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Artículo Invitado | Invited Article

A preformulation strategy for the selection of controlled-release components to simulate a subcutaneous implant

[Una estrategia de preformulación para la selección de componentes de liberación controlada para simular un implante subcutáneo]

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Abstract: Many chronic diseases require repetitive injections as maintenance treatment. It is therefore important to investigate a possible alternative. A simulated subcutaneous implant prototype was fabricated as a polymer matrix covered by cylinder-shape tubing having a porous membrane. Sucrose, bovine serum albumin, and gelatin were selected as matrix excipients. Eight APIs with different physiochemical properties were used to investigate the releasing mechanism. Drug release was tested through an *in vitro* dissolution apparatus. Drug release of eight APIs followed zero-order kinetics with a minimum 12-hour duration. Release rates also showed linear correlations with the APIs' solubilities under physiological pH. For releasing mechanism studies, different combinations of matrix and membrane were investigated in detail. A 144-hour continuous zero-order release of caffeine was achieved as the best controlled simulated prototype. The results showed that drug release of our simulated prototype was primarily achieved by drug diffusion rather than dissolution.

Keywords: Simulation; Subcutaneous implant; Preformulation; Controlled release; Drug diffusion; Drug dissolution

Resumen: Muchas enfermedades crónicas requieren inyecciones repetitivas como tratamiento de mantenimiento. Por lo tanto, es importante investigar una posible alternativa. Se fabricó un prototipo de implante subcutáneo simulado a partir de una matriz de polímero cubierta por un tubo en forma de cilindro que tiene una membrana porosa. La sacarosa, la albúmina de suero bovino y la gelatina se seleccionaron como excipientes matriciales. Se utilizaron ocho APIs con diferentes propiedades fisicoquímicas para investigar el mecanismo de liberación. La liberación del fármaco se probó a través de un aparato de disolución *in vitro*. La liberación del fármaco de las ocho APIs siguió una cinética de orden cero con una duración mínima de 12 horas. Las tasas de liberación también mostraron correlaciones lineales con las solubilidades de las APIs a pH fisiológico. Para los estudios de mecanismos de liberación, se investigaron en detalle diferentes combinaciones de matriz y membrana. El prototipo simulado con mejor control logró una liberación continua de cafeína de orden cero durante 144 horas. Los resultados mostraron que la liberación del fármaco del prototipo simulado ocurrió principalmente mediante la difusión del fármaco en lugar de la disolución.

Palabras clave: Simulación; Implante subcutáneo; Preformulación; Liberacion controlada; Difusión de drogas; Disolución de drogas

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INTRODUCTION

Chronic Disease is the leading cause of death and disability in the United States (Bauer *et al*., 2014). Repeated daily injections of maintenance medication are a problem for both patients and healthcare providers (Burnham *et al*., 2006). Not all maintenance medications can be given orally because of low bioavailability. Limited solubility, limited permeation through membranes or gastrointestinal degradation are the main obstacles for oral dosage forms (Muller & Keck, 2004). Subcutaneous implants are an alternative to resolve the issue of repeated injections for drugs that cannot be given orally. Drug delivery implants have been widely used in cancer treatment, female birth control, and hormone deficiency supplementation (Darney, 1994). Drug molecules in implants are usually released through matrix dissolution, osmotic pressure, or drug diffusion (Lee *et al*., 2010). Currently, implant treatment applications are limited due to: (1) passive drug release based on concentration gradient, (2) the drug release rate cannot be changed once administered under the skin, and (3) the drug release rate slowly decreases with time (FDA, 2001). These implant therapy systems may be improved through a better controlled mechanism of drug delivery that has the capacity to modify drug release rate after implant placement. In the short term, this would result in better therapeutic outcome and fewer adverse effects for patients. In the long term, this would make precision medicine and personalized medicine more feasible in the clinic. From the drug regulatory point of view, such innovation may also be eligible for facilitated regulatory approval in major regulatory agencies, including FDA and EMA (Liberti *et al*., 2016a; Liberti *et al*., 2016b).

It is therefore important to perform preformulation studies to select and investigate possible excipients and components that may contribute to an implant with (1) stable long-term zero-order drug release and (2) the capacity to change dosing after administration.

It was hypothesized that a slow dissolving matrix covered by a porous membrane should provide a controlled drug release. In addition, a long-term zero-order release could be achieved through the proper combination of an erodible matrix and a porous membrane. Therefore, the main objective of this project was to understand the drug release parameters to design an optimized prototype. All factors, including the membrane, the matrix, and the physical properties of the drugs themselves, need to be considered in such research. Flowchart No. 1 shows the proposed preformulation strategy for selection of excipients and components for the implant prototype. This research focuses on small molecule drugs. Small molecules were used because properties like membrane void fraction and matrix density could be studied without the cost associated with larger molecules. The final prototype is intended to be used on both small molecules and macro-molecules.

MATERIALS AND METHODS

Materials

Bovine serum albumin, fraction V, 97% pH 7, Lyophilized powder and Gelatin, type A, 175 Bloom Powder were purchased from Alfa Aesar. Sucrose (Ultra Centrifugation Grade) was provided by Fisher Biotech. Caffeine Monohydrate was acquired from MP Biomedicals. Guaifenesin, propranolol, and ibuprofen were provided by Spectrum Chemicals. Prednisolone and Metoprolol tartrate were provided by TCI Chemicals. Acetaminophen, formic acid, phosphoric acid, and sodium hydroxide were purchased from Sigma-Aldrich Company. Phosphate Buffered Saline (10X) and acetonitrile were purchased from Fisher Scientific. Deionized water was purified from tap water through a Thermal Fisher DI Water system. The Falcon® cell culture insert (24 well, 8, 3 and 0.4 µm pore size) and the polyethylene plug cap were ordered from Fisher Scientific.

High performance liquid chromatography

All samples generated were assayed through HPLC. an Agilent 1100 Series with autosampler injection and multi-wavelength detector was used for all HPLC assays. 50 MMol PH 3.0 OR 7.0 Phosphate Buffer was used in the mobile phase. The HPLC setting details are listed in supplementary No. 1.

