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RESEARCH ARTICLE

FORMULATION DESIGN AND EVALUATION OF CHEWABLE TABLET CONTAINING SUCRALFATE AND DICLOFENAC

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ABSTRACT

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. These tablets are intended to disintegrate smoothly in the mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most need of easy swallowing dosage forms like chewable tablets. The drug release of intact Diclofenac Potassium was found to be 98.09% the drug release was purely depend on the factor [b1] that was Crosscarmellose sodium. It indicates that increasing the concentration of Crosscarmellose sodium lads to increase in the drug release and increase in concentration of mannitol leads to decrease in the drug release. As the factor [b1] shows the positive number, which indicates that the Crosscarmellose Sodium has a positive impact on the drug release. And the factor [a1] showed the negative effect, which was mannitol. The relationship between variables that is [a1] Mannitol and [b2] Crosscarmellose sodium was further elucidated by using the response plot. The percentage release of intact Sucralfate tablet showed all values within limits, in which the [a1] showed the negative effect on the drug release and [b1] which is Crosscarmellose sodium shows the positive effect on the drug release. The coefficient value of [a1] was found to be less than that of [b1], which indicates that Crosscarmellose sodium has more effect of drug release than mannitol. The drug release of Sucralfate was found to be 97.02%, in which the [a1] was of mannitol, which indicates that it had a negative effect on drug release, and [a2] indicates that it had a good positive effect on the drug release.We can see that as the concentration of mannitol was increased, there was decrease in the dissolution seen, from which it was concluded that the mannitol had a negative effect on the drug release, and which was denoted by a (-) sign in the equation.The data clearly indicates that the drug release of crushed diclofenac potassium was dependent on the concentration of both mannitol and crosscarmellose sodium. .The coefficient [a1] and [b1] were found to be significant to the predicted release below 20min.The disintegration of all the tablets showed the disintegration time up to 5 min 40 sec, in which there were two polymers in which a [1] showed the negative effect, which was mannitol, and b [1] showed the positive effect, which means that Crosscarmellose sodium had a positive effect on the disintegration of tablets. As the concentration of mannitol increases the disintegration time. As its clearly seen that as the concentration of crosscarmellose sodium is increased there is increase in the disintegration time as per expectation, but as the concentration of mannitol was increased there was effect seen on the tablet disintegration.

Introduction:-

1. Introduction

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. [1] These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipient to perform a specific function in a tablet formulation such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic are one type of functional excipient commonly used in chewable tablet formulations to mask the unpleasant tastes and facilitate pediatric dosing. [2,3] Ideally upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets
before absorption from stomach. [4] Chewable tablet are often employed when the active ingredient is intended to act in a localized manner rather than systemically. Chewable tablet is one that is palatable and

may be chewed and ingested with little or no water. Manufacturing of chewable tablet is generally done using either wet granulation process or direct compression. Sucralfate exerts a generalized gastric cytoprotective effect by enhancing natural mucosal defense mechanisms. Studies conducted in animal and clinical trials in human have demonstrated that Sucralfate can protect the gastric mucosa against various irritants such as alcohol, acetylsalicylic acid, hydrochloric acid, sodium hydroxide or sodium taurocholate. In addition, sucralfate has been demonstrated to have a greater affinity for ulcerated gastric of duodenal mucosa than for non-ulcerated mucosa. Sucralfate produces an adherent and cytoprotective barrier at the ulcer site. This barrier protects the ulcer site from the potentialulcerogenic properties of acid, pepsin and bile. Furthermore Sucralfate blocks acid diffusion across the Sucralfate protein barrier and also complexes directly with pepsin and bile. The action of Sucralfate is non-systemic as the drug is only minimally absorbed from the gastrointestinal tract. The minute amounts of the sulfated disaccharide which are absorbed are primarily excreted in the urine. Each gram of Sucralfate contains approximately 200mg of aluminum. The aluminium moiety can dissociate at the low pH and aluminum release in the stomach can be expected; however, aluminium is poorly absorbed from the intact gastrointestinal tract. Following administration of 800mg of Sucralfate thrice a day to individual with normal renal function, approximately 0.001% to .017% of sucralfatesaluminium content is absorbed and excreted in urine. This results in an aluminium load of between 0.008mg and 0.136mg following a 3.2gm daily dose. Individuals with normal renal function excrete absorbed aluminium and can respond to an increased aluminium load by increasing urinary excretion.

Application of Chewable Tablets

1. **Local therapy:** Chewable tablet can release an active
substance at a controlled rate over an extended period of
time providing a prolonged local effect.
2. **Pain:** Successful treatment of minor pains, headaches,
pains of cold, muscular aches, etc. requires rapid absorption of therapeutic doses of the active substance.
Chewable tablet as a drug delivery system could be
beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the
risk of gastrointestinal side effects.
3. **Systemic Therapy:** Chewable tablet provides benefits to
systemic drug delivery, especially if the active substance
is absorbed through the buccal mucosa.
4. **Smoking Cessation:** Chewing gum formulations
containing nicotine, lobeline and silver acetate have been
clinically tested as aids to smoking cessation.
5. **Obesity:** Several chewing gum formulations containing

caffeine, guarana

Description:-This compound belongs to the class of organic compound known as phenyl acetic acid derivatives. These are compounds containing a phenyl acetic acid moiety, which consists of a phenyl group substituted at the second position by an acetic acid.

- **Pharmacokinetic profile:-**

a) Bioavailability: - Under goes first pass metabolism, only 50-60% of a dose reaches systemic circulation as an unchanged drug.
Peak plasma concentration attained within about 1hr.
b) Onset: - Single 50mg or 100mg dose of diclofenac potassium provide pain relief within 30min.
c) Duration: - Pain relief lasts up to 8hrs following administration of single 50mg or 100mg dose of diclofenac potassium.
d) Elimination root: - Diclofenac potassium is excreted in urine (65%) and in faeces biliary (35%) as metabolites.
e) Half life: - 1 to 2 hrs.

1. Therapeutic uses:-

2. Rheumatoid arthritis.
3. Osteoarthrosis.
4. Low back pain.
5. Migraine attack.
6. Acute muscular-skeletaldisorders and trauma such as periarthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures.
7. Ankylosing spondylitis.
8. Control of pain and inflammation in orthopedic, dental and other minor surgery.
9. Pyrophosphate arthropathy and associated disorders.
10. Acute gout.

Material and method:-

Table No. 1 List of Instruments

INSTRUMENTS	MODEL	MANUFACTURER
U.V. spectrophotometer	V-550	JASCO (JAPAN)
Digital balance	AUX-220	SHIMADZU (JAPAN)
Dissolution apparatus	Disso-2000	LABINDIA (INDIA)
FTIR spectrophotometer	FTIR-410	JASCO (INDIA)
Disintegration apparatus	VTD-D	VEEGO INSTRUMENT (INDIA)
Stability chamber	TI-710 SERIES	TEMPO INSTRUMENTS(INDIA)
Tablet punching machine	MC-200	FLUID PACK MINIPRESS Pvt.Ltd
Bulk density apparatus	L-6126	LAB. HOSP CORPORATION (INDIA)
Friability tester	-	LAB-HOSP

MATERIALS:-

Table No. 2 List of Materials

NAME OF MATERIAL	MANUFACTURER
Sucralfate	Surya Life Science (Gujarat)
Diclofenacpotassium	AaratiDrugs Ltd (Mumbai)
Magnesium hydroxide	Ace International (Mumbai)
Mannitol	Ace International (Mumbai)
Cross carmellose sodium	NavketanPharma. Pvt .Ltd. (Thane)
Aluminium hydroxide	Ace International (Mumbai)

DRUG POLYMER PROFILE:-

6.1 DRUG PROFILE:-

6.1.1. SUCRALFATE

- **Category :**Gastro-duodenal cytoprotective agent.

- **Structural formula :**

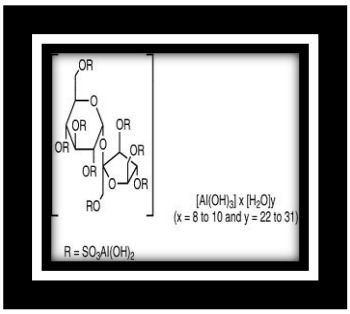


Fig. No. 1 Structure of Sucralfate

- **Molecular formula :**

$C_{12}H_{54}Al_{16}O_{75}S_8$

- **Molecular weight :**

2086.75 g/mol.

- **Chemical name :**

Hexdeca-hydroxytetracossahydroxy[8-[1,3,4,6-tetra-O-sulfo-D-fructofuranosyl-D-glucopyranoside tetrakis (hydrogen sulfate)8-)]hexadeca aluminum.

- **DOSE** :

800mg of drug thrice a day.

- **SOLUBILITY :**

Sucralfate is a metal salt of a sulfated disaccharide. It is soluble in dilute HCl and alkaline hydroxide but practically insoluble in water, boiling water.

- **MELTING POINT :**

196-204°C

- **STORAGE :**

It should be kept in a room temperature and should avoid direct contact with sunlight.

