DISCUSSION
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Preparation of Standard graph for Pantoprazole using 0.1 M Hydrochloric acid

The $\lambda_{\text{max}}$ of the pantoprazole in 0.1 M HCl was found to be 283nm. Calibration curve plotted by taking different concentrations ranging from 2 – 50 $\mu$g/ml appeared as a linear plot, with an $R^2$ value of 0.994, $y=0.015x + 0.015$.

Preparation of Standard graph for Pantoprazole using pH 6.8 phosphate buffer:

The $\lambda_{\text{max}}$ of the pantoprazole in 6.8 pH phosphate buffer was found to be 289 nm. Calibration curve plotted by taking different concentrations ranging from 2 – 50 $\mu$g/ml appeared as a linear plot, with an $R^2$ value of 0.993, $y = 0.039x + 0.037$.

PREFORMULATION STUDIES:

The first phase of the design of a pharmaceutical dosage form is the preformulation studies. These studies focus on the physicochemical properties of the drug compound that could affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design, or support the need for modifications. These formulation investigations may merely confirm that there are no significant barriers to the compound’s development.

Preformulation studies are prerequisite to study the physico–chemical properties of the active pharmaceutical ingredient – pantoprazole and other excipients, before subjecting them to formulation processing. Preformulation studies such as, solubility, organoleptic properties, physical characteristics, particle size, and thermal properties were to be determined.

Characterization of Drug Substance – Pantoprazole:

The following are the preformulation studies conducted on the active pharmaceutical ingredient. The purpose of these studies were to finalize specifications of active pharmaceutical ingredients (API), study the compatibility between active and
inactive ingredient and to characterize the reference product, thereby to maximize the chances in formulating an acceptable, safe, efficacious and stable product.

It is undoubted that the type of physical characterization tests for a drug or excipient depends very much on the material concerned as well as the processing involved. Material testing can be broadly divided into two types, namely physical testing and functionality testing. Physical testing, which is used to determine properties such as size, solubility, and crystal form is generally more direct and the procedures are better established. Functionality testing which evaluates, for example, lubricity, flow, creep, and tack is less well established but, if carried out, may yield useful information about the raw materials and their potential effects on the processing.

**Solubility of Pantoprazole:**

Solubility study of pantoprazole was conducted at times beyond the equilibration in order to verify the attainment of true equilibrium. The solubility estimations were carried out in water and phosphate buffer pH 6.8 in different time intervals to determine the real thermodynamic equilibrium.

The solubility of pantoprazole was found to be $38.47 \mu g/ml$ in water at $25^\circ C$ at 24 h and that of $39.29 \mu g/ml$ in water at $37^\circ C$ at 24 h. The solubility of the drug was found to be $49.16 \mu g/ml$ in phosphate buffer pH 6.8 at $25^\circ C$ at 24 h and that of $52.69 \mu g/ml$ in phosphate buffer pH 6.8 at $37^\circ C$ at 24 h. The solubility of pantoprazole in water and buffer at the end of 24 h is shown in table 24.

The solubility of pantoprazole in phosphate buffer was found to be greater than in water at both at $25^\circ C$ and $37^\circ C$ at 24 h. This complies with the fact that the solubility of pantoprazole increases with increase in the pH. This could be due to the increased ionization of the drug with increase in pH. A similar observation was reported by Zhang X et al, who found that the solubility of lansoprazole was found to be greater in buffer ($43.89 \mu g/ml$) compared to solubility in water ($33.57 \mu g/ml$).
Organoleptic properties:

The organoleptic characterization of pantoprazole was performed and it was found to be white in colour, odourless and bitter in taste. The drug source was in accordance with IP specifications. Hence, pantoprazole obtained from the supplier was used for further studies. The organoleptic characters of the drug are tabulated in table 25.

Physical characters:

The pH of the 10% aqueous solution was tested by using pH meter and it was found to be 9.82. This complies with the IP specifications of pH range between 9.0 and 11.5.

Loss on drying is recommended in EP, BP and USP. Although the loss in weight, in the samples so tested, is principally due to water, a small amount of other volatile materials will also contribute to the weight loss. The moisture balance combines both the drying process and weight recording. A moisture balance is suitable where large numbers of samples are handled and where a continuous record of loss in weight with time is required.

The loss in weight in the samples was tested by using digital moisture balance instrument. The observed LOD value complies with the IP specifications.

Melting point is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals, melting points are very sharp and constant. Since the crude drugs contain the mixed chemicals, they are described with certain range of melting point.

Melting point was determined by the melting point determining apparatus containing castor oil. Melting point temperature was found to be 139.5 and temperature value within the limit.

The physical characteristics of pantoprazole were tabulated in table 26.
Fourier Transform Infrared Spectroscopy:

The IR spectra of pantoprazole revealed its characteristic peaks at 1587 cm\(^{-1}\) due to C=N and C=C stretches, 1452 cm\(^{-1}\) showing CH\(_2\) bending, 1271 cm\(^{-1}\) corresponds to S=O stretches and peak at 1165 cm\(^{-1}\) reveals Sp\(^2\) C-O aromatic ether stretches.

Thermal analysis of Pantoprazole:

The DSC curve of pantoprazole obtained on heating rate of 10°C/min exhibits a sharp endothermic peak at 148.1°C. The obtained DSC curve of pantoprazole exhibited an endothermic peak which corresponds to the melting point of the drug and is immediately followed by the sharp symmetric exothermic peak. The observed melting peak temperature was 148.1 °C (T\(_{\text{onset}}\) = 134.1 °C) with an apparent heat of fusion of 221.3 J/g. The exothermic peak was observed at 193.8 °C (T\(_{\text{onset}}\) = 185.0 °C) with an apparent heat of fusion of 352.7 J/g.

The melting point of pantoprazole was reported differently by various manufacturers. The reason for these contradictory reports could be that the melting behaviour of sulfoxides known as proton pump inhibitors common due to significant heating rate dependence and melting of the substance is followed by decomposition of the substance, which makes the determination of the melting point very difficult. The other reason for inconsistency of reported data could be that different methods for determination have been applied. As a result, there is confusion in the melting point values quoted in the literature. In a recent study, Rosenblatt et al., reported on the thermal behaviour of one proton pump inhibitor – omeprazole. Using thermal and chromatographic analyses, the authors reported that the melting point depression at low heating rates is due to eutectic behaviour of the drug with its decomposition products formed at low heating rates\(^{113}\). At heating rates above 20°C/min, the melting point of pantoprazole becomes independent of the heating rate due to absence of decomposition products.
Powder X-ray diffractometry of Pantoprazole

The XRD spectra of pantoprazole show characteristics peaks at 7.330, 11.450, 13.011, 14.473, 16.589, 17.557, 18.450, 20.346, 22.395, 24.308, and 26.535. This data indicated that the drug is available as the most stable crystalline form and is in accordance with the standards.

Powder characterization of drug substance:

The powder characteristics including the particle size, bulk density, tap density, Hausner’s ratio and Carr’s index are tabulated in table 28.

The sizing of powders can be laden with problems such as non-reproducible results caused by cohesive nature of powders, poor control of ambient humidity, variable rate of introduction of particles, etc. Therefore, in order to avoid such problems encountered during measurement of particle size, wet feeder method was more preferred. From the particle size analysis, it could be inferred that the majority of the drug substances had particle size under 400 nm and the average particle size was found to be 231.4 nm.

Bulk density is defined as the mass of powder divided by the bulk density. It largely depends on practice shape, as the particles become more spherical in shape, bulk density increases. In addition as granules size increases, bulk density decreases. Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Measurement of bulk density and specific surface area is very sensitive to sample preparation, especially if the powder used has a small particle size like lansoprazole. The flowability of the powder is related to the particle size and shape. Hausner’s ratio and Carr’s index are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing
materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed\textsuperscript{116}.

From the SEM pictures (Figure 36, 37, & 38) and the values obtained for densities, according to the classification by Wells, for Hausner’s ratio and Carr classification for Carr’s index powder can be characterized as a poorly flowability and poorly compressible. A Hausner’s ratio of less than 1.20 indicates good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow\textsuperscript{117}. The Carr’s index values of 5-10, 12-16, 18-21, and 23-28 indicated, excellent, good, fair and poor flow properties of the material, respectively.

