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Impact of Formulation Variables on the Physical Performance of Oral Matrix Tablets

By

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Dedication

To my parents, my wife and my children E. Ahmed and A. Elrahman.
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Abstract

Introduction
It has been estimated that solid-dosage forms constitute about 80% of all pharmaceutical dosage forms, used to provide systemic administration of therapeutic agents. The matrix tablet is the most effective type of tablet in controlling drug release from tablet and so into systemic circulation, using polymers to perform this action.

Objectives
The aim of this study is to investigate that both, drug and polymer solubility properties and the difference in polymer source play a role in drug dissolution and diffusion from matrix tablets.

Methods
In this study, the 2³ full factorial was selected as an experimental design and utilized to examine the effects of three variables (set at two levels) on the physical performance of matrix tablets. These variables were the source of medium viscosity grade (4000 cps) of hydroxypropyl methylcellulose (Germany and China), source of polyvinyl pyrrolidone (K-30) (China and Germany) and drug solubility (free soluble and sparingly soluble drugs). Matrix tablets within experimental design runs were prepared by direct compression with equal ratios of drug and polymer, using laboratory tableting machine. Produced matrices were subjected to hardness, friability, swelling, erosion and drug release tests.

Results
The results have indicated that for insoluble drug, hydrophilic polymer has a profound effect on increasing the swelling profile of matrix systems compared to hydrophobic one. Moreover, variation in polymers source was shown to have a significant effect on tablet hardness and drug release behavior of both soluble and insoluble drugs. Furthermore, the hydrophilic polymer was found to be more efficient, compared to hydrophobic polymer, in controlling drug dissolution rate and so the drug release kinetics of tablet.
ملخص الدراسية

المقدمة

تشير الدراسات إلى أن المستحضرات الصيدلانية الصلبة تشكل حوالي 80% من كل أشكال المستحضرات الصيدلانية المستخدمة لإحداث التأثيرات بالمواد المعالجة. أنواع الأقراص المتراكس هي أكثر انتشار والاستخدام في التحكم في خروج المادة المعالجة من القرص، وبالتالي لداخل الجسم، وذلك باستخدام البوليميرات لإحداث هذا التغيير.

الأهداف

الهدف من هذه الدراسة هو تحقيق أن كلا من: الخصائص الذوبانية للبوليمر والمادة المعالجة، و الاختلاف في مصدر البوليمر، يلعب دورا في عملية الذوبانية للأقراص، و خروج المادة المعالجة من ها.

الطريقة

في هذه الدراسة، تم استخدام التصميم الأحصائي التجربي لاختبار تأثيرات متغيرات على الدواء الفيزيائي للأقراص وفق مستويين لكل متغير. هذه المتغيرات هي: مصدر الهيدروكسي بروبايل ميثيل سيليلوز متوسط الوزن الجزيئي 4000 متوسط الوزن الجزيئي 4000 (المانيا و الصين)، مصدر البولي فينيل بيروليدون 30-K (المانيا) و ذوبان المادة المعالجة (سريعة و ضعيفة الذوبان في الماء).

تم تصنيف الأقراص وفق التصميم الاحصائي لبعض الشكل الشائع الخصائص المثابرة لمستوى الذوبان و البوليمر، حيث تم اختيار الأقراص المنتجة لاختبارات: الصلايب، التقنيت، امتصاص الماء، التأكل، وانتشار المادة المعالجة من الأقراص.

النتائج

تشير نتائج هذا البحث إلى أنه بالنسبة ل المادة المعالجة ضعيفة الذوبان في الماء، فإن البوليمر عالي الامتصاص له تأثير فعال على زيادة امتصاص القرص للماء، مقارنة بالبوليمر ضعيف الامتصاص. كلاً فإن الاختلاف في مصدر البوليمر أظهر تأثيراً فعالاً على صلابة القرص وطريقة انتشار المواد من كل من المادة المعالجة سريعة و ضعيفة الذوبان في الماء. إضافة إلى ذلك، فإن البوليمرات عالية الامتصاص للماء أظهرت كفاءة أكثر في عملية التحكم في ذوبانية وانتشار المادة المعالجة من الأقراص مقارنة ببوليمرات قليلة الامتصاص للماء.
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1. Introduction and Literature Review

It has been estimated that solid-dosage forms constitute about 80% of all dosage forms used to provide systemic administration of therapeutic agents. This highlights the importance of these dosage forms in the treatment and management of disease states. The widespread use of tablets has been achieved as a result of their convenience and also the diversity of tablet types.

1.1. Types of Tablets

Based on the required target of action, stability of the loaded drug, patient acceptability, compliance and others, a variety of tablet types does exist and many methods can be used to categorize tablets.

1.1.1. Conventional Tablets

These tablets are designed to provide rapid disintegration and hence rapid drug release, and represent a significant proportion of tablets that are clinically used. The manufacture of these tablets involves the compression of granules or powders (both containing drug) into the required geometry. Following ingestion, the tablets will disintegrate within the gastrointestinal tract (stomach), allowing the drug to dissolve in the gastric fluid and, ultimately, be absorbed systemically. (1)

1.1.2. Multiple Compressed Tablets

These are tablets that are composed of more than one layer. Typically there are two designs of multiple compressed tablets, multiple-layered and compression coated. In the former design the first layer is formed by a relatively light compression of
the drug containing powder mix/granules. The next layer is then formed by compression of the powder/granule mix (containing drug) on top of the lightly compressed first layer. Additional layers are formed in a similar fashion. In the second approach the initial layer is prepared by light compression (as described above), removed and located in a second tablet press. The granules/powders of the second coat are fed into the press and allowed to form a constant mass around the surface (and edges) of the pressed tablet prior to compression to form the finished product. It is, of course, possible to prepare tablets containing more than two layers although, in so doing, the complexity of the manufacturing process is dramatically increased. (1)

1.1.3. Enteric Coated Tablets

These are tablets that are coated with a polymer that does not dissolve under acidic conditions (i.e. the stomach) but does dissolve under the more alkaline conditions of the small intestine (i.e. pH > 4). Enteric polymers are primarily employed as coatings of conventional tablet dosage forms and, by inhibiting the dissolution of the therapeutic agent within the stomach, offer protection against possible drug degradation (e.g. erythromycin) or irritation of the gastric mucosa (e.g. non-steroidal anti-inflammatory drugs). Following dissolution of the coating, the tablet will disintegrate and the drug will dissolve in the intestinal fluids (thereby facilitating absorption). This type of tablet is one of the delayed release dosage form. (1, 2)

