



Original Article

The impact of viscosity on the dissolution of naproxen immediate-release tablets

Dastan Salim Hassan, MSc^a, Hemin Jumaa Hasary, MSc^{b,*}

^a Hiwa Hospital, Sulaimani Directorate of Health, Sulaimani, Kurdistan Region, Iraq

^b Tehran University of Medical Sciences, Department of Pharmaceutics, Tehran, Iran

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المخلص

أهداف البحث: تعتبر زيادة لزوجة سائل المعدة نتيجة تناول الطعام أحد المعايير التي يمكن أن تؤثر سلباً على إذابة الأدوية التي يتم تناولها عن طريق الفم وقابليتها للذوبان. وبالتالي، من الأهمية بمكان إدراج هذه المسألة في تقييم ملف تعريف الحرائك الدوائية للتركيبات الفموية. في هذا العمل العلمي، أنواع مختلفة من معززات اللزوجة؛ تم تضمين كربوكسي ميثيل السلولوز والبكتين وصمغ الغوار والزانتان في تحضير وسائط مختلفة مشابهة للحالة البيولوجية بعد الوجبة وشاركت في فحص تأثيرها على معدل انحلال النابروكسين وقابلية ذوبانه في التشبع.

طرق البحث: تم استخدام مقياس اللزوجة "بروكفيلد" لتقييم السمات الانسيابية لقدرتين من كل معززات لزوجة مذابة في سائل معوي يحاكي حالة التغذية. بعد 24 ساعة من اهتزاز العينات، تم قياس قابلية ذوبان الدواء المختار في الوسط الذي تم تقييمه خلال استخدام مقياس الطيف الضوئي بالأشعة فوق البنفسجية وتم إجراء فحص ملف تعريف انحلال الدواء من خلال جهاز إذابة المجاذيف باستخدام 200 مل من السوائل.

النتائج: تم الكشف عن انخفاض كبير في قابلية الذوبان في التشبع للنابروكسين عند زيادة لزوجة الوسائط المختبرة وتم تسجيل أعلى انخفاض في الذوبان مع البكتين في حالة التغذية المحاكاة للسائل المعوي. وبالمثل، فإن ملف تعريف انحلال النابروكسين ينخفض مع زيادة لزوجة الوسائط التي تم فحصها.

الاستنتاجات: لا تعمل بنية البوليمر على تحسين لزوجة الوسائط فحسب، بل تتداخل أيضاً مع إذابة الدواء. نتيجة لذلك، من الضروري معالجة الجانب الإنسيابي في تصميم الوسائط المختبرية أثناء تقييم ملفات تعريف انحلال الدواء.

الكلمات المفتاحية: اللزوجة؛ تأثير الغذاء؛ النابروكسين؛ الامتصاص عن طريق الفم؛ حالة التغذية؛ الذوبان.

Abstract

Objectives: The increase in viscosity of gastric fluid as a result of food ingestion is one criterion that can negatively impact the dissolution and solubility of orally administered medications. Consequently, it is crucial to address this issue in the pharmacokinetic profile assessment of oral formulations. In this scientific work, various kinds of viscosity enhancers, namely carboxy methylcellulose, pectin, guar gum, and xanthan, were applied to the preparation of different media similar to the biological condition after a meal, and their impacts on the rate of naproxen dissolution and its saturation solubility were evaluated.

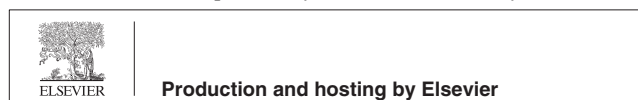
Methods: A Brookfield viscometer was used to assess the rheological features of two potencies of each viscosity booster dissolved in fed state simulated intestinal fluid (FeSSIF). After 24 h of samples shaking, the saturation solubility of the selected medicine in the assessed media was measured using an ultraviolet spectrophotometer, and investigation of the drug dissolution profile was performed with a paddle dissolution apparatus in 200 mL of fluid.

Results: Great reduction in the saturation solubility of naproxen was detected when the viscosity of the tested media was increased and the highest reduction of solubility was observed with pectin in FeSSIF. Similarly, the

* Corresponding address: Tehran University of Medical Sciences, Department of Pharmaceutics, Tehran, Iran

E-mail: hemin.hasary2@gmail.com (H.J. Hasary)

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dissolution profile of naproxen decrease with enhancement of the viscosity of investigated media.

Conclusion: A polymer structure not only enhances the viscosity of media but also interferes with drug solubilization. As a result, it is essential to address the rheological aspect in designing *in vitro* media during the assessment of drug dissolution profiles.