**COMPATIBILITY OF DRUG AND EXCIPIENT**

The selection of excipients is vital in the design of a quality drug product. Excipients and their concentration in a formulation are selected based not only on their functionality, but also on the compatibility between the drug and excipients.

An incompatibility may be defined as an undesirable drug interaction with one or more components of a formulation, resulting in changes in physical, chemical, microbiological or therapeutic properties of the dosage form. Excipient compatibility studies are conducted mainly to predict the potential incompatibility of the drug in the final dosage form. These studies also provide justification for selection of excipients, and their concentrations in the formulation as required in regulatory filings.

In the formulation of any pharmaceutical product, it is imperative to ensure that the ingredients used are compatible with one another. Incompatibilities can occur between drug and excipient as well as between the excipients themselves. Incompatibilities may be manifested through many modes, such as acid–base interaction and complex formation, resulting in lower potency and/or stability and eventually poor therapeutic efficacy of the product. It is therefore essential to avoid incompatibilities and this is achieved by carrying out studies to detect potential interactions between the components used in the formulation.

The observations made initially and at the end of 2\textsuperscript{nd} and 4\textsuperscript{th} week were tabulated in table 29.
All the ingredients when observed for physical changes at the end of 2nd and 4th week were found to have no change in the colour or texture or any other signs of incompatibility. Surelease, a latex formulation of ethyl cellulose, produced changes in its physical mixture which was revealed as darkening of the colour showing possible incompatibility between the polymer and the drug. However, the material was used for coating as seal coat was provided to the tablet preventing the incidence of physical contact between the two substances.

In order to resolve the occurrence of any chemical incompatibility between the drug and the ingredients, the physical mixture of drug with all the excipients were analyzed by IR spectroscopy. The IR spectra of pantoprazole revealed its characteristic peaks at 1587 cm$^{-1}$ due to C=N and C=C stretches, 1452 cm$^{-1}$ showing CH$_2$ bending, 1271 cm$^{-1}$ corresponds to S=O stretches and peak at 1165 cm$^{-1}$ reveals Sp$^2$ C-O aromatic ether stretches.

These characteristic peaks of the drug were found at the appropriate wave numbers of all the physical mixtures except Surelease. There were diminutive shift found in the physical mixture of other enteric polymers such as Acryl EZE, Sureteric, CAP and HPMCP. The reason could be due to the acidic nature of these polymers. Therefore, a seal coat may be necessary to avoid the direct contact between the polymer and the drug.

The common excipients used in the formulations are well compatible with the drug.

**Optimization of formulation method and additives:**

Systemic development of a formulation is needed to achieve a detailed and complete understanding of dosage forms in order to fulfil the requirements of regulatory bodies. Information from various categories such as the properties of the drug substances, excipients, and interactions between materials, unit operations and equipment are required$^{118}$. The drug substance’s physicochemical properties, as well as excipients all contribute to ensuring the desired therapeutic benefits.
formulation and the manufacturing processes of a pharmaceutical product are optimized by a specific approach, the scale up process and process validation can be very efficient.

**Formulation of core tablets by direct compression:**

The core tablets of pantoprazole formulations were prepared by direct compression method. The tablets were prepared after through screening of various tableting excipients such as Diluents, Binders, and Disintegrants using suitable experimental designs. The concentration of Diluents, Binders, and Disintegrants were optimized using ANOVA. The optimization of various excipient concentrations was carried out using pre & Post compression response variables such as Angle of Repose, Compressibility Index, Friability, Hardness and Disintegration Time.

Direct compression is a simple process being more economical and less stressful to ingredients in terms of heat and moisture exposure. Direct compression involves compressing tablets directly from powdered materials without modifying the physical nature of the materials. Direct compression vehicles can be used to produce good flow and compressible characteristics when drug alone does not have sufficient crystalline nature to generate good compression ability\(^1\). Pantoprazole though crystalline, pose poor compressible and flow properties which make it an unsuitable drug for direct compression. However, its dose being small, directly compressible diluents can be used to subject the drug for direct compression.

**Effect of formulation additives:**

The formula contains 40 mg of pantoprazole standard drug.

Proton-pump inhibitors (PPIs) are a group of drug compounds that has an acidic pKa.

For the pharmaceutical product development scientist, there is clearly a need for objective information about the practical performance of different excipients and their various grades. The small differences in primary material properties, such as molecular weight or particle size, can bring about significant changes in ultimate manufacturing performance, such as compressibility. Therefore, the effect of various diluents,
disintegrants and the binder were observed at various concentrations, up on the physicochemical properties of the tablet mass.

Magnesium stearate is primarily used as a lubricant in tablet formulations at the concentration between 0.25 to 5%. Because of its hydrophobicity it may retard the dissolution of a drug from a solid dosage form. Therefore, the lowest possible concentration is preferred to use\textsuperscript{56}. Colloidal silicon dioxide is a light fine and white amorphous powder, commonly used as a glidant in oral formulations. It may offer adsorbance for drying of hygroscopic powder or granules\textsuperscript{119, 120}.

The different diluents and disintegrants used in the study and the effect of their concentration on the performance of the tablets are discussed in the following sections.

**OPTIMIZATION OF DILUENTS**

A direct-compression formulation will require a diluent with good flow and compaction properties. If the material is extremely plastic, it is appropriate to add diluents that compact by brittle fracture; similarly, a brittle drug substance should be combined with plastic filler. The solubility of the drug substance should also be considered. A soluble drug is normally formulated with an insoluble filler to optimize the disintegration and dissolution process.

We have chosen to study the effect of the fillers that are most commonly used in the manufacture of immediate release tablets: microcrystalline cellulose (MCC) and lactose\textsuperscript{121}. Generally, MCC has good compression properties, imparting strength and robustness to tablet dosage forms. Thus, it is one of the most commonly used ingredients in tablet formulations. Lactose is also a first choice excipient for many tablets. Therefore microcrystalline cellulose, and lactose were considered for inclusion as diluents into the formulations.

Before subjecting the granulated blend containing different diluents to precompression characterization, some of the physical properties of the diluents were reviewed theoretically. Compact or powder solid fraction (SF) is a measure of the degree of compression because it increases with applied pressure. Mechanical
properties of powder compacts - tablet indices are dependent on SF and best compared at the same SF. About 0.85 SF is considered standard because it approximates the midpoint of the range typical of immediate release tablets (0.8–0.9).

The tablet indices characterization includes Compression stress, which is the punch pressure required to form a compact. It indicates the ease (i.e., the magnitude of the pressure) of forming compacts under standardized conditions.

**Dynamic indentation hardness** is a compact mechanical property that provides a measure of a material’s plasticity or ductility. Thus, during powder compaction, very ductile materials (i.e., having low hardness values) tend to deform to a greater extent than low ductility materials (i.e., having high hardness values).

A powder compact’s **Tensile strength** is the stress required to separate its constituent particles in tensile mode. Tablets that are manufactured on a traditional tablet press and that have high TS are considered ‘‘hard’’ and generally robust, and so this is a highly desired attribute for immediate release and other tablet types.

**The bonding index** is calculated from the dynamic indentation hardness and TS of powder compacts. It indicates the extent of particle bonding that remains after a tablet has been decompressed. This often results in reduced bonding contact area and perhaps bond rupture. The particle bonding that remains is represented by the bonding index: high values are significantly attributes because they indicate a high probability for forming strong, robust tablets.

**The brittle fracture index (BFI)** describes the propensity for particle bonds to relieve stress by fracturing. It is based on the ratio of the material’s TS to its ‘‘compromised’’ TS as measured on powder compacts without and with a macroscopic flaw manufactured into its structure, respectively. The BFI will approach zero for materials for which the regular and compromised TSs are nearly the same (i.e., their regular-to-compromised TS ratio approaches one). This is a highly desirable trait because it indicates a low probability for fracture (lamination or capping) during decompression in a tableting die.
By considering the above mentioned tablet indices the suitability of the diluents for inclusion in the core tablets was reviewed in correlation with the observations of precompression evaluations performed for the formulations.

The diluents were optimized by using $2^2$ factorial design by taking lactose and MCC as two factors and at two levels i.e., high and low. The angle of repose was considered as response factor. The ANOVA tables for optimization of diluents were shown in tables 30 & 31. The contour plots were given in figure 55. The final polynomial equation in terms of coded and actual factors were shown in equations 11 & 12 respectively.

The pre and post compression characteristics of all the formulation runs were in acceptable limits. The results of various evaluations were tabulated in table 32.