Among polymers that are used for enteric coatings are cellulose acetate phthalate, cellulose acetate butyrate, Hydroxypropylmethyl cellulose succinate and Methacrylic acid co-polymers (Eudragit®). (3)
1.1.4. Sugar Coated Tablets
These are conventional tablets that have been coated with a concentrated sugar solution to improve the appearance of the formulation and/or to mask the bitter taste of the therapeutic agent. The use of sugar coatings has dramatically decreased due to the advent of film-coated tablets (as a result of the improved mechanical properties of the latter coating). (1)
The coating may cover a bitter substance, conceal an unpleasant or mottled appearance, or provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice. While sugar coating a tablet may increase its weight by 50 to 100% of the core weight, the compression-coated tablet requires a coating that is about twice the weight of the core. If the cores are composed mainly of materials of low bulk density, such as fats and waxes, the amount of coating (by weight) must be even greater to assure a uniform volume of material surrounding the core. (4)

1.1.5. Film Coated Tablets
These are conventional tablets that have been coated with a polymer or a mixture of polymers (and, when required, a plasticizer to render the coating flexible). Film coatings show improved mechanical properties when compared to sugar coatings and, furthermore, film coatings may be deposited over embossed markings on the tablet surface. Film coatings are generally less elegant than sugar coatings. (1)
Examples of polymers that are used to film-coat tablets (and which dissolve in the stomach to enable tablet disintegration and drug dissolution) include; hydroxypropylmethylcellulose and Eudragit E100 (a co-polymer of butylmethacrylate, 2 dimethyl aminoethylmethacrylate and methylmethacrylate, 1:2:1). (1)
In addition to improving the appearance of conventional tablets, film coatings are employed to control the rate and duration of drug release or to target drug release to certain regions of the gastrointestinal tract, e.g. the colon. If the film coating is insoluble, the tablet will retain its shape during transit along the gastrointestinal tract. Drug release occurs by diffusion through the insoluble coating and subsequent partitioning into the gastrointestinal fluids. Examples for such class of polymers include ethylcellulose and methacrylate co-polymers (Eudragit® S & L). The use of film coatings to target drug release within the gastrointestinal tract requires the use of polymers that dissolve within certain pH ranges. For example, enteric coatings offer drug targeting to regions of the gastrointestinal tract in which the pH is greater than 5.5 (e.g. Eudragit L-100). Targeting drug release to the colon involves the use of polymer coatings that dissolve at higher pH values (> 7), e.g. Eudragit S-100. (1, 5)

1.1.6. Chewable Tablets
As indicated by the name, these tablets are chewed within the buccal cavity prior to swallowing. The main target applications for this dosage form are administration to children and adults who have difficulty in swallowing conventional tablets and antacid formulations in which the size of the tablet is normally large and the neutralization efficacy of the tablet is related to particle size within the stomach. Conversely, chewable tablets are not conventionally used if the drug has issues regarding taste acceptability. (1)

1.1.7. Effervescent Tablets
Effervescent tablets are added to aqueous solutions where they will rapidly disintegrate and produce either a drug suspension or an aqueous solution. The
disintegration of the tablet is due to chemical interaction that occurs between two components, namely, an organic acid (e.g. citric acid) and sodium bicarbonate in the presence of water. The evolution of carbon dioxide from this reaction results in tablet disintegration. The patient then consumes the solution/suspension. The main advantage of the use of effervescent tablets is the production of a dosage form from which the therapeutic agent is more rapidly absorbed than from alternative solid-dosage forms (e.g. conventional tablets). (1)

Conversely, the main disadvantages of this type of dosage form are the possible unavailability of water and the need to package these tablets in moisture-impermeable packaging (typically aluminium foil), to inhibit the interaction between the acid and sodium bicarbonate due to the presence of environmental moisture. (1)

1.1.8. Buccal and Sublingual Tablets

Buccal and sublingual tablets are dosage forms that are held within the oral cavity and slowly dissolve; the drug is absorbed across the buccal mucosa to produce a systemic effect. The type of tablet dictates the location within the oral cavity. Accordingly buccal tablets are positioned between the cheek and the gingiva whereas sublingual tablets are positioned underneath the tongue. These tablets are employed to achieve either rapid absorption into the systemic circulation (e.g. glyceryl trinitrate sublingual tablets) or, alternatively, to enable systemic drug absorption in situations where oral drug delivery is inappropriate, e.g. nausea. Drug absorption across the buccal mucosa avoids first-pass metabolism. Typically buccal and sublingual tablets should be formulated to dissolve slowly in vivo (and not disintegrate) and to be retained at the site of application and should not contain components that stimulate the production of saliva. (1)
1.1.9. Vaginal Tablets

These are ovoid-shaped tablets that are inserted into the vagina (using a special inserter). Following insertion, retention and slow dissolution of the tablet occur, releasing the therapeutic agent to provide the local pharmacological effect (e.g. for the treatment of bacterial or fungal infection). Vaginal tablets may also be used to provide systemic absorption of therapeutic agents. In a similar fashion to buccal/sublingual tablets, it is important that dissolution, and not disintegration, of the tablet occurs in vivo, as disintegration will reduce tablet retention within the vagina. (1)

1.2. Manufacture of Tablets

In general, there are four main methods for tablet manufacturing. These are wet granulation, dry granulation, direct compression (6) and roller compaction (chilsonisation) (1). The choice of manufacturing process employed is dependent on several factors, including the compression properties of the therapeutic agent, the particle size of the therapeutic agent and excipients and the chemical stability of the therapeutic agent during the manufacturing process.(1)

There are four steps which start with mixing of the therapeutic agents with the excipients followed by granulation of the mixed powders (this step is excluded in case of direct compression). The third step is mixing of the powders or granules with other excipients (most notably lubricants) and finally compression into tablets. However, the details of each of these steps will vary depending on the manufacturing method used. (1)
1.3. Pharmaceutical Polymers

Polymers are substances of high molecular weight made up of repeating monomer units. When all the monomer units are identical, the polymers are referred to as homopolymers. Examples include polystyrene, polyethylene, poly (vinyl alcohol) and polyvinylpyrrolidone. There may also be homopolymers with much smaller chains (oligomers). The different monomers can be arranged in a linear chain in either a random manner or in an alternating pattern along the chain. (7)

