ESTIMATION OF PARACETAMOL PRESENT IN A PHYSICAL MIXTURE CONTAINING KETOROLAC TROMETHAMINE SOLID DISPERSION WITH DIFFERENT POLYMERS

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Co-administration of combination of paracetamol with non-steroidal anti-inflammatory drugs showed synergistic effects leading to validation of clinical use of this combination in the treatment of majority of pain conditions. Controlled release drug delivery systems based on ketorolac tromethamine solid dispersion with Eudragit RS100, Eudragit RL100, and ethyl cellulose as polymers in a ratio of (1:3) drug:polymer with paracetamol in a physical mixture form were prepared in order to make use of the synergistic effect of this combination. An accurate simple and precise method was developed for simultaneous determination of ketorolac and paracetamol in the proposed solid dispersion preparation; a derivative spectrophotometric method was utilized. The method is based on measuring the first derivative amplitudes 1D at 338 and 249 for ketorolac and paracetamol in 0.1 N HCl using 0.1 N HCl as a blank with linearity ranges of 2-10 µg.ml⁻¹ and mean percent recovery not less than 99% and S.D not more than 0.03. Similarly, the first derivative values of absorbance ¹D at 304nm and 233 nm were measured for ketorolac and paracetamol respectively in phosphate buffer pH 7.4 using phosphate buffer pH 7.4 as a blank with concentration ranges of 2-10 and 3-10 µg.ml⁻¹ for ketorolac and paracetamol respectively.

The in-vitro drug release studies were performed for both drugs at different pH values. About 25% of ketorolac tromethamine combined with over 90% paracetamol were released at pH 1.2 whereas over 85% of ketorolac and 99% paracetamol were released at pH 7.4 all over the experimental time period. The obtained results can explain the synergistic effect of the proposed combination as well as the decreased gastrotoxic effects of ketorolac.

INTRODUCTION

Ketorolac, [(±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid], is a non-steroidal anti-inflammatory drug (NSAID) which has a strong analgesic activity¹. The drug can be administered intravenously, intramuscularly or orally as the water-soluble tromethamine salt.

The anti-nociceptive action of NSAIDs is primarily due to the inhibition of prostaglandin biosynthesis through the inhibition of cyclooxygenase enzymes: COX-1(constitutive) and COX-2 (inducible in inflammatory processes)²³. Several studies suggested of that ketorolac is comparable to opioids when used to treat acute pain⁴⁵.

Paracetamol has antipyretic and analgesic potential similar to NSAIDs; however, it is different from NSAIDs; it lacks anti-inflammatory, antiplatelet and gastrotoxic activities⁶. Paracetamol is often combined with NSAIDs in the management of acute and chronic pain⁶. Paracetamol exerts its action by inhibition of prostaglandin synthesis. Several clinical studies⁸⁹ have failed to show a reduction in peripheral prostaglandins in response to paracetamol. The drug is only a weak inhibitor of peripheral prostaglandin synthesis⁹. It was proposed that paracetamol exerted its analgesic action by inhibition of...
centrally situated isoform of cyclooxygenase enzymes\textsuperscript{10}.

Co-administration of combination of paracetamol with NSAIDs diclofenac, ibuprofen, ketoprofen, meloxicam, naproxen and nimesulide was studied by iso-bolographic analysis. The effective dose that produced 50\% anti-nociception was calculated\textsuperscript{11-13}. As shown by iso-bolographic analysis, all combinations were synergistic. The studies demonstrated potent interactions between paracetamol and NSAIDs and showed validation of the clinical use of combination of the tested drugs in the treatment of pain condition. The rationale underlying the practice of combining drugs in pain management is based mainly on the consideration that combining drugs that act at different pain mechanisms may enhance pain relief. NSAIDs block peripheral biosynthesis of prostaglandins by inhibiting the COX enzymes, whereas paracetamol act mainly on the brain and spinal cord; nevertheless, the exact mechanism of action of the later is still unknown\textsuperscript{14}.

