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DEVELOPMENT AND CHARACTERIZATION OF BILAYER ABUSE DETERRENT EXTENDED RELEASE TABLET USING VARIOUS MODEL DRUGS FOR OPIOIDS OVERDOSE CRISIS

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DEVELOPMENT AND CHARACTERIZATION OF BILAYER ABUSE DETERRENT EXTENDED RELEASE TABLET USING VARIOUS MODEL DRUGS FOR OPIOIDS OVERDOSE CRISIS

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ABSTRACT

DEVELOPMENT AND CHARACTERIZATION OF BILAYER ABUSE DETERRENT EXTENDED RELEASE TABLET USING VARIOUS MODEL DRUGS FOR OPIOIDS OVERDOSE CRISIS

Ankit Soni

The objective of present study is to develop bilayer abuse-deterrent extended-release tablets (ADERTs) using various model drugs for opioids overdose crisis. Bilayer ADERTs using various model drugs were fabricated by direct compression; consists of extended-release drug layer and pH modifying layer. To develop extended-release layer, various hydrophilic polymers evaluated for their abuse deterrent potential. Based on significantly higher viscosity at 100RPM and lower syringe-ability data, it was found that HPMC K100M could be used as abuse deterrent polymer. Along HPMC K100M, various diluents were evaluated for their abuse deterrent potential. Tablet formulations prepared with various type of diluents using metformin HCl as model drug. Based on outcomes, MCC KG-1000 was selected as diluent to provide tablets with physical and/or chemical barrier. Bilayer ADERTs were developed to minimize multiple-unit oral abuse using three model drugs based on similar pKa values to that of opioids, i.e., propranolol HCl (pKa 9.45), quinidine sulfate (pKa 8.5), dipyridamole (pKa 6.59). Various alkalizing agents evaluated for their abuse deterrent potential. Bilayer ADERTs using propranolol HCl as model drug were fabricated. Based on outcomes, magnesium hydroxide was selected as alkalizing agent, since it raised pH of dissolving media near to pKa of all model drugs. Additional amount of magnesium hydroxide was incorporated in extended-release layer to

minimize drug release in both FaSSGF and FaSSIF upon multiple-unit ingestion evaluated by in-vitro drug release study. Formulated bilayer ADERTs provided similar drug release profiles as compared to conventional extended-release tablets for single-unit ingestion. However, upon ingestion of multiple-unit bilayer ADERTs, fast-dissolving pH modifying layer increases pH in dissolving media, while extended-release layer increases micro-environmental pH within tablets for all model drugs tested. Retarding drug release owing to low solubility of basic drug at higher pH was observed. To minimize intravenous abuse, drug extraction study in various solvents were evaluated. Drug extraction was found to less than 2% for all the model drugs tested due to effect of alkalizing agent. Therefore, application of alkalizing agent has impact on pH-dependent solubility of drug like opioids and demonstrate its useful potential to be incorporated in bilayer ADERTs for opioids overdose crisis.

DEDICATION

The thesis is dedicated to my parents for their endless love, support and encouragement

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1. INTRODUCTION

There are approximately 100 million Americans suffering from chronic pain that costs up to $635 billion in medical costs (1). Opioid therapy is a necessary component of chronic pain management for many patients (2). Opioids are widely prescribed to treat most severe cases and over the past two decades, the number of prescriptions have also increased considerably (3). Consequently, while remaining as the major therapeutic option for the treatment of chronic pain, prescription opioids are the drugs of choice for abuse to increase the euphoric effect (e.g. feeling intense excitement and happiness). An estimated 25.4 million people have reported non-medical use of opioids in the last two decades and 18,893 drug overdose deaths involving prescription opioid in 2014 (4). Moreover, according to one of the national surveys, it has been reported that teenager group is the major constituent of non-medical use of opioids (5,6).

Opioids are available in various dosage forms including oral solutions, tablets, and capsules as well as parenteral solutions and can be abused via different methods to increase euphoric effect. For instance, oral solutions can be abused by ingesting high dose or by injecting the solution via parenteral route to achieve euphoria. Similarly, parenteral solutions can be injected in higher dose to get euphoric effect. Tablets are abused by different methods such as by crushing tablets to get smaller particles, which can be abused by nasal insufflation. Also, the intact tablets or manipulated tablets (being crushed into smaller particles) can be dissolved in commonly available solvents (e.g., water, vinegar, alcohol, and 70% isopropanol) making it suitable for parenteral administration. Among the different available dosage forms of opioids, oral tablets are

most commonly abused (7). Hence, there is critical need for the development of a suitable dosage form to help minimize abuse via parenteral, nasal and oral routes.

Recently, several dosage forms are being developed to decrease the abuse potential of opioid medications. Dosage forms equipped with these abuse deterrent features are commonly called abuse deterrent formulations. It is believed that these formulations have the potential to decrease abuse without limiting access of opioids to legitimate patients (8). In general, abuse deterrent formulations lower the abuse desirability of a medication by preventing physical (e.g., crushing, chewing of tablets) and chemical (e.g., drug extraction from tablets) tampering, prohibiting drug metabolism or binding, and/or incorporating aversive materials (e.g., bittering agents and mucous membrane irritants) into the product (9). Due to presence of higher dose in extended release formulations as compared to immediate release formulations, extended release formulations are at higher risk of abuse. As a result, it is recommended by the FDA to develop abuse deterrent properties for extended release formulations. The present investigation focuses on developing abuse deterrent extended release opioid tablets using excipients as physical and/or chemical barrier to minimize the potential problem of opioid abuse.

2. LITERATURE REVIEW

2.1. Abuse of opioids

Opioids act on the μ receptor in the spinal cord and brain to reduce pain (10). Activation of the μ receptor releases substance P in the spinal cord, this is the central neurotransmitter for pain which mediates analgesic effects (10–12). In addition, the μ receptor in the brain is dominant to euphoria (a feeling or state of intense excitement and happiness) that leads to abuse of opioids (12). Euphoria involves the dopaminergic system which is implicated in all addictive behavior, including that of alcohol and nicotine (13).

Majority of the currently available opioid dosage forms (e.g., tablets, capsules etc.) are designed for oral administration making tablets and capsules easy targets of abuse. Indeed, several recent drug preference studies have shown oral tablets to be the major source of abuse/misuse of prescription opioids. The opioids with most drug product approvals in the U.S. are oxycodone, hydrocodone, codeine and morphine. In addition, due to presence of higher dose in extended release opioid formulations, they are at higher risk for abuse over immediate release formulations. Drug abusers opt for various forms of abuse and product tampering. They may choose to ingest multiple doses of a drug product or may manipulate (e.g., crush, cut, chew, grind, heat, and/ or dissolve) the drug product to yield a high amount of opioid that could be easily abused via ingestion, nasal insufflation, injection, or smoking. The preferred route of abuse is governed by multiple factors such as the type of abusers and their tolerance level. For example, as a beginner, abuser starts with ingesting multiple oral tablets to get euphoric

effect. Over time, they might develop tolerance or look for quick euphoric effect developing preference for intravenous injection or nasal insufflation. For intravenous injection, abusers crush the tablets and dissolve it in various solvents (e.g., water, ethanol, and 70% isopropanol) making it suitable for injection. Also, they crush tablets to get smaller particles that are suitable for nasal insufflation and smoking (14,15).

To reduce opioid abuse, pharmaceutical manufacturers have responded to this public health concern by developing dosage forms resilient to various forms of tampering, best known as abuse deterrent formulations (ADFs). Although any type of dosage form can be formulated to deter abuse, oral dosage forms particularly oral solids, have seen the most use of novel technologies by applying various manufacturing methods and formulation designs. The ultimate goal of an ADF is to produce a product less favorable to abuse and misuse. This can be extended to include products with the ability to prevent, discourage or decrease the feeling of euphoria, high or rush sought after by abusers. A further challenge lies in making the product safe and effective when taken as directed. Hence, the purpose of this research is to develop a dosage form that would be resistant to all well-known methods of abuse and tampering.

2.2. Opioid products currently developed to have abuse deterrent properties

Opioid products, especially available in extended release dosage forms, are currently being developed to have abuse deterrent properties are described in Table 1. Based on Table 1, physical barrier using various polymers/excipients, such as polyethylene oxide (PEO), xanthan gum, hydroxypropyl methyl cellulose (HPMC),

lipids, fatty acids and wax, is the most commonly used approach to minimize drug abuse. These polymers/excipients have the ability to provide both physical barrier as well as extended drug release characteristics. Among these polymers/excipients, PEO is the most widely used one (i.e., eight out of twelve products listed in Table 1).

Another popular approach for abuse deterrence includes use of aversive agents used in seven out of twelve products listed in Table 1. The inclusion of aversive agents produces undesired effects when the product is abused. For example, sodium lauryl sulfate, a commonly used surfactant, irritates mucous membranes when tablet is crushed and abused via nasal insufflation. Also, the use of staining agents, which may stain the nasal and oral cavities when abusers snort or inhale the altered drug, causing embarrassment.

Although two extended release capsules and one immediate release tablet dosage forms are listed in Table 1, majority of the products being developed are extended release tablet dosage forms, as these are at higher risk of abuse due to higher drug content. Hence, the present investigation focuses in the development of abuse deterrent extended release tablet dosage forms using excipients to have physical and/or chemical barrier.

2.3. Formulation approaches of abuse deterrent extended release tablets (ADERT)

Various abuse-deterrent formulation approaches have been developed to minimize manipulation of the dosage forms. These approaches include 1) inclusion of physical barriers to prevent crushing and extraction, 2) chemical modifications to hinder excessive

drug release when manipulated, 3) inclusion of aversive agents to induce an unpleasant experience, and 4) use of antagonists to block the opioid effect when abused (16–19). However, in order to retain the extended release characteristics of abuse deterrent tablet formulation, polymers/excipients should be selected based on both abilities to provide physical barrier and extended drug release characteristics.

2.3.1. Selection of polymers

There are various classes of polymers, such as hydrophilic polymers, lipids, hydrophobic polymers and biodegradable polymers, utilized in preparation of extended release tablets. These polymers are described in Table 2. Hydrophilic polymers are the most widely used polymers to prepare extended release tablets. They are further classified into various categories such as natural gums, cellulose derivatives, non cellulose natural, non cellulose semi-synthetic polymers and polymers of acrylic acid. PEO is a hydrophilic polymer, which has been used to prepare extended release abuse deterrent tablets. Moreover, there are many hydrophilic polymers as described in Table 2, may have potential to provide not only the extended release characteristics but also abuse deterrent properties by acting as a physical and/or chemical barrier.

2.3.2. Effect of excipients as physical barrier on ADERT

Excipients as a physical barrier are classified into various categories based on their material characteristics which are poly(ethylene oxide), sucrose acetate isobutyrate, hyper-absorbent materials, lipids, foaming agents, and ceramic nanoparticles. In addition, novel microcrystalline cellulose grades have good compression characteristics that

increase hardness of tablets. The higher hardness of tablet may be beneficial to prepare abuse deterrent tablets making it difficult to crush into smaller particles.

2.3.2.1. Poly(ethylene oxide)

Poly(ethylene oxide) (PEO) is a high molecular weight polymer that undergoes ductile deformation rather than brittle fracture under mechanical stress, thereby preventing pulverization upon crushing and act as a physical barrier. PEO is also miscible and when it comes into contact with water, PEO hydrates rapidly and eventually turns into a viscous solution or gel which will make it difficult to extract the drug (20). PEO is available in a wide range of grades of differing viscosity with average molecular weights ranging from 100,000 to 7,000,000 manufactured by the Dow Chemical Company. Degree of swelling characteristics of PEO increases with increasing molecular weight (21,22).

2.3.2.2. Sucrose acetate iso-butyrate

Sucrose acetate isobutyrate (SAIB) is a hydrophobic, water-insoluble, thermally-stable, liquid and a biodegradable excipient (23). It is used in an extended-release formulation of a hard-shell gelatin capsule filled with an SAIB-based viscoelastic matrix. SAIB remains highly viscous over a wide range of temperature from 80°C to 100°C. The Remoxy® matrix is reported to have a viscosity of greater than 60,000 mPas, which is approximately 34 times more viscous than honey. This high viscosity prevents the Remoxy® formulation from being drawn or pushed through a syringe and prevent physical manipulation. Therefore, the formulation cannot be abused via intravenous

injection. Since it remains a viscous liquid when frozen, the Remoxy® formulation is also resistant to freezing and crushing (24).

2.3.2.3. Superabsorbent materials

Super-absorbents are cross-linked acrylic polymers such as polycarbophils or carbomers which can absorb a large quantity of water. Polycarbophils are cross-linked with divinyl glycol, while carbomers are cross-linked with either allyl sucrose or allyl pentaerythrol. Both polycarbophils or carbomers can absorb greater than 62 gm water/gm material per USP specifications, and both materials can swell to approximately 1000 times their original volume when exposed to a pH environment above 4–6. Hence, it will solidify upon contact with aqueous solvent and prevent syringe-ability and extraction.

Xanthan gum and hypromellose are present as the superabsorbent material in the MORPHABOND™ extended-release morphine sulfate tablet. This tablet was developed by Inspiron Delivery Technologies, LLC, and approved in 2015 that consists of an expansion layer, a barrier layer, a drug-containing diffusion layer, an extended-release coating, and a color coating (24).

2.3.2.4. Lipids

Lipid-based formulations can be useful in abuse-deterrent formulations, because of their lipophilicity and low solubility in ethanol. Hence, prevents extraction of drug upon dissolving in aqueous and hydroalcoholic solvents. In some cases, they have also demonstrated increased mechanical strength of the dosage forms (25–28). Examples of

waxes include carnauba wax and beeswax. Waxes are hydrophobic and have a melting point similar to that of fatty acids.

2.3.2.5. Ethyl cellulose

Cima Labs Inc. has developed OraGuard® process of including wax in coating layer of granules that gives crush resistant properties. In this technology, the core granules consist of opioid and cellulosic polymers such as hypromellose or ethyl cellulose, whereas the coating is composed of ethyl-cellulose and 10–30% glyceryl behenate. Coated granules can eventually be formulated in a matrix tablet with hypromellose and lactose. The inclusion of glyceryl behenate instead of magnesium stearate in the coating layer enabled an increased crush resistance. Crushed granules with lipids released less than 21% of the opioid in 30 minutes, which is less than crushed granules without lipids. Additionally, glycerides and waxes prevent dose dumping in ethanol, owing to their low solubility in ethanol (24).

2.3.2.6. Foam-forming agents

A foam-forming delivery system has been developed by Acura Pharmaceuticals to deter drug abuse (24). The foam-forming agents are composed of effervescent mixtures that contain an organic acid and base (e.g., citric acid and sodium bicarbonate), a surfactant (e.g., sodium lauryl sulfate), and high- and low-viscosity polymers formulated in a tablet. Polymers are added as a foam stabilizer. Low-viscosity polymers exhibit rapid hydration and gelation upon contact with a suitable media and can therefore entrap gas (e.g., CO_2) emitted by the effervescent agents into the foam. Due to its ability to stabilize

the foam more effectively, a high-viscosity polymer is preferred over a low-viscosity polymer. High viscous polymer prevents syringe-ability and extraction of drug and minimize abuse via parenteral route.

2.3.2.7. Titanium dioxide

Altair Nanotechnologies has developed proprietary technologies to manufacture nanoparticles of titanium dioxide and other related ceramic compounds. These ceramic structures are spherical and have a hollow core that allows for a high-loading drug coating. The hydrophilicity or hydrophobicity of the nanostructures can be adjusted to influence the nanoparticles' capacity to uptake the drug into the hollow core via chemical modification. These nanoparticles can be loaded with opioids using solvent evaporation or a melt-coating process. Extreme mechanical strength is associated with ceramic nanoparticles loaded with opioids and present a controlled-release delivery system. They are resistant to diversion attempts such as grinding and prevent abuse via nasal and parenteral route (24).

2.3.2.8. Microcrystalline cellulose

The novel microcrystalline cellulose (MCC) grades, such as MCC KG-802, KG-1000, UF-711 and UF-702, have good flow properties as well as good compatibility owing to their various particle shape characteristics. These novel polymers can give high hardness characteristics upon compression to get physical barrier. The most widely used MCC grades for oral solid dosage forms are PH grades. MCC PH-101 is the standard grade and most widely used for wet granulation tableting. PH-102 has larger particle size

with improved flow while maintaining compatibility and disintegration properties similar to PH-101 and used mostly for direct compression tableting.

The MCC UF grades contain porous structures and more spherical morphology of CEOLUS UF grades contribute to their effective plastic deformation and better flow. They are highly compactible and flowable. They are useful for direct compression. On the other hand, for MCC KG grade, the key to the compactibility of the CEOLUS KG grades lies in their needle-like particle shape. Needle-like particles, once compressed, have less elastic recovery and more particle-to-particle entanglements to provide greater tablet hardness. In particular, KG-1000, offers practically required tablet hardness and friability at concentrations of 10% or less.

2.3.3. Effect of excipients as chemical barrier on ADERT

The use of chemical barrier approach hinders excessive drug release when the dosage form is manipulated. There are many approaches available which includes salt formation between opioids free base and fatty acids that makes drug more lipophilic, complexation with ion exchange resin which will release drug by exchange of ions in gastrointestinal track. In addition, the use of alkalizing agent may serve as a chemical barrier that will reduce or hold drug release when multiple tablet is ingested.

2.3.3.1. Salt formation between opioids free bases and fatty acids

DETERx® was developed by Collegium Pharmaceutical Inc. in 2016 which is an abuse-deterrent drug delivery system is a capsule that contains microparticles consisting

of fatty acid salts of opioid free bases along with excess fatty acids and waxes. This technology minimizes drug extraction by altering solubility of drug. Fatty acids cause opioids to become much more lipophilic as compared to counter ions such as hydrochloride, sulfate, and bitartrate. With different carbon chain lengths of fatty acids, lipophilicity of the fatty acid salts can be adjusted. Fatty acid salt formation is accomplished by a melt process. During manufacturing, opioid free base is dissolved in molten fatty acid (e.g., stearic acid and myristic acid), which is in molar excess relative to the drug in order to achieve a homogeneous single phase (2–15 times). Waxes (e.g., beeswax and carnauba wax) can eventually be added to the molten solution, which is then converted into spherical particulates using a spray congealing process. The spherical particulates are then filled into hard gelatin capsule shells. The microparticles do not dissolve in water or organic solvents. Solubilization of opioids in the matrix enhances the abuse-deterrent properties of microparticles, as it is difficult to extract the drug from an intimately mixed composition. Since most of the drug remains associated with or entrapped within the fatty acid, the release of the drug is slow even if these microparticles are chopped or crushed (24).

2.3.3.2. Complexation with ion exchange resins

Drug delivery based on ion exchange resins (IERs) are used for taste masking and extended release (29–31). Ion exchange process is defined as the reversible interchange of ions between a liquid and a solid phase (32). IER-based formulations possess better dose dumping prevention properties than conventional polymeric formulations, since drug release from resinate is regulated by both ionic (chemical) and polymeric (physical)

mechanisms. Release of the active ingredient is triggered by ion exchange reaction with counter ions present in gastrointestinal tract. Acidic resins are used for delivery of opioids. Resins differ in their exchange capacity, permeability (related to their degree of cross-linking), swelling potential, and particle size. Strong acidic resins behave similarly to strong acids, and they are highly ionizable, producing many ions for the exchange process. On the contrary, weak acidic resins are weakly dissociated and have fewer ions available for exchange (33).

2.3.3.3. Alkalizing agent

Use of alkalizing agent in formulation, under normal dosing conditions, may allow complete and/or bioequivalent oral delivery of the desired drug dose from the formulation. However, when excess doses are ingested, either intentionally or unintentionally, the formulations may work to either slow or block release and subsequent absorption of the excessive doses. As opioid drugs are weakly basic in nature and have good dissolution in acidic environment (stomach), the dissolution of these drugs can be reduced by incorporating alkalizing agent in the tablet in sufficient amount that will release the drug under normal dosing condition. However, when the tablets taken in multiple dose, it will change the pH of stomach to hinder the release and absorption of the drug. The alkalizing agents will raise the pH of stomach and the drug will remain as insoluble particles. These alkalizing agents include sodium bicarbonate, magnesium hydroxide, calcium carbonate, magnesium carbonate, aluminum hydroxide (34). Also use of alkalizing agent in the tablet formulation leads to change in microenvironmental pH and which leads to reduction in drug release upon ingestion of multiple units.

2.3.4. Effect of antagonists on ADERT

The use of antagonist along with agonist (opioids) into the formulation has been proven to be a successful strategy to deter the abuse of opioid drugs. The euphoric effects of opioids can be blocked when these products are subject to tampering due to high concentration of antagonist in plasma. Antagonists can be categorized as available antagonist and sequestered antagonist. The term available antagonist refers to the antagonist being absorbed when opioid drugs are taken properly by patients. Otherwise, the term sequestered antagonist is used. Table 3 represents a list of products that contain antagonists. As shown in Table 3, naltrexone hydrochloride (five out of seven products as listed in Table 3) and naloxone hydrochloride (two out of seven products as listed in Table 3) are two commonly used antagonists. Because of its high bioavailability and high activity (2–9 times that of naloxone), naltrexone hydrochloride becomes very harmful to patients if absorbed along with opioids. Therefore, naltrexone hydrochloride is always sequestered.

2.3.5. Effect of aversion agents on ADERT

The inclusion of aversive agents is a formulation technique which is older than use of antagonists to produce undesired pharmacological effects when the product is abused. The immediate release LOMOTIL® tablet, approved in 1960 to treat diarrhea, contains 2.5 mg diphenoxylate hydrochloride as the therapeutic agent and 0.025 mg atropine sulfate as the aversive agent. Atropine sulfate, an anticholinergic agent, causes tachycardia (i.e., rapid pulse rate, shortness of breath, and dizziness) when an excessive number of tablets are ingested. Table 4 represents a list of commonly used aversion

agents. There are various categories of aversive agents such as bittering agent, emetic agent, gelling agent, irritant agent, laxative agent, staining agent and vasodilator. These aversive agent cause discomfort such as vomiting, induce pain/irritation, itching to abusers when they try to manipulate and abuse the dosage form. Hence, the use of aversive agent is another approach along with the use of physical and chemical barrier to prepare abuse deterrent extended release tablet to minimize abuse of opioids.

2.4. Selection of model drug as alterative of opioids

To avoid dealing with the complexity of controlled substance licensing and its management, various model drugs with similar physicochemical properties have been selected. Metformin HCl was selected as a model drug based on its aqueous solubility which is similar to a widely abused opioid drug oxycodone hydrochloride (35).

Also, various model drugs with similar dissociation constant (pKa) values to that of opioids have been selected. Opioids are weak bases with pKa values in the range of 6.5-9.5 (Table 6). In dissolution media, these drugs have different dissolution profiles depending on the pH of the media and their pKa value. For example, weakly basic drugs have a higher solubility in acidic media, and that leads to an increase in drug release from the tablet. On the other hand, there is a decrease in the solubility of opioids with an increase in the pH of the media, which leads to a decrease in drug release (36). For this reason, three model drugs were selected based on a similar pKa value that covers higher (9.5), median (8.6), and lower (6.5) pKa ranges compared to opioids. Propranolol HCl

(pKa=9.5), quinidine sulfate (pKa=8.5), and dipyridamole (pKa=6.4) were selected as model drugs.

3. RESEARCH OBJECTIVES AND SPECIFIC AIMS

The primary objective of this research is to develop abuse deterrent extended release metformin tablets using excipients as physical and/or chemical barrier to minimize the potential problem of opioid abuse.

Specific aims include

- To select suitable polymer and determine its effect as a physical and/or chemical barrier.
- To determine effect of diluents as a physical barrier.
- To study the effect alkalizing agent as a chemical barrier.
- To formulate tablet dosage form using selected extended release polymer, diluent using various model drugs.
- To study the effect of alkalizing agent as a chemical barrier on ADERT using various model drugs.

4. MATERIALS AND METHODS

4.1. Materials

Metformin HCl (≥ 99%), propranolol HCl (≥ 99%), quinidine sulfate dihydrate (≥ 98%), and dipyridamole were purchased from TCI America (Cambridge, MA). Xanthan gum, corn starch, gelrite gum, chitosan, locust bean gum, sodium carboxymethyl cellulose (Na CMC), hydroxypropyl cellulose (HPC) were purchased from Sigma Chemicals (St. Louis, MO). Carbopol 940 was purchased from Acros Organics (New Jersey, USA). Polyethylene oxide (PEO) and Hydroxypropyl methyl cellulose (HPMC) of various grades were kindly provided by DOW Chemicals (Midland, MI) and Ashland Pharmaceuticals (Wilmington, DE), respectively. Microcrystalline cellulose (MCC) PH grades were purchased from Sigma Chemicals (St. Louis, MO). MCC UF and KG grades were kindly provided as a gift sample by Asahi kasei corporation (Japan, Tokyo). Magnesium hydroxide, calcium carbonate, aluminum hydroxide, and calcium hydroxide were purchased from VWR International (Radnor, PA). All solvents utilized in the study were of analytical grade and were obtained from Thermo Fisher Scientific (Fair Lawn, NJ).

4.2. Analytical method for various model drugs

4.2.1. Metformin HCl

Analysis of metformin HCl was carried out by a UV spectrophotometer. The accurately weighed drug was dissolved in distilled water to prepare a stock solution of 1 mg/mL. The solution was further diluted to prepare solutions of 2-10 µg/mL. The diluted solutions were analyzed at an absorbance wavelength of 232 nm (35).The calibration

curve was generated using the concentration vs absorbance curve and represented in Figure 1.

4.2.2. Propranolol HCl

Propranolol HCl was analyzed using an HPLC system (Agilent Technologies Inc., Santa Clara, CA) equipped with HP1100 quaternary pump and autosampler. The system had a UV detector, which was set at 290 nm. Samples were analyzed for propranolol HCl concentrations using a C18, 4 µm 150×4.6 mm column (Phenomenex, CA). Isocratic conditions with a flow rate of 0.8 ml/min were used. The mobile phase was prepared by dissolving 0.5 g of sodium dodecyl sulfate (SDS) in 18 mL of 0.15 M phosphoric acid and adding 90 mL of acetonitrile and 90 mL of methanol to this mixture, this solution was then diluted with Nanopure® water to 250 mL, mixed, filtered, and degassed. The injection volume was 10 µL. Data acquisition and processing were performed using Chemstation® software (Agilent Technologies Inc., Santa Clara, CA) (37). Area under the peak was used to calculate the concentration of propranolol HCl and linearity over concentrations ranging between 25-1000 µg/ml, which was established as shown in Figure 2.

4.2.3. Quinidine sulfate

Quinidine sulfate was analyzed using an HPLC system with a 4 mm × 100 mm C-18 column with a particle size of 5 µm (ChromTech, MN). The mobile phase was composed of mixture of Nanopure® water, acetonitrile, methanesulfonic acid solution (35.0 mL of methanesulfonic acid added to 20.0 mL of glacial acetic acid, diluted with

water to 500 mL), and *diethylamine solution (*10.0 mL of diethylamine added in water to obtain 100 mL of solution) at ratio of 860:100:20:20. The pH of the mobile phase was adjusted to 3.2 with *diethylamine*. A flow rate of 1.2 ml/min was adjusted, and the quinidine sulfate content was detected at a wavelength of 331 nm (38). Area under the peak was used to calculate the concentrations of quinidine sulfate, and linearity over the concentrations ranging between 25-1000 µg/ml, which was established as shown in Figure 3.

4.2.4. Dipyridamole

Dipyridamole was analyzed using an HPLC system with a 3 mm × 150 mm C-18 column with a particle size of 4 µm (phenomenex, CA). The mobile phase consisted of 68% v/v methanol and 32% v/v of 0.5% v/v acetic acid aqueous solution. A flow rate of 0.8 ml/min was set, and dipyridamole content was detected at a wavelength of 284 nm (39). Area under the peak was used to calculate the concentrations of dipyridamole, and linearity over the concentrations ranging between 25-1000 µg/ml, was established as shown in Figure 4.

4.3. Effect of excipients as physical and/or chemical barrier on ADERT

Abuse deterrent potential of various polymers were evaluated by determining their effect as a physical barrier as described in following studies.

4.3.1. Effect of polymers as physical barrier to screen of type of polymer

Various hydrophilic polymers were selected by evaluation of their effect as a physical barrier by determining swelling, viscosity, and syringe-ability studies of polymeric solutions.

