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Research Article

Formulation And Development Of Bilayer Tablets Of Cimetidine And Sucralfate For Targeted Delivery

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ABSTRACT

For researchers, creating floating tablets with the necessary buoyancy, lag time, and drug release behavior control at the target spot is an incredibly intriguing and difficult challenge. The goal of this study is to develop effervescent floating controlled release tablets containing Cimetidine and Sucralfate to treat peptic ulcers. Nine formulations (F1–F9) were created, which were for bi-layered tablets. Hydroxypropyl methylcellulose (HPMC) K100M, HPMC K4M, HPMC K15M and sodium bicarbonate were used as the swelling and floating agents, respectively, during the direct compression method's preparation of these tablets. To guarantee the quality of the produced tablets, qualitative tests including thickness, hardness, weight fluctuation, friability, and content consistency were carried out. Every formulation had a floating lag time that varied between 14 and 20 seconds. While the tablets made with HPMC K4M (F1 & F3) had a total floating duration of less than 7 hours, the effervescent floating tablets with HPMC K100M (F7, F8, & F9) had a total floating time of more than 12 hours. The disparity in the two polymers' compaction and flow characteristics may be the cause of this discrepancy in floating behavior. When compared to formulations F1, F3, and F4 that use HPMC K4M as swelling and floating polymer, formulations F7 and F9 with HPMC K100M show somewhat more sustained drug release qualities. This may be explained by HPMC K100M's improved compaction. The produced tablets exhibit diffusion kinetics that are non-Fickian. All in all, these effervescent bilayers with floating controlled release and plain tablets may enhance the compliance and therapeutic outcomes of Cimetidine and Sucralfate in treatment of peptic ulcers

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INTRODUCTION

The pharmaceutical industry has become more interested in creating bilayer tablets, which combine two or more API in a single dose form, in the past ten years to improve patient compliance and convenience. To prevent chemical incompatibilities between API by physical separation and to facilitate the creation of distinct drug release profiles (immediate release paired with sustain release), bilayer tablets may be the principal choice. Despite their benefits, the mechanical structures of this drug delivery system have grown quite complex due to the use of various materials and intricate geometric boundaries between the adjacent layers. This has resulted in the need for complex tablet architectures and patient-friendly administration, which presents significant challenges to pharmaceutical scientists and engineers. The main obstacles to bilayer compression are covered in depth in this oral presentation, along with a logical plan of action to achieve the intended bilayer tablet performance.Delamination, or layer separation, is one of the main problems caused by inadequate bonding and adhesion at the interface between adjacent compacted layers. This is frequently the result of an interfacial crack caused by residual stresses in the tablet that propagate a finite distance within the tablet and may not always be noticeable right away after compaction (e.g., during storage, packaging, shipping). Additionally, an inadequate link between the compacted layers might result in impaired mechanical integrity if they are too soft or too rigid. Establishing the layer sequence order, layer weight ratio, elastic misfit of the neighboring layers, initial layer tamping force, and cross contamination between layers are further development obstacles. These elements will affect the bilayer compression process itself (an ineffective or uncontrolled one) as well as the quality characteristics of the bilayer tablets (enough mechanical strength to preserve the tablet's integrity and individual layer weight management), if they are not properly managed or optimized. Consequently, to allow the creation of a resilient product and process, it is imperative to get insight into the underlying reasons. Cimetidine is a member of the class of guanidine that consists of guanidine carrying a methyl substituent at position 1, a cyano group at position 2 and a 2-{[(5-methyl-1H-imidazol-4-yl) methyl]sulfanyl}ethyl group at position 3. It is an H2-receptor antagonist that inhibits the production of acid in stomach. It has a role as a H2-receptor antagonist, a P450 inhibitor, an anti-ulcer drug, an analgesic and an adjuvant. It is a member of guanidine's, a member of imidazole's, an aliphatic sulfide and a nitrile. Sucralfate is used to treat and prevent duodenal ulcers and other conditions as determined by your doctor. It works by forming a barrier or coat over the ulcer. This protects the ulcer from the acid of the stomach, allowing it to heal. Materials used in the study:- Cimetidine and Sucralfate was obtained from Virion Enterprise. All HPMC grade were obtained from Ashland India Pvt Ltd. Sodium Starch Glycolate was purchased from DFE Pharma Excipients. Croscarmellose and Sodium & Cross povidone were obtained from Hetero Labs Ltd. All the reagents, chemical and solvent were of analytical grade.

FORMULATION DEVELOPMENT:-

To formulate bilayer tablets, fast-release, and sustained-release layers were initially prepared separately to study the dissolution profile of each layer with an objective of selecting the optimized combination of excipients for the formulations. The optimized formulation of each layer was then compressed to bilayer tablet and further in vitro drug dissolution data

DEVELOPMENT OF CIMETIDINE SUSTAINED RELEASE (SR) TABLETS:-

Different batches of cimetidine sustained release tablets were formulated using different polymer in varying concentration of 26,28 and 30%w/w. cimetidine and excipients were passed through astm (American society for testing and materials) 40 mesh sieve (425 μ) and dry blended for 10 min in motor . aerosol 200P (0.5%w/w) and magnesium stearate (0.5%w/w) were sifted through ASTM 60 mesh sieve (250 μ) and added extra granularly and lubricated for 3 min. Compression was carried out using ten station single rotary tablet compression machine equipped with beveled flat-faced punches of 12.7 mm diameter at a tablet weight of 700 mg. Various excipients were screened and used in preparation of sustained release orally disintegrating tablets. The excipients chosen are as follows:

- Sustained Release Polymer:- HPMC K4M, HPMC K15M, HPMC K100M, HPMC E3LV
- Diluent:- Microcrystalline cellulose
- Lubricant:-Mg stearate, talc
- Carbon Dioxide Generating Agent:- sodium bicarbonate and citric acid

DEVELOPMENT OF SUCRALFATE (IR) TABLETS:-

Sucralfate IR tablet formulations (F1-F9) were prepared by dry granulation technique. All the powders were passed through ASTM 40 mesh sieve (425 μ). Required quantities of ciprofloxacin hcland super disintegrant were mixed thoroughly in motor Avicel PH 101 and lactose monohydrate were added to the above blend and mixed for 5 min. The powder was lubricated for 3 min with magnesium stearate (0.5 %w/w) and Aerosol 200 P (0.5%w/w) (ASTM 60 mesh sifted). The tablets were compressed at a weight of 550 mg on pilot press tablet compression machine equipped with beveled flat-faced punches 12.7 mm in diameter at a tablet weight of 300 mg.