Keywords: Dissolution; Fed state; Food effect; Naproxen; Oral absorption; Viscosity

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Introduction

Oral dosage form

Oral formulations are the most prescribed drug dosage form globally due to their many advantages, including patient convenience, higher level of stability compared to other dosage forms, and low cost of the manufacturing process.¹ However, various active pharmaceutical substances are not suitable for oral administration because of their poor bioavailability.^{2,3}

The United States Food and Drug Administration (FDA) defines bioavailability as “the rate and extent to which the active ingredient or therapeutic moiety is absorbed from a product and becomes available at the site of drug action”.² Consequently, any drug substance used to explore its therapeutic action should be available in an adequate

amount at the target site of action. Many drugs undergo direct enzymatic degradation when they are administered orally, such as insulin. Other drugs experience first pass metabolism after oral administration, preventing them from reaching the systemic circulation. The pharmacological effects of oral formulations can be achieved when the drug compound has the ability to overcome serious enzymatic barriers in the liver and gastrointestinal (GI) tract, and is thereby available at the site of action in an adequate amount.⁴ The detail of drug release from solid oral formulation is presented in Figure 1.

Solubility and drug dissolution

After ingestion of a solid oral drug formulation and release of the drug substance throughout disintegration of the drug formulation, drug particles should have enough solubility in GI fluid to change into the solution phase, causing it to pass through the biological membrane and reach the systemic circulation.⁵ The dissolution process of drug material in the GI lumen is a major element for drug absorption and as a result exploration of a pharmacological action.⁶

Dissolution can be defined as the process of dissolving drug substance in a solvent. The solubility process of any compound is directly correlated with the physicochemical feature of the compound and intended solvent as well. For example, the distinct extent of water solubility can be detected between various polymorphs of particular substance. Furthermore, the solubility element can be affected by other aspects such as pressure, pH, and temperature. The United States Pharmacopeia (USP) has classified compounds solubility into seven levels of solubility, which are shown in Table 1⁶

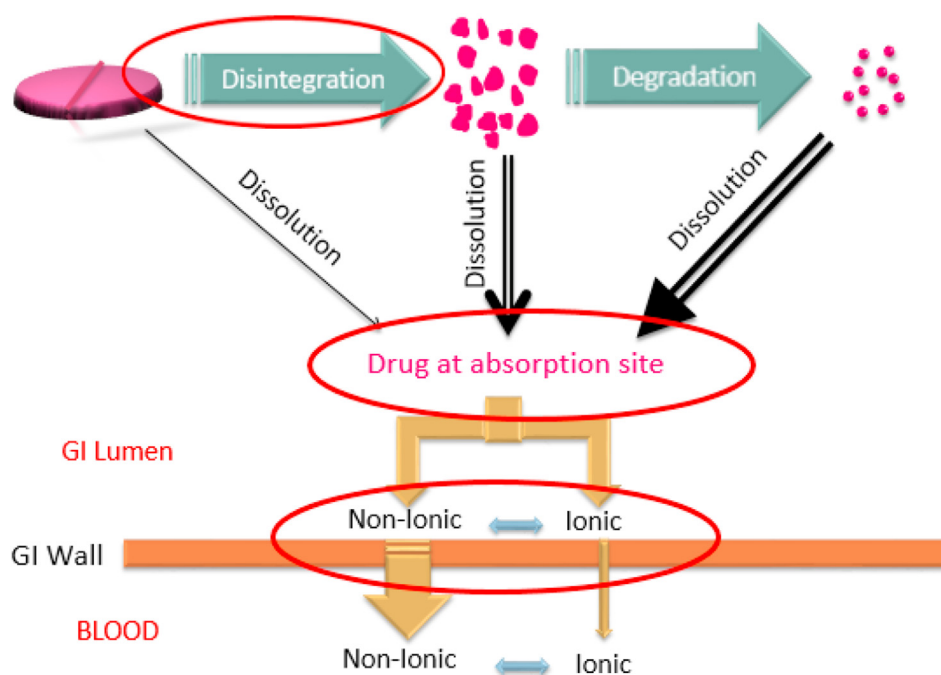


Figure 1: Schematic illustration the bioavailability process of orally administered drugs.

