. The polymers used in the final formulation were in good correlation with each other. The effect of various factors on response release exponent, T25, T90, and % swelling index were evaluated using DESIGN EXPERT 8.0.6.1 (STATEASE) demo version software. Each response was assessed by ANOVA and the individual parameter was evaluated using F-test. The optimized batch was obtained by applying limitations on responses and this optimized batch was evaluated and observed for the value of response to predicted values. All the batches exhibited good physical integrity furthermore; the drug content between the batches didn't differ by more than 1 %. Drug release from the tablets was completed for 24 hr. The determined regression coefficients demonstrated a greater r2 with the Higuchi model in all the cases. Mesalamine tablets were compressed successfully using the polymers as a mucoadhesive polymer and HPMC K100M as a release retardant polymer. F7 batch showed better results from factorial batches, the mucoadhesive property of F7 was the best. From the mucoadhesive strength investigations of the optimized batches, it was found that mucoadhesive property of optimized formulations was seen to be more noteworthy in vitro studies than ex vivo investigations. All the formulations were characterized using different kinetic modelsi.e. Zero-order kinetics, First-order kinetics, Korsmeyer Peppa's model, and Higuchi kinetics and exhibited Non-Fickian diffusion mechanism. The formulation F7 was selected as an optimized formulation with a 99.664 % release in 24 hours. Data for the

stability study indicate that there was no change in residual drug content for the selected formulation of F7.

KEYWORDS: Box-Behnken design, Mesalamine tablets, Colon delivery.

INTRODUCTION

Mesalazine, also known as **mesalamine** or **5-aminosalicylic acid** (**5-ASA**), a medication used to treat inflammatory bowel disease, including ulcerative colitis and Crohn's disease. It is generally used for mildly to moderately severe disease. It is taken by mouth or rectally. The formulations which are taken by mouth appear to be similarly-effective.

Common side-effects include headache, nausea, abdominal pain, and fever. Serious side-effects may include pericarditis, liver problems, and kidney problems. Use in pregnancy and breastfeeding appears safe. In people with a sulfa allergy certain formulations may result in problems.[1] Mesalazine is an aminosalicylate and anti- inflammatory.[1][9] It works by direct contact with the intestines.

Analytical characterization

This set of methods uses a scope of standards to uncover the compound arrangement, creation variety, crystal structure, and photoelectric properties of materials. Some general instruments include.

Determination of absorption maxima in 0.1N HCl

Mesalamine standard stock solution was produced by dissolving an accurate 10 mg drug to the small quantity of 0.1N HCl added in the flask of 100 ml. 100 ml volume was maintained utilizing 0.1 N HCl obtaining a stock solution of 100 µg/ml, then appropriate dilutions prepared and λmax was determined.

Calibration Curve of Mesalamine in 0.1 N HCl solution

Mesalamine (10 mg) precisely weighed, dissolved in little 0.1 N HCl quantity, maintained to 100 ml volume. Taken proper aliquots taken with various flask, maintained 10 ml using HCl solutions, a solution of 1 to 10 µg/ml concentration.

Determination of absorption maxima in water

Standard stock (Mesalamine) solution produced on the dissolution of 10 mg in small distilled water amount added in the flask of 100 ml. The volume maintained 100 ml using d.w. for

obtaining 100 µg/ml stock solution, then appropriate dilutions prepared and λmax was determined.

Calibration curve of Mesalamine in water

Mesalamine (10 mg) weighed precisely dissolved to water with a small amount furthermore, 100 ml volume was maintained. Proper aliquots used for various flasks and measurements maintained 10 ml with water, to have 1 to 10 µg/ml concentrations.

FTIR Spectroscopy

The range of FTIR is basic proof giving satisfactory details of the compound. FTIR technique gives a range containing a significant figure of the absorption band as of which information can be deduced about the design of an organic compound. The pellets were produced using 10 mg drug and 100 mg dry potassium bromide powder blend, compacted by using the pressure of 10 tons with a hydraulic press to yield a transparent pellet. The thin pellet was positioned in a pellet disk to obtain IR spectra.

