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Current developments in tablet coatings

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ABSTRACT

Surface coating on drug tablets is a widely practiced and commercially significant technology and is a workhorse of the pharmaceutical industry as far as post production protection of drug tablets and capsules is concerned. This technological area involves a highly sophisticated and complex end-use of surface coatings technology into pharmaceuticals which is of high value to the industry especially to the pharmaceutical and coatings technologist. While existing literature on this subject has focused upon the entirety of the area with respect to every minute factor such as types of the said coatings, the equipment involved, the biopharmaceutical aspects, the coloring and flavoring of the dosage forms and even the testing and stability evaluation of the dosage forms, this review focuses essentially on the latest developments in two main research areas namely the polymer chemistry of film coatings and the phenomenon of Controlled Release of an active pharmaceutical ingredient from the dosage form.

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INTRODUCTION

Coating of pharmaceutical dosage forms or simply 'medicines' as they were known earlier, during the times they developed, were employed primarily with a motive of masking unpleasant tastes and imparting a more elegant appearance, therefore making long-lasting gloss a primary requisite. The first reports on 'pill coating' date back from the Greek -Arabic civilization with mucilage of plantago psyllium and silver^[1] being used as the coating materials. Honey and later sugar followed as coating materials only to become popular with vast cultivation of sugar cane and sugar beet in Europe and North America in the 19th century. As technology developed and as the dosage forms employed became multifarious, coatings were required to be carried out to attain certain advanced objectives. They can be listed

as below:

1. Ensuring Controlled Release of the active ingredients with respect to the environment in which the dosage form is administered.
2. Avoidance of side effects.
3. Protection of the active ingredients against air, light and moisture.
4. Increasing mechanical stability during manufacture, packaging and shipment.
5. Increasing Drug safety by better identification.

The first two are the 'Primary' and 'on-site' objectives, the third is of intermediate significance and comes into play only when the dosage form is exposed to external conditions, while the final two are more advanced or 'Tertiary' objectives which are generally of importance on a bulk scale where storage, handling, packaging and distribution of the dosage forms is involved.

Types of coatings

While coatings on pharmaceutical dosage forms have been most broadly divided into Sugar coatings and Film coatings^[2], the area can be divided into two more classifications based mainly upon the method by which they are coated i.e. 'Hot melts' and 'Press coatings'. Out of these, the area of Film Coatings is the one which interests the coatings technologist most since it involves the direct applications of fundamentals of coatings technology. Film coatings consist mainly of polymers which are applied to the cores in the form of solutions or dispersions in which other excipients are dissolved or dispersed^[3]. A coating composition in a film coating consists of the film forming polymer, the requisite excipients or additives such as plasticizers, pigments, glidants and lubricants as well as dispersing agents. The desired composition is dictated by the end requirement as well the exact area of disintegration of the coating. Film coatings involve the use of mainly three types of polymers^[4] i.e. Rapid Release water soluble polymers coatings, enteric coatings and insoluble coatings.

Rapidly disintegrating film-coatings

Film coatings for rapidly disintegrating film-coated tablets consist either of water-soluble polymers or of mixtures of water-soluble and water insoluble polymers. The most widely used water-soluble film formers are Hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), Hydroxypropyl cellulose (HPC), Hydroxy ethylcellulose (HEC) and sodium carboxy methylcellulose (NaCMC), vinyl derivatives like polyvinyl alcohol and polyvinyl pyrrolidone and polyglycols and acrylate derivatives.

Of these, acrylate polymers with basic amino groups are used for flavoring and taste masking. They do not dissolve well in the saliva, and dissolve in the acid environment of the stomach. The product Eudragit E, poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) in the ratio of 1:2:1 is a rapid release polymer which disintegrates in water which does not require plasticizer addition but magnesium stearate may be used as a glidant.

Considering some solubility aspects of cellulose ethers, the powders swell strongly in water and thus tend to form lumps, but are less water soluble at higher temperature because of the reduced degree of hydra-

tion, they are first suspended in hot water and then cooled down with stirring. The pigments are homogenized separately from the polymer solution in suitable, usually high shear equipment and added just before use.

The plasticizer is a significant component of the film coating system and majority of the research carried out in the area of film coatings is based on investigating effect of different plasticizers on permeation, drug diffusion and release characteristics of the coatings. Plasticizers mainly reduce brittleness and increase flexibility and ductility of the film and ensure spreading and/or film capability. Migration of plasticizers from film coating polymers towards the core and to the storage medium could result in serious changes in the mechanical properties and permeability of coatings thus greatly influencing rate and extent of drug release.

The migration of water soluble triethyl citrate applied as a plasticizer in Acryl-Eze coating has been reported to be studied by Budavari et al. (New 8) Considerable migration of triethyl citrate towards the tablet cores has been reported. The extent of the triethyl citrate migration has been shown to be influenced by the relative humidity of the storage medium.