4.3.1.1. Dissolution/swelling behaviors of polymers

The effect of hydrophilic polymer swelling in commonly used solvents [0.1 N hydrochloric acid (HCl), water, 70% isopropanol (IPA), 10% ethanol, and 40% ethanol (EtOH)] was determined by dissolution/swelling behavior study for drug extraction. Hydrophilic polymers dissolve and swell in aqueous medium, and form gel which retards diffusion of drug from the hydrophilic matrix, and thereby tablets prepared with these polymers reduce drug extraction in various solvents. Solvent selection was based on the availability of solvents and has been used by abusers.

Polymeric solutions (2% w/v) were prepared by adding 2 gm of polymer in 100 mL of various solvents separately and kept on overnight stirring on magnetic stirrer at room temperature to achieve complete hydration of polymers. The 2% w/v polymeric solution represents a similar concentration of 1 crushed tablet dissolved in 5-10 mL of an aqueous solution. The dissolution/swelling behavior was determined by visual observation to screen the type of polymer. The polymers that dissolve and swell in all the given solvents, were selected to determine their viscosity study as a physical barrier.

4.3.1.2. Viscosity study

One common method of abusing tablet dosage form is extraction of the opioid from the tablets using a variety of commonly available solvents. Such extraction leads to a concentrated drug solution which can be used for parenteral abuse to achieve euphoria. The amount of solvent used by abusers is about 5-10 mL. The abusers also heat the solvents to get higher concentration solution. Hence, a polymer as a physical barrier should be selected based on their higher viscosity in various solvents in order to reduce the syringe-ability and reduce potential for intravenous injection.

Based on these considerations, the viscosity of 2% w/v polymeric solutions (represents one crushed tablet in 10 mL of aqueous solvent) were determined. Viscosity of 2% w/v screened polymeric solutions were determined in various solvents [0.1 N hydrochloric acid (HCl), water, 70% isopropanol (IPA), 10% ethanol, and 40% ethanol (EtOH)]. Viscosity of these polymeric solutions were evaluated using Brookfield Viscometer (AMETEK Brookfield, MA) with spindle number S-03 at room temperature (25°C) at spindle speed of 1-100 rpm (rotation per minute). The polymers were screened based on higher viscosity at 100 rpm compared to other polymers in all solvents, respectively. The screened polymers were evaluated for their heat-induced viscosity study and syringe-ability study.

4.3.1.3. Heat induced viscosity study

Viscosity of a liquid decreases with increase in temperature and the fluidity of a liquid (the reciprocal of viscosity) increases with temperature. The dependence of the

viscosity of a liquid on temperature is expressed approximately for many substances by an equation analogous to the Arrhenius equation of chemical kinetics (40).

$$\ln \eta = \ln A + \frac{Ea}{R} * \frac{1}{T} \qquad \text{Equation. 1}$$

where, η is viscosity, A is a constant, R is a gas constant, and T is the absolute temperature

The effect of temperature on viscosity of selected polymeric solutions were evaluated by heat-induced viscosity study based on the Arrhenius equation (Equation 1) of chemical kinetics. Heat-induced viscosity of screened 2% (w/v) polymeric solutions were determined in distilled water using Brookfield Viscometer with spindle number S-03 at spindle speed range of 1-100 rpm at 25, 37, 60, and 80°C to determine "activation energy (*Ea*)". *Ea* is the energy required to initiate flow between polymer molecules and can be obtained from the slope by plotting the natural logarithm of viscosity against reciprocal of temperature. The higher value of *Ea* leads to a reduction in the flow of polymeric solution and that might lead to a reduction in syringe-ability upon heating.

4.3.1.4. Syringe-ability study

Polymeric solutions (2% w/v) in commonly injectable solvents (water, 10% ethanol, and 40% ethanol) were used to determine syringe-ability. 15 mL of polymeric solution was transferred to a 20 mL scintillation vial and syringe-ability was performed by *TA.XTPlus Texture Analyzer (Texture Technologies Corp., Hamilton, MA)* equipped with a syringe assembly set. A 5 ml syringe fitted with a 21-gauge needle was used for each test. Tension mode was set for 1 mm/s test speed and 0.05 N trigger force. The

syringe plunger was set to move a distance of 40 mm in each direction with 30 seconds hold time in-between pulling and pushing. The target mode was set to record force that the sample plunger experience while pulling the solutions. Also, the volume withdrawn in the syringe was recorded by visual observation as one of syringe-ability parameters.

4.3.2. Preparation of metformin HCl-loaded ADERT

The screened polymers were selected to prepare tablets with various grades of microcrystalline cellulose as diluent. The composition of tablets was drug, polymer, MCC, and magnesium stearate at ratio of 8:30:61.5:0.5 (Table 9). Drug, polymer, diluent and lubricant were blended together by dry mixing using mortar and pestle and made into tablets by direct compression at a fixed compression force using Carver laboratory press tablet machine (Carver Inc, IN) equipped with 12 mm round, flat, and plain punches with compression pressure of 2500 lbs.

4.3.2.1. Abuse deterrent potential of metformin HCl-loaded ADERT

Abuse deterrent potential of prepared ADERT was characterized in terms of physical and chemical barrier studies.

4.3.2.1.1. Physical barrier: Screening of type of diluent

To formulate abuse deterrent dosage form, higher hardness of tablets is required to minimize drug abuse by snorting, as abuser crushes tablets into smaller particles to snort and achieve high blood concentration of opioids and subsequent euphoric effects. To achieve this, various microcrystalline cellulose (MCC) grades such as MCC PH-101,

PH-102, UF-702, UF-711, KG-802 and KG-1000 were screened for their better hardness characteristics as an excipient in tablet formulations.

4.3.2.1.1.1. Hardness testing

Tablet hardness or breaking force test is used to assess mechanical strength of ADERT and was determined using tablet hardness tester (Pharma Alliance group Inc, CA). The hardness is measured in terms of kg/cm^2. Three ADERTs were chosen randomly and tested for hardness from each formulation. The average hardness of triplicate determinations was recorded. The diluent that contributed to higher tablet hardness characteristic was selected for further studies.

4.3.2.1.1.2. Syringe-ability study

Powder sample (of prepared ADERT) of 500 mg (i.e., one tablet) from each formulation was weighed accurately and transferred into separate 20 ml scintillation vials, each containing 10 ml of commonly injectable solvents that are distilled water, 10%, and 40% ethanol, respectively, at room temperature. The scintillation vials were vortexed for 30 seconds and left for hydration for 30 min before the tests. Syringe-ability study of ADERT powder blend was performed using similar procedure as given in section 4.3.1.4.

4.3.2.1.2. Chemical barrier: Drug extraction study

Drug extraction study was performed to evaluate the chemical barrier of ADERT. Extraction studies were performed on intact formulations to evaluate drug extraction in

water, 10% and 40% ethanol. Briefly, an intact tablet was added to vial containing 10 mL of solvent (water or ethanol). The vial was vortexed for 3 minutes before withdrawing samples at 5 and 30 minutes and analyzed for drug content using method described in section 4.2.1. The study was performed in triplicate at room temperature.

4.3.3. Preparation of propranolol HCl-loaded ADERT

The propranolol HCl-loaded ADERT was prepared using similar procedure as given in section 4.3.2. with use of a similar amount (40 mg) of propranolol HCl as a model drug. 4.3.3.1. Abuse deterrent potential of propranolol HCl ADERT

Abuse deterrent potential of propranolol HCl-loaded ADERT was characterized in terms of physical and chemical barrier studies. The physical barrier was evaluated using hardness testing, evaluated by using a similar procedure as given in section 4.3.2.1.1.1. Whereas the chemical barrier was performed by drug extraction study on the intact tablet to evaluate drug extraction in water, 10%, and 40% ethanol, respectively. It was evaluated using similar procedure as given in section 4.3.2.1.2.

4.3.4. Preparation of quinidine sulfate-loaded ADERT

The quinidine sulfate-loaded ADERT was prepared using similar procedure as given in section 4.3.2. with use of similar amount (40 mg) of quinidine sulfate as a model drug.

4.3.4.1. Abuse deterrent potential of quinidine sulfate-loaded ADERT

Abuse deterrent potential of quinidine sulfate-loaded ADERT was characterized in terms of using physical and chemical barrier studies. The physical barrier was evaluated using hardness testing, performed using similar procedure as given in section 4.3.2.1.1.1. and chemical barrier was evaluated using a similar procedure as given in section 4.3.2.1.2.

4.3.5. Preparation of dipyridamole-loaded ADERT

The dipyridamole-loaded ADERT was prepared i using similar procedure as given in section 4.3.2. with use of similar amount (40 mg) of quinidine sulfate as a model drug.

4.3.4.1. Abuse deterrent potential of dipyridamole-loaded ADERT

Abuse deterrent potential of dipyridamole-loaded ADERT was characterized in terms of using physical and chemical barrier studies. The physical barrier was evaluated using hardness testing using similar procedure as given in section 4.3.2.1.1.1. and chemical barrier was evaluated using a similar procedure as given in section 4.3.2.1.2.

4.4. Effect of physical and/or chemical barrier on bilayer ADERT

In addition to the physical barrier and/or chemical barrier as discussed in above sections, the bilayer ADERT served to provide the additional advantage as a chemical barrier. Bilayer ADERT was developed using pH modifying layer and extended release layer containing drug to evaluate deterrence to abuse via multiple unit oral ingestion.

4.4.1 Effect of alkalizing agent as a chemical barrier on propranolol HCl-loaded bilayer ADERT

Incorporation of alkalizing agent in ADERT may help to minimize drug release in case of multiple unit oral ingestion of ADERT. Propranolol HCl (pKa=9.5) was selected as a model drug, since it has a similar pKa value (9.1-9.5) to that of the opioids (Table 6).

4.4.1.1. Preparation of propranolol HCl-loaded bilayer ADERT

Bilayer ADERT was prepared by direct compression method, with two layers. Bilayer ADERT was designed to have a pH modifying layer (top layer), consisting of the alkalizing agent which would help to modify the pH of the dissolution medium, when multiple units were added to the medium. On the other hand, the extended release layer (bottom layer) consisted of the propranolol HCl to achieve the extended release effect for a prolonged period.

4.4.1.1.1. pH modifying layer

Magnesium hydroxide, aluminum hydroxide, calcium carbonate, and calcium hydroxide were used as an alkalizing agent. Kollidon® CL-SF was used as a super disintegrant. The pH modifying layer contains an alkalizing agent, Kollidon® CL-SF, magnesium stearate, and MCC KG-1000 at a ratio of 50:5:0.5:44.5 (Table 12). Powder mixture for the pH modifying layer was prepared by blending all the ingredients by dry mixing using mortar and pestle.

4.4.1.1.2. Extended release layer

Based on the results of various studies provided in section 4.3.2.1, formulation F12 was selected as an extended-release layer. The extended-release layer contained model drug, HPMC K100M, MCC KG-1000, and magnesium stearate at a ratio of 8:30:61.5:0.5 (Table 12). The powder mixture of the extended-release layer was prepared by blending all the ingredients by dry mixing using mortar and pestle. Control formulation is a single layer ADERT contained similar composition as of an extended release layer.

4.4.1.1.3. Preparation of bilayer ADERT

Bilayer ADERT were compressed on a Carver Press using a 12 mm flat round set of die and punch tool. An illustration of the bilayer tableting process is shown in Figure 5.

Accurately weighed quantity of 500 mg powder (extended-release layer) was manually loaded into the die and compressed at a pressure, P1, of 200 lbs. to make the first tablet layer (Figure 5a). Without ejecting the first layer, 200 mg of a second powder (pH modifying layer) was again manually added to the die and the second (final) compression was carried out at P2, which was 2500 lbs. (Figure 5b). Finally, the bilayer tablet (ADERT) was ejected from the die by pushing the second layer downward with the punch (Figure 5c). Similarly, all other tablets were prepared.

4.4.1.2. Screening of alkalizing agent

Various alkalizing agents such as magnesium hydroxide, aluminum hydroxide, calcium carbonate and calcium hydroxide were screened to determine their effect as a chemical barrier via multiple unit's oral ingestion based on *in-vitro* drug release study.

4.4.1.2.1. *In-vitro* drug release study

4.4.1.2.1.1. Biorelevant dissolution media

For the *in-vitro* drug release, bio-relevant media has been widely used to adequately predict the *in-vivo* behavior of drug formulations by adapting simulation of gastrointestinal conditions (41). Fasted state simulated gastric fluid (FaSSGF) and fasted state simulated intestinal fluid (FaSSIF) were used as bio-relevant media for the *in-vitro* dissolution test. FaSSGF was prepared by dissolving 80 mM of sodium taurocholate, 20 mM of lecithin, 0.1 mg/mL of pepsin, and 34.2 mM of sodium chloride in distilled water. The pH of FaSSGF was adjusted to 1.6 with 6 N hydrochloric acid (HCl). FaSSIF was prepared by dissolving 3 mM of sodium taurocholate, 0.75 mM of lecithin, 3.438 g of sodium dihydrogen phosphate and 6.186 g of sodium chloride in 1 L of deionized water adjusted to pH 6.5 with 10 M sodium hydroxide (NaOH) solution (41). Double concentrated FaSSIF (2xFaSSIF) was obtained by using two times the amount of each ingredient of FaSSIF in deionized water, followed by adjusting pH to 6.5 with 10 M NaOH solution.

4.4.1.2.1.2. Protocol for *in-vitro* drug release

In-vitro drug release study was carried out using the two-stage bio-relevant drug release method which represents the gastrointestinal transfer. The study was performed using USP dissolution apparatus 2 (rotating paddle) with a paddle speed of 100 rpm, at 37 °C ± 0.5 °C, using an initial volume of 250 mL for FaSSGF (pH 1.6) for 2 h. Subsequently, 250 mL of 2×FaSSIF (pH 6.5) was added to achieve a final volume of 500 mL of FaSSIF. The pH of the final liquid in the dissolution vessel was adjusted to 6.5 using a 10 M NaOH solution .(41) The dissolution test was performed for 24 h. pH of the dissolution vessel was measured at various time points using a pH meter.

4.4.1.2.1.3. Single unit drug release

The single unit drug release study was carried out for a control formulation (without a pH modifying layer) and a bilayer ADERT for all the formulations using the protocol mentioned in section 3.4.2. Aliquots (1 mL) were withdrawn at specific predetermined time intervals from the medium and filtered through a 0.45 µm syringe filter. At each time point, an equal volume of fresh bio-relevant media was added to the dissolution vessels. Drug content was determined by the HPLC method as described previously for propranolol HCl, quinidine sulfate, and dipyridamole. The *in-vitro* drug release study was conducted in triplicate

4.4.1.2.1.4. Multiple-unit drug release

The *in-vitro* drug release study with multiple bilayer ADERT was carried out to evaluate deterrence to multi-dose abuse. This study was conducted by adding multiple bilayer ADERT (3-and 5-unit) in the dissolution vessel at a time. Further steps were conducted similar to the single unit drug release study.

4.4.2. Abuse deterrent potential of propranolol HCl-loaded bilayer ADERT

4.4.2.1. Physical and chemical barrier

Abuse deterrent potential of propranolol HCl-loaded bilayer ADERT was characterized in terms of physical and chemical barrier studies. Physical barrier was evaluated using hardness testing, by using similar procedure as given in section 4.3.2.1.1.1. Chemical barrier was evaluated by drug extraction study on the intact tablet to evaluate drug extraction in water, 10%, and 40% ethanol, respectively. It was evaluated using similar procedure as given in section 4.3.2.1.2. pH of the drug extraction media was also determined at the end of the study.

4.4.2.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of propranolol HCl-loaded bilayer ADERT

To minimize drug release upon multiple-unit ingestion (3-and 5-tablet) in both FaSSGF and FaSSIF, additional alkalizing agent (i.e., magnesium hydroxide) was incorporated in the extended-release layer (Table 13) which will not only raise the microenvironmental pH (i.e., pH at the diffusion layer surface), but also increase bulk media pH upon multiple unit abuse. This increased pH can lead to decreased solubility of

weakly basic drug and thereby hindering drug release. To achieve this shift in microenvironmental and/or bulk pH of the media, various amount of magnesium hydroxide (25, 50, and 75 mg) was added to the extended release layer (Table 13) and drug release study was performed for single, 3-and 5-unit bilayer ADERT using propranolol HCl as a model drug using similar method outlined in section 4.4.1.2.1

4.4.3 Effect of alkalizing agent as a chemical barrier on quinidine sulfate-loaded bilayer ADERT

Quinidine sulfate was selected as a model drug due to its similar pKa (8.1-8.7) as most opioids (Table 6). The bilayer ADERT containing quinidine sulfate was prepared according to Table 14, using similar method provided in section 4.4.1.1.

4.4.4. Abuse deterrent potential of quinidine sulfate-loaded bilayer ADERT

4.4.4.1. Physical and chemical barrier

Abuse deterrent potential of quinidine sulfate-loaded bilayer ADERT was characterized using physical and chemical barrier studies. Physical barrier was evaluated using hardness testing using similar procedure as given in section 4.3.2.1.1.1. Chemical barrier was determined by drug extraction study performed on the intact tablet to evaluate drug extraction in water, 10%, and 40% ethanol, respectively. It was evaluated using similar procedure as given in section 4.3.2.1.2. pH of the drug extraction media was also determined at the end of the study.

4.4.4.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of quinidine sulfate-loaded bilayer ADERT

To minimize drug release upon multiple unit ingestion, magnesium hydroxide was incorporated to the extended release layer (Table 15). The drug release studies of single and multiple units ADERT were performed using similar method outlined in section 4.4.1.2.1.

4.4.5 Effect of alkalizing agent as a chemical barrier on dipyridamole-loaded bilayer ADERT

Dipyridamole was selected as a model drug due to its similar pKa (6.5-7.1) to that of the opioids (Table 6). The bilayer ADERT containing quinidine sulfate was prepared according to Table 14, prepared similar to the method outlined in section 4.4.1.1.

4.4.6. Abuse deterrent potential of dipyridamole-loaded bilayer ADERT

4.4.6.1. Physical and chemical barrier

Abuse deterrent potential of dipyridamole-loaded bilayer ADERT was characterized using physical and chemical barrier studies. Physical barrier was evaluated using hardness testing using similar procedure as given in section 4.3.2.1.1.1. Chemical barrier was determined by drug extraction study performed on the intact tablet to evaluate drug extraction in water, 10%, and 40% ethanol, respectively. It was evaluated using similar procedure as outlined in section 4.3.2.1.2. pH of the drug extraction media was also determined at the end of the study.

4.4.6.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of dipyridamole-loaded bilayer ADERT

To minimize drug release upon multiple unit ingestion, *in-vitro* drug release studies of single and multiple units ADERT were performed using similar method as outlined in section 4.4.1.2.1.

4.5. Correlation of effect of pH and drug release

To correlate the effect of magnesium hydroxide on drug release and drug extraction, solubility of various model drugs at various pH were determined. Microenvironmental pH of various formulations were determined in water, FaSSGF and FaSSIF.

Further, based on Noyes-Whitney equation (Equation 2), the drug release from the matrix tablet was mainly controlled by concentration of the drug at solid-liquid interphase (diffusion layer) (Cs), concentration of the drug in the bulk media (C) and diffusivity of the drug from polymeric matrix (D) in the bulk media.

$$\frac{dC}{dt} = \frac{DS}{Vh}(Cs - C) \qquad \text{Equation 2}$$

where, *D* is the diffusion coefficient of the solute in solution, *S* is the surface area of the exposed solid, *h* is the thickness of the diffusion layer, *C*s is the solubility of the solid (i.e., concentration of a saturated solution of the compound at the surface of the solid and at the temperature of the experiment), and *C* is the concentration of solute in the bulk solution and at time *t*. The quantity *dC*/*dt* is the dissolution rate, and *V* is the volume of solution (42).

4.5.1. Determination of pH solubility of various model drugs

Solubility of various model drugs were determined over a pH range of 1.6–10.5. To avoid pH fluctuation during the experiments, an excess of model drug was added to the following solvent, respectively: acid phthalate buffer (pH 1.6–4), neutralized phthalate buffer (pH 4–5.8), phosphate buffer (pH 5.8–8.0), borate buffer (pH 8.0-10.5), 10% ethanol, and 40% ethanol. After equilibrating on shaker water bath (37 ± 1 °C) for 24 h, samples were filtered through 0.45 μm filter and the drug concentration in filtrate was determined by HPLC method. For comparison with theoretical values at various pH, an equation based on the pKa and intrinsic solubility of the drug was used.

$$\frac{S}{So} = (10^{pKa-pH}) + 1 \qquad \text{Equation 3}$$

where, S and So are solubility at test pH and at any pH above pKa, respectively. The value of So was determined experimentally at pH 10.5 for all model drug (39).

From Equation 3, the pH solubility profile of a weakly basic drug (opioid) can be predicted. Based on the pH-solubility of an opioid, drug release at higher pH values can be expected to be reduced due to reduction in the solubility. Since the pKa of the model drug is similar, similar pH-solubility profile may be expected to that of an opioid. According to this consideration, during the drug release of multiple unit bilayer ADERT, both bulk media, and microenvironmental pH increase, owing to the effect of alkalizing agent. This can lead to a reduction in the solubility of the drug and hence leading to a reduction in the drug release. Based on this, it can be assumed that drug release profile(s) with multiple unit ADERT prepared with model drug(s), may be similar to drug release profile as that of the opioid.

4.5.2. Estimation of microenvironmental pH of ADERT powder blend prepared using various model drugs

The microenvironmental pH of a drug-excipient blend for various formulations was estimated by adding 10 mL of various solvents (water, FaSSGF, and FaSSIF) to 400 mg of blend in a vial, mixing the suspension with a vortex mixer, and then recording the pH with a pH meter (43). With increase in the amount of alkalizing agent in the extended-release layer can lead to an increase in the microenvironmental pH, that will help to reduce drug release when multiple units ADERT ingested. This was based on the assumption that with multiple unit ADERT, since the amount of alkalizing agent will increase leading to an increase in both microenvironmental pH and bulk media pH under drug release study. At higher pH, the reduction in the solubility of weakly basic drug may lead to reduction in the drug release upon multiple unit ingestion.

4.6. Statistical analysis

To confirm statistically significant difference the statistical tool ANOVA (analysis of variance) and/or t-test was applied wherever applicable, considering appropriate parameter for comparison at an α value of formulations $p<0.05$, 0.01, 0.001, and 0.0001, respectively.

5. RESULTS AND DISCUSSION

5.1. Effect of excipients as physical barrier on ADERT

Abuse deterrent potential of various polymers were evaluated by determining their effect as a physical barrier by following studies.

5.1.1. Effect of polymers as physical barrier to screen of type of polymer

Various hydrophilic polymers were selected to screen type of polymer through their effect as a physical barrier by evaluation of following studies.

5.1.1.1. Swelling behaviors of polymers

Abusers use commonly available solvents to dissolve crushed tablets, making it suitable for parenteral route, also make a concentrated solution of the dissolved tablet to abuse via oral route. From Table 5 it was observed that methyl cellulose, Carbopol 907, Carbopol 940, methyl cellulose PEO 5M, PEO 7M, HPMC K15M, and HPMC K100M dissolved slowly and swelled in all the solvents used. The swelling of polymers in various solvents was attributed to diffusion of the solvent into the polymer molecule which leads to plasticization of the polymer by the solvent. This plasticization leads to formation of a gel-like swollen layer along with two separate interfaces, one between the glassy polymer and gel layer; and other between the gel layer and the solvent. The polymer dissolves after the induction time (time required for polymer to dissolve) since, hydration of polymer takes certain period and that is directly proportional to the molecular weight of polymers (43).

Also, being nonionic nature of methyl cellulose PEO 5M, PEO 7M, HPMC K15M, and HPMC K100M helps swelling of these polymers in various solvent. Whereas, chitosan showed dissolution/swelling only in 0.1N HCl (acidic environment). In acidic conditions, amino groups of chitosan can be partially protonated resulting in repulsion between positively charged macro chains, thereby allowing diffusion of water molecules and subsequent solvation of macromolecules (43). Also, due to its semi crystalline nature, derived mainly from inter- and intra-molecular hydrogen bonds, chitosan is water-soluble only at acidic pH environment (44,45). Locust bean gum, xanthan gum, corn starch, and gelrite gum did not swell/dissolve in 0.1N HCl. These are natural polymers that are anionic in nature (46). Being anionic polymers, they have reduced solubility at a pH value lower than their pKa. Abusers use commonly available solvents to dissolve crushed tablets, making it suitable for parenteral administration, they also make a concentrated solution of the dissolved tablet to abuse via oral route. To minimize the abuse, the tablets prepared with polymers (i.e., methyl cellulose, Carbopol 907, Carbopol 940, PEO 5M, PEO 7M, HPMC K15M, and HPMC K100M) that dissolve and swell in all the commonly available solvents were selected for further studies.

5.1.1.2. Viscosity study

The viscosity profile of selected polymeric solutions in various solvents are displayed in Figures 6-10. From Figure 6, it was observed that viscosity of polymeric solutions in water decreases as the with increase in spindle speed at various rpm (rotation per minute) increases. This could be attributed to the shear thinning property of the polymeric solution. The shear thinning property refers to the decrease in the viscosity of a

polymeric solution with increase in the applied shear rate, and the polymeric solution is called a pseudoplastic fluid (46).A portion of a curve from Figure 6 was enlarged in the same figure window at higher rpm (20-100 rpm), and the values of viscosity of polymers at 100 rpm was given in Table 7. From Table 1, it was observed that HPMC K100M showed significantly higher viscosity as compared to all the polymer used in the study ($p > 0.05$ as compared using ANOVA test). This may be observed due to the higher molecular weight of HPMC, since the action of HPMC on liquid uptake depends on the molecular weight. It has been reported that HPMC of a higher molecular weight has a greater liquid uptake capacity that leads to increase in viscosity of HPMC K100M (46).

Pseudoplastic behavior was observed for all the polymers in 10% ethanol, 40% ethanol, 0.1N HCl, and 70% isopropanol (Figure 7-10). From Figure 7,8 and 10, it was observed that viscosity of the polymers in hydroalcoholic solvent increases compared to water. This could be due to the decreased dielectric constant of the hydroalcoholic solutions owing to reduction in the volume of water in the hydroalcoholic solvent. This may have prompted the development of new bonds/structures between the polymer molecules and the solvating media as reported (47). On the other hand, increased ethanol content in the media could have led to formation of stronger gels. The interactions of the polymer solvated by the ethanol were far more prominent than the interactions of the polymer with water because of hydrogen holding and van der waal forces between the ethanol and polymer (48).

Also, HPMC K100M showed significantly higher viscosity compared to other polymers in all the solvents (Table 7). From Figure 9, it was observed that viscosity of all the polymers were reduced in 0.1N HCl compared to other solvents used. This was observed due to conversion of acidic group present on the polymers into protonated acid and that lead to reduction in swelling of the polymers under acidic environment. Viscosity of Carbopol 940 and 71G has not been reported in Figure 9, because viscosity was not detected due to limited torque generation with similar experimental conditions.

Since HPMC K100M showed higher viscosity compared to other polymers at higher rpm, it was selected for further studies. HPMC K100M was also compared with polyethylene oxide (PEO 7M), since PEO 7M has been widely used for abuse-deterrent formulations.

5.1.1.3. Heat induced viscosity study

Based on the results of heat-induced viscosity study as shown in Figure 11, the viscosity of HPMC K100M was observed to be significantly higher as compared to PEO 7M at various temperatures studied ($p > 0.05$ as compared using t-test). Also, it was observed that the viscosity of both polymeric solutions at 100 rpm was reduced with increase in temperature. This was observed due to molecular rearrangement in polymeric solutions at higher temperature. To initiate flow of a polymeric solution, energy (*Ea*) is required to break bonds in liquids composed of molecules that are associated through hydrogen bonds. These bonds are broken at higher temperatures by thermal movement and leads to decrease in viscosity and increase in flowability.

Ea values of HPMC K100 M and PEO 7M solutions were observed to be 4906 cal/mole and 1646 cal/mole at 100 rpm, respectively. This indicates that HPMC K100 M solution requires higher activation energy to initiate flow property. In other words, HPMC K100M would require more force to be withdrawn from a syringe.