The purpose of the present study was to make use of the synergistic effects reported between paracetamol and NSAIDs to obtain a combination of ketorolac tromethamine in the form of solid dispersion drug delivery systems containing Eudragit RS100, Eudragit RL100, and ethyl cellulose with paracetamol in order to obtain a formula facilitating patient compliance and exerting antipyretic as well as anti-inflammatory activity, simplifying prescribing, improving efficacy with decreasing adverse effects aiming that their co-administration will result in decreasing the individual doses of each drug. Both drugs are simultaneously estimated using a unique analytical technique.

**MATERIALS AND METHODS**

Ketorolac tromethamine (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt, Eudragit RL100 and Eudragit RS100 and Ethyl cellulose (in ratios of 1:3) drug to polymer were prepared. The method was achieved by dissolving 1500 mg of the polymer in a mixture of ethanol: dichloromethane in a ratio (1:1) in a glass vessel at 40\(^\circ\)C using Vortex Mixer (Maxi mix 11, Thermolyne Corporation, U.S.A.). The mixture was stirred at 400 rpm in a water bath (KOWELL N4, Germany) over 20 min. The obtained mixture was used as a solvent for the used polymers. 500 mg of drug was gradually added to the above mixture with stirring until completely dissolved. The rotation speed of the magnetic stirrer was continued until the solvent mixture was removed by evaporation. The dry film obtained was pulverized and passed through No 450 \(\mu\)m sieve in order to obtain a homogenous particle size\textsuperscript{15-17}. The obtained product was kept in a desiccator over silica gel under reduced pressure until used. Paracetamol was blended with the prepared solid dispersions in order to obtain a blend containing ketorolac tromethamine solid dispersions with paracetamol.

**Preparation of solid dispersion**

Three types of solid dispersion of ketorolac tromethamine with Eudragit RL100, Eudragit RS100 and Ethyl cellulose (in ratios of 1:3) drug to polymer were prepared. The method was achieved by dissolving 1500 mg of the polymer in a mixture of ethanol: dichloromethane in a ratio (1:1) in a glass vessel at 40\(^\circ\)C using Vortex Mixer (Maxi mix 11, Thermolyne Corporation, U.S.A.). The mixture was stirred at 400 rpm in a water bath (KOWELL N4, Germany) over 20 min. The obtained mixture was used as a solvent for the used polymers. 500 mg of drug was gradually added to the above mixture with stirring until completely dissolved. The rotation speed of the magnetic stirrer was continued until the solvent mixture was removed by evaporation. The dry film obtained was pulverized and passed through No 450 \(\mu\)m sieve in order to obtain a homogenous particle size\textsuperscript{15-17}. The obtained product was kept in a desiccator over silica gel under reduced pressure until used. Paracetamol was blended with the prepared solid dispersions in order to obtain a blend containing ketorolac tromethamine solid dispersions with paracetamol.

**Determinations of ketorolac and paracetamol in the prepared blend**

A derivative spectrophotometric method was developed. Since the zero-order spectra of the two drugs are overlapped, the determination of those ingredients using the conventional UV spectrophotometry has become invalid. Derivative spectrophotometry is an analytical technique of great utility for extracting both qualitative and quantitative information from spectra composed of unresolved bands. The derivative absorbance at certain chosen wavelengths allowed the concurrent determination of the two components without preliminary separation or extraction of any of them. The zero-crossing method is the most common procedure for conducting analytical calibration in derivative spectrophotometry\textsuperscript{18-21}.

**Instrumentation**

UV and derivative spectra of the solutions were recorded on double beam UV–Vis spectrophotometer Shimadzu 1800 using 10 mm path length quartz cells, scan range of
Preparation of standard solutions and construction of calibration curves

For paracetamol
Stock standard solution of paracetamol was prepared in 0.1 N HCl to give a final concentration of 1.0 mg.ml$^{-1}$. Different aliquots from this stock solution were taken and diluted with 0.1 N HCl to obtain solutions of paracetamol in the concentration range (2-10 µg.ml$^{-1}$). The zero order absorption spectra were recorded against 0.1 N HCl as a blank. The absolute values of the first order derivatives were obtained by zero-crossing technique.

Calibration curves were constructed by plotting the values of the first derivative absorbance ($'D'$) at zero-crossing point for paracetamol 249 nm against corresponding concentrations of standard solutions.