Differential Scanning Calorimetry (DSC)

A basic assessment of the effectiveness of absolute purity assurance is finished by DSC (SHIMADZU 60). The accuracy of purity acquired by the DSC is appeared to fall off quickly beneath purities of 99 mole %. DSC analysis was done with (Shimadzu-Thermal Analyzer DSC 60) sample of 2-5 mg. Selected samples were warmed using the exposed pan of aluminum with a rate of 10°C/min rate conducted over 30 to 300°C temperature with 2- bar pressure of N2 flow.

X-Ray Diffraction study

Diffractometer of powder (Philips X'Pert Pro MPD X-beam) was utilized. It was worked in diffraction mode of Bragg Brentano, and radiation which is monochromatized with Cu-Kα was produced with 40 kV voltage and 50 mA current. The essential beam of X-ray was a collimated slit having 0.250 divergences fixed and cover 15 mm. Slit of anti-cancer which is 0.250 and having 0.30 nm slit used for side beam diffracted another for counter proportional. Measured 2θ angle range was 3.0^0 to 52.0^0 C to match the graphs from the previously measured samples, having 0.04º size step and 2.0 s per step time for measurement. Using Cu sample holder different samples were prepared.

Loss on drying

It's a broadly utilized technique to decide moisture content; infrequently it might be unstable material from the example. LOD is directly measured by IR moisture balance (Mettler Toledo HB43-S). Firstly, the instrument calibrated by pressing the button and then distributed 5.00 g of powder into the sample pan uniformly and closes the unit. Set the temperature: IR moisture balance at 60°C - 10 minutes (Note: LOD determined at 60°C due to the drug has melting point at 102 to 105°C) and took the reading by start bottom and check LOD.

UV spectral analysis

Drug-excipients compatibility was done by preparing dilutions of the drug in HCl, then it is analyzed on UV spectroscopy in range (200-400 nm) and λmax has been recorded. Then, dilutions of formulation mixture were prepared in 0.1N HCl and it is analyzed by UV spectroscopy in range (200-400 nm) and λmax has been recorded.

FTIR analysis

Analysis of compatibility study of drug and excipients studied by FTIR . FT-IR graph (drug, HPMC K100M, Carbopol934P, Na CMC) comparison study has been done. By observing graphs, the weather there was a shift in the peak of the pure drug due to polymer interaction. Thus, the study will give compatibility between drug and polymer.

Formulation of Mesalamine

Mesalamine conventional tablet is present in the market. This tablet formulation was attempted to gain the objectives mentioned earlier. Development of a floating tablet was principally based on concentration and type of polymer and excipients were utilized to obtain a tablet with good physical properties including gastro retention.

Tablets HPMC K100M, Na CMC, Polyacrylic acid, and Xanthan gum; Sodium bicarbonate was compressed with direct compression via passing the blend via sieves of # 36. Citric acid and Mg stearate was gone through the sieve of # 60. Specified quantity of the drug was weighed just an every ingredient was moved to a bag of polythene and mixed about 10 minutes. Mixture was packed utilizing punches of round mold on the rotational press of ten stations. For compression, utilized punches estimating the diameter of 8 – 10 mm (170).

RESULTS AND DISCUSSION

CHARACTERIZATION OF DRUG

The drug sample obtained from Hetero Drugs Ltd (Baddi) was characterized by physical characters, micrometric characters, and analytical characters. Whereas results are discussed below.

Physical characterization

Physical characterization is the assurance of all the physical properties of a pharmaceutical medication (API), for example, a melting point. The principle reason for performing physical portrayal is to comprehend and control drugs: When developing up another medication product you need to ensure that it is steady during storage for a specific period (typically a few years). Therefore, it is applicable to recognize what happens when presented to, for example, higher temperature or humidity. Physical characterization of drug including all organoleptic characters (color, odor, and appearance), melting point, and solubility were characterized and results are discussed below

Organoleptic characteristics

Organoleptic properties are the aspects of creating experience via the senses — including taste, smell, and touch. Mesalamine received was studied for organoleptic characteristics for example color, odor, and appearance.