Polymer chains can be linear (forming random coils in solution) or branched. There may be cross-linking between chains to form three-dimensional networks. Highly branched polymers (dendrimers) built around a central core can be synthesised with a range of sizes depending on the generation of the dendrimer. Moreover, polymers do not form perfect crystals but have crystalline regions surrounded by amorphous regions. (7)

1.3.1. Types of Pharmaceutical Polymers

Owing to their aqueous solubility, polymers can be categorized into two classes, water soluble (hydrophilic) and water insoluble (hydrophobic) polymers. Hydrophilic polymers are widely utilized in pharmacy as suspending agents, emulsifiers, binding agents in tablets, thickeners of liquid dosage forms and in film coating of tablets. On the other hand, hydrophobic polymers are mainly used in packaging material and tubing, and in the fabrication of membranes and films. Important properties of hydrophobic polymers which affect their suitability for use in pharmacy are their permeability to drugs and gases and their tendency to adsorb drugs. (7)
1.3.2. Properties of Pharmaceutical Polymers
Pharmaceutical polymers are characterized by different properties that organize their selection and suitability for application in pharmaceutical technology. (7) The wide range of physicochemical properties offered by these materials may be utilized to improve both the clinical and nonclinical, (e.g., manufacturing, stability), properties of dosage forms. (3)

1.3.2.1. Bioadhesion
Bioadhesion arises from interactions between the polymer chains and the macromolecules on the mucosal surface based on the acquired charges on the surface of the molecules. This property is critical when selecting polymer for bioadhesive tablets that need optimum mucosal adhesion for most favorable physical performance of the dosage form. (8)

1.3.2.2. Crystallization and Amorphism
Defects in the crystals allow preparation of microcrystals, e.g. microcrystalline cellulose (Avicel) by disruption of larger crystals. (7) Polymers display different thermal, physical, and mechanical properties depending on their structure, molecular weight, linearity, intra- and intermolecular interactions. If the structure is linear, polymer chains can pack together in regular arrays. For example, polypropylene chains fit together in a way that intermolecular attractions stabilize the chains into a regular lattice or crystalline state. With increased temperature, the crystal cells start to melt and the whole polymer mass suddenly melts at a certain temperature. Above the melting temperature, polymer molecules are in continuous motion and the molecules can slip past one another. In many cases, the structure of a polymer is so irregular that crystal formation is thermodynamically infeasible. Such polymers form glass instead of crystal
domains. A glass is a solid material existing in a noncrystalline (i.e., amorphous) state. Amorphous structure is formed due to either rapid cooling of a polymer melt in which crystallization is prevented by quenching or due to the lack of structural regularity in the polymer structure. Rotation around single bonds of the polymer chains becomes very difficult at low temperatures during rapid cooling; therefore, the polymer molecules forcibly adopt a disordered state and form an amorphous structure. Amorphous or glassy polymers do not generally display a sharp melting point; instead, they soften over a wide temperature range. (9)

1.3.2.3. Degree of Chain Substitution

It’s the average number of hydroxyl group (%) substituted. e.g. by ester or ether groups, per monosaccharide unit in a polysaccharide. usually referring to cellulose. The properties of any of the many useful cellulose derivatives depend not only on the particular derivative but also on the degree of substitution which may vary from zero to three. The maximum value obtainable can be limited by steric crowding around the pyranose ring or by accessibility. (10)

Generally, this property is very useful in synthesis of polymers with specific physicochemical or rheological properties to serve in special types of manufacturing.

1.3.2.4. Viscosity

Viscosity is a measure of the resistance of a fluid which is being deformed by either shear stress or tensile stress. It describes a fluid's internal resistance to flow. (Wikipedia.org)

Viscosity of a polymer solution depends on concentration and size (i.e., molecular weight) of the dissolved polymer. By measuring the solution viscosity we should be able to get an idea about molecular weight.
Water-soluble hydrophilic polymer (e.g. HPMC), can affect the dissolution behavior and transport properties of drug molecules by an increase in solution viscosity. There has been considerable interest in the relationship between bulk solution viscosity and the rate of dissolution of a wide range of materials. A number of empirical equations have been proposed to describe the relationship of dissolution rate as a function of the viscosity of the dissolution medium. Generally, this type of polymers (hydrophilic) absorbs water to swell and form a gel. This gel serves as a barrier to drug diffusion. The controlled release behavior or the loaded drug is obtained from high viscosity of gel layer. (11)

So, the viscosity grade of the polymer affects the release of the drug from matrix system and also inhibits the crystallization of the drug by increasing the viscosity of crystallization medium.

1.3.2.5. Gel strength

The primary rate-controlling ingredients of a hydrophilic matrix are polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system. Robust swelling/gelling properties and straightforward manufacturing processes are to a large degree responsible for the versatility and performance of the system. The gel layer has been identified as the rate-controlling mechanisms. (12)

Generally, there are three layers, the dry core surrounded by glassy layer, then gel layer and finally the diffusion layer. However, gel strength within the dosage form can be compromised when polymers of low molecular weight are used. (12)

Recently, a self correcting HPMC-based matrix having strong gels was developed and showed insensitivity to both pH and stirring condition. (13, 14)
1.3.2.6. Swelling and erosion

Polymer swelling is a hydration or water uptake and the Erosion can be described as polymer dissolution or the disentanglement of polymer chains from the gel surface and transfer of the polymer to the bulk solution. Erosion can be used as disintegrant when designing a delivery system for insoluble drugs. Here, erosion is the main mechanism facilitating transfer of the insoluble drug out of the tablet matrix and into the dissolution medium. However, poor release characteristics such as variable burst release and dose dumping may be expected for a highly soluble drug that is formulated in a highly erodible dosage form. (15)

Hydrophilic matrices are widely used to develop oral sustained release formulations. They can be used for controlled release of both water soluble and insoluble drugs. The release of drugs varies with the nature of the matrix and also with the complex interaction of swelling, diffusion and erosion process. (16)

The swelling controlled release systems consist of a drug molecularly dissolved or dispersed at high concentration in a polymer matrix. If the drug has a limited solubility in the swollen polymer matrix, it is probable that an undissolved drug front will be observed within the continuously swelling polymer gel layer. (17)