From the polynomial equation obtained from factorial designs, the concentrations of diluents were optimized and optimized formula was given in table 5.

**Optimization of disintegrants:**

Once the tablet is taken by the patient, it must break up rapidly to ensure rapid dissolution of the active ingredient in immediate – release preparations. To overcome the cohesive strength produced by the compression process and to break down the tablet into the primary particles as rapidly as possible, the disintegrants are combined with other excipients during the tableting process. Super disintegrants, including Croscarmellose sodium (CCS), sodium starch glycolate (SSG), and Crospovidone (CP), display excellent disintegration activity at low concentrations and have better compression properties than starches.

Hence the super disintegrants were included in the formulations at the concentrations of 5%, 10% and 15% w/w. Thus nine formulations, FR5 to FR13 were prepared with three disintegrants in three different concentrations. Disintegrants were not used beyond 15% w/w due to fact that they are hygroscopic materials and will absorb moisture from the atmosphere, which could negatively affect the stability of moisture - sensitive drugs like pantoprazole.
The disintegrants were optimized using ANOVA and regression analysis by considering disintegration time and hardness as response variables. The Effect of Disintegrants like SSG, CCS, and Cross Povidone is represented using regression analysis, correlation plots and line fit plots which were given in tables 34 to 39 and figures 54 to 62. Among the Disintegrants cross povidine has better effect and also required in low concentrations with respect to both disintegration time and hardness when compared to SSG and CCS. Moreover there is a high coincidence of predicted hardness and actual hardness in case of cross povidone where as this coincidence was lack in croscarmellose sodium and sodium starch glycollate. Therefore cross povidone is optimized as disintegrant by performing ANOVA studies.

**Effect of Binders**

Binders are adhesives that are added to solid dosage formulations. The primary role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet. In a wet-granulation process, binders promote size enlargement to produce granules and thus improve flow ability of the blend during the manufacturing process. Binders may also improve the hardness of the tablets by enhancing intra-granular as well as inter-granular forces. In a direct compression process, binders often act as fillers and impart compressibility to the powder blend.

Polyvinylpyrrolidone (PVP) is versatile and one of the most commonly used binders. It is readily soluble in water and freely soluble in alcohol and many other organic solvents. It is available in a variety of grades of different molecular weights. PVP is generally used in the form of a solution; however, it can be added to the blends in the dry form and then granulated in situ. Aqueous or hydro-alcoholic solutions of PVP are used to granulate insoluble materials and alcoholic solutions are used for granulating soluble materials. It is used as a binder at concentrations between 0.5% and 5%. Low- to medium-viscosity grades are preferred since the high-viscosity grades of PVP have been known to cause dissolution problems. It is highly hygroscopic and picks up significant amounts of moisture at low relative humidity and can deliquesce at high relative humidity.
The binders were optimized using ANOVA and regression analysis by considering disintegration time and hardness as response variables. The Effect of binders like PVPk30 and PVPk90 is represented using regression analysis, correlation plots and line fit plots which were given in tables 41 to 44 and figures 63 to 66. Among the binders PVPk30 was selected as the best in the preparation of core tablets.

From the results shown in table 40 it was observed that with increasing concentration of binders i.e. PVP K30 & PVP K90 the hardness of tablets is increased but the time taken for disintegration also increased. Considering rapid release of the drug from the tablet it is essential to incorporate less concentration of binder where the hardness is not less than 4 kg/cm$^2$. In view with the results though PVP K90 is having better binding ability, PVP K30 was further optimized as the hardness of tablets is above 4 kg/cm$^2$ with a concentration of 3mg which is sufficient for oral tablets. To get Disintegration of less than 45 and by considering Both Hardness & Disintegration Optimized Concentration of PVP k30 is 3mg.

**Seal coating of core tablets:**

Seal coating has been proposed as a method to improve acid resistance for enteric coated dosage forms. Polymer sealcoats seal the substrate from the aqueous enteric film coating, thus preventing the migration of water-soluble drugs into polymeric film, as well as preventing drug polymer interactions$^{122}$.

In the case of substituted benzimidazole, Subcoating or seal coating has been described in a numerous patent literature as a barrier between an enteric coating and acid liable drug to prevent degradation of the compound, since the polymers for enteric film coatings contain free carboxyl groups which can increase degradation of acid liable drug. Direct contact of pantoprazole and few enteric coating polymers can lead to solid-solid interactions and degradation of pantoprazole, therefore the presence of Subcoating can be justified.

It has been demonstrated that the pH of the diffusion layer at the surface of a dosage form resembles that of a saturated solution of a drug and excipients in a dissolution media and represents the microenvironment pH of the system$^{123}$. During
dissolution, medium that may eventually penetrate the pellet core, or during storage moisture may penetrate into the core, resulting in a saturated solution of a drug and excipients. In the case of pantoprazole if the micro-environmental pH is too low, and moisture penetrates in the core, the drug will degrade and the initial amount of drug will decrease during storage. Too basic pH will create saturated diffusion layer at the surface which can cause ionization of the carboxylic groups of the enteric polymer. Presence of Subcoating can be essentially important in this case.

In the present work, the optimized core tablets of formulation OF3 which possessed the desired properties in terms of optimum drug content, mechanical strength, disintegration was selected for seal coating. The seal coating of tablets is necessary for the above mentioned reasons. Hence HPMC was used to sub coat the tablets. A 12% dispersion of the HPMC in organic solvents mixture of isopropyl alcohol and dichloromethane (2:1) was used for the purpose. The coating weight was increased to different levels and a portion of tablets were removed from the pan once the desired weight was achieved. Three different batches of the seal coated tablets were prepared with 2%, 4% and 8% weight gain. The tablets were then subjected for evaluation and compared to the properties of the core tablets. The results are tabulated in the table 46.

As the weight of the tablets increased from 200.14 mg to 216.38 mg based on the weight gain, the thickness of the tablets increased correspondingly from 4.14 to 5.1. The hardness of the tablets increased as well with reduction in the friability of tablets. The disintegration time increased as the weight gain increased due to the additional time required for the breakdown of seal coat. Based on the above results, 2% seal coat was considered optimum because, the tablets were completely enveloped which shall serve the purpose of preventing the direct contact between the drug and the polymer and also offer the required mechanical strength, with least disintegration time. Therefore tablets with 2% seal coat with HPMC were used for further coating with enteric polymers.
ENTERIC COATINGS:

Enteric coating systems are part of modified release film coatings, which are intended to remain intact and thus prevent any drug from being released or any acidic media being absorbed for different periods after ingestion, but ultimately to dissolve in order to permit the drug to be rapidly released thereafter. These formulations are also referred to as delayed release systems, where the delay in the onset of drug release, after ingestion, will depend on the type of the polymer used in the film coating and the transit of the dosage form through the gastro-intestinal tract. Although the United States Pharmacopoeia has set forward specific disintegration and dissolution.

An enteric coat resists disintegration or dissolution in acidic gastric media but disintegrates or dissolves in intestinal fluids. The film forming polymers for enteric resistance coating are macromolecules having a molecular weight range between 10,000 and several million Daltons and consist of a number of repeating units in its structure. They can cause a prolonged drug release in order to extend the intake intervals or enteric resistance in order to protect the drug against the acidic media in the stomach.

Choice between organic and aqueous coating

Polymers such as modified cellulose polymers and synthetic acrylic polymers are commonly known as enteric coating polymers. These polymers contain ionisable carboxylic groups. In the low pH stomach environment the carboxylic groups remain un-ionized so that the polymeric coat remains insoluble but disintegrates or dissolves at the higher pH of the intestinal environment to allow the release of drug contents. The coating process using organic solvents was reported to have an advantage so far as it takes a shorter processing time because of the low heat of vaporization characteristic of the solvents. Since the Tg of some polymers such as HPMCP, CAP was very high (more than 150 °C), it was difficult to produce solvent-free film coating from these polymers.

The use of organic solvents in the coating of pharmaceutical dosage forms has become problematic due to regulatory requirements, flammability and limits on solvent residues in the coated product. The alternative aqueous coating systems can overcome
these problems but suffer from certain limitations. This created a renewed interest in the use of water as a solvent and vehicle for the coating process. Initially, aqueous systems were viewed with scepticism because of their lengthy processing times and because the appearance of products coated with aqueous films was inferior to that one of products coated using organic systems\textsuperscript{38}.