- Super disintegrants: Sodium starch glycolate, Cross povidone Cross carmellose sodium
- Diluent: Microcrystalline cellulose
- Lubricant: Mg stearate, Talc

COMPOSITION OF FORMULATION BATCHES:-

SUSTAIN RELEASE LAYER :-

Table No. 1:- Sustain Release Layer

INGREDIENTS	F1 [MG]	F2 [MG]	F3 [MG]	F4 [MG]	F5 [MG]	F6 [MG]	F7 [MG]	F8 [MG]	F9 [MG]
CIMETIDINE	400 MG								
HPMCK4M	182 MG	196 MG	210 MG	-	-	-	-	-	-
HPMCK15M	-	-	-	182 MG	196 MG	210 MG	-	-	-
HPMCK100M	-	-	-	-	-	-	182 MG	196 MG	210 MG
SODIUM BICARBONATE	25 MG								
CITRIC ACID	25 MG								
MCC	q.s to 700 mg								
MG STERATE	0.5%(700mg)								
TALC	1% (700mg								

Optimization Of Carbondioxide Releasing Agent To Achieve Desired Floating Time :-

Table No. 2:- Optimization Of Carbondioxide Releasing Agent

INGREDIENTS	F1 [MG]	F2 [MG]	F3 [MG]	F2 [MG]
CIMETIDINE	400 MG			
HPMCK15M	210 MG			
SODIUM BICARBONATE	25 MG	30 MG	35 MG	40 MG
CITRIC ACID	25 MG	30 MG	35 MG	40 MG
MCC	q.s to 700 mg			
MG STERATE	0.5%(700mg)			
TALC	1% (700mg			

OPTIMIZATION OF IR TABLET :-

Table No. 3:- Optimization Of Super Disintegrants

INGREDIENTS	F1 [MG]	F2 [MG]	F3 [MG]	F4 [MG]	F5 [MG]	F6 [MG]	F7 [MG]	F8 [MG]	F9 [MG]
SUCRALFATE	250 MG								
CROSSPOVIDONE	10.5 MG	12.5 MG	14.5 MG	-	-	-	-	-	-
SODIUM STARCH GLYCOLATE	-	-	-	10.5 MG	12.5 MG	14.5 MG	-	-	-
CROSS CARMELLOSE SODIUM	-	-	-	-	-	-	10.5 MG	12.5 MG	14.5 MG
MCC	q.s to 300MG								
MG STERATE	0.5% (300MG)								
TALC	1% (300MG)								

OPTIMIZED FORMULA:-

Table No. 4:- Optimized Formula

Sustained Release Layer	
Ingredient	**Quantity (Mg)**
Cimetidine	400 Mg
Hpmck15m	210 Mg
Sodium Bicarbonate	35 Mg
Citric Acid	35 Mg
MCC	Q.S To 700 Mg
Mg Stearate	0.5% (700mg)
Talc	1% (700mg)
Immediate Release Layer	
Ingredient	**Quantity (Mg)**
Sucralfate	250 Mg
Crosspovidone	12.5 Mg
MCC	Q.S To 300 Mg
Mg Stearate	0.5% (300mg)
Talc	1% (300mg)

EVALUATION:-

EVALUATION OF TABLET BLEND:

1. **Bulk density**

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the inter particulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The equation for determining bulk density is

$$\rho b = m/ V$$

where, m= Weight of sample taken, Vb= Bulk volume

2. **Tapped density**

It is the maximum packing density of a powder [or blend of powders] achieved under the influence of well defined, externally applied forces. The tapped density is a limiting density attainedafter"tapping down," usually in a device that lifts and drop volumetric measuring cylinder containing thepowder a fixed distance. The tapped density is calculated using the equation:

$$\rho t = m/ V$$

where, m = Weight of sample taken, Vt = Tapped volume

3. **Compressibility**

Compressibility is indirectly related to the relative flow rate, cohesiveness and particlesize distribution of the powder. Powders with compressibility values lesser than 20% have been found toexhibit good flow properties. Tapped [ρt] and Apparent Bulk density [ρb] measurements can be used toestimate the compressibility of a material. It is often referred to as Carr's Index.

4. **Compressibility index =**
   Tapped density – Bulk density
   Tapped density X 100

5. **Angle of repose**

The angle of repose gives an indication of the flow ability of the substance. Funnel was adjusted such that the stem of the funnel lies 2 cm above the horizontal surface. The drug powder was allowed to flow from the funnel under the gravitational force till the apex of the pile just touched the apex of the funnel, so the height of the pile was taken as 2 cm. Drawing a boundary along the circumference of the pile and taking the average of six diameters determined the diameter of the pile. These values of height and diameter were then substituted in the following equation:

Angle of repose [θ] = tan -1[2h/d]

6. Hausner's ratio 51

Hausner's ratio is an indication of the flowability and compressibility of a powder. It measures the friction condition in a moving powder mass. It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio less than 1.5 indicates good flowability.

Hausner's Ratio = Vb / Vt

EVALUATION OF TABLET:-

1. **Weight variation**

Twenty tablets were randomly selected and individually weighed, the average weight and standard deviation of 20 tablets was calculated.

2. **Thickness**

The thickness of each tablet was measured using digital Vernier calliper.

