Enhancement of Etodolac Solubility Using Solid Dispersion Technique: Full Factorial Design Optimization and In Vitro Release Studies

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Abstract

Etodolac (ETD) is a non-steroidal anti-inflammatory drug (NSAIDs). It has anti-inflammatory, analgesic, and anti-pyretic properties. The adverse effects of NSAIDs on the gastrointestinal tract (GIT) are gastric irritation and ulceration. So, in our research, we aim to enhance solubility which will lead to reducing side effects using the inclusion of complex techniques. Cyclodextrins (CDs) were used at a 1:1 drug:excipients molar ratio. All formulations were investigated by solubility and drug content studies and drug-polymer interactions by using thermal gravimetric analysis (TGA), and infrared spectroscopy (IR). The formulations showed improvement in insolubility. The extent of solubility enhancement was arranged in order as follows: HP-β-CD > α -CD > Sorbitol. IR studies approved no interaction between the drug and the carrier. TGA study approved the conversion of the drug to an amorphous state. It was concluded that α -CD and HP-β-CD can be used to improve the solubility of ETD.

Keywords

Etodolac, Inclusion complex, cyclodextrins, Sorbitol

1. Introduction

Etodolac is a non-steroidal anti-inflammatory drug (NSAIDs). It has anti-inflammatory, analgesic, and anti-pyretic properties. It is a poorly water-soluble drug, that belongs to class II drugs; that is, characterized by low solubility and high permeability (Abdelbary et al., 2013).

One of the most difficult parts of formulation creation is the drug’s solubility behaviors. Poor solubility is well recognized to result in decreased medication bioavailability due to a slow dissolution rate. As a result, we adopted a solid dispersion approach with Sorbitol and cyclodextrin as carriers to improve ETD solubility. This method works by dispersing a hydrophobic active medicinal component within a hydrophilic carrier. As a result, the API's wettability improves, and an amorphous form with high apparent aqueous solubility emerges.

SDs is achieved using a variety of procedures, including solvent evaporation, melting, and kneading. As a result, this approach permits the employment of carriers with extremely high melting points. The medication and carrier are dissolved in a volatile solvent for uniform mixing,
which is the core premise of this approach. SDs is obtained by evaporating the solvent while agitating it constantly. The solid SD is crushed and sieved after that (Milne, 2017).

Carriers used in solid dispersions are usually pharmacologically inert and can interact with API molecule by weak physical bonds such as hydrogen bonds, Van der Waals forces, and electrostatic interactions to form a more soluble complex, and hence improve the aqueous solubility and thereby dissolution and oral bioavailability (Chiou & Riegelman, 1971).

Cyclodextrins (CDs) are cyclic oligosaccharides that are produced from starch or starch derivatives. Alpha-cyclodextrin (α-CD; alfadex) and beta-cyclodextrins (β-CD; betadex) are natural occurring containing 6 and 7 glucose units, respectively, 2-hydroxypropyl-β-CD is a hydrophilic CD derivative (Conceição et al., 2018). The CD molecules are having hydrophilic cavities with enough space to incorporate the lipophilic drug as a guest which fits the outer side of the host molecule forming an inclusion complex. Thus, the molecular encapsulation of the drug has greatly improved aqueous solubility and rate of dissolution. previously using CDs information for solid dispersion was considered2nd Generation SDs (Mir & Khan, 2017) but recently for this special mechanism using CDs to enhance solubility is considered a separate technique from solid dispersion called the inclusion complex technique (Bikiaris, 2011). Physicochemical characterizations were performed to ensure the formation of the inclusion complex and compared it with pure drugs.

Etodolac is used in the management of rheumatoid arthritis and osteoarthritis. and also in postoperative pain (dental, obstetric, or orthopedic surgery), and non-surgical pain (lower back pain, tendonitis, sports injury, or gout) (Shah et al., 2002). But its poor solubility led to limited bioavailability after oral administration, so this study aims to improve the solubility of etodolac with the help of a water-soluble carrier by solid dispersion technique using the co-evaporation method.