In the present study, enteric polymers Cellulose acetate phthalate (CAP), Hydroxy propyl methyl cellulose phthalate (HPMCP) and Opadry enteric were used as organic coating solutions. Acryl EZE, Sureteric and Nutrateric (Combination of NS enteric and Surelease) were used as aqueous enteric coatings to be laid upon the seal coated tablets of pantoprazole. The compositions of different coating material, their preparation and the coating methodology were discussed in detail in the experimental section.

In the following sections the performance of the enteric polymers in terms of various evaluations such as disintegration time, acid uptake, drug release, and thermal analysis and stability studies.

**COATING WITH CELLULOSE ACETATE PHTHALATE**

Cellulose acetate phthalate enteric coating material is a pH sensitive cellulose derivative designed for coating pharmaceutical tablets and granules. It may also be used as a matrix material in solid dosage forms. CAP enteric coating material withstands prolonged contact with acidic gastric fluids, but dissolves readily in the neutral environment of the intestine. It can be applied to tablets from solutions of organic solvents. It is a hygroscopic substance, practically insoluble in water, alcohols, hydrocarbons and chlorinated hydrocarbons but soluble in dilute solutions of alkalis, a number of ketones, esters, ether alcohols, cyclic ethers and in certain solvent mixtures such as acetone : ethanol, acetone : methanol or ethyl acetate : isopropanol. The relative molecular weight of CAP is ca. 30,000.

Many factors can influence the preparation of enteric coated dosage forms e.g. the properties of the substrate such as the nature of drugs, additives or core. The
properties of the polymer such as molecular weight, pH-dependent solubility, the pKa value, the total free carboxylic acid content or the degree of substitution of the polymer can also affect the preparation. The type of the incorporated drug had an important affect on the stability of the CAP film coated product. The ionic strength of the dissolution fluid, the thickness of the coat, the permeability to gastric fluid and the presence or absence of plasticizers, other non-enteric components in the coat and defects can influence the dissolution of enteric coats\textsuperscript{126, 37}. Since it was reported that the Tg of pure CAP was very high, the addition of a suitable plasticizer was necessary to reduce the Tg to a temperature at which a coating process can be performed. In the present study triethyl citrate was used as the plasticizer and talc was used as a separating excipient.

Increasing alcohol or water content will change the solubility of CAP in the solvent system and could retard the drying rate. For most rapid solution and to obtain gel-free organic solvent solutions, the enteric polymer should be added slowly to the solvent mixture with stirring. After the polymer has dissolved in the solvent mixture, either solvent component can be increased simply by adding more to the solution with mixing. A solvent mixture of isopropyl alcohol and dichloromethane (1:1) was used to prepare the organic solution of the polymer. The coating material deposits were increased to obtain different weight gains such as 5\%, 8\% and 12\% from its original weight and were coded as CAP1, CAP2 and CAP3. The tablets were then subjected to all the physicochemical evaluations including, disintegration, acid uptake, drug release and stability analysis and thermal analysis. The results of the evaluations were presented in table 47.

\textit{Disintegration:}

All the batches of tablets CAP1 to CAP3 were imparted to disintegration test studies in 0.1M HCl for 2h and then in phosphate buffer pH 6.8. CAP1 which was prepared with 5\% weight gain could not resist the acid media and disintegrated with in 2 h of the test. Therefore the batch was considered to have failed the test. But with an intention to determine the disintegration time in buffer, fresh tablets were placed in the phosphate buffer pH 6.8 where it disintegrated at about 4 min. CAP2 and CAP3 prepared by coating 8\% and 12\% of weight gain remained stable and acid resistant for
2h in 0.1 M HCl while in phosphate buffer pH 6.8, they disintegrated at 4.86 and 5.6 min respectively. It is evident from the following figure that the increase in the enteric coating weight (up to 12 %) resulted in non disintegration of the tablets in the acid media (0.1 N HCl) during the study period (2 h). Thomas and Bechtold, reported about the minimum thickness of CAP films coated on tablets from an aqueous coating system and an organic system in order to have a swelling of less than 10 % and a resistance to 0.1 N HCl. Their statement was that a high thickness of 110 µm CAP film from an aqueous system was necessary for a resistance to an acidic medium, whereas the thickness of 40 µm was sufficient from an organic system. The observed data is in agreement with the reported data showing the potential of these polymers to prevent disintegration in acidic media.

Assessment of Acid uptake:

The tablets after coating with different weight gains with Sureteric were subjected to two hours in 0.1N HCl or pH 4.5 acetate buffer. CAP1 disintegrated completely both in 0.1 M HCl and acetate buffer 4.5, therefore fails the acid uptake test. CAP2 and CAP3 showed up to 4.6% and 2.6% uptake in 0.1 M HCl while in acetate buffer 4.5, they showed an increased uptake at about 8.76% and 5.75% respectively. Thus increase in the coating thickness of the organic coating could reduce the acid uptake and swelling. The results of the acid uptake study is tabulated in the following table 48.

In vitro Drug release:

Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the formulations. As CAP1 coated tablets with 5% weight gain failed the disintegration test, they were not engaged for dissolution test. In vitro drug release was carried out for formulations with 8 % and 12% weight gain of enteric coated tablets (CAP2 and CAP3) in 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 60 min. It is evident from the figure that all the formulations demonstrated excellent physical resistance to the acid medium with the drug release less than 1.28% to 3.65% in 0.1M HCl up to 2h. Altering the media to basic (phosphate buffer-pH 6.8) leads to rapid release of pantoprazole.
from the tablets. CAP2 released about 94.24% while CAP3 released 85% at the end of 45 min. The slower release of CAP3 could be drawn to the reason of having additional polymeric film thickness. Similar observation was recorded by Amit. Patel and group, who found that formulations demonstrated excellent physical resistance to the acid medium with the acid uptake value in 2h rapidly released the drug in the alkaline media\textsuperscript{128}.

\textit{Release kinetics:}

The release profile of the optimized formulation CAP3 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

\textit{Stability studies:}

The results obtained for the disintegration, acid uptake and the in vitro dissolution studies revealed that formulation CAP3, coated up to 12% weight gain held most desirable properties. Hence CAP3 was subjected to accelerated stability studies to assess its long term keeping properties by storing up to 3 months in a humidity chamber at at 40 ± 2 °C and 75 ± 5 % RH. The samples were tested at regular intervals to examine any possible changes in the physico chemical properties, disintegration, drug content and release pattern.

The stability studies showed there was significant reduction in the assay and dissolution rate of the formulation. The possible reason could be that under prolonged storage at high temperatures and high humidity CAP will slowly hydrolyze, increasing the free acid content. CAP can be easily degraded by a hydrolysis. The relative humidity has a greater effect on the storage stability of CAP powder than temperature.

Eshra has reported on the stability of CAP film prepared from organic or aqueous formulations. In freshly prepared films of CAP from organic solution 3.2 % of free phthalic acid was measured, whereas films from an aqueous system 4.0 % free phthalic acid was found\textsuperscript{129}. After stress storage conditions at room temperature and 100 % RH, the content of free phthalic acid in films from aqueous systems reached 8.0 %.
Films from organic systems on the other hand had only 6.2 % free phthalic acid. Eshra also showed the effect of the pKa and the solubility in water of the drug incorporated in the free films on the hydrolysis of phthalyl groups of the polymer. The hydrolysis increased when the pH of the water-soluble drug increased. Eshra found that these tablets were not resistant to the acidic medium after storage. The reason for this result was the migration of the drug, especially the water soluble one, into the outer film layer containing CAP. The stability of enteric coated tablets was also studied by Thoma and Krautle. They have found that applying a barrier coat prior to the enteric coating consisting of aqueous dispersion of hydroxypropyl methylcellulose phthalate or CAP resulted in reduced swelling of the tablets130.

COATING WITH HYDROXY PROPYL METHYL CELLULOSE PHTHALATE (HPMCP):

An enteric coating agent is used to protect drugs from degradation by gastric acid or to present them from causing side effects in the stomach. The chemical structure of HPMCP is a phthalic half ester of hydroxy propyl methylcellulose, and the threshold pH value for rapid disintegration of HPMCP can be controlled by varying the phthalyl content. HP-55 is a special type of HP-55 which is distinguished by its higher molecular weight, higher film strength and higher resistance to simulated gastric fluid, has also been introduced. The following mixed solvents are used in general: methylene chloride/ethanol, acetone/ethanol. Triethyl citrate is used as the plasticizer in the coating composition. The method of preparation and the coating methodology is detailed in the experimental section. Triethyl citrate is used as the plasticizer in the coating composition. Isopropyl alcohol and dichloromethane in the ratio in 60: 40 ratios is used as the solvent mixture for the polymer.

