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Effect of Indion Complexation on the Stability and Bioavailability of Some Non-steroidal Anti-inflammatory Drugs

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Abstract

Ion exchange resins are commonly used for masking of drug objectionable taste. Our work aimed to study the effect of this complexation on the drug stability and bioavailability in rabbits. In this work, paracetamol and ibuprofen complexes with indion 204 were prepared; drug stability and bioavailability from the prepared complexes were studied and compared with that of the commonly used commercial tablets Tylenol and Motrin respectively. The clinical protocol and information about drugs were discussed with a group of healthy albino rabbits. The results showed that t_{max} of both drugs were kept constant at 1.5hrs and 2hrs without any change from the reference standards Tylenol and Motrin respectively. The calculated pharmacokinetic parameters Cp_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ respectively for paracetamol were 0.431µg/ml, 3.535µg.hr/ml and 3.756µg.hr/ml from the prepared complexes in comparison to 0.494µg/ml, 4.083µg.hr/ml, 4.198µg.hr/ml from Tylenol, and 0.743µg/ml, 5.380µg.hr/ml, 5.559µg.hr/ml from the prepared ibuprofen complexes in comparison to 0.803µg/ml, 6.272 µg.hr/ml, 6.432 µg.hr/ml from Motrin. The relative bioavailability of both drugs from the prepared complexes were calculated using Tylenol and Motrin as reference standards and the 90 % confidence intervals of the geometric mean values for the test/reference ratios for Cp_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ were within the bioequivalence acceptance range of 80–125 % according to the European Guideline. Statistical analysis (ANOVA) indicated a significance difference between the calculated pharmacokinetic parameters for both drugs. From these results we can conclude that indion complexation of drugs significantly affects their pharmacokinetics and retards their bioavailability.

Keywords: Paracetamol, Ibuprofen, Ion exchange, Indion 204, Bioavailability.

Introduction

The bitter nature of many orally administered drugs creates an objectionable feeling in the mouth. This results in patient incompliance to these medicines especially in children and elderly, thereby retarding the effectiveness of the pharmacotherapy [1].

The American Academy of Pediatrics estimates that compliance in children is as low as 53%, indicating that children frequently fail to take medications properly. Noncompliance can cause extended symptoms, excessive doctor visits and may be hospitalizations, relapses, additional medications may be prescribed, increased healthcare cost and in cases of infectious diseases resistant organisms may be developed [2].

One of the popular approaches in the taste masking of bitter drugs is based on Ion exchange resins; which is one of the most exciting technologies for the pediatric industry and can be described as an ideal process where the taste of bitter medicament can be successfully masked. [3, 4]

Ion exchange resins are solid water insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly. Typically, the ionized drug form and the ion-exchange resin form a stable complex and the drug be unavailable for taste sensation hence taste masking occur. The average pH of 6.7 and cation concentration in the saliva (about 40meq/L) are not able to break the drug resin complex and this complex prevents the drug release in the saliva, thus resulting in absolute taste masking with no after taste. [3] Low gastric pH, increased ionic concentration of the GIT, larger volume of the release media and/or increased gastric residence time all cause drug release from the ion-exchange resin into the surrounding media and is, thus, be available for absorption [4] paracetamol and ibuprofen are used as drug models for this application.

Paracetamol (which in some countries is called acetaminophen) has been safely used for many years to help with mild to moderate pain and fever for babies over 1 month of age and up to adult age. paracetamol must be given with caution to a sick child, for too long time otherwise, it may be harmful. Ibuprofen is a newer drug than paracetamol to relief fever and mild to moderate pain in children and adults, but not suitable for children under 3 months of age. [5]

Acetaminophen is an odorless, slightly bitter taste white crystalline powder. It is soluble in organic solvents but slightly soluble in water. It's pH range is 5.5 - 6.5 based on saturated aqueous solution. It, chemically N-(4-Hydroxyphenyl) acetamide. Acetaminophen is a nonprescription analgesic and antipyretic drug similar to aspirin. But acetaminophen is not an NSAID (Nonsteroidal Anti-inflammatory Drug) as it doesn't participate in the inflammatory response as it cannot inhibit cyclooxygenases in the presence of peroxides. Paracetamol has almost no adverse effects on the stomach or esophagus. [6]

Following oral administration it is rapidly absorbed from the gastrointestinal tract, and depending on drug dose the systemic bioavailability ranging from 70 to 90%. Its rate of oral absorption is predominantly dependent on the rate of gastric emptying. Paracetamol is effectively absorbed from the rectum. It rapidly distributes throughout most tissues and fluids with volume of distribution of approximately 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. Paracetamol is extensively metabolized, mainly in the liver as sulphate and glucuronide conjugates. [7]

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), is a propionic acid group member. It is a white to off-white crystalline powder that melts at about 74° to 77°C. It is practically insoluble in water (<0.1 mg/ml), but readily soluble in organic solvents. Ibuprofen has a pKa of 4.43±0.03. It is chemically (±)-2-(p-isobutyl phenyl) propionic acid. Its molecular formula is $C_{13}H_{18}0_2$. [6] Ibuprofen works by reducing hormones of inflammation and pain in the body as analgesic and to relief of symptoms of arthritis, dysmenorrhea, fever. [8]

