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Comparative Study of Compartmental Modeling of Sustained Release Oral Dosage Forms and Intramuscular Injection

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Abstract

This study has been performed to compare the compartmental modeling of two types of extravascular routes, sustained-release (SR) oral dosage forms and intramuscular (IM) injection. Twenty healthy volunteers received a single dose of 100 mg Diclofenac Sodium (DS) sustained-release tablet, then 75 mg DS Intramuscular injection after two weeks washout period. The concentrations of DS in plasma were measured using reverse-phase high-performance liquid chromatography (HPLC). The data analyzed using compartmental modeling, with single time-variant input and output. Primary kinetic parameters for both formulations, ($AUC_{0\rightarrow\infty}$, C_{max},T_{max}) and other kinetic parameters were evaluated. The result shows that the IM injection needs a shorter time to reach the maximum concentration with convergent bioavailability to SR oral dosage forms, in another hand the data of IM injection fitted to single-compartment model with a correlation coefficient of 0.93 and the data of SR tablet fitted to two-compartment models with a correlation coefficient of 0.97.

Keywords: Compartmental Analysis, Bioavailability, Sustained-Release Drug, Intramuscular Injection.

دراسة مقارنة للتحليل الحيزي للحبوب مستمرة الطرح مع الحقن العضلية

خولة حميد رشيد

الخلاصة:

أجريت هذه الدراسة لمقارنة النمذجة بواسطة التحليل الحيزي لنوعين من جرعات الدواء اللاوريدية ، اقراص الطرح المستمر والحقن العضلية. عشرون متطوع يتمتع بصحة جيدة اخذو جرعة واحدة من 100 ملغ من اقراص الدايكلوفيناك صوديوم المستمرة الطرح ثم 75 ملغ من الحقن العضلية بعد اسبوعين من اخذ الاقراص.

تم قياس تراكيز ديكلوفيناك الصوديوم كروموتوفي السائل عالي الاداء. تم مقارنة النتائج بواسطة التحليل الحيزي بواسطة متغير زمني واحد للمدخلات والمخرجات. تم حساب عوامل الحركية الدوائية الاساسية مثل المساحة تحت المنحني من صفر الى ما لانهاية والتركيز الاعلى والوقت اللازم للوصول لأعلى تركيز وغيرها. النتائج اظهرت الحقن العضلية احتاجت الى وقت افل للوصول الى اعلى تركيز بالمقارنة مع الاقراص مستمرة الطرح، بالإضافة الى ان منحني التراكيز مع الزمن للحقن العضلية تطابق مع نموذج الحيز الواحد بمعامل توافق 0.93 بينما منحني الاقراص مستمرة الطرح تطابق مع نموذج الثنائي الحيز بمعامل توافق 0.97.

1. Introduction

Pharmacodynamics and Pharmacokinetic (PK/PD) analyses are the major parts of drug development and discovery process. [1], [2] When a drug is given to a patient, the drug generally passes through absorption, distribution, and metabolism, and elimination phases respectively. [3] The bioavailability of a drug could be defined as" the rate and extent to which the active ingredient of the drug is absorbed and becomes available to the body".[4]

Intramuscular drug delivery is examples of parenteral routes which administrated outside the gastrointestinal tract, these types of routes still undergo absorption into the bloodstream, generally, loose capillary membranes at their site of administration allow Paracellular penetration even of a large drug and/or polar molecules. [5] another hand oral administration convenience makes it the most common route of drug administration. Through this route capsule, tablet, syrups, suspensions are administrated. [6]

Extended-release, prolonged action, controlled release, sustained-release, all are idioms used to characterize drug delivery systems that are manufactured to achieve the prolonged therapeutic effect by releasing medication continuously over an extended time period after a single drug dose [7]. When drugs are administered to subjects, their body acts as a series of compartments. In many cases, the drug distributes from the blood into the tissues rapidly, and pseudo drug movement equilibrium between blood and tissues is established. When this

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occurs, a single-compartment model can be applied to describe the serum concentrations of a drug. This means that all tissues assumed to be one-compartmental, i.e., well mixed with a well-defined concentration.[8]

The simplest multi-compartment model is a two-compartment model, although these compartments have no anatomical or physiological meaning, Drug distribution occurs very quickly in the tissues that make up the central compartment into which the medication is administered, it comprises highly perfused tissues like lungs, heart, kidneys, brain, and liver. But the distribution of a significant drug amount to other tissues occurs at a slower rate. The latter tissues make up the peripheral compartment into which drug distributes. It comprises less perfused tissues like fat, skin, and muscle.[9]

The concept of the compartment is important to describe the plasma concentration against time data accurately and adequately, the model selection depends on the drug properties of distribution following its administration. The required equation to describe the plasma concentration versus time profile depends on the chosen compartment model and the way of drug administration. The selected model should permit accurate predictions in clinical situations.[10]

DS is a non-steroidal anti-inflammatory drug prescribed for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. DS is available in many dosage forms that can be given orally, rectally, or intramuscularly. [11][12]. This work aims to determine the difference in compartmental modeling of two types of extravascular drug delivery systems (intramuscular injection and sustained-release oral dosage forms).