- **MECHANISAM OF ACTION :**

Sucralfate produces distinct morphologic and functional changes in the normal gastric mucosa: mucus release, changes in ion transport and increased release of luminal prostaglandins. Several studies have shown that it can increase the synthesis and release of prostaglandin E_2 from the mucosa. The mechanism may in part explain its effective cytoprotective properties.

Laboratory and clinical studies indicate that Sucralfate promotes the healing of gastric and duodenal ulcer by three way action:-

1. Formation of a chemical complex that bind to the ulcer site to establish a protective barrier.
2. Direct inhibition of the action of pepsin and bile.
3. Blockage of the back diffusion of gastric acid across the barrier.

- **PHARMACOKINETIC PROFILE**

1	Onset of action:	30 to 50min after dosing
2	Absorption:	It is seen that 55% of Sucralfate is absorbed orally and rest of the drug is absorbed in the stomach.
3	Duration:	The duration of the drug is up to 6hrs due to high affinity for defective mucosa
4	Bioavailability:	The absolute bioavailability is approximately 50% with no substantial loss by first pass metabolism.
5	Excretion:	Approximately, 40 to50% of an orally administered dose is excreted in urine as unchanged drug.

- **CONTRAINDICATIONS :-**

1. Use in pregnancy:-

Teratogenicity studies have been performed in mice, rats and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

2. Pediatric use:-

Clinical experience in children is limited. Therefore, sucralfate therapy cannot be recommended for children under 18 unless, in the

judgment of the physician, anticipated outweigh the potential risk.

- **PRECAUTIONS :-**

Sucralfate must not be administered intravenously. Inadvertent intravenous administration of insoluble excipient may induce fatal complications including pulmonary and cerebral emboli. Other severe complications including aluminium intoxication are reported after intravenous administration.

The following should be taken into account before treating patients with sucralfate:

a) Recurrence may be observed in patients after a successful course of treatment for gastric or duodenal ulcers. While the treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the underlying cause o ulcer disease.

b) Proper diagnosis is important since symptomatic response to sucralfate therapy does not rule out the presence of a gastric malignancy.

c) Isolated reports of sucralfate tablet aspiration with accompanying respiratory compliance have been received. Therefore, sucralfate should be used with cautions by patients who have known conditions that may impair swallowing, such as recent or prolonged intubation, tracheostomy, prior history of aspiration, dysphasia or any other conditions that may alter gag and cough reflexes, or diminish oropharyngeal coordination or motility.

d) Due to carbohydrate content of sucralfate suspension excipients, episodes of hyperglycemia have been reported in diabetic patients. Close monitoring of glycemic in diabetic patients. Close monitoring of glycemic in diabetic patients treated with sucralfate suspension is recommended. Adjustment of the anti –diabetic treatment dose during the use of sucralfate suspension might be necessary.

- **DRUG INTERACTION** :-

a) Antacid should not be taken within half an hour before or after sucralfateintake because of the possibility of decrease binding with the gastro-duodenal mucosa as a consequence of a change of intra gastric pH.

b) Animal studies have shown that simultaneous administration of sucralfate with tetracycline, phenytoin or cimetidine results in statistically reduction in the bioavailability of these agents. Cimetidine absorption was not reduced in humans.

c) In clinical trials, the concomitant administration of sucralfate reduced the bioavailability of digoxin. In case of simultaneous administration, the extent of absorption of phenytoin, warfarin, fluroquinolone antibiotics is also reduced. These interactions appear to be non-systemic and to result from the binding of sucralfate the concomitantly administered drug in the gastro intestinal tract. In all cases, complete bioavailability was restored by separating the administration of sucralfate from that of the other agent by 2 hours.

d) Sucralfate, administered respectively 30 and 60 minutes before ASA or ibuprofen did not alter the bioavailability of these agents. In a study comparing the prior administration of a single dose of sucralfate tablets on the bioavailability of naproxen, indomethacin or ketoprofen versus administration in the absence of sucralfate, it was shown that the total amount of these drugs absorbed was not altered; however, the peak concentration was delayed. A single dose of sucralfate suspension administered one-half hour before naproxen had a similar effect on the bioavailability of naproxen.

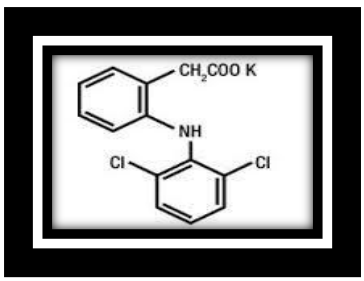
e) The physician should consider the possible clinical implications of these interactions. It is recommended to separate the administration of a drug from that of sucralfate when the potential for altered bioavailability is felt to be critical to the effectiveness of that drug.

Unless specified, the above data are based on studies carried out with sucralfate tablets.

6.1.2. DICLOFENAC POTASSIUM:-

- **Category:-**

Non-steroidal anti inflammatory drug.



- **Structural formula**:-

Fig. No. 2 Structure of Diclofenac Potassium

- **Molecular formula :-**

$C_{14}H_{10}C_{12}NKO_2$

- **Molecular weight :-**

334.239

- **Chemical name :-**

2-[(2, 6-dihlorophenyl) amino] benzene acetic acid, monopotassium salt.

- **Dose :-**

50mg 0f drug two to three times a day.

- **Solubility :-**

Soluble in water (0.00447 mg/ml)

- **Melting point :-**

283-285

- **Storage :-**

Store at 20 degree, under desiccating conditions and away from direct contact with sunlight . The product can be stored for up to 12 months.

- **Mechanism of action :-**

The anti-inflammatory effect of diclofenac is believed to be due to inhibition of both leukocyte migration and the enzyme cyclo-oxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors for the analgesic effect of diclofenac.Anti pyretic effect may be due to action on the hypothalamus, resulting in peripheral dilation, increased coetaneous blood flow and subsequent heat dissipation.

- **Contraindications :-**

➢ Hypersensitivity to diclofenac or any of the excipients.

➢ Active, or history of recurrent peptic ulcer/ hemorrhage (one or more distinct episodes of proven ulceration or bleeding).

➢ NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, other non-steroidal anti-inflammatory drugs.

➢ Severe heart failure, hepatic failure and renal failure.

➢ History of gastro-intestinal bleeding or perforation, relating to previous NSAID therapy.

➢ During the last trimester of pregnancy.

- **Precautions:-**

➢ **Cardiovascular, Renal and Hepatic impairment:**

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal action, cardiac impairment, liver dysfunction, those taking diuretics and the elder patients. Renal functions should be monitored in these patients.

➢ **Hepatic :-**

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestation occurs, diclofenac potassium should be discontinued. Hepatic may occur without prodromal symptoms. Use of diclofenac potassium tablets in patients with hepatic porphyria may trigger an attack.

➢ **Hematological:-**

Diclofenac potassium tablets may reversibly inhibit platelet aggregation. Patients with defects of homeostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

➢ **Long term treatment:-**

All patients who are receiving long term treatment with non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Patients appear to be at the highest risk for these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac potassium should be discontinued at the first appearance o skin rash, mucosal lesions or any other signs of hypersensitivity.

➢ **Impaired female fertility:-**

The use of diclofenac potassium tablets may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties in conceiving or who are undergoing investigation of infertility, withdrawal diclofenac potassium tablets should be considered.

- **Drug interaction :-**

➢ **Anti-hypertensive**: Reduced anti-hypertensive effect.

➢ **Diuretic**s: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

➢ **Cardiac glycosides**: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

➢ **Lithium**: Decreased elimination of lithium.

➢ **Methotrexate**: Decreased elimination of Methotrexate.

➢ **Cyclosporine**: Increased risk of nephrotoxicity.

- **Mifepristone**: NSAIDs should not be used or 8-12 days after Mifepristone administration as NSAIDs can reduce the effect of Mifepristone.
- **Corticosteroids**: Increases risk of gastrointestinal ulceration or bleeding.
- **Anti-coagulant**: NSAID may enhance the effect of anti-coagulants such as warfarin.
- **Quinolone antibiotics**: Animal data indicates that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- **Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)**: Increased risk of gastrointestinal bleeding.
- **Tacrolimus**: Possible increased risk of nephrotoxicity when NSAIDs are given with Tacrolimus.
- **Zidovudine**: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV positive hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- **Ant diabetic agents**: clinical studies have shown that diclofenac potassium tablet can be given together with oral ant diabetic agents without influencing their linical effect. However there have been isolated reports of hypoglycaemic and hyperglycemic effects which have required adjustment to the dosage o hypoglycemic agents.

7.1. Preformulation Study:

7.1.1. Drug Authentication:

- **IR spectroscopy:**

IR spectroscopy of sucralfate and diclofenac potassium was done by using FT-IR spectrophotometer (JASCO FT/IR). The spectra were scanned over wavelength region 4000 to 400cm^{-1}. The procedure consisted of dispersing samples in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

- **UV spectroscopy:**

50mg of sucralfate and diclofenac potassium was dissolved in HCl respectively and was diluted up to 100ml with respective solvents. Dilute 2ml of solution to 50ml of solvent. And the sample was examined between 200nm-400nm, and the absorption maximum was determined.