In the present study, three different batches of tablets HP1, HP2 and HP3 were produced by coating the seal coated tablets up to weight gain of 5%, 8% and 10%. The coated tablets were subjected to all the physico-chemical evaluations including, disintegration, acid uptake, drug release and stability analysis and thermal analysis. The results of the evaluations were presented in the following table 50.
**Disintegration:**

All the batches of tablets HP1 to HP3 were imparted to disintegration test studies in 0.1M HCl for 2h and then in phosphate buffer pH 6.8. HP1 which was prepared with 5% weight gain could not resist the acid media and disintegrated within 4.7 min in the phosphate buffer. HP2 and HP3 prepared by coating 8% and 12% of weight gain remained stable and acid resistant for 2h in 0.1 M HCl while in phosphate buffer pH 6.8, they disintegrated at 5.23 and 6.8 min respectively. It is evident from the following figure that the increase in the enteric coating weight (up to 12%) resulted in non disintegration of the tablets in the acid media (0.1 N HCl) during the study period (2 h).

**Assessment of Acid uptake:**

The tablets after coating with different weight gains with HPMCP were subjected to two hours in 0.1N HCl or pH 4.5 acetate buffer. HP1 took up 12.8% in both in 0.1 M HCl and in acetate buffer 4.5, disintegrated within 2 hours. HP2 and HP3 showed up to 6.6% and 8.6% uptake in 0.1 M HCl while in acetate buffer 4.5, they showed an increased uptake at about 8.6% and 3.24% respectively. Thus increase in the coating thickness of the organic coating could reduce the acid uptake and swelling. The results of the acid uptake study is tabulated in the following table 51.

**In vitro Drug release:**

Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the formulations. HP1 coated with 5% weight gain released about 14% of the drug in the acidic media which is beyond the limits prescribed by the USP. The tablets of the batch released 96% of the drug within 30 min in the phosphate buffer, indicating the thin increments of coating given with HPMCP. In vitro drug release was carried out for formulations with 8% and 12% weight gain of enteric coated tablets (HP2 and HP3) in 0.1 N HCl for 2 h evidenced that that all the formulations demonstrated physical resistance to the acid medium with the drug release less than 5% in 0.1 M HCl up to 2h. Altering the media to basic (phosphate buffer-pH 6.8) leads to rapid release of pantoprazole from the tablets. HP2 released about 95% while HP3 released 86% at the
end of 45 min. The slower release of HP3 could be drawn to the reason of having additional polymeric film thickness. Similar observation was recorded by Amit A. Patel and group, who found that formulations demonstrated excellent physical resistance to the acid medium with the acid uptake value in 2h rapidly, released the drug in the alkaline media.\textsuperscript{128}

\textbf{Release kinetics:}

The release profile of the optimized formulation HP2 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

\textbf{Stability studies:}

The results obtained for the disintegration, acid uptake and the in vitro dissolution studies revealed that formulation HP2, coated up to 12% weight gain held most desirable properties. Hence HP2 was subjected to accelerated stability studies to assess its long term keeping properties by storing up to 3 months in a humidity chamber at at $40 \pm 2 \, ^{\circ}C$ and $75 \pm 5 \, % \, RH$. The samples were tested at regular intervals to examine any possible changes in the physico chemical properties, disintegration, drug content and release pattern.

The stability studies showed there was slight reduction in the assay and dissolution rate of the formulation. The possible reason could be that under prolonged storage at high temperatures and high humidity, HPMCP will slowly hydrolyze, increasing the free acid content.

\textbf{COATING WITH OPADRY ENTERIC:}

Opadry Enteric is a family of fully formulated, delayed release coating systems for solid oral dosage forms, which are applied by organic or hydro-alcoholic processing techniques. Specific Opadry Enteric coating formulations have been developed from a choice of enteric polymers, with solubility as a function of the environmental pH in the gastro-intestinal tract.
Opadry Enteric- 94series is formulated using the delayed-release polymer “Methacrylic Acid- Methyl Methacrylate Copolymer (1:1)”. Methacrylic acid copolymers have excellent stability against hydrolysis unlike other phthalate esters such as CAP or HPMCP\textsuperscript{131,132}. This system may be applied using organic or hydro-alcoholic processing techniques. It is generally considered that enteric protection is achieved with 5 – 6\% coating weight gain on tablets, although it is to be determined on a case-by-case basis based on the substrate nature and intended release profile.

**Disintegration:**

The tablets were subjected to disintegration in a disintegration test apparatus for 2h using 0.1N HCl as the media. All the batches of tablets remained intact without any visible changes on the surface such as peeling or cracking, thus remained unaltered in appearance. When changed to phosphate buffer pH 6.8, the tablets began breaking down rapidly. Changes in film permeability caused by salt formation of the carboxylic acid groups in the polymer with anions in the buffer media results in loss of integrity of the enteric film coating, causing the tablets to disintegrate\textsuperscript{133}. The disintegration time varied from 6 min to 10 min depending on the coating thickness. Enteric coated tablets with higher coating weight gains had longer disintegration times than those enteric coated at lower levels when tested in the same disintegration test medium. Longer disintegration times from films of higher thickness could also be attributed to a longer time taken to solubilise a thicker film.

**Assessment of Acid uptake:**

The ability of the coating to protect the active ingredient from the effects of gastric acid was determined by measuring the percent fluid uptake of the coated tablets when reciprocated in acid media for 2 hours in a disintegration apparatus. The test was carried out using two different media, namely, 0.1 M HCl and acetate buffer pH 4.5. All the batches of tablets showed less than 5\% of uptake in 0.1 M HCl, with the highest taken up by OE1 with least coating. In acetatebuffer pH 4.5, OE1 tablets showed up to 6\% uptake while the batch OE3 resisted the acid uptake less than 2\%. Fluid uptake of the coated tablets in all tested media decreased with increase in coating weight gain. This effect was observed until a certain minimum coating weight gain was achieved after which the effect was less pronounced. These results indicated that there was a
minimum coating thickness required to delay the drug release until a specific pH target, or to effectively protect an acid-labile drug. These results are in agreement with other reports documented in literature\textsuperscript{134}. The methacrylate type A polymer starts to ionize and dissolve at pH of around 6.0\textsuperscript{135}. In lower pH media, the polymer is not ionized and hence remains insoluble with low fluid uptake by the enteric coated dosage form. Low levels of fluid uptake at higher enteric coating weight gain may also be explained by the lower porosity, higher tortuosity and increased diffusion path length for the fluid\textsuperscript{133}.

\textit{In vitro Drug release:}

The release of pantoprazole from enteric coated tablets of Opadry enteric dispersion was evaluated in a USP dissolution apparatus using 0.1M HCl for 2 hours followed by test phosphate buffer pH 6.8 for 60 min. The drug release in 0.1M HCl was timid. OE1 release about 1.8% of drug at the end of 2h while OE2 and OE3 did not release any appreciable amount of drug in HCl. On transferring the tablets to phosphate buffer pH6.8, the tablets swell immediately and OE1, OE2 and OE3 released up to 98%, 94% and 89% by the end of 45 min. Slower release was obtained in the first 15 minutes in pH 6.8 buffer media for tablets coated with a 12% weight gain as compared to those with a 5% weight gain. Thereafter, rapid release of the drug in the buffer media was obtained for enteric coated tablets at both 5% and 12% weight gains. Slower initial release could be attributed to the longer time taken to solubilize a thicker film produced at higher coating levels than a thinner film produced at lower coating weight gains. At 12% enteric weight gain, the coat is initially semi-permeable allowing limited drug release, after which it becomes sufficiently weak to allow disintegration to occur\textsuperscript{134}. Once the enteric coat is sufficiently dissolved, rapid disintegration and release of the drug was obtained.