5.1.1.4. Syringe-ability study

Figure 12 represents the syringe-ability profile which was plotted based on the data as shown in Table 8, respectively. Based on Table 8, syringe-able force of 2% w/v polymeric solution of HPMC K100M and PEO 7M in water was found to be 14.6 ± 0.7 N and 13.5 ± 2.0 N, respectively (displayed in Figure 12 on positive y-axes). In 10% ethanol, the syringe-ability was found to be 15.5 ± 1.0 N, 13.3 ± 0.9 N, and in 40% ethanol, the syringe-ability was found to be 16.1 ± 0.3 N, 14.7 ± 1.2 N for HPMC K100M and PEO 7M, respectively. Also, the syringe-able force increased with 10% and 40% ethanol compared to water. It was observed due to increase in viscosity of the given polymers in hydroalcoholic solvent (observed from section 5.1.1.2.), which have more swelling capacity in hydroalcoholic solvent and thus requires higher force to be withdrawn by a syringe (i.e., provides higher resistance to syringe-ability). The syringe-able force for HPMC K100M was higher in all the solvents to that of PEO 7M and that indicates HPMC K100M may provide a stronger physical barrier as compared to PEO 7M.

Additionally, as given in Figure 12, the intercept of the curve on negative x-axes represents the volume of solution withdrawn into the syringe through the needle and

values of the volume withdrawn is given in Table 8. It was observed that PEO 7M was syringe-able among all the polymeric solution into the syringe. Whereas, HPMC K100M solution could not be withdrawn into a syringe. Based on this, 2%w/v polymeric solution of HPMC K100M act as a better polymer with physical barrier characteristics compared to PEO 7M. Furthermore, these two polymers were used to prepare abuse deterrent extended release tablet with various type of diluent.

5.1.2. Abuse deterrent potential of metformin HCl ADERT

Abuse deterrent potential of prepared ADERT was characterized using physical and chemical barrier studies.

5.1.2.1 Physical barrier: Screening of type of diluent

Physical barrier of metformin ADERT was characterized by evaluation of Hardness and syringe-ability studies.

5.1.2.1.1 Hardness testing

Hardness of the formulations F1-F12 are displayed in Table 9. Hardness of all the formulations was found to be more than 30 kg. This was attributed to the presence of high molecular weight polymers (PEO 7M or HPMC K100M) in higher amount (150 mg) which act as binders, respectively. As per Table 9, tablet hardness was found to be higher in the formulations F5, F6, F11, and F12, where MCC KG-802 and KG-1000 were used as diluent, respectively. This might be attributed to the needle shape of these novel MCC

grades, which leads to high compression characteristics with lower elastic recovery and makes tablet with higher hardness.

5.1.2.1.2. Syringe-ability study

Figure 13 represents the syringe-ability profile which was plotted based on the data as shown in Table 10, respectively. Based on Table 10, syringe-able force of formulations F7-F12 that contains HPMC K100M was higher (16-20 N) compared to formulation F1-F6 (14-16 N) that contains PEO 7M, and it was increased for all the formulations in hydroalcoholic solvents (10%, and 40% ethanol) compared to water. Both of these observations can be correlated to the viscosity study in which solution of HPMC K100M have higher viscosity compared to PEO 7M solution, and due to increase in swelling capacity of the polymer in hydroalcoholic solvent, it requires higher force to be withdrawn by the syringe. Also, it was observed that similar force was required for formulation F1-F6 and F7-F12 in same solvent. For example, syringe-able force for formulation F1-F6 was found to be around 14 N in water, 14.5 N in 10% ethanol, and 15 N in 40% ethanol. From the data, it was observed that the effect of type of diluent (various type of MCC) has minimum and/or similar impact on syringe-able force.

Corresponding volumes withdrawn (Table 10) during syringe-ability test were found in the range of 1-3.5 mL for formulation F1-F6, and it was less than 1 mL for formulation F7-F12 in all the solvent used. This data corelates to the syringe-ability data (as given is section 5.1.1.4.) for polymeric solutions of HPMC K100M and PEO 7M, where it was found that PEO 7M polymeric solution was more syringe-able as compared

to HPMC K100M. This explains that upon mechanical manipulation of tablets (crushing) and dissolving the powder in various solvents, it would form a gel resulting in difficulty to be withdrawn from the syringe when formulations contain HPMC K100M.

5.1.2.2. Chemical barrier: Drug extraction study

Results for drug extractions are displayed in Figure 14 and Table 11. The viscosity and syringe-ability studies of polymeric solutions (PEO 7M and HPMC K100M) can be correlated with the type of solvent used for drug extraction. For instance, increasing alcohol content (i.e., from 10% to 40%) in the solvent resulted in decreased drug extraction from all formulations (Table 11) as compared to water. As the viscosity of these polymers increases in presence of 10% and 40% ethanol, swelling of polymer increases, respectively. The swollen polymer retards drug diffusion from the polymeric matrix and subsequently reduces drug extraction.

The drug extraction study suggests that both HPMC K100M and PEO 7M have the potential to provide a chemical barrier to minimize extraction in various solvents. However, addition of novel type of diluent, i.e., KG-1000 grades to the formulation (formulation F6 and F12, respectively) increases the hardness of the tablet and leads to reduction in the pores on the surface of a tablet and that results in reduction of drug diffusion and thereby drug extraction (Table 11).

Note: Based on the screening viscosity, syringe-ability, and tablet hardness, and drug extraction studies, it was observed that HPMC K100M could provide better physical

and/or chemical barriers as compared to PEO 7M. Also, MCC KG-1000 grade serves as a better diluent to increase the mechanical strength of tablets (Formulation F12). Hence, Formulation F12 was selected for their abuse deterrent potential with use of various type of model drugs.

5.1.3. Abuse deterrent potential of propranolol HCl ADERT

Abuse deterrent potential of propranolol HCl ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the propranolol HCl ADERT (Formulation P) was found to be 45.7 ± 0.6 kg, which is similar to formulation F12. Drug extraction study of formulation P is displayed in Figure 15. The drug extraction of Formulation P showed similar trend to that of formulation F12.

The hardness and drug extraction were similar for formulation P and F12 since the polymeric matrix are similar. The only difference between formulation P and F12 is the drug, and based on Equation 3, drug solubility is the only parameter that modifies the diffusion of the drug. Propranolol HCl is freely soluble at ~pH 7 of the drug extraction media (Figure 19B). Drug extraction was reduced despite high solubility of drug in hydroalcoholic media (189 ± 9 mg/mL in 10% ethanol and 232 ± 11 mg/mL in 40% ethanol) due to presence of swollen polymer which retards drug diffusion.

5.1.4. Abuse deterrent potential of quinidine sulfate ADERT

Abuse deterrent potential of quinidine sulfate ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the quinidine sulfate ADERT (Formulation Q) was found to be 44.5 ± 0.9 kg. Drug extraction of formulation Q was found to be similar to formulation P (Figure 15). pH of extraction media was found to be around 7, drug solubility is 6.4 ± 0.2 mg/mL at pH 7.1(Figure 27). The solubility of quinidine sulfate in 10% ethanol and 40% ethanol was found to be 44 ± 2 mg/mL and 112 ± 8 mg/mL, respectively. The reduced drug extraction in hydroalcoholic solvent was due to higher swelling of polymer in the media.

5.1.5. Abuse deterrent potential of dipyridamole ADERT

Abuse deterrent potential of dipyridamole ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the dipyridamole ADERT (Formulation D) was found to be 44.6 ± 0.6 kg. As shown in Figure 15, the drug extraction of dipyridamole in water was found to be significantly lower as compared to formulation P and Q. This was observed due to poor solubility of the drug at pH 7, i.e. 0.04 mg/mL (Figure 35). However, the drug extraction of dipyridamole in hydroalcoholic media was similar to formulations P and Q. The solubility was found to be 39 ± 2 mg/mL and 53 ± 3 mg/mL in 10% ethanol and 40% ethanol, respectively.

5.2. Effect of physical and/or chemical barrier on bilayer ADERT

Propranolol HCl (pKa 9.5), quinidine sulfate (pKa 8.5), and dipyridamole (pKa 6.4) loaded bilayer abuse deterrent extended release tablet of were prepared along with alkalizing agent, respectively, to determine their abuse deterrent potential as a chemical barrier.

5.2.1 Effect of alkalizing agent as a chemical barrier on propranolol HCl-loaded bilayer ADERT

Propranolol HCl-loaded bilayer abuse-deterrent extended-release tablets (ADERT) were prepared to screen type of alkalizing agent (Table 12).

5.2.1.1 Screening of alkalizing agent

The alkalizing agent was screened based on ***in-vitro*** drug release study of formulation P1-P4 were carried out in in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours for single unit as well as and multiple units. The drug release profiles, and pH of the release media during drug release are depicted in Figure 16 and 19, respectively. Based on Figure 16, it was observed that the drug release of the formulation P1-P4 was found to be similar to the control formulation for 1, 3, and 5 unit, respectively. No reduction in drug release was observed upon multiple unit drug release study. It was observed due to minimal shift in bulk media pH (Figure 19), and drug solubility was not altered at this pH of the media (i.e., pH of the intestinal media was found to be in a range of 6.5 to 6.8, and the drug solubility of propranolol HCl observed at pH 6.8 was

69.33±2.50 mg/mL). Due to higher solubility of the drug, no reduction in drug release was observed upon multiple unit release study.

The first two hours of the two-stage drug release study reflect the release in FaSSGF of pH 1.6, and the amount of drug released at the end of two hours is represented in Figure 19. In this acidic environment 13.67±1.62 mg of the drug was released after 2 hours from the control ADERT. Based on Equation 2, the drug release from the matrix tablet was majorly controlled by the concentration of the drug at the solid-liquid interphase (diffusion layer) (Cs), concentration of the drug in the bulk media (C) and diffusivity of the drug from polymeric matrix (D) in the bulk media. The pH of the media after two hours was found to be 1.64±0.08 (Figure 19) and the solubility of propranolol HCl at this pH 183.8±3.7 mg/mL (Figure 20). Based on solubility data, the drug is freely solubilized in the acidic environment, and thereby the drug release should not be hindered by the solubility of the drug. However, the limited drug release (i.e. 32.7±1.9%) in FaSSGF was attributed to the presence of high molecular weight HPMC K100M as a release rate controlling polymer. HPMC K100M swells in the media and releases the drug in a controlled manner by slow diffusion from the polymeric matrix.

Similarly, drug release from single unit bilayer ADERT from formulation P1 reflected similar drug release in FaSSGF after the initial two hours (13.10±0.78 mg). The pH modifying layer containing $MgOH_2$ disintegrated quickly (within 30 seconds) once the bilayer ADERT came in contact with the FaSSGF. The pH of the media was found to be 1.92±0.10 after two hours. There was a minimal shift in pH in dissolution media from

single bilayer ADERT to that of the control tablet. This was attributed to the presence of a large quantity of FaSSGF (250 mL) and a limited amount of $MgOH_2$ (100 mg) that is not sufficient to shift the pH of the media. Also, the release profile of formulation P1 in FaSSIF was similar to the control ADERT, due to the similar composition of ingredients in the extended-release layer. Hence, the drug release controlled majorly by the rate-controlling polymer HPMC K100 M in the FaSSIF as well.

To evaluate multidose oral abuse, the drug release study was performed by placing multiple unit bilayer ADERT (3-and 5-unit) at once in the dissolution vessel. Based on Figure 19, the drug release from 3 unit and 5 units of formulation P1 after two hours were found to be 36.76±5.18 mg and 46.95±5.0 mg, respectively. Also, based on Figure 19 A, the pH of the media was raised to 5.45±0.78 and 9.42±0.49 after two hours when 3- and 5-unit bilayer ADERT were studied, respectively. This increase in pH was due to the presence of a higher amount of $MgOH_2$ in the dissolution vessel, which is sufficient to shift to higher pH. Drug release from 3 units was found to be similar to the 3-unit control formulation ADERT, and drug release did not decrease even when a higher amount of alkalizing agent (300 mg of $MgOH_2$) was available to modify pH of the media. This was attributed to solubility of drug at pH 5.45 that is 126.3±5.4 mg/mL, drug release did not decrease as there was presence of sufficient media for complete dissolution of the drug that was released from the ADERT. However, drug release from 5-unit bilayer ADERT of formulation P1 was reduced significantly compared to control formulation. This reduction in the drug release was attributed to reduced solubility (0.72±0.02 mg/mL) of the drug at increased pH of the dissolution medium (pH of 9.4).

As represented in Figure 20, no significant reduction in the drug release was observed for formulation P2, P3, and P4 compared to control ADERT for single and multiple unit ADERT in the FaSSGF. This was attributed to pH shift of the bulk media, none of the alkalizing agents (aluminum hydroxide, calcium carbonate, and calcium hydroxide) raised pH more than 6.5 after 2 hours (Figure 19). Moreover, the solubility of the drug was found to be 83.0±2.1 mg/mL at pH 6.5 and due to high solubility of the drug, the drug release did not decrease in FaSSGF for formulation P2, P3, and P4 for both single as well as multiple unit bilayer ADERT drug release study.

Magnesium hydroxide was selected as an alkalizing agent for further studies, since it shifts pH of media from acidic (pH 1.6) to alkaline (pH 9.2) form drug release studies in FaSSGF compared to aluminum hydroxide, calcium carbonate, and calcium hydroxide. Since $MgOH_2$ can increase bulk media pH up to 9.2 with multiple unit drug release study, it has the potential to act as a chemical barrier that will reduce the solubility of weakly basic drugs.

5.2.2 Abuse deterrent potential of propranolol HCl-loaded bilayer ADERT

5.2.2.1. Physical and chemical barrier

Abuse deterrent potential of propranolol HCl-loaded bilayer ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the formulations P1, P2, P3, and P4 was found to be 46.18 ± 0.37, 46.56 ± 0.94, 47.51 ± 0.82, and 46.06 ± 1.22 kg, respectively. The hardness was similar to the control formulation (formulation P) since MCC KG1000 as a

diluent was used in pH modifying layer and similar compression pressure (2500 lbs) was used to prepare bilayer tablet.

Drug extraction of formulation P1-P4 and their comparison with control formulation (Formulation P) is presented in Figure 20. Based on Figure 20 A, it was observed that the drug extraction of formulations P1-P4 was reduced significantly (less than 1 mg extracted) compared to the control formulation in all solvents. This was observed due to presence of alkalizing agents in all the formulations, the bilayer ADERT disintegrate and raises the pH of the extraction media (Figure 19 B). Solubility of the drug decreases at higher pH (Figure 20) which leads to reduction in drug extraction in water. Also, drug extraction from P1-P4 was found to be reduced in hydroalcoholic solvents compared to control formulation, due to increased pH of the extraction media and increased swelling of polymers in hydroalcoholic solvents resulting in reduction in rug extraction.

5.2.2.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of propranolol HCl-loaded bilayer ADERT

Magnesium hydroxide was incorporated in extended-release layer to minimize drug release upon multiple-unit ingestion (3- or 5-tablet) in both FaSSGF and FaSSIF. Formulations P25, P50, and P75 with various amount of magnesium hydroxide (Table 13) were developed and hardness was found to be 45.21 ± 0.53, 44.15 ± 0.75, and 44.55 ± 0.80 kg for formulations P25, P50, and P75, respectively. Drug extraction of formulation P25, P50, and P75 was not performed due to presence of similar pH

modifying layer as that of formulation P1. Similar pH modifying layer may lead to similar (increased) pH of the extraction media and the drug extraction can be predicted based on the solubility of the drug at higher pH (from Equation 3) and which leads to reduction in diffusion of the drug. Hence, based on the pH values found in Figure 19 B, the drug extraction would be found similar for formulations P25, P50, and P75 as formulation P1.

Drug release from single unit bilayer ADERT is presented in Figure 22. The drug release profiles from formulation P25, P50, and P75 were found to be of similar to the control formulation and formulation P1. However, with increase in the amount of magnesium hydroxide in the extended release layer (formulations P25, P50, and P75) the amount of propranolol HCl released was decreased compared to control formulations. This was due to presence of magnesium hydroxide which leads to increase in microenvironmental pH of formulations P25, P50, and P75 compared to control formulation. Based on the results from Table 16, the microenvironmental pH for the control formulation was found to be 5.56±0.05, 2.85±0.14, and 6.57±0.04 in water, FaSSGF, and FaSSIF, respectively. On the other hand, the values of microenvironmental pH were around 8, 8.4, and 9 for formulations P25, P50, and P75, respectively, in both FaSSGF and FaSSIF (Table 16). Hence, due to increased microenvironmental pH, diffusion of the drug from polymeric matrix reduced slightly from formulations P25, P50, and P75, respectively compared to control formulation.

In-vitro drug release profiles from single and multiple-unit of propranolol HCl-loaded bilayer ADERT of formulation P25, P50, and P75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation are presented in Figure 26. Significant reduction in propranolol HCl release from multiple-unit (3- and 5-tablets) of formulations P25, P50, and P75 compared to multiple-unit of control formulation was observed. In addition, from Figure 26A, it was observed that increasing the amount of magnesium hydroxide in the extended release layer, the amount of propranolol HCl released at 2 hours in FaSSGF was decreased compared to control formulations. Similar results were observed during the additional 22 hours in FaSSIF (Figure 26B).

This reduction in drug release was due to an increase in both microenvironmental pH and bulk media pH which leads to reduction in solubility of propranolol HCl. The values of microenvironmental pH were 8, 8.4, and 9 for formulations P25, P50, and P75, respectively, in both FaSSGF and FaSSIF (Table 16). pH in bulk media with 3-unit bilayer ADERT were 8.7, 8.9, and 9.1, respectively, from formulations P25, P50, and P75 in FaSSGF at 2 hours and 7.8, 8.1, and 8.6 in FaSSIF at additional 22 hours (Figure 27). Also, the values of pH with 5-unit bilayer ADERT were 9.3, 9.35, and 9.4, respectively, from formulations P25, P50, and P75 in FaSSGF at 2 hours and 8.6, 8.8, and 9.2 in FaSSIF at additional 22 hours (Figure 27).

Hence, based on Equation 3, the changes of pH led to reduction in solubility of drug (Figure 21) which leads to reduction in the diffusion of the drug from the various

ADERT formulations. Thus, by change in microenvironmental pH as well as bulk media pH, the drug release can be reduced significantly upon multiple unit drug release study compared to control formulation ADERT. Thus, administering multiple-unit ADERT of formulations P25, P50, and P75 formulated with an opioid drug with pKa of 9.5 (like propranolol HCl) might lead to a reduction in euphoric effect of opioids.

5.2.3 Effect of alkalizing agent as a chemical barrier on quinidine sulfate-loaded bilayer ADERT

In-vitro drug release study of quinidine sulfate loaded bilayer ADERT was determined. The *in-vitro* drug release profiles from quinidine sulfate-loaded bilayer ADERT were found to be similar to that of propranolol HCl-loaded bilayer ADERT. From Figure 28, it was observed that drug release profile of formulation Q1 was similar to control formulation for 1 and 3-unit ADERT. The drug release profile for 5-unit bilayer ADERT of formulation Q1, was significantly less compared to 5-unit control formulation (Figure 28). This reduced drug release in FaSSGF was attributed to increased bulk media pH from 1.6 to 9.21±0.6 (Figure 37) and solubility of quinidine sulfate was reduced to 0.25±0.02 mg/mL at pH 9.2 (Figure 31). Hence, due to reduction in solubility of the drug reduces drug diffusion from the polymeric matrix. However, drug release from 5-unit bilayer ADERT of formulation Q1 was not reduced in FaSSIF. This was attributed to pH of the bulk media which remained around pH 6.9 (Figure 37) and the solubility of quinidine sulfate was found to be 9.15±0.18 mg/mL (Figure 31) at this pH. Due to this high solubility of the drug, drug release was found to be similar for 5-unit ADERT of both control and Q1 formulation s in FaSSIF.

5.2.4. Abuse deterrent potential of quinidine sulfate-loaded bilayer ADERT

5.2.4.1. Physical and chemical barrier

Abuse deterrent potential of quinidine sulfate-loaded bilayer ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the formulations Q1 was found to be 46.80 ± 0.80 kg.

Drug extraction of formulation Q1 was found to be similar to formulation P1. Drug extraction of formulation Q1 and their comparison with control formulation (Formulation Q) is presented in Figure 26. Based on Figure 30 A, it was observed that the drug extraction of formulation Q1 was reduced significantly (less than 1 mg extracted) compared to control formulation in all the solvents. This was observed due to presence of magnesium hydroxide in all the formulations which raises the pH of the extraction media (Figure 30 B). Solubility of the drug decreases at higher pH (Figure 37)which leads to reduction in drug extraction in water.

5.2.4.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of quinidine sulfate-loaded bilayer ADERT

Similar to propranolol HCl-loaded bilayer ADERT, to minimize drug release for multiple unit (3-and 5-unit) study, various amounts of magnesium hydroxide were added to extended release layer of the bilayer ADERT (Table 15). Hardness of the formulations Q25, Q50, and Q75 was found to be 45.76 ± 0.76, 44.23 ± 0.83, and 44.00 ± 1.91 kg, respectively.

From Figure 32, similar trend in drug release profiles were observed for single unit ADERT of various formulations Q25, Q50, and Q75 to that control formulation, and drug release was found to be similar for single unit formulations containing propranolol HCl (P25, P50, and P75). From Figure 32, a slight reduction in drug release with increased amount of magnesium hydroxide in the formulations was observed. This reduced drug release was due to increase in microenvironment pH. The values of microenvironmental pH were around 7.9, 8.4, and 9.3 for formulations Q25, Q50, and Q75, respectively, in both FaSSGF and FaSSIF (Table 16) and due to increased microenvironmental pH, the diffusion of the drug from polymeric matrix was reduced slightly from formulations Q25, Q50, and Q75, respectively compared to control formulation.

In-vitro drug release profiles from single and multiple-unit of propranolol HCl-loaded bilayer ADERT of formulation Q25, Q50, and Q75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation are presented in Figure 34. Similar to the formulations prepared with propranolol HCl, there was significant reduction in release profiles from multiple-unit (3- and 5-unit) of formulations Q25, Q50, and Q75 as compared to multiple-unit of control formulation were observed. Also, from Figure 36 A and B, it was observed that with increase in the amount of magnesium hydroxide in the extended release layer, amount of quinidine sulfate released at 2 hours in FaSSGF and at additional 22 hours in FaSSIF were decreased compared to control formulations.

Due to the presence of magnesium hydroxide in both the layers, reduction in drug release was observed. This was attributed to increase in both microenvironmental pH and bulk media pH which leads to reduction in solubility of quinidine sulfate. The values of microenvironmental pH were 7.9, 8.4, and 9.3 for formulations Q25, Q50, and Q75, respectively, in both FaSSGF and FaSSIF (Table 16). Also, the bulk media pH with 3-unit bilayer ADERT were 8.7, 8.9, and 9.1, respectively, from formulations Q25, Q50, and Q75 in FaSSGF at 2 hours and 7.8, 8.2, and 8.6 in FaSSIF at additional 22 hours (Figure 37). Bulk media pH with 5-unit bilayer ADERT were 9.3, 9.35, and 9.4, respectively, from formulations Q25, Q50, and Q75 in FaSSGF at 2 hours and 8.6, 8.8, and 9.2 in FaSSIF at additional 22 hours (Figure 37).

The change in both bulk media and microenvironmental pH values led to reduction in solubility of drug (Figure 31) which leads to reduction in diffusion of the drug from various ADERT formulations. Accordingly, consuming multiple-unit ADERT of formulations Q25, Q50, and Q75 formulated with an opioid drug with pKa of 8.5 (like quinidine sulfate) might lead to a reduction in euphoric effect of opioids.

5.2.5 Effect of alkalizing agent as a chemical barrier on dipyridamole-loaded bilayer ADERT

5.2.5.1. Abuse deterrent potential of dipyridamole-loaded bilayer ADERT

Abuse deterrent potential of dipyridamole-loaded bilayer ADERT was characterized using hardness testing as a physical barrier and drug extraction study as a chemical barrier study. Hardness of the formulations D1 was found to be 45.90 ± 0.70 kg.

Drug extraction of formulation D1 is presented in Figure 42. Based on Figure 42 A, it was observed drug extraction was reduced in all the solvents used as compared to the control formulation. It was reduced due to increased pH of the extraction media (Figure 42 B) due to presence of magnesium hydroxide. This increased pH (>10.3) leads to reduced solubility of dipyridamole (Figure 43) and thereby resulting in reduced drug diffusion from the polymeric matrix.

5.2.5.2. Effect of magnesium hydroxide on in-vitro drug release from oral multiple-unit abuse of dipyridamole-loaded bilayer ADERT

Drug release profiles for single and multiple unit ADERT from control and D1 formulations are presented in Figure 38. Based on Figure 38, drug release profile for single unit control formulation was incomplete and 15.5±0.9 mg of drug released at the end of 24 hours of study. This incomplete drug release was observed due to shift in pH by use of FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and thereby solubility of dipyridamole changed with change in media. From Figure 40, it was observed that after addition of FaSSIF, the pH of the media shifted to 6.5. Due to limited solubility of dipyridamole in the FaSSIF at pH 6.5 [solubility of 0.051±0.011 mg/mL at pH 6.5 (Figure 43)] which leads to incomplete release of dipyridamole (due to saturation of the drug in the dissolution vessel) from the single unit control and D1 formulations.

Also, drug release from 3-and 5-unit control formation showed higher drug release in the FaSSGF and the drug release reduced in the FaSSIF. This type of drug

release was observed due to higher solubility of dipyridamole in FaSSGF (27.0±0.9 mg/mL in FaSSGF pH 1.6) and reduced solubility in FaSSIF (0.051±0.011 mg/mL in in FaSSGF pH 6.5). Thereby, based on Equation 2, reduced solubility of the drug in FaSSIF resulted in reduced drug release in FaSSIF. On the other hand, drug release from 3-and 5-unit D1 formation showed minimal drug release in both the medias. This minimal drug release was due to release of higher amount of magnesium hydroxide leading to increased pH of the media, thereby reduced solubility of dipyridamole.

Figure 33 reflects effect of alkalizing agents on *in-vitro* drug release profiles from oral multiple-unit of dipyridamole-loaded bilayer ADERT of formulation D1 in FaSSGF for 2 hours and their comparison with control formulation. Drug release was found to be similar for single unit control and D1 formulations in FaSSGF. Limited amount of magnesium hydroxide released and pH of the media (Figure 41) was found to be similar for both the formulations. However, with multiple unit (3-and 5-unit) drug release study in FaSSGF significant reduction in drug release was observed (Figure 40). This was attributed to increase in the pH of bulk medium at 5.12 ±0.12 and 9.24±0.10 for 3-and 5-unit of D1 formulation, respectively. Drug solubility at pH 5.1 was found to be 0.23±0.03 mg/mL and at pH 9.2 to be 0.015±0.001 mg/mL. Based on Equation 3, these reduced solubilities at various pH leads to precipitation of the drug and thereby reduction in drug release was observed.

The change in bulk media pH in FaSSGF led to reduction in solubility, and lower solubility of drug in the FaSSIF leads to reduction in diffusion of the drug from the D1

formulation with multiple unit release study. Accordingly, administering multiple-unit ADERT of formulations D1 formulated with an opioid drug with pKa of 6.5 (like dipyridamole) might lead to a reduction in euphoric effect of the opioid.

6. CONCLUSION

In this investigation, bilayer ADERTs of opioids could be successfully developed from an HPMC K100M matrix and novel MCC KG-1000 formulated in extended release layer coupled with an alkalizing agent in pH modifying layer using various model drugs. HPMC K100M and MCC KG-1000 were selected based on preliminary studies i.e., hardness, syringe-ability, and drug extraction. Bilayer ADERTs were developed and based on multiple-unit *in-vitro* drug release studies, magnesium hydroxide was selected as an alkalizing agent that was incorporated not only in pH modifying layer, but also in extended-release layers of bilayer ADERTs. The singe-unit drug release for the bilayer ADERTs was found to be similar to that of control formulation. whereas the multiple-unit drug release revealed that the drug release was reduced significantly compared to control formulation for all the model drugs. This indicates that the bilayer ADERTs approach could minimize oral multiple-unit abuse by modifying both micro-environmental and bulk media pH resulted in low solubility of drug suggesting their potential to minimize drug abuse.

SUGGESTIONS FROM COMMITTEE MEMBERS

1. Perform drug release study for Formulations F6 and F12

Drug release study for formulations F6 and F12 was performed as per similar method as described in section 4.4.1.2.1 and the result of drug release study shown in Figure 44. Based on the drug release study, it was observed that both the formulations show similar drug release profile. This could be attributed due to high molecular weight of both PEO 7M (present in formulation F6) and HPMC K100M (present in formulation F12) and it leads to swelling of polymers in the aqueous environment. The drug release slowly from high swellable polymeric matrix and releases drug up to 24 hours. Also, similar drug release study supports the drug extraction study where both formulations shown similar drug extraction in all the solvent used. Hence, HPMC K100M can be a better alternative compared to PEO based on better abuse deterrent potential and similar drug release behavior.

