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Research Article

**FORMULATION AND EVALUATION OF MESALAMINE
TABLETS FOR COLON DRUG DELIVERY SYSTEMS****Raghvendra Singh Yadav*¹, Dr. Madhusudhan Reddy A²**Department Of Pharmaceutics ,Princeton College Of Pharmacy, Pocharam, Hyderabad,
Telangana 500088.**Abstract:**

Objective of the current study is to develop colon targeted drug delivery systems for Mesalamine. Eudragit S-100 and Ethyl cellulose is used as polymers in this drug delivery system. The colon targeted tablet was prepared by direct compression technique. Study of the Preformulation characteristics and FTIR studies indicates that there was no interaction between Mesalamine and excipients used. The formulated tablets were tested for both pre-compression parameters and post compression parameters as per requirements of standards. Pre-compression parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and compressibility index. The results obtained indicate that it has good flow property for direct compression. From among the entire batches, formulation F4 showed 98.90% drug release at 24 hrs. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the trial F4 was considered as best formulation.

Keywords: Mesalamine, Eudragit S-100, Ethyl cellulose, and colon targeted drug delivery systems.

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INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery and the design of dosage forms must be developed within the intrinsic characteristics of GIT physiology, pharmacokinetics and pharmacodynamics and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

TABLETS:⁵

Tablets are solid dosage forms each containing a unit dose of one or more medicaments. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets.

Tablets are usually solid, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may exist in other shapes like triangular, rectangular, etc also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking.

Advantages of Tablets:⁶

- ✓ They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- ✓ They are in general the easiest and cheapest to package and strip of all oral dosage forms.
- ✓ They may provide the greatest ease of swallowing with the least tendency for “hang-up” above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.

- ✓ They lend themselves to certain special release profile products, such as enteric or delayed release products.
- ✓ They are better suited to large-scale production than the other unit oral forms.
- ✓ They have the best-combined properties of chemical.
- ✓ Cost is low.
- ✓ Lighter and compact.
- ✓ Easy to swallowing with least tendency for hang-up.
- ✓ Sustained release product is possible by enteric coating.
- ✓ Objectionable odour and bitter taste can be masked by coating technique.
- ✓ Suitable for large scale production.
- ✓ Greatest chemical and microbial stability over all oral dosage form.
- ✓ Product identification is easy and rapid requiring no additional steps when employing an embossed and or monogrammed punch face.

Disadvantages of the tablets:

- ✓ Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low density character.
- ✓ Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features are very challenging for the formulators.
- ✓ Difficult to swallow in case of children and unconscious patients.
- ✓ Bitter tasted drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

Various Types of Tablets:⁷

Based on the route of administration or the function, the tablets are classified as follows.

Tablets ingested orally.

- a) Compressed tablets
- b) Multiple compressed tablets
 - I) Layered tablets
 - II) Compression coated tablets
- c) Repeat action tablets
- d) Delayed action and enteric coated tablets
- e) Sugar and chocolate coated tablets
- f) Film coated tablets
- g) Chewable tablets

2. Tablets used in the oral cavity.

- a) Buccal tablets
- b) Sublingual tablets
- c) Troches and Lozenges
- d) Dental cones

Tablets administered by other routes.

- a) Implantation tablets
- b) Vaginal Tablets

Tablets used to prepare solution.

- a) Effervescent tablets
- b) Dispensing tablets
- c) Hypodermic tablets
- d) Tablets triturates

PHARMACEUTICAL INGREDIENTS USED IN THE FORMULATION OF TABLETS:**1. Active ingredients**

A drug substance is the Active Pharmaceutical Ingredient (API) or component that produces pharmacological activity.

2. Fillers/diluents

Diluents are used as excipients for direct compression formulas have been subjected to prior processing to give them flow ability and compressibility.

Eg: Lactose, Dibasic calcium phosphate, Dextrose, Calcium carbonate, Magnesium carbonate, Starch, Sucrose, Mannitol.

3. Binders

Binders are agents which are used to impart cohesive qualities to the powdered material. Binders are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets.

Eg: Povidone, Acacia, Gelatin, HPMC, Polyvinyl pyrrolidone, Hydroxypropylcellulose.

4. Disintegrants

Disintegrants are substances or a mixture added to a tablet formulation to facilitate its breakup or disintegration of the tablet after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution.

Eg: Microcrystalline cellulose, Starch, Crosscarmellose sodium, Sodium starch glycolate.

5. Lubricants⁸

During compression lubricants acts as to reduce the interface between the face of the die and the surface of the tablet and act to reduce the friction at this interface during ejection of the tablet from the tablet press. Inadequate lubrication of this interface results in the production of tablets with a pitted surface and is due to their ability of the tablet surface to detach from the surface of the tablet die. There are two main categories of lubricants: (1) insoluble and (2) soluble. Insoluble lubricants are added to the final mixing stage prior to the tablet compression. Eg: Magnesium stearate, Stearic acid, Glyceryl palmitostearate.

Soluble lubricants are principally employed to overcome the possible deleterious effects of their insoluble counterparts on the time required for tablet disintegration and drug dissolution. Eg:

Polyethylene glycol, Polyethylene stearate, Lauryl sulphate salt.

6. Glidants⁹

Glidants are added to the formulation in order to improve the flow properties of the material to be fed into the die and sometimes aid in particle rearrangement within the die during the early stages of compression. They may act by interposing their particles between those of the other components and so, by virtue of their reduced adhesive tendencies, lower the overall interparticulate friction of the system.

Eg: Talc, Colloidal silicon dioxide.

7. Adsorbents

Adsorbents are used whenever it is required to include a liquid or semisolid component, e.g. a drug or a flavour, within the tablet formulation. As the production of tablets requires solid components, the liquid/semisolid constituent is adsorbed on to a solid component which, in many cases, may be one of the other components in the tablet formulation (e.g. diluent) during mixing. If this approach is not possible, an adsorbent is specifically included in the formulation.

Eg: Magnesium oxide/Carbonate, kaolin/Bentonite.