3. **Friability**

It is the ability of tablets to withstand mechanical shocks during handling and transportation. Friability of the tablets was measured in Roche friabillator. Twenty pre-weighed tablets are placed in the friabillator that revolves at 25 rpm, dropping the tablets at a distance of six inches with each revolution. Normally, it is operated for 100 revolutions. The tablets are then dusted and reweighed.

4. **Drug content**

Three tablets were crushed and powder weight equivalent to one tablet weight was accurately weighed. The powder was dissolved in 100ml of pH 6.8 phosphate buffer and sonicated for about 20 mins. An aliquot was withdrawn and diluted with pH 6.8 phosphate buffer and measured at λ 320 nm.

5. **In vitro dissolution**

In vitro dissolution studies were performed on the optimized tablets. In vitro drug release was studied up to 12 hrs using USP Type 2 [Paddle] dissolution apparatus in 900 ml of pH 1.2 Acidic buffer at 37.5°C ±0.5°C. The stirring speed was set at 50 rpm. Five millilitre sample was withdrawn at intervals of 1hr and replaced with fresh dissolution medium. After appropriate dilution, the samples were analyzed by UV-visible spectrophotometer at 245 & 281 nm.

MATHEMATICAL TREATMENT OF IN VITRO RELEASE DATA

Several mathematical equations which generally define the dissolution profile. Once an appropriate function has been selected, the evaluation of dissolution profile can be carried out and hence the drug release profile can be correlated with drug release kinetic models. Various mathematical models are employed to understand drug release kinetics which is explained below.

- The model dependent approaches include:
- Zero order kinetic models
- First order kinetic model
- Higuchi model

STABILITY INDICATING HPLC METHOD DEVELOPMENT AND VALIDATION

High Performance Liquid Chromatography [HPLC] is a form of column chromatography that pumps a sample mixture or analyte in a solvent (known as the mobile phase) at high pressure through a column with chromatographic packing material (stationary phase). The main purposes for using HPLC are for identifying, quantifying and purifying the individual components of the mixture. A stability-indicating assay is a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product. A stability-indicating assay accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities.

APPARATUS AND CHROMATOGRAPHIC CONDITIONS:

FOR CIMITIDINE

Equipment:

High Performance Liquid Chromatography [Isocratic]

Mobile phase :

methanol : HPLC water [80:20]: 0.3% phosphoric acid

Flow rate :

1ml/min Injection volume 25µL

Detection wavelength:

218 nm Retention time: 2.88 mins

FOR SUCRALFATE

Equipment:

High Performance Liquid Chromatography [Isocratic]

Mobile phase:

solutionA:B (70:30): 0.3ML formic acid

Solution A

Dissolve 17.418g of Dipotassium hydrogen phosphate in 1000mL of water (pH 8.9). Filter through 0.45µ or finer porosity membrane filter.

Solution B

Take Acetonitrile in 1000mL beaker and degas it to remove air bubbles

Flow rate: 1ml/min Injection volume 25µL

Detection wavelength:

276 nm Retention time: 2.37 mins

FORCED DEGRADATION

- Forced degradation plays an important role in the development of stability indicating analytical methodology. In addition to demonstrating specificity, forced degradation studies can be used to determine the degradation pathways and degradation products of the APIs that could form during storage and facilitate formulation development, manufacturing and packaging.
- The drug products were subjected to forced degradation at various stressed conditions like Hydrolytic degradation under acidic

condition, Hydrolytic degradation under alkaline condition, Photolytic degradation & Oxidative degradation. All the samples were placed at reflux at elevated temperature i.e 60ºC for a period of 24 hours separately. The degraded samples are then neutralized using suitable acid, base or buffer to avoid further decomposition. The samples were then analysed with HPLC for the degradation.

HYDROLYTIC DEGRADATION UNDER ACIDIC CONDITIONS:-

The stock solution of Cimetidine and Sucralfate was prepared having a concentration of 1 mg/ml with water in 100 ml of volumetric flask. A 25ml of the above drug solution was placed in 50 ml of round bottom flask, to it 25ml of 1M solution of HCl was added. Then the round bottom flask was kept at the 60°C for reflux for 24 hours and further, it was neutralized with 1M NaOH. The resultant solution was filtered with 0.45 microns syringe filters and placed in the vials.

HYDROLYTIC DEGRADATION UNDER ALKALINE CONDITIONS:-

The stock solution of Cimetidine and Sucralfate was prepared having a concentration of 1mg/ml with water in 100ml of volumetric flask. A 25ml of the above drug solution was placed in 50ml of round bottom flask, to it 25ml of 1M solution of NaOH was added. Then the volumetric flask was kept at 60°C for reflux for 24 hours and further, it was neutralized with 1M HCl. The resultant solution was filtered with 0.45 microns syringe filters and placed in the vials.

OXIDATIVE DEGRADATION:-

The stock solution of Cimetidine and Sucralfate was prepared having a concentration of 1mg/ml with water in 100 ml of volumetric flask. A 25 ml of the above drug solution was placed in 50 ml of volumetric flask, to it 25ml of 1% solution of H2O2 was added. Then the volumetric flask was kept at the 60°C for reflux for 24 hours. The resultant solution was filtered with 0.45 microns syringe filters and placed in the vials.

VALIDATION OF HPLC METHOD

1. LINEARITY

100 mg of Cimetidine and 1000mg Sucralfate was placed in 100 ml of volumetric flask and dissolved with the mobile phase to get 1000 ppm and 10,000 ppm respectively. 1 ml of the solution from the stock solution was transferred and diluted to 10ml with sufficient mobile phase so as to get 100 ppm and 1000 ppm solution. Then 0.2 ml, 0.4 ml, 0.6ml, 0.8ml, 1.0ml, 1.1 ml,1.2 ml, 1.4ml was taken in 10 ml volumetric flask and diluted with mobile phase to get 2,4,6,8,10,12,14 ppm solutions of cimetidine and 500,1000,1500,2000 ppm solution respectively. A plot of peak area against concentration was calculated and subjected to linear regression.