Table 1: Classification of compounds solubility according to the United States Pharmacopeia.⁶

Definition of terms	Parts of solvent required for one part of solute	Solubility range (mg/ml)
Very soluble (VS)	<1	>1000
Freely soluble (FS)	From 1 to 10	100–1000
Soluble	From 10 to 30	33–100
Sparingly soluble (SPS)	From 30 to 100	10–33
Slightly soluble (SS)	From 100 to 1000	1–10
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1
Practically soluble (PS)	>10,000	<0.1

Physicochemical factors affecting drug dissolution

During drug formulation, great attention is paid to the physical and chemical properties of the proposed active pharmaceutical ingredient. The solubility criterion of a drug substance can be significantly affected by the characteristic features of drug compound. Many considerations influence the solubility aspect of the drug material, which are described below.⁷

1. Particle size

It is obvious that the process of dissolution develops at the particle surface of the drug material; as a result, the active surface area of a substance can markedly affect drug dissolution. As a consequence, enhancement of the effective surface area leads to an increase in dissolution rate of a compound. Therefore, the high dissolution rate of a drug can be attained via particle size reduction.

2. Aqueous solubility

There is a great variation in the affinity of compounds for different solvents; for instance, sugar and salts freely transform into solution form in water, while low water solubility can be detected with mineral oil, which could be attributed to the structural diversity of compounds.

3. pH of media

Since there are considerable variations in the pH of the GI tract, beginning with the low pH of the stomach to the slightly alkaline environment of the small intestine, extensive focus on the pH aspect has been highlighted in the formulation process of the oral dosage form. Basic drugs mimic greater solubility in the acidic environment, whereas acidic drugs are highly soluble in alkaline medium.

Polymorphism and solvate state

The ability of a compound to exist in various crystalline forms is called polymorphism. The different polymorphs of a substance may exhibit differences in physical properties such as melting point, density, and solubility. Furthermore, some compounds may present in a solvate state, existence of solvent or water in drug molecules, which markedly affects the solubility properties of these materials.

The biopharmaceutical classification system

Hydrophilicity and lipid solubility features of compounds are two basic requirements for a drug substance to reach blood circulation, allowing exploration of drug action to be achieved.⁴ All drug materials do not possess a high level of solubility and optimum membrane permeability profiles; thus, the Biopharmaceutical Classification Scheme (BCS) was developed by Amidon and his colleagues as an attempt to classify drug compounds according to solubility and permeability properties.⁸ In addition, this classification scheme is efficiently used in the drug development process to categorize a new active agent from the initial steps of the process and is markedly implicated in the determination of proper dosage form for new chemical entities.

Biorelevant media – simulated intestinal fluids

The drug development process is composed of several parts, and formulation design is considered an important part of the process. During dosage form design, the *in vitro-in vivo* correlation is potentially involved in the investigation of dissolution rate of a new candidate drug and correlate the attained data from *in vitro* study to assume *in vivo* response.⁸ The medium of GI tract is described as a multicomponent fluid rather than clear aqueous environment, which consists of ingested food, various digestive enzymes, and natural surfactant. The constituent of GI fluid has been studied by Dressman⁹ and co-workers in different conditions to develop a medium that simulates the GI environment. The authors proposed that preparation of biorelevant media requires the addition of bile salt and lecithin with implication of glycerol, fatty acids, and triglyceride for the simulation of fed state, whereas preparation of medium simulating fasted condition needs fewer quantities of these compounds. Another factor that should be taken into account during development of dissolution media is the pH variation of GI fluid.

Furthermore, different parameters change between the fasted condition of GI tract and fed state. Similarly, many changes can be observed between stomach medium and intestine environment such as pH, concentration and occurrence of surfactant, osmolality aspect, enzymatic agents, and rheological properties of the medium. Consequently, designing medium for testing the drug dissolution rate should be similar to the normal physiological environment.¹⁰

Therefore, many experiments have been conducted to develop dissolution medium that simulates the GI condition; these studies recommended that the addition of surfactant, sodium lauryl sulfate for instance, is needed to design fasted dissolution medium in order to reduce the surface tension, similar to the biological environment.^{9–12} Despite these developed media, it was later confirmed that they do not fully simulate gastric dissolution because of the greater concentration of the containing surfactant.¹² Thus, Vertzoni and colleagues designed Fasted Stated Simulated Gastric Fluid (FaSSGF) throughout the use of pepsin and low amount of natural surfactant and lecithin.¹³

Regarding simulated intestinal fluid (SIF), in the initial stage the USP Simulated Intestinal Fluid with optimization, the medium pH at 6.8 was applied for the dissolution study.¹⁴ After extensive research by Dressman et al.,⁹ biorelevant media representing various states of the upper part of small intestine

have been developed that comprise both fed State Simulated Intestinal Fluid (FeSSIF) and FaSSIF.