Its mode of action, like other NSAIDs, is not clearly understood, but may be related to prostaglandin synthetase inhibition. In the body the [-]R-enantiomer of ibuprofen undergoes interconversion to the [+]S-form. The biological activities of ibuprofen are associated with the [+]S-enantiomer. Although ibuprofen is a non-selective cyclooxygenase (COX) inhibitor, its analgesic, antipyretic and anti-inflammatory effects are achieved principally through COX-2 inhibition. [9-11]

Ibuprofen is absorbed from the gastro-intestinal tract and peak plasma concentrations are reached within about 1 to 2 hours after ingestion. Bioavailability is ≥ 80%. 99% of ibuprofen is bound to plasma proteins, 90% is transformed to 2 inactive metabolites and it has a plasma half-life of about 2 ± 0.5 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen. Studies in febrile children have established the proportionality at doses of 5 and 10 mg/kg of ibuprofen. Studies in adults have established the proportionality of ibuprofen at a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug [12]

It is claimed that complexation of exchange resins with drugs for masking their objectionable taste not affect their bioavailability as these complexes are weak enough to break down by hydrochloric acid present in the stomach without neglicable effect on their bioavailability. [3] They also possess modifying release properties and commonly used for sustaining drug action. [13] This work aims to investigate the effect of indion complexation on the bioavailability and also the stability of drugs. Paracetamol and Ibuprofen were selected as drug models and indion 204 was selected as a resin model for this work.

Materials and Methods

Materials

Ibuprofen and Paracetamol were received as gift samples from El-Nasr Pharmaceutical Chemical Co., Abo-Zaabal, Cairo, Egypt. Indion 204 was received as gift samples from EPCI, Beni-Suief, Egypt. Propyl paraben (Sigma Chemical Co., USA). Methanol and Acetonitrile (HPLC grade, Romil Chemical Co., England). Children s Tylenol Meltaways (80mg paracetamol chewable tablets, McNeil Consumer Healthcare, USA). Motrin Junior Strength (100mg ibuprofen chewable tablets, McNeil Consumer Healthcare, USA). All other solvents and chemicals used throughout the study are official and of analytical grades and were used as received.

Methods

Preparation of drug indion complexes

Batches of drug resinate mixtures were prepared at optimized conditions for maximum loading capacity [14]:

For this purpose, adequate quantities of acid activated resin (indion 204) were placed in different beakers containing adequate quantities of deionized water and allowed to swell for 30 min. Paracetamol and Ibuprofen were separately added to each beaker at 1:3 drug: resin ratio and stirred using a magnetic stirrer for six hours at 80ºC. The mixtures were filtered and residues were washed with adequate quantities of deionized water and drug content was determined as follows:

Accurately weighed amounts of the prepared resinate complexes equivalent to 10 mg of each drug were separately added to 100 ml of 0.1 N HCl and stirred at 100 rpm for 1 h, till the entire drug leached out. The solutions were filtered through a filter paper No. 41 and the drug content was determined spectrophotometrically at λ_{max} 243nm and 222nm for paracetamol and ibuprofen respectively after suitable dilution. [15]

Determination of drug release rate

Accurately weighed amounts of the prepared drug resinate complexes equivalent to the normal dose of each drug as well as crushed commercial Motrin and Tylenol tablets were subjected to in-vitro dissolution studies using USP dissolution apparatus II at 100 rpm with temperature of 37±0.5ºC and 900 ml dissolution medium (0.1 N HCl for paracetamol and phosphate buffer pH 7.2 for ibuprofen). Aliquots of 5 ml were withdrawn at specific pre-determined time interval of 5, 10, 15, 20, 30, and 45 minutes with replacement. The amount of the drug in each sample was measured spectrophotometrically at λ_{max} 243nm and 222nm for

paracetamol and ibuprofen respectively. The mean of six determinations was considered.

The effect of excipients on the release rate of both drugs from the commercial tablet mixture Tylenol and Motrin was considered. Where the dissolution rate of plain drugs paracetamol and ibuprofen under the experimental conditions was calculated and compared.Bioequivalence was assessed based on comparison of dissolution parameters like t_{50} (50%dissolution) and calculation of similarity factor (f_2). The similarity factor, f_2 used as the mathematical model for comparing the bioequivalence of the nine brands was calculated using the following formula:

$$f_2 = 50 \bullet \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\overline{R}(t) - \overline{T}(t) \right]^2}{n}}} \right]$$

Where, f_2 = Similarity factor; n = Number of time points; R *(t)* = Mean percent drug dissolved e.g. a reference product; T *(t)* = Mean percent drug dissolved of e.g. a test product. Not more than one mean value of >85% dissolved for each formulation. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. [16]