Hydroxypropyl methyl cellulose has been extensively studied among all the rapid release water soluble polymers. Quessi et al.^[5] have demonstrated that the incorporation of different concentrations of HPMC into shellac coatings, due to the increasing of pores, could considerably increase the drug release from the pellets in purified water. Additionally, PVA results in small cracking in the films and much more diffusion of drug in water. Lee et al.^[6] have reported that unlike the uncoated and conventionally coated HPMC tablet, dual drug-loaded HPMC matrix tablets give a biphasic linear release. The biphasic release profiles of dual drug-loaded HPMC matrix tablet were highly modified, depending on the amount and type of five plasticizers. This goes on to demonstrate that the current dual drug-loaded HPMC matrix tablet, showing biphasic release profiles may provide an alternative to deliver drugs with circadian rhythmic behaviors in the body. Frohoff-Hulsmann et al.^[7] have investigated release mechanisms of theophylline pellets coated with an aqueous ethyl cellulose (EC) dispersion containing plasticizers and hydroxypropyl methylcellulose (HPMC) as a water

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soluble pore former along with the effect of curing and storage conditions of coated pellets on the drug release rate. The release mechanisms have been shown to depend on the glass transition temperature of the ethyl cellulose and therefore on the migration of the plasticizers and the pore former. Another similar study^[8] has been conducted to investigate the properties of sprayed films prepared from aqueous ethyl cellulose dispersions (ECD) containing hydroxypropyl methylcellulose (HPMC) and plasticizers of different water solubility in order to clarify the drug release mechanisms of pellets coated with the respective material. The results reported demonstrate that the glass transition temperature T_g and the softening temperature T_s of these films after swelling are dependent on the water solubility of the plasticizer. The T_g of ECD films plasticized with triethyl citrate is above the swelling temperature of 37°C after migration of the plasticizer, transforming the polymer in the glassy state. In contrast, dibutyl phthalate-containing ECD films demonstrate a T_g below the swelling temperature, leaving the polymer in the rubbery state. Qussi et al.^[9] have investigated the effect of triethyl citrate (TEC) and different molecular weights and concentrations of polyethylene glycol (PEG), in addition to the effect of different water-soluble polymers and dispersions at different levels, hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), polyvinyl alcohol (PVA), ethyl cellulose (EC), on the mechanical and thermal properties, drug permeability, and porosity of free shellac films. The addition of plasticizer was shown to cause a decrease in both elastic modulus and glass transition temperature T_g and an increase in elongation at break of free shellac films. It has also been reported that the drug permeability is directly related to the mechanical properties and T_g of shellac films. Saringat et al.^[10] have reported the investigation of the effect of plasticizers PEG400, PEG1000 and triacetin on mechanical properties, glass transition temperature and water vapor transmission of free films prepared from HPMC and/or HPMC:PVA blends, to develop suitable coating system for tablets, and to determine the release profiles of the coated tablets. Addition of both grades of polyethylene glycol (PEG400 & PEG1000) increased the moisture permeability of HPMC films but the films containing triacetin provided a more rigid barrier to moisture compared to unplasticized HPMC films. Presence of the

three plasticizers as well as PVA and PEG400 together improved the coating properties of HPMC films and made it more suitable as a non-functional coating material. Kwok et al.^[11] have investigated vinyl pyrrolidone/vinyl acetate copolymer (S630) as plasticizer for its influence on HPMC film coating parameters, comparing the results with a commonly used plasticizer, polyethylene glycol and another copolymer, polyvinyl alcohol. The moisture permeation was slightly reduced but not to the same extent as polyethylene glycol. This may be attributed to the water soluble-water insoluble combination of vinyl pyrrolidone-vinyl acetate. A 10% concentration of S630 increased the adhesive strength and toughness of the HPMC film coat. The anti-tack action of polyvinylpyrrolidone (PVP) on hydroxypropylmethylcellulose (HPMC) solution has been elucidated by Chan et al.^[12]. The addition of PVP was shown to reduce the tack of the HPMC solution when used at low concentrations, without affecting the state of hydration of HPMC. Lower molecular weight PVP was more effective as an anti-tack agent owing to suitable hydrodynamic size to intersperse among the HPMC chains. The degree of reduction in tack values was more pronounced for HPMC that showed a greater extent of interaction between polymer chains such as when high concentration of HPMC or low solution temperature was employed, which was attributed to the net reduction in the extent of hydrogen bonding between HPMC chains. This in turn, has been correlated to the changes of viscosity and surface tension of the HPMC solutions but not to the glass transition temperatures of the polymers prepared as solid films.

Enteric coatings

An enteric coating resists dissolution in acidic gastric media, but dissolves in the alkaline intestinal environment. Enteric coatings are useful for protecting the stomach wall from the effect of active ingredients in dosage form. For example, if aspirin is directly exposed to gastric mucosa, it can cause corrosion of the stomach wall. Enteric coatings are also used to protect active ingredients in the tablet core from chemical attack from stomach acids and digestive enzymes. Enteric coatings can also be used to promote the delivery of active ingredients in the core tablet to a particular region of the intestine such as the upper part of the small

intestine, in order to enhance the bioavailability of the active ingredient.

Polymers with free carboxylic groups are insoluble in acid media and dissolve by salt formation above pH 5-6. They are used for enteric film coatings. Polymers such as hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate trimellitates (CAT), Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS), carboxymethyl ethylcellulose (CMEC), polymethacrylates and polyvinyl acetate phthalate (PVAP), and certain acrylic polymers, in both aqueous and organic coating formulations. In the low pH stomach environment, the carboxylic acid groups in the polymers remain un-ionized. Therefore, the polymeric coating remains insoluble in gastric fluid. The polymeric coating disintegrates or dissolves in the higher pH intestinal environment to allow dissolution of the tablet core in the small intestine. The active ingredients are absorbed through the intestinal wall for delivery to the blood stream.

Enteric coatings materials are used for taste masking and stability improvement as well as for odour protection. They are specifically indicated, however to avoid incompatibility reactions in the stomach with aggressive drugs that may cause nausea and irritation of the gastric mucosa^[3]. Enteric coatings may also be used for controlled delivery to the small intestine and the colon. Some enteric coatings are combined with a non-irritational initial dose released in the stomach to ensure an immediate onset of therapeutic action.