7.1.2. Authentication of polymers and excipient by FT-IR and other identification tests given in BP 2007:

7.1.2.1 FT-IR Spectroscopy: IR spectroscopy of mannitol, crosscarmellose sodium, magnesium hydroxide was done by using FT-IR spectrophotometer (JASCO FT/IR).

7.1.3. Compatibility studies:

The proper design and formulation of a dosage form requires consideration of physical, chemical and biological characteristics of all drugs substances and excipient, which are to be used in fabricating the product. The drug and the excipient must be compatible with other excipients and should be stable, effective, attractive, easy to administer and safe.

The drug and the excipient in same ratios were equally distributed and kept in well closed containers. The samples were kept at room temperature. The samples were drawn at intervals of 0th and 4th week, and were analyzed for its physical appearance and the drug stability was checked by UV scanning.

7.2. ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF MULTICOMPONENTS IN TABLET DOSAGE FORM:

1. Instrument, Chemicals and Reagents:

A new method was developed by using U.V. visible spectrophotometer with 1 cm matched quartz cells, over the range of 200-400nm. A Shimadzu electronic analytical balance (AUX-220) was used for weighing the sample.

Pure sample of Sucralfate and Diclofenac Potassium (Surya Life Science Pvt. Ltd andAarati Drugs Ltd.) were used in the study. Methanol was used as a solvent, which was obtained from Merck Chemicals. The pharmaceutical dosage form used in this study was my own formulated Chewable tablet, which contained 700mg of Sucralfate and 50mg of Diclofenac Potassium.

2. Selection of Solvent:

According to the solubility characteristics of drug, 0.1N HCl was selected for analysis. From the scanning of both the drug by UV spectra, wavelengths were selected for estimation of Sucralfate at 283nm and for Diclofenac Potassium at 276nm.

3. Preparation of Standard Stock Solution:

Accurately weighed 10mg of each drug was dissolved in little quantity of methanol and the volume was adjusted to 100ml with the same, the obtained standard solution having concentration of 100 µg/ml. The standard solutions of these drugs were obtained by dilution of the respective stock solution with 0.1N HCl. The aliquots of 0.1, 0.2, 0.3, 0.4, 0.5 µg/ml was prepared by using this stock solution.

4. Preparation of sample stock solutions:

1ml (100µg/ml) of standard stock solution was diluted with 100ml 0.1N HCl, the concentration of the sample stock solution was 1µg/ ml. As needed the sample stock solution was diluted to obtain the concentrations of 0.1, 0.2, 0.3, 0.4, 0.5µg/ml respectively.

5. Determination of λ_{max}:

The standard solutions of Sucralfate and Diclofenac Potassium were separately scanned at different concentration in the range of 200-400 nm and the $\lambda_{max}$was determined. From the scanning of both the drugs by U.V.Spectra, wavelengths were selected for estimation of Sucralfate at 283nm and Diclofenac Potassium at 276nm.

6. Method validation:

The method was validated according to ICH Q2B guidelines for validation of analytical procedures in order to determine linearity, sensitivity, precision and accuracy for the analyte.

a) Linearity:

Sucralfate and Diclofenac Potassium exhibited linearity with absorbencies in the range of 0.1-10µg/ml at their respective selected wavelengths that are at 283nm and 276nm respectively. From this calibration curve was plotted. (Refer Table no: 14 and 15 and Fig. No: 13, 14and 15, 16)

b) Precision:

Repeatability of method was established by analyzing various replicates of sample. All the solutions were analyzed thrice, in order to record intra-day and inter day variation in the result. The results obtained for intra-day variations are shown in the table No. 17 to 20.

c) Assay results:

A tablet dosage form of Sucralfate and Diclofenac Potassium was analyzed by simultaneous equation method, the percentage in dosage form were determined and results obtained are referred in table No. 21 to 23.

d) Recovery:

Accuracy was determined by recovery study. The recovery experiment was carried out by spiking the already analyzed sample of the tablets with their different known concentration of my formulated tablet considering it as standard.

To evaluate the accuracy of the method, known amount of pure drug was added to the pre-analyzed sample of tablet powder and the mixture was analyzed for the drug content using the proposed method. The recovery experiments indicated the absence of interference from the commonly encountered pharmaceutical additive and excipients. Results of recovery studies are shown in table No. 24 to 27.

7.3. Formulation and Optimization of Formulation:1.Formulation of trial batches:

Table No. 4. Trial batches of formulation

Ingredients(mg)	**B1**	**B2**	**B3**	**B4**
Sucralfate	**700**	**700**	**700**	**700**
Diclofenac potassium	**50**	**50**	**50**	**50**
Magnesium hydroxide	**50**	**50**	**50**	**50**
Starch	**50**	**-**	**-**	**-**
Chitosan	**-**	**50**	**-**	**-**
Microcrystalline cellulose	**-**	**-**	**50**	**-**
Crosscarmellose sodium	**-**	**-**	**-**	**50**
Mannitol	**120**	**120**	**120**	**120**

Various batches of different concentrations were prepared, each batch was properly and thoroughly mixed and was triturated in a mortar and was

passed in a sieve for the uniform particle size, and then the tablets were punched.

The Batch B1 contains starch, B2 contains Chitosan, B3 contains Microcrystalline cellulose and B4 contains Crosscarmellose sodium having the same concentration.

7.4. Formulation of batches for Chewable tablets:

7.3.1. Optimization of process variables:

It is desirable to develop an expectable pharmaceutical in the shortest period of time using minimum man power and raw materials. In addition to the art formulation, full factorial design is an efficient method of indicating the relative significance of a number of variables and their interaction. Batches were made with the aid of factorial design. In the present study, effect of two variables was considered.

Two variables were considered at three levels, lower level (-1), middle level (0) and upper level (1), hence it was a 3^2 factorial design.

7.3.2. Selection of independent variables:

Following are the independent variables, which were selected in this study.

- **Crosscarmellose sodium.**
- **Mannitol.**

Both the polymer concentrations were taken in milligrams. The three levels for these independent variables were selected on the basis of trail batches.

a) Polymer concentration:

As it's the chewable tablet, the polymers play an important role in as an excipient in the manufacturing of chewable tablets. It has got the special property of negative heat of solution, which is the important property in preparation of chewable tablets. Polymer used in this formulation has got various other properties like sweetness, mouth feel and also improves the flow property of other materials. Mannitol is commonly used as an excipient in the manufacturing of chewable tablet formulation.

b) Concentration of super disintegrant:

The concentration of super disintegrant is also very important in the formulation. There are different mechanisms of differentdisintegrants. The appropriate disintegrant was selected depending on its mechanism. As the concentration of the super disintegrant varies the release profile of the drug also varies.

7.4. Factorial design:

A 3^2 full factorial design with two independent variables was employed for study. 3^2 factorial designs were used for study between polymer concentration and freezing time.

a) **Independent variables:**

X_1 = polymer concentration.

X_2= super disintegrant.

b) **Dependent variables:**

In-vitro drug release.

Table No. 5. Independent variables

Coded values	**Actual values**	
	X_1	X_2
-1	100	20
0	110	30
1	120	40

Table No. 6. Scheme for factorial design

Batches	**Polymer concentration(mg)**	**Disintegrant concentration(mg)**
F1	100	20
F2	110	20
F3	120	20
F4	100	30
F5	110	30
F6	120	30

F7	100	40
F8	110	40
F9	120	40

The composition of different formulation of batches containing excipients has been shown above.

Table No.7. Formulation batches

Ingredients	**Formulation batches**								
Batches	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sucralfate (mg)	700	700	700	700	700	700	700	700	700
Diclofenac potassium(mg)	50	50	50	50	50	50	50	50	50
Crosscarmellose sodium(mg)	20	20	20	30	30	30	40	40	40
Mannitol(mg)	100	110	120	100	110	120	100	110	120
Magnesium hydroxide(mg)	10	10	10	10	10	10	10	10	10

7.5. Characterization of Granules:

7.5.1. Angle of Repose:

The angle of repose of the granules was determined by the funnel method the accurately weighed were taken in funnel. The height of the funnel was adjusted in such a way that the tip of funnel just touched the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation:

$\tan \Theta = h/r$…….(0)

Hence, $\Theta = \tan^{-1} h/r$

Where,

Θ = angle of repose.

h = height of the funnel from the surface.

r = radius of the formed circle.

7.5.2. Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2gm powder was introduced in to a 10ml measuring cylinder, which was allowed to fall under its own weight onto a hard surface from height nearly of 5cm, the tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas:

LBD =weight of the powder/volume of the packing.

TBD = weight of the powder/tapped volume of the packing.

7.5.3. Carr's Index:

The compressibility of the granules was determined by Carr's compressibility index:

Carr's index(%) = [(TBD-LBD)×100]/ TBD

7.5.4. Drug content:

Granules equivalent to 10mg of drugs were weighed accurately and dissolved in suitable quantity of appropriate solvents. Samples were filtered through Whatman filter paper no. 41. The drug content was determined at 283nm and 276nm by UV-Visible spectrophotometer (V-550, JASCO).

7.6. Preparation and Evaluation of Tablets:

The granules were recompressed on a tablet press into tablet of weight 900mg in view of the proportion of ingredients as aforesaid; each tablet contained 700mg of sucralfate, 50mg diclofenac potassium and rest were the polymers and other excipients. The tablets were subjected to different tests.