2. Perform inject-ability study for formulations F6 and F12

Powder sample (of prepared ADERT) of 500 mg (i.e., one tablet) from F6 and F12 formulations was weighed accurately and transferred into separate 20 ml scintillation vials, each containing 10 ml of commonly injectable solvents that are distilled water, 10%, and 40% ethanol, respectively, at room temperature. The scintillation vials were vortexed for 30 seconds and left for hydration for 30 min before the tests. The prepared solution was manually inserted into the syringe and needle was attached to the syringe. Inject-ability study of ADERT powder blend was performed by *TA.XTPlus Texture Analyzer (Texture Technologies Corp., Hamilton, MA)* equipped with a syringe assembly

set. A 5 ml syringe fitted with a 21-gauge needle was used for each test. Tension mode was set for 1 mm/s test speed and 0.05 N trigger force. The syringe plunger was set to move a distance of 40 mm in plunging direction. The target mode was set to record force that the sample plunger experience while pushing the solutions.

The results of inject-ability study are shown in Figure 45 and force required to push the syringe is displayed in Table 17. Based on the results it was observed that formulation F12 shows higher force in all the solvents used compared to that of formulation F6. This was observed due to presence of HPMC K100M in formulation F12, which has higher swelling capacity compared to PEO 7M (present in formulation F6). Apart from that, the Also, the force was increased in hydroalcoholic solvents compared to water. This supports the viscosity study in hydroalcoholic solvents, since the viscosity of both polymers increases in hydroalcoholic solvents that leads to increased force for inject-ability.

3. Limitation of the research

The objective of the research is to minimize opioid overdose crisis. The studies conducted were aimed to minimize abuse potential for multiple-unit oral ingestion and reduce intravenous injection abuse.

Based on the outcome of the studies, when multiple-unit intact bilayer ADERTs taken, the drug release will be reduced based on reduced solubility of the drug at higher pH environment. However, when crushed ADERTs taken orally, it will reduce drug release up to 2 hours, and thereafter the higher amount of drug will be available for the

absorption. Hence, the concept of bilayer ADERT with alkalizing agent is effective to reduce multiple-unit drug release only when intact bilayer tablets taken.

Also, even the hardness of the tablets was found to be around 50 kg, they can still be reduced in smaller particles by using coffee grinder and can be abused by nasal insufflation. Particle size distribution of formulation F12 was carried out by performing physical manipulation. A coffee grinder (Brew berry, Bangkok) was used for physical manipulation of the ADERT. The ADERT (10-units) were subjected to high shear grinding for 2 min using a coffee grinder and the resultant material was subjected to particle size distribution by sieve analysis. The crushed material was applied to sieve stack which included U.S. Standard sieves no. 35 (500 μm), no. 40 (425 μm), no. 50 (300 μm), no. 80 (180 μm), no. 120 (125 μm), and no. 170 (90 μm). The sieves were set on an electric sieve shaker for 5 minutes that operates in both vertical and horizontal tapping. After that, the materials were collected from each sieve and the percentage weight of powder collected on each sieve was determined. The percent of particles with size less than 500mm was also recorded. Similar study was performed on cured ADERT where, ADERTs subjected for 130 ºC for 30 minutes in hot air oven to increase physical strength in terms of hardness and cool down for 30 minutes and subjected to particle size distribution study.

The results of particle size distribution study are displayed in Table 18. Based on the outcomes it was observed that more than 40% of the crushed particles found to be less than 500 micron for both before and after curing at higher temperature. There was no significant difference observed after curing ADERTs at higher temperature. It was observed due to high glass transition temperature of the polymer HPMC K100M and that

leads to minimum impact on the hardness. Hence, the selected formulation F12 can be abused via nasal insufflation if the ADERTs are subjected to particle size distribution using coffee grinder.

7. TABLES

Table 1: Opioid products with abuse deterrent properties

Product	Active ingredient	Polymer as extended release	Abuse deterrent approaches		Product status	References
			Physical barrier	Other		
OxyContin® extended-release tablets	Oxycodone HCl	PEO	PEO	Staining agent (Aversive agent)	Approved -2010	(24,49–52)
EXALGO® extended-release tablets	Hydromorphone HCl	PEO/ Cellulose acetate	PEO/ Cellulose acetate	Staining agent (Aversive agent)	Approved -2010	(24,51,53)
OPANA® ER extended-release tablets	Oxymorphone HCl	PEO	PEO	-	Approved -2011	(24,54)
NUCYNTA® ER extended-release tablets	Tapentadol HCl	PEO	PEO	Staining agent (Aversive agent)	Approved -2011	(24,55)
ZOHYDRO® ER extended-release capsules	Hydrocodone bitartrate	PEO	PEO	Staining agent (Aversive agent)	Approved -2013	(24,56)
TARGINIQ® ER extended-release tablets	Oxycodone HCl and Naloxone HCl	PEO	PEO	-	Approved -2014	(24,51,52)

HYSINGLA™ ER extended-release tablets	Hydrocodone bitartrate	PEO	PEO	-	Approved-2014	(24,51,52,57)
XARTEMIS® XR extended-release tablets	Oxycodone HCl and acetaminophen	PEO	PEO	-	Approved-2014	(24)
MORPHABOND™ extended-release tablets	Morphine sulfate pentahydrate	Xanthan gum/ HPMC	Xanthan gum/ HPMC	Staining agent (Aversive agent)	Approved-2015	(24,52,58)
Xtampza® ER controlled-release capsules	Oxycodone free base	Fatty acid/wax	Fatty acid/wax	Staining agent (Aversive agent)	Approved-2016	(24,52,59)
ARYMO® ER extended-release tablets	Morphine sulfate penthydrate	Ethyl-cellulose	Cetostearyl alcohol/ ethyl-cellulose	-	NDA filed in 2015.	(24,52,60,61)
Vantrela® extended-release tablets	Hydrocodone bitartrate	Lipids	Lipids	-	NDA filed in 2015	(24,52,61)

REMOXY® extended-release capsules	Oxycodone base or HCl salt	Sucrose acetate isobutyrate	Sucrose acetate isobutyrate	-	NDA filed in 2016	(24)
Egalet 002 ER extended-release tablets	Oxycodone HCl	Ethyl-cellulose	Cetostearyl alcohol/ ethyl-cellulose	-	Phase 3	(24,52)
LEVOCAP® ER extended-release capsules	Levorphanol tartrate	Lipids	Mixed lipids	-	Phase 2	(24,52)
FT227 extended-release tablets	Hydromorphone HCl	Ethyl-cellulose	Castor oil/PEG 40 hydrogenated castor oil/ ethyl-cellulose	-	Phase 2	(24,52)
OXAYDO® immediate-release tablets	Oxycodone HCl	-	PEO	Irritant agent (Aversive agent)	Approved -2011	(24,62,63)

Table 2: Classification of polymers used for extended release characteristics

Sr. No.	Class of material		Example	References
1	Hydrophilic polymers			
	1.1	Natural gums	Guar gum, locust bean gum, tragacanth, pectin, xanthan gum, gelrite gum	(64–68)
	1.2	Cellulose derivatives	Methyl cellulose, hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC) K4M, K15M, K100M, sodium carboxy methyl cellulose (Na CMC)	(64,65,67–71)
	1.3	Non cellulose natural	Alginates, carob gum, chitosan, modified starches	(64,65,68–70)
	1.4	Non cellulose semi-synthetic	Polyethylene oxide (PEO)-100000, PEO-300000, PEO-1M, PEO-3M, PEO-7M homopolymers and copolymers of acrylic acid, derivatives of methacrylic acid	(64,65,67,68,72)
	1.5	Polymer of acrylic acid	Carbopol-934, carbopol-907, carbopol-940	(64–69)
2	Lipids		Carnauba wax in combination with stearyl alcohol, beeswax, Compritol®, Gelucire® 43/01, 39/01, 33/01, 50/02, and 54/02	(65,69,73,74)
3	Hydrophobic polymers		Ethylcellulose, hypromellose acetate succinate, cellulose acetate, cellulose acetate propionate, methacrylic copolymers, polyvinyl acetate, polyethylene	(65–67,69)
4	Biodegradable polymers		Poly lactic acid (PLA), poly glycolic acid (PGA), poly (lactide-co-glycolide) (PLGA), polyhydroxybutyrate (PHB), poly (e-caprolactone) (PCL), polyamide, polyanhydrides, proteins, polysaccharides.	(65,67,69,75)

Table 3: Commercial available opioid products containing antagonist (24)

Product	Manufacturer	Active ingredient	Antagonist	Design features	Product status
Talwin® Nx Oral tablet	Sanofi Aventis	Pentazocine HCl	Naloxone HCl	Immediate release tablet	FDA approved in 1982
Embeda® ER capsule	King Pharmaceuticals Inc.	Morphine sulfate	Naltrexone HCl	Extended-release oral capsules	Approved in 2009
Suboxone® Sublingual film	Reckitt Benckiser Pharmaceuticals Inc.	Buprenorphine HCl	Naloxone HCl	IR tablet and film	Approved: tablet in 2002 film in 2010
Zubsolve® Sublingual tablet and film	OREXO AB	Buprenorphine HCl	Naloxone HCl	IR tablet with improved bioavailability	Approved in 2013
Bunavail® Buccal film	BioDelivery Sciences International, Inc	Buprenorphine HCl	Naloxone HCl	IR film	Approved in 2014
Targiniq® ER tablet	Purdue Pharma	Oxicodone HCl	Naloxone HCl	Extended-release tablet	Approved in 2014
ALO-02	Pfizer, Inc	Oxicodone HCl	Naltrexone HCl	Extended-release oral capsules	NDA filed in 2015

Table 4: List of common aversion agents used in abuse deterrent formulations (24)

Type	Aversive agent examples	Undesired pharmacological effects
Bittering agent	Denatonium benzoate, eucalyptus oil, menthol, sucrose octa-acetate and other sucrose derivatives	Causes a bitter taste to reduce abuse by oral or inhalation
Emetic agent	Cephaeline, ipecac, zinc sulfate	Causes vomiting if greater than prescribed amount is ingested
Gelling agent	Carbomer, HPMC, poly(vinyl alcohol), PEO	Produce nasal discomfort upon gelling in contact with mucous membrane
Irritant agent	Capsaicin and other capsaicinoids, citric acid and other acids, surfactants (e.g. sodium lauryl sulfate, poloxamer, sorbitan monoesters, glyceryl mono-oleates)	Induces pain and irritation of abuser's mucous membrane and/or respiratory passageway tissue
Laxative agent	Aloin, bisacodyl, casanthranol, castor oil, senna, sodium dioctyl sulfosuccinate	Causes stools to loosen and/or increase bowel movements if greater than prescribed amount is ingested
Staining agent	Beta-Carotene, food, drug and cosmetic color (e.g., indigo carmine) and other dyes and lakes	Stain tissues in contact with staining agent upon manipulation or administration
Vasodilator	Niacin	Causes warm flushing syndrome, itching and sweating effects

Table 5: Effect of polymeric solutions (2% w/v) as a physical barrier: Swelling behavior of polymers (data are presented as mean ± standard deviation, n = 3)

Polymer type	Swelling behavior				
	Water	10% Ethanol	40% Ethanol	70% IPA	0.1N HCl
Xanthan gum	√	√	√	√	X
Corn Starch	√	√	√	√	X
Gelrite gum	√	√	√	√	X
Chitosan	X	X	X	X	√
Locust bean gum	√	√	√	√	X
Na CMC	√	√	√	√	X
Methyl cellulose	√	√	√	√	√
Carbopol 907	√	√	√	√	√
Carbopol 940	√	√	√	√	√
PEO 5M	√	√	√	√	√
PEO 7M	√	√	√	√	√
HPMC K15M	√	√	√	√	√
HPMC K100M	√	√	√	√	√

Note: √ represents swelling in given solvent, and X represents did not swell in given solvent

Table 6: Physicochemical properties of various opioid and model drugs

Drug	Molecular weight (gm/mole)	pKa	log P	Aqueous solubility (mg/L)	References
Opioids					
Dextropropoxyphene HCl	357.93	9.52	4.06	4.19	(76)
Codeine phosphate	397.40	9.19	1.40	100000	(77)
Methadone	309.44	9.12	4.14	5.90	(78)
Morphine sulfate	668.80	9.12	0.89	10200	(79)
Fentanyl	336.47	8.77	4.05	24	(80)
Hydrocodone bitartrate	449.46	8.61	2.13	62000	(81)
Hydromorphone HCl	321.80	8.59	0.11	4390	(82)
Oxycodone HCl	351.80	8.53	1.04	100000	(83)
Oxymorphone	301.33	8.21	0.83	25600	(84)
Meperidine HCl	283.79	8.16	2.90	62000	(85)
Remifentanil	376.40	7.10	1.75	591	(85)
Alfentanil HCl	471.00	6.50	2.20	252	(85)
Model drugs					
Propranolol HCl	295.80	9.45	2.58	50000	(86)
Quinidine sulfate	746.90	8.50	2.82	11000	(87)
Dipyridamole	504.60	6.40	1.52	922	

Table 7: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in various solvents at 100 rpm

Polymer	Viscosity at 100 rpm				
	Water	10 % ethanol	40 % ethanol	0.1 N HCl	70 % IPA
PEO 7M	286 ± 11	306 ± 32	423 ± 29	200 ± 3	330 ± 4
Carbopol 940	287 ± 52	330 ± 7	485 ± 25	NA	377 ± 10
Carbopol 71G	117 ± 8	145 ± 12	262 ± 15	NA	217 ± 25
HPMC K15M	288 ± 25	317 ± 4	415 ± 15	199 ± 3	200 ± 9
Methyl cellulose	73 ± 2	128 ± 7	229 ± 11	81 ± 5	121 ± 5
PEO 5M	202 ± 6	208 ± 8	302 ± 6	108 ± 10	217 ± 25
HPMC K100 M*	737 ± 22	820 ± 16	952 ± 13	609 ± 49	502± 28

*Represents significantly different from other polymers $p<0.05$; data are presented as mean ± standard deviation, n = 3

Table 8: Effect of polymeric solutions (2% w/v) as a physical barrier: Syringe-ability parameters of polymeric solutions (data represent mean ± standard deviation, n = 3-5)

Formulation code	Syringe-ability					
	Force (N)	Volume withdrawn (ml)	Force (N)	Volume withdrawn (ml)	Force (N)	Volume withdrawn (ml)
HPMC K100M	14.6 ± 0.7	-	15.5 ± 1.0	-	16.1 ± 0.3	-
PEO 7M	13.5 ± 2.0	3.1 ± 0.6	13.3 ± 0.9	2.9 ± 0.9	14.7 ± 1.2	1.0 ± 0.2

Table 9: Comparison of hardness of tablet formulations, formulated with screened polymers containing 40 mg metformin HCl in each tablet (data represent mean ± standard deviation, n = 3).

Formulation code	Type of polymer	Type of diluent	Hardness (kg)
F1	PEO 7M	MCC PH-101	33.3 ± 1.1
F2	PEO 7M	MCC PH-102	33.1 ± 0.2
F3	PEO 7M	MCC UF-702	35.6 ± 0.5
F4	PEO 7M	MCC UF-711	37.0 ± 1.0
F5	PEO 7M	MCC KG-802	41.6 ± 1.8
F6	PEO 7M	MCC KG-1000	41.1 ± 0.8
F7	HPMC K100 M	MCC PH-101	29.6 ± 1.2
F8	HPMC K100 M	MCC PH-102	28.6 ± 0.6
F9	HPMC K100 M	MCC UF-702	31.9 ± 1.6
F10	HPMC K100 M	MCC UF-711	35.2 ± 1.3
F11	HPMC K100 M	MCC KG-802	40.2 ± 0.7
F12	HPMC K100 M	MCC KG-1000	42.8 ± 0.8

Composition of tablets was drug, polymer, MCC, and magnesium stearate at ratio of 8:30:61.5:0.5.

Table 10: Syringe-ability parameters of metformin HCl-loaded ADERT in various solvents (data represent mean ± standard deviation, n = 3-5)

Formulation code	Syringe-ability parameters					
	Water		10% Ethanol		40% Ethanol	
	Force (N)	Volume withdrawn (mL)	Force (N)	Volume withdrawn (mL)	Force (N)	Volume withdrawn (mL)
F1	14.1 ± 0.8	3.5 ± 0.2	13.8 ± 2.1	3.0 ± 0.4	15.8 ± 0.8	1.7 ± 0.1
F2	14.4 ± 0.8	2.6 ± 0.5	14.88 ± 1.0	2.3 ± 0.4	15.1 ± 1.0	1.7 ± 0.5
F3	14.2 ± 2.0	3.0 ± 0.4	14.7 ± 1.6	2.2 ± 0.1	14.3 ± 2.0	1.8 ± 0.2
F4	12.8 ± 2.4	2.8 ± 0.2	14.1 ± 2.0	2.8 ± 0.1	13.7 ± 1.8	0.9 ± 0.4
F5	13.5 ± 1.3	2.2 ± 0.2	15.3 ± 1.4	2.1 ± 0.4	14.6 ± 4.0	2.2 ± 0.1
F6	14.8 ± 1.2	1.6 ± 0.5	14.4 ± 2.6	2.5 ± 0.3	14.7 ± 0.6	2.2 ± 0.3
F7	16.3 ± 1.6	0.9 ± 0.1	17.3 ± 1.0	0.7 ± 0.1	18.7 ± 3.0	0.3 ± 0.2
F8	16.6 ± 1.1	0.6 ± 0.1	18.1 ± 1.3	0.5 ± 0.1	18.5 ± 2.3	0.3 ± 0.1
F9	16.5 ± 0.6	0.7 ± 0.3	17.7 ± 0.3	0.4 ± 0.1	19.3 ± 1.4	0.3 ± 0.2
F10	17.9 ± 3.2	0.5 ± 0.3	18.6 ± 0.5	0.5 ± 0.0	20.2 ± 5.1	0.2 ± 0.0
F11	16.0 ± 0.5	0.8 ± 0.2	16.3 ± 0.6	0.4 ± 0.2	18.3 ± 0.7	0.4 ± 0.1
F12	17.0 ± 0.4	0.6 ± 0.2	17.4 ± 0.1	0.4 ± 0.0	19.8 ± 2.0	0.2 ± 0.0

Table 11: Effect of excipients as a chemical barrier: drug extraction study of metformin HCl-loaded ADERT in various solvents (data represent mean ± standard deviation, n = 3-5)

Formulation code	Water (%)		10% ethanol (%)		40% ethanol (%)	
	5 min	30 min	5 min	30 min	5 min	30 min
F1	2.9 ± 0.1	6.0 ± 0.5	2.3 ± 0.1	5.1 ± 0.3	1.5 ± 0.1	4.7 ± 0.3
F2	3.2 ± 0.2	7.8 ± 0.3	2.6 ± 0.1	5.9 ± 0.7	1.9 ± 0.2	5.5 ± 0.7
F3	2.9 ± 0.2	7.3 ± 0.2	2.0 ± 0.4	5.5 ± 0.6	1.7 ± 0.2	5.5 ± 0.4
F4	2.7 ± 0.4	7.1 ± 0.7	2.1 ± 0.2	5.6 ± 0.6	0.9 ± 0.1	3.3 ± 0.4
F5	2.6 ± 0.2	5.5 ± 0.5	2.6 ± 0.1	4.5 ± 0.2	2.3 ± 0.2	4.0 ± 0.5
F6	2.3 ± 0.1	5.9 ± 0.6	1.9 ± 0.3	5.5 ± 0.2	1.3 ± 0.2	3.9 ± 0.1
F7	3.8 ± 0.2	10.1 ± 0.4	2.8 ± 0.1	7.3 ± 0.5	1.9 ± 0.2	4.6 ± 0.2
F8	3.9 ± 0.3	10.9 ± 0.2	3.2 ± 0.2	8.05 ± 0.3	2.6 ± 0.2	5.6 ± 0.6
F9	3.7 ± 0.2	8.9 ± 0.4	2.8 ± 0.1	7.9 ± 0.7	1.7 ± 0.1	5.7 ± 1.6
F10	3.2 ± 0.3	8.8 ± 0.4	2.7 ± 0.3	8.0 ± 0.5	2.0 ± 0.3	5.8 ± 0.3
F11	3.1 ± 0.4	8.3 ± 0.3	2.8 ± 0.1	7.0 ± 0.3	2.0 ± 0.1	5.0 ± 0.2
F12	2.3 ± 0.2	6.5 ± 0.1	1.8 ± 0.1	5.7 ± 0.2	1.7 ± 0.1	3.8 ± 0.2

Table 12: Screening of alkalizing agent to be incorporated in pH modifying layer of propranolol hydrochloride-loaded bilayer ADERT

Composition	pH modifying layer			
	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)
Kollidon® CL-SF	10	10	10	10
Magnesium stearate	1	1	1	1
Magnesium hydroxide ($MgOH_2$)	100	-	-	-
Aluminum hydroxide [$Al(OH)_3$]	-	100	-	-
Calcium carbonate ($CaCO_3$)	-	-	100	
Calcium hydroxide [$Ca(OH)_2$]	-	-	-	100
MCC KG-1000	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200

Note: All formulations contain similar extended release layer (total amount: 500 mg) composed of propranolol hydrochloride (40 mg), HPMC K100M (150 mg), magnesium stearate (2.5 mg), and MCC KG-1000 (307.5 mg). Control formulation contains similar composition as of an extended release layer

Table 13: Formulation compositions of propranolol hydrochloride-loaded bilayer ADERT formulated with various amount of magnesium hydroxide in extended release layer

Composition	Extended release layer		
	P25 (mg)	P50 (mg)	P75 (mg)
Propranolol HCl	40	40	4
HPMC K 100M	150	150	150
Magnesium stearate	2.5	2.5	2.5
Magnesium hydroxide	25	50	75
MCC KG-1000	q.s. to 500	q.s. to 500	q.s. to 500

All formulations contain similar pH modifying layer (total amount: 200 mg) composed of Kollidon® CL-SF (10 mg), magnesium hydroxide (100 mg), magnesium stearate (1 mg), and MCC KG-1000 (89 mg). Control formulation contains similar composition as of an extended release layer

Table 14: Formulation compositions of quinidine sulfate and dipyridamole-loaded bilayer ADERT

Composition	Extended release layer	
	Q1 (mg)	D1 (mg)
Quinidine sulfate	40	-
Dipyridamole	-	40
HPMC K 100M	150	150
Magnesium stearate	2.5	2.5
MCC KG-1000	q.s. to 500	q.s. to 500

All formulations contain similar pH modifying layer (total amount: 200 mg) composed of Kollidon® CL-SF (10 mg), magnesium hydroxide (100 mg), magnesium stearate (1 mg), and MCC KG-1000 (89 mg). Control formulation contains similar composition as of an extended release layer

Table 15: Formulation compositions of quinidine sulfate-loaded bilayer ADERT formulated with various amount of magnesium hydroxide in extended release layer

Composition	Extended release layer		
	Q25 (mg)	Q50 (mg)	Q75 (mg)
Quinidine sulfate	40	40	40
HPMC K 100M	150	150	150
Magnesium stearate	2.5	2.5	2.5
Magnesium hydroxide	25	50	75
MCC KG-1000	q.s. to 500	q.s. to 500	q.s. to 500

All formulations contain similar pH modifying layer (total amount: 200 mg) composed of Kollidon® CL-SF (10 mg), magnesium hydroxide (100 mg), magnesium stearate (1 mg), and MCC KG-1000 (89 mg). Control formulation contains similar composition as of an extended release layer

Table 16: Microenvironmental pH for various formulations (data represent mean ± standard deviation, n = 3)

Drug	Solvent	Formulation code			
		Control	P25	P50	P75
Propranolol HCl	Water	5.56 ± 0.05	7.93 ± 0.14	8.56 ± 0.11	8.88 ± 0.15
	FaSSGF	2.85 ± 0.14	7.95 ± 0.13	8.39 ± 0.10	8.95 ± 0.14
	FaSSIF	6.57 ± 0.04	7.89 ± 0.16	8.30 ± 0.15	8.84 ± 0.16
Quinidine sulfate	Water	6.00 ± 0.20	7.85 ± 0.10	8.21 ± 0.10	9.32 ± 0.20
	FaSSGF	3.90 ± 0.03	7.90 ± 0.12	8.40 ± 0.24	9.19 ± 0.16
	FaSSIF	6.56 ± 0.06	7.98 ± 0.08	8.38 ± 0.24	9.25 ± 0.12

Table 17: Effect of polymeric solutions (2% w/v) as a physical barrier: Inject-ability force of polymeric solutions (data represent mean ± standard deviation, n = 3)

Formulation code	Solvent	Force (N)
F6	Water	4.73 ± 1.58
	10% ethanol	7.40 ± 0.67
	40% ethanol	9.05 ± 1.91
F12	Water	13.23 ± 2.53
	10% ethanol	19.81 ± 2.16
	40% ethanol	21.80 ± 2.40

Table 18: Particle size-distribution of crushed tablets (data represent mean ± standard deviation, n = 3)

Sieve no.	Particle Size (um)	% Particle retained before curing	% Particle retained after curing
35	500	39.01 ± 2.52	44.11 ± 5.64
40	425	7.77 ± 1.46	6.18 ± 0.94
50	300	11.66 ± 0.75	10.12 ± 2.00
80	180	11.39 ± 0.46	9.10 ± 1.65
120	125	6.16 ± 0.70	4.78 ± 1.22
170	90	5.90 ± 0.35	5.76 ± 0.39
Pan	-	18.07 ± 0.85	20.00 ± 4.85