Effects of various formulation and processing parameters such as plasticizer content, coating level and curing conditions on the resulting drug release kinetics from theophylline matrix pellets coated with aqueous hydroxypropyl methylcellulose acetate succinate (HPMCAS) dispersions were studied by Siepmann et al. (New 1) Due to the micrometer range size of the HPMCAS particles, their coalescence was particularly crucial and not complete upon coating. It has been demonstrated that at low coating levels continuous water-filled channels connected the bead cores with the release medium through which the drug could rapidly diffuse, resulting in high release rates even at low pH. At high coating levels such continuous connections did not exist (due to the increased number of polymer particle layers), and drug release was controlled by diffu-

sion through the macromolecular network resulting in much lower release rates. An elevated temperature curing was demonstrated to be responsible for further polymer particle coalescence, resulting in a change of the underlying drug release mechanism and significantly reduced drug release rates.

The anion-controlled drug release mechanism through the cationic coating polymer Eudragit RS 30 D as a function of the anion attraction toward the polymer's quarternary ammonium group (QAG), anion valence, and film composition has been reported by Wagner et al. (New 2). An instant exchange of chloride against the medium's anion species after an immediate penetration of dissolution medium into the polymer at completely different rates compared with the drug release constituted the mechanism of drug release. A water flux was induced by back and forth exchanging anions depending upon the attraction of the anion towards the Quarternary Ammonium Group (QAGs). Strong attraction (as in cases of nitrate and sulfate ions) resulted in a low water flux while weak attraction resulted in a high flux (as in case of acetate ions and succinic acid). The water flux increased at increasing number of QAGs. Plasticizer acted as a diluent in respect of the number of QAGs, thus higher plasticizer concentrations led to lower drug release.

Menjoge et al.^[13] have reported miscible blends of a newly synthesized reverse enteric polymer (NREP) with enteric and pH-independent polymers. The interactions between NREP and these polymers have been ranked in the order EC (ethylcellulose) < ES (Eudragit S) < HPMCP (hydroxypropyl methylcellulose phthalate). The comparison of interactions in blends has been proven to help explain the release pattern of cefuroxime axetil (CA), a very strong antibacterial, at gastric pH and tailor the release of other drugs according to their pharmacokinetic characteristics. The understanding has been reported to provide a more rational approach for selection of polymers and their content in the coating compositions, rather than an empirical approach. The interactions of Cefuroxime axetil (CA) with the polymers hydroxypropyl methylcellulose phthalate, cellulose acetate trimellitate, and Eudragit E result in the generation of unacceptable amounts of impurities and degradation. Thus, formulations, which mask the bitter taste of CA and release it immediately in the stomach, have

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therefore not been possible. Thus, a study subsequent to the previous one, by the same team has reported a self-associated cationic polymer (NREP) containing methyl methacrylate (MMA), 2-hydroxy ethylmethacrylate (HEMA), and 4-vinyl pyridine (4-VP), in an attempt to overcome the interaction with the same drug CA. The hydrogen bonding between the pyridine nitrogen and the hydroxyl groups of HEMA has been demonstrated to result in strong intrachain associations, prevent interactions between NREP and CA, and inhibits degradation of CA. These self-associations restrict polymer chain motions, enhance biocompatibility, and lead to a higher T_g, which ensures that NREP does not become tacky in processes involving heat. The judicious choice of the hydrophobic and hydrophilic monomers renders the polymer hydrophobic enough as to mask the bitter taste of CA at near neutral pH. Incorporation of the basic monomer 4-VP ensures rapid dissolution of the polymer and release of CA at the acidic pH prevalent in the stomach. The work indicates an approach to design pH-sensitive polymers for dosage forms that meet the pharmacokinetic requirements of the drug. Work in the same direction, has been patented by Ibanez et al.^[14] wherein they disclose composition comprising cefuroxime axetil in particulate form such that the particles are coated with integral coatings of a lipid or mixture of lipids which are insoluble in water and which disperse or dissolve on contact with gastrointestinal fluid, a bulk sweetener a binding agent and a texture modifier such as polyvinylpyrrolidone, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, which serves to mask the bitter taste of cefuroxime axetil upon oral administration.

Dittmar et al.¹⁵ have patented a novel bilayered pharmaceutical composition in a solid unit dosage form for oral administration. The composition consists of an active pharmaceutical ingredient or drug, an inner and outer coating layer. The inner coating layer comprises poly (methacrylic acid, methyl methacrylate) 1:2 (Eudragit S), or other enteric polymer material which has the same pH release characteristics in aqueous media as Eudragit®S, an anionic copolymer derived from methacrylic acid and methyl methacrylate, with a ratio of free carboxyl groups to the ester groups of approximately

1:2, and a mean molecular weight of approximately

135,000. The outer coating material can be any coating material that dissolves or is removed in the gastrointestinal tract prior to the inner coating layer. The outer coating layer is either a single coating or multiple coatings of either an enteric polymer material or film coating material. The function of the outer coating layer is to prevent or minimize fractures of the inner coating layer during formulation processing, manufacturing, and packaging, and the function of the inner coating layer is to maintain the desired point of release of the therapeutic active agent in the gastrointestinal tract. Plasticizers may also be added to the coating composition to facilitate the coating process and to obtain an even coating film with enhanced physical stability. The outer coating layer may consist of non-enteric as well as enteric polymers such as hydroxypropyl methylcellulose, carboxymethylcellulose, carboxymethylcellulose, hydroxyethyl cellulose or cellulose acetate maleate, polyvinyl alcohol phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose hexahydrophthalate, polyvinyl acetate phthalate.