8. Sweetening agents/flavours

Sweetening agents and flavours (in accordance with other dosage forms) are employed to control the taste and hence the acceptability of tablets. These agents are of particular importance if the conventional tablet contains a bitter drug or, more importantly, if the tablet is a chewable tablet.

Eg: Aspartame, Sucralose, Sucrose, Glycerine, Mannitol, Sorbitol, Acesulfame potassium. Flavouring agents are incorporated into the formulation to give the tablet a more pleasant flavour or mask an unpleasant one. Eg: Chocolate, Peppermint, Pineapple and Vanilla flavour.

9. Colours

Colorants do not contribute to the therapeutic activity and to improve the product bioavailability or stability. Their main role is to facilitate identification and to enhance the aesthetic appearance of the product. All colorants used in pharmaceuticals must be approved and certified by the FDA. Some commonly used Pharmaceutical colorants are,

Eg: Erythrosine, Tartrazine, Sunset Yellow, Brilliant blue.

TABLET PROCESSING:

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation, or dry granulation methods. Method chosen depends on the ingredients, individual characteristics like flow property, compressibility etc. Right choice of method requires thorough investigation of each proposed ingredient in the

formula for comprehensive approach for

interactions and stability.

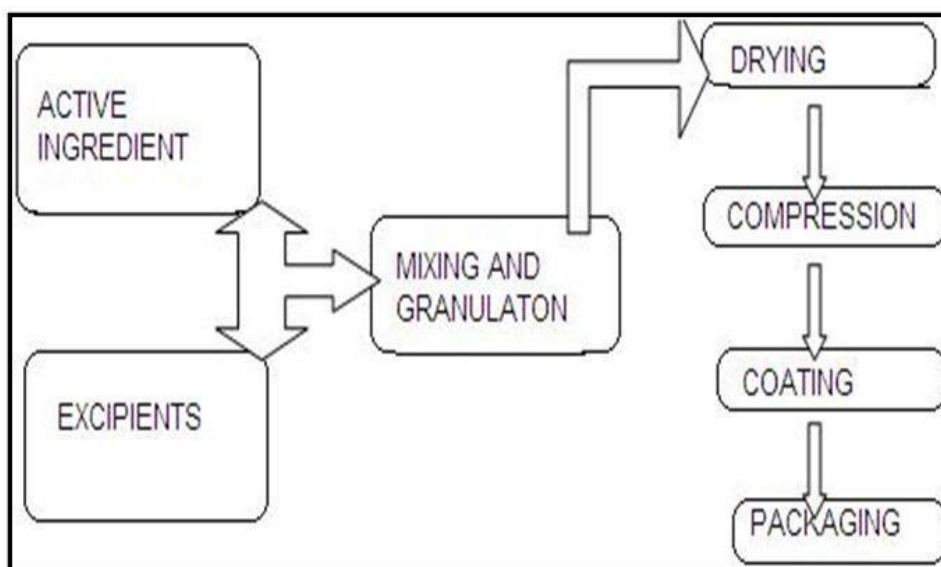


Figure.1. Various Unit Operation Sequences In Tablet Manufacturing

Table No:1 Tablet manufacturing methods – advantages and Limitations

Methods	Advantages	Limitations
Direct compression	Simple, Economical process No heat/moisture, good for unstable compounds.	Not suitable for all API, generally limited to lower dose compounds Segregation potential Expensive excipients.
Wet granulation Aqueous	Robust process suitable for most compounds. Imparts flowability to a formulation. Can reduce elasticity problems. Coating surface with hydrophilic polymer can improve wet-ability. Binds API with excipients thus reduce in segregation potential.	Expensive, Time and energy consuming process. Specialized equipments required. Stability issues for moisture sensitive and thermolabile API with aqueous granulation.
Wet granulation Non- aqueous	Suitable for moisture sensitive API. Vacuum drying techniques can remove or reduce need for heat.	Expensive equipment. Need organic facility. Solvent recovery issues. Health and environment issues.
Dry granulation	Eliminates exposure to moisture and drying.	Dusty procedure. Not suitable for all compounds. Slow process.

MANUFACTURING DEFECTS IN TABLETS:

During the routine production of tablets, so many defects arise with the finished tablets which may be due to either some faults in the formulation or in the tablet equipment and sometimes due to both of these reasons. Some defects are noticed immediately during

manufacturing, but others may be noticed on storage as in the case of capping. Therefore it is important to perform tests at the start and during production in order to make prompt remedial action. The defects are:

a) Defects during the processing of tablets are

- Capping
- Lamination
- Cracking

b) Defects due to excipients

- Picking
- Sticking
- Binding
- Chipping

c) Defects due to other factors are

- Mottling

d) Defects due to machine are

- Poor flow pattern
- Double impression

COATING OF TABLETS

The application of coating is usually based on one or more of the following:

- To mask the taste, odour or colour of the drug.
- To provide physical and chemical protection to the drug.
- To control the release of the drug.

Types of coating:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Extended release coating

Layers of coating in the formulation:

1. **Tablet core**
2. **Seal coating** acts as an inert intermediate layer between the core and outer layer (which are not compatible with one another).
3. **Enteric coating** acts as an outer layer which is resistant to gastric juice.

Enteric coatings:¹⁰

Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intention is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by

* To protect acid-labile drugs from the gastric fluid.

* To protect gastric distress or nausea due to

- To protect the drug from the gastric environment of the stomach with an acid-resistant coating.
- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.
- To provide pharmaceutical elegance by use of special colour.

irritation of gastric mucosa. The coatings that are used now a day to produce enteric effects are primarily mixed acid functionality and acid ester functionality, synthetic, or modified natural polymers. The most extensively used polymers are Cellulose acetate, polyvinyl acetate, polyhydroxy propyl methyl cellulose, Methacrylic acid copolymers. All these polymers have the common feature of containing the dicarboxylic, phthalic acid in partially esterified form. These polymers, being acid esters are insoluble in gastric media that have the pH of about

4. And then leave the stomach and enter into the duodenum (pH 4-6) and further along the small intestine, where the pH is increased to a range of (pH 7-8). The primary mechanism, by which these polymers lose their integrity, is there by admitting the releasing drug to the intestinal fluid. In this ionization of the residual carboxyl groups on the chain and subsequent hydration.