Viscosity

Rheology is an essential aspect of the processing and performance of pharmaceuticals. The rheological property of dissolution media is an important biological parameter that is greatly influenced by food intake; thus, it is essential to evaluate this feature, as it may affect dissolution rate of oral medications.¹⁵ The exact definition of viscosity is resistance of liquid to flow; fluid with greater viscosity has higher resistance.⁶ As rheological properties can have notable effects on the consistency of the final product as well as its smoothness, different characteristics can markedly affect several elements, bioavailability, product stability, and patient perspective.¹⁶ Consequently, the assessment of rheological properties of final drug product is considered a fundamental prerequisite in pre-marketing quality control.⁶

Naproxen belongs to class II BCS, which has features of high permeability and poor water solubility. Therefore, this drug has solubility issues, which influences its bioavailability.¹⁷ As a result, naproxen is considered a suitable drug to study the effect of viscosity on drug bioavailability.

The aim of this study was to assess the impact of viscosity elevation on the dissolution process of orally formulated drugs. Naproxen was chosen as the investigational drug to determine the effects of changing rheological properties on drug dissolution.

Materials and Methods

Materials

Naproxen (meets USP testing applications), xanthan gum (from *Xanthomonas campestris*), pectin (from apple), carboxy methylcellulose (meets USP testing applications), and guar gum were obtained from Sigma–Aldrich (St. Louis, MO, USA). The surface active agent, sodium dodecyl sulfate (SDS), was purchased from Alfa Aesar Chemicals (Haverhill, MA, USA). Naproxen 250 mg tablets were ordered from a pharmacy.

Naproxen

Naproxen is a non-steroidal anti-inflammatory drug that belongs to the arylacetic category of cyclooxygenase inhibitors. It is broadly prescribed for the treatment of moderate to severe levels of pain in various clinical issues, particularly rheumatoid arthritis. However, from a formulation point of view, this compound has low level of solubility in aqueous media and high permeability properties.¹⁸ Consequently, the drug is categorized as BCA Class II.

Methods and equipment

Calibration curve construction and lambda max (λ_{max}) measurement

Generally, ultraviolet (UV)/visible spectrophotometry and high-performance liquid chromatography (HPLC) are

two major analytical procedures involved in the assessment of drug solubility and dissolution profiles. The most prevalent and applicable technique for quantitative analysis is the UV method, which is widely applied in pharmaceutical research.¹⁹ This type of analytical procedure depends on the determination of absorbed light by drug molecules in an investigated sample solution; thus, the measurement of concentration can be readily performed using Beer Lambert's Law, which is presented in the below equation:

$$A = \epsilon bc,$$

where A is absorbance, ϵ represents molar absorptivity of the absorbing species, c is concentration, and b is path length of the sample.

Practically, with the implication of calibration curve, the amount of solute can be easily calculated. The technique includes plotting many concentrations versus their absorbance, and throughout use of the obtained graph, the concentration of solute in a sample can be easily determined. Lambda max (λ_{max}) is a wavelength used to explore the high absorbance of drug particles on the UV spectrum. Exclusion of solvent, which is to dissolve drug particles, interference absorption with the solute particle is an essential element and methanol is generally considered a suitable vehicle for most drugs.²⁰

Regarding the laboratory procedure, a stock solution of naproxen was prepared by dissolving 10 mg naproxen powder in 10 mL methanol to produce a stock solution of 1 mg/1 mL. Then several dilution factors were performed from the stock solution to prepare different solutions at different concentrations. Thereafter, the obtained solutions were scanned over a 200–400 nm range by employing the Jenway 7315 spectrophotometer to measure λ_{max} and the initial concentration for construction of the calibration curve. As a result, the best dilution factor was determined to produce stock drug solutions of 32 and 46 $\mu\text{g/mL}$. Consequently, serial dilution was attained for the construction of naproxen calibration.

Preparation of media

The aim of this experiment was to assess the effect of rheological alteration due to food ingestion on drug solubility and dissolution rate, and the medium of interest was FeSSIF. Preparation of the medium was according to the procedure proposed by Dressman⁹ and colleagues; however, SDS was used instead of bile salt due to economic reasons. Since the pH aspect should be taken into account, the solution pH was optimized to 5.0 ± 0.05 with 1 N HCl or 1 N NaOH. When blank medium was prepared, 2.95 g lecithin and 8.25 g SDS were added to the mixture with continuous stirring. The obtained admixture was suspended on a magnetic stirrer for 4 h to produce a micellar solution that was clear to marginally cloudy, and the obtained preparation was stored in the fridge.