Figure 1. Chemical structure of etodolac. 1, 8-diethyl-1, 3, 4, 9-tetrahydropyran-[3,4-b] indole-1-acetic acid

2. Results

2.1. Infrared spectroscopy

The IR spectra were carried out to investigate the possible interaction between the drug and the host molecules in the solid-state. The spectrum of the drug (figure 2, trace A) showed characteristic bands of Etodolac at wave number 1744.93 cm⁻¹. The CDs spectra (figure 2, trace B) showed mainly abroad vibrational band of free OH between 3300-3700 cm⁻¹ or more specifically at 3408.1: and 3390.92 cm⁻¹ for α-CD, and HP-β-CD. The IR spectra of the physical mixture of the investigated cyclodextrins (figure 2, trace C) showed peaks of both etodolac and cyclodextrins with a decrease in the peak intensity. In the case of solid complexes (figure 2, trace D), there are small shifts in the position of some peaks about (2-3 cm⁻¹) as well as a reduction of the intensity and broadness of the peaks.
2.2. Thermal gravimetric analysis

The thermogram of the untreated drug (trace A in all CD) showed an endothermic peak at 152.78 °C corresponding to the melting point of the drug. Regarding the curves of CDs, it was observed that they are characterized by broad endothermic peaks in the range of 104 °C and 81 °C for α-CD and HP-β-CD (trace B). Thermograms of Etodolac/CDs physical mixtures showed the presence of an endothermic peak of the drug. Inclusion complexes with α-CD (Figures 3, trace C) showed similar results to that obtained by the corresponding physical mixture. Regarding the thermogram of drug/HP-β-CD complex, complete disappearance of drug endothermic peak is observed (Figure 3, trace D); But in the case of Sorbitol, TGA showed the existence of the endotherm beak of the drug with little effect on its.
2.3. Factorial Design and response Surface Analysis (Drug content measurement)
The drug content in all the formulations was estimated spectrophotometrically at 277 nm.

Figure 3. TGA of etodolac (A), CDs & Sorbitol (B), physical mixtures (C), and inclusion complexes (D)

Figure 4. Response surface plots of formulation factors effects on (a) Drug content %, (b) Solubility % and ETD release % after 30 min.
2.4. *In vitro* dissolution studies

The cumulative amount of dissolved etodolac from the inclusion complexes as well as the corresponding physical mixture after 30 minutes was obtained in figure 4 (c). It is observed that solid inclusion complexes of HP-β-CD exhibited higher dissolution rates of 61%, compared with the pure drug.

3. Materials and Methods

3.1. Materials

Etodolac was kindly gifted by Pharco Pharmaceutical Co. (Alexandria, Egypt) (code no.13170-lot no.18900). α-CD and HP-β-CD (batch no.5994075) were supplied by Sigma-Aldrich Co. (St. Louis, USA). Ethanol and Sorbitol (batch no.6120880) were purchased from El-Nasr Pharm. Chem. Co., (Cairo Egypt).

3.2. Preparation of physical mixtures.

Physical mixtures of ETD with selected cyclodextrins (α-CD and HP-β-CD) and Sorbitol are prepared separately at an equimolar ratio by blending using a mortar and pestle. The obtained mixtures were sieved and then stored in a desiccator till further studying.

3.3. Preparation of etodolac solid dispersion

Solid dispersion of Etodolac/CDs in 1:1 ratio and Etodolac/Sorbitol were prepared in 1:1 and 1:3 molar ratio using the co-evaporation (CE) method. For the preparation of CE product, equimolar amounts of Etodolac, Sorbitol dissolved in a minimum volume of Ethanol, and CDs were dissolved in distilled water and mixed then sonicated till a clear solution results. The solvents were removed by keeping the mixture at room temperature till complete drying and the residue was kept in desiccators for further investigations. The solid mass was ground and stored After passing through a 100 mesh sieve (145-125 μm particle size range) (Hirlekar & Kadam, 2009).

3.4. Optimization of the prepared CDs by factorial design

According to the model it contained 2 independent variables at 3 levels, +1, and -1. The different independent variables were α and HP-β-CDs ($X_1$) and Sorbitol ($X_2$) with their drug to CDs ratio, and nine formulations were prepared. The factor levels were chosen to their relative alteration was acceptable to have powder bulk with flow property. The dependent factor included drug content, solubility, and the amount released at 30 min. The significant response polynomial equations generated by Minitab 17 were used to validate the statistical design. Response surface plots were generated to visualize the simultaneous effect of each variable on each response parameter. The constant and regression coefficients were also calculated using the software.