Important reasons for enteric coating are as follows:

irritation from drug.

* To deliver drugs intended for local action in the intestines.

* To provide a delayed release component to repeat actions.

* Protect the drugs from harmful effect of the gastric contents; some of the drugs

Ideal enteric coating materials should have the following properties:

- * Resistance to gastric fluids.
- * Ready susceptibility to or permeability to intestinal fluids.
- * Compatibility with most coating solution components and the drug substrates.

Enteric Coating Materials:

Enteric coatings polymers are selectively insoluble substances. They won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine. Most enteric coatings won't dissolve in solutions with a pH lower than 5.5.

Commonly-used enteric coating polymers:

- * Methacrylic acid copolymers

The earliest enteric coatings utilized formalized gelatin, this was unreliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac, disadvantage was polymerization with time, and

➤ **Cellulose Acetate Phthalate (CAP) :**

Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

➤ **Poly Vinyl Acetate Phthalate (PVAP) :**

Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrates at pH 5.

➤ **Hydroxy Propyl Methyl Cellulose Pthalate (HPMCP):**

It is available in two grades HP50 and HP55. HP55 solutions are more viscous than HP50. HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5.

EVALUTION OF TABLET

Tablets formulated may undergo physical and chemical changes thereby altering the bioavailability of the dosage form. The tablets are to be evaluated before dispensing to maintain their stability and bioavailability throughout its shelf life. Evaluation of tablets can be carried as follows:

are prone to be hydrolyzed in acid media (Eg, omeprazole, pantaprazole)

* The film should not change on aging.

* Formation of continuous film.

* Non-toxicity.

* Low cost.

* Ease of application.

* Cellulose acetate (and its succinate and phthalate version)

* Polymethacrylic acid/acrylic acid copolymer

* Hydroxypropyl methyl cellulose phthalate (HPMCP)

* Polyvinyl acetate phthalate (PVAP)

* Hydroxy ethyl cellulose phthalate

* Cellulose acetate tetra hydro phthalate

resulting in poor dissolution of the coating. The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.

It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer.

➤ **Methacrylic acid copolymers: ¹¹**

Two grades are available A, B and C which differs in the ratio of free carboxyl to ester groups therefore:

Type A - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio 1: 2: 0.2 and soluble in intestinal fluid from pH 6.

Type B - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio of 1:2:0.1 and soluble in intestinal fluid from pH 7.

Type C - Poly (methacrylic acid, ethyl acrylate) 1:1 and soluble in intestinal fluid from pH 5.5.

a) Unofficial tests

- Tablet appearance
- Organoleptic properties
- Identification markings on tablet
- Size and shape of the tablet
- Thickness of tablet
- Hardness of tablet
- Friability of tablet

b) Official tests

- Weight variation test
- Content uniformity test

MATRIX TABLET^{12,13}

Matrix tablets may be defined as the “oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants”. These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. **ADVANTAGES OF MATRIX TABLET:**

- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.

DISADVANTAGES OF MATRIX TABLET

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

CLASSIFICATION OF MATRIX TABLETS:

On the Basis of Retardant Material Used:
Matrix tablets can be divided into 5 types.

1. Hydrophobic Matrices (Plastic matrices)¹⁴

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug

- Disintegration test
- Dissolution test.

- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improve the bioavailability of some drugs.
- Improve of the ability to provide special effects.

is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices¹⁵

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices¹⁶

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable

controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy ethylcellulose; Hydroxy propylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix¹⁷⁻²⁰

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. Macro porous Systems: In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm . This pore size is larger than diffusant molecule size.

2. Micro porous System: Diffusion may occurred in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 $\text{\AA}$, which is slightly larger than diffusant molecules size.

3. Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

POLYMERS USED IN MATRIX TABLET²¹

- **Hydrogels** Polyhydroxyethylmethacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
- **Soluble polymers** Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
- **Biodegradable polymers** Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters
- **Non-biodegradable polymers** Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)
- **Mucoadhesive polymers** Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
- **Natural gums** Xanthan gum, Guar gum, Karaya gum, Locust bean gum

EFFECT OF RELEASE LIMITING FACTOR ON DRUG RELEASE:²²⁻²³

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A. Polymer hydration:

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-

polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility:

Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility:

In view of *in-vivo* (biological) sink condition maintained actively by hem perfusion, it is logical that all the *in-vitro* drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of *in vitro* drug release profile with *in- vivo* drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy

MATERIALS

Aceclofenac-Provided by SURA LABS, Dilsukhnagar, Hyderabad, Deflazacort Procured From Manus Aktteva Biopharma LLP ,India. Provided by SURA LABS, Dilsukhnagar, Hyderabad.Eudragit S-100 Merck Specialities Pvt Ltd, Mumbai, India,Ethyl Cellulose-Merck Specialities Pvt Ltd, Mumbai, India,Hydroxypropyl Cellulose-Yarrow Chem. Products, Mumbai, India,Lactose-Shakti Chemicals, Mehsana, India,PVP K30 Merck Specialities Pvt Ltd, Mumbai, India,Magnesium stearate-S. D. Fine Chemicals Ltd., Mumbai, India,Talc-S. D. Fine Chemicals Ltd., Mumbai, India

METHODOLOGY

a) Determination of absorption maxima:

100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL

(10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve:

100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10, 20, 30, 40 and 50 µg/ml of Deflazacort per ml of solution. The absorbance of the above dilutions was measured at 244 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

9.2. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

$$h = \text{Height of the cone ,}$$

r = Radius of the cone base

Formulation composition for tablets

INGREDIENTS (mg)	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9

Deflazacort	6	6	6	6	6	6	6	6	6
Ethyl Cellulose	5	10	15	-	-	-	-	-	-
Eudragit S 100	-	-	-	5	10	15	-	-	-
Hydroxypropyl Cellulose	-	-	-	-	-	-	5	10	15
Lactose	71	66	61	71	66	61	71	66	61
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total Tablet Weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION:

The present study was aimed to developing Controlled release tablets of Deflazacort using various polymers. All the formulations were evaluated for physicochemical properties and *in*

vitro drug release studies.