8. FIGURES

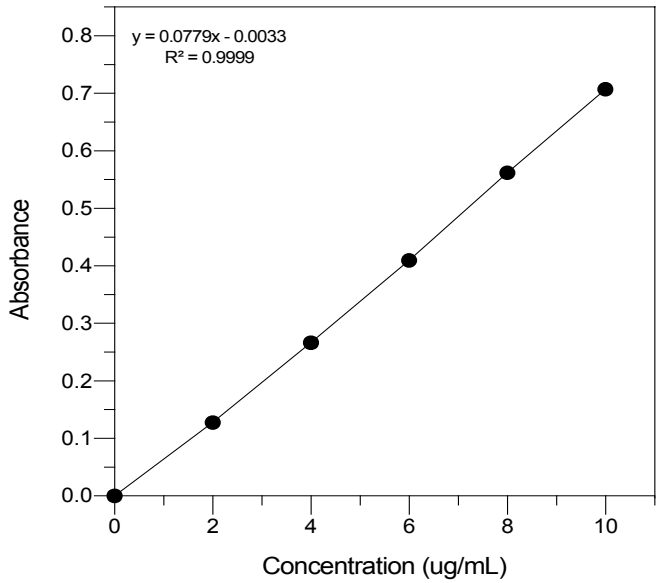

Figure 1. Calibration curve of metformin HCl assayed by UV-spectroscopy

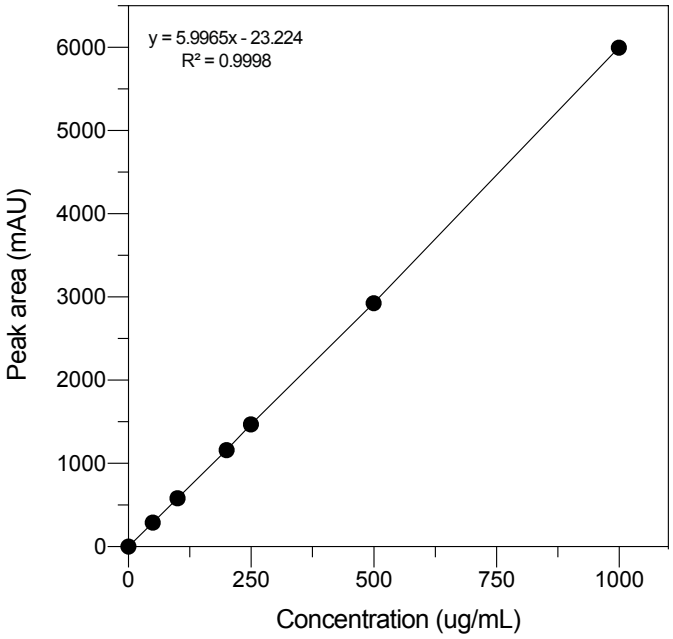

Figure 2. Calibration curve of propranolol HCl assayed by HPLC method

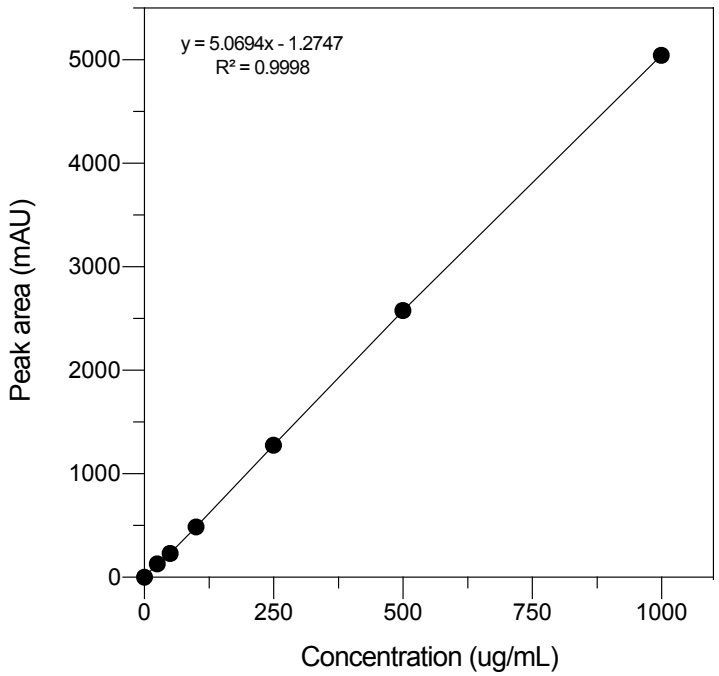

Figure 3. Calibration curve of quinidine sulfate assayed by HPLC method

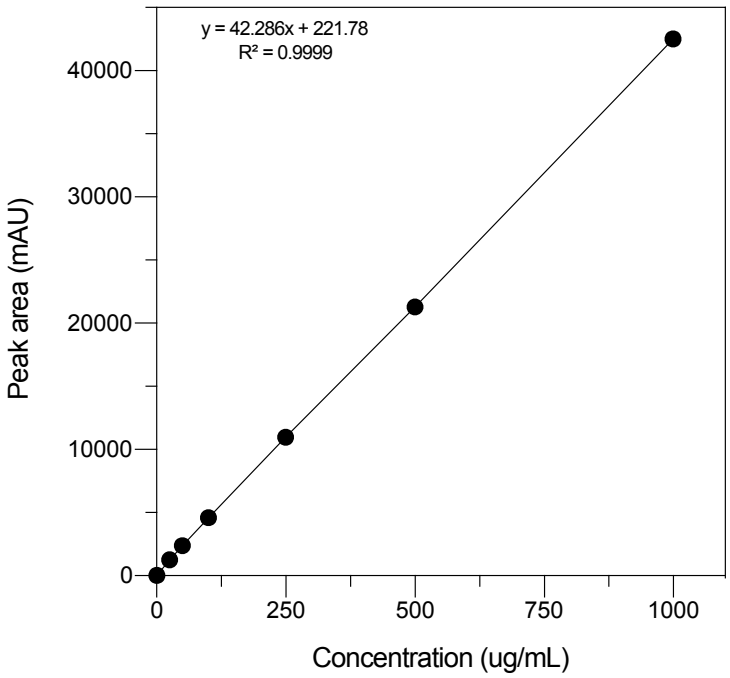

Figure 4. Calibration curve of dipyridamole assayed by HPLC method

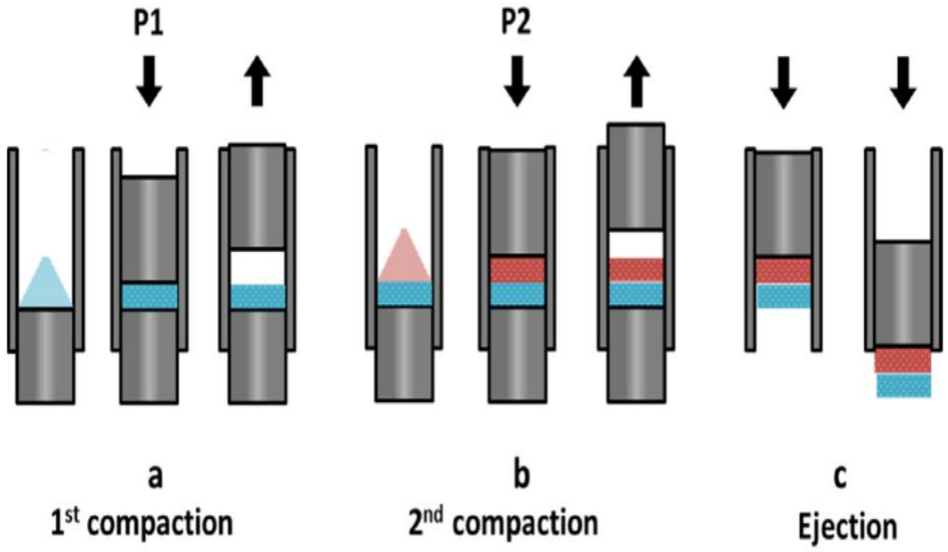

Figure 5. Illustration of the process for making bilayer ADERT. (a) Compression of first layer; (b) addition and compression of second layer; (c) Ejection of bilayer tablet from die. P1: compression pressure 1 (200 lbs); P2: compression pressure 2 (2500 lbs) [Figure adapted from reference: (88)]

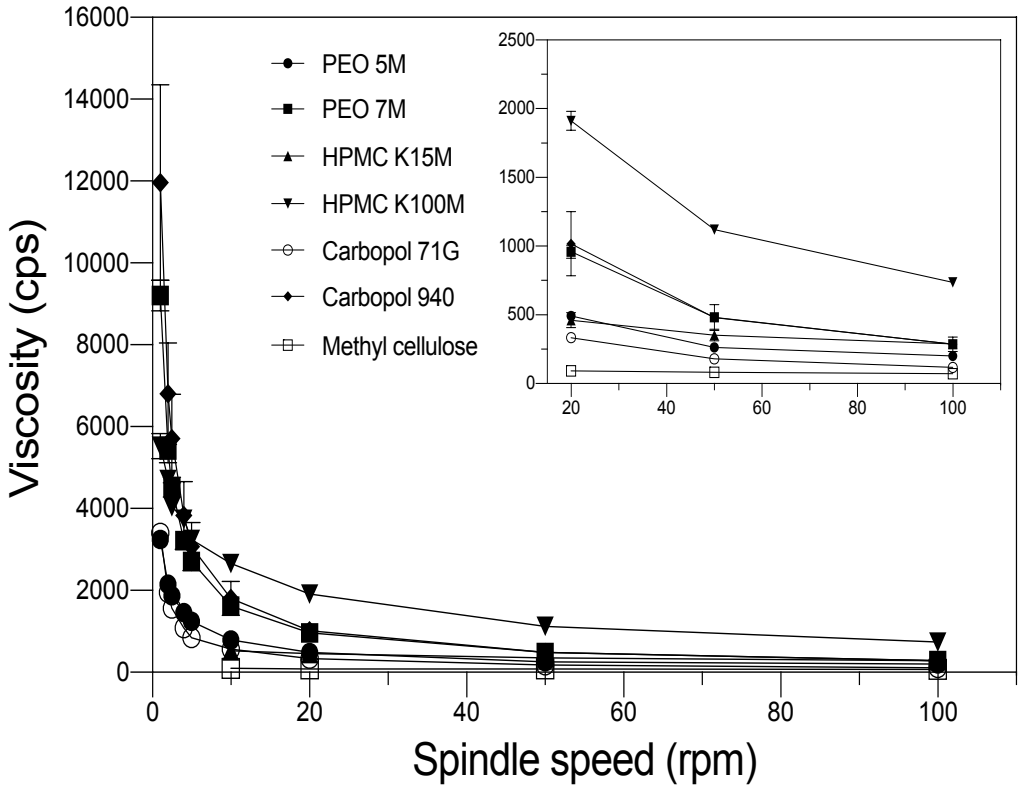

Figure 6: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in water (data represent mean ± standard deviation, n = 3)

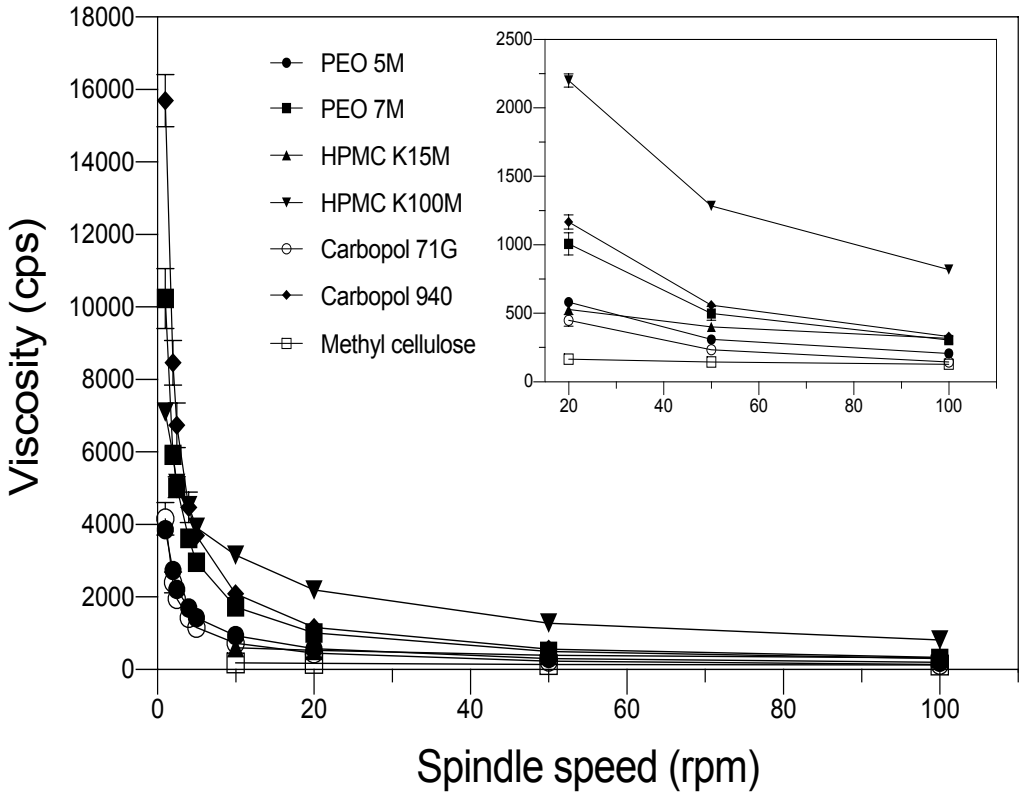

Figure 7: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in 10% ethanol(data represent mean ± standard deviation, n = 3)

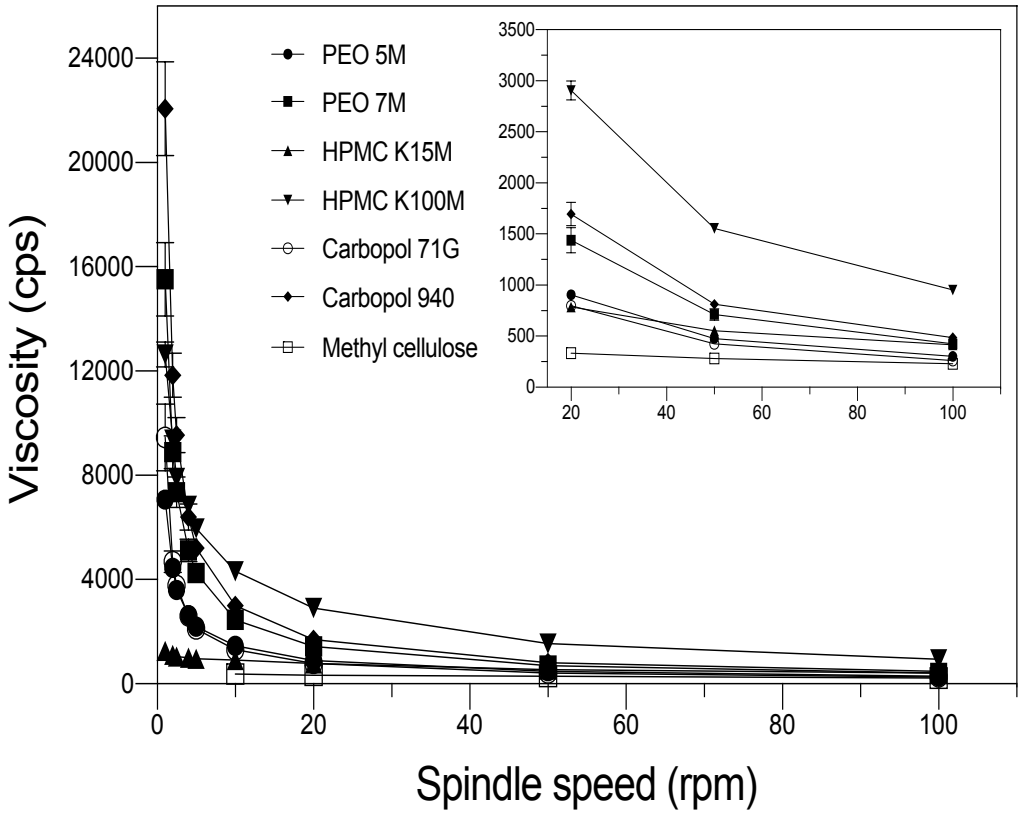

Figure 8: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in 40% ethanol (data represent mean ± standard deviation, n = 3)

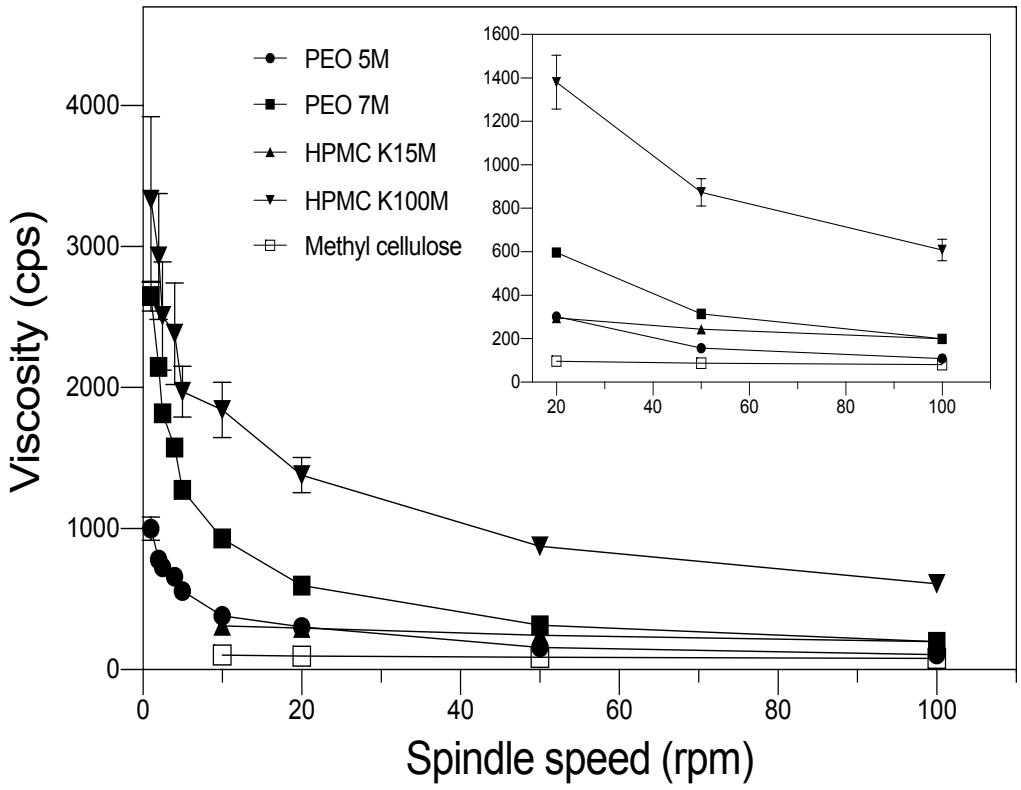

Figure 9: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in 0.1N HCl (data represent mean ± standard deviation, n = 3)

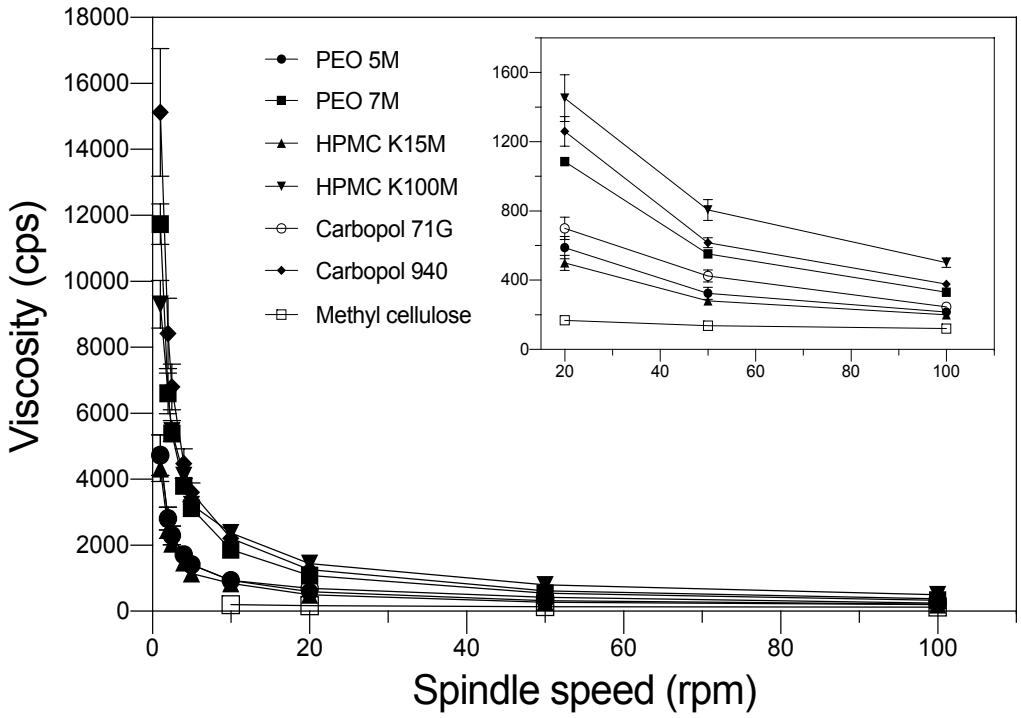

Figure 10: Effect of polymeric solutions (2% w/v) as a physical barrier: Viscosity of polymers in 70% isopropanol (data represent mean ± standard deviation, n = 3)

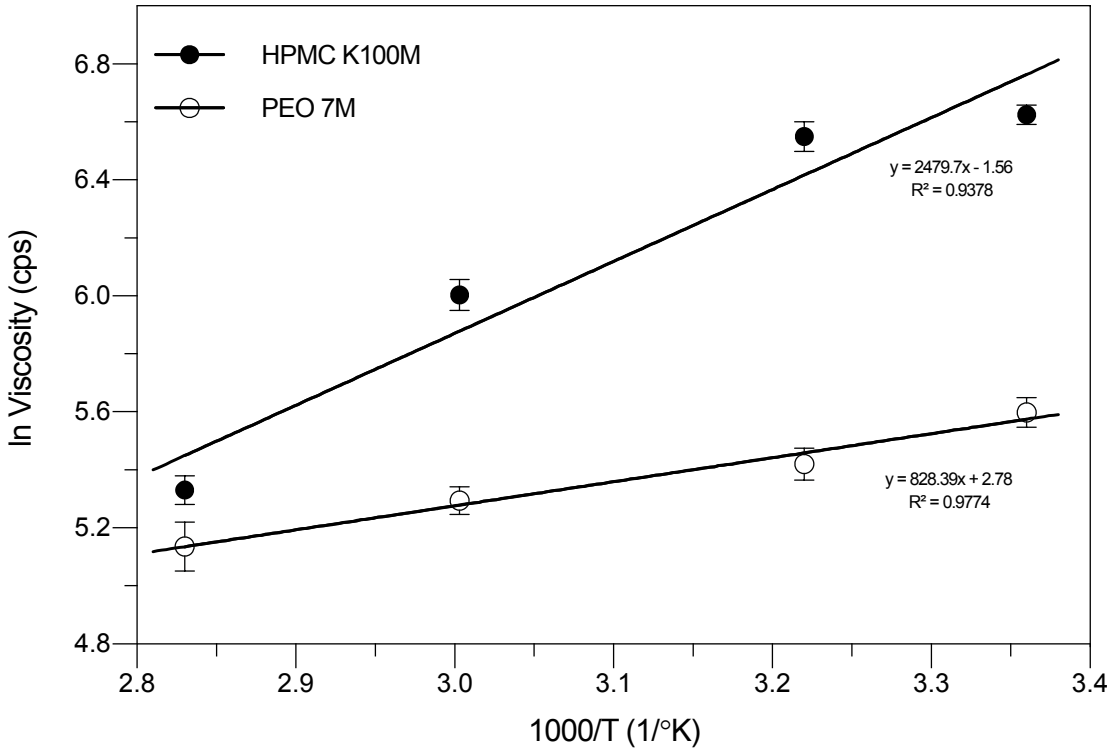

Figure 11: Effect of polymeric solutions (2% w/v) as a physical barrier: Heat induced viscosity at 100 rpm (data represent mean ± standard deviation, n = 3)

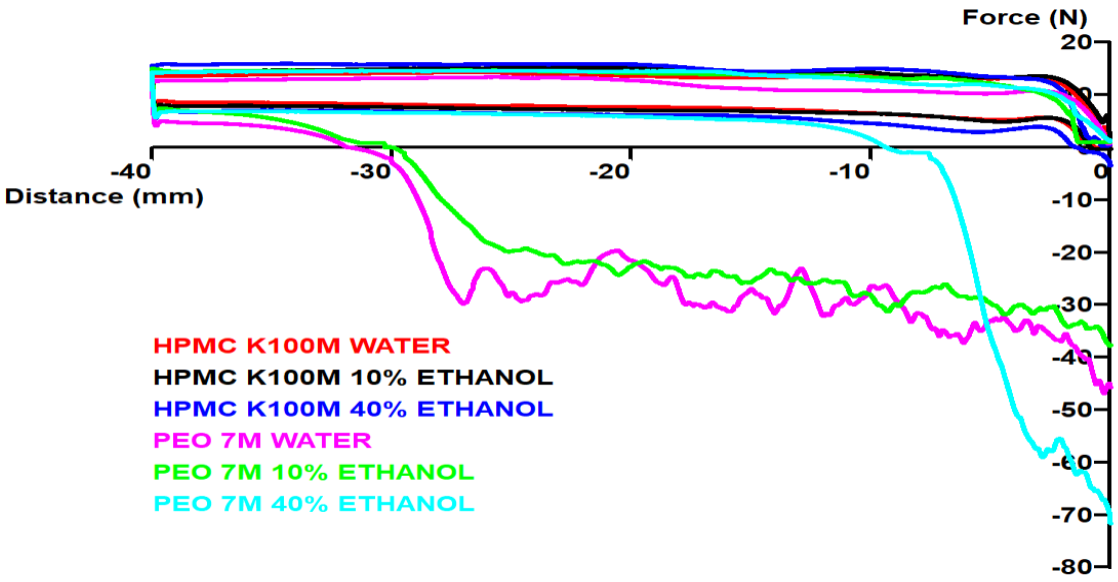

Figure 12: Effect of polymeric solutions (2% w/v) as a physical barrier: Syringe-ability profiles in various solvents. (data represent mean, n = 3-5)

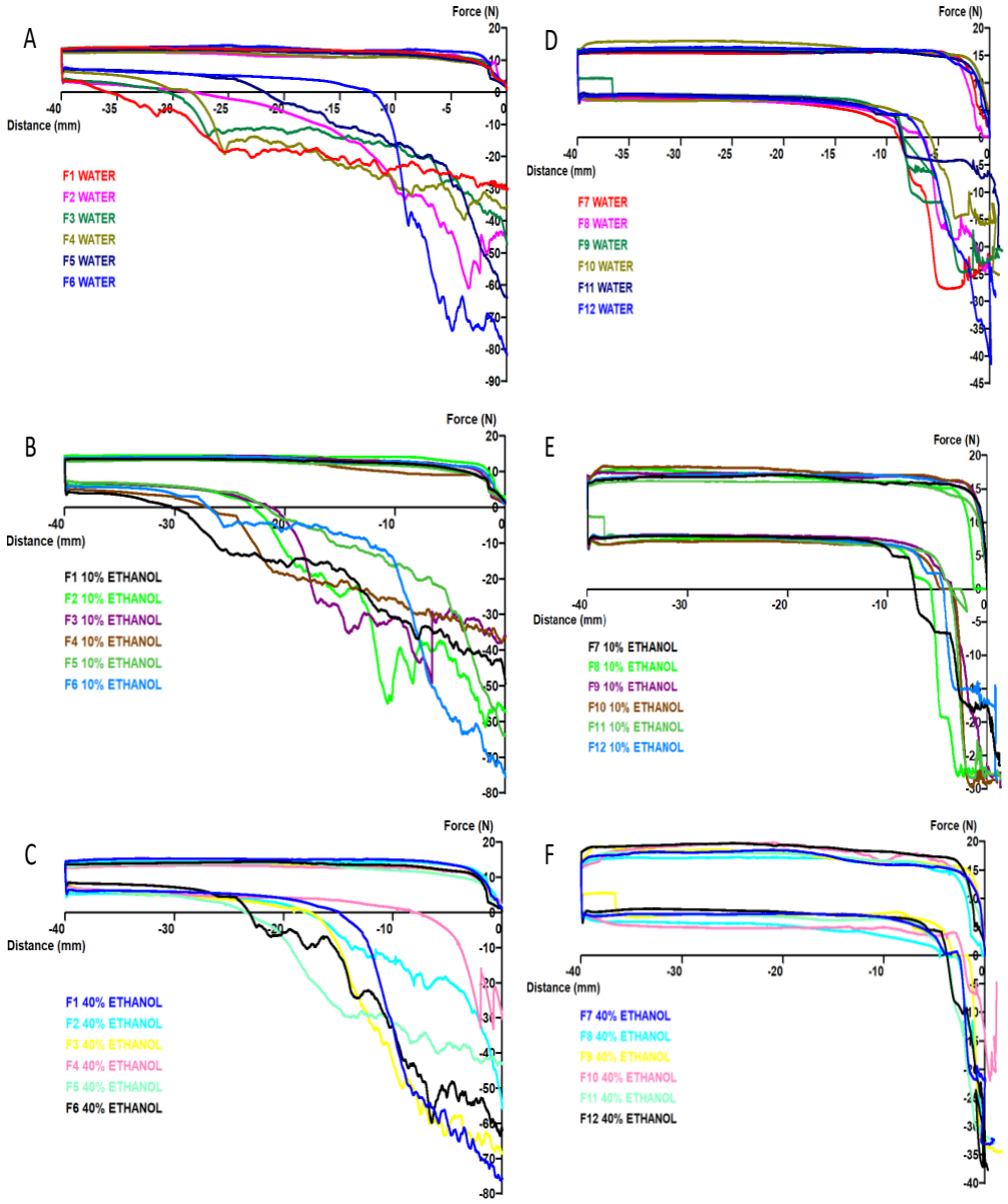

Figure 13: Effect of excipients as a physical barrier: Syringe-ability profile of formulations F1-F12, A: water (F1-F6), B: 10% ethanol (F1-F6), C: 40% ethanol (F1-F6), D: water (F7-F12), E: 10% ethanol (F7-F12), and F: 40% ethanol (F7-F12). Data shown as mean ± standard deviation, n=3-5