2. ACCURACY

Accuracy was determined by calculating recovery of Cimetidine and Sucralfate by the standard addition method. The standard solution was added at 80, 100 and 120% were injected into chromatographic systems and calculated the amount found and amount added for Cimetidine and Sucralfate and further calculated the individual recovery.

3. PRECISION

- Interday and intraday precision was carried out by injecting the standard solutions of 60, 80 and 100 µg/ml of cimetidine and 500, 1000,1500 µg/ml of Sucralfate in triplicates twice a day.
- Next day same concentration 60, 80 and 100 µg/ml of cimetidine and 500, 1000,1500 µg/ml of Sucralfate were injected and evaluated to find the concentrations based on the responses [Area]. Standard deviation and % Relative standard deviation were calculated.

LIMIT OF DETECTION [LOD] AND LIMIT OF QUANTITTATION [LOQ] 61

Detection limit [DL] expressed as: DL = 3.3 σ/ S
Where,
σ = Standard deviation of the response
S = Slope of the calibration curve Quantitation limit [DL]

STABILITY STUDIES:

Stability testing of pharmaceutical formulations is one of the key aspects of formulation development. It is performed at various stages of formulation development on drug substances and products. In early stages, accelerated stability testing [at relatively higher temperature and/or humidities] can be used for "worst case" evaluation to determine what types of degradation products may be found after long term storage. Testing under gentle conditions [long term shelf storage] slightly elevated temperatures can be used to determine a product's shelf life and expiration dates. During stability testing, the products are tested for content uniformity, degradation products, dissolution time, appearance. The optimized formulation of Cimetidine and Ciprofloxacin HCL were subjected to accelerated stability studies testing under storage condition. The formulation was placed in an Alu-Alu pack at a condition of 250C ± 2˚C/60% RH ± 5% ; 300C ± 2˚C/65% RH ± 5% RH & 40˚C ± 2˚C/75% RH ± 5% RH for a period of one month.

RESULT AND DISCUSSIONS

Different types of studies ranging from physicochemical to in vitro assay were performed in order to optimize and to assess the potential of the drug delivery system developed. Results along with detailed discussion are being given here with justification in support of the rationale for development of the delivery system.

PREFORMULATION STUDIES:

ORGANOLEPTIC EVALUATION:-

Cimetidine were examined for their organoleptic properties like colour and odour. Cimetidine sample is a white, odorless amorphous powder.

Table No. 5:- Organoleptic Properties Of Cimetidine

PARAMETERS	OBSERVATION
Color	White
Oduor	Odorless
Physical appearance	crystal
Texture	Smooth
Taste	bitter

Sucralfate was examined for its organoleptic properties like colour and odour. Sucralfate sample is a white, odorless amorphous powder.

Table No. 6:- Organoleptic Properties Of Sucralfate

PARAMETERS	OBSERVATION
Color	White
Odour	Odourless
Physical appearance	Amorphous
Texture	Smooth
Taste	bitter

MELTING POINT DETERMINATION:

- The melting point determination of a drug is done as it is an important property that proves the authentication of the drug since presence of relatively small amount of impurity can lower as well as widen the melting point range. The melting point of cimetidine was found to be 142°C.

- The melting point determination of a drug is done as it is an important property that proves the authentication of the drug since presence of relatively small amount of impurity can lower as well as widen the melting point range. The melting point of Sucralfate was found to be 232°C.

PH SATURATED SOLUBILITY:

Table No. 7:- Solubility Of Cimetidine In Different Media

SR. NO.	SOLVENTS	Solubility (mg/ml)
1	pH 1.2 Acid Buffer	10.24
2	pH 4.6 Acetate Buffer	19.51
3	pH 6.8 Phosphate Buffer	10.36
4	pH 7.5 Phosphate Buffer	5.42
5	Distilled Water	6.26

CIMETIDINE shows maximum solubility in pH 4.6 Acetate Buffer

Table No. 8:- Solubility Of Sucralfate In Different Media

SR. NO.	SOLVENTS	Solubility (mg/ml)
1	pH 1.2 Acid Buffer	0.573
2	pH 4.6 Acetate Buffer	0.366
3	pH 6.8 Phosphate Buffer	0.163
4	pH 7.5 Phosphate Buffer	0.274
5	Distilled Water	0.035

Sucralfate shows maximum solubility in pH 1.2 phosphate buffer

DRUG EXCIPIENT COMPATIBILITY STUDY:-

The drug and excipients were found to be compatible with each other and did not show any change in their physical properties.

AUTHENTICATION OF CIMETIDINE AND CIPROFLOXACIN HCL:-

UV SPECTRUM OF THE CIMETIDINE

- Simple, sensitive, accurate, precise and rapid ultraviolet spectrophotometric method was developed for estimation of cimetidine. The aim was to develop accurate, precise and sensitive UV spectrophotometric method for estimation of cimetidine by UV- visible spectrophotometer.
- Determination of λ max: The absorption maxima of cimetidine was determined by scanning the drug solution using double beam ultraviolet spectrophotometer.
- Procedure: Accurately weighed 100 mg of cimetidine was dissolved in pH 1.2 phosphate buffer in 100 ml of volumetric flask and then made up the volume up to 100 ml with pH 1.2 phosphate buffer. 1 ml of the solution was diluted to 10 ml with pH 1.2 phosphate buffer in 10 ml volumetric flask to obtain concentration of 10 µg/ml. The spectrum of this solution was run between 200- 400 nm range using UV- visible spectrophotometer. The absorption maximum was found to be 245 nm.

λmax = 245nm

UV SPECTRUM OF THE SUCRALFATE

- Simple, sensitive, accurate, precise and rapid ultraviolet spectrophotometric method was developed for estimation of sucralfate. The aim was to develop accurate, precise and sensitive UV spectrophotometric method for estimation of ciprofloxacin HCL by UV-visible spectrophotometer.

- **Determination of λ max:**

The absorption maxima of ciprofloxacin HCL was determined by scanning the drug solution using double beam ultraviolet spectrophotometer.