10.1. Analytical Method

Graphs of Deflazacort were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 244 nm respectively.

Table 10.1: Observations for graph of Deflazacort in 0.1N HCl

Concentration [µg/mL]	Absorbance
0	0
10	0.149
20	0.258
30	0.357
40	0.472
50	0.589

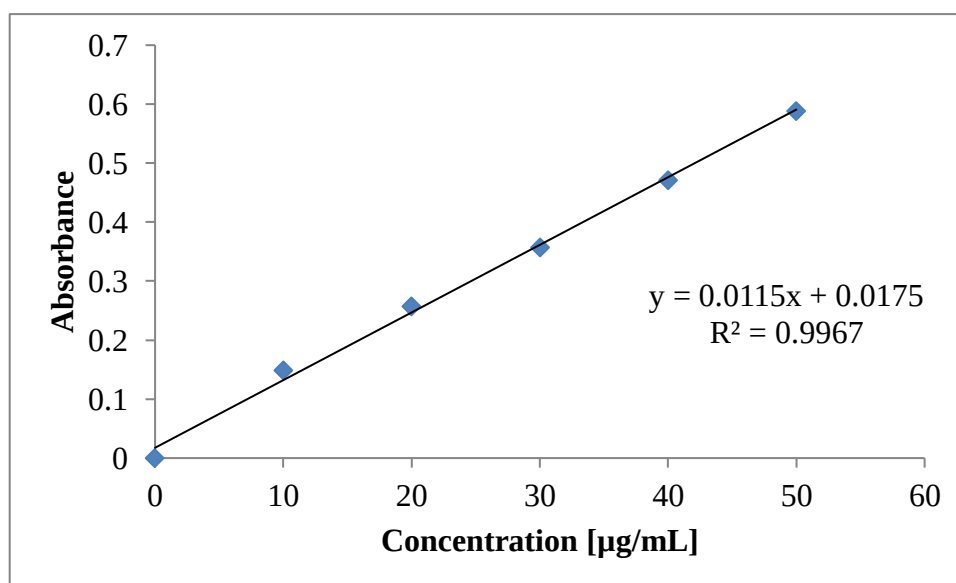


Figure : Standard graph of Deflazacort in 0.1N HCl

Table : Observations for graph of Deflazacort in p H 6.8 phosphate buffer

Conc [µg/ml]	Abs
0	0
10	0.161
20	0.295
30	0.445
40	0.571
50	0.698

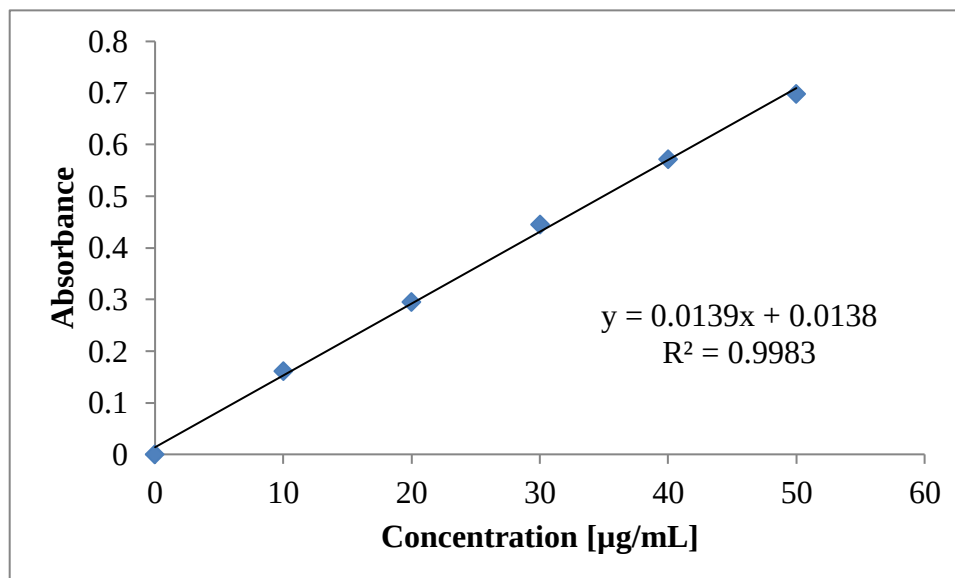
**Figure: Standard graph of Deflazacort pH 6.8 phosphate buffer (244 nm)****Preformulation parameters of powder blend****Table : Pre-formulation parameters of Core blend**

Table : Pre-compression parameters					
Formulations	Bulk Density(gm/cm ²)	Tap Density (gm/cm ²)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Θ)
F1	0.47±0.001	0.53±0.005	14.11±0.10	1.13±0.011	28.76±0.14
F2	0.44±0.003	0.66±0.003	30.45±0.07	1.55±0.007	5.64±0.20
F3	0.41±0.004	0.59±0.004	18.75±0.09	1.22±0.011	7.01±0.13
F4	0.58±0.004	0.52±0.005	8.27±0.28	1.01±0.010	4.28±0.13
F5	0.55±0.003	0.65±0.002	9.52±0.09	1.14±0.009	31.58±0.24
F6	0.42±0.002	0.58±0.002	19.89±0.11	1.26±0.011	4.22±0.22
F7	0.49±0.004	0.51±0.003	19.33±0.050	1.23±0.010	0.19±0.23
F8	0.56±0.006	0.64±0.005	13.63±0.08	1.14±0.010	2.26±0.07
F9	0.43±0.003	0.57±0.002	18.95±0.12	1.05±0.007	7.03±0.16

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41±0.004 to 0.58±0.004 (gm/cm³) showing that the powder has good flow properties. The tapped density of all the

formulations was found to be in the range of 0.51±0.003 to 0.66±0.003 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 8.27±0.28 to 30.45±0.07 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging

between 1.01 ± 0.010 to 1.55 ± 0.007 indicating the powder has good flow properties.