Stability study

Accurately weighed amounts of the prepared complexes of paracetamol resinate and ibuprofen resinate equivalent to the normal dose of each drug as well as the commercial forms Tylenol and Motrin were separately packed in transparent glass jars with plastic closures and subjected to stress accelerated stability studies. Jars were stored at different temperatures (namely: 40ºC ± 0.5, 50ºC ± 0.5 and 60ºC ± 0.5) for a time period of six months. The humidity was fixed at 75% relative humidity at all temperatures. Samples of the prepared complexes of paracetamol resinate and ibuprofen resinate as well as the commercial forms Tylenol and Motrin were withdrawn, at specified pre-determined time intervals (namely: 1, 2, 3, 4, 5 and 6 months) during the storage period and evaluated as follows:

Determination of drug content: (fresh and stored)

Samples of paracetamol resinate and ibuprofen resinate as well as the commercial forms Tylenol and Motrin were separately transferred to a 100-ml volumetric flask, and the volume was completed with methanol (HPLC grade). The solution was filtered, the first 20 ml were rejected then 1 ml of the filtrate was diluted to 100 ml by methanol. One ml aliquot of the prepared solution was transferred to 10-ml volumetric flask, 0.5 ml internal standard (propyl paraben) was added and the volume was completed with methanol.

The unknown concentration of ibuprofen in each chewable tablet was calculated as follows:

Q = (R/A ± B) x dilution factor

Where, Q is the drug concentration, R is the peak area ratio (drug/internal standard), A is the slope of the calibration curve and B is the Y-intercept.

Kinetic analysis of data and expiry date determination

The stability data of drugs from the prepared indion complexes was kinetically analyzed by means of a personal computer using linear regression according to zero- and first-order kinetic models; the correlation coefficient (r) was determined. Using Garett-Karper method; the decomposition rate constant (K) was calculated according to the determined order at each of the three temperatures. The (K) values at different temperatures were plotted against the reciprocal of the corresponding absolute temperatures on the logarithmic scale according to the Arrhenius plot for the determination of the predictive shelf life at room temperature.

In-vivo evaluation studies

Animals:

The clinical protocol and information about drugs were discussed with a group of healthy rabbits. Fifteen male albino rabbits weighing 2.5-3.0 kg, taking the same diet along the time of the study, fasted overnight before drug administration and allowed free access to water. They are used in this study to determine the bioavailability of drugs from the prepared indion complexes as well as assuring the bioequivalence of these prepared complexes in comparison to the commercial chewable tablets; Motrin Junior Strength and Tylenol. The animal dose of drugs was calculated with reference to Paget and Barnes table which relates the animal dose to the human daily dose. [17]

Study design

The study was performed on three phases according to a randomized crossover design. A washout period of one week separated between the phases. At the beginning of the study a control sample of 2 ml blood was withdrawn from each rabbit before drug administration.

Accurately weighed amounts of the prepared drug resinate complexes of each drug as well as crushed commercial Motrin and Tylenol tablets equivalent to the calculated animal dose were suspended in minimal volume of water and administered to rabbits by the aid of insulin syringe. Suspensions of both plain paracetamol and ibuprofen equivalent to the calculated animal doses were also prepared and administered to rabbits as control to detect the excipients effect on the bioavailability of both drugs from the commercial tablet mixtures Tylenol and Motrin. Blood samples were obtained at specified pre-determined time intervals (namely 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24) hours post dose. All the samples were collected in heparinized tubes and immediately centrifuged at 3000 rpm for 15 minutes and the plasma was frozen and stored at –20ºC until the analysis.

Analytical procedure for determination of drug in plasma

Simple and sensitive HPLC methods for the determination of drug in plasma were used. In case of ibuprofen; the mobile phase composed of acetonitrile: methanol: phosphate buffer pH 3.2 (50:10:40 v/v) and in case of paracetamol; the mobile phase composed of acetonitrile: methanol: phosphate buffer pH 6.3 (17.5:17.5:65 v/v). The mobile phase was filtered through 0.45 µm pore size filter. The flow rate was 1 ml/min in all cases, the detection wavelength was 264nm in ibuprofen and 254nm in paracetamol and the sensitivity was set at 0.0001 AUFS. After extraction from plasma, the drug was chromatographed on a C-18 reverse phase column.

Pharmacokinetics parameters (namely Cp_{max}, T_{max}, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, $t_{1/2}$, and K) for both drugs from the prepared indion complexes and commercial Tylenol and Motrin formulae were calculated and compared. The Relative bioavailability of drugs was also calculated using the commercial formulae as reference standards.

Pharmacokinetic Parameters and Statistical Analysis of Data

The calculated pharmacokinetic parameter including Cp_{max}, T_{max}, $[AUC]_{0-24}$, $[AUC]_{0-\infty}$, $t_{1/2}$ and K was subjected to statistical analysis of variance (ANOVA) according to student t-test. $P < 0.05$ was considered statistically significant in all calculations. For [AUC] and Cp_{max}, a 90 % parametric confidence interval was defined for the ratio test/reference using the residual variability obtained from the ANOVA. According to the european guidance [18]; Bioequivalence assessment was based on a predefined acceptance criterion of 80–125 % for the ratio test/reference and its 90 % confidence interval for the log-transformed data of $AUC_{(0-24)}$, $AUC_{(0-\infty)}$ and Cp_{max}.