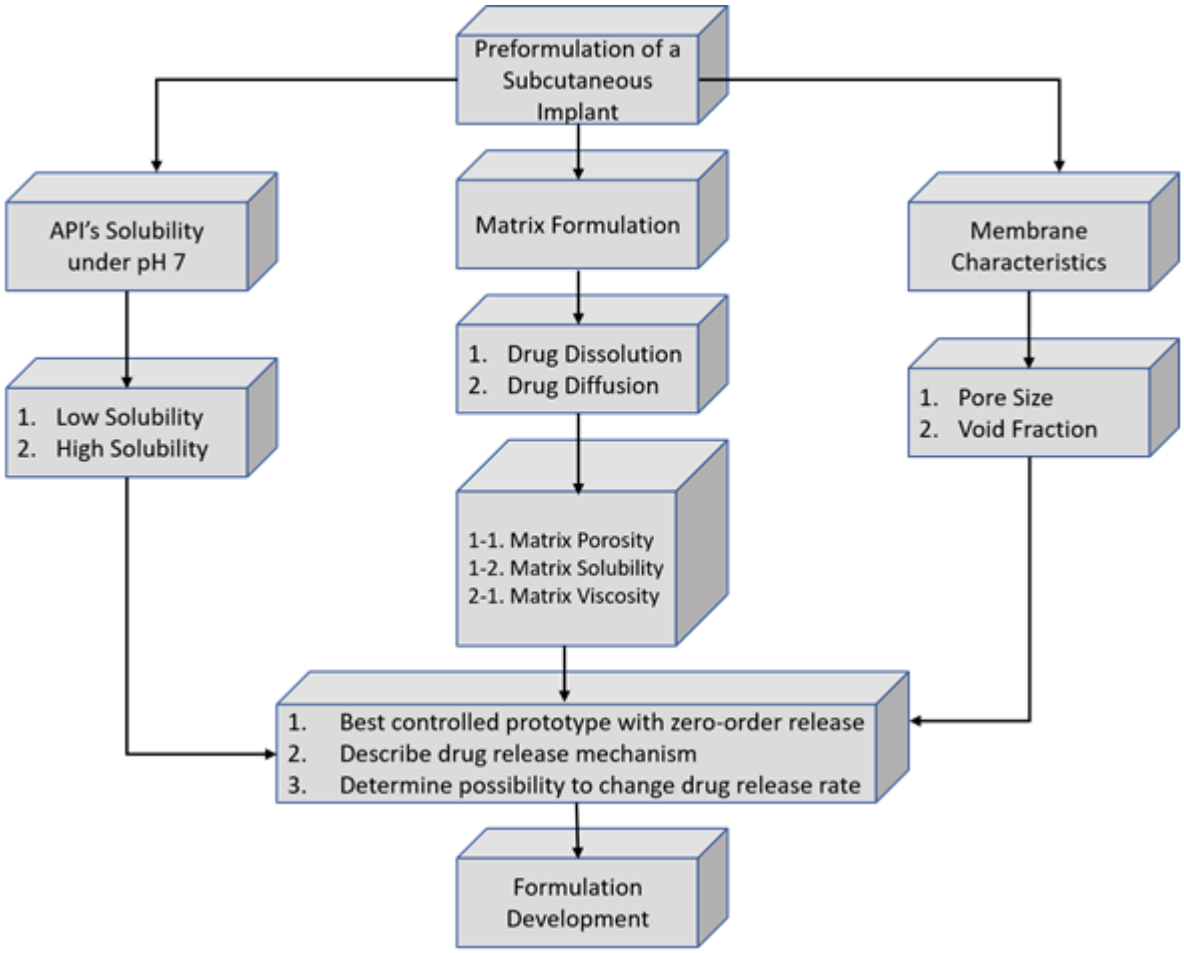
Matrix preparation: polybag blending

Small batch blending was performed using a polyethylene bag and a vortex blender (Fisher Scientific). Specifically, a Warning® Commercial High-Speed Blender was used to blend the excipients at “High Speed” for 10 minutes to a uniform fine particle size. The excipients were mixed with the APIs in a polyethylene bag (4” long and 6” high). The bag was purged with helium before sealing to

improve flowability. The polybag was vortexed for 10 minutes to ensure complete mixing. A visual inspection was performed for blending quality.

Matrix preparation: lyophilization

For water-soluble drugs, a uniform mixture of API and excipients may be prepared through a complete dissolution followed by lyophilization. Caffeine monohydrate matrix was prepared through this method. All excipients and caffeine were dissolved in a stainless-steel beaker. After forming a clear solution, the beaker was transferred into a -80°C freezer for one hour. This temperature and time were selected to ensure complete freezing. Lyophilization was performed on Labconco FreeZone lyophilizer. The temperature was set to -44°C and pressure to 0.150-0.05 Torr. Overnight lyophilization was performed.



Flowchart No. 1
Proposed preformulation strategy for selection of excipients and components for implant prototype

Compaction of powder

The lyophilizing cake or fine blender were compacted via a Carver® Lab Press Model C. The diameter of the tablet mold was 7.12 mm. The goal is to create a tablet-shape matrix. The handle was pressed slowly to avoid any sharp increase in the compacting pressure. Pressure was maintained at readable zero throughout the process. The final product was a tablet shape matrix of 7.12 mm diameter and 80 to 90 mm height. Figure 1 shows the

steps to prepare the matrices for the different APIs.

Fabrication of Tablet-in-Insert (TII) Prototype

A preliminary estimate of a fully developed implant used the dimensions of a 3-inch implant administered by a 16-gauge needle. Using this as a preliminary specification, the implant would have a volume of 0.085 ml and a surface area of 2.88 cm^2. The last step in fabrication was to put the tablet matrix into a Falcon® Cell Culture Insert. The Falcon inserts were used preliminarily to attain the flux and to calculate the estimated drug release rate. These inserts have a volume of approximately 0.3 ml and a surface area of 0.3 cm^2. A spring was placed vertically in the insert. The spring was used to prevent the tablet from flipping inside of the prototype and to maintain contact with the porous membrane. The spring is not intended to add any force to the tablet. The spring occupies only a very small volume and thus should not influence buffer filtration. The insert was sealed with a plastic plumb cap and the membrane was the only exchange surface with the external environment (Figure No. 1). This is a Tablet-in-Insert (TII) device. Several prototypes were fabricated and tested. Detailed information is provided in Table No. 1.