Quality control parameters for tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

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Table: 10.4. *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm ²)	Friability (% lose)	Thickness (mm)	Drug content (%)
F1	98.32	5.7	0.79	2.03	99.73
F2	97.54	5.4	0.48	2.16	97.42
F3	97.22	5.1	0.12	2.79	99.10
F4	99.15	5.8	0.85	2.32	97.89
F5	98.10	5.5	0.55	2.55	98.55
F6	95.48	5.2	0.28	2.78	97.23
F7	98.39	5.9	0.94	2.11	99.91
F8	97.56	5.6	0.68	2.24	99.62
F9	100.02	5.3	0.33	2.47	98.34

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 10.4. The average tablet weight of all the formulations was found to be between 95.48 to 100.02. The maximum allowed percentage weight variation for tablets weighing >100 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 2.03 to 2.79.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 10.4. The average hardness for all the formulations was found to be between (5.1 to 5.9) Kg/cm² which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion

during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 10.4. The average percentage friability for all the formulations was between 0.12 to 0.94 which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 10.4. The drug content values for all the formulations were found to be in the range of (97.23 to 99.91). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table : Dissolution Data of Deflazacort Tablets

	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
In dissolution media 0.1 N HCL									
0	0	0	0	0	0	0	0	0	0
1	27.72	19.85	14.62	23.8	27.69	24.72	17.3	16.75	19.35
2	33.39	20.22	18.21	36.4	30.75	37.54	24.4	23.89	25.92
In dissolution media 6.8 Phosphate Buffer									
3	43.75	26.80	23.85	47.3	43.82	49.35	32.6	24.73	33.55
4	56.49	38.35	28.76	53.4	54.46	53.41	38.8	33.27	37.28
5	59.75	43.24	33.93	64.6	65.21	61.46	46.2	38.10	42.10
6	63.12	44.87	34.24	76.5	73.96	68.38	54.4	44.61	48.83
7	74.69	56.42	45.75	83.14	78.43	77.57	57.95	55.46	53.79
8	85.24	59.96	56.36	94.59	82.22	83.26	61.44	63.75	57.97
9	94.14	64.29	67.24		98.43	94.38	65.82	77.51	65.41
10	93.86	76.34	78.10			99.19	74.49	80.28	71.11
11		83.89	80.96				78.20	88.31	72.52
12		88.21	84.75				86.15	96.94	78.63

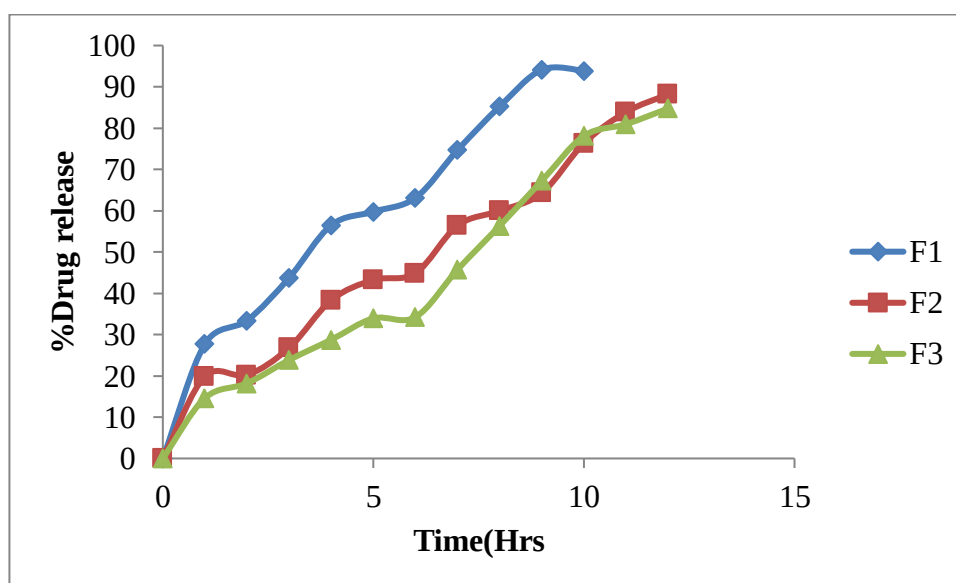


Fig : Dissolution profile of Deflazacort (F1, F2, F3 formulations).

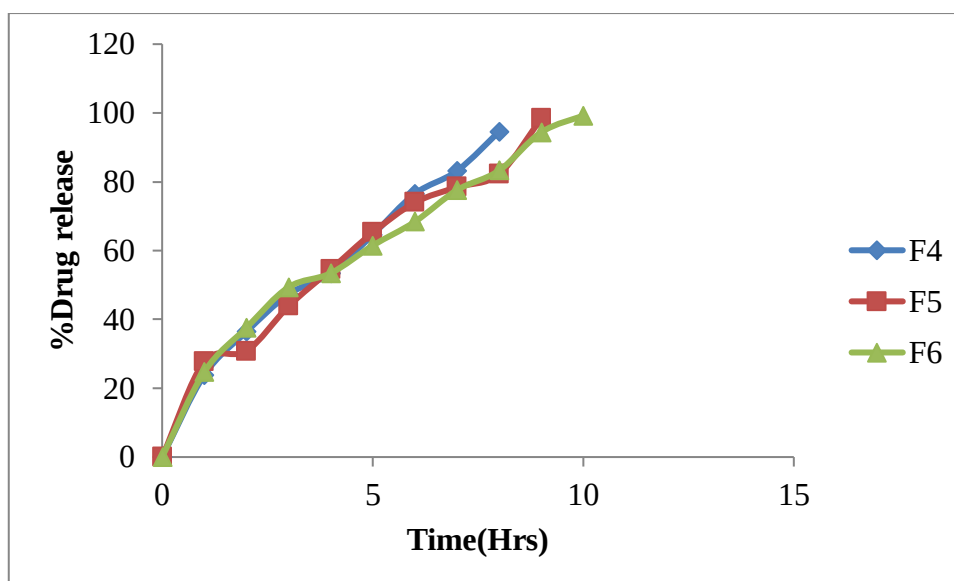


Fig : Dissolution profile of Deflazacort (F4, F5, F6 formulations)