Similarly stock standard solution of paracetamol was prepared in phosphate buffer pH 7.4 to give a final concentration of 1 mg.ml$^{-1}$. Different aliquots from this stock solution were taken and diluted with the buffer to obtain solutions of paracetamol in the concentration range (2-10 µg.ml$^{-1}$). The zero order absorption spectra were recorded against phosphate buffer pH 7.4 as blank.

Calibration curves were constructed by plotting the values of the first derivative absorbance ($'D'$) at 233 nm against corresponding concentrations of standard solutions.

For ketorolac
Stock standard solution of ketorolac was prepared in distilled water to give a final concentration of 1 mg.ml$^{-1}$. Different aliquots from this stock solution were taken and diluted with 0.1 N HCl to obtain solutions of ketorolac in the concentration range (2-10 µg.ml$^{-1}$). The zero order absorption spectra were recorded against 0.1 N HCl as a blank.

Calibration curves were constructed by plotting the values of the first derivative absorbance ($'D'$) at 338 nm against corresponding concentrations of standard solutions.

Similarly stock standard solution of ketorolac was prepared in phosphate buffer pH 7.4 to give a final concentration of 1 mg.ml$^{-1}$. Different aliquots from this stock solution were taken and diluted with the buffer to obtain solutions of ketorolac in the concentration range (2-10 µg.ml$^{-1}$). The zero order absorption spectra were recorded against phosphate buffer pH 7.4 as blank.

Calibration curves were constructed by plotting the values of the first derivative absorbance ($'D'$) at 304 nm against corresponding concentrations of standard solutions.

In-vitro drug release studies
The dissolution rate of ketorolac tromethamine solid dispersions equivalent to (10 mg) as well as (500 mg) of paracetamol in a physical mixture form was studied using USP dissolution test apparatus employing paddle type (Paddle type, Copley, England). Each sample was placed in 900 ml of the dissolution media, pH 1.2 (0.1 N HCl) and pH 7.4 (phosphate buffer). Paddle speed of 100 rpm and temperature of 37.5±0.2°C were employed. Aliquots (5ml) were withdrawn, filtered through 0.45 membrane filter at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min and replaced with equal volumes of prewarmed fresh medium to maintain constant volume and keep sink condition. The drugs concentration and the percentage drug released were determined with respect to time spectrophotometrically. Studies were performed in triplicate for each sample and the results were reported as mean ±SD.

Assay of the prepared blend
Simultaneous determination of Ketorolac and Paracetamol
Five ml of dissolution media at predetermined time intervals was withdrawn and replaced with free media.

The zero order spectrum of this aliquot of dissolution medium was recorded against 0.1 N HCl (dissolution medium 1) or pH 7.4 (dissolution medium 2) as blank.

For dissolution medium (1): the $'D'$ value was recorded at 249 and at 338 nm for determination of paracetamol and ketorolac respectively then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve.

For dissolution medium (2): the $'D'$ value was recorded at 233 and at 304 nm for
determination of paracetamol and ketorolac respectively, then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve.

RESULTS AND DISCUSSION

Since the zero-order spectra of ketorolac tromethamine and paracetamol in phosphate buffer (pH 7.4) and in 0.1 N HCl (pH 1.2) are overlapping as shown in figure 1(A) and figure 2(A) respectively, the determination of both ingredients utilizing the conventional UV spectrophotometry has become invalid. A first derivative spectrophotometric method was adopted for their simultaneous determination where the first derivative spectra revealed zero-crossing point for paracetamol allowing the measurement of ketorolac tromethamine and the contrary zero-crosses points for ketorolac tromethamine allowing the measurement of paracetamol figure 1(B) and figure 2(B).

Fig. 1: Overlain of zero-order spectra (A) for ketorolac (1) & paracetamol (2) and 1st order spectra (B) for ketorolac (1) & paracetamol (2) in phosphate buffer (pH 7.4).

Fig. 2: Overlain of zero-order spectra (A) for ketorolac (1) & paracetamol (2) and 1st order spectra (B) for ketorolac (1) & paracetamol (2) in 0.1N HCl (pH 1.2).
Validation of the proposed first derivative spectrophotometric method

The validity of the method was tested regarding linearity, specificity, accuracy, and precision according to ICH guidelines (ICH-Q2B, 2005)\textsuperscript{22}.