2. Materials and method

2.1 The sampling procedure:

1. The samples of blood were drawn from the vein of the twenty healthy volunteers arms (ten females and ten males), their ages ranging from 25 to 40 years .
2. They collected at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after single dose of 100mg oral sustained release DS (Novartis Pharmaceuticals) then after washout period of two weeks the volunteers received 75mg IM injection (Novartis Pharmaceuticals) and the samples collected at the same time points .
3. The blank samples of blood were taken in all volunteers .
4. At each time of sampling, 5mL of blood was drawn using a disposable syringe.
5. The collected samples of blood were placed in EDTA tubes and transformed into special glass centrifuge tubes .
6. then the separated plasma stored below -20°C until used for the analysis of DS.

2.2 Chemicals:

To extract the Diclofenac sodium (Ds) from blood samples and to prepare the standard and mobile phase. The following chemicals were used, (Ds) standard (samara Iraq), Acetonitrile, ammonium acetate (Merk, Germany), nitrogen gas.

2.3 Equipment:

The following equipment was used to test the samples, High-Performance Liquid Chromatography (HPLC, KNAUER), the HPLC UV (Ultraviolet) spectrophotometer (UV 1601 Shimadzu, Japan), HPLC column ODS (C18) (KNAUER), 0.45µm pore size Membrane filters (Sartorius, Germany).

2.4 HPLC assay:

An HPLC procedure was developed and used to determine the area under the curve for each sample, the system of HPLC equipped with a UV detector was set at 283nm and C18 (5µm) reversed-phase column (250 × 4.6 mm) used. The mobile phase composed of a mixture of 0.01M ammonium acetate buffer and acetonitrile with a 40:60 ratio, the optimum flow rate was 1.5 mL/min, pH of mobile phase was kept at 3.4 by glacial acetic acid. Further, the method was approved by the establishment of standard solution (10µg/ml) diclofenac sodium, diclofenac sodium standard solutions (10µg/ml) were prepared fresh every day by dissolving the standard solution in the mobile phase. 2ml of acetonitrile and 1mL of plasma samples to precipitate the proteins then placed in the vortex for 1 minute, then placed in centrifuge for 5 minutes at 3500 rpm, after the centrifugation, floating layer was relocated to another test tube and evaporated until dryness under nitrogen gas flux, the residue was then dissolved in mobile phase (400µl) and 20µl injected into the injection port. DS concentrations in serum were measured by reversed-phase HPLC with an ultraviolet detector at a wavelength of 283, the retention time of DS was 4.3 to 4.8minutes the area under the curve (AUC) of samples was obtained for all volunteer at each sampling time points.

3. Results and discussion

The Mean Plasma DS Concentration against Time curves of Twenty Volunteers of both drug delivery systems was calculated as shown in Table (1).

Table (1): The Concentration of DS in Each Volunteer Samples with Respect to their Sampling Times and type of drug delivery system.

Time (hr)	Mean Plasma Concentration of sustained-release tablet	Mean Plasma concentration of IM injection
0	0.025	0.004
0.5	0.09879	0.8706
1	0.21	2.112
1.5	0.3967	1.5433
2	0.6002	1.4832
3	0.7289	1.2095
4	0.4889	0.9049
6	0.3787	0.4421
8	0.2308	0.3768
10	0.0989	0.04
12	0.079	0.005

The mean plasma concentration of DS with respect to their sampling time was plotted for each drug delivery as shown in Figure (1, 2).

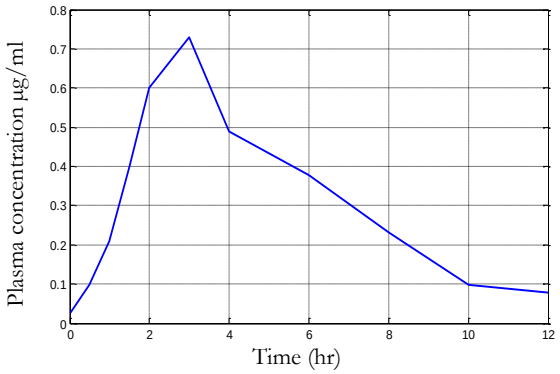

Figure (1): Mean plasma concentration against time after sustained release 100mg DS.