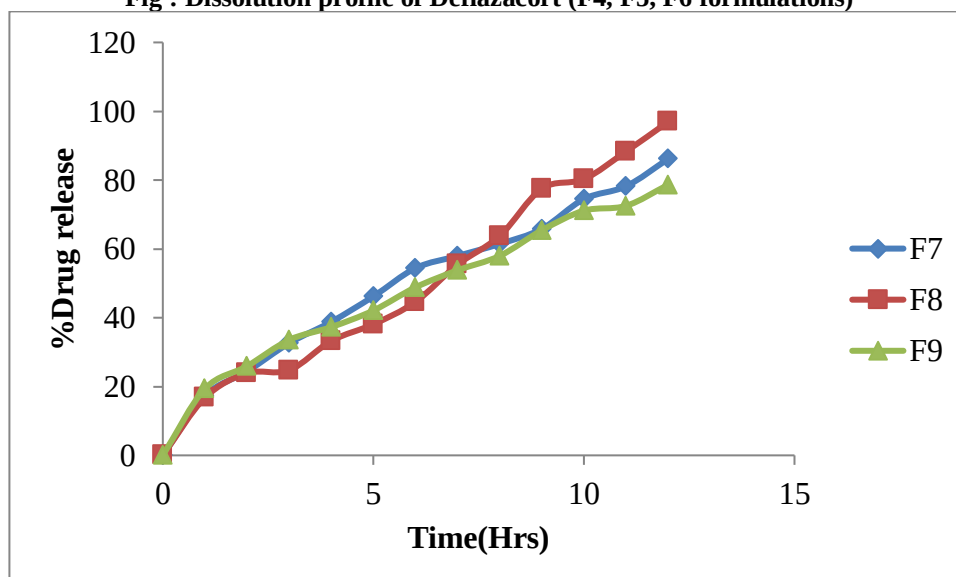


Fig : Dissolution profile of Deflazacort (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Ethyl Cellulose polymer (high concentrations) were able to retard the drug release up to desired time period i.e., 12 hours. The formulations prepared with Eudragit S100 were unable retarded the drug release. They were not shown total drug release. Hence they were not considered.

Whereas the formulations prepared with Hydroxypropyl Cellulose were retarded the drug release in the concentration of 10 mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.94 % in 12 hours with good retardation.

From the above results it was evident that the formulation F8 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 10.6: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3- Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
16.75	1	1.000	1.224	0.000	1.920	16.750	0.0597	-0.776	83.25	4.642	4.366	0.275
23.89	2	1.414	1.378	0.301	1.881	11.945	0.0419	-0.622	76.11	4.642	4.238	0.404
24.73	3	1.732	1.393	0.477	1.877	8.243	0.0404	-0.607	75.27	4.642	4.222	0.419
33.27	4	2.000	1.522	0.602	1.824	8.318	0.0301	-0.478	66.73	4.642	4.056	0.586
38.1	5	2.236	1.581	0.699	1.792	7.620	0.0262	-0.419	61.9	4.642	3.956	0.686
44.61	6	2.449	1.649	0.778	1.743	7.435	0.0224	-0.351	55.39	4.642	3.812	0.830
55.46	7	2.646	1.744	0.845	1.649	7.923	0.0180	-0.256	44.54	4.642	3.545	1.097
63.75	8	2.828	1.804	0.903	1.559	7.969	0.0157	-0.196	36.25	4.642	3.310	1.332
77.51	9	3.000	1.889	0.954	1.352	8.612	0.0129	-0.111	22.49	4.642	2.823	1.819
80.28	10	3.162	1.905	1.000	1.295	8.028	0.0125	-0.095	19.72	4.642	2.702	1.940
88.31	11	3.317	1.946	1.041	1.068	8.028	0.0113	-0.054	11.69	4.642	2.270	2.372
96.94	12	3.464	1.987	1.079	0.486	8.078	0.0103	-0.013	3.06	4.642	1.452	3.190