In addition, Peppas indicated that in swellable matrix tablets, drug dissolution might be responsible for an observed zero-order release mechanism. (18)

On the other side, swelling and erosion behaviors and drug solubility control the release kinetic of matrix system. Depending on drug solubility, three fronts can be observed; swelling front, diffusion front and erosion front. In the last front there is an identifying boundary between matrix and dissolution medium. (19)

Generally, there are three cases for the effect of swelling and erosion rates on drug release kinetics. The 1\textsuperscript{st} one is that the swelling rate is faster than erosion rate, this indicates delayed release kinetics. The 2\textsuperscript{nd} case is that erosion rate is larger than swelling rate, and this indicates immediate release kinetics. The 3\textsuperscript{rd} one is that the
swelling and erosion rates are equal indicating that much of the kinetics depends on drug solubility. It’s a complicated process to indicate the exact relationship between swellings, erosion and release kinetics of the drug, because there are many other factors influencing this relationship. (3)

Depending on the properties of the polymer used, drug release from the tablets may be swelling-controlled, erosion-controlled, multiple mechanism controlled.

1.3.3. Applications of Polymers in Drug Delivery
The following sections deals with how deep polymers contribute to the pharmaceutical and formulation technology.

1.3.3.1. Film Coating
Polymer solutions allowed to evaporate produce polymeric films which can act as protective layers for tablets or granules containing sensitive drug substances or as a rate-controlling barrier to drug release. Film coats have been divided into two types: those that dissolve rapidly and those that behave as dialysis membranes allowing slow diffusion of solute or some delayed diffusion by acting as gel layers.(7) The application is utilized for enteric, colonic and target drug delivery.

1.3.3.2. Matrix Forming
Utilization of polymer as matrixing agent for controlled release non conventional tablets might be the most interesting application and many relevant reports have attributed this utilization to the biocompatibility of these polymers.

1.3.3.2.1. A non-eroding matrix
The mechanism of sustained release is the passage of drug through pores in the matrix if this is made of water-insoluble polymer (hydrophobic matrices), or by
another way, entry of water into the polymer matrix followed by swelling and gelation and then diffusion of drug through the viscous gel when water-soluble matrices (hydrophilic matrices) are used. (7)

1.3.3.2.2. An eroding matrix
Drug is released when the polymer matrix in which a drug is dissolved or dispersed erodes by either bulk erosion or surface erosion. (7)

1.3.4. HPMC (Hypermellose)
Hypermellose is cellulose hydroxypropyl methyl ether [9004-65-3]. It’s an odorless and tasteless, white or creamy white fibrous or granular powder. It has many synonyms as benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose and Tylopur. (20)

The PhEur 2005 describes hypermellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 208C. Hypermellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypermellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis. Molecular weight is approximately 10000-150000 Da. The JP 2001
includes three separate monographs for hypromellose: HPMC 2208, 2906, and 2910, respectively. (20)

The polymer has been extensively used as coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder and viscosity-increasing agent. (20)

Hypromellose has many applications in pharmaceutical formulation or technology as widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, (21) in film-coating, (22) and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an
adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products. (20)

1.3.5. PVP (Povidone)

Povidone is 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]. It occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. It has many synonyms as E1201; Kollidon; Plasdone; poly [1-(2-oxo-1-pyrroldinyl) ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer. (23) The polymer has extensively been used as disintegrant, dissolution aid, suspending agent and tablet binder. (23)

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. (24, 25) Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. (26-28) Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. (23)
1.3.6. Factors affecting drug release from matrix tablets

A matrix system consists of active and inactive ingredients that are homogeneously mixed in the dosage form. It is the most commonly used oral controlled release technology.

There are many factors affecting drug release from matrix systems. The most effective one is the Type and the solubility of the polymer present inside the matrix system to form either hydrophobic or Hydrophilic matrix system. The hydrophobic is the only system where use of a polymer is not essential to provide controlled drug release, although insoluble polymers have been used. To modulate drug release of this system, it may be necessary to incorporate soluble ingredients such as lactose into the formulation. The hydrophilic system contains polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system, which would be responsible for release rate of the drug. (12)

The source is one of the factors that affect the release kinetic by which content %, fineness, degree of substitution and water content vary from one source to another and so influencing the physical properties that affect the controlled release rate and/or kinetic of the loaded drug.

Viscosity grade of polymer is also an effective factor in drug release rate. In which the viscosity grade is controlling the release mechanism and the physiochemical performance of the gel layer (Gel Strength). Also the erosion and swelling % are affected by viscosity grade of the polymer.

The solubility of the loaded drug also interferes with polymers fitted inside the matrix system to either increase or decreases the rate of dissolution and diffusion of the drug to dissolution medium.

1.4. Controlled release oral dosage forms
The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties. The technologies behind oral drug delivery have emerged from the mainstream pharmaceutical industry and have become influential forces in their own right, as evidenced by the burgeoning “drug delivery companies” that are at the forefront of innovation and hold their own niche market. Drug delivery companies and their pharmaceutical industry partners are poised to reap the rewards of the multibillion-dollar drug delivery market, which has grown to about $70 billion by 2005. (29)

Benefit behind utilization of oral controlled release drug delivery systems are numerous and include (but not limited to) less fluctuation in blood drug concentration, reduction in adverse drug side effects, improvement in tolerability (30), enhancement of patient compliance and reduction of healthcare cost (31).