Polymer solution preparation

Various polymeric substances were used in this study, namely, pectin, carboxy methylcellulose, guar gum, and

xanthan. During the study, two polymeric concentrations were used for each polymer: 0.5% and 1%, in FeSSIF. The following preparation procedures of all solutions were conducted at room temperature.

1. Two different weights, 0.5 and 1 g of each polymer powder, were weighed on a sensitive balance.
2. The weighed compounds were gradually added to a beaker containing 100 mL investigational medium followed by continuous stirring of the mixture with the use of a glass rod.
3. To get rid of the sources of contamination, the obtained admixtures were covered and the complete hydration of polymeric substances was attained by storing the preparations for 24 h at room temperature, leading to dissolution of the polymer.
4. The pH was adjusted to 5.0 ± 0.05 using the calibrated Mettler Toledo pH meter.

Viscosity determination

The used viscosity enhancers in this study do not follow the Newtonian fluids law and therefore a proper kind of viscometer should be selected. One precise viscometer that is applicable for the evaluation of rheological properties of different liquid properties is the Brookfield viscometer, which is provided by the Brookfield Engineer of Laboratories Inc. The model type of the evolved viscometer for the assessment of the prepared solutions viscosity was the cup and bob geometry. Temperature consideration is one of the intrinsic elements that can severely affect viscosity measurement. Therefore, all processes of viscosity investigation were performed at room temperature to exclude the impact of temperature. Furthermore, pH can also affect the readings of viscosity, and consequently the rheological properties of the prepared solutions were measured at two distinct pH conditions (5 and 7) to determine their effects on the viscosity.

The viscosity measurement was initiated by adding 100 mL of the prepared polymer solution into a 100 mL beaker with a small diameter. Then the sample was suspended on the viscometer and the device was turned on. The fixed reading shown on the screen was recorded for each polymer solution.

Solubility tests

Solubility tests were done using the incubator shaker technique at room temperature. The process included the addition of excess drug material to 5 mL test media in a glass vial. The drug powder was uniformly distributed throughout the investigated viscous media using a glass rod. Thereafter, all test vials were covered to eliminate any sources of contamination and suspended on a shaker for 24 h. After shaking, the specimens were removed from the shaker and evaluated to assess the dissolution state of the tested drug substance. The content of each vial was transferred to a test tube for centrifugation, which was set at 3500 rpm for 20 min. A 3 mL micropipette was used to collect the supernatant from each vial. Eventually, the obtained samples were

diluted with suitable media and analyzed using a UV spectrophotometer.

Dissolution tests

The dissolution determinations were performed using the Caleva dissolution tester, which is apparatus 2 of the USP dissolution test rotating paddle method. The temperature aspect was set at 37 °C using a water bath and the speed of rotating paddles was 50 rpm. The process included the filling of a round dissolution vessel with 200 mL of the investigated media and a table of the examined drug was positioned at the bottom of the round vessel after the fixation of rotating paddles level. Thereafter, the process was initiated throughout collection of 5 mL of each investigated media at predefined time intervals (5, 15, 20, 30, 45, 60, 90, and 120 min). At each time point after the samples were taken, 5 mL fresh media was added to the dissolution vessel to maintain the volume of studied media at a constant level. Then the collected specimens were first exposed to the centrifugation process to facilitate the next step, which was filtration. Eventually, analysis of the samples was performed with a UV spectrophotometer (see Figure 2).

Findings and study of data

Measurement of λ_{\max} and the construction of calibration curves

The λ_{\max} was assessed in methanol medium, which is used for most drugs, and the peak absorbance of naproxen was detected at 232 nm. Then the absorbance of serially diluted samples was recorded and the attained readings was plotted against their corresponded concentration to construct calibration curves, which is presented in Figure 3. A linear relationship was noted between absorbance and concentration (see Figure 4).

Viscosity assessments

The rheological properties of prepared polymeric solutions, pectin, xanthan, guar gum, and sodium carboxy methylcellulose at different concentrations were assessed at two distinct pH values (5 and 7) using the Brookfield viscometer. The polymeric materials were solubilized in FeSSIF. It is worth noting that increasing the concentration of polymer solutions from 0.5% to 1% led to a significant

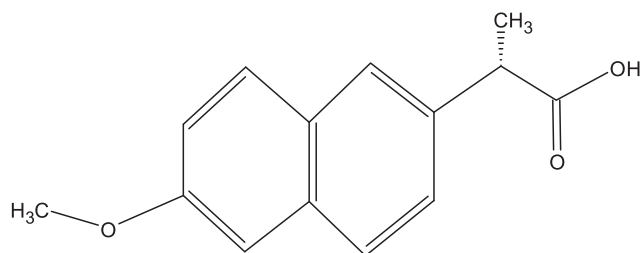


Figure 2: Chemical structure of naproxen.