- **Characterization of tablets:7.6.1. Thickness:**

Thickness of tablets was determined using determined using Vernier Caliper. Five tablets from batches were used, and average values were determined.

7.6.2. Weight variation:

Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

7.6.3. Drug content:

Granules equivalent to 10mg of drugs were weighed accurately and dissolved in suitable quantity of appropriate solvents. Samples were filtered through Whatman filter paper no. 41. The drug content was determined at 283nm and 276nm by UV-Visible spectrophotometer (V-550, JASCO).

7.6.4. Hardness:

For each formulation, hardness of 6 tablets was determined using the Pfizer hardness tester.

7.6.5. Friability:

The friability of 6 tablets was determined using the Roche friabilator. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 0.5-1% in weight is generally considered acceptable. Percent friability (%F) was calculated as follows,

%F =loss in weight/Initial weight × 100

7.6.6. Disintegration:

The disintegration time for chewable tablet was carried using USP disintegration apparatus. The limit for disintegration was not more than 20 minutes, at a temperature between 36 to 38°C. For study, six tablets from eachbatch were taken. Tablets were placed individually in each tube of disintegration test apparatus and the disc was placed. The water was maintained at 37°C. Mean of three readings were taken and considered as disintegration time of each batches.

7.6.7. Dissolution:

The release rate of chewable tablet was carried out by using USP Dissolution Testing Apparatus 2 (Paddle type equipped with auto sampler). The dissolution test was performed using 900ml of 0.1N HCl, at 37±0.5ºC and 50 rpm. A 5ml sample of the solution was withdrawn from the dissolution apparatus every 5 min for 20 min. Absorbance of these solutions were measured at 276nm and 283nm for Diclofenac Potassium and Sucralfate respectively using UV spectrophotometer (V-550, JASCO).

RESULT AND DISCUSSION:

8.1. ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF TABLET DOSAGE FORM AND PREFORMULATION STUDY:

8.1.1. Sucralfate Authentication:

- **Description:**

Sucralfate USP: The sample obtained was white in colour with no characteristic odour.

- **Melting point:**

Melting point was found to be 199-204°C by using digital melting point apparatus. This complies with the melting point as given in USP.

- **UV Spectroscopy:**

Maximum absorbance of sucralfate was found at 283nm. This is characteristic property of sucralfate in its pure form. So conformation can be made here regarding authentication of drug. So finally above results complies with specifications of sucralfate in USP and so drug sample considered as authentic.

a) Scanning in Methanol:

UV spectroscopic scanning of sucralfate in methanol showed maximum absorbance at wavelength of 283nm.

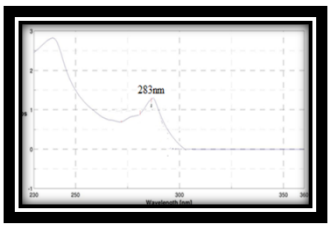


Fig. No.6 UV Spectrum of Sucralfate in Methanol

- **FTIR spectroscopy:**

IR spectrum showed dominant characteristic peaks of Sucralfate. The Ether link, C-C bend, OH group, C-H stretch, C-H bend were seen at 1100,700, 2900, 2800, 800.

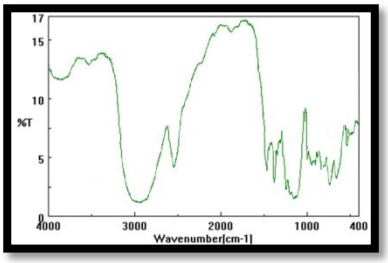


Fig. No.7. IR Spectrum Of Sucralfate

Table No.8Authentication of Sucralfate by IR Spectroscopy

Sr. No.	Observed IR peaks (cm^{-1})	
1	C-C bend	800
2	OH group	2900
3	C-H stretch	2800
4	C-H bend	700
5	R-O-R	1100

8.1.2. Diclofenac Potassium Authentication:

- **Description:**

Diclofenac potassium was white in colour with no characteristic odour.

- **Melting point:**

Melting point of drug was found to be 283-285°C by using digital melting point apparatus. This complies with the melting point as given in USP.

- **UV spectroscopy:**

Maximum absorbance of diclofenac potassium was found at 276nm. This is characteristic property of diclofenac potassium in its pure form. So confirmation can be made here regarding authentication of drug. So finally above results complies with specifications of diclofenac potassium in USP and so drug sample considered as authentic.

a) Scanning in methanol:

UV spectroscopic scanning of diclofenac potassium in methanol showed maximum absorbance at wavelength of 276nm.

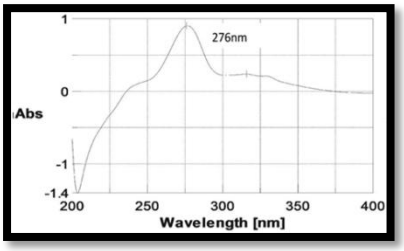


Fig.No.8 UV Spectrum of Diclofenac Potassium in Methanol.

- **FTIR Spectroscopy:**

IR spectrum showed dominant characteristics peaks of diclofenac potassium. Especially R-Cl, C=O, aromatic ring, secondary amine, C-O at 600, 1600, 2800, 1650, 3200.

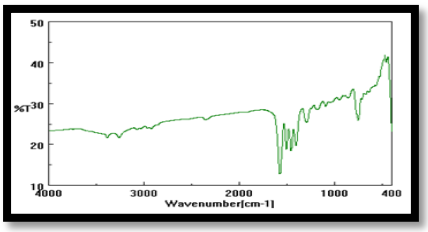
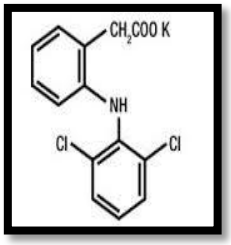


Fig.No. 9 IR Spectrum of Diclofenac Potassium.

3	C-H Stretch		2954
4	C-O		1058

Table No. 9 Authentication of Diclofenac Potassium by IR Spectroscopy

Sr. No.	Observed I.R. Peaks		
1	R-Cl		754.031
2	C=O		1576.52
3	Aroma. Ring		3260
4	C-O		1094.4
5	R-CH_2		3310.26

8.2. POLYMER AND EXCIPIENT AUTHENTICATION:

8.2.1. Mannitol:

IR spectrum shows dominant characteristic peaks of mannitol. Especially at CH_3-OH,C-C stretch, C-H stretch, C-O which were found at 2800, 3000,2954,1058. Which confirms polymer sample was authentic one.

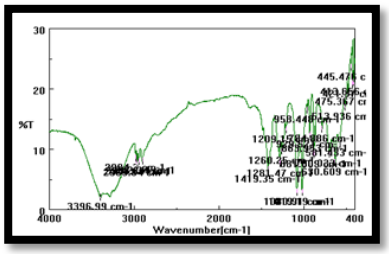
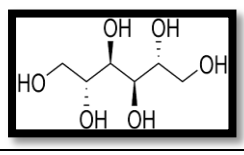


Fig.No.10 IR Spectrum of Mannitol.

Table No. 10 Authentication of Mannitol by IR Spectroscopy

Sr. No.	Observed IR peaks (cm^{-1})		
1	R-OH		3396.99
2	C-C Stretch		2994.609

8.2.2. Crosscarmellose sodium:

IR spectrum shows dominant characteristics peaks of crosscarmellose sodium at 1750, 1000, 3200 for C=O, C-O-C, C-C stretch.

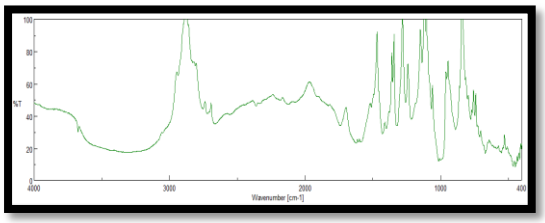
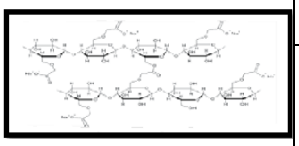


Fig.No.11 IR Spectrum of Crosscarmellose Sodium.

Table No. 11 Authentication of Crosscarmellose Sodium by IR Spectroscopy

Sr. No.	Observed IR peaks (cm^{-1})		
1	C=O		1750
2	C-O-C		1000
3	C-C Stretch		3200

8.2.3. Magnesium Hydroxide:

IR spectrum shows dominant characteristics peaks of magnesium hydroxide at 3443 for OH group.