- **Procedure:**

Accurately weighed 1000 mg of sucralfate was dissolved in pH 1.2 phosphate buffer in 100 ml of volumetric flask and then made up the volume up to 100 ml with pH 1.2 phosphate buffer. 1 ml of the solution was diluted to 10 ml with pH 1.2 phosphate buffer in 10 ml volumetric flask to obtain concentration of 100 µg/ml. The spectrum of this solution was run between 200- 400 nm range using UV- visible spectrophotometer. The absorption maximum was found to be 281 nm.

λmax = 281nm

FOURIER-TRANSFORM INFRA RED SPECTROSCOPY [FTIR]:

- The sample of Cimetidine showed a characteristic vibrational peak for N-H stretching at 3226 cm-1. IR peaks at 1622 cm-1 were assigned to C=N stretching, respectively. The C=N-C=C asymmetric stretching was assigned to peak at 1586 cm-1, N-SH bending vibration peak was attributed to peak at 1506cm-1, and C-C stretching peak was assigned to peak at 1425-1426 cm-1. The absorption peaks at 1387 and 668 cm-1 were assigned to CH3 bending and C-S asymmetric stretching, respectively.
- The sample of Sucralfate showed a characteristic vibrational peak for C=O stretching at 1641.68 cm−1. IR peaks C=C pyridine ring stretching at 1463.44 cm−1, respectively. The C=C stretching in furan ring at 1600.74 cm−1. The C=C bending in ring at 1620.93, The O-H stretching at 3483 cm−1.

CALIBRATION CURVE OF CIMETIDINE: -

Calibration curve was plotted and the correlation coefficient ‘r²’values were calculated. The important parameters are listed in Table 15. The method for estimation of cimetidine showed linear relationship in the concentration range 2 to 18 µg/ml as shown in figure no. 13.

Parameter	Result
Linearity range	20 to 180 µg/ml
slope	0.0051x+0.01155
r2	0.9978

Calibration data of Cimetidine

Table No.9:- Calibration Reading Of Cimetidine

Concentration (µg/ml)	Absorbance
20	0.11
40	0.202
60	0.312
80	0.432
100	0.516
120	0.623
140	0.745
160	0.81
180	0.908

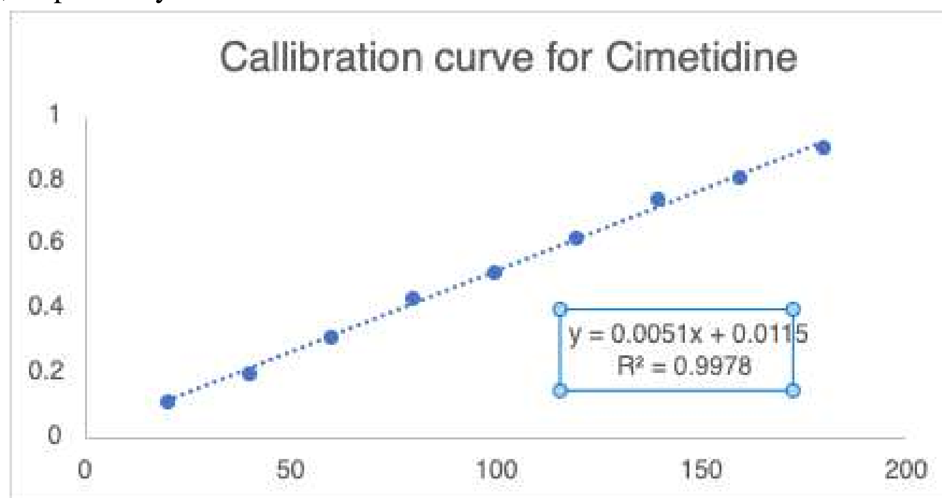

Figure no. 1:- Calibration curve of Cimetidine

Calibration curve was plotted and the correlation coefficient ‘r^2’values were calculated. The important parameters are listed in Table 15. The method for estimation of SUCRALFATE showed linear relationship in the concentration range 2 to 18 µg/ml as shown in figure no. 13

Parameter	Result
Linearity range	20 to 180 µg/ml
slope	0.0051x+0.01155
r2	0.9978

Calibration data of SUCRALFATE

Table No.10:- Calibration Reading Of Sucralfate

Concentration (µg/ml)	Absorbance
500	0.189
1000	0.346
1500	0.59
2000	0.758
2500	0.954

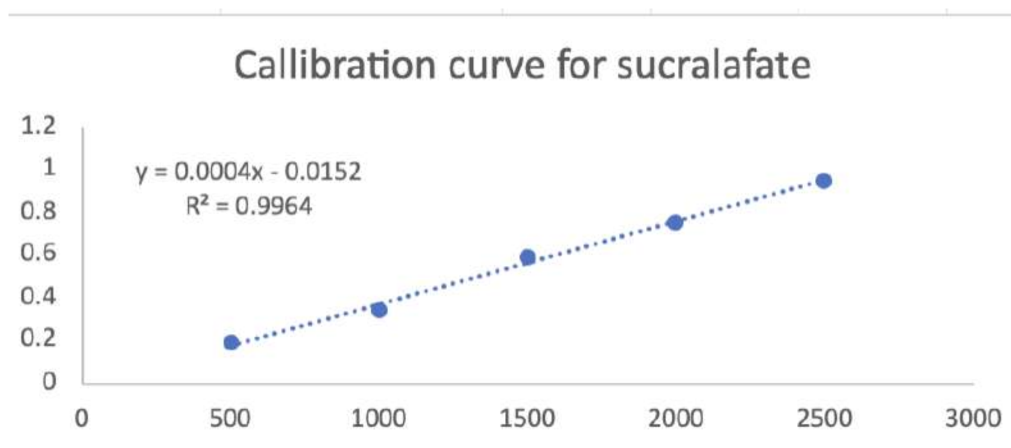

Figure No. 2:- Calibration Curve Of Sucralfate

EVALUATION:

EVALUATION OF TABLET BLEND:

The powder blend before tablet compression was evaluated for various parameters such as bulk density, tapped density, Carr’s compressibility index, Hausner’s ratio and angle of repose. Bulk density was found in the range of 0.64 g/ml and the tapped density between 0.69 g/ml indicating both parameters were found to be within the limits. Using the above two density data, Carr’s compressibility index was determined. The compressibility index and Hausner’s ratio were found to be 6.333 ± 0.57 and 1.068 ± 0.005 respectively indicating that the powder blend showed significantly acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found to be 32.2˚. The results of angle of repose showed all powder blends exhibited good to acceptable flow property.