1.4.1. Currently utilized oral controlled release systems

Advances in oral controlled-release technology are attributed to the development of novel biocompatible polymers and machineries that allow preparation of novel design dosage forms in a reproducible manner. The main oral drug-delivery approaches that have survived through the ages are coating technology using various polymers for coating tablets, matrix systems made of swellable or nonswellable polymers, slowly eroding devices and osmotically controlled devices. Conventional tablet formulations are still popular in the design of single-unit, matrix-type controlled release dosage forms. The advancement of granulation technology and the array of polymers available with various physicochemical
properties (such as modified cellulose or starch derivatives) have made the
development of novel oral controlled release systems possible. (29)
Matrix devices made with cellulose or acrylic acid derivatives, which release the
homogeneously dispersed drug based on the penetration of water through the
matrix, have gained steady popularity because of their simplicity in design. The
drawback of matrix-type delivery systems is their first-order drug delivery
mechanism caused by changing surface area and drug diffusional path length with
time. This drawback has been addressed by osmotic delivery systems, which
maintain a zero-order drug release irrespective of the pH and hydrodynamics of the
GI tract. Multiparticulate systems are gaining favor over single-unit dosage forms
because of their desirable distribution characteristics, reproducible transit time, and
reduced chance of gastric irritation owing to the localization of drug delivery. (29)
Although several technologies for the production of microparticulate systems have
been designed, thus far the mainstream technologies are still based on spray-
drying, spheronization, and film-coating technology. (29)

1.5. Design of Experiment (DOE)
Experimentation is carried out to determine the relationship (usually in the form of
a mathematical model) between factors acting on the system and the response or
properties of the system (the system being a process or a product, or both). The
information is then used to achieve, or to further, the aims of the project. So, the
experimental design (DOE) can be defined as the strategy for setting up
experiments in such a manner that the information required is obtained as
efficiently and precisely as possible. (32)
1.5.1. Full factorial designs in two levels
A design in which every setting of every factor appears with every setting of every other factor is a full factorial design. A common experimental design is one with all input factors set at two levels each. These levels are called ‘high’ and ‘low’ or ‘+1’ and ‘-1’, respectively. A design with all possible high/low combinations of all the input factors is called a full factorial design in two levels. If there are k factors, each at 2 levels, a full factorial design has $2^k$ runs.

Full factorial designs not recommended for 5 or more factors. When the number of factors is 5 or greater, a full factorial design requires a large number of runs and is not very efficient, the fractional factorial design or a Plackett-Burman design a better choice for 5 or more factors. (33)

1.6. Chlorpheniramine Maleate
It is one of $H_1$-receptor antagonist that has antihistaminic action. The powder is white or almost white, crystalline form which is freely soluble in water and ethanol. (BP, 2007)

Based on the water solubility behavior and simplified assay method (U. V. spectrophotometric analysis), the drug is selected as a model drug in this project.

1.7. Atenolol
Atenolol is beta-adrenoceptor antagonist acts as hypotensive agent. It’s white or almost white powder, sparingly soluble in water, soluble in ethanol, slightly soluble in methylene chloride. (BP 2007)

Based on the water insolubility behavior and simplified assay method (U. V. spectrophotometric analysis), the drug is selected as a model drug in this project.
1.8. Similarity factor ($f_2$)

FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC (Supplemental Post Approval Changes) related changes, or with different strengths, helps assure similarity in product performance and signals bioinequality. (34)

Among several methods investigated for dissolution profile comparison, $f_2$ is the simplest. Moore and Flanner proposed an independent mathematical model approach to compare the dissolution profile using two factors, $f_1$ and $f_2$. (35)

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} \right\} \times 100$$

$$f_2 = 50 \log \left[ \left( 1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right)^{0.5} \times 100 \right]$$

Where $R_t$ and $T_t$ are the cumulative percentage dissolved at each of the selected $n$ time points of the reference and test product respectively. The factor $f_1$ is proportional to the average difference between the two profiles, whereas factor $f_2$ is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The factor $f_2$ measures the closeness between the two profiles. Because of the nature of measurement, $f_1$ was described as difference factor, and $f_2$ as similarity factor. In
dissolution profile comparisons, especially to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure which is more sensitive to large differences at any particular time point. For this reason, the $f_2$ comparison has been the focus in Agency guidance. When the two profiles are identical, $f_2=100$. An average difference of 10% at all measured time-points results in an $f_2$ value of 50. FDA has set a public standard of $f_2$ value (between 50 and 100) to indicate similarity between two dissolution profiles. \(34, 35\)
Scope of the Work

Generally, the objective of this project is to study the effect of the some formulation variables on the physical performance of oral matrix tablets. This is by applying $2^3$ full factorial design in order to study the impact of three factors on the drug release from matrix system. Specifically, these factors are the supplier source of the polymers, solubility of the polymers and solubility of the loaded drugs. Moreover, the study is designed in away to permit the analysis of the influences these factors might have on the drug release rate and drug release kinetics.
2. Materials and Methods

2.1. Materials
The following materials have been utilized during the experimental part of the research:
HPMC (K4M 4000 cps, pharmaceutical grade) was obtained from two different sources. One is a product of Bulk Medicines & Pharmaceuticals (Germany), and the other is a product of Taian Ruitai Cellulose Co., Ltd “Alcapharm” (China). In both sources, the polymer is used as received.

PVP (K-30, pharmaceutical grade) was obtained also from two different sources. One is the product of Bulk Medicines & Pharmaceuticals (Germany) and has been donated by Amipharma Laboratories Ltd. (Sudan) and the other is a product of Nanfang Industrial Co., Ltd. (China) and was donated by Citypharm Pharmaceutical IND. (Sudan).

Mg stearate is a product of Huzhou Zhanwang Pharmaceutical Co., Ltd. (China) and donated by Shanghai-Sudan Pharmaceutical Co., Ltd. (Sudan).

Model drugs used in this study (Chlorpheniramine Maleate and Atenolol) were pharmaceutical grade products of Supriya Chemicals Pvt. Ltd and Ipca Laboratories Ltd (Mumbai, India), respectively and were received as a gift from Amipharma Laboratories Ltd. (Sudan).

Other materials and reagents were analytical grade obtained from different commercial sources.
2.2. Instruments and Apparatus

The following instruments were used in the experimental part of the research:
Single Punch Tablet Compression Machine (Cadmach®, Ahmedbad-8, India); Analytical Balance (Sartorius®, AG CP 124S, Germany); Tablet Friability Tester (ERWEKA® TA, Germany); Tablet Hardness Tester (ERWEKA® GmbH, Hensenstamm, Germany); Tablet Dissolution Tester (ERWEKA®, Germany); U.V. Spectrophotometer (double beam UV-1800, Shimadzu, Japan).