Determination of absorption maxima in 0.1N HCl

UV spectroscopy is about the spectroscopic absorption, adjoining noticeable spectral areas. This suggests it utilizes light in the noticeable and ranges nearby. The retention or reflectance in the range of visible straightforwardly influences the apparent shade of the synthetic compounds included. The λmax was determined in a 0.1N HCl solution by producing a stock solution of 100 µg/ml, and running on UV spectra between 200 – 400nm.

Calibration curve of Mesalamine in 0.1N HCl

In analytical chemistry, a calibration curve, also known as a standard curve, is a general strategy for deciding the concentration of a substance in unknown example by contrasting unknown with a lot of standard examples of known concentration. The drug Mesalamine showed maximum absorption at 245.188 nm wavelength, thus considered as λmax of drug and calibration curve of the dilutions was run at this wavelength, and the result is shown in figure.

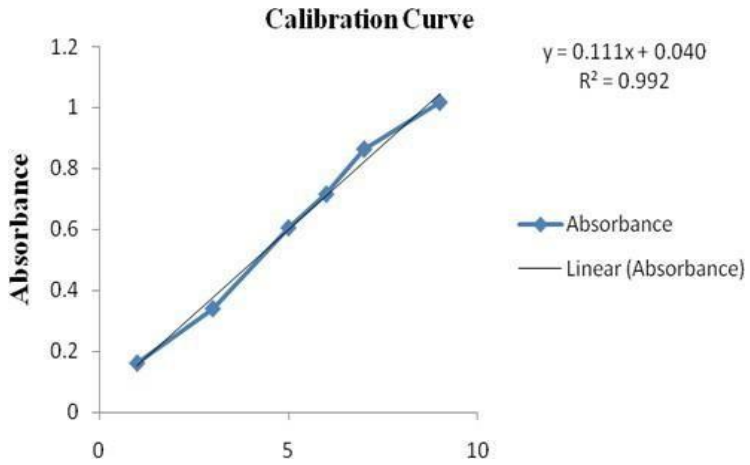


Fig. 1: Calibration curve of Mesalamine in 0.1N HCl.

Result: During the Mesalamine calibration curve, the dilutions were made at 2, 4, 6, 8, and 10 and the correlation coefficient of 0.992 was observed.

Table 1: Determination of uniformity of weight of preliminary batches.

Batch Code	Uniformity of weight (mg)
PF1	320±0.13
PF2	294±0.21
PF3	263±0.11
PF4	275±0.37
PF5	244±0.18
PF6	215±0.15
PF7	262±0.16
PF8	244±0.14

Friability test

Friability of all eight preliminary batches was determined. Tablets compressed lose weight below 1% are acceptable commonly. Each formulation attempted reduction of weight under 1% subsequently satisfactory. Results of the friability test of all preliminary batches are determined in table.

Table 2: Determination of friability of preliminary batches.

Batch code	Friability (%)
PF1	0.2569±0.02
PF2	0.1860±0.07
PF3	0.2785±0.01
PF4	0.4570±0.01
PF5	0.1054±0.01
PF6	0.3279±0.01
PF7	0.1499±0.04
PF8	0.3305±0.02