With the gradual elimination of all organic solvents, such as acetone and methanol, in the pharmaceutical industry from the manufacturing of pharmaceutical drug products, there has been a growing need for aqueous-based coating technologies. One of the early records of developing aqueous formulations for enteric coatings on drug tablets has been given by Sophie-Dorothee et al. Novel formulations of an aqueous-soluble salt of CAP which can be coated onto tablets producing a film that is insoluble in acid but soluble in an alkaline buffer. The formulations can be used for any drug that requires an enteric film coating such as the manufacture of delayed release articles. The process can be briefly described as follows. The polymer/salt forming agent (SFA) formulation is prepared by dispersing the polymer in about half of the total amount of required water. SFA, from about 35% of polymer is then poured into the dispersion and the mixture agitated for about 4 hours to allow for complete dissolution of the polymer. The plasticizer is then added at 20% levels, based on polymer, preferably about 25%, and water is added to reach the final weight. The solution is then agitated for about one 30 minutes to about one hour, preferably about 30 minutes, to achieve plasticization of the polymer and

then optionally passed through a 20-60-mesh screen, resulting in a plasticized polymer/SFA solution which is clear, free from any insoluble material and used within 24 hours following preparation.

One of the early quantitative descriptions of drug release was presented by Ozturk SS with the help of a mathematical model that describes the dissolution of the polymer coating and release kinetics of weakly acidic drugs from enteric-coated tablets in buffered media. This model can also be used to predict the time of onset of core disintegration. The dissolution of the enteric coating was found to depend on the intrinsic solubilities and pKa's of the drug and polymer and the medium properties. The release rate of the drug was demonstrated to depend on the intrinsic solubilities and pKa's of drug and polymer, the medium properties, i.e., pH and buffer capacity, and a mass transfer coefficient.

With an objective to provide an aqueous enteric coating composition containing a water soluble salt of a film-forming enteric polymer wherein the film coating provides a higher water resistance than was previously achievable and maintains good mechanical strength, Wayne et al.^[16] have developed and patented an enteric film coating composition such that, while maintaining good mechanical strength, its water and acid resistance is increased beyond that which was previously achievable via solids loading by way of loading an aqueous solution of its salt with a dispersion of a particular concentration of solid flake filler material and a hydrophobic compound containing aliphatic carbon atoms. The approximate weight percents of the required composition are 35%-50% weight percent of a enteric polymer with a solubilizing amount of a water-soluble base to provide an aqueous solution or dispersion of a salt of the enteric polymer and, dispersing about 30 weight percent of a hydrophobic and about 25 weight percent of a water insoluble flake material (water-insoluble, inorganic mineral) in the aqueous polymer solution.

HPMCP is not considered advantageous because it may cause environmental problems due to the use of an organic solvent. Although aqueous dispersions of acryl copolymers are commercially available, they are not natural products but synthetic polymers and have physical properties for films inferior to HPMCP. Accordingly, there has been an increasing demand on the development of novel environment-friendly products.

A novel method of preparing an aqueous dispersion of hydroxypropyl methylcellulose phthalate (HPMCP) nanoparticle composition has been patented by Baek et al.^[19] The nanoparticles prepared by this method claim to offer physical properties for enteric coatings without an ion exchange process, which is the cause of increased manufacture cost. In doing so, it has been found out that an HPMCP nanoparticle composition prepared by an aqueous neutralization-emulsification process, in which use of an emulsifier and a plasticizer is selectively controlled, can solve the solid content decrease and a problem of long process time due to the ion exchange process and offer physical properties such as dissolution and disintegration for use as enteric films and coatings. The process described briefly as follows. Purified water, HPMCP an emulsifier and a plasticizer are taken in a reactor. The neutralizing agent which is extremely important for nanoparticle synthesis is added slowly for 30 minutes. Aqueous ammonia solution has been used as the neutralizing agent. The reaction has been reported to be performed for 2-4hrs. at 40-60°C to prepare a 10 to 30% aqueous dispersion of HPMCP. The evaluation of the enteric property was evaluated by coating a diclofenac sodium tablet, which is widely used as anti-inflammatory drug with the prepared aqueous HPMCP dispersion. When a disintegration test was performed at pH 1.2 for 2 hours, no disintegration was observed, which suggests that it has superior physical properties for enteric coatings.

Insoluble coatings

The third major class of coatings used for coating pharmaceutical dosage forms is that of 'Insoluble Coatings' which consists of cellulose derivatives, acrylates and vinyl derivatives.

For permeable, delayed release coatings copolymers of methyl methacrylate and ethyl methacrylate 2:1 are used, which additionally contain trimethylammonioethyl methacrylate chloride in proportion of 5% (Eudragit® RS) or 10% (Eudragit® RL) as hydrophilic monomer units.

Sungthongjeen et al.^[17] have reported the preparation and evaluation of a tablet system consisting of cores coated with two layers of swelling and rupturable coatings as pulsatile drug delivery system. Cores containing buflovedil HCl as model drug were prepared and were

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then coated sequentially with an inner swelling layer containing a superdisintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. The effect of core composition, level of swelling layer and rupturable coating was reported to reveal that increasing levels of the ethylcellulose coating retarded the water uptake and thus prolonged the lag time. A pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion Aquacoat® ECD has been developed by Mohamad et al.^[18]. A rupturable pulsatile drug delivery system consists of

- (1) a drug core;
- (2) a swelling layer, comprising a superdisintegrant and a binder;
- (3) an insoluble, water-permeable polymeric coating.

Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release. The release after lag time was fast and complete, when cross-linked carboxymethyl cellulose (AcDiSol) was used as a swelling agent and a sustained release was achieved after the lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab) were used as swelling agents. Outer membrane, formed using aqueous dispersion Aquacoat ECD was reported to be brittle and ruptured sufficiently to ensure fast drug release, compared to ethylcellulose membrane formed using organic solution. The addition of talc has been demonstrated to increase brittleness of membrane and has been proved to be very advantageous because of (i) reduced sensitivity of lag time on variations in the coating level and (ii) fast and complete drug release. The swelling characteristics of various swellable polymers in swelling layers that induce the rupturing of an outer polymer coating in pulsatile drug delivery systems (DDS) have been investigated by Bussemer et al.^[20] The swelling energy of several excipients was shown to decrease in the following order:

Croscarmellose sodium (Ac-Di-Sol) > Low-substituted hydroxypropyl cellulose (L-HPC®) > Sodium starch glycolate (Explotab®) > Crospovidone (Kollidon® CL) > Hydroxypropyl methylcellulose (Methocel® K100M).

A linear correlation was shown to exist between the swelling energy and the water uptake. A diffusion-controlled swelling force development, predominantly

controlled by the penetration rate of the medium for the excipients tested has been proved. The use of blends of gastrointestinal tract (GIT)-insoluble and enteric polymers (ethyl cellulose and Eudragit L) as coating materials for multiparticulate controlled release dosage forms has been demonstrated by Lecomte et al.^[21]. In the same study, effects of the polymer blend ratio and coating level on the resulting drug release patterns were also studied along with an explanation of the observed phenomena based on the physicochemical properties of the systems. A broad range of drug release patterns from coated pellets was demonstrated to be obtained by varying the GIT-insoluble:enteric polymer blend ratio. The drug release mechanisms from pellets coated with pH sensitive blends of a water-insoluble and an enteric polymer, ethylcellulose:Eudragit L and Eudragit NE:Eudragit L, respectively have been demonstrated by Lecomte F et al.^[21] (New 3) It has been demonstrated that by varying the type of polymer blend and blend ratio, drug release mechanisms can be effectively altered. As an example, at low pH drug release has been demonstrated to be primarily controlled by diffusion through the intact film coatings in Eudragit NE:Eudragit L blends, whereas crack formation has been shown to be of major importance in ethylcellulose:Eudragit L-coated systems. At high pH, the (partial) leaching of the enteric polymer out of the coatings plays an important role.

Coatings for tablets for drug delivery in the gastrointestinal tract

Since tablets are employed primarily for oral drug delivery, the target region for these dosage forms is the Gastrointestinal Tract. Controlled release of active ingredients in specified regions of the the Gastrointestinal Tract is required for the following reasons:

- Local side effects provoked by concentration peaks of the active ingredients.
- Instability of the active ingredients under the influence of digestive fluids.
- Local treatment of diseases of the digestive fluids.

The digestive tract itself consists of a number of regions, each characterized by varying conditions of pH, absorption area and secretion. The major regions of the digestive tract can be listed as follows: Mouth, Esophagus, Stomach, Small Intestine, which is divided

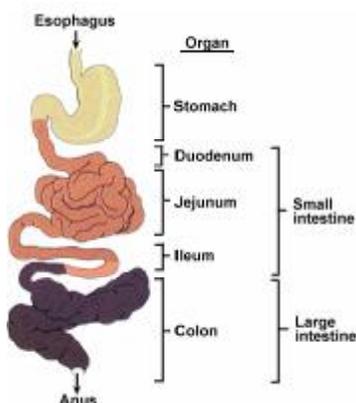


Figure 1 : The gastrointestinal tract

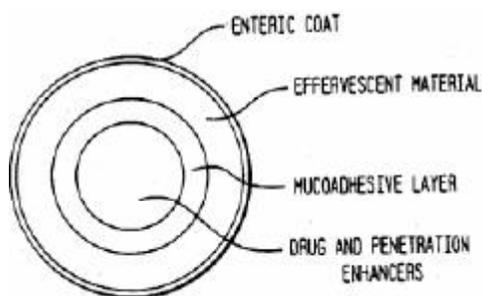


Figure 2 : A composition utilizing effervescence as means of drug delivery for drugs of low bioavailability

into 3 parts namely the Duodenum, Jejunum and Ileum, the colon and the rectum.

Out of these most research has been carried out on coatings of tablets for the stomach i.e. the enteric coatings and the colon. For targeting the mouth region, practically all enteric coatings can be used. The next region is the stomach region. There is a myriad of factors which affect the pH value of the stomach environment from 1.0 to 5.0, and thus the effectiveness of a coating formulation must be independent of the pH conditions from 1.0 to 5.0. A pharmaceutical composition for oral administration containing a pharmaceutically active ingredient coated with an amount of a polymer combination of an enteric polymer and an ammonio methacrylate copolymer to effectively mask the taste of the active ingredient has been patented by Chuanbin et al.^[22]. The polymer weight ratio of the enteric polymer to the ammonio methacrylate copolymer is about 60:40. The pharmaceutical coating composition is soluble in the acidic pH of the stomach, which is generally about 1.0 to 3.0, but relatively insoluble at the non-acidic pH of the mouth, which is typically about 5.0. The coatings

provide for rapid release and absorption of the drug, which is generally desirable in the case of liquid dosage forms. The Eudragits RL 100, RL PO, RL 12.5, RL 30 can be used for this purpose. These compositions can be developed by any standard technique involving aqueous or organic solvents.