Table No. 1
Components of All Tested Porotypes (A to L)

Prototype	Pore (µm)	Membrane Void Fraction (%)	Sucrose (mg)	Albumin (mg)	Gelatin (mg)	API (mg)	Total Matrix (mg)
A	**8**	**12.06%**	**125**	**125**	**0**	**25**	**275**
B	**3**	**22.61%**	**125**	**125**	**0**	**25**	**275**
C	**8**	**12.06%**	**187.5**	**62.5**	**0**	**25**	**275**
D	**3**	**22.61%**	**187.5**	**62.5**	**0**	**25**	**275**
E	**0.4**	**1.00%**	**100**	**150**	**0**	**25**	**275**
F	**0.4**	**1.00%**	**75**	**175**	**0**	**25**	**275**
G	**0.4**	**1.00%**	**50**	**200**	**0**	**25**	**275**
H	**0.4**	**1.00%**	**25**	**200**	**25**	**25**	**275**
I	**0.4**	**1.00%**	**0**	**200**	**50**	**25**	**275**
J	**0.4**	**1.00%**	**0**	**175**	**75**	**25**	**275**
K	**0.4**	**1.00%**	**125**	**125**	**0**	**25**	**275**
L	**0.4**	**1.00%**	**187.5**	**62.5**	**0**	**25**	**275**

In vitro drug releasing test

All drug releasing tests were performed on a Vankel 7010 dissolution system. All experiments used a USP apparatus I - basket. The rotation speed was 50 RPM. Temperature was controlled at 37°C. The media used was 50 mMol pH 7.4 phosphate buffer. All samples were extracted by auto-sampler.

Statistical Analysis

All experiments were performed in triplicate. All data were analyzed in GraphPad Prism 5 software and are reported as mean± standard error.

RESULTS

Pilot study: Multi-drug in vitro release

We tested 8 small molecule drugs with prototype A's excipients and components. All prototypes were fabricated with 125 mg sucrose, 125 mg albumin, 25 mg APIs and 8 µm membrane with 12.06% void fraction. The releasing rate is shown in Figure No. 2A. All 8 drugs followed a zero-order release for 24 hours. The releasing rates vary based on drug properties. Supplementary No. 2 is the comparison of drug releasing rate and physiochemical properties of all APIs (DrugBank, 2019; Mani *et al.*, 2003; Valko *et al.*, 2003; Shaw *et al.*, 2005; Bhowmick *et al.*, 2013; Morris & Dunham, 2019). A regression analysis was performed between drug release rate and drug solubility. Drug release rates for all APIs are considered statistically significant. Drug release rates were linearly related to solubility for prednisolone, benzoic acid, ibuprofen, acetaminophen, propranolol hydrochloride, guaifenesin and caffeine (Figure No. 2B).

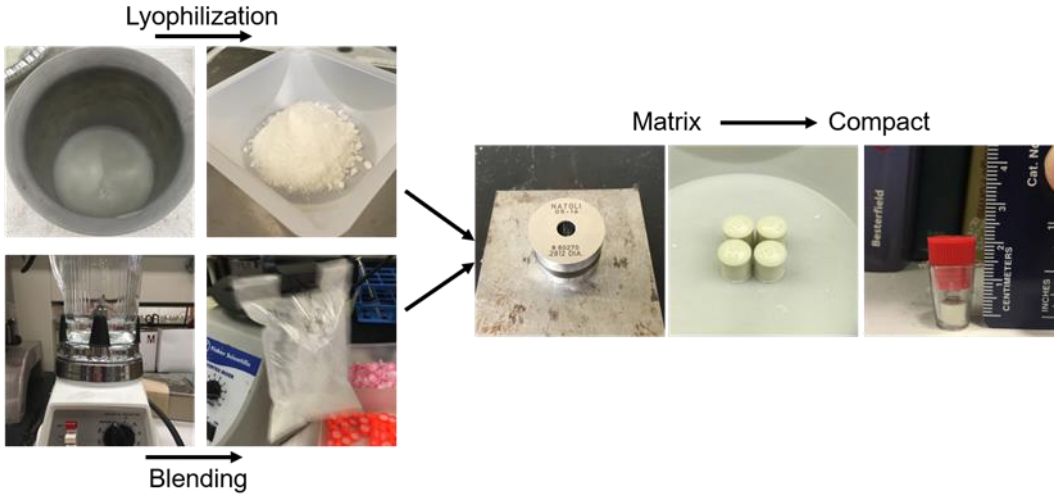


Figure No. 1
Fabrication Process of Implant Prototype.

Effect of membrane void fraction on caffeine release

Caffeine was chosen as the high solubility model drug because it was hypothesized that the effect of drug dissolution would be minimized, and the diffusion aspects of the excipients could be better evaluated.

In initial experiments, it was observed that caffeine release was faster with higher void fraction membrane. Figure No. 3A is the *in vitro* caffeine release with the same matrix but different membrane void fractions. Zero-order release was achieved for 16 hours for those 5 prototypes. Prototype D had the fastest caffeine release rate, and maintained zero-order release for 16 hours before slowing down. The decrease in caffeine release was due to the depletion of the matrix since more than 80% of the total drug was released. Supplementary No. 3 contains detailed prototype information and release rates sorted by membrane void fraction. Figure No. 3B shows data for caffeine release rate and flux with the different prototypes. We also calculated the maximum estimated caffeine release rate if using a 3-inch implant administered by a 16-gauge needle.

Effect of matrix composition on caffeine release

The effects of the matrix were investigated after the correct membrane void fraction was determined from the previous section. From **Figure No. 3A**, it can be observed that prototype C with more sucrose had a more rapid drug release than prototype B, while prototype C had smaller membrane void fractions. This phenomenon indicated that the matrix composition might have a more important role than the membrane void fraction for some prototypes.

Prototypes E through G showed that reduction of the amount of sucrose reduces the drug release rate of caffeine from the matrix (Figure No. 4A).

In prototypes H through J, the amount of gelatin was increased. The drug release rate of caffeine was reduced for these prototypes. Additionally, a zero-order drug release was observed for prototype I over 144 hours. This makes it a viable option for extremely long drug release. Figure No. 4B shows data for caffeine release rate and flux. We also calculated the maximum estimated caffeine release rate if using a 3-inch implant administered by a 16-gauge needle. Supplementary No. 4 provides details of the caffeine release rate and the modification of the matrix.