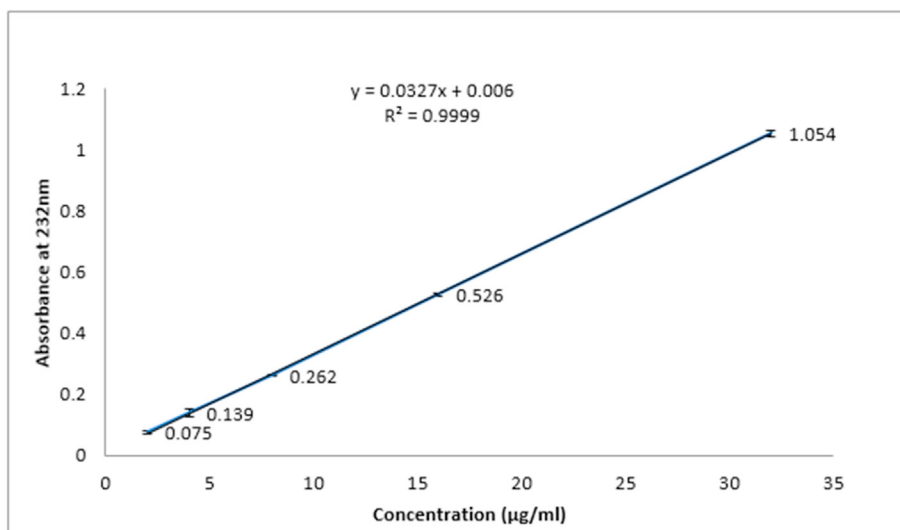


Figure 3: Calibration graph of various concentrations of naproxen versus their corresponding absorbance ($n = 3$, mean \pm standard deviation).

rise in the viscosity of the solutions. However, the findings showed that the rheological properties of all FeSSIF based media were markedly affected by pH alterations; for instance, there was a notable increase in the viscosity of 0.5% pectin between pH 5 and 7, which was 45.6 and 108 cp, respectively. In addition, greater viscosity was recorded with guar gum in FeSSIF-based medium at pH 5, whereas the lowest viscosity was reported with pectin solution at the same pH conditions.

Solubility test

Solubility measurement was first performed in FeSSIF medium alone without inclusion of viscosity enhancer agents to determine the solubility of naproxen in the medium, and it was found that the saturation solubility of the drug was (316 µg/mL) at pH 5. Naproxen was evaluated in FeSSIF including two distinct potencies of polymeric materials,

0.5% and 1%. The saturation solubility of the tested medication was reduced in FeSSIF medium co-existing with polymer compounds.

Depending on statistical analyses, the induction of polymeric compounds led to an observable decline in drug solubility, with the exception of 0.5% guar gum medium. However, alteration in the concentration of viscosity enhancer agents considerably affects the drug solubility; for example, duplication of xanthan concentration resulted in a 52% reduction in naproxen solubility. Only FeSSIF medium containing pectin showed greater solubility naproxen with a rise in the polymer concentration. Additionally, the greatest decline in drug solubility was reported with 1% of xanthan solution.

Dissolution tests

Dissolution assessment was performed in FeSSIF alone and also with the addition of polymer compounds. The pH of

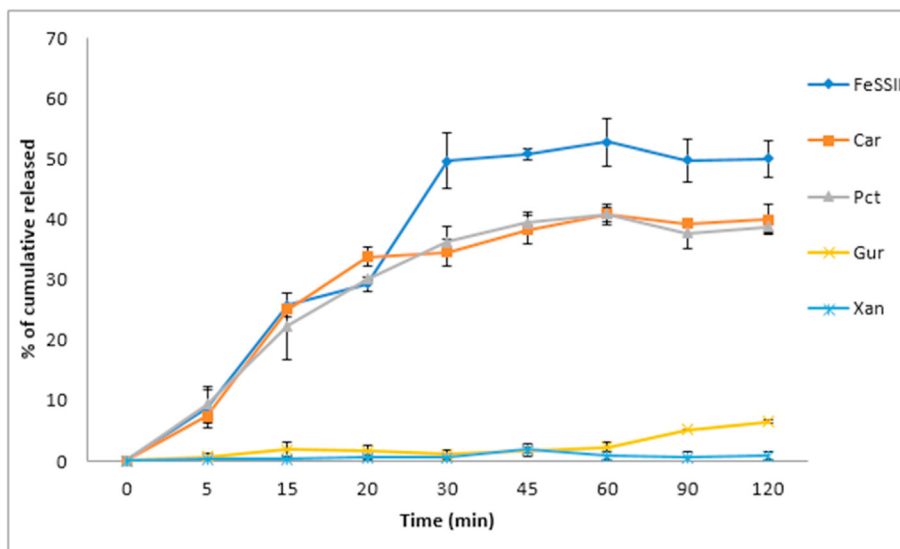


Figure 4: Measurement of naproxen dissolution profiles in FeSSIF-based medium and FeSSIF-based media containing 0.5% of various viscosity enhancing agents, namely, carboxy methylcellulose (Car), pectin (Pct), guar gum (Gur), and xanthan gum (Xan).