A pharmaceutical composition comprising orally administrable dosage forms that use effervescence as a penetration enhancer for drugs known, or suspected, of having poor bioavailability has been patented by Indiran et al.^[23] Effervescence can occur in the stomach, once the tablet or other dosage form is ingested. In addition to effervescence in the stomach, or as alternative technique, by the use of appropriate coatings and other techniques, the effervescence can occur in other parts of the gastrointestinal tract, including, the esophagus, duodenum, intestinal and colon. The site of effervescence and drug release is chosen to correspond with the segment of the gastrointestinal tract displaying mainly maximal absorption of the formulated drug. The effervescent penetration enhancers evolve gas by means of a chemical reaction which takes place upon exposure to water and other fluids. Such water-activated materials must be kept in a generally anhydrous state and with little or no absorbed moisture or in a stable hydrated form, since exposure to water will prematurely disintegrate the tablet. The composition may also include in amounts additional to that required for effervescence a pH adjusting substance. For drugs that are weakly acidic or weakly basic, the pH of the aqueous environment can influence the relative concentrations of the ionized and the unionized forms of the drug present in solution. This composition mainly uses enteric coating polymers which were discussed earlier.

For delayed drug release in the colon, coatings with a dissolution pH around 7 can be used. Since the transfer of drugs in the large intestine is slow and continuous, it is also possible to achieve time-delayed drug release effectively with coatings dissolving around pH 7.

Khan et al. (New 9) used Eudragit L100-55 and Eudragit S100, by spraying from aqueous systems in various combinations to coat Lactose-based placebo tablets which were later tested in vitro for their suitability for pH dependent colon targeted oral drug delivery. The same coating formulations were then applied on tablets containing mesalazine as a model drug and evalu-

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ated for *in vitro* dissolution rates under various conditions. The polymer combination used to coat the tablets, pH of the disintegration media, and the coating level of the tablets were reported to influence the disintegration rate of the tablets. It has been reported that the release profiles of the drug can be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high gastrointestinal (GI) pH variability among individuals. The potential of a combination of Eudragit L100-55 and Eudragit S100 successfully used from aqueous system to coat tablets for colon targeted delivery of drugs has been demonstrated and the formulation has been shown to be able to be adjusted to deliver drug at any other desirable site of the intestinal region of the GI tract on the basis of pH-variability.

A combination of pH-dependent (Eudragit S100 and Eudragit L100) and time-dependent (Eudragit RS) polymers as a single coating for design of colon delivery system of indomethacin pellets has been studied by Akhgari et al. (New 10) The drug release in colon has been demonstrated to be controlled by addition of Eudragit RS to the pH-dependent polymers. The lag time prior to drug release was shown to be highly affected by coating level. With combination of two factors, i.e. the percent of Eudragit RS and coating level, the optimum formulation was found to be the one containing 20% Eudragit RS, 64% Eudragit S and 16% Eudragit L, and a coating level of 10%. Time- and pH-dependent colon-specific drug delivery systems (CDDS) in form of tablet coatings of ethylcellulose for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA), respectively have been studied by Cheng G. et al. (New 11) The *in vitro* release behavior of the DS coated tablets and 5-ASA coated pellets were examined, and then *in vivo* absorption kinetics of DS coated tablets in dogs were further studied. The pH of the dissolution medium did not influence the release profile of time-dependent DS coated tablets, but the lag time of DS release was primarily shown to be controlled by the thickness of the coating layer. In view of the pH-dependent 5-ASA coated pellets, 5-ASA release was significantly demonstrated to be governed

by pH. Moreover, the 5-ASA release features from the coated pellets have been shown to depend upon both the combination ratio of the Eudragit L100 and S100 pH-sensitive copolymers in the coating formulation and the thickness of the coating layer. The two types of CDDS, prepared by means of the regular coating technique, have been shown to be capable of achieving site-specific drug delivery targeting at colon following oral administration, and providing a promising strategy to control drug release targeting the desired lower gastrointestinal region.

Colon-specific compression coated systems of 5-fluorouracil (5-FU) for the treatment of colorectal cancer using xanthan gum, boswellia gum and hydroxypropyl methylcellulose (HPMC) as the coating materials have been reported by Sinha et al. (New 17) Different coat weights (230, 250, 275 and 300 mg) and different ratios (1:2, 2:1, 1:3, 1:7 and 3:4) of boswellia gum and xanthan gum and different ratios (1:1, 1:2, 2:1, and 2:3) of boswellia gum and HPMC were evaluated *in vitro* and out of these ratios, ratio 1:3 demonstrated the best release profile with the lowest coating weights of 230 mg (7.47 +/- 1.56% in initial 5h). Further increase in the coat weights to 250, 275 and 300 mg showed a release profile of 5.63 +/- 0.53%, 5.09 +/- 1.56% and 4.57 +/- 0.88%, respectively, in the initial 5 h and 96.90 +/- 0.66%, 85.05 +/- 1.01% and 80.22 +/- 0.35%, respectively, in 24h. Of the combination boswellia gum and HPMC, the ratio 2:3 was reported to give the best results among the initial trial batches (7.80 +/- 0.57% in 5 h) and a drug release of 6.5 +/- 0.27%, 3.70 +/- 2.3% and 2.99 +/- 0.72%, respectively, in the initial 5 h and 96.90 +/- 0.66%, 85.05 +/- 1.01% and 80.22 +/- 0.35%, respectively, in 24h, when the coat weights were increased to 250, 275 and 300 mg thus laying a basis for use of compression coating of 5-FU as a tool for delaying the release of the drug.