Table No.11 Evaluation Of Blend

Evaluation Parameters	Observation
Bulk density[g/ml]	0.42 ± 0.005
Tapped density[g/ml]	0.49 ± 0.001
Angle of repose	31.2˚
Carr’s index [%]	10.75 ± 0.34

Hausner's Ratio	1.34 ± 0.062

EVALUATION OF TABLET:

WEIGHT VARIATION:-

The weight variation for optimized tablet formulation was found to be 999.65 mg and result is summarized in Table No 21. The tablets passed weight variation test as the % weight variation was within the pharmacopeial limits [<5%].

THICKNESS:-

Optimized formulation was evaluated for their thickness using "Vernier callipers". The average thickness of the optimized formulations was found to be 12.7 mm which is within the allowed limit of deviation i.e. 5% of the standard value.

HARDNESS:-

Tablet hardness is one of the critical parameter to evaluate resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. Hardness test was performed by "Monsanto hardness tester". The hardness was found to be between 5-5.2 kg/cm2.

FRIABILITY:-

Friability is determined to evaluate ability of tablets to withstand abrasion during packing, handling and transportation. Friability of optimized tablets was determined by using Roche friabilator. The sustained release matrix tablets were evaluated for percent friability and the result is shown in table no 21. The percent friability for all tablet formulations was found to be 0.428% within the pharmacopoeial limit [i.e. less than 1%].

DRUG CONTENT:

The percentage of the drug content for optimized formulation was found to be between 98.5 %w/w and 101.0%w/w. It complies with official specifications. The results are shown in table no 2 Current issues in edible oil adulterations:

Admixing cold press oil with refined one: Refined oils are used in the adulterations of cold press oil. During refining processes, trans fatty acids and steradienes are formed which are generally absent in cold press oil. Trans fatty acids are not essential and they do not promote good health. The consumption of trans fatty acids increases risk of coronary heart disease.

High price oil adulterations with low price oil:

The substitution of more expensive oil by cheaper one is so profitable for producers and there are inspires to do it oil. Some oils are more prone to be adulterated due to their higher price and limited accessibility.

Mustard oil adulterated with argemone oil

In number of cases, adulteration of Argemone mexicana (Family: Papaveraceae) seed oil in edible oils has been reported as cause of epidemic dropsy.

MATERIAL AND METHODS

For edible oil samples there are number of methods is used to detect adulteration like physicochemical test, Laboratory test (chemical test), and analytical test. In physicochemical test density measurement, Boiling point determination, Moisture content, Peroxide value, Acid value, Saponification value, Iodine value. In laboratory test Modified nitric acid test, Nitric acid test, Azo dye test, Sodium azide test, Molybdate test, Halphen's test, Modified Boudouin test, Hexabromide test, Solvent partition method.

Physicochemical test:

The following physicochemical tests are performed for detection of physicochemical characteristics that determine the quality and help to describe the present condition of oils.

Density Measurement:

Densities of all oil samples were measured by a Relative Density (R.D) bottle or density bottle with a capacity of 10 ml, according to the following formula:

Density (ρ) = Mass of the oil sample (M) /Volume of the R.D bottle (V) g/ml

Moisture content:

Ten grams of the oil sample were added to each of three crucibles after they had been weighed. The samples were weighed after being cooled in desiccators and dried to consistent weights at 105°C in an oven. For every sample, the process was carried out three times, and the average value was ascertained.(13)

Boiling point determination:

The boiling point of all oil samples were determined by a thermometer ±1°C using Thiele tube. The boiling point depends upon the degree of unsaturation of fatty acids.(14)

Saponification number:

The saponification value is determined by taking 1.0 g of the oil sample into a conical flask, Adding 25 ml of 0.5 N alc. KOH and heating it in a special condenser for 30-40 minutes to ensure that sample was completely dissolved. After cooling the sample, titrated with 0.2 N HCL using Phenolphthalein as an indicator until a pink endpoint was obtained. An empty sample is determined with the same time conditions.(15)

Saponification value = (B-T) × N × 56.1/WB= ml of HCL required by blank

T= ml of HCL required by oil sample

N=Normality of HCL

W=Weight of oil in gram

Peroxide value:

Peroxide value is determined by taking 5gm of oil into 500 ml conical flask and dissolved in 30 ml acetic acid: chloroform (3:2) mixture and added 0.5 ml saturated KI solution mix well And stand for 1min then added 30 ml of water and titrated against 0.01 N Sodium thiosulphate using starch solution as an indicator with vigorous shaking until blue colour disappear.(16)

Peroxide value = (S-B) ×W×N

S = Volume of sodium thiosulphate consumed by the sample oil

B = Volume of sodium thiosulphate used for blank

W = Weight of oil sample

N = the Normality of sodium thiosulphate

Acid value:

Approximately 5g of oil was introduced into a 250 ml conical flask. Then, 25 ml of neutral ethyl alcohol is added to it and then brought to a boil in a water bath. Phenolphthalein indicator solution (1-2 drops) was added and then the mixture, while still warm, was titrated with a stirred potassium hydroxide standard solution. Endpoints were recorded until the first pink persisted for 30 seconds.(17)

Acid value = V×N×56.1/W

V = Volume of standard KOH solution in ml

N = Normality of standard KOH solution.