Tablets with higher Opadry enteric coating weight gains had longer disintegration times than those coated at lower coating weight gains. Dissolution rate was dependent upon both the pH of the dissolution medium and the thickness of the applied coat. Enteric coating using Opadry Enteric (94 Series) provided good acid resistance in 0.1N HCl at an enteric coating of 12% by weight of tablets. Therefore, formulation OE3 was selected for stability studies.
Release kinetics:

The release profile of the optimized formulation OE3 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

Stability Studies:

Tablet assay, dissolution and free salicylic acid were determined for coated tablets after 1, 2, and 3 months storage at accelerated temperature and humidity conditions 40°C/75%RH. Minimal change was observed in assay values of pantoprazole and dissolution results as compared to the initial results obtained. The enteric coating provided good protection in acid phase and greater than 80% release in 30 minutes even after 3 months at 40°C/75% RH.

COATING WITH ACRYL EZE:

Enteric polymer coatings contain ionisable carboxylic groups which shall remain insensitive to the acidic state of the stomach, nevertheless dissolves or disintegrates readily in the alkaline surroundings of the intestine. The different release characteristics of the enteric polymers have profound impact upon the pharmacokinetic parameters of the drug\textsuperscript{136, 137}. An ideal enteric polymer should possess a hydrophilic and hydrophobic monomeric unit. Methacrylic acid and methyl methacrylate could make an ideal hydrophilic and hydrophobic unit respectively. Such compositions of polymer are essentially insoluble in gastric fluids and may help transportation of drugs across the proximal alimentary tract without degradation\textsuperscript{138}. The Acryl-EZE is an anionic copolymer based on methacrylic acid and ethyl acrylate which suits the criterion of an acceptable enteric polymer. It is an optimized, pre-mixed excipient blend of aqueous acrylic system belonging to methacrylic acid copolymer type C (Eudragit \textsuperscript{®} L 100-55) for enteric film-coating. The polymer is insoluble in acidic media and dissolves step-wise at pH values greater than 5.5\textsuperscript{139}. Furthermore, Acryl-EZE \textsuperscript{®} is an excellent candidate for thermal processing since the polymer is pre-plasticized with triethyl citrate. The use of such aqueous polymer dispersion is advantageous from a toxicological and processing point of view but is critical with respect to film formation and storage stability\textsuperscript{140}. 

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Acryl-EZE is readily dispersible in water for easy application. The coating system can be pigmented to meet marketing requirements and provides consistent, reproducible delayed release profiles. Acryl-EZE MP is reconstituted to 20% w/w solids dispersion for use. Recommended weight gains of Acryl-EZE MP start at 10% for enteric performance depending on the shape, size and surface area of the multi-particulate. Individual product and machine functions should be taken into account and conditions altered as required.

The objective of this study was to investigate the enteric performance of aqueous enteric-coated tablet formulations containing proton pump inhibitors (PPI’s) in bio-relevant media, which better simulates the gastric environment of a patient on a multiple dose regimen of PPI. In the present study, Acryl EZE coating composition is produced by dispersing the Acryl EZE powder in water. A sub-coat may be required to separate strongly acidic or basic drugs from the enteric polymer or to strengthen the dosage form prior to enteric coating. The optimized formulation with good mechanical strength was seal coated using 12% HPMC dispersion. The seal coated tablets were then enteric coated with Acryl EZE dispersion in water. The method of preparation of the coating dispersion and coating procedure were detailed in chapter. The coating material deposit was increased to obtain different weight gains such as 8%, 10% and 16% from its original weight. The tablets were selected at random and checked for the weight gain before and after the application of specified time of coating in order to verify the attainment of desired weight. The three batches of tablets prepared AE1, AE2 and AE3 with different weight gains up to 8%, 10% and 16% respectively, were subjected to the evaluations such as thickness, weight, integrity, disintegration, fluid uptake, drug release, release kinetics, thermal analysis and accelerated stability studies.

Disintegration:

The tablets were subjected to disintegration in a disintegration test apparatus for 2h using 0.1N HCl as the media. All the batches of tablets remained stable and acid resistant for 2 hours in 0.1 N HCl without signs of peeling or discoloration of media. The coated tablets however disintegrated rapidly in phosphate buffer pH 6.8. The disintegration time varied from 4 min to 8 min depending on the coating thickness.
Thus as the coating thickness increases from 8% to 16%, the disintegration time increases correspondingly. This could be due to the fact that as the thickness increases, the polymer requires more time to solubilise and then to allow the tablet to disintegrate. The effect of weight gain up on the disintegration time is shown in the following figure 91.

**Assessment of Acid uptake:**

The tablets after coating with different weight gains with Acryl – EZE were subjected to two hours in 0.1N HCl or pH 4.5 acetate buffer. The percent acid uptake for the enteric coated tablets is shown in table 57 and Figure 92.

Although all the batches of tablets showed acid uptake than the prescribed limit, tablets AE1, AE2 and AE3 took up 6.2%, 4.9% and 2.26% respectively in 0.1M HCl while in the acetate buffer 4.5 the acid uptake was slightly on the greater side due to the exposure to higher pH. About 8.4%, 7.2% and 4.5% of acetate buffer was taken up by AE1, AE2 and AE3. Therefore, AE3 with highest coating thickness showed less acid uptake. AE2 tablets can also considered good which shows acid uptake well with the limits, taking in to account the lesser amount of coating thickness.

**In vitro Drug release:**

The drug release properties of the enteric coated tablets of pantoprazole at various weight gains were tested in 0.1 N HCl for 2 hours followed by testing in pH 6.8 phosphate buffer for 1 hour in a USP dissolution bath. Tablets of all the batches had less than 2% of drug release in acid media at the end of 2 hours and released more than 82% in phosphate buffer pH 6.8 with in 45 min. The release profile of the prepared tablets met with the criteria of the monograph of releasing less than 10% in acid media after 2 hours and more than 80% in intestinal media at 45 min. The tablets with greater weight gain, 12% and 16%, slightly delayed the released than tablets with 8% weight gain (Figure 104). Such an influence of polymer weight gain on the release pattern of tablets was also observed by Missaghi and his team, who found a slower release for enteric coated Rabeprazole tablets at 14% weight gain. The tablets with 12%
theoretical weight (AE2) were ascertained to be optimized formulation due to their acceptable dissolution profile and hence used for further studies.

**Release kinetics:**

The release profile of the optimized formulation AE2 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

**Stability studies:**

The accelerated stability studies performed for optimized AE2 batch tablets up to 3 months in a humidity chamber at at 40± 2 °C and 75± 5 % RH, revealed that the tablets held its properties with out much changes and the results were found satisfactory, well with in the limits. The study disclosed the absence of any significant transformation in the physical properties such as colour, appearence, hardness and disintegration time of the enteric coated tablets. The assay and the dissolution rate of the tablets which are considered as important assessments did not reveal any remarkable changes. The percentage of dissolution and assay were well with in the acceptable limits.

**COATING WITH SURETERIC:**

The pH of the stomach, even in the fed condition, will seldom reach a pH level of 5-6 but will surpass this level in the duodenum, where secretion of bicarbonate neutralizes the acidic chyme, leaving the stomach. Thus, a polymer with a dissolution threshold pH in the range 5 to 6 is considered suitable for use as an enteric coat142. The proportion of ionisable monomers in the polymer chain is probably the most important determinant of threshold dissolution pH, but other factors play a role in delineating this pH143. The quality of the enteric film formed by the coating composition is controlled by a number of factors, such as, tensile strength of the film which is dependent up on the properties of the polymer, the elasticity of the film, which depends on the quantity of the plasticizer used and the film- tablet surface interaction which is affected by every ingredient used in the making of the coating composition10.
Polyvinyl acetate phthalate (PVAP) is one of the most preferred materials for designing enteric formulations in terms of performance and acceptability\textsuperscript{144}. PVAP is the product obtained as a result of reaction between polyvinyl alcohol and phthalic anhydride\textsuperscript{56}. Aqueous dispersions of enteric polymers have gained importance over the organic solutions in the recent times, with regard to manufacturing safety concerns, toxicological and ecological deliberations\textsuperscript{145}. Sureteric is a specially blended optimized aqueous film coating combination of polyvinyl acetate phthalate, plasticizers and other processing ingredients, designed to meet the enteric coating needs of the solid oral dosage forms. However, the major limitation of many aqueous enteric coating formulations is the risk of premature drug release through the enteric coat in the stomach. This can be due to an increased permeability of aqueous film coatings\textsuperscript{42, 146}. Therefore, this section of the present study aimed at formulation and evaluation of enteric coated pantoprazole tablets using an aqueous based Sureteric enteric polymer system and thereby, to assess the potential of the polymeric system to protect the drug from the adverse effect of the gastric environment and its ability to favour its release in the intestine.