3.5. Characterization of the prepared solid dispersion

3.5.1. Measurement of drug content

20 mg of the prepared mixtures were dissolved in 20 ml ethanol. After 24 hours, the solution was filtered using Titan™ Polypropylene Syringe Filters. The filtrate was diluted up to the appropriate dilution then drug concentration was evaluated spectrophotometrically at 277 nm using a double beam spectrophotometer (EMC-61PC-UV Germany). Percent drug content was calculated for each sample by using the following formula (Trivedi et al., 2014):

$$\text{%Drug content} = \frac{\text{Actual amount of the drug in the formula}}{\text{Theoretical amount of the drug in the formula}} \times 100$$

3.5.2. In-vitro dissolution studies

All measurements were performed using 6 paddles USA Hanson dissolution tester. An accurately weighed amount (20 mg) of pure drug or equivalent number of physical mixtures or solid dispersion was dispersed over 500 ml distilled water which is immediately stirred at the speed of 50 rpm and temperature of (37°C ± 0.1). At different time intervals, 5 ml samples were withdrawn and filtered through a membrane filter (0.45μm), and the corresponding concentrations of Etodolac were analyzed by measuring their absorbance at 277nm. An equal volume of pre-warmed fresh dissolution medium was added to the cells to keep the volume of the dissolution medium constant. The results are the average of three independent experiments ± SD.
3.5.3. Infrared spectroscopy

The IR spectra of pure drug, Sorbitol, cyclodextrins, solid dispersions, and physical mixtures at a range of 4000-400 cm\(^{-1}\) using the KBr disk method (Shimadzu IR Tracer, Japan). To investigate the existence of any interaction of drug with the carriers (Mukne & Nagarsenker, 2004).

3.5.4. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) of the pure drug, CDs, Sorbitol, physical mixtures, and solid dispersion was performed using Shimadzu thermal analyzer, DTG-60H, Japan, calibrated with indium. Samples of about 4-5 mg were heated under a nitrogen atmosphere on a sealed aluminum pan at a rate of 10°C/minute over the temperature range of 20 - 500 °C to investigate the crystallinity of the drug.

4. Discussion

4.1. Infrared spectroscopy

The spectrum of the drug (figure 2, trace A) showed characteristic bands of Etodolac at wave number 1744.93 cm\(^{-1}\) corresponding to (C=O) stretching vibration of the carboxylic group, 3344.51 cm\(^{-1}\) due to single -NH stretching vibration of the amine group and 2972.58 cm\(^{-1}\) corresponding to C-H stretching. These data are in good accordance with the previously reported data (Shah et al., 2002).

The CDs spectra (figure 2, trace B) showed mainly a broad vibrational band of free OH between 3300-3700 cm\(^{-1}\) or more specifically at 3408.1: and 3390.92 cm\(^{-1}\) for α-CD, and HP-β-CD.

The IR spectra of the physical mixture of the investigated cyclodextrins (figure 2, trace C) showed peaks of both etodolac and cyclodextrins with a decrease in the peak intensity, due to the inclusion of the drug and formation of amorphous form.

In the case of solid complexes (figure 3, trace D), there are small shifts in the position of some peaks about (2-3 cm\(^{-1}\)) as well as a reduction of the intensity and broadness of the peaks. For example, the stretching band at 3344.51 cm\(^{-1}\) appeared as a single broad peak at 3346.48 and 3345.12 cm\(^{-1}\) for α-CD and HP-β-CD complexes. Moreover, the intensity of the C=O band (at 1744.93 cm\(^{-1}\)) is decreased in all prepared complexes.

This broadening of the peak and the decreased intensity of C=O bands in complexes indicated the breakdown of intramolecular hydrogen bonds of the drug molecules and the formation of intermolecular hydrogen bonds between the drug and CD molecules. In addition, the results proved the monomeric dispersion of drug molecules and their entrapment in the hydrophobic cavity of cyclodextrins.

ON the other hand, the physical mixture of ETD/Sorbitol showed the characteristic band of Sorbitol (3322.00 cm\(^{-1}\)) corresponding to –OH stretching) clearly and a characteristic band of ETD, indicating a little interaction between etodolac and cyclodextrins in the physical mixture.

In the case of ETD/Sorbitol solid dispersions showed little effect on the intensity of the C=O band and the broadness of the characteristic –NH of etodolac which indicates little interaction between drug and carrier.

4.2. Thermal gravimetric analysis

Further supporting evidence for the formation of inclusion complexes between the drug and CDs was obtained from the thermograms (Figure 3). The thermogram of the untreated drug (trace A in all CD) showed an endothermic peak at 152.78 °C corresponding to the melting point of the drug.

Regarding the curves of CDs, it was observed that they are characterized by broad endothermic peaks in the range of 104 °C and 81 °C for α-CD and HP-β-CD, due to the release of water molecules that were entrapped inside the cavity or those existing as residual humidity (trace B).

Other observed peaks indicate the degradation of cyclodextrins.