W = Weight of oil sample in grams.

Iodine value:

The iodine value of oils was determined according to AOAC method. About 0.25 g oil sample was taken in a conical flask and dissolved in 10 ml CCl4. 30 ml Hanus solution was added and the mixture was allowed to stand for 45 min in dark with occasional shaking. 10ml 10% KI solution and 100 ml distilled water were added and washed down any free iodine on the stopper. The iodine was titrated with previously standardized Na2S2O3 solution which added starch indicator was added and titration was continued until blue color entirely disappeared. Bottle was shaken violently so that any iodine remaining in solution in the CCl4 might be taken up by the KI solution. The volume of Na2S2O3 solution required for the experiment was noted. A blank experiment was conducted along with the sample.(18) Percent weight of iodine absorbed by the oil sample was calculated by the following formula:

1 ml 1N Na2S2O3 = 0.127 g I2

Iodine value = (B-A) × N × 0.127 × 100/W

B = ml of 0.1N Na2S2O3required by blank

A = ml of 0.1N Na2S2O3 required by oil sample

N = Normality of Na2S2O3

W = Weight of oil in gm.

Chemical test (Laboratory test):

IS: 548 (Part-II)-1976 addresses the common qualitative techniques for adulterant detection. The majority of these techniques rely on the precipitate's or turbidity's characteristic colour or appearance developing.(19)

Detection of Synthetically Made Artificial Mustard Oil:(20)

To synthesize synthetic mustard oil, some inexpensive vegetable oils are coloured with oil soluble yellow dye, and then the necessary amount of synthetic allyl isothiocyanate is added. The mixed oil has the same appearance and scent as real mustard oil, but its production costs are significantly lower, making it advantageous for dishonest producers and distributors.

Sodium Azide Test:

Take 100 ml of the mustard oil sample suspected of being artificial mustard oil, mix in 100 ml of Sodium Azide solution (2 gram per 100 ml), and heat the oil mixture upto 3 hours on a hot plate or by direct heating. Allow the aqueous and oil layers to separate by cooling the flask and transferring the contents to a 250 ml separating funnel. Discard the oily layer and collect the lower aqueous layer in a beaker. To eliminate any remaining oily substance, wash the aqueous layer twice with 50 ml of Diethyl ether each time. Filter this aqueous solution and boil it to reduce it to around half its original volume. In a test tube, put 1 ml of bismuth nitrate solution and 1 ml of the above-mentioned concentrated solution. If a bright yellow precipitate forms, the oil sample contains synthetic mustard oil. When natural mustard oil is tested in the same way, it gives a negative result.

V = Volume of standard KOH solution in ml

N = Normality of standard KOH solution.

W = Weight of oil sample in grams

Detection of Argemone Oil:

It is occasionally discovered that edible oils, particularly mustard oil, contain argemone oil (Argemone mexicana Linn). But horrible diseases like dropsy, necrosis, high tension glaucoma, diarrhea, vomiting, and anemia are brought on by argemone oil. There are reports of the oil causing toxic symptoms, and the presence of alkaloid sanguinarine and dihydro- sanguinarine is thought to be the cause of toxicity.(21)

Modified nitric acid test:(22)

5 ml of oil sample in a dry test tube and mix it successively with 0.5 ml of 2% salicylic acid in methanol, Add 2 ml of conc. Nitric acid, followed by 2 - 4 drops of conc. sulphuric acid, and shake. A crimson-red or deep orange-red colour develops within 20-30 seconds if Argemone oil adulteration is present in edible oil. The crimson red or orange-red colour formation is due to the formation of nitrosalicylate salt of hydrolysed sanguinarine.

Detection of Rice Bran Oil:(23)

Rice bran oil is used as edible oil in Japan, China, India and other rice producing countries. Physically refined rice bran oil is similar to mustard oil in colour and density. Rice bran oil is price wise cheaper to mustard oil so it is frequently used as an adulterant in mustard oil. The literature describes a quick and easy colorimetric technique for identifying rice bran oil in vegetable oil.(24) Oryzanol is one of the significant minor components in rice bran oil that Tsuchiya discovered.

Azo Dye Test:

In this procedure, 1 ml of rice bran oil containing oil sample is mixed with 2-4 ml of 10% (w/v) sodium hydroxide solution in a dry test tube and shake for 5-10 minutes to formed an emulsified solution (a). In a separate dry test tube, dissolve 1-2 drops of aniline in dilute hydrochloric acid. After cooling to 0-5°C, add 2-3 ml of 5% (w/v) sodium nitrite solution and shake, resulting in the formation of benzene diazonium chloride solution (b), combine solution (a) and solution (b). Within 10-20 seconds, if orange-red colour develops, indicating the presence of rice bran oil as an

adulterant in edible oil sample. In this method, aniline is first undergo diazotization to produce benzene diazonium chloride in the presence of dil. hydrochloric acid and sodium nitrite solution at temperatures between 0 to 5 degrees Celsius. Following that, the coupling reaction of compound and compound in a basic solution medium that leads to the formation of a reddish orange colored dye, phenylazo-ɤ-oryzanol or phenylazoferulic acid.

Detection of Sesame Oil:

Modified baudouin test: (25)

Take a 25 ml measuring cylinder (or test tube) with glass stopper, put 5 ml sesame oil, Add 5ml Hydrochloric acid, and 0.4 ml furfural solution. Shake vigorously for two minutes after inserting the glass stopper. Allow the mixture to separate for a few minutes. The presence of sesame oil is indicated by the formation of a pink colour in the acid layer. Add 5 ml of water and shake again to confirm. Sesame oil is present if the colour in the acid layer persists. If the colour vanishes, the adulterant is no longer present. In above test the pink colour is formed due to the formation of addition compound by the reaction of sesamol with furfural in presence of hydrochloric acid. This test is sensitive to the extent of 0.2% of sesame oil in other oils. This test is sensitive to the extent of 0.2% of sesame oil in other oils.