Results

Drug release rate

Release rate of Paracetamol and Ibuprofen from the prepared resinate complexes in comparison to the commercial formulae Tylenol and Motrin against the dissolution profiles of plain drugs are shown in figures 1and 2. Histograms of the half lives of dissolution of both drugs are illustrated in figure 3. It is clear from these results that there was a significant delay in the drug release rate of both drugs; where the percentage of paracetamol released after 45 minutes from resinate complex reached 96.13% with half life of 8.15 minutes in comparison to 99.25% from Tylenol with half life of 6.72 minutes; and the percentage of Ibuprofen released also after 45 minutes from its resinate complex reached 97.21% with half life of 7.78 minutes in comparison to 99.57% with half life of 6.02 minutes from Motrin tablets. The results also indicate that the effect of excipients in both Tylenol and Motrin tablet mixtures on the dissolution rates of both drugs was neglicable. The calculated dissolution parameters for comparison (similarity factors, f_2 and T_{50}) for paracetamol and ibuprofen from the prepared resinate complexes and commercial forms Tylenol and Motrin is shown in Table 1. All results still fall within the acceptable range of 50–100. [16]

Stability study

Figure 4 and 5 shows histograms of the percentage of drug remained after storage at different conditions (namely 40ºC±0.5, 50ºC±0.5 and 60ºC±0.5) for a time period of six months. the percentage drug remained in all cases was higher than 90% without any considerable difference in drug content between resinate complexes and commercial forms of both drugs at all storage conditions, where the percentage paracetamol remained after six months was 93.97, 93.65, and 91.24% in Tylenol in comparison to 93.51, 93.34, and 90.64% in resinate complex; and the percentage Ibuprofen remained was 94.83, 92.84, and 91.15 in Motrin in comparison to 93.78, 91.87, and 90.53% in resinate complex when stored at 40ºC±0.5, 50ºC±0.5 and 60ºC±0.5 respectively.

Kinetic analysis of the stability data of both drugs from the stored formulae (commercial and resinate complexes) revealed that; the degradation followed first-order kinetics at all storage conditions. The predictive shelf life (t_{90}) was calculated for Paracetamol and was found to be 1.10 and 1.05 years for resinate complex and Tylenol respectively; while the predictive shelf life (t_{90}) for Ibuprofen was found to be 1.09 and 1.12 years for resinate complex and Motrin respectively; The results are shown in Tables 2 and 3.

In-vivo evaluation studies:

The bioavailability of Paracetamol and Ibuprofen from their corresponding tested commercial chewable tablet formulae Tylenol and Motrin respectively in comparison to the prepared resinate complexes was determined using plasma data obtained from

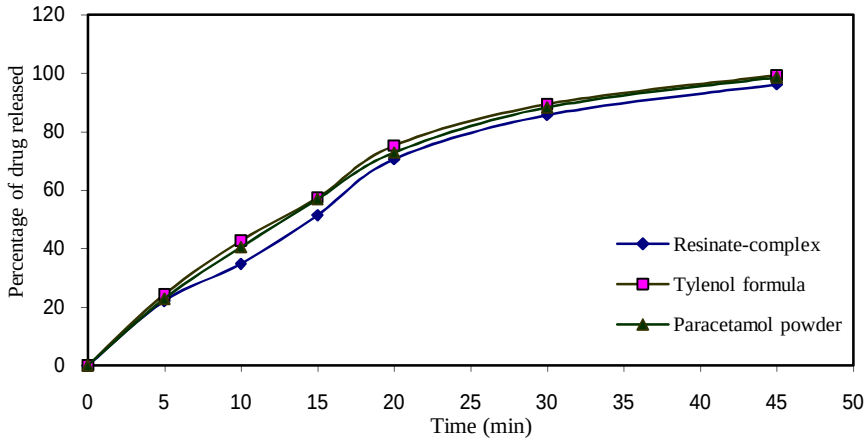

Figure 1: Dissolution profiles of paracetamol.

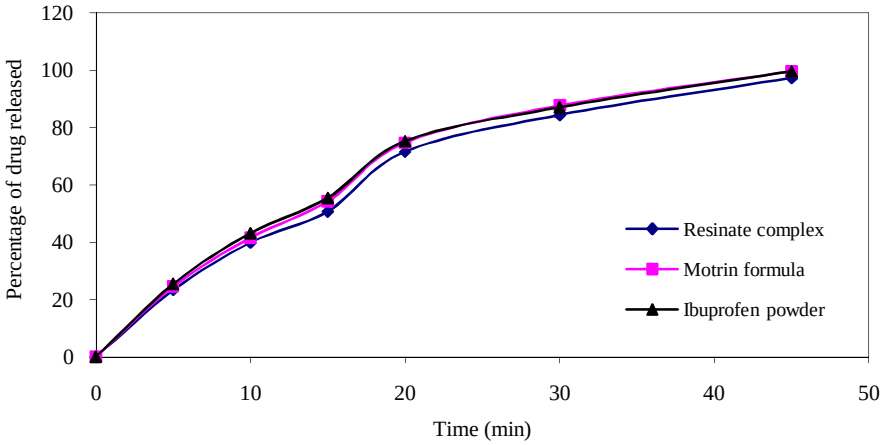

Figure 2: Dissolution profiles of ibuprofen.