The *in vitro* the release of 5-aminosalicylic acid (5-ASA) or diclofenac sodium (DS) from matrices based on chitosan (Ch) or Ch hydrochloride (Ch-HCl), planned to be introduced into enteric-coated capsules for controlled release to the colon has been studied by Zambito et al. (New 12) The Ch-HCl-based matrices, were observed to swell in the dissolution medium without disintegrating. Drug release were shown to be diffusion-controlled and follow square-root-time kinetics.

The internal pH of the swollen Ch-HCl-based matrix was acidic, so 5-ASA solubility and release were influenced by penetration of salts from the external buffer. In the Ch-HCl-based matrix DS was converted into the scarcely soluble diclofenac free acid, which prolonged the time for release of 50 % dose excessively. The enzymatic action of rat cecal microflora was reported to accelerate drug release from the Ch-HCl-based matrix.

A colon-targeted drug delivery system for 5-fluorouracil using pectin combined with microcrystalline ethylcellulose as a film coat has been developed by Wei et al.(New 13) The coated pellets with pectin or ethylcellulose alone with Theoretical Weight Gained (TWG, as measure of film thickness) as 20% were shown to be incapable to control the drug release in the first 5 h of the dissolution study in the simulated gastric and small intestinal conditions. When the ratio of pectin to ethylcellulose was 1:1(w/w) and film coat TWG-20%, the release was shown to be rapid and was accompanied by splitting of the coat. When the ratio of pectin to Surelease was 1:2(w/w) and film coat TWG-13% and TWG-20%, the formulations were reported to release 9.8+/-0.7% and 4.1+/-0.4%, respectively, of 5-fluorouracil in the first 5h of the dissolution study in the simulated gastric and small intestinal conditions. When the dissolution study was continued in simulated colonic fluids for another 19h, the film coat with the formulations of TWG-13% and TWG-20% were reported to release 96+/-1.3% and 85.0+/-0.3%, respectively, of 5-fluorouracil in simulated colonic fluids at the end of 24 h of the dissolution study, whereas in the control study the formulations had released 51.4+/-1.0% and 34+/-0.5%, respectively, of 5-fluorouracil in absence of rat caecal contents at the end of 24h. The results of the study have shown that the formulation of TWG-20% (pectin to ethylcellulose 1:2, w/w) is most likely to provide targeting of 5-fluorouracil for local action in the colon, as it released only 4.1+/- 0.4% of the drug in the simulated gastric and small intestinal conditions, and it released 85.0+/- 0.3% of 5-fluorouracil in simulated colonic fluids at the end of 24h.

Khaya and albizia gums have been evaluated as compression coatings for target drug delivery to the colon using indometacin(a water insoluble drug) and paracetamol (a water soluble drug) as model drugs by

Odeku et al.(New 14) The core tablets were compression-coated with 300 and 400mg of 100% khaya gum, 100% albizia gum and a mixture of khaya and albizia gum(1:1). Khaya and albizia gums were capable of protecting the core tablet in the physiological environment of the stomach and small intestine, with albizia gum showing greater ability than khaya gum. The fact that the release from tablets coated with the mixture of khaya and albizia gums was midway between the two individual gums, indicated that there is no interaction between the two gums. The gums were shown to be susceptible to degradation by the colonic bacterial enzymes, leading to release of the drug, indicating their potential.

Colon-targeted drug delivery systems for ornidazole using guar gum as a carrier have been developed by Krishnaiah et al.(New 15). Compression-coated tablets of ornidazole containing various proportions of guar gum in the coat and evaluated for hardness and drug content uniformity and were subjected to in vitro drug release studies. Compression-coated tablets with 85%, 75%, and 65% of guar gum coat released about 21%, 38%, and 73% of ornidazole, respectively, in simulated colonic fluids indicating the susceptibility of the guar gum formulations to the rat caecal contents. The compression-coated ornidazole tablets with either 65% or 75% of guar gum coat have been shown to be most likely to provide targeting of ornidazole for local action in the colon owing to its minimal release of the drug in the first 5hr. The same group (New 16) has reported novel tablet formulations for site-specific delivery of 5-fluorouracil to the colon without the drug being released in the stomach or small intestine using guar gum as a carrier. Compression coated fast-disintegrating 5-fluorouracil core tablets compression coated with 60% (FHV-60), 70% (FHV-70) and 80% (FHV-80) of guar gum, and were subjected to in vitro drug release studies. Guar gum compression-coated tablets released only 2.5-4% of the drug in simulated GI fluids. In simulated colonic fluids the compression-coated FHV-60, FHV-70 and FHV-80 tablets released another 70, 55 and 41% of the 5-fluorouracil respectively. The results of the study show that compression-coated tablets containing 80% (FHV-80) of guar gum have been demonstrated to be most likely to provide targeting of 5-fluorouracil for local action in the colon, since they released only 2.38% of the drug in the physiological environment of the stom-

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ach and small intestine.

Amylose combined with the water-insoluble polymer ethylcellulose, in different proportions to produce film coatings of various thicknesses for application to mesalazine (mesalamine or 5-aminosalicylic acid)-containing tablets has been demonstrated as a promising vehicle for drug delivery to the colon by Wilson et al.^[24] The rate and extent of drug release has been demonstrated to be related to the ratio of amylose to ethylcellulose in the film and the thickness of the coating. Increasing the proportion of ethylcellulose in the film and/or the thickness of the coating depressed the rate of drug release in the conditions of the upper gastrointestinal tract.