the tested media was set at 5, and only FeSSIF-based media containing 0.5% concentration of polymeric materials was selected to assess the drug dissolution profiles. Furthermore, assessment of the drug dissolution rate was carried out at two distinct time point, t_{15} and t_{90} , to obtain more understandable data. The percentage of naproxen release at t_{15} in FeSSIF-based media was 25.7% in the absence of viscosity enhancer agents, whereas the amount of the drug release in media containing xanthan and guar gum was 0.3% and 1.9%, respectively. However, the portion of the drug release in media incorporating pectin and sodium carboxy methylcellulose was 22.3% and 25% accordingly. The greater decline in naproxen release was shown with xanthan solution, only 0.7% at t_{90} , and in the case guar gum medium was 5.2%, whereas reduction in naproxen solubility in the presence of pectin and sodium carboxy methylcellulose was 40%. On the other hand, roughly 50% of naproxen was released at t_{90} in FeSSIF.

Discussion

Viscosity aspect and naproxen consideration

Meal constituents, rheological properties of luminal fluid and/or a particular window of drug adsorption are all factors that affect how food changes drug absorption *in vivo*. The viscosity of GI fluid is markedly altered by food intake, which is substantially dependent on the meal content and location along the GI tract. The alteration in drug dissolution and absorption due to food viscosity is significantly correlated with the type of viscosity promoting agent, degree of rheological changes, and the window of drug absorption. For example, the consumption of meal containing high amount of hydrophilic fiber can affect absorption of some drugs whereas it has no impact on other drugs.²¹

λ_{max} measurement and calibration curve construction

Methanol was used as a solvent for the preparation of calibration curves, which was the most applicable solvent for various drugs. First, λ_{max} was monitored in a methanol-based preparation and the peak absorbance of naproxen was 232 nm. However, when FeSSIF-based medium containing naproxen substance was assessed, there was a significant shift in λ_{max} , from 232 nm in methanol-based medium to 274 nm in FeSSIF preparation. This shifting criterion is called bathochromic shift, which is a shift in shorter wavelength to longer. The main reason behind this change in λ_{max} of naproxen can be ascribed to alterations in the polarity of applied media; water is the applied solvent for the preparation of FeSSIF, which is considered more polar than methanol. This outcome is in accordance with an experiment conducted by Bani-Yaseen et al.²² on the photo physicochemical characteristic features of fluoroquinolones. El-badrawy and colleagues reached the same finding during the study of solvent effects on the UV-visible absorption of some new chemicals.²³

The viscosity stimulator agents

Since the aim of this experiment was to evaluate the effect of rising viscosity by ingested food stuff on the process of drug release in the GI tract, three distinct kinds of natural viscosity inducers, xanthan, guar gum, and pectin, were selected to simulate foodstuffs. However, sodium carboxy methylcellulose, which is a synthetic polymer, was also applied in this study.

The rheological features of the evolved polymer substances were evaluated in FeSSIF and at two distinct pH conditions, 5 and 7. Obviously, elevation of polymer concentration leads to an increase in viscosity of the polymer solutions. However, the range of increasing viscosity differs among the used viscosity enhancer agents. In addition, it was observed that the viscosity of polymeric substances in FeSSIF media was significantly greater, which can be attributed to the occurrence of lecithin and SDS in the FeSSIF admixture. These findings are in accordance with a study conducted by Tung et al.,²⁴ which evaluated the effect of micellar framework on viscosity and showed that lecithin solution led to a five-fold elevation in viscosity via supplementation of bile salt because of micelles creation.