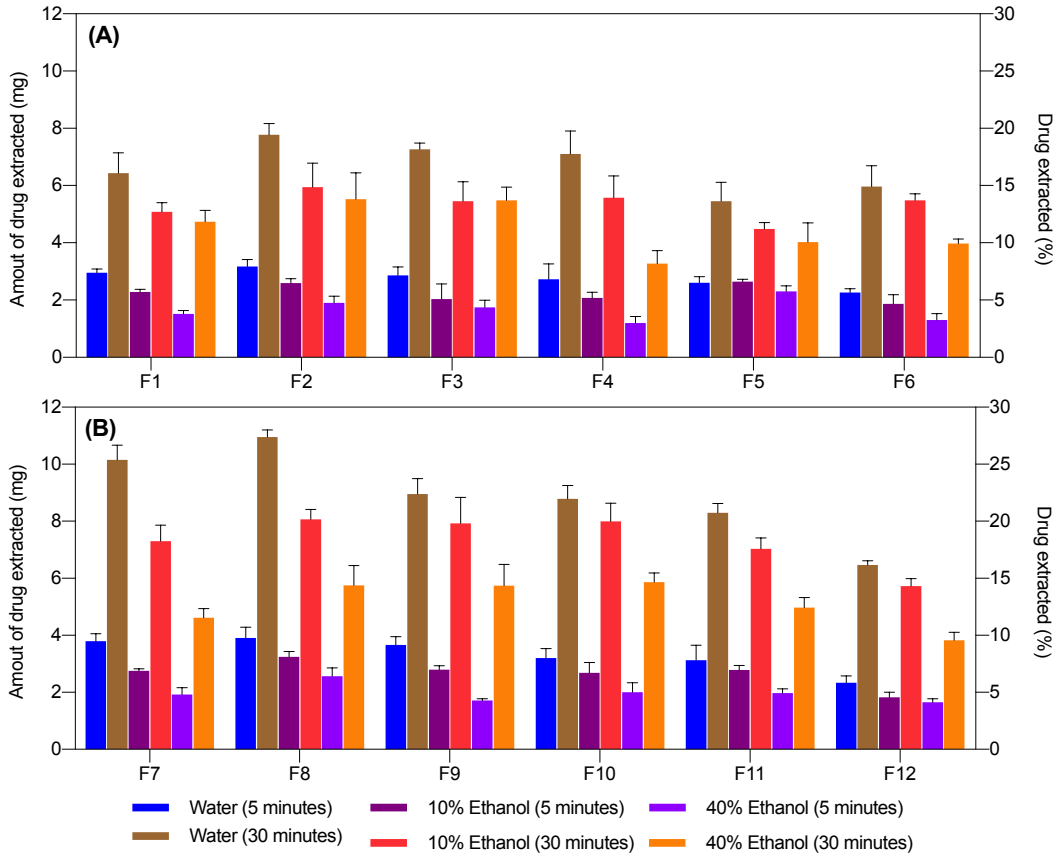

Figure 14: Effect of excipients as a chemical barrier: drug extraction study in various solvents, A) formulation F1-F6, B) formulation F7-F12 (data represent mean ± standard deviation, n = 3)

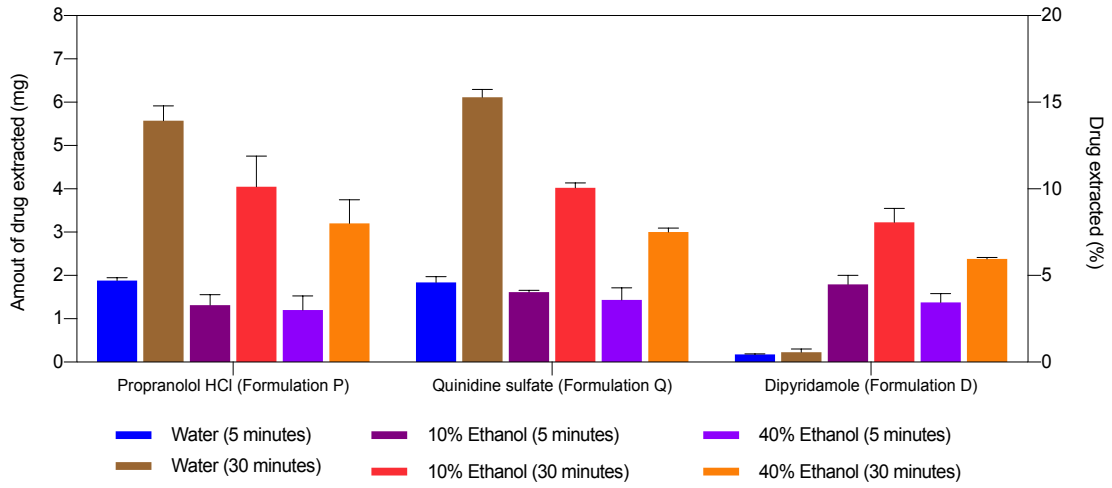

Figure 15: Effect of excipients as a chemical barrier: drug extraction study from formulations P, Q, and D in various solvents (data represent mean ± standard deviation, n = 3)

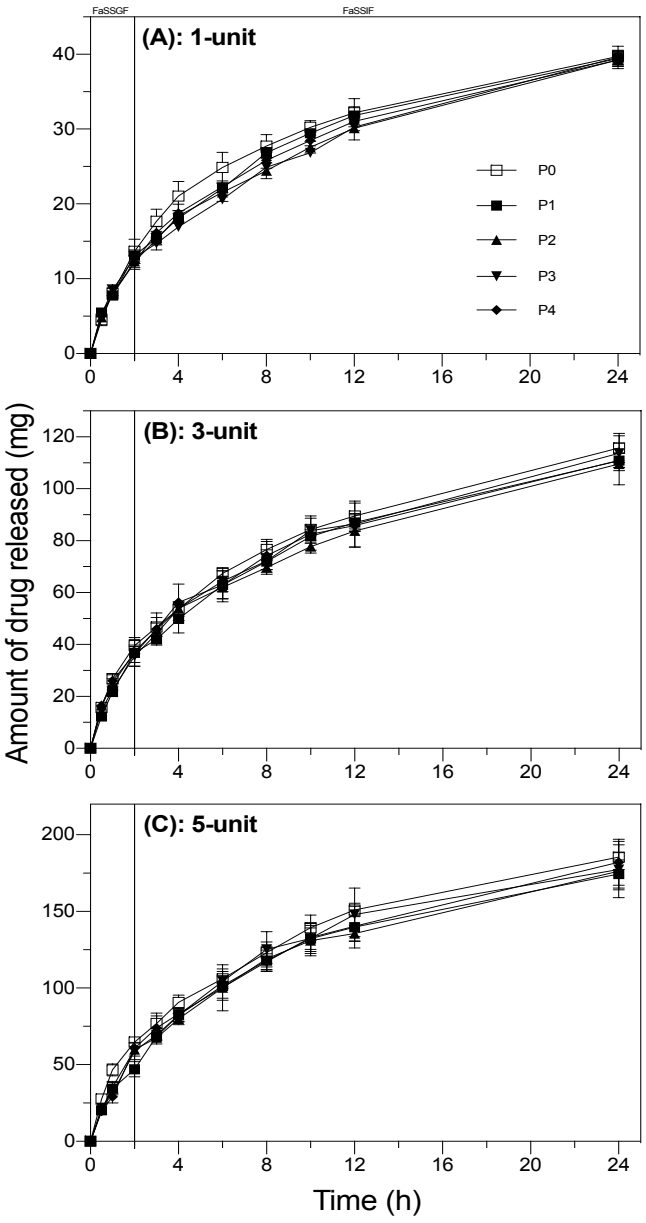

Figure 16: *In-vitro* drug release profile of propranolol HCl-loaded bilayer ADERT of formulation P1, P2, P3, and P4 from A) 1-unit, B) 3-unit, and C) 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

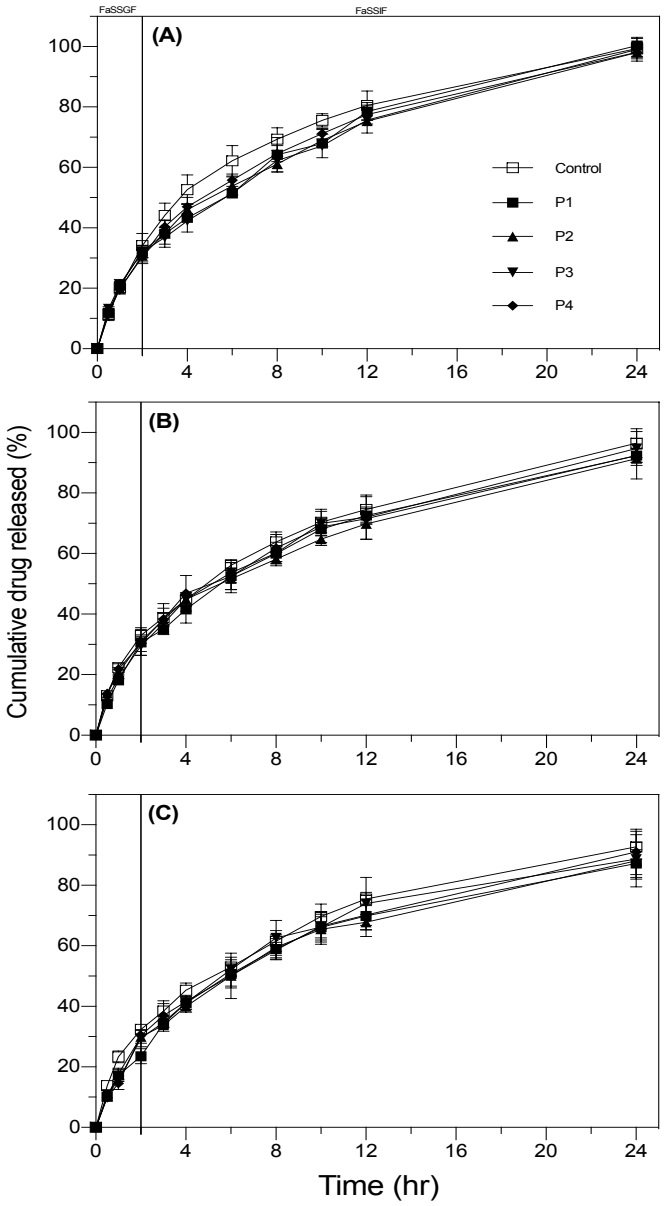

Figure 17: Cumulative % *In-vitro* drug release profile of propranolol HCl-loaded bilayer ADERT of formulation P1, P2, P3, and P4 from A) 1-unit, B) 3-unit, and C) 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

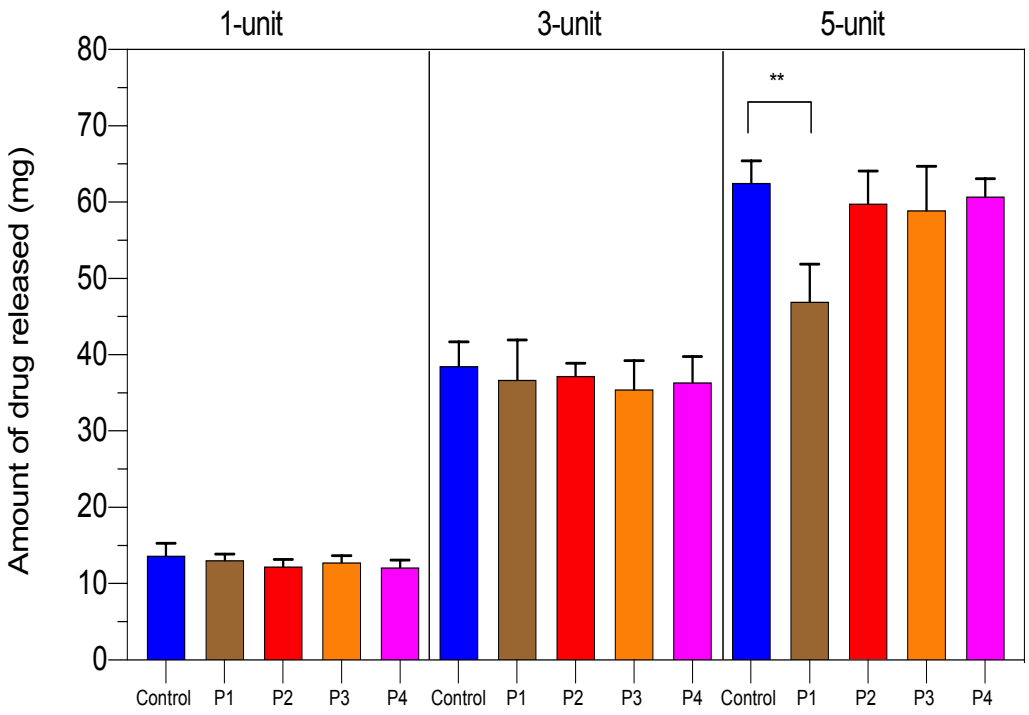

Figure 18: Effect of alkalizing agents on in-vitro drug release profiles from oral multiple-unit of propranolol HCl-loaded ADERT of formulation P1, P2, P3, and P4 in FaSSGF for 2 hours and their comparison with control formulation to minimize the potential abuse. (** represents significantly different from other formulations $p<0.005$; data are presented as mean ± standard deviation, n = 3; control formulation represents formulation P)

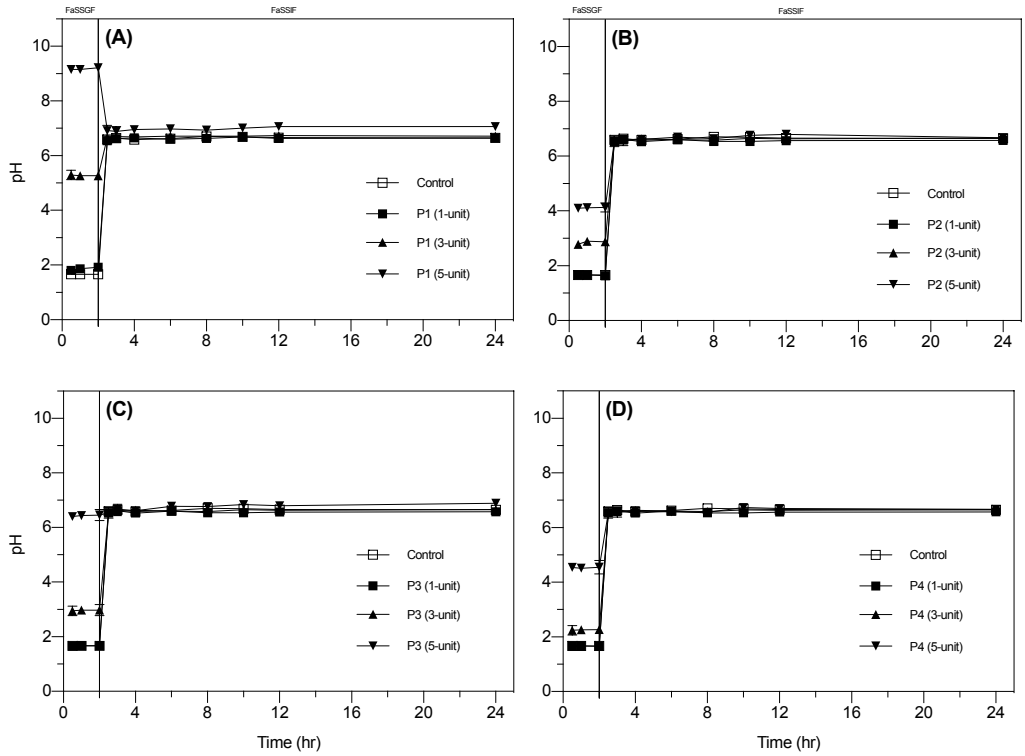

Figure 19: Effect of alkalizing agents on pH of *in-vitro* drug release media from oral multiple-unit of propranolol HCl-loaded bilayer ADERT of A) formulation P1, B) formulation P2, C) formulation P3, and D) formulation P4, in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

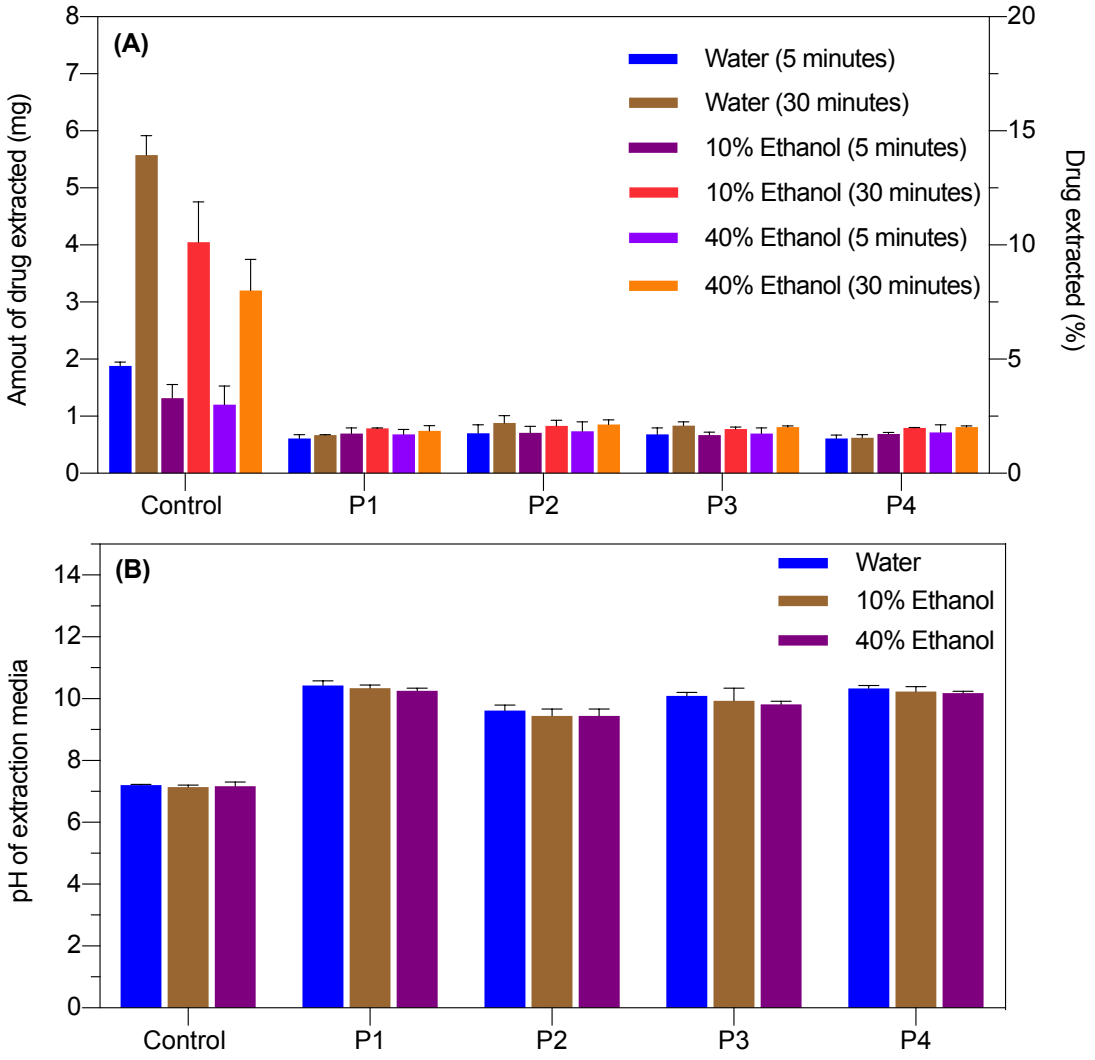

Figure 20: Effect of excipients as a chemical barrier: A) drug extraction study from formulations P1, P2, P3, and P4 in various solvents B) effect of alkalizing agents on pH of drug extraction media at 30 minutes and their comparison with control formulation to minimize the potential abuse (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

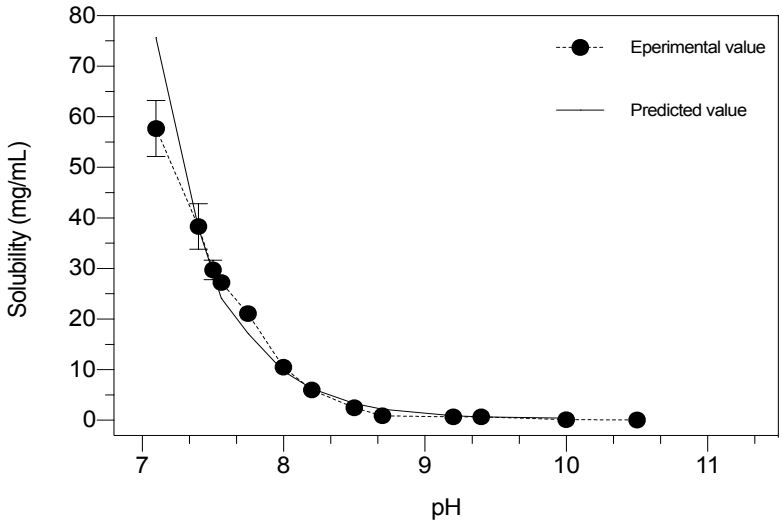

Figure 21: pH-dependent solubility profile of propranolol HCl (data represent mean ± standard deviation, n = 3)

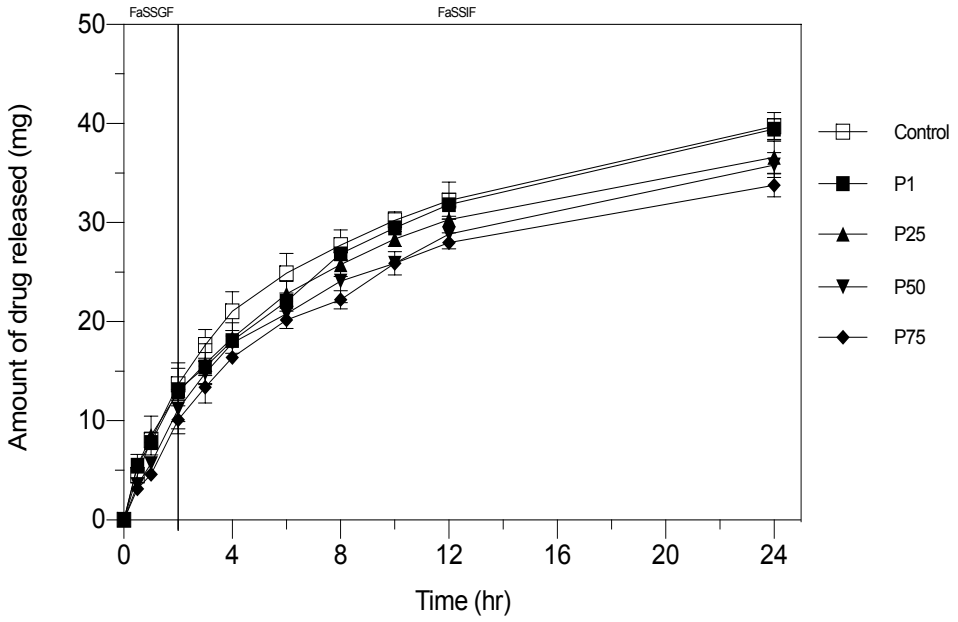

Figure 22: Effect of amount of magnesium hydroxide on *in-vitro* drug release profiles from oral single-unit of propranolol HCl-loaded bilayer ADERT of formulation P25, P50, and P75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

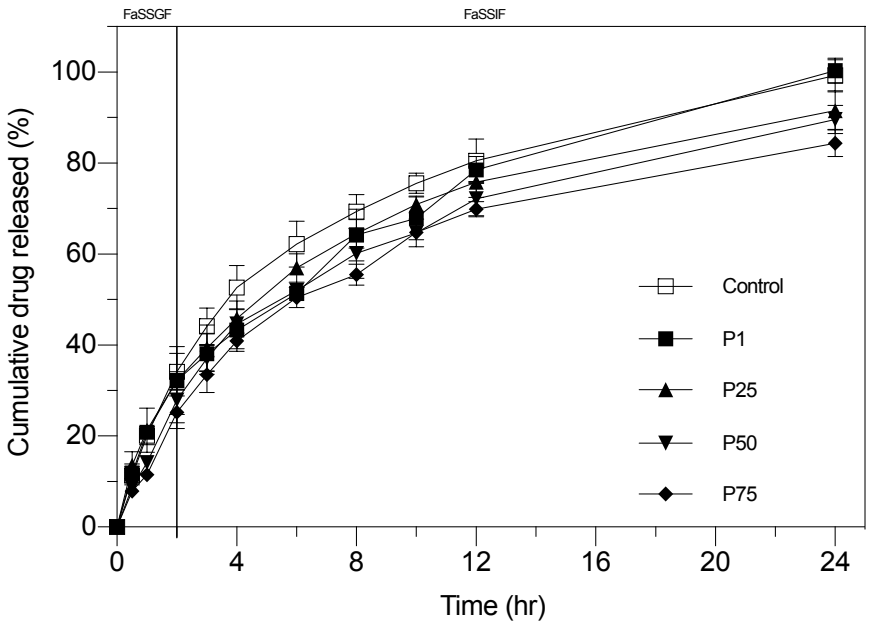

Figure 23: Effect of amount of magnesium hydroxide on cumulative % *in-vitro* drug release profiles from oral single-unit of propranolol HCl-loaded bilayer ADERT of formulation P25, P50, and P75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

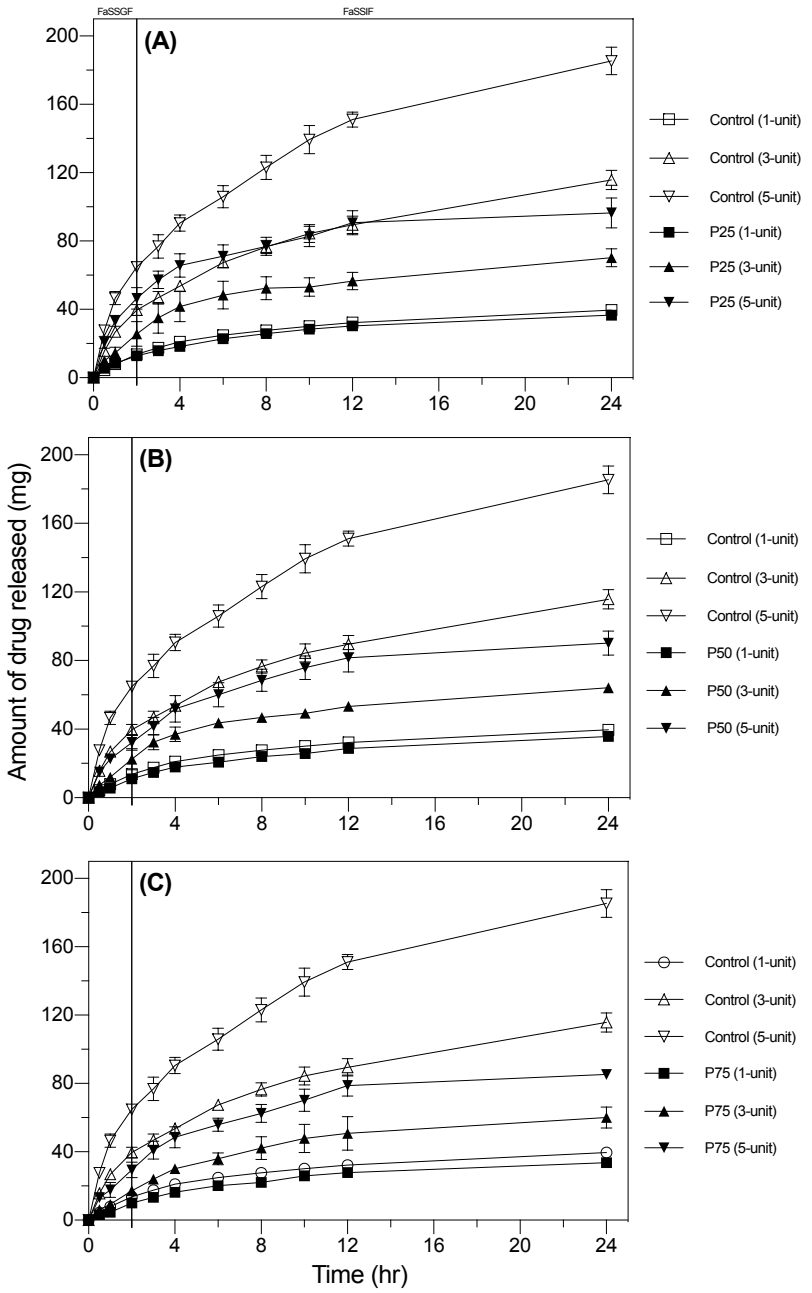

Figure 24: Effect of amount of magnesium hydroxide on *in-vitro* drug release profiles from oral multiple-unit of propranolol HCl-loaded bilayer ADERT of A) formulation P25, B) formulation P50 and C) formulation P75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3, control formulation represents formulation P)