Table 1: Dissolution data of paracetamol and ibuprofen.

Drug	PARACETAMOL			IBUPROFEN		
Formula	Control	Tylenol	Resinate	Control	Motrin	Resinate
T_{50} (min)	6.64	6.72	8.15	5.88	6.02	7.78
F_2		51.293			51.494	

Table 2: Kinetic data of accelerated stability testing of paracetamol after storage at different temperatures for six months.

K Values at the Following Temperatures (°K) on Logarithmic Scale				K_{25} (months^{-1})	$t_{1/2}$ at 25°C (years)	t_{90} at 25°C (years)
Temp. (K)	313°K	323°K	333°K			
Resinate	0.0115	0.0138	0.0161	0.00792	7.29	1.10
Tylenol	0.0115	0.0115	0.0138	0.00831	6.94	1.05

Table 3: Kinetic data of accelerated stability testing of ibuprofen after storage at different temperatures for six months.

K Values at the Following Temperatures (°K) on Logarithmic Scale				K_{25} (months^{-1})	$t_{1/2}$ at 25°C (years)	t_{90} at 25°C (years)
Temp. (K)	313°K	323°K	333°K			
Resinate	0.0115	0.0138	0.0138	0.008002	7.21	1.09
Motrin	0.0092	0.0115	0.0115	0.0078095	7.39	1.12

Table 4: The mean pharmacokinetic parameters of paracetamol following the oral administration to rabbits.

Parameters	Control	Resinate	Tylenol
T_{max} (hr)	1.5±0.00	1.5±0.00	1.5±0.00
Cp_{max} (µg/ml)	0.475±0.07	0.431±0.08	0.494±0.05
$AUC_{(0-24)}$ (µg.hr/ml)	3.977±0.06	3.535±0.09	4.083±0.06
$AUC_{(0-\infty)}$ (µg.hr/ml)	4.139±0.07	3.756±0.06	4.198±0.03
$t_{1/2}$ (hr)	3.21±0.03	3.89±0.07	3.18±0.05
K (hr^{-1})	0.228±0.09	0.179±0.02	0.238±0.12

Table 5: The mean pharmacokinetic parameters of ibuprofen following the oral administration to rabbits.

Parameters	Control	Resinate	Motrin
T_{max} (hr)	2.0±0.00	2.0±0.00	2.0±0.00
Cp_{max} (µg/ml)	0.797±0.08	0.743±0.03	0.803±0.02
$AUC_{(0-24)}$ (µg.hr/ml)	6.069±0.02	5.380±0.09	6.272±0.05
$AUC_{(0-\infty)}$ (µg.hr/ml)	6.268±0.05	5.559±0.08	6.432±0.06
$t_{1/2}$ (hr)	1.68±0.04	2.08±0.01	1.79±0.03
K (hr^{-1})	0.378±0.07	0.334±0.02	0.391±0.01

Table 6: Bioequivalence assessment summary of paracetamol following the oral administration of its resinate and commercial Tylenol formulae to rabbits.

Parameter	Paracetamol Formulae	
	T/R Ratio (%)	90% CI (%)
Cpmax	87.25	86.44–88.21
AUC (0-24)	86.59	85.16-87.12
AUC (0-∞)	89.471	88.41-90.35

Table 6: Bioequivalence assessment summary of ibuprofen following the oral administration of its resinate and commercial Motrin formulae to rabbits.

Parameter	Ibuprofen Formulae	
	T/R Ratio (%)	90% CI (%)
Cpmax	92.53	89.45-96.15
AUC (0-24)	85.78	85.08-86.36
AUC (0-∞)	88.63	86.38-90.88

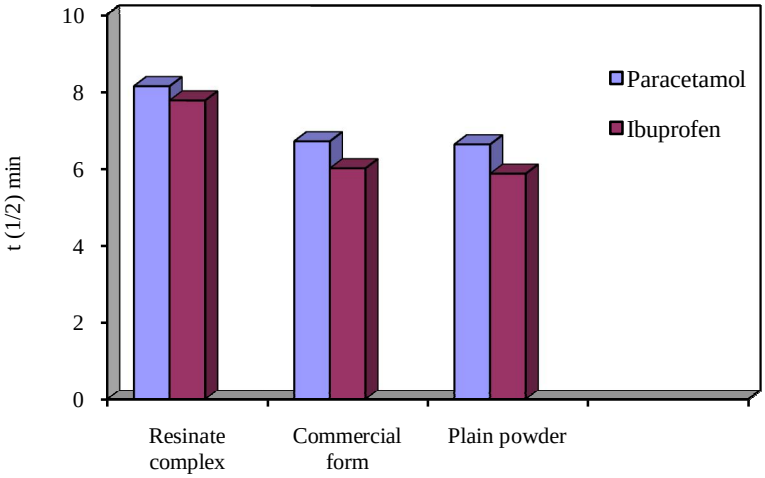

Figure 3: Histogram of $t_{1/2}$ values of the dissolution of paracetamol and ibuprofen