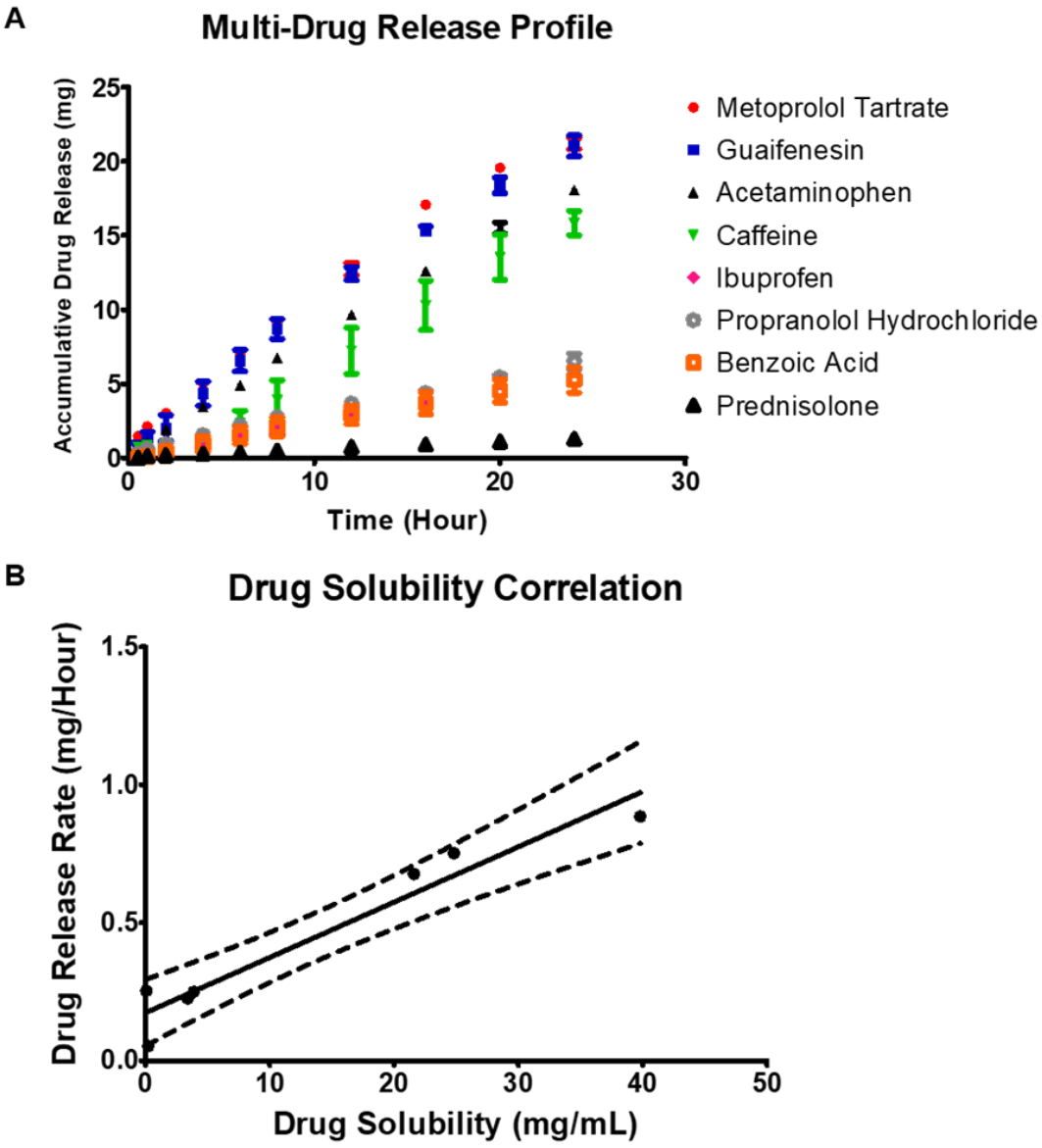


Figure No. 2

Multi-drug *in vitro* release result of prototype A. 2-A: Diffusion profile. Data are expressed as mean ± SEMs. 2-B: Solubility and drug release rate correlation for prednisolone, benzoic acid, ibuprofen, acetaminophen, propranolol hydrochloride, guaifenesin and caffeine. R2=0.9339. Dotted lines indicate 95% confidence band. Data are expressed as mean ± SEMs