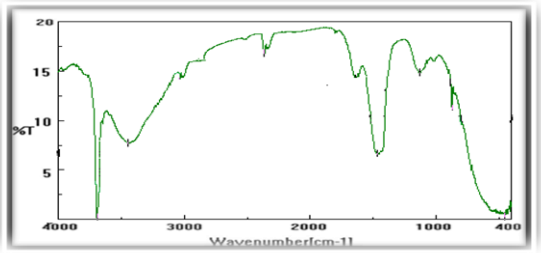
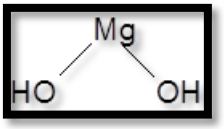


Fig.No.12 IR Spectrum of Magnesium Hydroxide

Table No. 13 Authentication of Magnesium Hydroxide by IR Spectroscopy

Sr. No.	Observed I.R. Peaks (cm^{-1})		
1	OH group		3443.28

8.3.COMPATIBILITY STUDIES:

Compatibility study was carried out by using UV Spectrophotometer at 0^{th} week and fourth week. The scanning values were found in the range of 283 to 286 for sucralfate and 276 to 279 for diclofenac potassium. The change in the λ_{max} was due to possible interaction between crosscarmellose sodium and drugs. While this change remains constant throughout testing. Therefore it is enough to consider that drug is compatible with given excipient.

Table No.13. Compatibility study by UV-Visible Spectrophotometer

Sr. No.	Name	λ_{max} at 0^{th} week (nm)	λ_{max} after 4^{th} week (nm)
		Room temp.	Room temp.
1.	Sucralfate+Mannitol	283	283
2.	Sucralfate+C.C.S	283	285
3.	Sucralfate + $Mg(OH)_2$	283	283
4.	Diclofenac + Mannitol	276	276
5.	Diclofenac+ C.C.S.	276	278
6.	Diclofenac + $Mg(OH)_2$	276	276
7.	Sucralfate+ Diclofenac	283 and 276	283 and 276

8.4.METHOD VALIDATION:

The method was validated according to ICH Q2B guidelines for validation of analytical procedure in order to determine linearity, sensitivity, precision, LOD, LOQ and accuracy for the analyte.

1. Calibration Curve:

1.1. Calibration curve of Sucralfate at 283nm and 276nm

Table No. 14 Absorbance of Sucralfate at (a) 283nm and (b) 276nm.

Sr. No.	Concentration (µg/ml)	Absorbance (283nm)	Absorbance (276nm)
1	0.1	0.0816±0.0122	0.0268±0.0291
2	0.2	0.1586±0.0261	0.0423±0.0254
3	0.3	0.2476±0.0232	0.0648±0.0176
4	0.4	0.3294±0.0198	0.0839±0.0298
5	0.5	0.4118±0.0375	0.1020±0.0317

*mean S.D n = 3

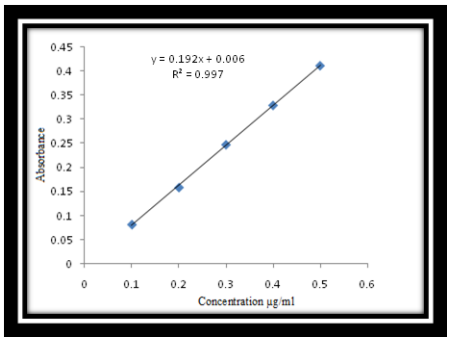


Fig.No.13 Calibration Curve of Sucralfate at 283nm

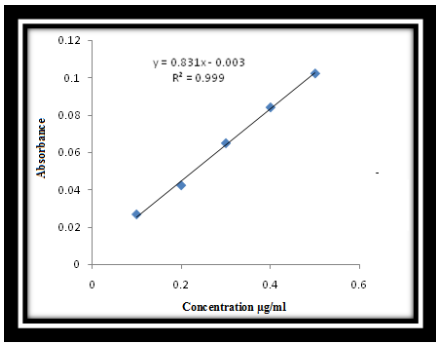


Fig.No.14Calibration curve of sucralfate at 276nm

1.2.Calibration curve of Diclofenac Potassium at 283nm and 276nm

Table No. 15Absorbance of Diclofenac Potassium at (a) 283 nm and (b) 276nm

Sr. No.	Concentration (µg/ml)	Absorbance (283 nm)	Absorbance (276 nm)
1	0.1	0.0345±0.0317	0.1043±0.0412
2	0.2	0.0624±0.0128	0.1804±0.0127
3	0.3	0.0939±0.0119	0.2522±0.0361
4	0.4	0.1238±0.0325	0.3457±0.0112
5	0.5	0.1554±0.0223	0.4375±0.0422

***mean S.D n = 3**

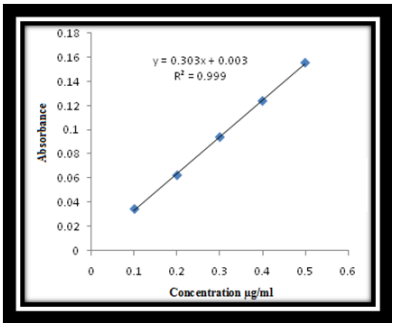


Fig.No. 15Calibration curve of Diclofenac Potassium at 283nm

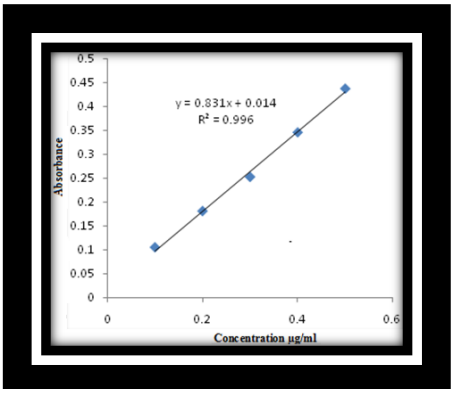


Fig. No.16 Calibration Curve of Diclofenac Potassium at 276nm

Table No. 16. Absorptivity Values for Sucralfate and Diclofenac Potassium

Components	Absorptivity at 283.0 nm	Absorptivity at 276.0 nm
Sucralfate (x)	8161.52 (ax_1)	2212.61 (ax_2)
Diclofenac Potassium (y)	2754.87 (ay_1)	7301.28 (ay_2)

SIMULTANEOUS EQUATIONS:

SIMULTANEOUS EQUATIONS:

$$C_{SUC} = \frac{A_2a_{y1} - A_1 a_{y2}}{a_{x2} a_{y1} - a_{x1} a_{y2}} \quad \text{----------(1)}$$

$$C_{DP} = \frac{A_1a_{x2} - A_2a_{x1}}{a_{x2} a_{y1} - a_{x1} a_{y2}} \quad \text{---------- (2)}$$

2. Precision:

The method was established by analyzing various replicates of sample. The solutions were analyzed thrice, in order to record intra-day and inter-day variation in the result. The result obtained for mean are good, standard deviation is within the range and percentage relative standard deviation was found below 2% signifies the precision of the method. The results obtained for intra-day precision are shown in table No.17, 18, 19 and 20.

Table No.17. a) Intraday precision for Sucralfate at 283 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	%RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.1582	0.1586	0.1550	0.1572	0.0681	0.1651
0.3	0.2471	0.2476	0.2477	0.2474	0.0125	0.2068
0.4	0.3298	0.3294	0.3299	0.3297	0.0256	0.0310

***mean S.D n = 3**

b) Intraday precision for Sucralfate at 276 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	%RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.0419	0.0423	0.0426	0.0422	0.0010	0.4732
0.3	0.0638	0.0648	0.0647	0.0644	0.0031	0.9984
0.4	0.0836	0.0839	0.0835	0.0837	0.0012	0.3010

***mean S.D n = 3**

Table No.18. a) Intraday precision for Diclofenac Potassium at 283 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.0621	0.0622	0.0624	0.0622	0.0023	0.4942
0.3	0.0936	0.0933	0.0939	0.0936	0.0071	0.1928
0.4	0.1241	0.1244	0.1238	0.1241	0.0025	0.0428

***mean S.D n = 3 b) Intraday precision for Diclofenac Potassium at 276 nm**

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.1804	0.1807	0.1810	0.1807	0.0030	1.4255
0.3	0.2522	0.2499	0.2521	0.2514	0.0041	1.0448
0.4	0.3457	0.3450	0.3448	0.3451	0.0015	1.5573

***mean S.D n = 3**

Table No.19. a) Interday precision for Sucralfate at 283 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.1498	0.1586	0.1556	0.1547	0.0110	0.2409
0.3	0.2412	0.2476	0.2487	0.2458	0.0023	0.8806
0.4	0.3250	0.3294	0.3266	0.3270	0.0065	0.2053

***mean S.D n = 3**

b) Interday precision for Sucralfate at 276 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.0399	0.0422	0.0416	0.0412	0.0114	0.6632
0.3	0.0641	0.0639	0.0633	0.0637	0.0028	0.8978
0.4	0.0810	0.0817	0.0811	0.0813	0.0031	0.2220

***mean S.D n = 3**

Table No.20. a) Interday precision for Diclofenac Potassium at 283 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.0625	0.0619	0.0620	0.0621	0.0133	1.367
0.3	0.0940	0.0936	0.0945	0.0940	0.0127	0.7431
0.4	0.1233	0.1211	0.1239	0.1227	0.0012	0.2543

***mean S.D n = 3**

b) Interday precision for Diclofenac Potassium at 276 nm

Conc. (µg/ml)	Absorbance (283 nm)			Mean	±S.D.	% RSD
	Trail 1	Trail 2	Trail 3			
0.2	0.1791	0.1821	0.1855	0.1822	0.0110	0.3180
0.3	0.2499	0.2531	0.2512	0.2514	0.0180	1.6553
0.4	0.3411	0.3466	0.3144	0.3340	0.0140	0.6157

***mean S.D n = 3**

3. Analysis of prepared formulation:

My formulationcontained, 700 mg of Sucralfate and 50 mg of Diclofenac Potassium, which were used for analysis. The statistical data obtained after replicate determinations (n = 3) is shown below.