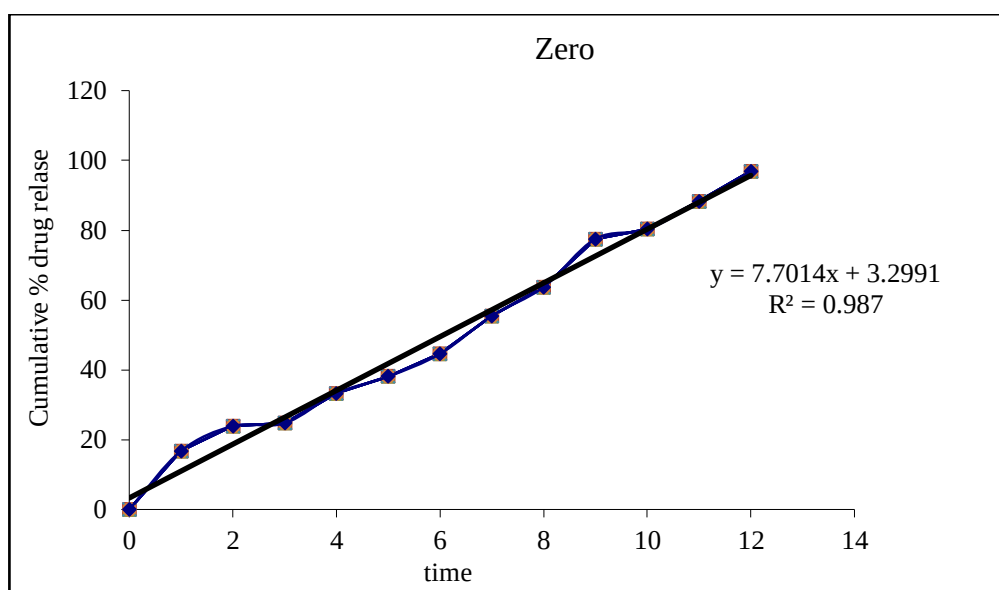
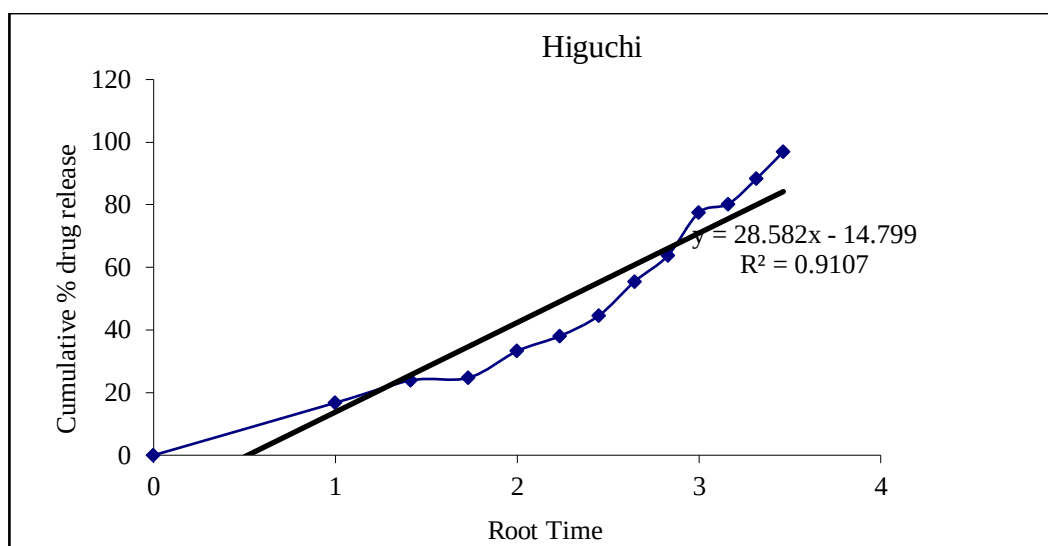
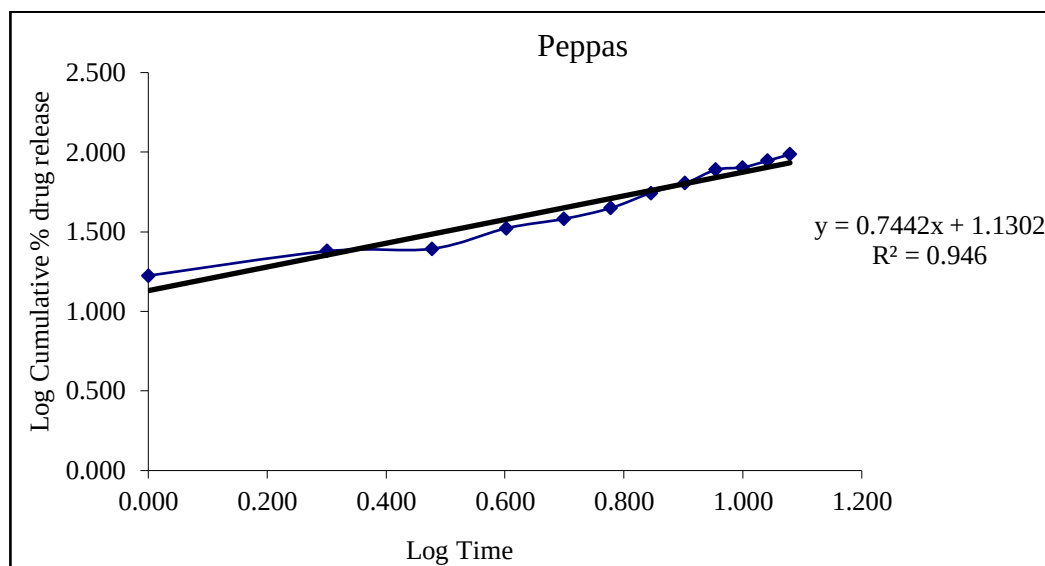
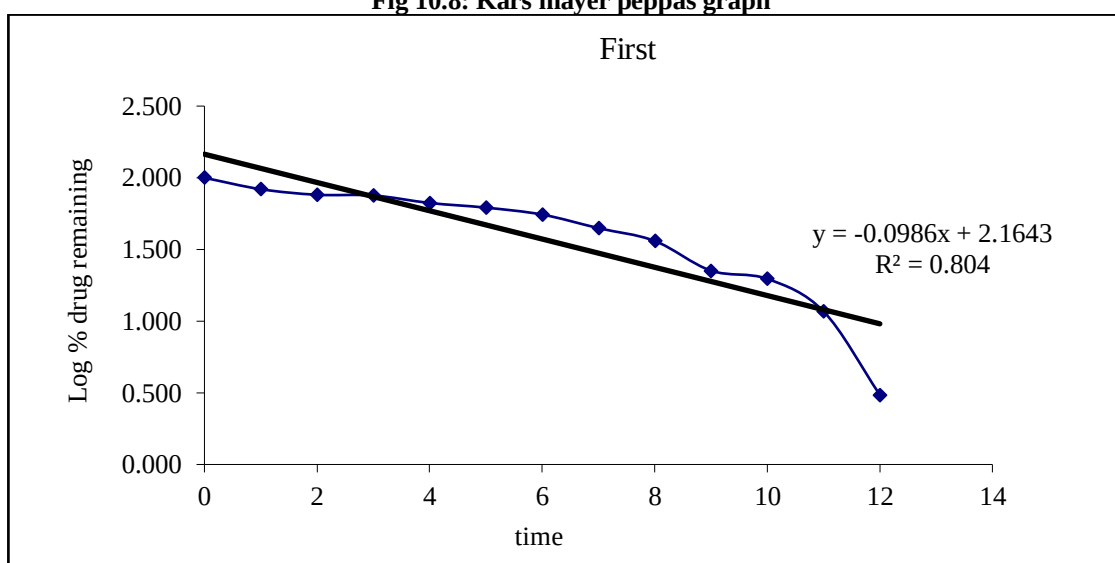