Linearity and range

The calibration graphs for the determination of ketorolac and paracetamol by the proposed method were constructed by plotting the derivative amplitudes versus the concentrations. The graphs were found to be rectilinear over the concentration ranges cited in Table 1.

Statistical analysis of the data gave high values of correlation coefficients of the regression equations, small values of the standard deviations of intercept (Sa), and of slope (Sb). These data proved the linearity of the calibration graphs and the agreement of the result with Beer’s law.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The limit of detection (LOD) was determined by evaluating the lowest concentration of the analyte that can be readily detected, while the limit of quantitation (LOQ) was determined by establishing the lowest concentration that can be measured above which the calibration graph is nonlinear.

The results are shown in Table 1. LOQ and LOD were calculated according to the following equations\textsuperscript{22}.

\[
\text{LOQ} = 10 \times \frac{S_a}{b}, \quad \text{LOD} = 3.3 \times \frac{S_s}{b}
\]

Where Sa is the standard deviation of the intercept of regression line, and b is the slope of the calibration curve.

Accuracy and precision

To prove the accuracy of the proposed methods several synthetic mixtures of paracetamol and ketorolac in the ratio 1:1 were analyzed.

Statistical analysis of the results involving the mean percent recoveries of both drugs in these mixtures are summarized in Tables 2&3.

Intraday (repeatability) and inter-day (intermediate) precisions were assessed using three concentrations and three replicates of each concentration. The standard deviations were found to be very small indicating good repeatability over the entire concentration range, which revealed the precision of the proposed method as shown in Table 3.

Table 1: Statistical data of calibration curves of ketorolac tromethamine and paracetamol by the proposed first derivative spectrophotometric method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>In pH 1.2</th>
<th>In pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketorolac</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Linearity Range, µg.ml\textsuperscript{-1}</td>
<td>2-10</td>
<td>2-10</td>
</tr>
<tr>
<td>Regression equation</td>
<td>\textsuperscript{1}D\textsubscript{335}=0.014x</td>
<td>\textsuperscript{1}D\textsubscript{249}=0.012x+0.02</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.99990</td>
<td>0.9990</td>
</tr>
<tr>
<td>SD about slope</td>
<td>0.000003</td>
<td>0.00019</td>
</tr>
<tr>
<td>SD about intercept</td>
<td>0.00020</td>
<td>0.001200</td>
</tr>
<tr>
<td>LOD, µg.ml\textsuperscript{-1}</td>
<td>0.30000</td>
<td>0.31000</td>
</tr>
<tr>
<td>LOQ, µg.ml\textsuperscript{-1}</td>
<td>0.9000</td>
<td>1.9500</td>
</tr>
</tbody>
</table>
Table 2: Recovery of synthetic mixtures of ketorolac tromethamine and paracetamol by the proposed method.

<table>
<thead>
<tr>
<th>drug</th>
<th>Concentration taken, µg.ml⁻¹</th>
<th>Mean* % recovery</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In pH 1.2</td>
<td>In pH 7.4</td>
<td></td>
</tr>
<tr>
<td>ketorolac</td>
<td>2.0</td>
<td>99.00 ± 0.04</td>
<td>102.00 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>99.10 ± 0.10</td>
<td>99.57 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td>100.40 ± 0.05</td>
<td>100.20 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>paracetamol</td>
<td>2.0</td>
<td>100.50 ± 0.01</td>
<td>99.50 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>99.85 ± 0.03</td>
<td>100.14 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td>99.77 ± 0.02</td>
<td>99.88 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

*average of three determinations ±S.D.

Table 3: Precision data for the determination of ketorolac tromethamine and paracetamol in mixtures by the proposed method.