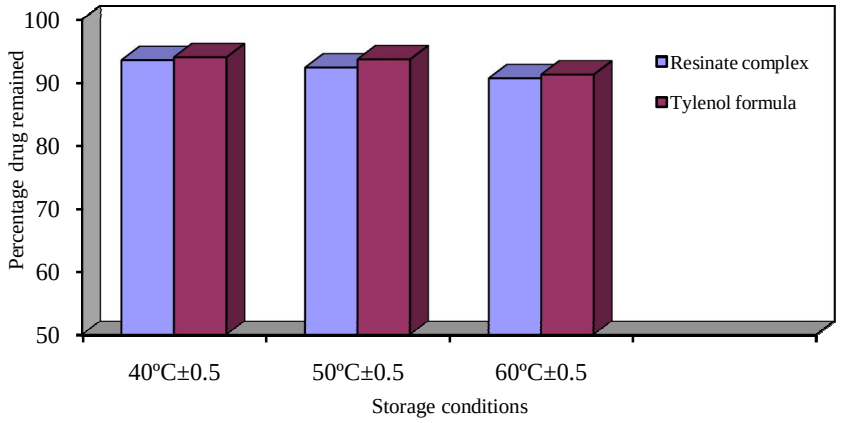

Figure 4: Histogram of the percentage of paracetamol remained after storage at different conditions for six months.

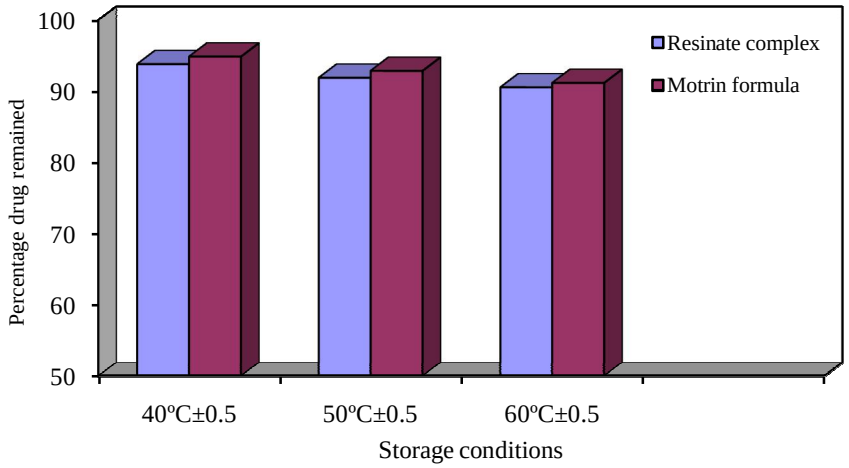

Figure 5: Histogram of the percentage of ibuprofen remained after storage at different conditions for six months.

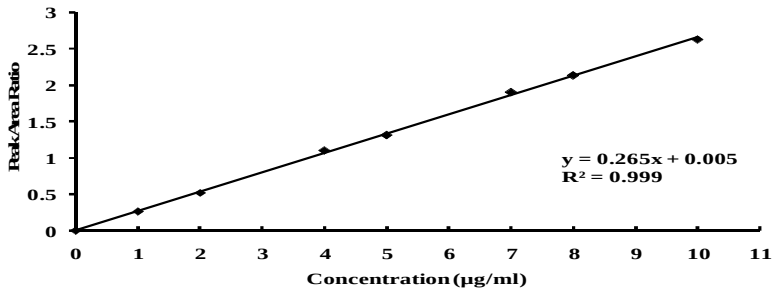

Figure 6: Calibration curve of paracetamol in plasma at λ_{max} 254 nm using HPLC method.

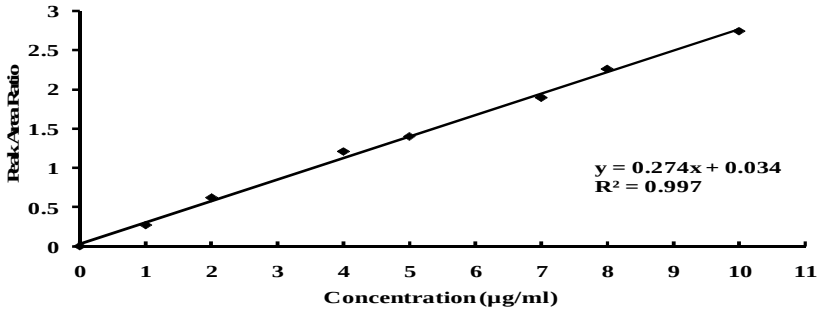

Figure 7: Calibration curve of ibuprofen in plasma at λ_{max} 264 using HPLC method.