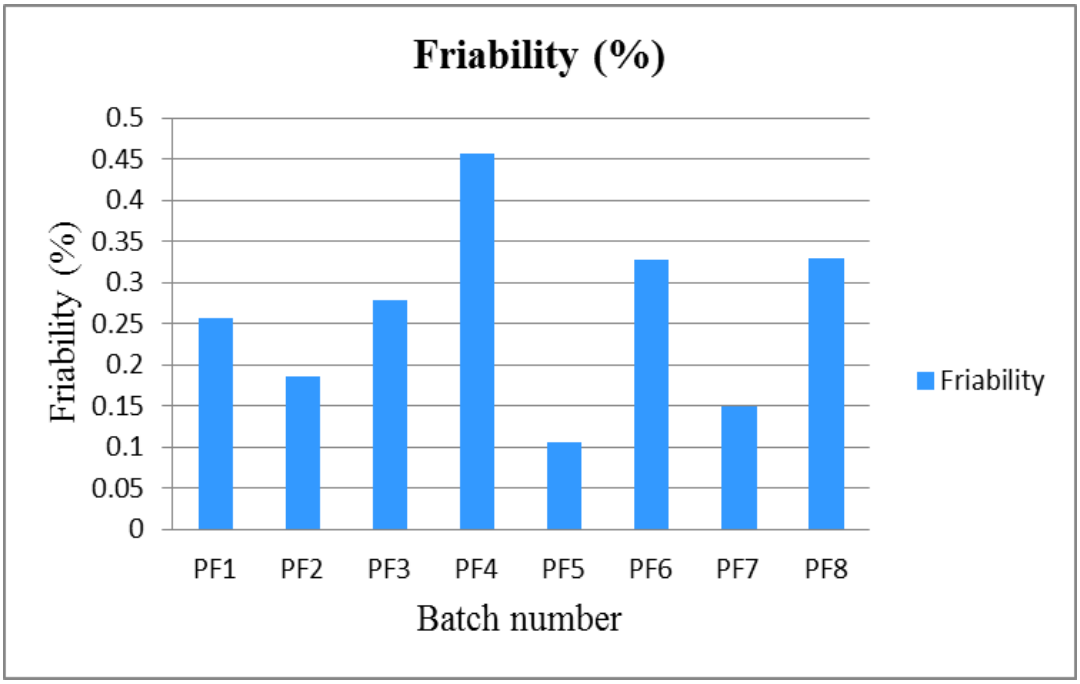


Fig. 2: Determination of friability of the preliminary batches.

All the preliminary batches were subjected for friability test and from results obtained can be concluded that PF7 showed best friability results determined.