**Disintegration:**

Tablets were subjected to disintegration and acid uptake evaluations. All the batches of tablets remained stable and acid resistant for 2h in 0.1 M HCl while in phosphate buffer pH 6.8, the disintegration time varied from 4.5 min for ST1 with lowest weight gain to 9 min for ST4 with highest weight gain up to 15%. All the formulations demonstrated reproducible tablet break up, well within 10 min. The time for disintegration slightly increased as the actual coating weight gain increased. (Table 59 and figure 99).

**Assessment of Acid uptake:**

The tablets after coating with different weight gains with Sureteric were subjected to two hours in 0.1N HCl or pH 4.5 acetate buffer. The criterion for acid uptake was not more than 10 percent drug loss after 2 hours in 0.1N HCl or pH 4.5 acetate buffers. The percent acid uptake for the enteric coated tablets is shown in table 60 and Figure 100.
Formulation ST1, coated with weight gain up to 5% was the only batch which resulted in more than 12% acid uptake while the other formulations with greater weight gain exhibited less than 5% of acid uptake in 0.1 M HCl. In the acetate buffer 4.5 the acid uptake was slightly on the greater side due to the exposure to higher pH. About 15.6%, 7.8%, 4.5% and 2.8% of acetate buffer was taken up by ST1, ST2, ST3 and ST4. Therefore ST1, which took up more than the prescribed limit is considered to have failed the acid uptake test while ST4 with highest coating thickness showed less acid uptake.

In vitro drug release:

The solubility characteristics of polyvinylacetate phthalate produce a rapid breakdown of the enteric coating when the drug has passed from the stomach into the intestine allowing for release of the active ingredient. Six tablets each from four different formulations coated with different weight gains, i.e. 5%, 8%, 10% and 15% were subjected to in vitro dissolution testing in 0.1 N HCl for 2h followed by testing in pH 6.8 phosphate buffer for 1 hour in a USP dissolution bath. Tablets showed complete acid resistance for 2h, except ST1 tablets coated with least amount of polymer, which let about 12.13% of drug released in acid media at the end of 2 h. However, the release of pantoprazole in buffer pH 6.8 met the criteria outlined in this study i.e. not less than 80% dissolved after 60 minutes. All the tablet formulations released the drug rapidly on exposure to the alkaline media, although the percentage of drug released at a given time point was ascertained by the amount of polymer used for coating the tablets. Hence, ST1 with least weight gain released at a faster rate while ST3 fabricated with 15% polymer weight gain, released at a slower pace (Figure 101). Such an observation was made by Abdel and Aiman for enteric coated Diclofenac sodium tablets using Sureteric, which released more than 80% of drug with 30 min in alkaline media. Thus manipulation of performance by variation of the quantity of the applied enteric-coating agent has a powerful part to play.
**Release kinetics:**

The release profile of the optimized formulation ST2 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

**Stability Studies**

The results obtained for the disintegration, acid uptake and the in vitro dissolution studies revealed that formulation ST3, coated up to 10% weight gain held most desirable properties. Hence ST3 was subjected to accelerated stability studies to assess its long term keeping properties by storing up to 3 months in a humidity chamber at 40 ± 2 °C and 75 ± 5 % RH. The samples were tested at regular intervals to examine any possible changes in the physicochemical properties, disintegration, drug content and release pattern. Poly (vinyl acetate phthalate) is not hydrophilic due to its vinyl backbone, making it less subject to water vapour effects. The study disclosed the absence of any significant transformation in the physical properties such as colour, appearance, hardness and disintegration time of the enteric coated tablets. The drug content and the dissolution behaviour remained the same without any significant changes. The percentage of dissolution and assay were well within the acceptable limits as shown in the Figure 106.

**COATING WITH NUTRATERIC:**

Nutrateric, is a novel nutritional enteric coating system and an aqueous delayed release coating system designed specifically for nutritional supplements. It is comprised of an aqueous ethyl cellulose dispersion and NS enteric.

Surelease is a complete, optimally plasticized aqueous dispersion for modified release and taste masking applications. Ethyl cellulose is a water insoluble polymer with good ability to form films and excellent safety profile. Using ethyl cellulose as the rate controlling polymer, Surelease delivers dependable and reproducible extended release profiles that are consistent from laboratory to pilot and production scale processes. Surelease is a fully formulated and optimally plasticized system supplied at 25% w/w solids content. For best results, the product should be diluted to 15% w/w
Surelease is prepared by blending with ethyl cellulose with plasticizer, then extruded and melted. The molten plasticized ethyl cellulose is then directly emulsified in ammoniated water in a high shear mixing device under pressure. Ammonium oleate is formed in-situ to stabilize and form the dispersion of plasticized ethyl cellulose particles.

NS enteric is a nutritional enteric component, a dry powder containing sodium alginate. The sodium alginate functions as a pore former within the ethyl cellulose film to provide delayed release functionality.

The aim of this section of the present study were to investigate the influence of incorporating different levels of NS enteric as a pore forming agent into the aqueous ethyl cellulose system on the release of the freely water soluble pantoprazole from coated tablets. The method of preparation of the coating dispersion and the coating methodology were presented in detail in chapter 7. Two different ratios of Surelease: NS enteric were used. NSL comprised of 85 parts of Surelease and 15 parts of NS enteric while NSH comprised of 75 parts of Surelease and 25 parts of NS enteric. Each of the NSL and NSH were then used to prepare three formulations by coating up to different weight gains, such as 3%, 5% and 9% to study the best coating thickness required for the delayed release formulations of the pantoprazole drug. Six batch of the tablets thus prepared were subjected to various physico chemical evaluations such as thickness, hardness, friability, disintegration, acid uptake and drug release. The physico chemical properties of the tablets were found to be well within the acceptable limits (Table 62 and 63).

The physico chemical properties of the tablets were found to be well within the acceptable limits.

**Disintegration**

The disintegration time of the coated tablets was determined using the The USP model disintegration apparatus (EI). Six tablets were placed in the basket rack assembly, and was run for 2 hours in 0.1 N HCl media with the discs. The tablets were removed from the solution, gently dried by bloating. The test was then continued by
placing the tablets in phosphate buffer pH 6.8. The disintegration time of NSL were found to be slightly higher than the NSH which were prepared higher quantity of pH sensitive pore former. Both NSL1 and NSH 1 prepared with 3% weight gain of the coating composition failed the test as they disintegrated in the acid phase with in two hours. The disintegration time of NSL2 and NSL3 was found to be 7.8 min and 9.2 min respectively, while The disintegration time of NSL2 and NSL3 was found to be 5.9 min and 6.3 min respectively. In both cases, as the coating thickness was increased the disintegration time was prolonged.

**Assessment of acid uptake:**

Fluid uptake evaluation s provide an indication of the ability of the coating to protect the active drug from the effects of the gastric juice. As observed in the disintegration test, NSL1 and NSH 1 coated with least polymer thickness disintegrated in the aid media and hence fail to qualify the acid uptake test. NSH2 and NSH3 showed upto 4.6% and 3.25% acid uptake in 0.1 N HCL and about 12.8% and 9.1% in acetate buffer respectively. NSL2 and NSL3 showed upto 5.4% and 4.2% acid uptake in 0.1 N HCL and about 14.9 and 10.6% and 5.1% in acetate buffer, respectively. The results show that as the concentration of the pore forming agent was increased, the acid uptake slightly decreases which could be the property due to NS enteric to resist the acid. As the coating thickness increases the acid uptake in both 0.1 M HCl and acetate buffer decreases significantly (Table 64 and figure 108).

**In vitro Drug release**

The release of pantoprazole from the nutrateric coated enteric tablets were dependent up on the amount of NS enteric present in the formulation and the thickness of the polymeric film. The formulations NSL 1 nad NSH1 which were coated up to 3% weight gain could not resist the acidic environment and therefore disintegrated well with 2h. NSL 2 and NSL3 which were prepared with 15 parts of pore forming agent and 85 parts of ethylcellulose, showed a maximal acid uptake of 4.6% and 1.7% of acid uptake in the 0.1 M HCl in 2 h. On transfering to alkaline media, NSL2 released 86% while NSL3 released 68% of drug at the end of 3h. This slow release could be attributed to the release ratrding nature of ethyl cellulose. NSH 2 and NSH3 which were prepared
with 25 parts of pore forming agent and 85 parts of ethylcellulose, showed a maximal acid uptake of 2.7% and 0.9% of acid uptake in the 0.1 M HCl in 2 h. On transfering to alkaline media, NSH2 released 96% while NSL3 released 88% of drug at the end of 3h. Hence NSH 2 with 25 parts of NS enteric and 75 parts of EC at 5% weight gain was considered optimum for the delayed release of pantoprazole.