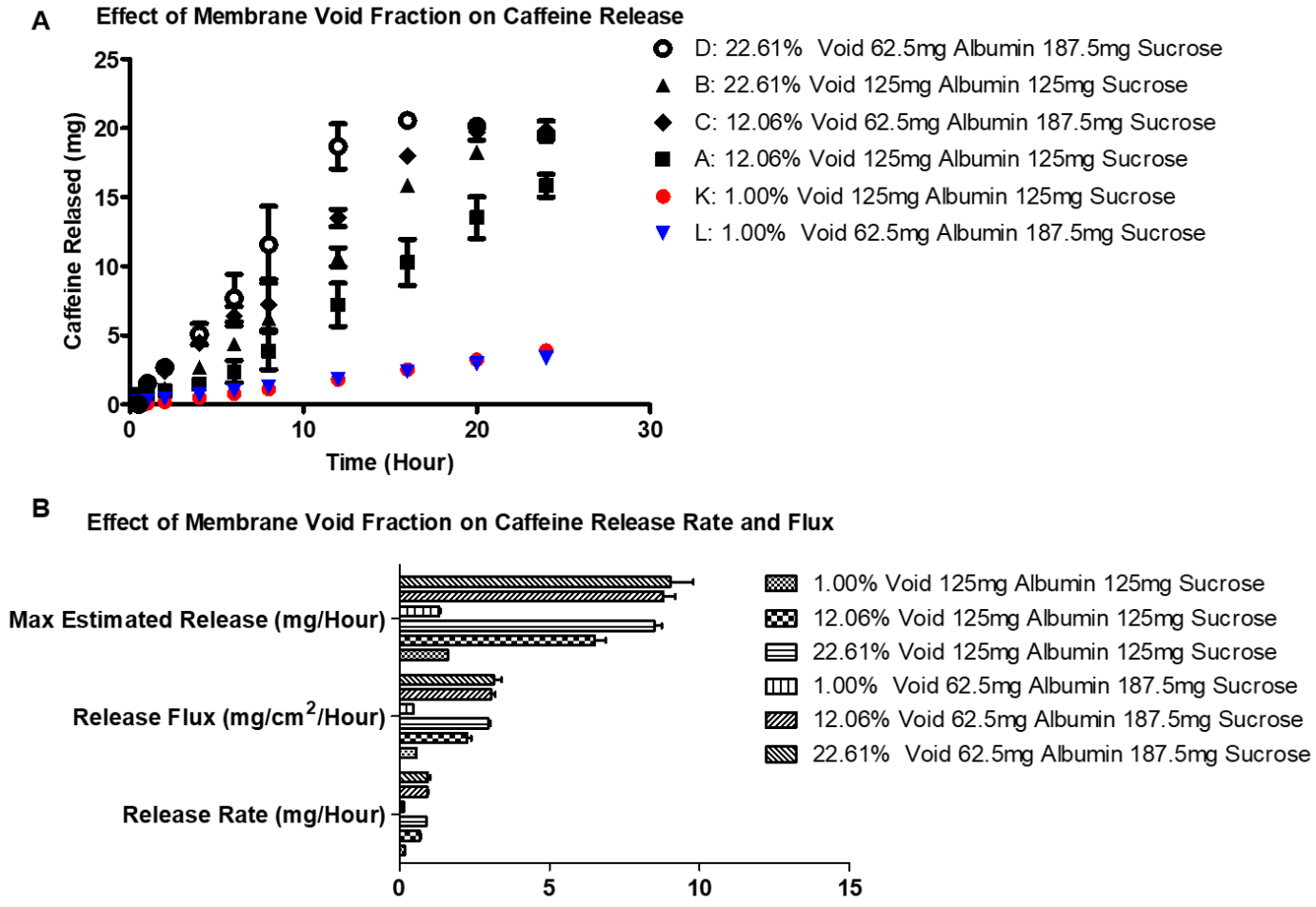


Figure No. 3
***In vitro* caffeine release with different membrane**
3-A: Effect of membrane void fraction on caffeine release. Data are expressed as mean ± SEMs. 3-B: Effect of membrane void fraction on caffeine release rate and flux. Data are expressed as mean ± SEMs

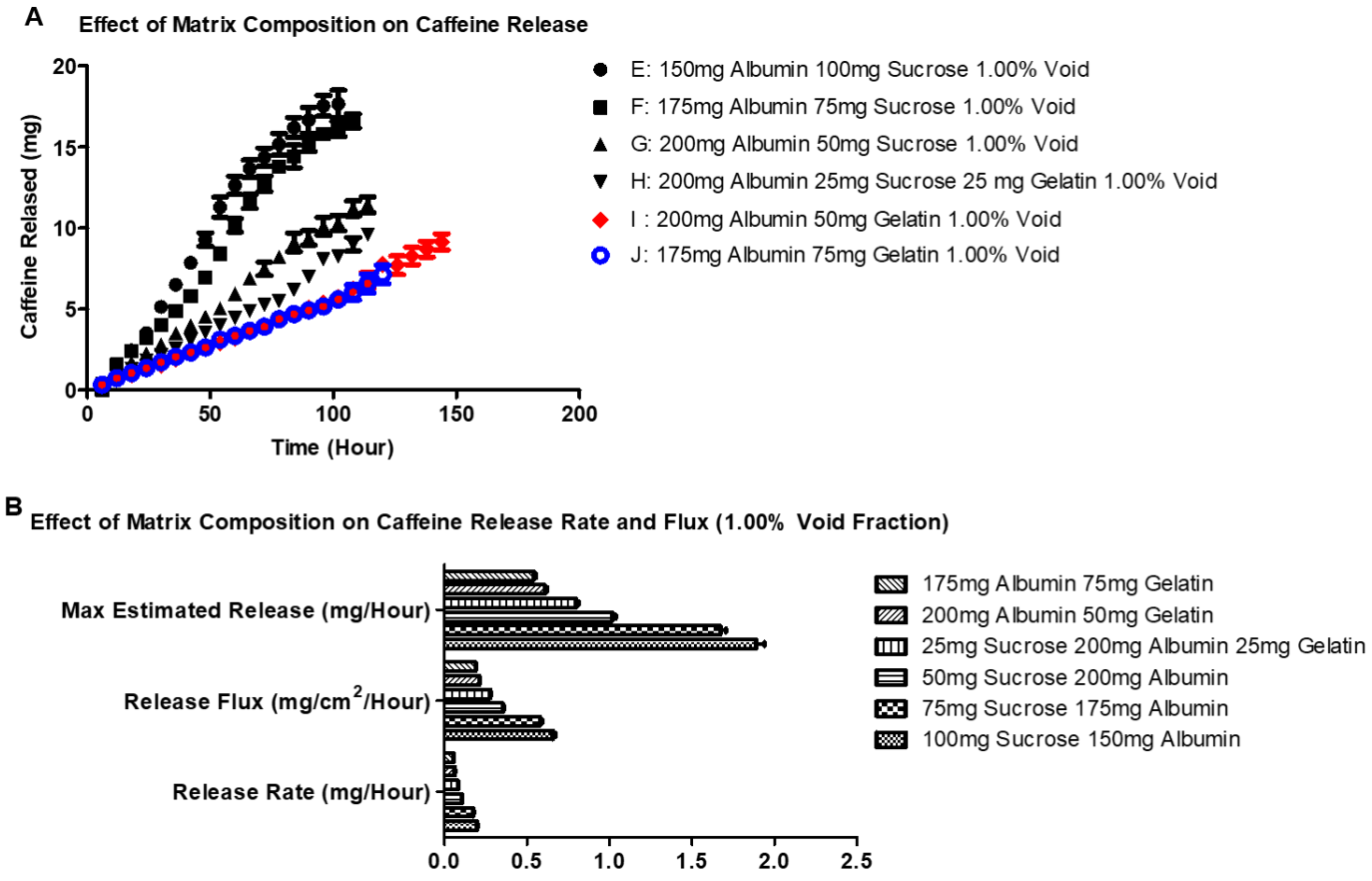


Figure No. 4
***In vitro* caffeine release with different matrix**
4A: Effect of matrix composition on caffeine release. 4B: Effect of matrix composition on caffeine release rate and flux. Data are expressed as mean ± SEMs

DISCUSSION

Drug release mechanism

The intended device has a limited volume but a variable surface area. In this study, Falcon inserts were used because they have a limited volume and a set surface area. Therefore, the limits of formulation and the drug release mechanism can be determined. In addition, these inserts allow us to visualize the drug release process (Figure No. 5A).

If the Noyes-Whitney equation is considered (Equation No. 1), two of the important factors are Drug Solubility (C_s) and surface area (A). C_s is the maximum limit of C_2. In our study, low-solubility drugs definitely show that C_s is a rate-limiting mechanism. The low solubility of Benzoic acid, prednisone, and propranolol definitely show that solubility controls the drug release rate (Figure No. 2A). The higher solubility drugs do not show as much time dependence since the drug totally dissolves in the media and C_s is not reached (Figure No. 5B). Therefore, drug load in the matrix becomes the important term to determine C_2 (Smith, 2015).

Solubility and dissolution-controlled drug release have been reported by many publications. It has been reported by Bettini *et al*. (2001), that drugs with higher solubility were released at a faster rate from a HPMC-based hydrogel. Similarly, Li *et al*. (2008), reported faster drug release from Polyethylene Oxide (PEO) matrix tablets for higher soluble drugs. The importance of drug solubility and its influence have been widely investigated. Technologies have been discovered in the past

decade to improve drug solubility in order to provide greater drug bioavailability (Leuner & Dressman, 2000; Khadka *et al*., 2014).