Liquid suspensions of reverse enteric polymer coated dosage forms that mask the unpleasant taste of the active agent have been reported by Danny et al.^[25] The liquid suspensions can be swallowed without producing a bitter taste in the mouth, but the coated agent is immediately bioavailable upon exposure to the pH levels found in the stomach. The coating consists of a blend of dimethylaminoethyl methacrylate and neutral methacrylic acid ester (MM/MAE) copolymer and a cellulose ester, in an aqueous vehicle, wherein the polymer weight ratio of the cellulose ester to the MM/MAE is about 60: 40. The liquid composition utilizes a "reverse enteric coating" which is soluble in the acid pH's of the stomach, generally about 1.0 to 4.0, but relatively insoluble at the non-acidic pH's of the mouth. Reverse enteric coatings are those which are not water soluble at non-acidic pH's as are present in the mouth, but are soluble in the acid pH levels of the stomach. The cellulose acetate component, the solubility of which is pH independent, and the MM/MAE component, the solubility of which is pH dependent, are mixed in a ratio which provides the desired diffusion characteristics. The polymer coating material is dissolved in an organic solvent to make a solution for use in the fluidized bed coating process. Siew et al.^[26] have reported the investigation of amylose-ethylcellulose film coatings obtained from organic-based solvents as potential vehicles for colonic drug delivery. Under upper gastrointestinal tract conditions, the rate and extent of drug release have been reported to be related to the thickness of the coating and the ratio of amylose to ethylcellulose within the film. Coatings with a thick film and/or low amylose content

were demonstrated to be relatively impermeable and able to delay drug release under conditions mimicking the upper gastrointestinal tract. Under simulated colonic conditions, drug release was more pronounced from coating formulations containing higher proportions of amylose. Colon-specificity can therefore be achieved using such systems by judicious choice of the appropriate ratio of amylose to ethylcellulose and coat thickness. The same team has reported a study carried out with a purpose to establish the physico-mechanical and digestibility properties of water-miscible organic solvent-based amylose-ethylcellulose films as potential coatings for colonic drug delivery^[27]. Resultant mixed films were characterised in terms of tensile strength and elasticity, polymer miscibility, permeability, and digestibility under simulated colonic conditions. Films containing higher concentrations of amylose displayed increasing weakness and softness and faster permeation to hydrogen ions compared to films with lower amylose content. The films were found to be susceptible to digestion by bacterial enzymes within a simulated colonic environment. The extent of digestion has been demonstrated to be directly proportional to the amount of amylose present within the film. Overall, the results suggest that such amylose-ethylcellulose films could be used as coatings for drug delivery to the colon.

Process development and modelling

Process Optimization and scale up are extremely important aspects of sound development of any technology. Thus, a thermodynamic film-coating model for aqueous and/or organic-based systems which predicts exhaust stream conditions, has been elucidated by am Ende MT et al. (New 4) The first law of thermodynamics and conservation of mass principles have been effectively used to complete a material-energy balance on the coating unit operation for a closed, non-isolated system. Heat loss from the coating pan is incorporated into the model through a parameter called a heat loss factor (HLF) that is directly related to the heat transfer coefficient and pan surface area. The outlet air temperature and humidity have been demonstrated to be most notably affected by the coating composition and the inlet drying air temperature, which controls the evaporative cooling rate. With an ability to predict T_{air} successfully within 3°C for a given coating pan, and

within 6°C scaling up from 1 to 220kg pans for both organic and aqueous based coatings, this model has been also proved useful for probing process and formulation variable sensitivity critical to establishing process robustness. The development of another mathematical model to predict air and product temperatures, product moisture, and air humidity during an aqueous coating process using a Bohle Lab-Coater has been elucidated in detail by Page et al. (New 5). 4 balance equations could be set up describing the change of the air humidity, the product moisture, the enthalpy of the air, and the enthalpy of the product in each zone for the drying and spraying zones involving the knowledge regarding heat and mass transfer and also the motion of the tablets. Based on the considerations of the heat and mass transfer, a set of first-order coupled ordinary differential equations (ODEs) was developed which could be solved numerically. In the subsequent report of the same study, (New 6) this model was demonstrated to predict the air and product temperatures, the product moisture, and air humidity during a coating process in the Bohle Lab-Coater using round, biconvex tablets. An instrumented and automated pan-coating system, including historical data storage capability and a novel air-flow measurement system, which is a useful tool for controlling and characterizing the tablet film-coating process has been developed by Ruotsalainen et al. The instrumentation system was shown to provide comprehensive and quantitative information on the process parameters monitored. The measured process parameters and the responses of the film-coated tablet batches showed that the coating process is reproducible. The inlet air-flow rate was shown to influence the coating process and the subsequent quality of the coated tablets. Increasing the inlet flow rate accelerated the drying of the tablet surface. At high inlet flow rate, obvious film-coating defects (ie, unacceptable surface roughness of the coated tablets) were observed and the loss of coating material increased. Monitoring of critical process parameters has been shown to increase the overall coating process efficiency and predictability.

CONCLUSION

The area of surface coatings on pharmaceutical dosage forms displays enormous potential for advanced

drug delivery to the gastrointestinal region as well as other complex and unaccessible regions of the human body. With the advent of more biodegradable and biocompatible polymers for this purpose and advances technology such as pseudo latex coatings, the field is a promising technology for surface coating technologists as well pharmaceutical technologists. The complex and equipments required for operations involved for the coating activity also offer tremendous scope for further development.

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