Thermograms of Etodolac/CDs physical mixtures showed the presence of an endothermic peak of the drug which confirms its crystallinity. These observations may be attributed to little interaction
between the pure components in the physical mixture. Inclusion complexes with α-CD (Figures 3, trace C) showed similar results to that obtained by the corresponding physical mixture.

Regarding the thermogram of drug/HP-β-CD complex, complete disappearance of drug endothermic peak is observed (Figure 3, trace D) which may be attributed to the complete transformation of the drug from crystalline to amorphous state. So, the considerable increase in the dissolution rate may be attributed to both complex formation and conversion of the drug to an amorphous state.

But in the case of Sorbitol TGA showed the existence of the endotherm beak of the drug with little effect on its intensity which indicates a partial transformation of the drug from crystalline to amorphous state.

4.3. Factorial Design and response Surface Analysis (Drug content measurement)

The drug content of the prepared solid dispersion was found to be in the range of 52% to 61% except ETD/Sorbitol in the range of 15% to 20%. Figure 4(a).

4.4. In vitro dissolution studies

The results indicated that the dissolution rate of the drug from inclusion complexes is higher than physical mixtures and both are higher than that of the plain drug. The same results were obtained with the Torsemide inclusion complex. The increase in the dissolution of etodolac when it is physically mixed with CDs may be due to an improvement in the wettability and solubility of the drug in the aqueous CDs solutions (Conceição et al., 2018). The impact of different agents on the dissolution of the drug was arranged in the following descending order: HP-β-CD < α-CD < Sorbitol.

5. Conclusion

In comparison to plain medication or other equivalent physical mixes, the produced inclusion complexes showed the greatest increase in dissolving rate. HP-CD had the greatest effect on increasing the drug's dissolving rate, which was explained by the CDs' hydrophilicity and high amorphous nature, which was later validated by IR and TGA analyses. These findings suggest that CDs could be used as carriers to improve ETD bioavailability and formulation in oral drug delivery systems.

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تحسين قابلية ذوبان الايتودولاك باستخدام تقنية التشتت الصلب: تحسين التصميم الشامل للعوامل

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الإيتودولاك هو عقار مضاد للالتهاب غير ستيرويدي (NSAIDs) له خصائص مضادة للالتهابات ومسكنات ومضادة للحرارة. الآثار الضارة لمضادات الالتهاب غير الستيروئيدية على الجهاز الهضمي (GIT) تهيج وتقرح المعدة. لذلك نهدف في عقارنا إلى تعزيز قابلية الذوبان التستؤدي إلى تقليل الآثار الجانبية باستخدام تقنية المعقدة التضمين. تم استخدام في عقار ١: ١: نسبة السواغات المولية. تم فحص جميع التركيبات من خلال دراسات الذوبان ومحتوى الدواء وتفاعلات الدواء مع البوليمر باستخدام تحليل الجاذبية الحرارية (TGA) والتحليل الطيفي بالأشعة تحت الحمراء (IR). أظهرت التركيبات تحسنًا في قابلية الذوبان (α-HP-β-CD). وافقت دراسة TGA على تحويل الدواء إلى حالة غير متبلورة. تم استنتاج أنه يمكن استخدام α-HP-β-CD لتحسين قابلية ذوبان الايتودولاك.

الكلمات المفتاحية
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المراجعات
جاء في مقدمة البحثية (١٨٩٢٢٩١، عمار الجارحى٢، حمدى عبد القادر٢، علاء الخياط١) عن عقار مضاد للالتهاب غير ستيرويدي (NSAIDs) يسمى الإيتودولاك. له خصائص مضادة للالتهابات ومسكنات ومضادة للحرارة. الآثار الضارة لمضادات الالتهاب غير الستيروئيدية على الجهاز الهضمي (GIT) تهيج وتقرح المعدة. لذلك نهدف في عقارنا إلى تعزيز قابلية الذوبان التستؤدي إلى تقليل الآثار الجانبية باستخدام تقنية المعقدة التضمين. تم استخدام في عقار ١: ١: نسبة السواغات المولية. تم فحص جميع التركيبات من خلال دراسات الذوبان ومحتوى الدواء وتفاعلات الدواء مع البوليمر باستخدام تحليل الجاذبية الحرارية (TGA) والتحليل الطيفي بالأشعة تحت الحمراء (IR). أظهرت التركيبات تحسنًا في قابلية الذوبان (α-HP-β-CD). وافقت دراسة TGA على تحويل الدواء إلى حالة غير متبلورة. تم استنتاج أنه يمكن استخدام α-HP-β-CD لتحسين قابلية ذوبان الايتودولاك.

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