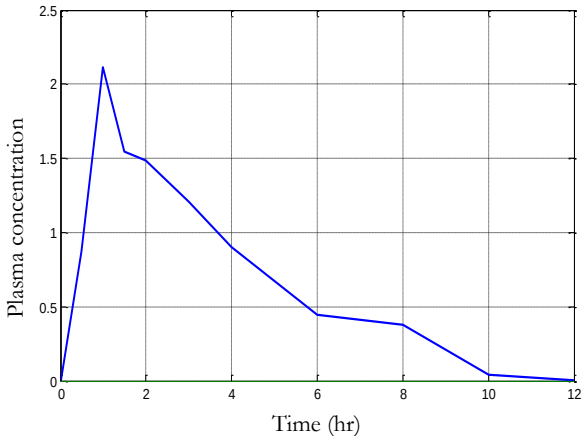

Figure (2): Mean plasma concentration against time after 75mg DS IM injection**.**

3.1 Compartmental analysis:

Compartment models are hypothecal structures that describe the movement of solute inside the body. [13] it applied to plasma concentration versus time profile:

a) To find how many compartments describe the plasma concentration against time profiles.

b) To compare the behaviors of two drug delivery systems inside the body.

Fig. (3) is a semilogarithmic plot of a plasma concentration against time for a sustained release DS tablet. It shows clearly the presence of three phases, these phases include absorption, distribution, and post-distribution, observe that there is a clear differentiation between the distribution and post-distribution phases. Where Fig (4) is a semilogarithmic plot of a plasma concentration versus time data of single-dose 75mg IM injection, and it shows clearly that there's no clear and recognizable distinction between these phases.

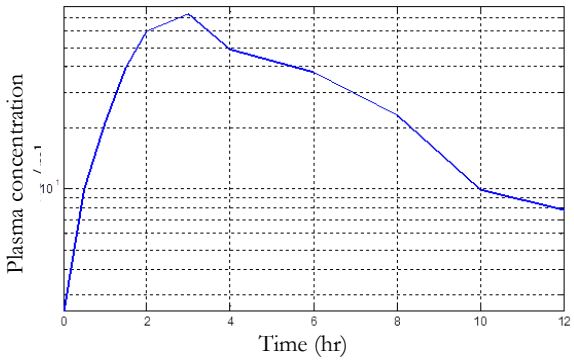

Figure (3): The semilogarithmic plot of a plasma concentration against the time of sustained-release DS tablet.

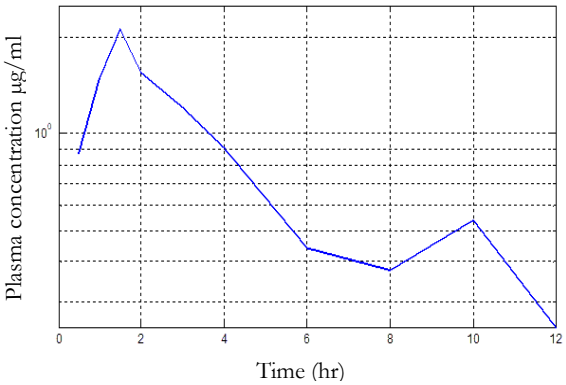

Figure (4): The semilogarithmic plot of a plasma concentration against the time of DS IM injection.

The number of compartments that represents plasma concentration versus time profile is could be calculated from the number of exponential terms that represents the post absorption phase. [14] The data of sustained-release tablets. On a log scale, data exhibit a bi-exponential decay which describes the sum of two first-order processes: distribution and elimination so it's fitted to two-compartment model using nonlinear regression analysis as shown in Fig. (5).

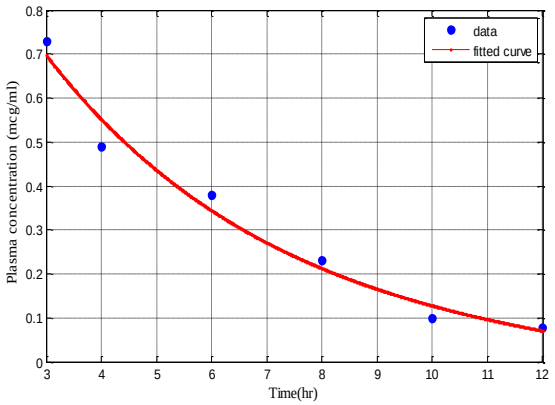

Figure (5): Fitting the post absorption phase of a plasma concentration against time profile to a two-term exponential function.