2.3. Methods

2.3.1. Experimental Design:
Based on the aim and the data of this project, \(2^3\) full factorial was selected as an experimental design, in which 3 factors were examined at two levels (two sources of HPMC 4000 cps, two sources of PVP-30 and two different solubility profiles’ drugs. The design composed of 8 experimental runs and the layout is shown in Table I
### Table I
Experimental runs layout for the $2^3$ design

<table>
<thead>
<tr>
<th>Run</th>
<th>Source of HPMC(^a)</th>
<th>Source of PVP(^a)</th>
<th>Drug solubility(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>[+1]</td>
<td>[+1]</td>
<td>[+1]</td>
</tr>
<tr>
<td>Run 2</td>
<td>[-1]</td>
<td>[+1]</td>
<td>[+1]</td>
</tr>
<tr>
<td>Run 3</td>
<td>[+1]</td>
<td>[-1]</td>
<td>[+1]</td>
</tr>
<tr>
<td>Run 4</td>
<td>[-1]</td>
<td>[-1]</td>
<td>[+1]</td>
</tr>
<tr>
<td>Run 5</td>
<td>[+1]</td>
<td>[+1]</td>
<td>[-1]</td>
</tr>
<tr>
<td>Run 6</td>
<td>[-1]</td>
<td>[+1]</td>
<td>[-1]</td>
</tr>
<tr>
<td>Run 7</td>
<td>[+1]</td>
<td>[-1]</td>
<td>[-1]</td>
</tr>
<tr>
<td>Run 8</td>
<td>[-1]</td>
<td>[-1]</td>
<td>[-1]</td>
</tr>
</tbody>
</table>

\(^a\) -1 and +1 stand for Germany and China, respectively; \(^b\) -1 and +1 stand for water soluble and water insoluble, respectively.

### 2.3.2. Preparation of Tablets

For all runs, the drug: polymer ratio is kept 1:1 similarly to HPMC: PVP ratio, with mg stearate content (as a lubricant) fixed as 1% w/w. For each formulation run, the constituents of 100 tablets were mixed separately using mortar and pestle for 10 minutes, lubricated and compressed into tablets using single punch tableting machine equipped with size 9 mm flat punch. The cleaning of the machine is carried out after preparation of each formulation run using ethanol. Each formulation run is packaged in tightly closed glass bottle, and then labeled with the number of the run. Produced tablets are weighed and have an average of 202mg containing 100mg of loaded drug per unit dosage.
2.3.3. Friability Test
Tablets within all runs were subjected to friability testing (USP, 2010) where 10 tablets from each produced tablets batch were weighed and introduced in the right drum of tablet friability tester and same number in the left drum. The device was turned on at 25 r/min speed for 4 minutes and the dust is removed after test. The tablets were weighed after test and the friability was calculated using the average % loss from the two drums.

2.3.4. Hardness Test
10 tablets from each formulation runs were placed in hardness tester. The device measures hardness in N (Newton) and diameter in mm. The measured values and statistics of these values were calculated and recorded automatically by computer program connected to the device.

2.3.5. Swelling and Erosion Tests
Tablets sample from each formulation run were investigated for swelling and erosion performance in order to correlate the observed drug release phenomena with the rates of polymer hydration, swelling and erosion. Weighed tablets were placed in the beaker of 100 ml distilled water. After 0.25, 0.5, 0.75, 1, 2, 3, 4 and 5 h, each tablet is removed from beaker using spatula, blotted to remove excess water and weighed on an analytical balance. The wet tablet were then dried in an oven at 50 °C for 24 h, allowed to cool and finally weighed until constant weight was achieved (final dry weight). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The
increase in weight due to absorbed liquid \((Q)\) was estimated at each time point from the following equation:

\[
Q = \frac{W_w - W_f}{W_f} \times 100
\]

Where \(W_w\) is the mass of the hydrated sample before drying and \(W_f\) the final weight of the same dried and partially eroded sample. The percentage erosion \((E)\) was estimated from the following equation:

\[
E = \frac{W_i - W_f}{W_i} \times 100
\]

Where \(W_i\) is the initial dry sample weight.

2.3.6. Dissolution Test
The dissolution test was carried out using apparatus 1 (Basket apparatus) (USP 2010) set at 100 r/min and complete sink condition. In order to reproduce the digestive physiological phases, 1000 ml samples of dissolution medium were used at 37 ± 0.5°C. 0.1 N HCl (pH 1.2) was used as dissolution medium and 6 tablets from each batch were subjected to the test. Dissolution samples were withdrawn at predetermined time points, filtered and analyzed spectrophotometrically at 275 and 265nm for Atenolol and Chlorpheniramine Maleate, respectively, considering sample taken at zero time as a blank sample. The mean cumulative percentage of drug was calculated and plotted against time.
2.3.6.1. Drug Release Kinetics:

Data derived from dissolution test were subjected to model fitting and statistical analysis in order to explore the kinetics of the drug release. The model selected was Korsmeyer and Peppas equation where dissolution data <60% drug release were fitted to the model and the fitting process aided by the software PCP Disso V3 (36) in order to determine the diffusional exponent \( n \) that is used to characterize the drug transport mechanism.
3. Result

3.1. Friability Test
Table II shows average friability of tablet formulation runs in the experimental design and the result indicated that all of tablet formulations investigated were within the acceptable pharmacopoeial limit of friability (less than 1%, BP 2010).

<table>
<thead>
<tr>
<th>Formulation Run</th>
<th>Average Friability (%)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>0.12</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Run 2</td>
<td>0.02</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Run 3</td>
<td>0.05</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Run 4</td>
<td>0.17</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Run 5</td>
<td>0.20</td>
<td>Chlorpheniramine Maleate</td>
</tr>
<tr>
<td>Run 6</td>
<td>0.35</td>
<td>Chlorpheniramine Maleate</td>
</tr>
<tr>
<td>Run 7</td>
<td>0.05</td>
<td>Chlorpheniramine Maleate</td>
</tr>
<tr>
<td>Run 8</td>
<td>0.05</td>
<td>Chlorpheniramine Maleate</td>
</tr>
</tbody>
</table>

3.2. Hardness Test
Average hardness of tablet formulations in the factorial design are shown in figure 1 and it is apparent that all formulations investigated have met the pharmacopoeial criteria for uncoated tablet where the accepted hardness range is considered as 39-98 N (BP, 1998)
Formulation Runs (1-4) and (5-6) represent Atenolol and Chlorpheniramine Maleate respectively.

Fig. 1
Average tablet hardness of formulation runs in the experimental design. Each value is the average of 10 determinations with error bars indicating values of standard deviations.