**Release kinetics:**

The release profile of the optimized formulation NSH2 was fitted to zero-order, first-order, Higuchi, Korse-meyer and Peppa’s for deciding the most appropriate model to predict the mechanism of drug release.

**Stability studies:**

The results obtained for the disintegration, acid uptake and the in vitro dissolution studies revealed that formulation NSH2, coated up to 5% weight gain held most desirable properties. Hence NSH2 was subjected to accelerated stability studies to assess its long term keeping properties by storing up to 3 months in a humidity chamber at at 40 ± 2 °C and 75 ± 5 % RH. The samples were tested at regular intervals to examine any possible changes in the physico chemical properties, disintegration, drug content and release pattern. The study disclosed the absence of any significant transformation in the physical properties such as colour, appearance, hardness and disintegration time of the enteric coated tablets. The drug content and the dissolution behaviour remained the same without any significant changes. The percentage of dissolution and assay were well within the acceptable limits as shown in the Figure 114.

**Release kinetics of coated tablets:**

The regression values of zero order are very near to 1 than the other kinetic models. Thus it could be inferred that the drug release from the coated tablets follows zero order. The coated tablets disintegrate and released drug in alkaline media and have shown lag time in 0.1 N HCl (stomach pH) confirming delayed release.
Selection of Optimized formulation:

In the present research work, the core tablets with optimal properties were sealed using HPMC dispersion. The tablets were produced in bulk and used in parts for further coating with different enteric polymers. Three different polymer types namely, organic (CAP and HPMC), hydroalcoholic (Opadry) and aqueous (Acryl Eze, Sureteric, Nutrateric) coating compositions were used. For each of the enteric polymer, formulation variables were altered and evaluated for their physicochemical properties. Based on the evaluations, an optimized formulation coated with each of these polymers were selected which had most desired properties in terms of their stability and performance. Each of the polymer used could be successfully used to prepare a stable delayed release tablets of pantoprazole.

The performance of the polymers however greatly depend upon the nature of the polymers, its solubility in a particular pH and the coating level and coating method used. While some polymer assure acid resistance at low coating levels, others might show the same resistance at higher coating level. While CAP dissolves at pH >6, Sureteric dissolves at pH 5. In case of Nutrateric, only the pore former dissolves while sureteric erodes slowly. So comparison of the performance of a polymer with other polymers may not be fair. However, as the coating with aqueous polymers was considered more advantageous from, ecological and ecnomic prospects, attempt was made to compare the performace of tablets, one from organic, hydroalcoholic and aqueous types each. Thus the optimized formulations of CAP, opadry enteric based on methacrylic polymer and sureteric based on PVAP were chosen for thermal analysis and gastro intestinal transit behaviour studies.

Thermal analysis:

The DSC Thermogram of pantoprazole is shown in the figure 115. The DSC curve of pantoprazole obtained on heating rate of 10°C/min exhibits a sharp endothermic peak at 148.1°C. The obtained DSC curve of pantoprazole exhibited an endothermic peak which corresponds to the melting point of the drug and is immediately followed by the sharp symmetric exothermic peak. The observed melting peak temperature was 148.1°C ($T_{onset} = 134.1 \, ^\circ C$) with an apparent heat of fusion of 221.3 J/g.
The DSC Thermograms of the CAP polymer, the optimized formula CAP3 were shown in the figures 116 & 117. The characteristic peak of the drug was found in the formulation Thermogram at 147.5°C, very prominently, revealing the unchanged nature of drug. The characteristic peak of the polymer was found to be less prominent considering the smallest quantity of polymer used to coat the tablet. Hence, the formulations are considered to have retained the properties of the acid liable drug without the incidence of any potential incompatibilities.

The DSC Thermograms of the Opadry enteric polymer, the optimized formula OE3 were shown in the figures 118 & 119. The characteristic peak of the drug was found in the formulation Thermogram at 152.2°C, very prominently, revealing the unchanged nature of drug. The characteristic peak of the polymer was found to be less prominent considering the smallest quantity of polymer used to coat the tablet. Hence, the formulations are considered to have retained the properties of the acid liable drug without the incidence of any potential incompatibilities.

The DSC Thermograms of the Sureteric polymer, the optimized formula ST3 were shown in the figures 120 & 121. The characteristic peak of the drug was found in the formulation Thermogram at 155°C, very prominently, revealing the unchanged nature of drug. The characteristic peak of the polymer was found to be less prominent considering the smallest quantity of polymer used to coat the tablet. Hence, the formulations are considered to have retained the properties of the acid liable drug without the incidence of any potential incompatibilities.

**Gastro intestinal transit behaviour:**

Based on the physico chemical properties, invitro release performance and stability aspects, the optimized formulations coated with sureteric and opadry enteric selected for the study of their in vivo performance. CAP coated tablets were also used as a comparison of aqueous coatings to that of organic coating polymers.

The GI transit behaviour of the formulation was visualized using fluoroscopy under the supervision of a radiologist. The tablets containing radio-opaque marker (barium sulphate) were prepared by replacing the drug using 3mm biconvex punches
using same proportion of ingredients in a similar manner to optimized formulations. The tablets were administered to each animal with sufficient of water after the animals had fasted overnight. During the experiments the animals remained in a sitting or upright posture in neck stock cages. All X-ray films were taken in anterior positions at regular intervals up to 3 h from the time of administration to detect the intactness or disintegration of the test formulations.

The radiographic images of the tablets coated with Opadry, Sureteric and CAP are shown in the figures 122, 123 and 124. Opadry and Sureteric coated tablets were seen prominently in the anterior side of the animal up to 120 min confirming the rigidity of the tablets in the acidic stomach. At 150 min, however, the traces of the tablets were not seen ensuring the complete disintegration of the tablets in the intestine.

The tablets coated with CAP, although intact till 120 min in the stomach region, showed the traces of tablets at the end of 150 min in the intestinal region. This shows the increased pH and time required for the CAP coated tablets to release its contents.

PHARMACOKINETIC AND BIOAVAILABILITY EVALUATION CAP COATED OPTIMIZED FORMULATIONS

Enteric coated tablets of Pantoprazole using Sureteric, Opadry and CAP exhibited markedly better gastric resistance when compared to the tablets prepared using various other polymers. Among the three polymers CAP exhibited much gastric resistance and delayed drug release. Therefore in order to understand the pharmacokinetic behaviour of optimized formulations they are further subjected to in vivo pharmacokinetic and bioavailability assessment in rabbits.

Pharmacokinetic parameters estimated following the oral administration of Pantoprazole and its Enteric coated Tablets are given in Table 69. The elimination rate constant ($K_{el}$) for Pantoprazole was found to be 0.199 hr$^{-1}$ and the corresponding biological half-life ($t \frac{1}{2}$) was found to be 3.47 hrs after the oral administration of Pantoprazole.
The absorption of Pantoprazole was found to be absorbed well when given orally and a peak serum concentration ($C_{\text{max}}$) of 1.912 ng/ml was observed at 2.0 hr following oral administration. Whereas the absorption of Pantoprazole from Enteric coated tablets is much slower and peak serum concentration ($C_{\text{max}}$) of 1.213 ng/ml was observed at 9.16 hr following oral administration.

All the pharmacokinetic parameters of absorption (Table 69) namely $C_{\text{max}}$, $T_{\text{max}}$, % absorbed to various times and AUC indicated slower absorption and good bioavailability of Pantoprazole when administered as Geomatrix Tablets from GVG 6 Formulation. lower $C_{\text{max}}$ and longer $T_{\text{max}}$ values were observed with Pantoprazole Geomatrix Tablets when compared to those of Pantoprazole as such. AUMC was also much higher in the case of Pantoprazole enteric coated Tablets when compared to Pantoprazole. AUMC was increased from 84.71 ng-hr/ml for Pantoprazole to 256.52 ng-hr/ml for Pantoprazole enteric coated Tablets.