<table>
<thead>
<tr>
<th>drug</th>
<th>Concentration used µg.ml⁻¹</th>
<th>Intra-day *</th>
<th>Inter-day *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentration found µg.ml⁻¹</td>
<td>Concentration found µg.ml⁻¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In pH 1.2</td>
<td>In pH 7.4</td>
</tr>
<tr>
<td>ketorolac</td>
<td>2.0</td>
<td>1.99 ± 0.04</td>
<td>1.99 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>7.02 ± 0.10</td>
<td>7.00 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td>8.99 ± 0.05</td>
<td>8.99 ± 0.02</td>
</tr>
<tr>
<td>paracetamol</td>
<td>2.0</td>
<td>1.99 ± 0.01</td>
<td>2.00 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>6.98 ± 0.03</td>
<td>6.99 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td>9.01 ± 0.02</td>
<td>8.99 ± 0.03</td>
</tr>
</tbody>
</table>

*average of three determinations ±S.D.

**In-vitro drug release**

The release profile of ketorolac tromethamine solid dispersions prepared from different types of polymers (Eudragit RS100, Eudragit RL100 and ethyl cellulose) as well as the dissolution of paracetamol present as a physical mixture are presented in tables 4&5 (pH 1.2 and pH 7.4) respectively.

It is clear from table 4 that the percentage of ketorolac released from the solid dispersions over the experimental time period (120 min) were 17.50±0.31, 31.28±0.43 and 27.92±0.35 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively. The percentage of paracetamol dissolved from the physical mixture contained with solid dispersions were 97.41±0.27, 94.50±0.87 and 94.73±0.41 respectively. The observed dissolution behavior of both drugs may give an answer on the exact mechanism of the synergistic action of paracetamol on different anti-inflammatory drugs where paracetamol rapidly dissolves at the acidic gastric pH followed by its absorption in the stomach exerting its effect on the brain and spinal cord6 accompanied by gradually increasing amounts of ketorolac which acts by blocking the peripheral biosynthesis of prostaglandins by inhibiting the cyclooxygenase enzyme. At the same time, paracetamol lacks the antiplatelet and gastro-toxic activities13.

The speed of release and absorption in addition to the high bioavailability of paracetamol (63-89%), also the drug is not subjected to a large degree of first-pass metabolism in the liver23. All these postulations can describe the importance of the practice of combining both drugs in one formulation.
These results are in agreement of the studies which performed and showed the effect of such combination on increasing the analgesic effect and pain relief which necessitated the reduction of the anti-inflammatory dose by 37%-46%\textsuperscript{24-27}.

From table 5, it is obvious that at pH 7.4 a controlled process of ketorolac percentage release from the solid dispersions and the subsequent dissolution began by 50.60±0.22, 52.63±0.75 and 58.63±0.42 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively after 5min. After 120 min the percentages were 70.16±0.42, 71.83±0.55 and 90.46±0.51 respectively, this means that a controlled drug release all over the experimental time is obtained. From tables 4 and 5, it is clear that over 80% of ketorolac tromethamine is available to be released and absorbed from the intestine under the effect of the polymers chosen for the solid dispersion.

These results can describe the effect of the solid dispersion technique in reducing to a great extent the ulcerogenic activity as well as the other gastrototoxic side effects of the drug.

In a previous study in our laboratory the authors proved that there is no interaction between ketorolac tromethamine and the polymers used in this study\textsuperscript{28}. Also many references reported that there is no interaction between paracetamol and ketorolac from ethamine.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% Drug Dissolved*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Polymeric used in Solid Dispersion</td>
</tr>
<tr>
<td>a 5 b</td>
<td>3.18 ± 0.43</td>
</tr>
<tr>
<td>a 10 b</td>
<td>3.50 ± 0.87</td>
</tr>
<tr>
<td>a 15 b</td>
<td>4.00 ± 0.19</td>
</tr>
<tr>
<td>a 20 b</td>
<td>4.20 ± 0.54</td>
</tr>
<tr>
<td>a 30 b</td>
<td>4.82 ± 0.42</td>
</tr>
<tr>
<td>a 45 b</td>
<td>5.70 ± 0.93</td>
</tr>
<tr>
<td>a 60 b</td>
<td>6.20 ± 0.22</td>
</tr>
<tr>
<td>a 90 b</td>
<td>8.50 ± 0.88</td>
</tr>
<tr>
<td>a 120 b</td>
<td>17.50 ± 0.31</td>
</tr>
</tbody>
</table>