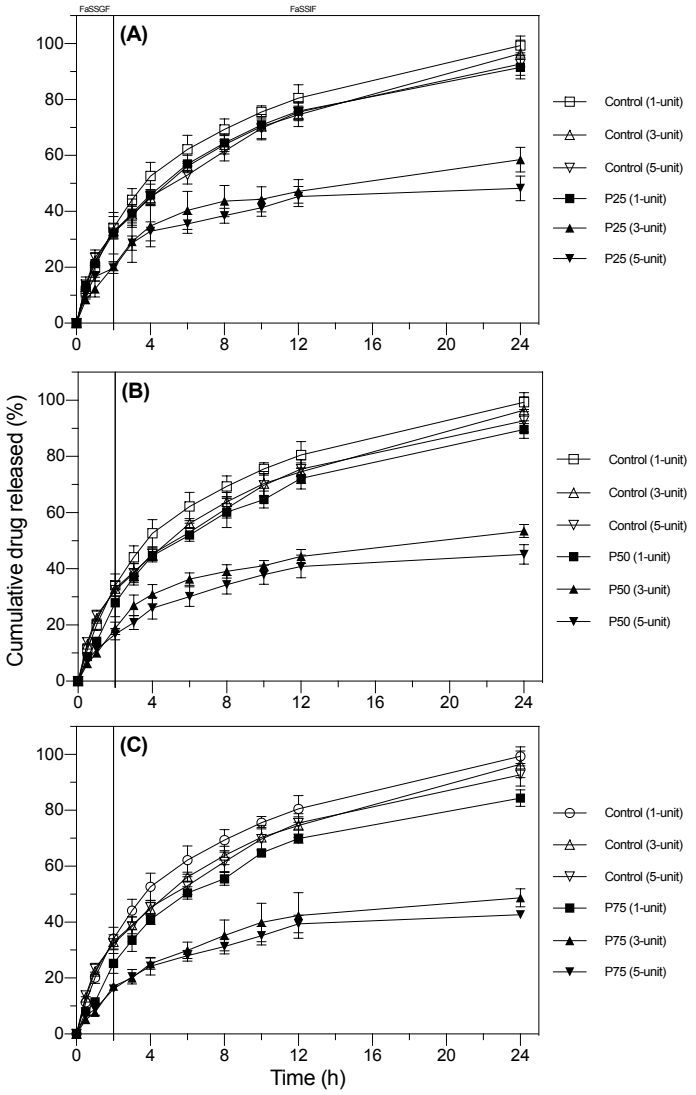

Figure 25: Effect of amount of magnesium hydroxide on cumulative % *in-vitro* drug release profiles from oral multiple-unit of propranolol HCl-loaded bilayer ADERT of A) formulation P25, B) formulation P50 and C) formulation P75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3, control formulation represents formulation P)

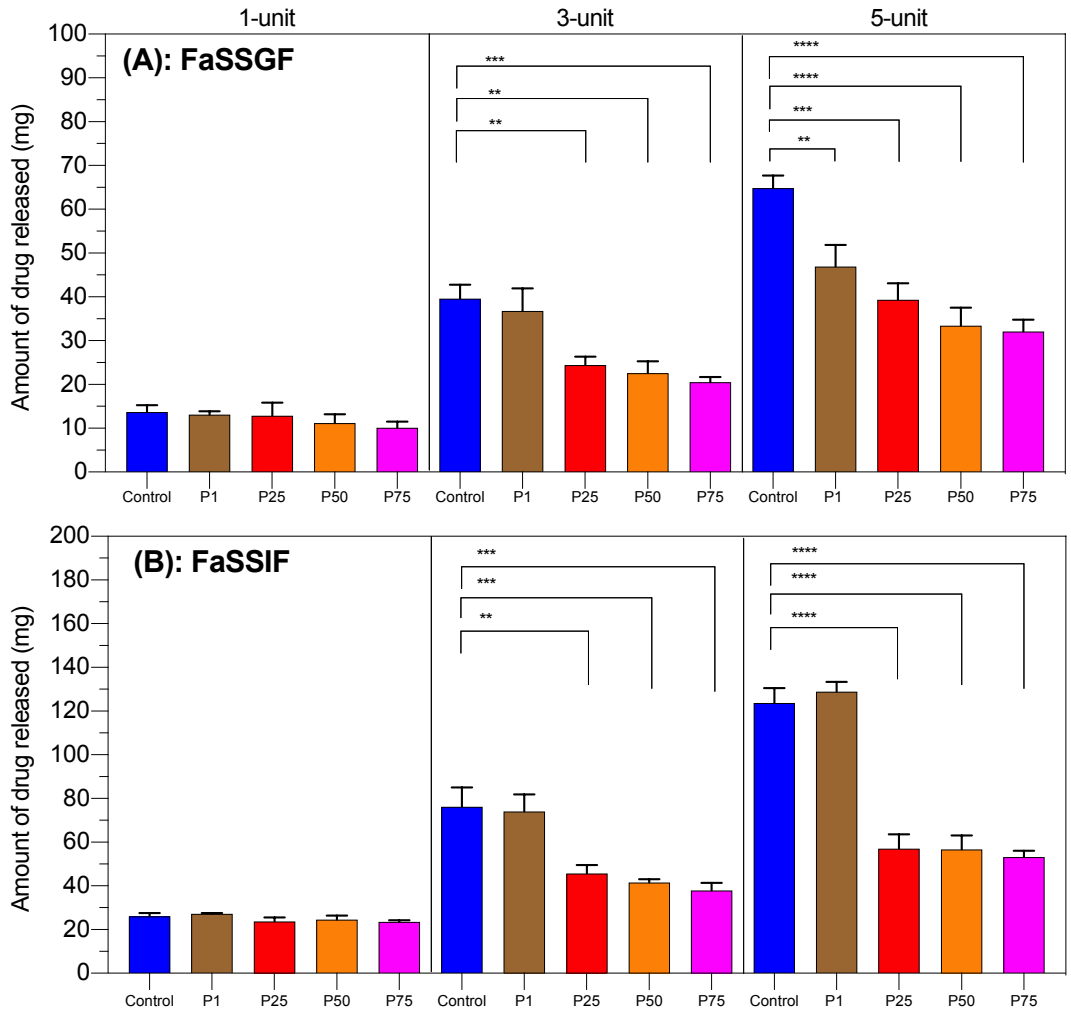

Figure 26: Effect of amount of magnesium hydroxide on amount of drug release A) at 2 hours in fasted state simulated gastric fluid (FaSSGF) and B) at additional 22 hours in fasted state simulated intestinal fluid (FaSSIF) from oral multiple-unit of propranolol HCl-loaded bilayer ADERT of formulations P25, P50 and P75 and their comparison with the control formulation. (**, ***, and **** represents significantly different from other formulations $p<0.005$, 0.005, and 0.0005, respectively; data are presented as mean ± standard deviation, n = 3; control formulation represents formulation P)

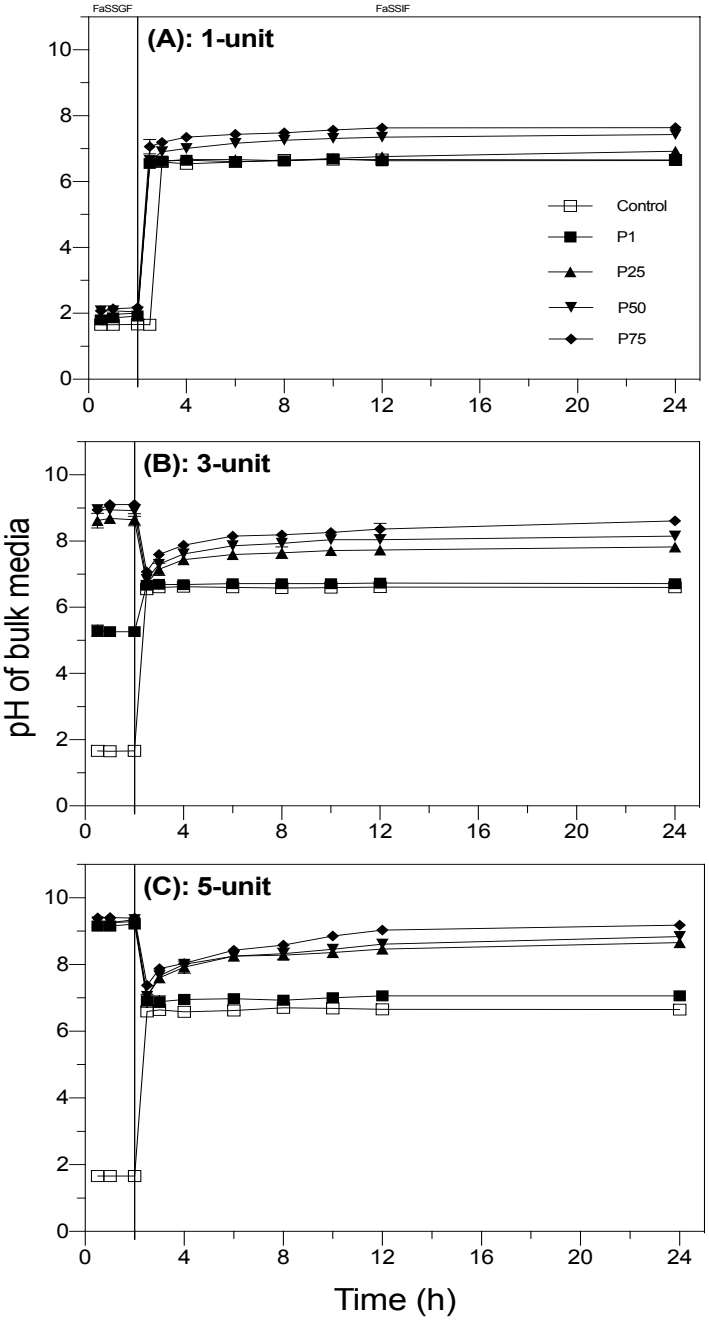

Figure 27: Effect of alkalizing agents on pH of *in-vitro* drug release media from propranolol HCl-loaded bilayer ADERT of A) 1-unit, B) 3-unit, and C) 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

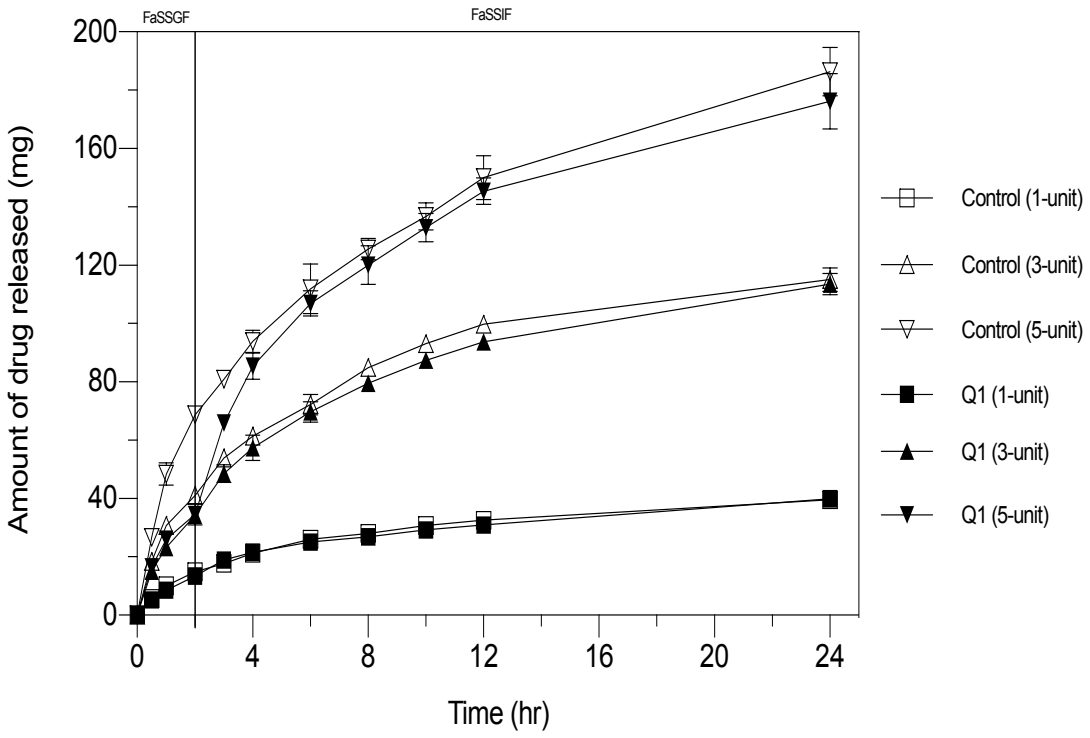

Figure 28: In-vitro drug release profile of quinidine sulfate-loaded bilayer ADERT of formulation Q1 from 1, 3, and 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

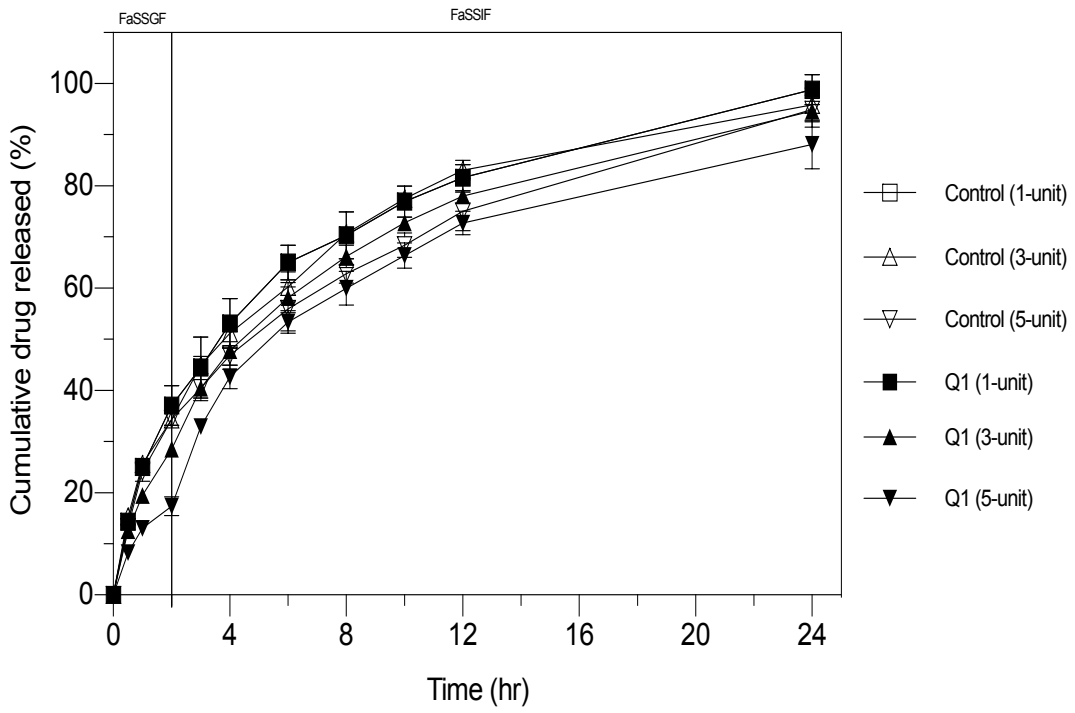

Figure 29: Cumulative % *in-vitro* drug release profile of quinidine sulfate-loaded bilayer ADERT of formulation Q1 from 1, 3, and 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

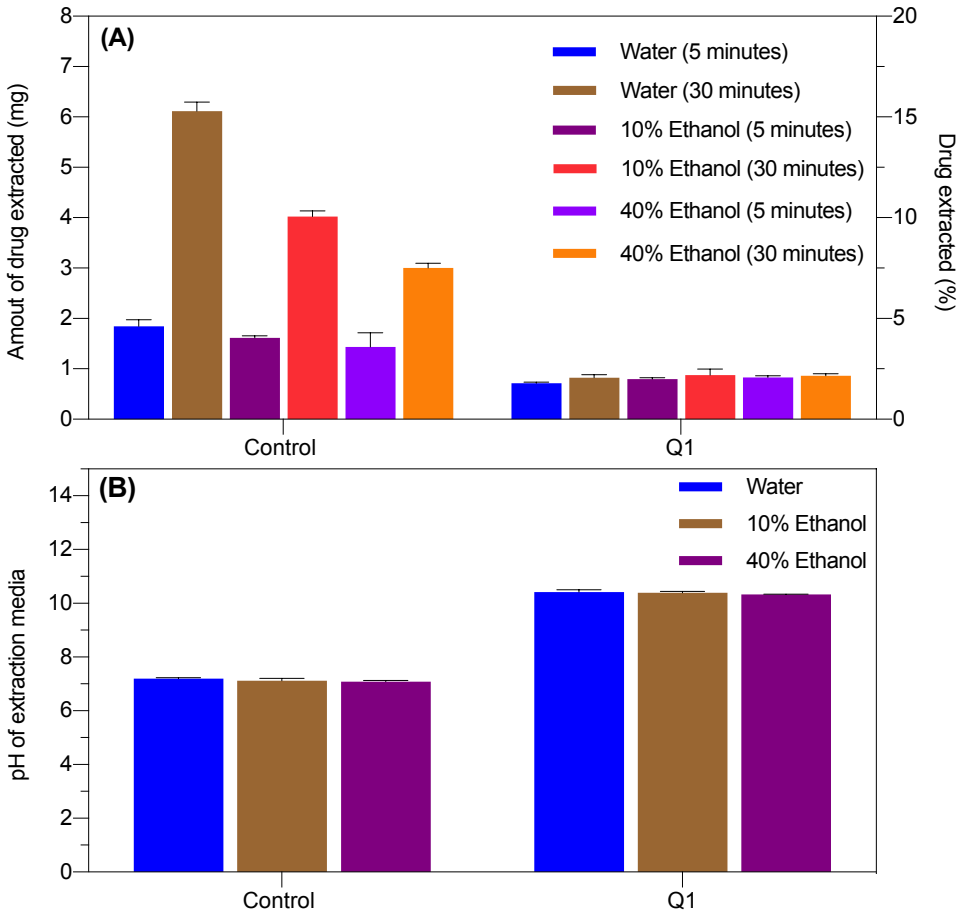

Figure 30: Effect of excipients as a chemical barrier: A) drug extraction study from formulation Q1 in various solvents B) effect of alkalizing agents on pH of drug extraction media at 30 minutes and their comparison with control formulation to minimize the potential abuse (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

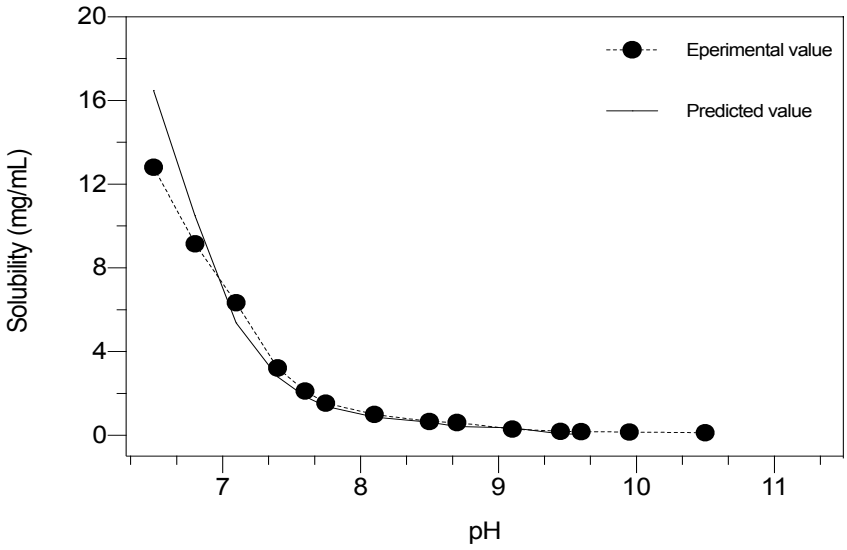

Figure 31: pH-dependent solubility profile of quinidine sulfate (data represent mean ± standard deviation, n = 3)

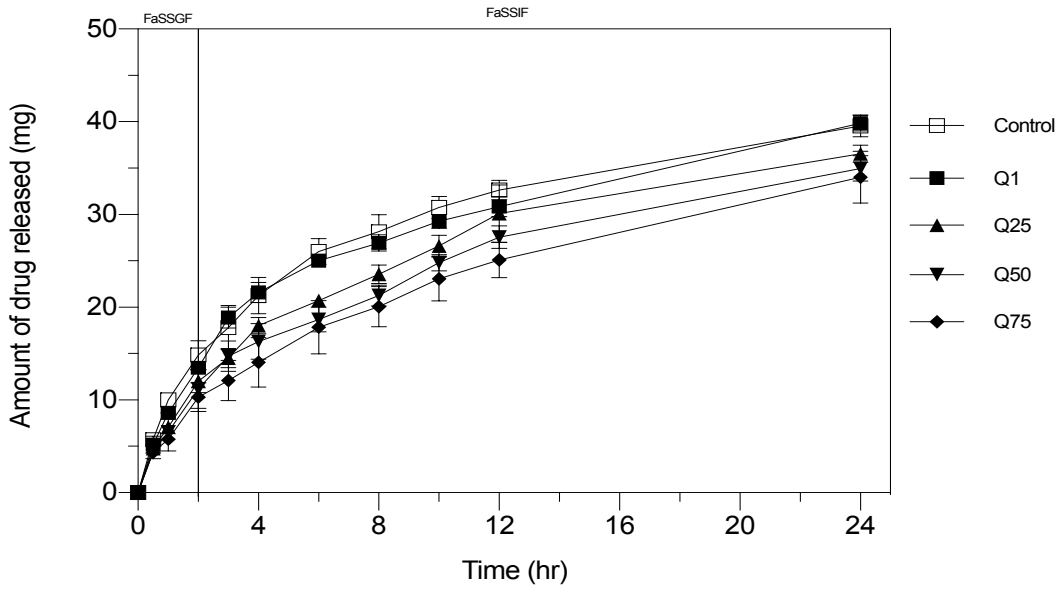

Figure 32: Effect of amount of magnesium hydroxide on *in-vitro* drug release profiles from oral single-unit of quinidine sulfate-loaded bilayer ADERT of formulation Q25, Q50, and Q75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

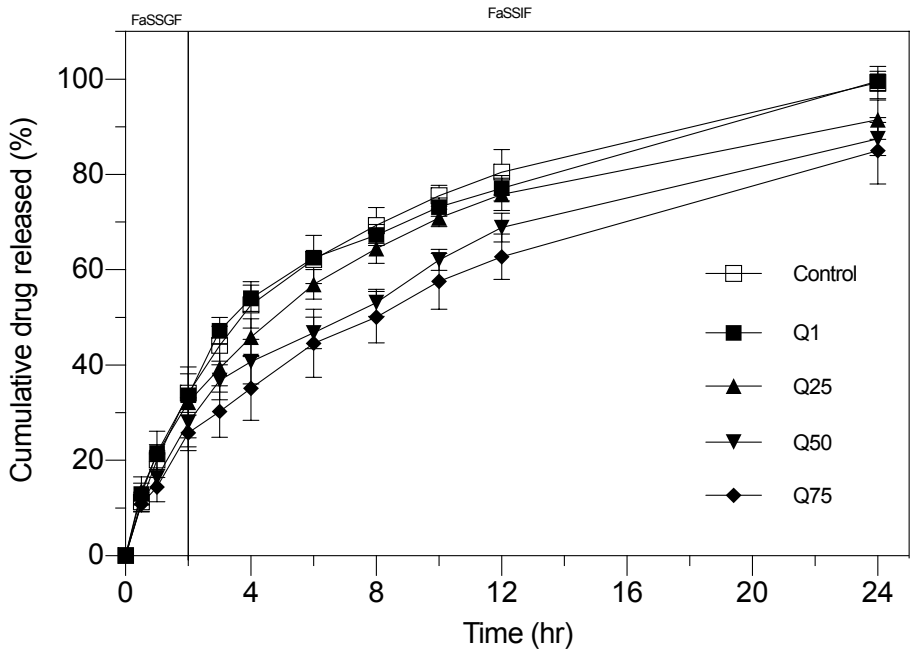

Figure 33: Effect of amount of magnesium hydroxide on cumulative % *in-vitro* drug release profiles from oral single-unit of quinidine sulfate-loaded bilayer ADERT of formulation Q25, Q50, and Q75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

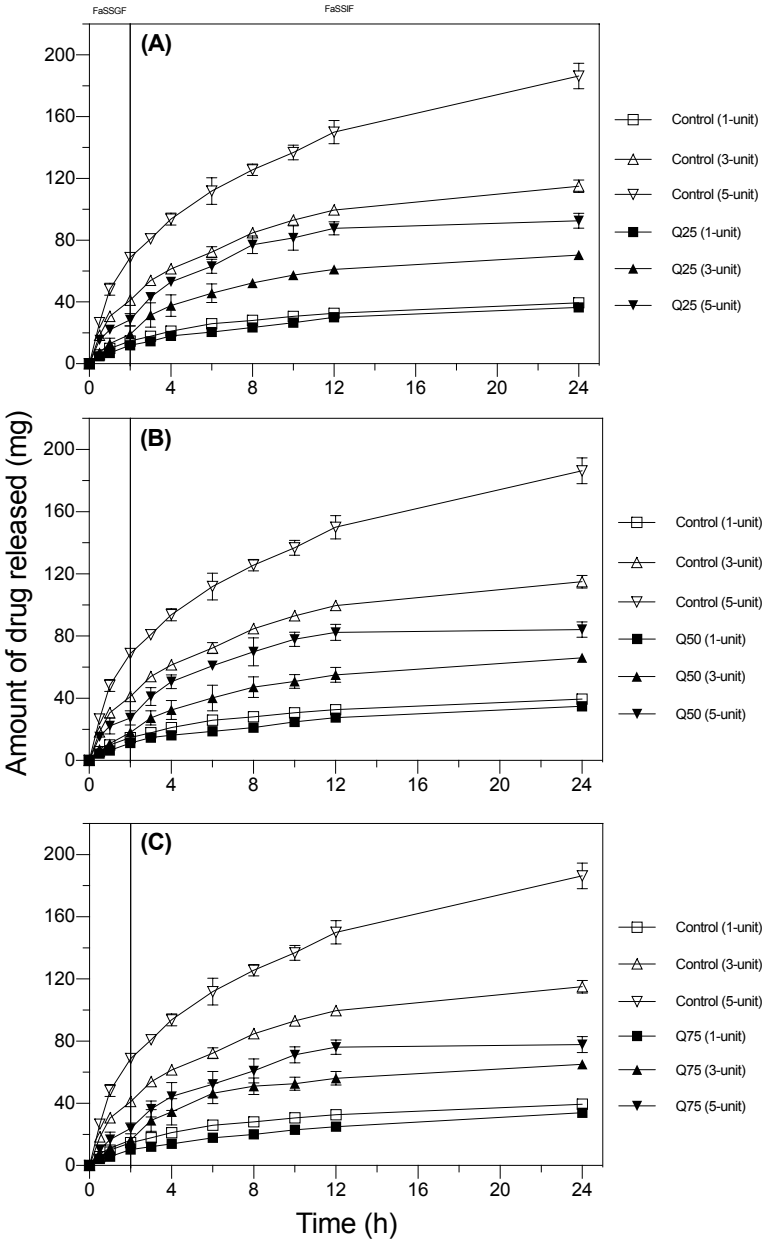

Figure 34: Effect of amount of magnesium hydroxide on *in-vitro* drug release profiles from oral multiple-unit of quinidine sulfate-loaded bilayer ADERT of A) formulation Q25, B) formulation Q50 and C) formulation Q75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