3.3. Swelling and Erosion Tests
For formulation runs 5, 6, 7 and 8 which are specified to load soluble drug (Chlorpheniramine Maleate), the tablets immediately start to form gelatinous substratum foundation after 15 – 20 minutes upon immersion in distilled water. So the test was not continued for these formulation runs.
Figure 2 illustrates the swelling behaviors of tablets within formulation runs 1-4 that loaded with the insoluble drug Atenolol.
Swelling profile of tablet within formulation runs 1-4 loaded with Atenolol.

Fig. 2

Erosion profile of tablet within formulation runs 1-4 loaded with Atenolol.

Fig. 3
3.4. Dissolution Test
Following the procedure described in the methods section, the data obtained as measures from U.V. spectrophotometric device for dissolution samples were arranged in tables and analyzed by PCP Disso V3 (36) computer software program to calculate the diffusional exponent (n) and rate constant (k) that characterize drug release process. The data analyzed are those corresponding to less than 60% release and graphs of release profile were thus generated.

3.4.1. Standard calibration curves of Atenolol and Chlorpheneramine maleate in 0.1 N HCl
Figure 4 shows the plot of atenolol different concentrations (μg/ml) and their respective UV absorbance at 275 nm (BP, 2007). A linear correlation between atenolol concentration and absorbance with high determination coefficient was achieved in the concentration range of 10—500 μg/ml (R² =1).
For chlorpheneramine maleate, Figure 5 shows the plot of chlorpheniramine maleate different concentrations (µg/ml) and their respective UV absorbance at 265 nm (BP 2007). There is a linear correlation between chlorpheniramine maleate concentration ranged 1-100 µg/ml and absorbance with high determination coefficient ($R^2 = 1$).
3.4.2. Release Profile of Atenolol

Atenolol is the insoluble drug module used in the formulation runs 1, 2, 3 and 4. Figure 6 revealed Atenolol release % versus time (hr) for formulation run 1, 2, 3 and 4 respectively. The release % data taken were less than 60 % where data can be effectively utilized to determine values of the diffusional exponent, $n$ and the release constant, $k$. Estimated values for both components of release kinetics and the respective determination coefficient are summarized in Table III.
Fig. 6
Release profile of Atenolol from tablet formulation runs 1-4

Table III
Values of release kinetics components, n and k, for Atenolol and Chlorpheneramine maleate from different tablet formulation runs

<table>
<thead>
<tr>
<th>Formulation Run</th>
<th>N</th>
<th>k</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>0.4920</td>
<td>28.6798</td>
<td>0.9992</td>
</tr>
<tr>
<td>Run 2</td>
<td>0.4956</td>
<td>28.3471</td>
<td>0.9981</td>
</tr>
<tr>
<td>Run 3</td>
<td>0.4979</td>
<td>27.9818</td>
<td>0.9932</td>
</tr>
<tr>
<td>Run 4</td>
<td>0.4997</td>
<td>28.4998</td>
<td>0.9992</td>
</tr>
<tr>
<td>Run 5</td>
<td>0.6965</td>
<td>97.4890</td>
<td>1</td>
</tr>
<tr>
<td>Run 6</td>
<td>0.7030</td>
<td>97.6199</td>
<td>1</td>
</tr>
<tr>
<td>Run 7</td>
<td>0.6498</td>
<td>97.6567</td>
<td>1</td>
</tr>
<tr>
<td>Run 8</td>
<td>0.7388</td>
<td>93.9171</td>
<td>1</td>
</tr>
</tbody>
</table>

(n) Diffusional exponent; (k) Constant; ($R^2$) Determination Coefficient
3.4.3. Release Profile of Chlorpheniramine Maleate

Chlorpheniramine maleate is the soluble drug model used in the formulation runs 5, 6, 7 and 8. Figure 7 shows the release pattern of chlorpheniramine maleate (as release %) versus time (hr) for formulation runs 5, 6, 7 and 8. Once more, the accepted release % data were those less than 60 % and values for release kinetics components are summarized in Table III.

![Graph showing release profile of Chlorpheniramine maleate from tablet formulation runs 5-8](image)

**Fig. 7**

Release profile of Chlorpheniramine maleate from tablet formulation runs 5-8
4. Discussion, Conclusion and Recommendation

4.1. Discussion

4.1.1. The Influence of Swelling and Erosion Percent on Dissolution Behavior of Insoluble Drug (Atenolol)

In order to examine the effects that swelling and erosion rates might have on dissolution behavior of insoluble drug (atenolol), a three directional surface plot was generated. The data utilized were those associated with 1 hour time interval for the three nominated variables as shown in figure 8.

Drug release % = 24.6757 + 0.1619(swelling) - 0.3494(erosion)

Fig. 8
Surface Plot for the effect of Swelling and Erosion on Dissolution Behavior of Insoluble Drug (Atenolol)
The surface plot revealed a proportional relation between drug release and % swelling. Moreover, analysis of coefficients of regression equation associated with the two variables shown in the figure support the dominance of the inhibitory effect of erosion on the drug release compared to the positive one exhibited by the swelling, as evident by the magnitude and sign of coefficients associated with the two variables.

The previous discussion shows that the effect of the hydrophilic polymer (HPMC) on uptake of water and swelling % is stronger than the effect of hydrophobic polymer (PVP). This might explain the increase of percentage drug released owing to increase in swelling % as well as the increase in gelling layer causing the drug diffusion. Consequently, both hydrophilic and hydrophobic polymers control the rate diffusion of the drug from matrix system by swelling and erosion actions. This is in agree with the findings of Li., et al, (2006) where authors were able to show that the dual release processes make hydrophilic matrices more suitable for insoluble molecules than other diffusion-controlled systems.(37).

Furthermore, the addition of PVP K-30 (hydrophobic) to HPMC (Hydrophilic) tablets improved the HPMC matrix structure so as to release the drug in constant amounts in each time interval. This has been mentioned in relevant published work (Saeio, et al., 2007) where authors attributed such release profile to the enhanced swelling-erosion balance of the matrix. (38)

4.1.2. The Influence of Polymers Source on Tablet Hardness of Insoluble Drug (Atenolol)

According to the experimental design (Table I), formulation runs 1, 2, 3 and 4 contain atenolol as insoluble drug model. These formulation runs contain the same
type of polymer with the same ratio; 100 mg of atenolol, 100 mg of polymer divided into 50 mg HPMC and 50 mg PVP, but with different source.