Fig 10.6 : Zero order release kinetics graph

**Fig 10.7 : Higuchi release kinetics graph****Fig 10.8: Kars mayer peppas graph****Fig 10.9: First order release kinetics graph**

To study the release rate kinetics and the release mechanism of the drug from the tablet formulations, the Optimised *in vitro* drug release data were treated with the mathematical equation such as first order kinetics equation, zero-order kinetics equation

Drug and excipient compatibility studies

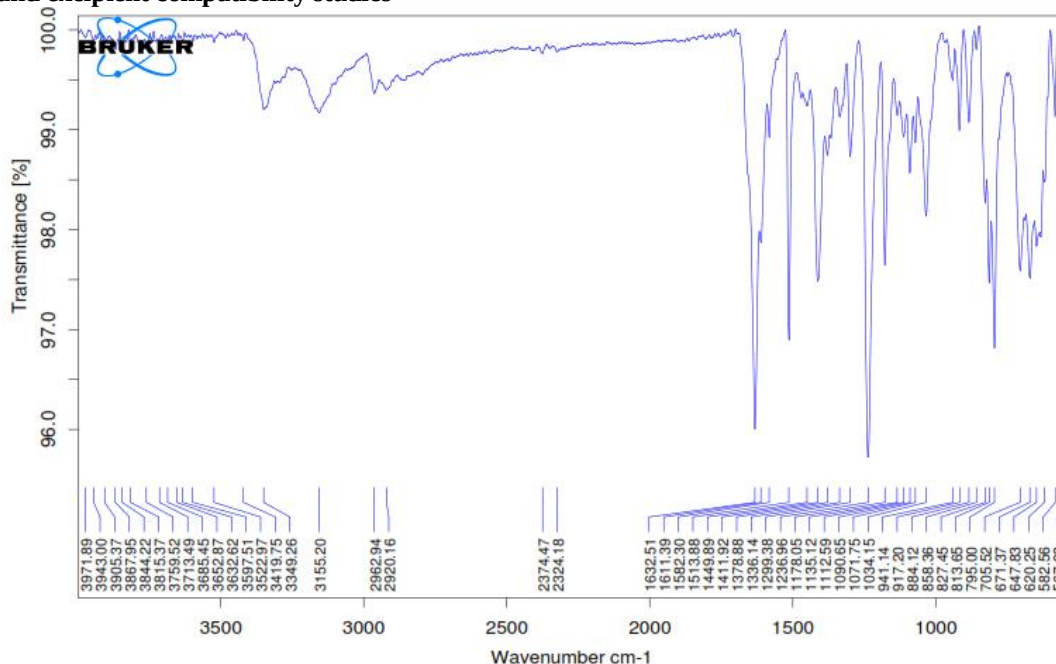


Figure 10.10: FT-IR Spectrum of Deflazacort pure drug

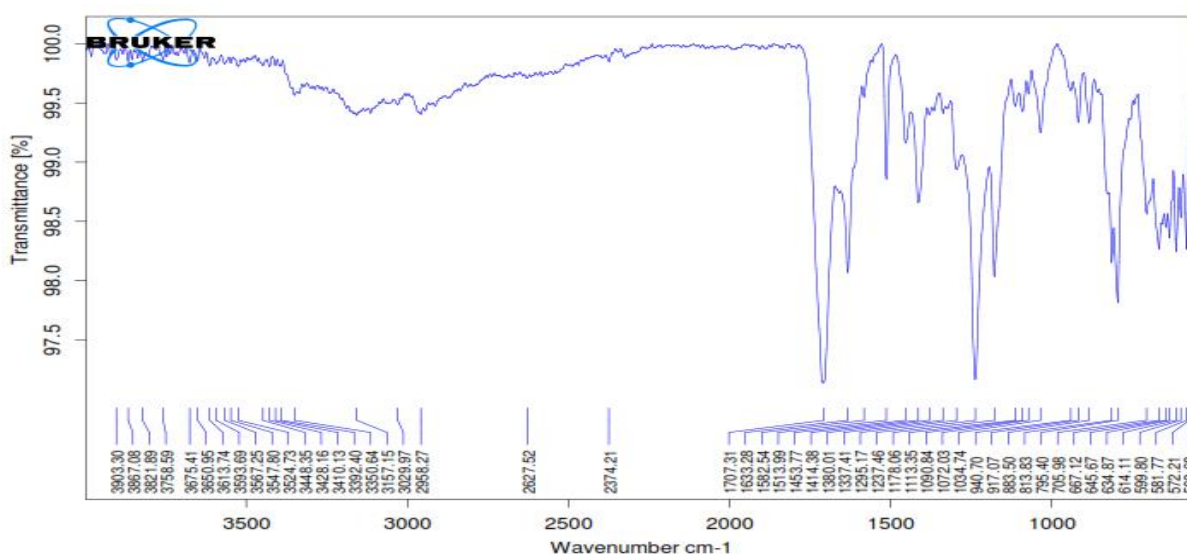


Figure 10.11: FT-IR Spectrum of Optimised Formulation

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra.

CONCLUSION:

Preformulation studies were performed to study the nature of Mesalamine and compatibility of Mesalamine with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between Mesalamine and all the excipients selected.

The Mesalamine matrix tablets were successfully formulated by direct compression method using the

selected excipient quantities. The formulated tablets were evaluated for both pre-compression and post-compression parameters as per requirements of standards. And the results were complied with the pharmacopoeia specification. The formulated Mesalamine matrix tablets were coated with enteric polymer Eudragit FS 30D and Ethyl cellulose by pan coating method.

From among the entire batches, formulation F4

showed 98.90% drug release at 24 hrs. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the trial F4 was considered as best formulation. From the results obtained, it can be concluded that formulation F4 containing enteric coated matrix tablet of Mesalamine would be a promising formulation to achieve the purpose which treat inflammatory bowel diseases (ulcerative colitis)

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