For high-solubility drugs, drug diffusion is controlled by either the void fraction of the rate-limiting membrane or the erosion of the drug matrix. Membrane void fraction may indirectly change the surface area (A) of diffusion (**Equation No. 1**). For example, in prototype D, for caffeine, the matrix has a high sucrose content, a low albumin content, and a high void membrane. While drug release may be zero-order in the beginning, the release rate slows at the end of the study due to drug reservoir depletion. Prototype L has the same composition as Prototype D, but the drug release rate is much reduced because of the use of a low void fraction membrane (Figure No. 3A).

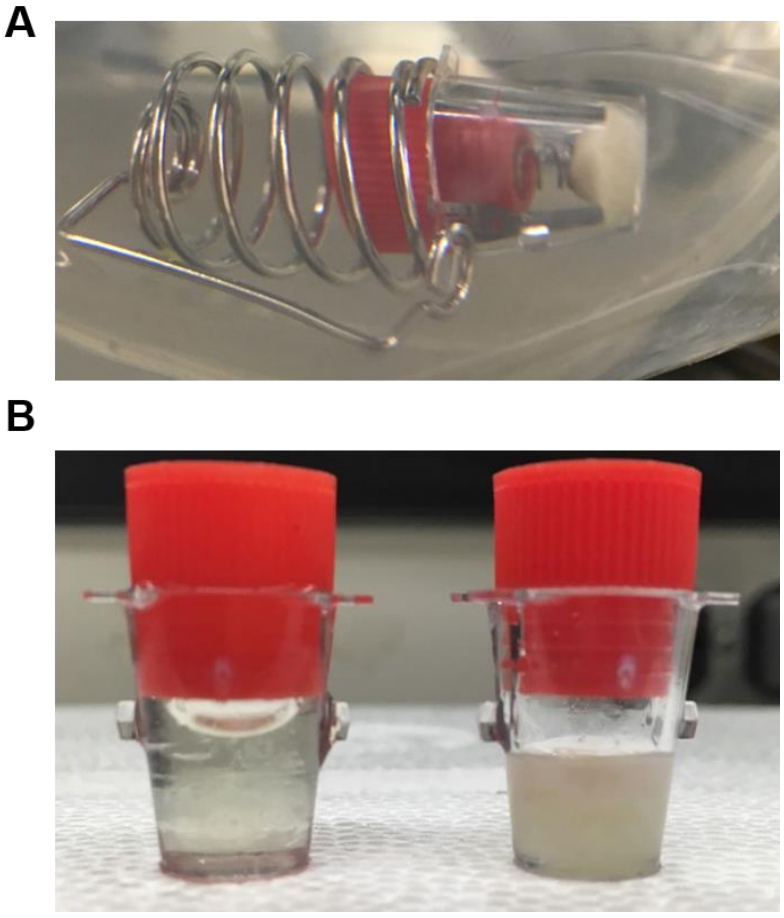


Figure No. 5
Visual observation of experimental prototypes. 5A: Demonstration of buffer infiltration into prototype using capsule Sinker. 5B: Visual inspection for prototypes of guaifenesin (Left) and benzoic acid (Right)

Membrane control via a change in surface area has been discussed in many research articles. Jeon et al. described a method using electrical current to induce change in membrane void fraction. Drug release rate was significantly lowered with a lower membrane void fraction (Jeon *et al*., 2011). Membrane coating was also used in tablet dosage forms to provide controlled drug release (Colombo *et al.*, 1990; Conte *et al*., 1993). Bayraktar *et al*. (2005), reported using silk fibroin as a coating material for the tablet to provide controlled release of theophylline. It is commonly recognized that drug release is controlled by membrane void fracture and channels in solid dosage forms.

$$\frac{dm}{dt} = A\frac{D}{L}(C_2 - C_1)$$

Equation No. 1

Noyes-Whitney Equation: (dm/dt is the rate of dissolution. A is the surface area of the solid. C_1 is the concentration of the solid in the bulk dissolution media. C_2 the concentration of the solid in the diffusion layer surrounding the solid. D is the diffusion coefficient. L is the diffusion layer thickness.)

The effect of the matrix is more complicated. Erosion of the matrix slows drug release through increasing the diffusion coefficient (D) due to viscosity (Equation No. 1). As excipient material diffuses out of the matrix the viscosity of the solution drops and allows for the release of the drug.

In our matrix formulation, we used three different materials to control matrix erosion. This is an indirect change in surface area (A). These excipients were sucrose, albumin, and gelatin. Sucrose does increase viscosity and also makes a compressible matrix, but it diffuses quickly out of the matrix with minimal modification in viscosity. Albumin is a globular protein with a molecular weight of 66,463 Da. An albumin matrix dissolves slowly, slows the diffusion of the drug delivered, and also forms a viscous matrix which limits drug diffusion. However, there is a limit to which albumin can slow drug release. Albumin itself will eventually dissolve and diffuse out of the matrix. This reduces viscosity and allows for drug release. Since albumin is globular, the molecular radius is fixed and swelling of the protein is limited.

Sucrose has been widely used to increase matrix porosity (Selkirk & Ganderton, 1970; Mohanta *et al*., 2014). A high sucrose tablet matrix usually disintegrates very quickly (Lieberman *et al*., 1989; Adolfsson & Nyström, 1996; Shivanand & Sprockel, 1998). In addition, sucrose is highly used as a lyo-protectant to protect protein conformation (Ressing *et al*., 1992; Johnson *et al*., 2002). Albumin is widely discussed as a drug delivery carrier (Stehle *et al*., 1997; Kosasih *et al*., 2000). Elsadek and Kratz (2012), reviewed albumin-based drug products which are approved in clinical trials and in research stage. They also pointed out the common drug binding sites of albumin. Elzoghby *et al*. (2012a), discussed the application of albumin in nanoformulations. Most globular proteins have the capacity to maintain structure without unfolding in a mild environment (Murphy *et al*., 1990; Elzoghby *et al*., 2012b).

Gelatin is denatured collagen and is in the form of a random coil. Gelatin will limit drug release but is much slower to leave the matrix because as a random coil, swelling of the protein occurs. Swelling increases viscosity more than albumin and also slows the erosion of the matrix by filling the entire volume of the matrix (Figure No. 4A). Using gelatin alone would not be advised because compression of the matrix would be difficult, and the matrix would have almost no erosion.