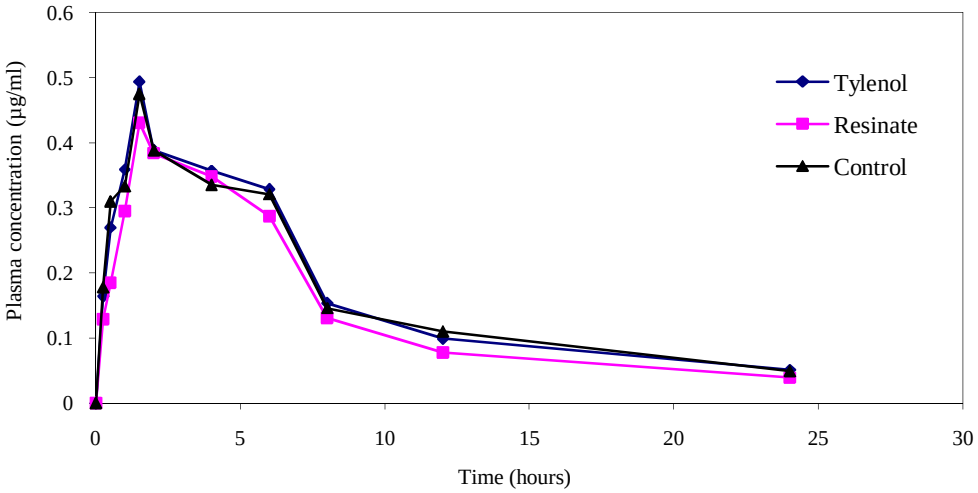

Figure 8: Mean plasma concentration-time curves of paracetamol following the oral administration to rabbits.

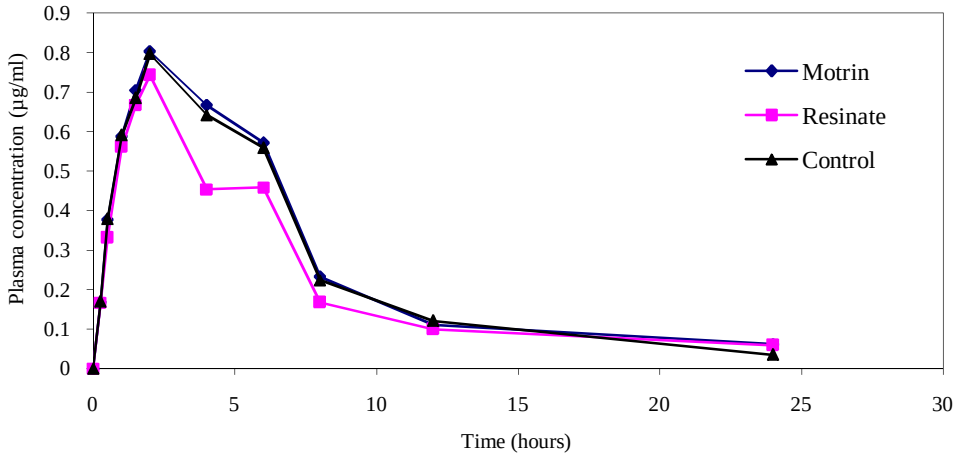

Figure 9: Mean plasma concentration-time curves of ibuprofen following the oral administration to rabbits.

fifteen male albino rabbits. The calculated drug doses of each formula was administered orally to the rabbits and the drug plasma concentrations were determined by an accurate and sensitive HPLC assay method.

HPLC chromatograms in plasma, in the presence of propyl paraben as internal standard indicated that, the retention times of paracetamol and the internal standard were 3.24 and 3.99 minutes respectively, while the retention times of the ibuprofen and the internal standard were 3.12 and 3.95 minutes respectively. The percentage recovery was calculated to indicate the suitability of the assay, the mean percentage recovery of paracetamol was 99.84% with coefficient of variation of 2.98% and of ibuprofen was 99.90% with coefficient of variation of 2.47%.

Figures 6 and 7 show the plasma calibration curve of paracetamol and ibuprofen respectively in the range of 1-10 µg/ml. The equations of linear regression of the curves were Y = 0.265 X + 0.005 and Y = 0.274 X + 0.034; where, X is the drug concentration in µg/ml and Y is the ratio of the area of drug peak to the area of internal standard peak. The correlation coefficient were 0.999 and 0.997 which suggests the accuracy of the assay.

Figure 8 shows the mean plasma concentration-time curves after the oral administration of the prepared Paracetamol-resinate complex and Tylenol chewable tablet formula against plain paracetamol suspension as a control to the rabbits and the mean pharmacokinetic parameter of the drug from both formulae and plain drug suspension were listed in Table 4, from which it was found that, the time required to reach the peak plasma concentration (T_{max}) was 1.5 hours in all cases. The same results

were obtained for Ibuprofen as shown in Table 5 and graphically illustrated in figure (9) where the time required to reach the peak plasma concentration (T_{max}) was kept constant at 2 hours in all tested samples.

Regarding the drug maximum plasma concentration following oral administration of both drugs; results in Tables 4 and 5 and figures 8 and 9 show that Paracetamol and Ibuprofen reached higher plasma concentrations from Tylenol and Motrin formulae respectively than from resinate complexes where the maximum plasma concentration of Paracetamol and Ibuprofen was 0.494µg/ml and 0.803µg/ml from Tylenol and Motrin in comparison to 0.431µg/ml and 0.743µg/ml from their resinate complexes respectively.