Table No.21.Analysis of Tablet formulation.

Sr. No.	Label Claim (mg)		Amount found (mg)		% of Label Claim	
	Sucralfate	Diclofenac Potassium	Sucralfate	Diclofenac Potassium	Sucralfate	Diclofenac Potassium
1.	700	50	700.00	50.26	100.00	100.52

2.	700	50	700.70	50.15	100.10	100.30
3	700	50	700.45	49.98	100.06	99.96

Table no.22.Absorbance values for the Tablet

Sr. No.	A_1 (283.0 nm)	A_2 (276.0 nm)
1.	0.3190	0.2778
2.	0.3191	0.2781
3.	0.3193	0.2781
Mean	0.3192	0.2780

Table no.23.Statistical Validation of Tablet formulation

Component	Mean	±SD	% RSD	Standard Error
Sucralfate	100.05	0.9028	0.8953	0.5212
Diclofenac Potassium	100.26	1.007	0.9984	0.5812

Recovery:

Recovery studies were carried out by standard addition method at three levels, 80%, 100%, and 120%. In this method known amounts of standard drug solution was added to pre-analyzed tablet solution and absorbance was measured at 283 nm and 276 nm. At each level three determinations were performed,the results of mean, standard deviation were within the range and percentage relative standard deviation was below 2 %, which signifies that percentage recovery was in the limit. Result of recovery study isshown below.

Table no. 24: a) Recovery studies for Sucralfate

Level of % Recovery	Amount present (mg/tab)		Amount added (mg)		Amount Found of Sucralfate	% Recovery
	Sucralfate	Diclofenac Potassium	Sucralfate	Diclofenac Potassium	At 283 nm	Sucralfate
80	700	50	560	0	1238.96	98.33
	700	50	560	0	1280.91	101.66
	700	50	560	0	1252.94	99.44
100	700	50	700	0	1266.3	100.5
	700	50	700	0	1393	99.5
	700	50	700	0	1390.2	99.3

120	700	50	840	0	1556.79	101.09
	700	50	840	0	1548.32	100.54
	700	50	840	0	1534.30	99.62

Table no. 25: b) Statistical Validation for recovery studies of Sucralfate

Level of %Recovery	%Mean Recovery	Standard Deviation	%RSD	Standard error
	Sucralfate	Sucralfate	Sucralfate	Sucralfate
80	99.81	1 .696	1.6992	0.9789
100	99.76	0.6429	0.6445	0.3712
120	100.42	0.7374	0.7343	0.4257

Table no. 26 a): Recovery studies for Diclofenac Potassium

Level of % Recovery	Amount present (mg/tab)		Amount added (mg)		Amount Found of Sucralfate	%
	Sucralfate	Diclofenac Potassium	Sucralfate	Diclofenac Potassium	At 276 Nm	D
80	700	50	0	40	90.495	
	700	50	0	40	89.496	
	700	50	0	40	90.747	
100	700	50	0	50	100.25	
	700	50	0	50	100.5	
	700	50	0	50	99.75	
120	700	50	0	60	109.725	
	700	50	0	60	110.495	
	700	50	0	60	109.85	

	Batch B1		Batch B2		Batch B3		Batch B4	
Time (min)	**Intact**	**Crushed**	**Intact**	**Crushed**	**Intact**	**Crushed**	**Intact**	**Crushed**
5	36.89	59.96	33.90	44.34	52.61	66.96	41.68	54.99
10	79.49	93.76	57.27	81.76	95.24	96.21	79.63	93.71
15	92.81	--	84.26	93.10	--	--	91.42	--
20	--	--	91.44	--	--	--	--	--

Table no. 27 b): Statistical validation for Diclofenac Potassium

Level of % Recovery	% Mean Recovery	Standard Deviation	% RSD	Standard Error
	Diclofenac Potassium	Diclofenac Potassium	Diclofenac Potassium	Diclofenac Potassium
80	100.27	0.7351	0.73312	0.4244
100	100.16	0.3819	0.38129	0.2205
120	100.02	0.3912	0.39118	0.2259

4. Method validation parameter:

All parameters are validated as per ICH guidelines. Accuracy, precision and Linearity are checked. Result of validation is shown below.

Table no.28: Summary of the present study Result (UV –method)

Parameters	Sucralfate	Diclofenac Potassium
Detection Wavelength	283.0nm	276.0nm
Beers Law Limit	0.1-10µg/ml	0.1-10µg/ml
Absorptivity	gm/100ml	gm/100ml
Regression Equation	y = mx + c	y = mx + c
Slope	0.192	0.831
Intercept	+0.006	+0.014
Correlation Coefficient	0.997	0.996

Y=A+B*C, where C is the concentration in µg/ml and Y is absorbance unit

8.5. Disintegration of Trial Batches:

Table No. 29. Disintegration of trail batches

Batch No.	Disintegrant	Time
1	Starch	2 min 58 sec
2	Microcrystalline Cellulose	7 min 25sec
3	Chitosan	1 min 53 sec
4	Crosscarmellose Sodium	4 min 18 sec

8.6. DRUG RELEASE STUDY OF TRIAL BATCHES:

Table No. 30. Drug dissolution study of trial batches of Sucralfate. [B1 to B4]

Table No. 31. Drug dissolution study of trial batches of Diclofenac Potassium. [B1 to B4]

Total four batches were formulated in the trial batches, all the four batches were having different ingredients but the concentration was kept the same. In batch B1 there was Starch used, in batch B2 there was Microcrystalline cellulose used, in batch B3 there was Chitosan added and in the last, batch 4 there was Crosscarmellose sodium used.

% Drug release study of trial batches.								
	Batch B1		Batch B2		Batch B3		Batch B4	
Time (min)	**Intact**	**Crushed**	**Intact**	**Crushed**	**Intact**	**Crushed**	**Intact**	**Crushed**
5	53.64	59.26	41.22	50.42	55.62	61.92	49.51	59.62
10	93.11	95.94	79.76	78.09	94.91	96.44	84.72	97.91
15	--	--	89.76	96.12	--	--	96.66	--
20	--	--	94.21	--	--	--	--	--

The batch B4 was the appropriate batch, which showed the maximum drug release,but more important was its taken time for disintegration, which fits my aim of having maximum drug release within 20min and also due to its slow disintegration, the patient will not have any problem, which is found when there is complete rupture of tablet within few seconds after ingestion. In spite of its less drug release as compared to other batches.

8.7. EVALUATION OF FORMULATED GRANULES:

The flow properties of powders are important for preparing dosage forms, when fluidity is poor, it must be improved by granulation or addition of excipients.

8.7.1. Bulk density and Tapped density:

Bulk density may influence compressibility and flow properties. The bulk density of the powder was found 0.53 ± 0.11 gm/cm^3 .The tapped density was found to be 0.49 ± 0.01 gm/cm^3. Shows good compressibility of powder. The values of individual batches are listed in table number 29.

8.7.2. Carr's Index:

The value of Carr's Index is between 5-15%, which shows excellent compressibility properties but readings above 23% indicate poor compressibility. Carr's index was found to be 6.981± 0.23 indicating excellent compressibility properties. The values of individual batches are listed in table number 29.

8.7.3. Hausner's Ratio:

It was 1.16± 0.05 for the formulated batch, they had good flow properties. Hausner's ratio is simple method to estimate flow properties. Low range (less than 1.11) was observed of Hausner's ratio that indicates good flow property. The values of individual batches are listed in table number 29.

8.7.4. Angle of Repose:

The angle of repose of powder was determined by the funnel method. The 10gm of accurately weighed powder blends were taken in funnel. The height of the funnel was adjusted 2 cm above the tip off the funnel which just touches the heap of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. The values of individual batches are listed in table number 29.

$$\tan\Theta = h/r$$

Table No. 32. Micromeritics properties of Formulation Batches

Batch	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index	Hausner's Ratio	Angle of Repose (Θ)
F1	0.54 ±0.12	0.60 ±0.01	8.42 ±0.42	1.14 ±0.02	21.01 ±0.50
F2	0.43 ±0.03	0.62 ±0.01	7.12 ±0.68	1.11 ±0.04	21.12 ±0.12
F3	0.52 ±0.04	0.61 ±0.03	8.11 ±0.19	1.14 ±0.07	21.92 ±0.48
F4	0.58 ±0.03	0.49 ±0.04	8.66 ±0.12	1.15 ±0.02	27.9 ±0.11
F5	0.55 ±0.03	0.67 ±0.02	6.88 ±0.43	1.12 ±0.06	20.87 ±0.29
F6	0.51 ±0.09	0.51 ±0.02	7.79 ±0.29	1.14 ±0.03	23.91 ±0.13
F7	0.53 ±0.11	0.49 ±0.01	6.98 ±0.23	1.16 ±0.05	21.96 ±0.49
F8	0.59 ±0.01	0.67 ±0.03	7.11 ±0.20	1.15 ±0.02	18.45 ±0.32
F9	0.52 ±0.08	0.63 ±0.01	7.42 ±0.23	1.14 ±0.07	21.26 ±0.34

***mean S.D n = 3**

8.8. EVALUATION OF TABLET FORMULATION:

8.8.1. Weight variation:

The percentage deviation of all tablets weight was found to be within the limits of IP specifications. This shows uniform die fill during tablet compression. The results are shown in table No.33.