The equation that represents this model can be written as:

$$\boldsymbol{Cp = -0.04432e^{-0.8804t} + 0.2647e^{0.811t}} \ldots (1)$$

So the equation of the single-compartment model can be written as:

$$Cp = 3.138(e^{-0.2722t} - e^{1.34t}) \quad \ldots (2)$$

Where Cp is the plasma concentration and t is time, The data of IM injection fitted to the two-compartment model using nonlinear regression analysis as shown in Fig. (6)

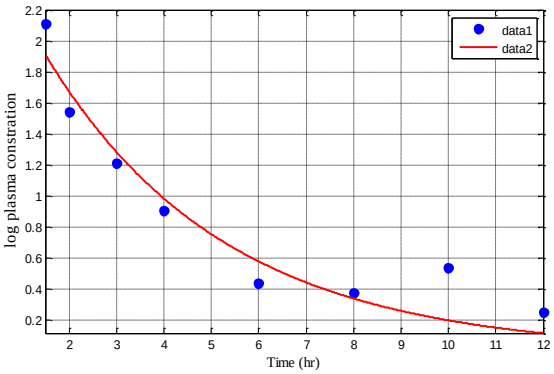

Figure (6): Fitting the post absorption phase of a plasma concentration versus time profile of IM injection to one term exponential function.

Table (2) shows the pharmacokinetic parameters of sustained-release two-compartment models, and Table (3) shows the pharmacokinetic parameters of the IM injection single-compartment model.

Table (2): The pharmacokinetic parameters of sustained-release two-compartment models.

Parameter name	Parameter value Mean± SD
AUC0→t (µg. h/ml)	3.892±0.228
AUC0→∞ (µg. h/ml)	4.224±0.162
AUMC0→∞ (µg. h^2/ml)	24.871±0.134
Tmax (h)	3±0.5
Cmax (µg/ml)	0.7289±0.121
k21	0.25±0.211
k12	-0.287±0.13
k10	-0.05941±0.24
α	0.8804 ±0.5
β	-0.811 ±0.331
$t_{1/2}$(h)	2.603 ± 0.514
MRT(h)	6.736±1.07
Vd/F (L)	89.995±1.48
Cl/F(L/h)	21.674±0.790

Where, AUC0→t is the area under plasma concentration against time the curve from time zero to t, AUC0→∞ area under the plasma concentration against time curve from zero to infinity, AUMC0→∞ area under the plasma concentration against time curve from zero to infinity, Tmax is the time needed to reach the maximum concentration, Cmax the maximum plasma concentration, K21 the first-order release rate constant for transfer from the peripheral to the central compartment, K12 the first-order release rate constant for transfer from the central to the peripheral compartment, K10 the first-order rate constant for elimination of drug from the central compartment, α is the fast disposition rate constant (usually representing the rate of drug distribution), β the slow disposition rate constant, t1/2 half-life time, MRT mean residence time, Vd/F volume of distribution, Cl/F clearance.

Table (3): The pharmacokinetic parameters of the Ds IM injection single-compartment model.

Parameter name	Parameter value Mean± SD
AUC0→t (µg. h/ml)	3.122±0.228
AUC0→∞ (µg. h/ml)	3.824±0.162
AUMC0→∞ (µg. h^2/ml)	24.871±0.134
Tmax(h)	0.5±0.5
Cmax(µg/ml)	1.912±0.331
Ka(h^{-1})	1.34 ±0.162
Kel(h^{-1})	0.2722 ±0.162
$t_{1/2}$(h)	1.65 ± 0.514
MRT(h)	4.736±1.07

Where, AUC0→t is the area under the curve from time zero to time t, AUC0→∞ area under the curve from zero to infinity, AUMC0→∞ area under the curve from zero to infinity, Tmax is the time needed to reach the maximum concentration, Cmax the maximum plasma concentration, Ka absorption rate constant, Kel elimination rate constant, t1/2 half-life time, MRT mean residence time.

4. Conclusion

This study shows that DS plasma concentration values after IM Administration best fitted to single-compartment model, the IM data has correlation coefficient of 0.932 with single compartment model equation, while the DS plasma concentration after sustained-release tablet is best fitted to a two-compartment model .and it has correlation coefficient of 0.97 with two-compartment model equation, the IM DS has a faster absorption parameters than sustained-release tablet, (Cmax, Tmax are 0.5hr, 1.912 (µg/ml) and 3hr,0.728(µg/ml)) for IM and sustained-release tablets respectively [15]. at the same time the correlation between the plasma concentration against time profiles of IM injection and the sustained release tablets where 0.807 which means that both formulations have convergent bioavailability inside the human body and that is clear from the values of AUC0→t and AUC0→∞ of both drug delivery systems which are (3.122, 3.824 and 3.892, 4.224) for IM and sustained release tablet respectively[16].

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