![Graph showing the relationship between polymers source and hardness of insoluble drug (Atenolol)](image)

*Chi: China source, Ger: Germany, X: Y for HPMC: PVP*

**Fig. 9**

**The Relationship between Polymers Source and Hardness of Insoluble Drug (Atenolol)**

Although the four formulations runs (1-4) have the same content and type of the polymers, and compressed under the same loading level, differences in tablets hardness were observed. Under such conditions, variation in hardness could possibly be attributed to the different source of the polymers (Germany and China). Generally, the Germany polymer source results in tablets with lower hardness compared to those prepared with Chinese one.

In fact, this variation could be explained in terms of the differences in percentage humidity, purity percent (content %), particle size and viscosity grade that the same polymer of different source might have.
4.1.3. The Influence of Polymers Source on Dissolution Behavior of Insoluble Drug (Atenolol)

To determine the possible effects of polymers source on dissolution behavior of insoluble drug, a column chart was created using the drug release percent at the same time point (6 hours) for all four formulation runs as shown in figure 10.

![Column Chart](image)

*Chi: China source, Ger: Germany, X: Y for HPMC: PVP*

**Fig. 10**

*The Effect of Polymers Source on Dissolution Behavior of Atenolol*

Evidenced from the figure that the difference in polymer source affect the drug release behavior of atenolol tablet. This effect has been very clear in run number 4 that revealed 67% drug release at 6 hr time interval compared to the other three run which achieved 100% drug release at the same time interval.

At least under the present experimental condition where other variables kept the same, one could conclude that the difference in polymers source might be the reason for the revealed variation in atenolol dissolution rate. Once again such findings could possibly be explained in terms of the variation in content, humidity
and particle size that the same polymer might measure when imported from different sources.

Although, the manufacture process of polymer was done in specific and known condition. But, the difference in tablet physical performance of the same drug can be observed.

4.1.4. The Influence of Polymer Source and Hardness on Dissolution Behavior of Soluble Drug (Chlorpheniramine Maleate)

In order to examine the effects that polymer source and hardness might have on dissolution behavior of soluble drug (chlorpheniramine maleate), a three directional surface plot was generated. The data utilized were those associated with 1 hour time interval for the three nominated variables as shown in figure 11.
Drug release % = 17.3701-7.5214(Polymer Source)+0.9193(hardness)

-1 and +1 stand for Germany and China, respectively.

Fig. 11

The effect of Polymer Source and Hardness on Dissolution Behavior of soluble drug

(Chlorpheniramine Maleate)

The surface plot revealed a proportional relation between German source and drug release %, in which the polymer from Germany has more diffusional properties than Chinese one. Moreover, analysis of coefficients of regression equation associated with the two variables shown in the figure support the dominance of the effect of difference in polymer source compared to the tablet hardness effect on drug release %, as evident by the magnitude and sign of coefficients associated with the two variables.
The previous discussion shows that the effect of the difference in polymer source is stronger than tablet hardness effect. This might explain the increase of percentage drug released owing to bias to German source.

The tablet hardness also has an effect on percentage drug release, which is detected by coefficient associated with y axis.

It has been published that not only the swelling property of the polymer but also its hydrophobicity and the hardness of the tablet played an important role in retardation of drug release. (38)

### 4.1.5. Similarity factor (f₂)

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Reference Run 1 Mean</th>
<th>Test Run 4 Mean</th>
<th>Reference Run 5 Mean</th>
<th>Test Run 8 Mean</th>
<th>Reference Run 1 Mean</th>
<th>Test Run 5 Mean</th>
<th>Reference Run 4 Mean</th>
<th>Test Run 8 Mean</th>
</tr>
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<td>58.02</td>
<td>99.95</td>
<td>57.53</td>
<td>99.99</td>
</tr>
</tbody>
</table>

Mean represents mean of 6 observations (released %) for every time point for each formulation.

Similarity factor determination for different drug release profiles in the experimental design is depicted in Table IV. Similarity factor (f₂) for run 1 and run 4 is 98.2. Both runs contain 100 mg insoluble drug (atenolol) and the same
polymers with the same ratio (1:1). Two formulation runs have different polymers source (Chinese polymers for run 1 and German polymers for run 2), yet, they are comparable with regard to drug release profile ($f_2 = 50$-100). Consequently, the difference in polymers source has no (or a little) effect on dissolution behavior of tablets containing insoluble drug.

For run 5 and run 8, $f_2$ is equal to 35.9 which support the non similarity. Although the condition of both formulations is similar to that of run 1 and 4, yet, drug solubility is different. This might indicate the effect the drug solubility might have on dissolution behavior,

To illustrate the influence of drug solubility on dissolution of the drug from matrix system (3rd factor in the experimental design), the $f_2$ value is calculated for run 1 and run 5 (same polymers, same ratio and same source (China) and also for run 4 and run 8 (same polymers, same ratio and same source (Germany), the calculated $f_2$ values are 20.4 and 14.1 respectively. The findings greatly support the fact that each pair of runs (1, 5) (4, 8) are significantly different with regard to drug release profiles and that the drug solubility is the main reason behind such dissimilarity. This is in agree with relevant published works concerning the influence of drug solubility on the drug release from glyceryl monooleate matrices (39), polyethylene glycol (40) and HPMC based matrices (41).
4.2. Conclusion
Based on the findings of this study, one might conclude that for insoluble drug, hydrophilic polymer has a profound effect on swelling profile of matrix systems compared to hydrophobic one. Moreover, variation in polymers source was shown to have a weighty impact on tablet hardness and drug release behavior of both soluble and insoluble drugs. Furthermore, the hydrophilic polymer was found to be more efficient, compared to hydrophobic polymer, in controlling drug dissolution rate and so the drug release kinetics of the matrix.
In general, the solubility of the drug, solubility of the polymer and the source of the same material all have been shown to influence significantly the dissolution rate of a drug from matrix system.

4.3. Recommendation
Although, hydrophilic polymer has a profound effect on swelling profile of matrix systems compared to hydrophobic one, the researchers should still undergo some improvements for the role of hydrophobic polymers in controlling swelling behavior of matrix tablets. Also, the failure of chlorpheniramine maleate tablets to swell is expected to be due to the variation in drug source. So, I recommend more focusing in this manner. The effect of polymer source variation on physical performance of matrix tablet should be further linked by more researches with the influence on variation of drug (Active constituent) source.
References