8.8.2. Thickness:

There was no much variation in thickness of tablets in formulation. It shows that granules and powder blends were consistent in particle size and uniform behavior during compression process. The results are shown in table No.33.

8.8.3. Hardness:

The hardness of tablet was measured by Pfizer hardness tester. The results are shown in table No.33.

8.8.4. Disintegration time:

Disintegration time of tablets formulation was 5min 42sec ± 0.98. This is well within limit of IP specification of chewable tablet. The results are shown in table No.33.

8.8.5. Friability:

Friability was found to be 0.15± 0.03. As friability was well below 1% tablets in each formulation can withstand the mechanical shocks.The results are shown in table No.33.

8.8.6. Drug Content:

The drug content of Sucralfate was found to be 98.56% ± 0.71, and that of Diclofenac Potassium was found to be 99.92% ± 0.73. The results of other batches are shown in table No. 33.

Table No. 33.Evaluation of tablets.

Batch	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration time	Drug Content (%)	
						Sucralfate	Diclofenac Potassium
F1	6.6 ±0.06	899.97 ±0.04	7.8 ±0.23	0.21 ±0.04	7 min 05 sec ±0.12 sec	98.42 ±0.69	99.24 ±0.43
F2	6.5 ±0.01	899.99 ±0.06	7.9 ±0.34	0.36 ±0.09	7 min 39 sec ±0.72 sec	97.62 ±0.26	99.56 ±0.23
F3	6.4 ±0.08	899.99 ±0.08	7.9 ±0.31	0.37 ±0.02	8 min 21 sec ±0.32 sec	98.12 ±0.84	99.45 ±0.67
F4	6.5 ±0.07	899.96 ±0.09	7.8 ±0.42	0.13 ±0.05	6 min 21 sec ±0.59 sec	98.86 ±0.57	98.67 ±0.65
F5	6.4 ±0.09	899.98 ±0.02	7.7 ±0.14	0.16 ±0.02	6 min 45 sec ±0.28 sec	98.21 ±0.41	99.00 ±0.82
F6	6.5 ±0.02	899.97 ±0.12	7.8 ±0.16	0.09 ±0.01	6 min 58 sec ±1.31 sec	97.98 ±0.63	99.11 ±0.61
F7	6.6 ±0.08	899.97 ±0.10	7.8 ±0.12	0.15 ±0.03	5 min 42 sec ±0.12 sec	98.56 ±0.71	99.92 ±0.73
F8	6.7 ±0.01	899.98 ±0.11	7.8 ±0.22	0.46 ±0.02	5 min 59 sec ±0.20 sec	98.11 ±0.32	99.16 ±0.44
F9	6.4 ±0.01	899.99 ±0.06	7.9 ±0.23	0.38 ±0.02	6 min 11 sec ±1.22 sec	97.77 ±0.55	99.09 ±0.89

***mean S.D n = 3**

8.9. DISINTEGRATION STUDY:

8.9.1. DISINTEGRATION STUDY OF FORMULATED BATCH:

Table No. 34.Disintegration study of formulated batches.

Batches	Time of Disintegration in Min. and Sec.
F1	7 min. 05 sec.
F2	7 min. 39 sec.
F3	8 min. 21 sec.
F4	6 min. 21 sec.
F5	6 min. 45 sec.
F6	6 min. 58 sec.
F7	5 min. 42 sec.
F8	5 min. 59 sec.
F9	6 min. 11 sec.

]

***mean S.D n = 3**

8.10. DRUG RELEASE STUDY FOR SUCRALFATE:

Table No. 35.Drug dissolution study of formulated batches for sucralfate. [F1 to F4]

% Drug release study of formulated batch								
	Batch F1		Batch F2		Batch F3		Batch F4	
Time (min)	Intact	Crush	Intact	Crush	Intact	Crush	Intact	Crush
5	28.76 ±0.07	46.87 ±0.32	28.51 ±0.46	46.80 ±0.12	27.11 ±0.06	46.05 ±0.04	29.60 ±0.43	47.47 ±0.19
10	51.26 ±0.23	68.45 ±0.2	50.66 ±0.14	68.15 ±0.33	50.52 ±0.41	67.63 ±0.26	56.62 ±0.51	83.63 ±0.33
15	69.86 ±0.08	91.61 ±0.17	69.64 ±0.21	89.10 ±0.24	69.27 ±0.26	88.43 ±0.18	75.12 ±0.07	94.21 ±0.12
20	89.08 ±0.42		88.42 ±0.32		86.56 ±0.25		93.15 ±0.25	

***mean S.D n = 3**

Table No. .Drug dissolution study of formulation batches for sucralfate. [F5 to F6]

%Drug release study of formulated batch								
	Batch F5		Batch F6		Batch F7		Batch F8	
Time (min)	Intact	Crush	Intact	Crush	Intact	Crush	Intact	Crush
5	29.01 ±0.26	47.39±0 .55	29.02 ±0.26	46.94 ±0.22	34.30 ±0.39	49.55 ±0.59	30.76 ±0.68	48.51 ±0.11
10	56.25 ±0.32	83.03 ±0.32	55.80 ±0.43	82.58 ±0.31	58.55 ±0.54	86.16 ±0.23	57.96 ±0.31	84.52 ±0.34

15	71.50 ±0.06	93.15 ±0.54	71.35 ±0.54	92.87 ±0.12	80.35 ±0.08	97.02 ±0.11	79.01 ±0.45	96.42 ±0.21
20	91.54 ±0.44	--	90.40 ±0.24	--	95.11 ±0.12	--	94.41 ±0.24	--

***mean S.D n = 3**

Table No..Drug dissolution study of formulation batches for sucralfate.[F9]

Batch F9		
Time (min)	**Intact**	**Crush**
5	29.61 ±0.06	48.06 ±0.43
10	57.66 ±0.43	83.70 ±0.59
15	77.08 ±0.21	95.64 ±0.08
20	94.01 ±0.14	

***mean S.D n = 3**

8.11.DRUG RELEASE STUDY OF DICLOFENAC POTASSIUM:

Table No. 36. Drug dissolution study of formulation batches for Diclofenac Potassium [F1 to F9]

% Drug release study of formulated batch								
	Batch F1		**Batch F2**		**Batch F3**		**Batch F4**	
Time (min)	**Intact**	**Crush**	**Intact**	**Crush**	**Intact**	**Crush**	**Intact**	**Crush**
5	32.61 ±0.07	50.10 ±0.32	31.16 ±0.46	49.61 ±0.41	30.41 ±0.12	49.50 ±0.39	37.26 ±0.25	50.55 ±0.61
10	61.46 ±0.23	72.11 ±0.21	59.21 ±0.33	69.66 ±0.33	51.16 ±0.26	64.11 ±0.12	72.18 ±0.21	79.17 ±0.33
15	85.12 ±0.42	92.16 ±0.17	84.61 ±0.14	91.84 ±0.24	76.42 ±0.11	90.11 ±0.41	86.27 ±0.53	94.61 ±0.87
20	91.52 ±0.39	-	90.69 ±0.32	-	89.91 ±0.04	-	93.12 ±0.62	-

***mean S.D n = 3**

Table No. Drug dissolution study of formulation batches for Diclofenac Potassium.[F5 to F8]

%Drug release study of formulated batch								
	Batch F5		**Batch F6**		**Batch F7**		**Batch F8**	
Time (min)	**Intact**	**Crush**	**Intact**	**Crush**	**Intact**	**Crush**	**Intact**	**Crush**
5	35.12 ±0.12	50.41 ±0.22	33.16 ±0.34	50.16 ±0.51	41.99 ±0.08	51.22 ±0.23	41.87 ±0.34	51.10 ±0.55
10	72.10	77.71	69.11	74.16	76.42	86.18	74.12	85.16

	±0.45	±0.31	±0.58	±0.09	±0.31	±0.43	±0.45	±0.43
15	85.91 ±0.32	93.12 ±0.43	83.99 ±0.12	92.87 ±0.64	89.61 ±0.42	98.66 ±0.31	88.79 ±0.18	97.92 ±0.22
20	92.46 ±0.61	-	92.12 ±0.49	-	98.09 ±0.11	-	96.01 ±0.62	-

***mean S.D n = 3**

TableNo. Drug dissolution study of formulation batches for Diclofenac Potassium.