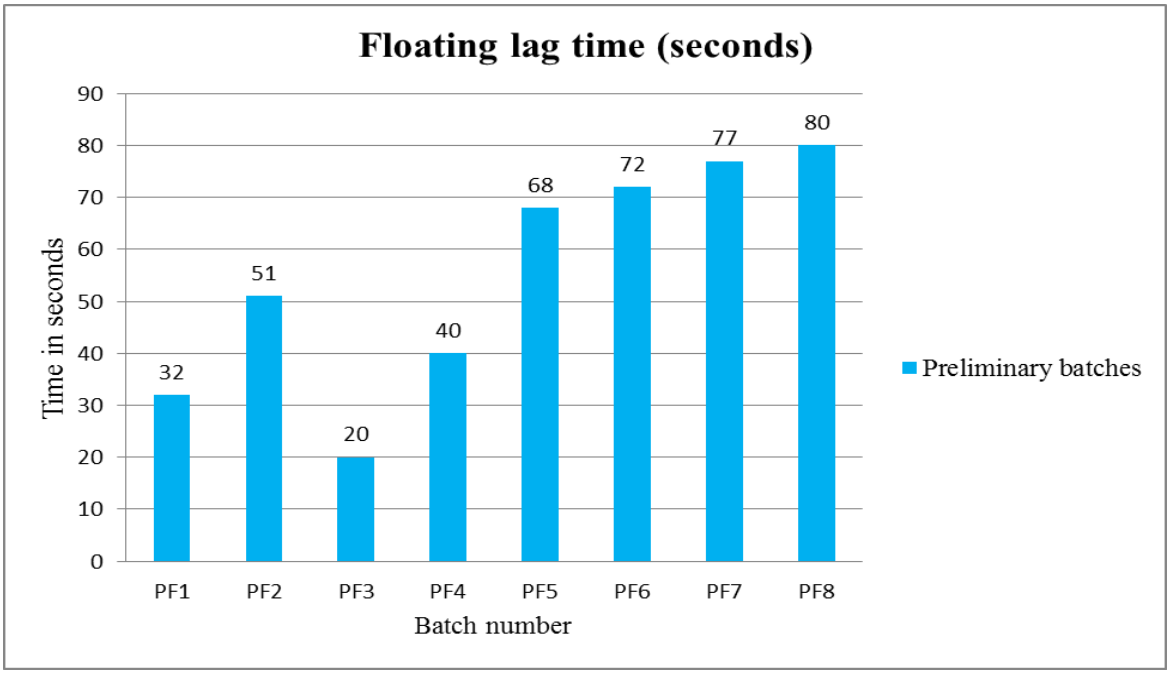
Floating lag time

Duration required for the tablet to float on outside for dissolution medium, after its presentation into the medium. Measurements structure thickness may be related to floating behavior. All the 8 preliminary batches of floating tablets were assessed for FLT and the outcomes acquired are as determined in table 6.25 below:

Table 3: Determination of the floating lag time of preliminary batches.

Sr. No.	Batch No.	Floating lag time(seconds)
1	PF1	32±1.13
2	PF2	51±1.10
3	PF3	20±0.09
4	PF4	40±0.98
5	PF5	68±1.15
6	PF6	72±1.12
7	PF7	77±1.04
8	PF8	80±1.03

Fig. No. 3: Determination of floating lag time of preliminary batches From the above observations, it is seen that preliminary batch number PF3 showed best FLT which was 20 seconds, thus said to be the best one.



Determination of swelling index

Swelling index of each preliminary batch was performed for 24 hours results are shown in table

Table 4: Swelling indices of preliminary batches.

Formulation	% Swelling index			
	4 hr	8 hr	16 hr	24 hr
PF1	162.86±1.08	245.56±0.99	302.46±1.08	525.44±0.99
PF2	169.63±0.99	232.44±0.91	319.31±0.91	464.00±1.08
PF3	157.92±0.91	241.85±	291.46±0.99	392.87±1.09
PF4	174.06±0.99	363.05±1.08	420.53±0.99	409.79±1.05
PF5	195.99±0.98	281.78±0.91	385.97±1.08	452.35±1.04
PF6	167.16±0.91	246.06±0.98	348.52±0.98	371.40±0.93
PF7	224.27±0.98	353.88±0.98	486.38±1.08	425.03±1.02
PF8	196.10±0.91	298.30±0.98	307.85±0.99	441.74±0.91

CONCLUSION

Eight preliminary batches were manufactured via changing the level of polymers (HPMC K100M, carbapol 934P, and four responses) and assessed for thickness, hardness, uniformity of weight, friability, FLT, TFT, determination of swelling index, measurement of bioadhesive strength, drug content, in addition to in vitro dissolution examination. A total of eight batches were subjected for hardness test and lies between 2.0 to 4.6 Kg/cm^2 and the batch PF4 has maximum stiffness of 4.6 Kg/cm^2. The width of all eight batches w as determined and lies between 3.54 to 4.11 mm and the batch PF4 has more thickness 3.93±0.129 mm than

others. Uniformity of weight was done according to an authorized method and the percentage of average deviation of total the preparation had between the limits (according to pharmacopoeial std. deviation ought not to be over 5% of the tablet which taking mass 350 mg). The outcomes of total batches were recorded, and they lie between 215±0.15 to 320±0.13 mg. Friability of all eight preliminary batches was determined. Compacted tablets had lost weight than less than 1 % of the original mass have commonly suitable. For Total preparation attempted now the mass reduction had less than 1% subsequently satisfactory. Results of the friability test of total preliminary batches are determined and the outcome of the PF4 batch was 0.4570 % which was seen the best. The period taken by a tablet to reach the layer of the fluid has FLT, PF8 batch taken 80 seconds to reach the surface which was the maximum, and the PF3 batch takes 20 seconds whereas PF4 takes 40 seconds and considered as the best. Time for which tablet remains floating on the layer is called the total floating time, for batch PF4 and PF3, it was observed that more than 20 hours. Swelling has an important element to confirm the dissolution of drug, buoyancy, and similar impact of drug discharge kinetics.

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