Table 4: Simultaneous dissolution of ketorolac tromethamine solid dispersion in combination of paracetamol physical mixture at pH 1.2.

a: ketorolac tromethamine
b: paracetamol
The results are the mean of 3 readings ± SD.
Table 5: Simultaneous dissolution of ketorolac tromethamine solid dispersion in combination of paracetamol physical mixture at pH 7.4.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Drug</th>
<th>% Drug Dissolved *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Eudragit RS 100</td>
</tr>
<tr>
<td>5 a</td>
<td>50.60 ± 0.22</td>
<td>52.63 ± 0.75</td>
</tr>
<tr>
<td>10 b</td>
<td>52.73 ± 0.78</td>
<td>54.31 ± 0.42</td>
</tr>
<tr>
<td>15 b</td>
<td>56.34 ± 0.17</td>
<td>55.23 ± 0.60</td>
</tr>
<tr>
<td>20 b</td>
<td>58.41 ± 0.74</td>
<td>56.49 ± 0.43</td>
</tr>
<tr>
<td>30 b</td>
<td>59.52 ± 0.32</td>
<td>58.43 ± 0.08</td>
</tr>
<tr>
<td>45 b</td>
<td>60.92 ± 0.98</td>
<td>60.14 ± 0.87</td>
</tr>
<tr>
<td>60 b</td>
<td>62.44 ± 0.54</td>
<td>65.34 ± 0.65</td>
</tr>
<tr>
<td>90 b</td>
<td>65.33 ± 0.23</td>
<td>69.16 ± 0.18</td>
</tr>
<tr>
<td>120 b</td>
<td>70.16 ± 0.42</td>
<td>71.83 ± 0.55</td>
</tr>
</tbody>
</table>

a : ketorolac tromethamine  
b : paracetamol  
The results are the mean of 3 readings ± SD.

REFERENCES

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تعني تركيز الباراسيتمول الموجود في مخلوط طبيعي مع الكتيرولاك تروميثامين

في مثبت صلب في مواد عديدة الجليدات

سناء عبد الغني الجيزاوي۱ - عصمت السيد زين الدين۲ - شرين فاروق حماد۳ -
هبة احمد باتین۴

قسم التكنولوجيا الصيدلية ، وقسم الكيمياء التحليلية ، كلية الصيدلة ، جامعة طنطا

أظهر تناول الباراسيتمول في أن واحد مع مضادات الالتهاب غير استرودية تأثيراً اكلينيكياً
غير عادي مما دعي لاستخدام هذه الصيغة لعلاج عدد كبير من حالات الألم.
تم تحضير صيغ صيدلية مبية علي الكتيرولاك تروميثامين مع إيدرايبيت أر إس ۱۰۰ ،
وايدرايبيت أر إس ۱۰۰ وكذا ايثيل سييلوز على شكل مثبت صلب ثم اضافة الباراسيتمول لهذه
الصيغ على شكل مخلوط طبيعي، وذلك للحصول على صيغة صيدلية متحكمة الانطلاق وللاستفادة من
التأثير الاكلينيكي لتناول العقارين معاً.
تم استنباط طريقة سهلة ودقيقة لتعيين العقارين المستخدمين في أن واحد ، وتعتمد هذه الطريقة
علي قياس المشتق الأول الإكستروفوتومترى لكل من العقارين المستخدمين في اس هيروجيني ۱،۷،۵ وکذا ۷،۷،۴.
تمت متابعة الانطلاق المعملي للعقارين المستخدمين في اس هيروجيني ۱،۷ وکذا ۷،۷،۴ ، ولقد
أثبتت النتائج ان حوالي ۵۰٪ من عقار الكتيرولاك وكذا حوالي ۹۰٪ من الباراسيتمول قد تم انطلاقهما
من الصيغ المستخدمة عند اس هيروجيني ۱،۷ ، بينما تم انطلاق أكثر من ۸۵٪ من الكتيرولاك مع
حوالي ۹۹٪ من الباراسيتمول في اس هيروجيني ۷،۴ طوال فترة التجربة.