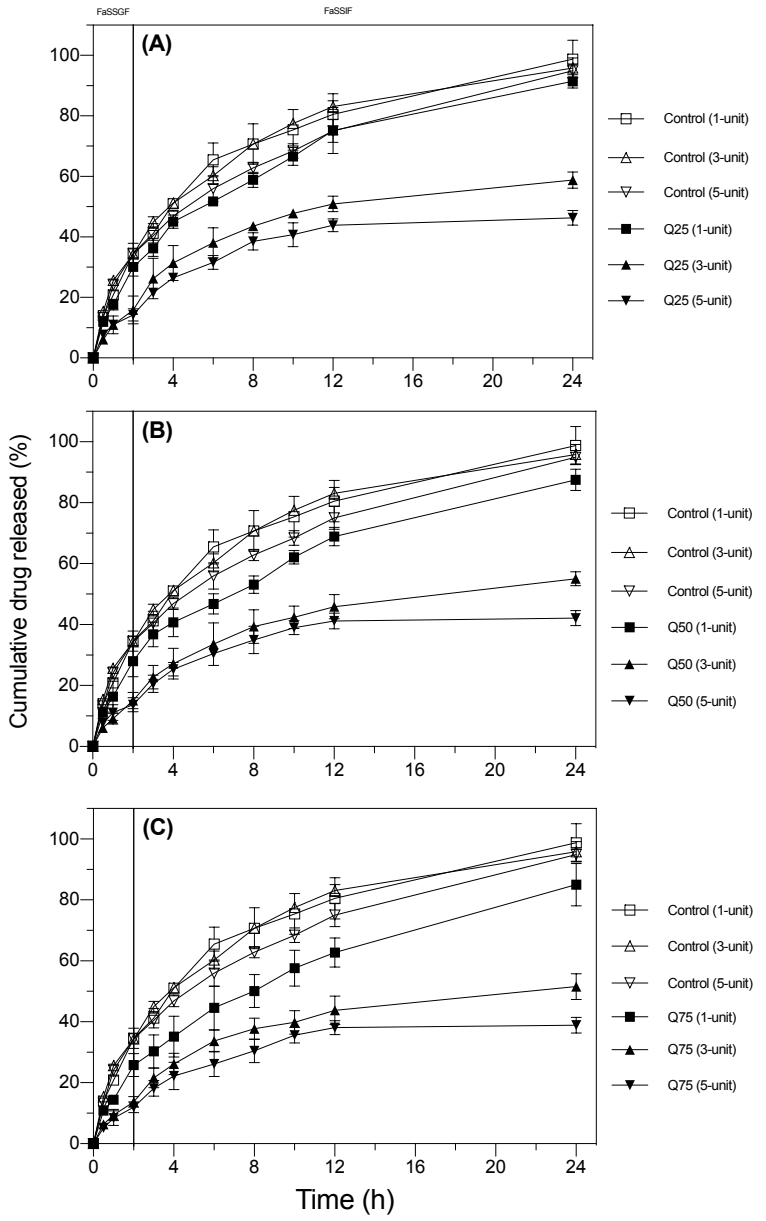

Figure 35: Effect of amount of magnesium hydroxide on cumulative % *in-vitro* drug release profiles from oral multiple-unit of quinidine sulfate-loaded bilayer ADERT of A) formulation Q25, B) formulation Q50 and C) formulation Q75 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

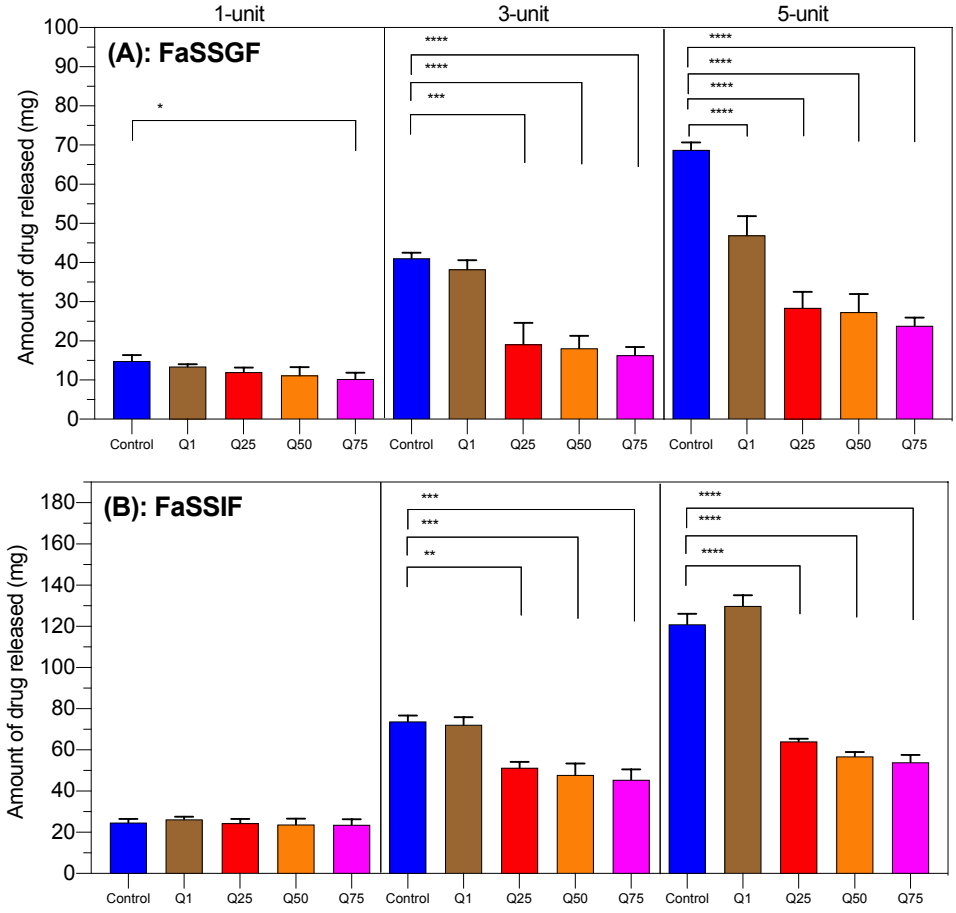

Figure 36: Effect of amount of magnesium hydroxide on amount of drug release A) at 2 hours in fasted state simulated gastric fluid (FaSSGF) and B) at additional 22 hours in fasted state simulated intestinal fluid (FaSSIF) from oral multiple-unit of quinidine sulfate-loaded bilayer ADERT of formulations Q25, Q50 and Q75 and their comparison with the control formulation. (*, **, ***, and **** represents significantly different from other formulations $p<0.05$, 0.005, 0.005, and 0.0005, respectively; data are presented as mean ± standard deviation, n = 3; control formulation represents formulation Q)

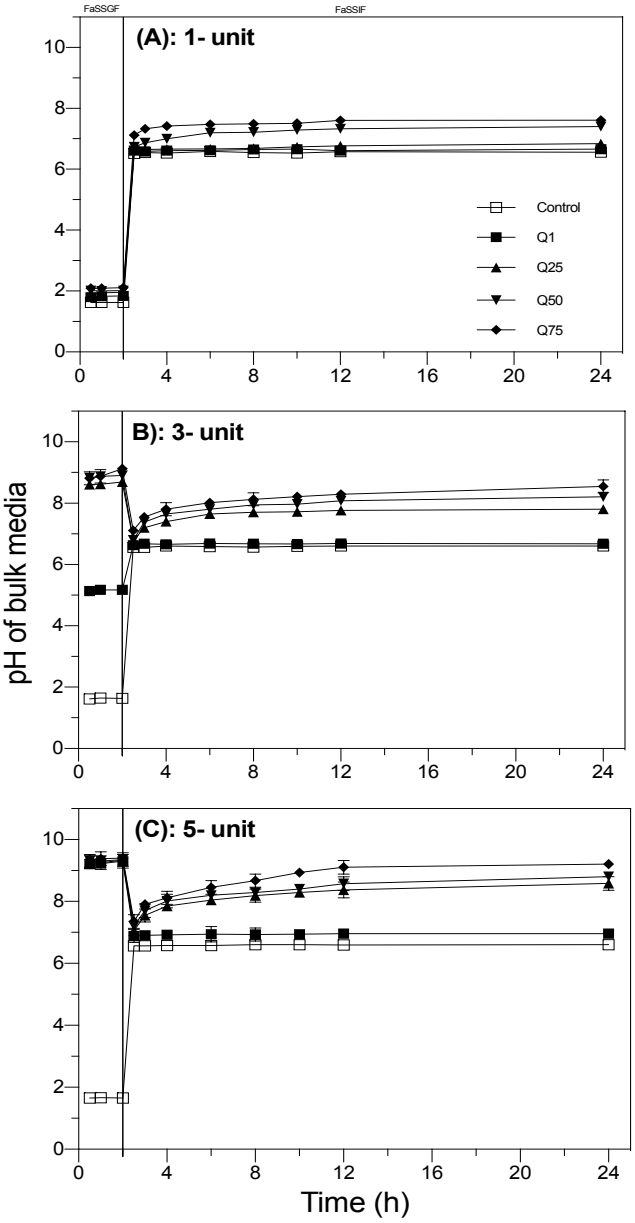

Figure 37: Effect of alkalizing agents on pH of *in-vitro* drug release media from propranolol HCl-loaded bilayer ADERT of A) 1-unit, B) 3-unit, and C) 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation Q)

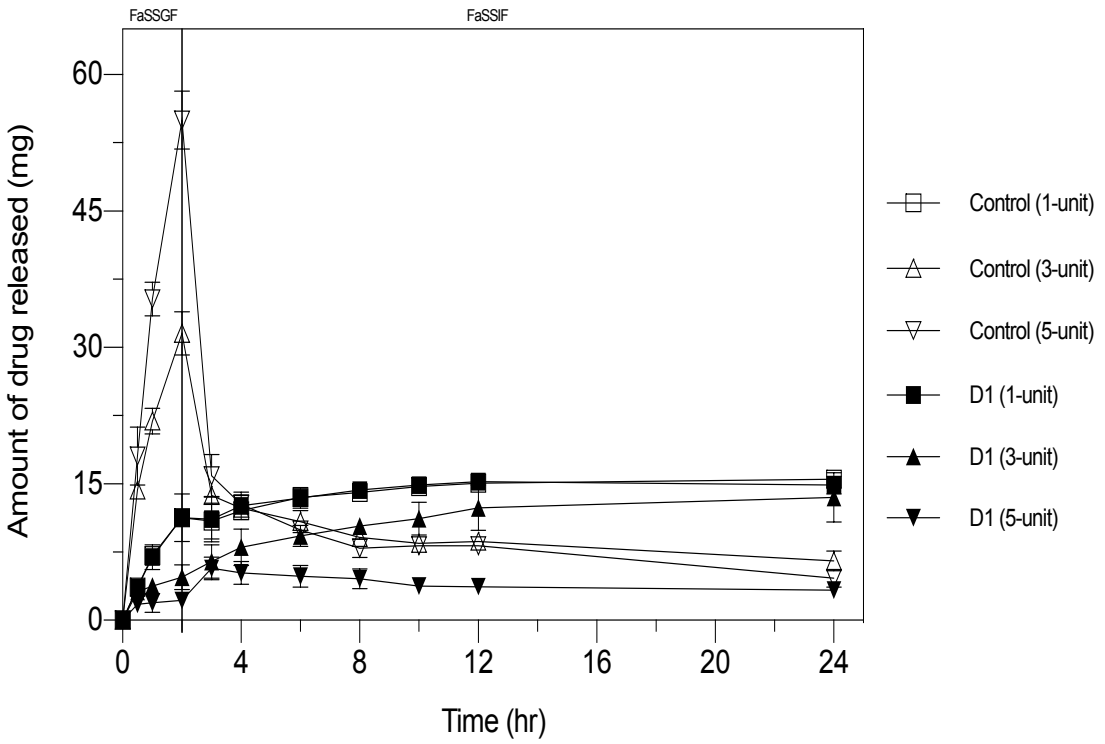

Figure 38: *In-vitro* drug release profile of dipyridamole-loaded bilayer ADERT of formulation D1 from 1, 3, and 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation D)

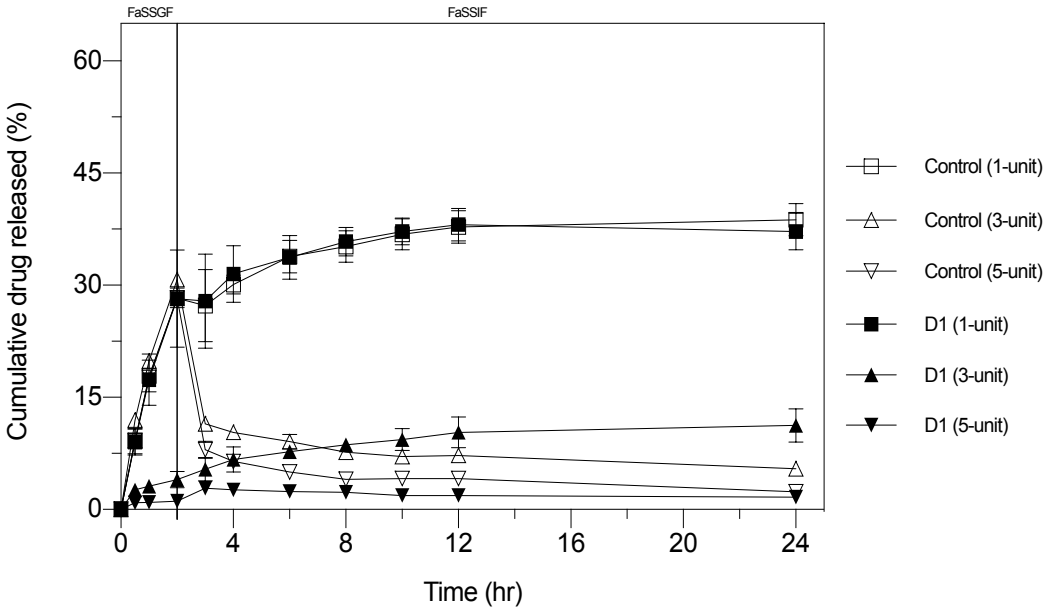

Figure 39: Cumulative % *in-vitro* drug release profile of dipyridamole-loaded bilayer ADERT of formulation D1 from 1, 3, and 5-unit in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation. (data represent mean ± standard deviation, n = 3; control formulation represents formulation D)

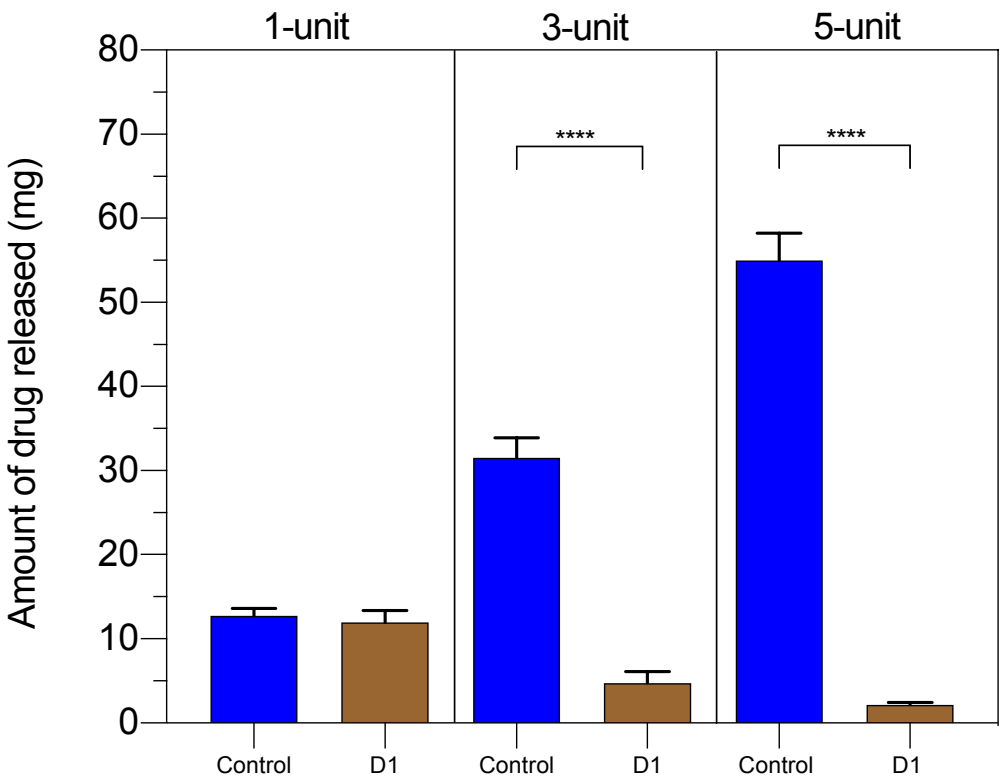

Figure 40: Effect of alkalizing agents on *in-vitro* drug release profiles from oral multiple-unit of dipyridamole-loaded ADERT of formulation D1 in FaSSGF for 2 hours and their comparison with control formulation to minimize the potential abuse. (**** represents significantly different from other formulations $p < 0.0005$; data are presented as mean ± standard deviation, n = 3; control formulation represents formulation Q)

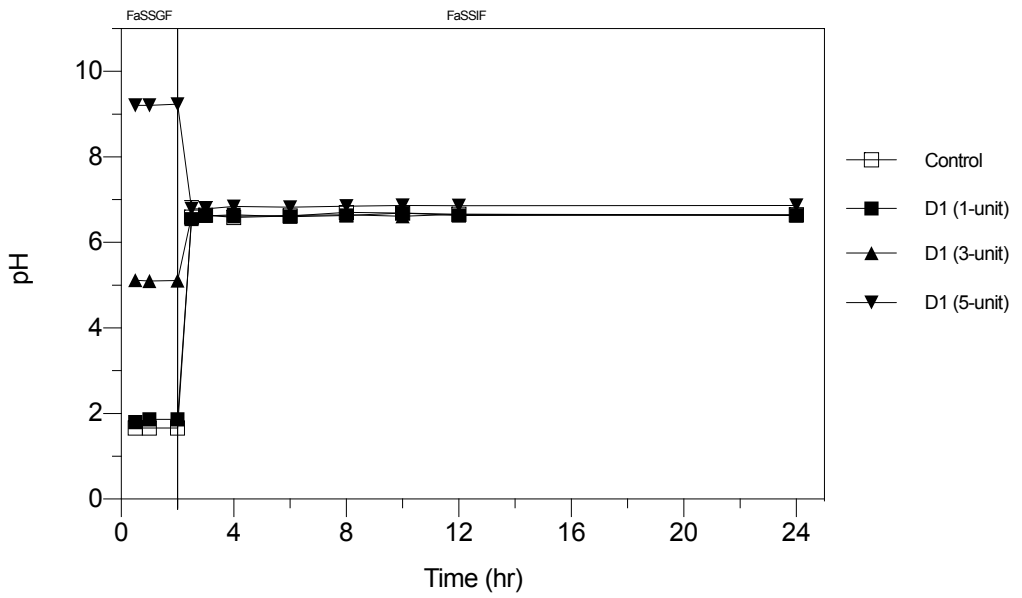

Figure 41: Effect of alkalizing agents on pH of *in-vitro* drug release media from oral multiple-unit of dipyridamole-loaded bilayer ADERT of formulation D1 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours and their comparison with control formulation to minimize the potential abuse. (data represent mean ± standard deviation, n = 3; control formulation represents formulation D)

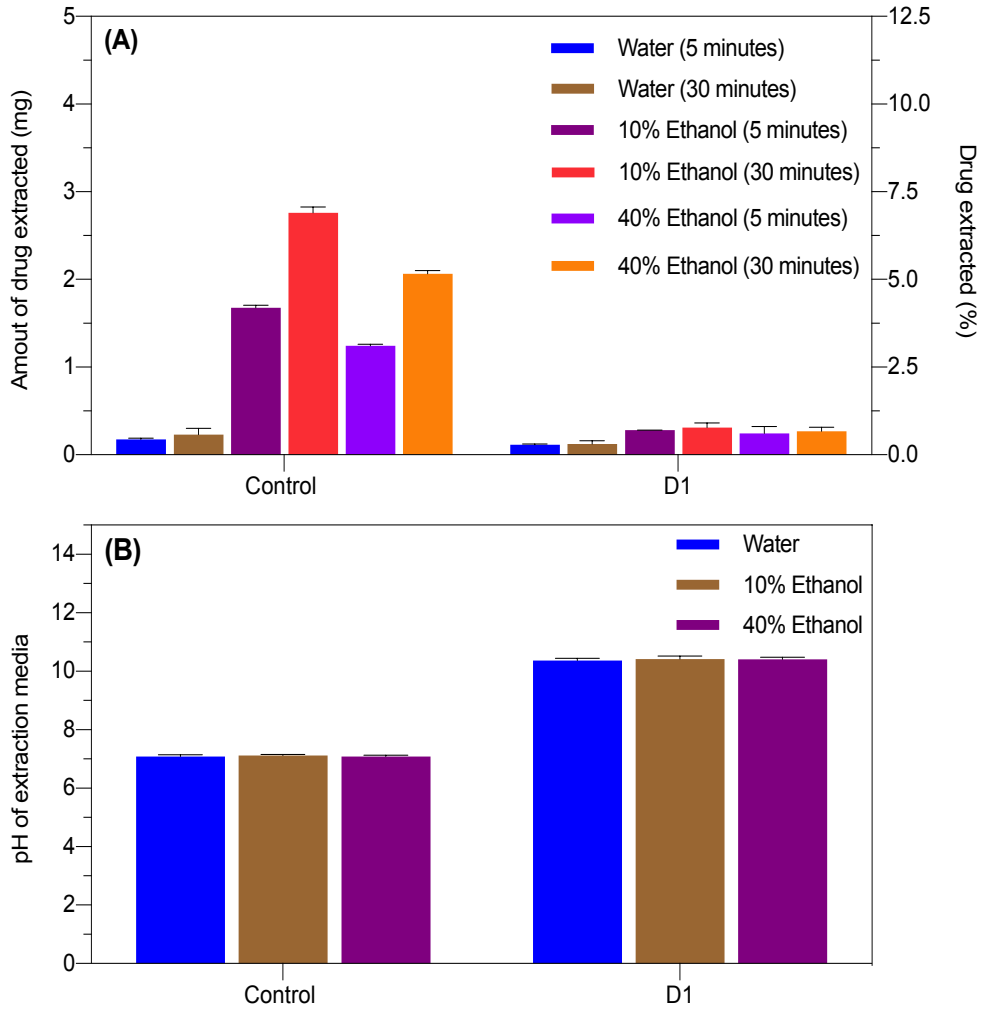

Figure 42: Effect of excipients as a chemical barrier: A) drug extraction study from formulation Q1 in various solvents B) effect of alkalizing agents on pH of drug extraction media at 30 minutes and their comparison with control formulation to minimize the potential abuse (data represent mean ± standard deviation, n = 3)

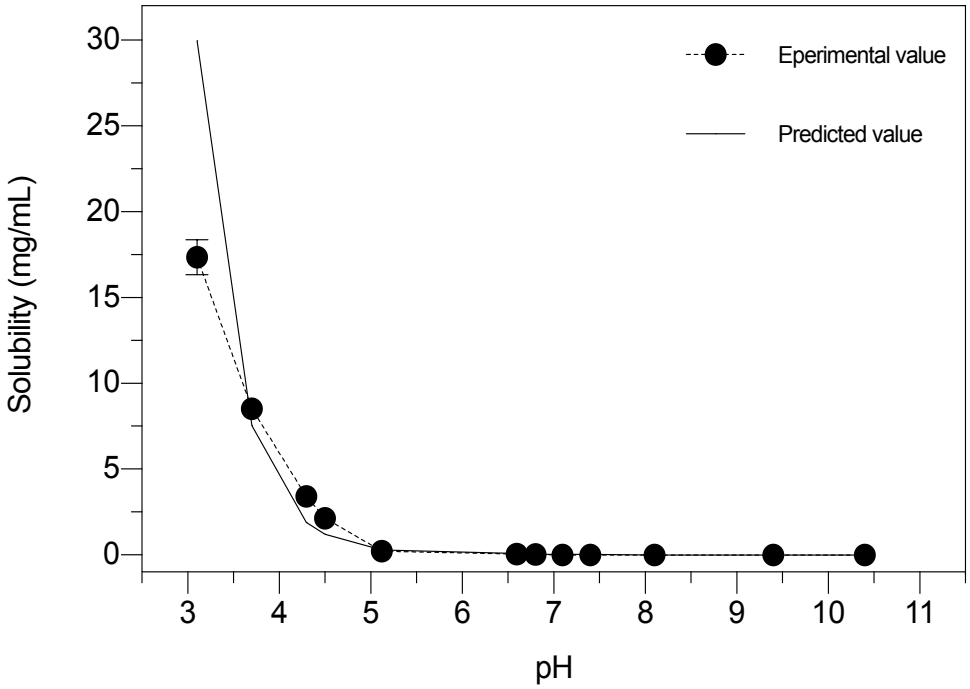

Figure 43: pH-dependent solubility profile of dipyridamole. (data represent mean ± standard deviation, n = 3)

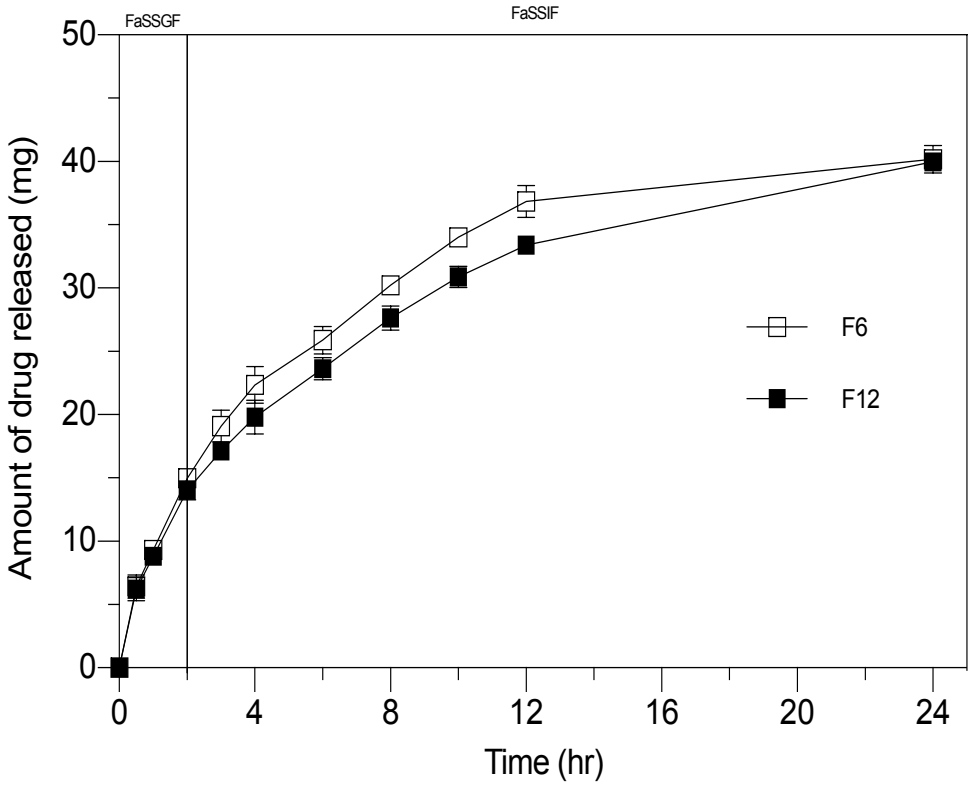

Figure 44: *In-vitro* drug release profiles from oral single-unit of metformin HCl-loaded ADERT of formulation F6 and F12 in FaSSGF for 2 hours followed by FaSSIF for additional 22 hours. (data represent mean ± standard deviation, n = 3; control formulation represents formulation P)

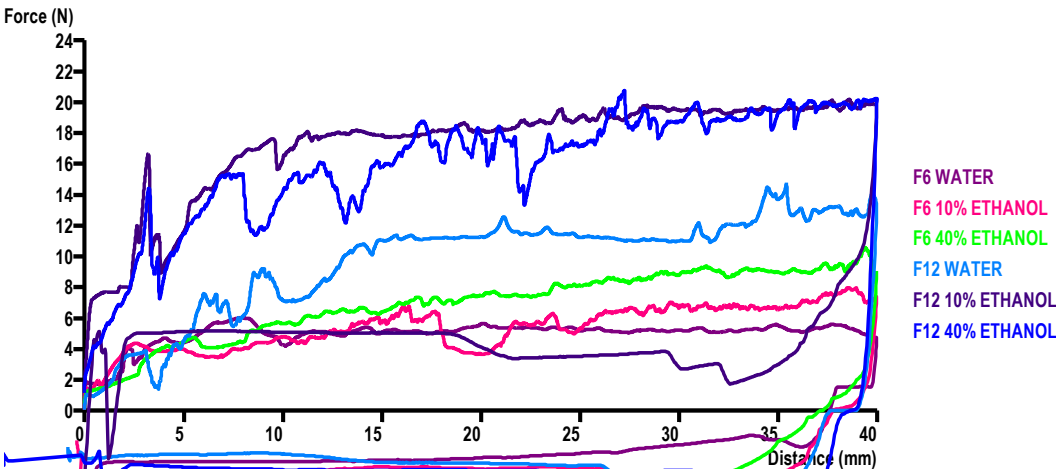

Figure 45: Effect of polymeric solutions (2% w/v) as a physical barrier: Syringe-ability profiles in various solvents. (data represent mean, n = 3-5)

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