In our formulations, gelatin was functioning similarly to a noncovalent polymer (Tanford *et al*., 1967). Ofner and Schott noticed that buffer solution absorbed by every unit of gelatin is a function of time (Ofner & Schott, 1986). Years later, Wlez and Ofner noticed that gelatin could be crosslinked to improve its control over drug release. Northrop and Kunitz pointed out that gelatin swelling increases with the temperature and concentration of gelatin (Northrop & Kunitz, 1930). All of their explanations are consistent with the decreasing caffeine release rate from prototypes G through I. In addition, Vazquez *et al*. (1995), used gelatin as a swelling frame to successfully perform polymer grafting. Similar to albumin, gelatin nanoparticles also provide controlled drug release through swelling (Bajpai & Choubey, 2006).

For this particular insert prototype, sucrose, albumin, and gelatin were used to provide for a zero-order drug release. Sucrose promoted the initial drug release and reduced lag-time for the insert. Albumin formed the bulk of the matrix and gelatin was used to slow drug release from the matrix more effectively than albumin. The membrane void fraction can be used to further control the diffusion from the matrix.

Summary and projection

In summary, drug release from our prototype is dominated by diffusion. Our preformulation prototype can be considered as a hybrid of reservoir and monolithic devices. Drug molecules should diffuse out of the matrix first, then diffuse through the porous membrane. The overall drug release will follow zero-order kinetics if under sink condition. The slow step will control the release rate and the ultimate release should follow Equation No. 2:

$$M_t = AD_m K \frac{C_d - C_0}{\delta} t$$

Equation No. 2

Drug release model from diffusion controlled device (A is the surface area of membrane, D_m is the diffusion coefficient, C_d is the API concentration in solution form inside of the device, C_0 is the API concentration in the buffer. Under sink condition, C_0 equals to 0. δ is the thickness of porous membrane)

Our prototype may be designed to deliver different APIs. Specific API's solubility under pH 7 and 25°C will determine the starting point of the design. For a specific API with a target releasing rate, a Design of Experiment (DOE) is needed to calculate the composition of excipients and membrane.

This preformulation research indicated two potential strategies to adjust drug release rate after implant placement. The first method is through adjusting the membrane void fracture. This method could be achieved by adjusting membrane pore size or total surface area. Jeon *et al*. (2011), successfully changed a membrane's pore size using electric power, which could be utilized for future research. The other method to adjust drug release rate is through modifying the drug matrix. Unfortunately, with the current composition, it would be difficult to change the ratio of sucrose, albumin, and gelatin. A "matrix adjustor" needs to be discovered first before executing this idea.

CONCLUSION

In this article, we built a preformulation simulated prototype for potential use as a long-term drug delivery implant system. Even though this prototype is conceptual, we still consider it as a convincing starting point. The drug release mechanism was fully explained by the dissolution and diffusion processes. Visual inspection and experimental data support our hypothesis. We also proposed methods to apply this prototype to an unknown API and to change the drug release rate after implant placement. Future research will expand this preformulation strategy to other molecules, including peptides and proteins, and will seek to refine methods to control drug release rate after administration. In addition, formulation developments using 3-D printing technology will be evaluated. Revotek Co., Ltd, a leading 3D bio-printing company headquartered in Memphis, Tennessee, will be collaborating in future research.

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REFERENCES

Adolfsson Å, Nyström C. 1996. Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads. **Int J Pharm** 132: 95 - 106. **https://doi.org/10.1016/0378-5173(95)04336-5**

Bajpai AK, Choubey J. 2006. Design of gelatin nanoparticles as swelling controlled delivery system for chloroquine phosphate. **J Mater Sci Mater Med** 17: 345 - 358. **https://doi.org/10.1007/s10856-006-8235-9**

Bauer UE, Briss PA, Goodman RA, Bowman BA. 2014. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. **The Lancet** 384: 45 - 52. **https://doi.org/10.1016/s0140-6736(14)60648-6**

Bayraktar O, Malay Ö, Özgarip Y, Batıgün A. 2005. Silk fibroin as a novel coating material for controlled release of theophylline. **Eur J Pharm Biopharm** 60: 373 - 381. **https://doi.org/10.1016/j.ejpb.2005.02.002**

Bettini R, Catellani PL, Santi P, Massimo G, Peppas NA, Colombo P. 2001 Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. **J Control Rel** 70: 383 - 391. **https://doi.org/10.1016/s0168-3659(00)00366-7**

Bhowmick M, Sengodan T, Nitin D, Gaidhane KR, Sivakumar T. 2013. Metoprolol tartrate-an ideal drug candidate for transdermal antihypertensive therapy: It's preliminary preformulation screening. **Asian J Chem** 25: 1501 - 1504. **https://doi.org/10.14233/ajchem.2013.13108**

Burnham R, McNeil S, Hegedus C, Gray D. 2006 Fibrous myopathy as a complication of repeated intramuscular injections for chronic headache. **Pain Res Manag J Can Pain Soc** 11: 249 - 252.

https://doi.org/10.1155/2006/198751

Colombo P, Conte U, Gazzaniga A, Maggi L, Sangalli ME, Peppas NA, La Manna A. 1990. Drug release modulation by physical restrictions of matrix swelling. **Int J Pharm** 63: 43 - 48. **https://doi.org/10.1016/0378-5173(90)90099-p**

Conte U, Maggi L, Colombo P, La Manna A. 1993. Multi-layered hydrophilic matrices as constant release devices (GeomatrixTM Systems). **J Control Rel** 26: 39 - 47. **https://doi.org/10.1016/0168-3659(93)90207-l**

Darney PD. 1994. Hormonal implants: Contraception for a new century. **Am J Obstet Gynecol** 170: 1536 - 1543.

DrugBank Drugs. 2019. **DrugBank**. https://www.drugbank.ca/drugs. Accessed 9 Jun 2019

Elsadek B, Kratz F. 2012. Impact of albumin on drug delivery - New applications on the horizon. **J Control Rel** 157: 4 - 28. **https://doi.org/10.1016/j.jconrel.2011.07.031**

Elzoghby AO, Samy WM, Elgindy NA. 2012a. Albumin-based nanoparticles as potential controlled release drug delivery systems. **J Control Rel** 157: 168 - 182. **https://doi.org/10.1016/j.jconrel.2011.07.031**

Elzoghby AO, Samy WM, Elgindy NA. 2012b. Protein-based nanocarriers as promising drug and gene delivery systems. **J Control Rel** 161: 38 - 49. **https://doi.org/10.1016/j.jconrel.2012.04.036**

Falcon Falcon® Cell Culture Inserts. 2019. Https://ecatalog.corning.com/life-sciences/b2c/US/en/Permeable-Supports/Inserts/Falcon%C2%AE-Cell-Culture-Inserts/p/falconCellCultureInserts. Accessed 25 Jul 2019