Batch F9		
Time (min)	**Intact**	**Crushed**
5	41.23 ±0.09	50.61 ±0.26
10	73.96 ±0.42	84.22 ±0.51
15	88.61 ±0.35	95.79 ±0.07
20	94.91 ±0.27	-

***mean S.D n = 3**

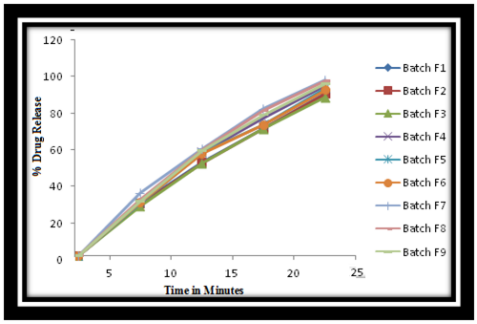


Fig.No.17.In-Vitro Drug Release Study of Intact Sucralfate Tablet.

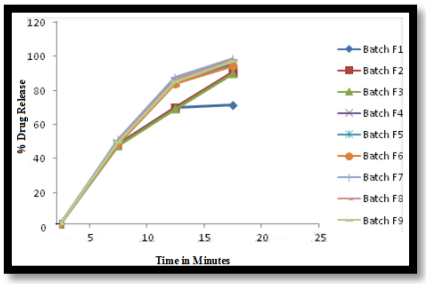


Fig.No 18.In-Vitro Drug Release Study of Crushed Sucralfate Tablet.

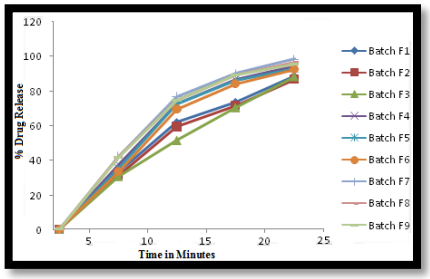


Fig.No. 19.In-Vitro Drug Release Study of Intact Diclofenac Potassium Tablet.

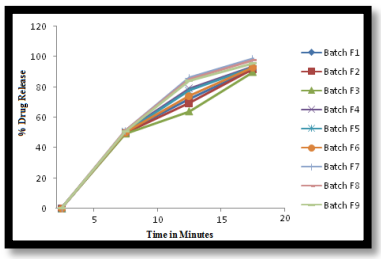


Fig.No.20.In-Vitro Drug Release Study of Crushed Diclofenac Potassium Tablet.

8.12.FACTORIAL DESIGN WITH SURFACE PLOT AND OPTIMIZATION OF PROCESS VARIABLES:

Table No. 37. Coded and Actual Values

Coded values	Actual values	
	X_1	X_2
-1	100	20
0	110	30
1	120	40

Table No. 38. 3^2 full factorial design layout of Sucralfate Drug Release.

Batch No.	Variable level in coded form		% Drug Release	
	X_1	X_2	Intact	Crushed
F1	-1	-1	89.08±0.42	91.61±0.17
F2	0	-1	88.42±0.32	89.10±0.24
F3	1	-1	86.56±0.25	88.43±0.18
F4	-1	0	93.15±0.35	94.21±0.12
F5	0	0	91.54±0.44	93.15±0.54
F6	1	0	90.40±0.24	92.87±0.12
F7	-1	1	95.11±0.12	97.02±0.11
F8	0	1	94.41±0.24	96.42±0.21
F9	1	1	94.01±0.14	95.64±0.08

***mean S.D n = 3**

Table No .39.3^2 full factorial design layout of Diclofenac Potassium Drug Release.

Batch No.	Variable level in coded form		% Drug Release	
	X_1	X_2	Intact	Crushed
F1	-1	-1	91.52±0.39	92.16±0.17
F2	0	-1	90.69±0.32	91.84±0.24
F3	1	-1	89.91±0.04	90.11±0.41
F4	-1	0	93.12±0.62	94.61±0.87
F5	0	0	92.46±0.61	93.12±0.43
F6	1	0	92.12±0.49	92.87±0.64
F7	-1	1	98.09±0.11	98.66±0.31
F8	0	1	96.01±0.62	97.92±0.22
F9	1	1	94.91±0.27	95.79±0.07

***mean S.D n = 3**

An interactive statistical second-order complete model equation was generated to evaluate the selected response which is as follows:

$$Yi = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2\ b_{22}X_2^2$$

Where Y is the predicted response, b_0 is the arithmetic mean response of 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low value to its high value. The interaction (X_1X_2) shows how percentage drug release of formulation changes when tow factors are simultaneously changed, and the exponential terms (X_1^2 and X_2^2) represent the curvature. The coefficient corresponding linear effect ($b_1$and b_2), interaction (b_{12})and the quadric effect (b_{11} and b_{12}) were determined from the result of the experimental design. The % rug release from the 9 batch experiments were used generate predictor equations for sucralfate and diclofenac potassium with independent variable as polymer concentration (X_1) and disintegrant concentration (X_2). The result of multiple regression analysis of variance test (ANOVA) are summarized below.

Conclusion- All the tablets showed satisfactory results with respect to hardness, friability, assay and *in vitro* dissolution studies. The trial 'DC' *i.e.* tablet prepared by direct compression method had the better dissolution rate when compared to trial 'NAQ' and 'AQ' *i.e.* prepared by non aqueous and aqueous methods, respectively.The drug release of intact Diclofenac Potassium was found to be 98.09% the drug release was purely depend on the factor [b1] that was Crosscarmellose sodium. It indicates that increasing the concentration of Crosscarmellose sodium lads to increase in the drug release and increase in concentration of mannitol leads to decrease in the drug release. As the factor [b1] shows the positive number, which indicates that the Crosscarmellose Sodium has a positive impact on the drug release. And the factor [a1] showed the negative effect, which was mannitol. The relationship between variables that is [a1] Mannitol and [b2] Crosscarmellose sodium was further elucidated by using the response plot. The percentage release of intact Sucralfate tablet showed all values within limits, in which the [a1] showed the negative effect on the drug release and [b1] which is Crosscarmellose sodium shows the positive effect on the drug release. The coefficient value of [a1] was found to be less than that of [b1], which indicates that Crosscarmellose sodium has more effect of drug release than mannitol. The drug release of Sucralfate was found to be 97.02%, in which the [a1] was of mannitol,

Reference:-

1. Health and Safety Executive. EH40/2002: Occupational Exposure Limits Sudbury; Health and Safety Executive, 2002. (http://www.hse.gov.uk/press/2003/c03014.htm) .
2. Lachman L., Liberman H. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, Bombay. 1987: 3(6): 297-299.
3. Adultone M.E. Pharmaceutics- The Science of Dosage from Design, 1998, 1(6), Churchill Livingstone. 247-248, 603-606.
4. Rudnic, EM and Schwartz, J.D. Oral Dosage Forms Remington: The Science and Practice of PharmacyGennaro AR(Eds), Lippincott Williams and Wilkins, USA, page 858.
5. Gohel, M.C., A Review of co-processed Directly Compressible Excipients JPharma PharmaceutSci.,8, 76-93.
6. Rubinstein, MH., 2000 Tablets In: "Aulton" , ME(Ed.), Pharmaceutics, The Science Of Dosage Form Design Churchill Livingstone, Edinburgh London Melbourn and New York, page 305.
7. Lindgren S., Janzon L., Prevalence of swallowing complaints and clinical findings. Medical clinics of North America, 1993; 77: 3-5.

Bannwarth B, Gaucher A, Burnel D, Netter P, Longterm sucralfate therapy J Rheumatol, 1986;13(6):1187.

8 Bolin TD, Davis AE, Duncombe VM, Billingon B.,Role of maintenance sucralfate in prevention of duodenal ulcer recurrences, Am J Me 1987 sep;83(suppl 3B)91-94.
9 Borella LE, Seethaler K, Lippmann W, Sucralfate-antipeptic, antiulcer activities and antagonism of gastric emptying,Arzneimittelforschung 1979;29:793-798.
10 Brandstaetter G, Kratochvil P, Comparison of two sucralfate dosages (2gm twice a day versus 1gm four times a day) in duodenal ulcer healing, Am J Med 1985 Aug 30;79(suppl 2C):36-38.
11 Burgess E, Muruve D,Significant increase in serum aluminium levels during sucralfate therapy in patients with chronic renal disease increased renal Al clearance., Presented at the National Kidney Foundation Annual Scientific Meeting, 30-Dec-1990.
12 Becker C, Dressaman JB, Junjinger HE, Kopp S, Midha KK, Shah VP, Stavchansky SA, Barends DM., Biowaiver monographs for immediate release solid oral dosage forms: Prednisolone, J PharmaSci 96:27-37.
13 Riess W, Stierlin H, Degen P, Faigle JW, Greardin A, Sulc M, Theobald W, Wagner J. 1978. Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren,Scand J RheumatoSppl 22:17-29.
14 Hendriksen BA, Sanchez Felix MV, Bolger MB., The composite solubility versus pH profle and its role in intestinal absorption prediction, AAPS Pharma Sci. 2003;5:1-15.
15 Tantishaiyakul V. Prediction and characterization of a range of diclofenac salts using PLS and molecular modeling,Int J Pharm 275: 2004;133-139.
16 O'Connor KM, Corrigan OI, Preparation and characterization of a range of diclofenac salts,Int J Pharma 226;2001;163-179.
17 Moore N.,Diclofenac potassium 12.5mg tablets for mold to moderate pain and fever: A review of its pharmacology, clinical efficacy and safety.Clin Drug Invest 27: 2007;163-195.