Regarding the effect of pH aspect on FeSSIF-based polymer, it was found that elevation of pH led to an increase in the viscosities of the vast majority of polymer solutions, with the exception of 0.5% xanthan and 1% guar gum. Silva et al.²⁵ showed that the addition of SDS to hydroxyl propyl methylcellulose (HPMC) solution resulted in molecule aggregation around HPMC. Consequently, the swelling of HPMC was observed because of the negative charge repulsion between the surface active agent and polymer chains, leading to an increase in viscosity to a particular point and critical aggregation concentration. Thereafter, the viscosity started to decrease due to greater electrostatic repulsion, exposing polymeric molecule shrinkage. Depending on this outcome, carboxylic groups on the polymer chain non-ionized form at low pH conditions due to lower negative charge repulsion with SDS molecules leads to viscosity reduction of the solution. As a result, greater viscosity can be reported with higher pH. However, the reduction of 1% guar gum viscosity might be ascribed to greater electrostatic repulsion during duplication of the polymer concentration.

Solubility measurements for naproxen in FeSSIF-based media

Viscosity aspect can be accounted for the main reason of decrease in drug solubility, since FeSSIF-based preparations show higher viscosity. In addition, when viscosities of polymer solutions were elevated, higher decline in naproxen solubility was observed with most evolved solutions. The most reduction in drug solubility was recorded with pectin solutions, and this may be attributed to linear properties of pectin molecules.²⁶

Dissolution determinations for naproxen in FeSSIF-based media

A great decline in naproxen release was observed with FeSSIF-based media comprising polymer substances. The inclusion of the hydrophobic moiety of pectin and carboxy methylcellulose by SDS reduces the interference ability of polymeric substances with naproxen dissolution.^{27,28} Consequently, the higher dissolution rate of the drug can be detected with pectin and carboxy methylcellulose dissolved in FeSSIF. However, formed micelles in test solutions of xanthan and guar gum do not show significant effects on the polymeric compounds. Therefore, great reduction in the drug release noted with xanthan and guar gum solutions.

The rate of drug release can be markedly influenced by viscosity aspect.²⁹ In this study, the obvious reduction of naproxen release was detected. This decline in drug dissolution rate can be attributed to the ability of polymeric compounds to produce a coat layer surrounding naproxen tablets and thereby inhibition of the solvent diffusion to the drug compound. The mechanism of this criterion can be explained via implication of Noyes and Whitney equation after further medication of the equation by Levich and Nernst-Brunner³⁰:

$$\frac{dXd}{dt} = \frac{AD}{\delta} \left(C_s - \frac{Xd}{V} \right)$$

where A is the effective surface area of the drug substance, D represents the diffusion coefficient of the drug, δ symbolizes the thickness of diffusion boundary layer, C_s refer to the saturation solubility of the drug in intestinal lumen, X_d is the amount of medication in solution state, and V is the volume of the dissolution media.

The rising of viscosity throughout the addition of various polymeric substances leads to reduction of the diffusion coefficient (D), and as a result, a greater decline in dissolution rate of naproxen was detected with increasing the viscosity of evolved dissolution media.

Furthermore, the differences in impacts of viscosity inducer agents in the reduction of naproxen dissolution rate can be linked to variation in the capacity of polymeric compounds to build a barrier layer. Different viscosity enhancers have various physiochemical properties, for instance, the degree of hydration, coil overlap concentration, and form of polymer chain.²⁶

Moreover, the incorporation of viscosity enhancer agents in the applied dissolution media not only increases the viscosity of the investigated media but also interferes with the drug dissolution rate. Guar gum and xanthan gum are hydrophilic polymers with high molecular weights, and as a result, the polymers have the ability to form a thick hydrate layer upon being present in the hydrophilic solvent. Consequently, the higher reduction of naproxen dissolution rate was recorded with guar gum and xanthan.^{31,32}

Conclusion

The concomitant administration of oral drugs with food intake can result in a considerable alteration in the drug

release process by affecting various physiological parameters. The rheological properties GI fluid can be markedly affected by food ingestion, which could influence drug pharmacokinetic profiles.

In this experiment, four distinct kinds of viscosity stimulator agents were solubilized in media to simulate foodstuff impacts. Study outcomes explore that viscosity elevation may negatively affect the drug dissolution process. However, the extent of impact on solubility and drug dissolution rate were different depending on many factors, such type of tested polymer and the selected concentration of the used viscosity enhancer. This finding indicates that viscosity element is an essential factor, which can affect the drug dissolution process in GI fluid and its effects considerably depend on type of ingested food. Consequently, viscosity aspect of designed biorelevant for *in vitro* drug dissolution measurements is an important consideration that required to be taken into account to simulate the biological conditions.

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Ethical approval

This study did not need ethical approval.

Author contributions

Conceptualization, **HJH** and **DSH**; laboratory work, **HJH**; writing the article, data analysis, supervision and editing, **HJH** and **DSH**; both authors have critically reviewed and approved the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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