FDA. 2001. **Nexplanon** (etonogestrel implant) Label - FDA

Jeon G, Yang SY, Byun J, Kim JK. 2011. Electrically actuatable smart nanoporous membrane for pulsatile drug release. **Nano Lett** 11: 1284 - 1288. **https://doi.org/10.1021/nl104329y**

Johnson RE, Kirchhoff CF, Gaud HT. 2002. Mannitol–sucrose mixtures-versatile formulations for protein lyophilization. **J Pharm Sci** 91: 914 - 922. **https://doi.org/10.1002/jps.10094**

Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J. 2014. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. **Asian J Pharm Sci** 9: 304 - 316. **https://doi.org/10.1016/j.ajps.2014.05.005**

Kosasih A, Bowman BJ, Wigent RJ, Ofner CM. 2000. Characterization and *in vitro* release of methotrexate from gelatin/methotrexate conjugates formed using different preparation variables. **Int J Pharm** 204: 81 - 89. **https://doi.org/10.1016/s0378-5173(00)00476-2**

Lee SS, Hughes P, Ross AD, Robinson MR. 2010. Biodegradable implants for sustained drug release in the eye. **Pharm Res** 27: 2043 - 2053. **https://doi.org/10.1007/s11095-010-0159-x**

Leuner C, Dressman J. 2000. Improving drug solubility for oral delivery using solid dispersions. **Eur J Pharm Biopharm** 50: 47 - 60. **https://doi.org/10.1016/s0939-6411(00)00076-x**

Li H, Hardy RJ, Gu X. 2008. Effect of drug solubility on polymer hydration and drug dissolution from polyethylene oxide (PEO) matrix tablets. **AAPS Pharm Sci Tech** 9: 437 - 443. **https://doi.org/10.1208/s12249-008-9060-x**

Liberti L, Breckenridge A, Hoekman J, Leufkens H, Lumpkin M, McAuslane N, Stolk P, Zhi K, Rägo L. 2016a. Accelerating access to new medicines: Current status of facilitated regulatory pathways used by emerging regulatory authorities. **J Public Health Policy** 37: 315 - 333. **https://doi.org/10.1057/jphp.2016.8**

Liberti L, Breckenridge A, Hoekman J, Leufkens H, Lumpkin M, McAuslane N, Stolk P, Zhi K, Rägo L. 2016b. **Practical aspects of developing, implementing and using facilitated regulatory pathways in the emerging markets.** Poster Drug Information Association Annual Meeting, Philadelphia, PA, USA.

Lieberman HA, Lachman L, Schwartz JB. (Eds). 1989. **Pharmaceutical dosage forms: tablets.** Dekker, New York, USA.

Mani N, Jun HW, Beach JW, Nerurkar J. 2003. Solubility of guaifenesin in the presence of common pharmaceutical additives. **Pharm Dev Technol** 8: 385 - 396. **https://doi.org/10.1081/pdt-120024692**

Mohanta K, Kumar A, Parkash O, Kumar D. 2014. Processing and properties of low cost macroporous alumina ceramics with tailored porosity and pore size fabricated using rice husk and sucrose. **J Eur Ceram Soc** 34: 2401 - 2412. **https://doi.org/10.1016/j.jeurceramsoc.2014.01.024**

Morris J, Dunham A. 2019. **Metoprolol.** In: StatPearls. StatPearls Publishing, Treasure Island, Florida, USA.

Muller RH, Keck CM. 2004. Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles. **J Biotechnol** 113: 151 - 170.

https://doi.org/10.1016/j.jbiotec.2004.06.007

Murphy K, Privalov P, Gill S. 1990. Common features of protein unfolding and dissolution of hydrophobic compounds. **Science** 247: 559 - 561. **https://doi.org/10.1126/science.2300815**

Northrop JH, Kunitz M. 1930. Swelling and hydration of gelatin. **J Phys Chem** 35: 162 - 184.

Ofner CM, Schott H. 1986. Swelling studies of gelatin I: Gelatin without additives. **J Pharm Sci** 75: 790 - 796. **https://doi.org/10.1002/jps.2600750814**

Ressing ME, Jiskoot W, Talsma H, van Ingen CW, Beuvery EC, Crommelin DJA. 1992. The influence of sucrose, dextran, and hydroxypropyl-β-cyclodextrin as lyoprotectants for a freeze-dried mouse IgG2a monoclonal antibody (MN12). **Pharm Res** 9: 266 - 270. **https://doi.org/10.1023/a:1018905927544**

Selkirk AB, Ganderton D. 1970. An investigation of the pore structure of tablets of sucrose and lactose by mercury porosimetry. **J Pharm Pharmacol** 22: 79S - 85S. **https://doi.org/10.1111/j.2042-7158.1970.tb08584.x**

Shaw LR, Irwin WJ, Grattan TJ, Conway BR. 2005. The effect of selected water-soluble excipients on the dissolution of paracetamol and ibuprofen. **Drug Dev Ind Pharm** 31: 515 - 525. **https://doi.org/10.1080/03639040500215784**

Shivanand P, Sprockel O. 1998. A controlled porosity drug delivery system. **Int J Pharm** 167: 83 - 96. **https://doi.org/10.1016/s0378-5173(98)00047-7**

Smith BT. 2015. **Remington education: physical pharmacy**. Pharmaceutical Press, USA.

Stehle G, Sinn H, Wunder A, Schrenk HH, Schütt S, Maier-Borst W, Heene DL. 1997. The loading rate determines tumor targeting properties of methotrexate albumin conjugates in rats. **Anticancer Drugs** 8: 677 - 685. **https://doi.org/10.1097/00001813-199708000-00006**

Tanford C, Kawahara K, Lapanje S. 1967. Proteins as random coils. I. intrinsic viscosities and sedimentation coefficients in concentrated guanidine hydrochloride. **J Am Chem Soc** 89: 729 - 736. **https://doi.org/10.1021/ja00980a001**

Valko K, Nunhuck S, Bevan C, Abraham MH, Reynolds DP. 2003. Fast gradient HPLC method to determine compounds binding to human serum albumin. Relationships with cctanol/water and immobilized artificial membrane lipophilicity. **J Pharm Sci** 92: 2236 - 2248. **https://doi.org/10.1002/jps.10494**

Vázquez B, Gurruchaga M, Goñi I. 1995. Hydrogels based on graft copolymerization of HEMA/BMA mixtures onto soluble gelatin: swelling behaviour. **Polymer** 36: 2311 - 2314. **https://doi.org/10.1016/0032-3861(95)95312-o**