Detection of Linseed Oil(26) (Hexabromide Test):

When highly unsaturated fatty acid such as linolenic acid containing oil, e.g. linseed oil, is treated with bromine in chloroform and then with alcohol and ether, the formation of a precipitate of hexabromide indicates the presence of linseed oil in other oil sample.

Detection of Cottonseed Oil:

Raw cottonseed oil contains two unordinary fatty acids, i.e. malvalic acid and sterculic acid. Both acids belong to the category of cyclopropenic acids which is responsible for the traditional Halphens reaction. High levels of cyclopropenic acids (specially sterculic acid) could show toxicity.

Halphen colour test:

In a dry test tube, place 5 ml of filtered and dried oil, then add an equal volume of Sulphur 1.0 % (w/v) solution in carbon disulfide, followed by an equal volume of amyl alcohol. Shake completely before heating in a water bath (70-80°C) for a few minutes, shaking occasionally, until carbon disulfide is cooked out and foaming stops. Place the tube in oil bath or a saturated brine bath at 110-115°C and let it there for 1 to 2 hours. The presence of cottonseed oil is shown by a red color at the end of this period.(27)

Detection of Castor Oil (Molybdate Method):

Molybdate method is a rapid test for the detection of castor oil to an extent up-to 1.0% or more in other oils. In this test take 1ml of the oil in a dry test tube and dissolve it in 10 ml petroleum ether. Shake vigorously for 2 minutes and add 1-2 drops of molybdate reagent (Dissolve 1.25 g of ammonium molybdate in 100 ml of conc. sulphuric acid). Instantaneous development of white turbidity indicates presence of castor oil as an adulterant in test sample.

Determination of antioxidant activity (DPPH method)

The antioxidant properties of each oil sample were also investigated by determining the free radical scavenging activity of the DPPH radical. Briefly each oil sample was diluted upto 10µg/ml with ethanolic solution, to this 1ml of DPPH solution was added. 0.004% DPPH solution in ethanol was used as a free radical. The mixture was vigorously shaken and left to stand for 15min in the dark (until the absorbance stabilized). The reduction of the DPPH radical was determined by measuring the absorbance of the mixture at 517 nm. The radical scavenging activity (RSA) was calculated as the percentage of DPPH discoloration using the following equation.[27]

%RSA = (AbC) – (AbS) / (AbC) × 100

Whereas is the absorbance of the solution when the sample extract is added at a particular level and ADPPH is the absorbance of the DPPH solution.

DISCUSSION:

The above physicochemical parameters are reported in Table no.1, here is the sample of edible oils such as Soyabean oil, Peanut oil, Mustard oil, Olive oil, Sunflower oil, Sesame oil, Ricebran oil which shows the quality and safety of edible oils, also give information about present condition about edible oils.(27) The above laboratory or chemical tests are reported in Table no.2, here is the sample of edible oils such as Soyabean oil, Peanut oil, Mustard oil, Olive oil, Sunflower oil, Sesame oil, Ricebran oil which shows which type of adulterant is present in edible oil samples.(27)

Table 1:2 Physicochemical characteristics of edible oil samples

	Peroxide value	Acid value	Saponification value	Density	Boiling Point (^{0}C)	Moisture content (%)	Iodine value
Soybean oil	2.2	0.561	186	0.927	226	0.27	126
Peanut oil	7.6	0.78	183	0.926	236	0.21	105
Mustard oil	2.0	0.561	172	0.917	179	0.23	95
Olive oil	4.2	0.44	191	0.924	189	0.11	91
Sunflower oil	8.6	0.897	189	0.935	225	0.18	133
Sesame oil	3.4	1.009	196	0.931	210	0.13	106
Rice bran oil	3.1	1.28	3.1	0.929	246	0.11	99

Table 13: chemical test for adulteration detection of edible oil samples

	Modified nitric acidTest	Azo dye Test	Sodium Azide Test	Molybdate Test	Halphens Test	Modified Bouidene Test	Nitric acid Test
Soybean oil	+	+		–	–	–	+
Peanut oil	–	+		–	–	–	–
Mustardoil	–	–	–	–	–	–	–
Olive oil	–	–		+	–	+	–
Sunfloweroil	+	+		+	–	–	+
Sesame oil	–	+		–	–		–
Rice branoil	–	+		–	–	–	–

CONCLUSION:

The floating drug delivery system (bi-layer tablets) of cimetidine & sucralfate were successfully prepared by direct compression method. Preformulation studies revealed that there was no sign of any interaction between drug and polymers and all formulation showed good flow properties. All formulations were evaluated for physiochemical properties and the result was found within the limit. Among all the formulation F4 showed better buoyancy and drug release profile. The release of drug from the prepared formulations was found to follow zero order. In vitro dissolution revealed that drug release rate was increased as the concentration of polymer increased. HPMC K15M showed a greater drug release rate as compared to HPMC K4M and HPMC K100M. Stability studies showed that there were no significant changes in the buoyancy, drug release rate and physical appearance. The results

of the present study for F4 on evaluation of long-term stability studies, and investigations on in vivo performance using Pk simulation software.

The conclusions that were derived from the above research work include:

- Compatibility studies showed no significant interactions between Cimetidine and Sucralfate and excipients.
- Hydrophilic polymers used in sustained release of Cimetidine showed reproducible effects.
- Developed Cimetidine and Sucralfate tablets gave an initial burst release up to 40% in first two hours of dissolution study when only hydrophilic polymers were used to control the release.
- The optimized formulation showed satisfactory disintegration time and In vitro drug release. Use of super disintegrants such as Croscarmellose sodium, Sodium starch glycolate & cross povidone is important for improving disintegration.
- After one month of stability studies, there was no significant change found in the appearance and integrity of the optimized formulation.
- The physical characteristics of the tablets such as weight of the tablet, thickness, hardness, friability, and In vitro drug release of tablets at 25 ℃ /60% RH, 30 ℃ /65% RH & 40℃/75% RH were found to be within given specifications.

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