Area under the plasma concentration-time curve [AUC] of Paracetamol and Ibuprofen from commercial forms Tylenol and Motrin in comparison to the prepared resinate complexes is also listed in Tables 4 and 5. from the results we can note that drug-resinate complexation caused lowering of the total amount of drug absorbed as indicated by [AUC] values; where Paracetamol showed $AUC_{(0-\infty)}$ values of 3.756 µg.hr/ml and 4.198 µg.hr/ml for resinate complex and Tylenol respectively while Ibuprofen showed $AUC_{(0-\infty)}$ values of 5.559 µg.hr/ml and 6.432 µg.hr/ml for resinate complex and Motrin respectively.

Results of vivo study as listed in Tables 4 and 5 and illustrated in figures 8 and 9 indicate that the effect of excipients in both Tylenol and Motrin tablet mixtures on pharmacokinetic parameters and bioavailability of both drugs was neglicable. Where the plasma concentration time curves of both drugs from Tylenol and Motrin tablet mixtures were almost identical and about to superimpose with that of plain drug suspensions.

Two-way analysis of variance (ANOVA) test was performed in order to determine the significance of the detected difference between the calculated pharmacokinetic parameters (namely: Cp_{max}, $T_{1/2}$, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ of both drugs from the commercial formulae and their resinate complexes at probability level (ℓ) equals 0.05. Results of variance analysis clearly detected a significant difference between all tested pharmacokinetic parameters at the specified probability level for both drugs.

Finally; the percentage relative bioavailability of Paracetamol and Ibuprofen from the prepared resinate complexes was calculated using the commercial formulae (Tylenol and Motrin) respectively as reference standards and accepted to be bioequivalent. The 90 % confidence interval for the ratio of the logarithmically transformed values of primary variables [$AUC_{(0-t)}$, $AUC_{(0-24)}$ and Cp_{max}] laid between the predefined range of 80–125 %. [18] Results are presented in Tables 6 and 7

Discussion

Paracetamol and ibuprofen are non steroidal anti-inflammatory drugs that are commonly used in controlling fever and other inflammatory conditions in children. the problem of objectionable taste of both drugs act as a great challenge for most formulators and greatly affects the physician choice during prescription. Solid oral formulations including orodispersible and chewable tablets taken a great consideration in recent experiments to overcome the problem of bad taste of liquid formulations and difficulty of swallowing of conventional tablets so many taste masking techniques were applied for this purpose including loading onto ion-exchange resin. In this work our aim was to investigate the effect of this complexation on the bioavailability and stability of these drugs.

The effect of indion drug complexation on the drug stability was neglicable where the percentage drug released in both formulae and expiry date of both drugs were almost the same.

It is documented that drug release from these complexes is dependent mainly on the electrolyte concentration in the release media which in turn affects the absorption rate and extent and may sustain the drug release [3 and 13]; we correlated the drug release rate data of both drugs from the prepared resinate complexes with indion (a cationic exchange resin) with the calculated pharmacokinetic parameters. In case where > 85% of the drug is dissolved within 15 minutes, dissolution profiles are usually accepted as similar without further mathematical evaluation [16]; the dissolution profile of paracetamol and ibuprofen did not achieve these results so parameters like t_{50} and similarity factor (f_2) derived from the dissolution profile were used as estimators for the bioavailability of both drugs [19], Our results showed that; drug indion complexation markedly affected the release rate where mainly the mean half life of dissolution rate was significantly prolonged and the calculated values of similarity factors for both drug was extremely law indicating poor similarity of dissolution profiles and hence poor bioequivalence between the prepared resinate complexes and commercial forms.

To prove two or more drug products are bioequivalent, a similarity in the rate and extent to which the drug in dosage form become available for absorption need to be demonstrated based on the analysis of the calculated variance AUC and Cp_{max} are indicators of the extent of drug absorbed while the time for maximum drug concentration in plasma (T_{max}) is an indicator of the absorption rate.

Results of ANOVA test reflected a significant delay in the almost all pharmacokinetic parameters of both drugs; where the elimination half lives were prolonged and the maximum drug plasma concentrations were significantly lowered and finally the overall amount of absorbed drug as represented by the area under the plasma concentration time curves was decreased.

The calculated relative bioavailability indicated that; despite this significant effect of indion complexation on pharmacokinetic parameters of both drugs and based upon 90 % confidence interval for the ratio of geometric means (test/reference) of logarithmically transformed $AUC_{(0-24)}$. $AUC_{(0-\infty)}$ and Cp_{max}, they still bioequivalent as the 90 % confidence intervals for the ratio of $AUC_{(0-24)}$. $AUC_{(0-\infty)}$ and Cp_{max} were within the acceptable FDA bioequivalence limits (85 to 125%).

Conclusion

Drug loading onto indion (as a cationic exchange resin model) significantly retarded the release rate of both drugs but the release

profile still follows first order kinetics. The stability of both drugs was not affected by resinate complexation. Despite the detected variance between the calculated pharmacokinetic parameters was statistically significant, The calculated percentage relative bioavailability of the logarithmically transformed values of primary variables [$AUC_{(0-t)}$, $AUC_{(0-24}$ and Cp_{max}] was within accepted European limits at the predefined probability level and 90% confidence interval. This all laid to the final conclusion that indion complexation as a technique for masking of objectionable taste is accepted but we recommend it as inferior technique for taste masking due to the expected significant effect on drug bioavailability.

Conflict of Interest

There is no conflict of interest

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