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Study on Dissolution test and the correlation factors that lead to different Bioavailability of Drugs

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الخلاصة:

استهدف البحث دراسة الخصائص الفيزياوية والكيمياوية لفحص الاذابة باستخدام ثلاث أنواع من الأدوية هي: (Chlorpromazine tablet), Simvastatin tablet, Clopidegrol tablet مختلفة المنشأ فرنسي, أردني, هندي , ألماني , يوناني , سوري , لبناني بموجب المواصفة الأمريكية (U.S.P30) معياراً للحصول على نتائج القراءات الاولية وقد اسفرت نتائج المقارنات المعنوية لتحليل التباين في اختبار تطابق متوسطات قراءات الاذابة مايلي:

1 – إرتفاع نسبة الإذابة للمنتج الفرنسي وبفارق:
   أ – عالي المعنوية ($P < 0.01$) مع المنتج الهندي .
   ب – غير معنوي ($P > 0.05$) مع المنتج الاردني .
   ج – معنوي عالي ($P < 0.01$) لنسبة الإذابة بالمنتج الأردني مقارنة مع المنتج الهندي باستخدام الدواء Simvastatin
2 – بينت نتائج الفروقات المعنوية الى ارتفاع نسبة الاذابة باستخدام الدواء clopidegrol للمنتج الاردني وبفارق معنوي ($P < 0.05$) بالمقارنة مع المنتج الهندي.
3 – كذلك حققت نتائج المقارنات المعنوية فروقا عالية ($P < 0.01$) مابين المنتج الالماني الذي حقق ارتفاعا نسبيا بالمقارنة مع المنتج اليوناني وبفارق غير معنوي ($P > 0.05$) بالمقارنة مع المنتج الهندي.
4 – اسفرت نتائج المقارنات المعنوية عن وجود فرق عالي المعنوي ($P < 0.01$) بارتفاع نسبة الاذابة للمنتج اللبناني بالمقارنة مع المنتج السوري باستخدام الدواء chlorpromazine ايضا في اختبار التطابق لمستويات قراءات الاذابة باستخدام اختبار t.

Abstract:

The aim of this work is to study the physical and chemical characteristics solubility testing by using three types of drugs which are: (Clopidegrol tablet, Simvastatin tablet, Chlorpromazine tablet).

From different sources (France, Jordan, India, Germany, Creek, Syria and Lebanon) according to American standard (U.S.P30) to obtain the results to the primary solubility testing data the result of the significant level comparison to analysis the variation for the test of equal means of the data of solubility as following:

1 - The solubility of the French drug is the heights with significant level differences at:
   A - With a highly significant level ($P < 0.01$) Compared with the Indian product.
   B - With a non significant level at ($P > 0.05$) Compared with Jordan product.
   C - A highly significant level at ($P < 0.01$) according to the solubility of Jordan product by using Simvastatin.
2 - The results of significant difference is based on the highest solubility by using Clopidegrol drug at ($P < 0.01$) compared with the Jordan and with significant level ($P < 0.05$) compared with Indian drug .
3 - Also the result of significant level comparison given high significant level ($P < 0.01$) between the German product which gives a high significant difference level compared with the Greek product and with un significant level ($P > 0.05$) compared with Indian product .
4 - Show that their exist a significant difference ($P < 0.05$) with the highly solubility for the Lebanon product compared with Syrian product by also using chlorpromazine in similarly test for average reading of solubility by using t-test.

Introduction:

Pharmaceutical industries are subjected to an increased interest from both public groups and governments to save costs and consistently deliver to the market safe and efficient products. Therefore quality control must be able to separate kinds of products that is not suitable and at the same time acts as tool to control the production process [1].

In vitro dissolution testing serves as an important tool for characterizing the biopharmaceutical quality of a product at different stages in its lifecycle.

In early drug development in vitro dissolution properties are supportive for choosing between different alternative formulations **candidates for** further development and for evaluation of active ingredients /drug substances.[2]

Dissolution tests are used nowadays in the pharmaceutical industry in a wide variety of applications,[3]

To help identify which formulations will produce the best results in the clinic,

To release product to the market, to verify batch-to-batch reproducibility,[4]

To help identify whether changes made to formulations or their manufacturing procedure after marketing.[1]

Materials and Methods:

Methods:

Three drugs are selected clopidegrol, simvastatin and chlorpromazine Hcl tablets. Dissolution test was done to different company for each drug, one company of each drug are not comply in the test and the test was done with pharmacopoeia specification U.S.P.30

*for clopidegrol tablet(Hydrochloric acid buffer PH 2,padlle,50 rpm,30 mint,1000 ml)limit N.L.T.80%Q,detected by U.V. at 240 nm.

*for simvastatin tablet (phosphate buffer PH 7, padlle, 50 rpm, 30 mint, 900 ml) limit N.L.T.75%Q detected by U.V. at 247 nm. And 257nm.

*for chlorpromazine Hcl tablet (0.1N Hcl,basket,50 rpm,30 mint,900 ml)limit N.L.T80%Q , detected by U.V. at 254 nm. [2]

Instruments:

Dissolution apparatus (pharma test), U.V spectrophotometer, PH meter, Ultra sound shaker and Balance.

Materials:

*Mono basic sod. Phosphate powder

*Sod.dodecyl sulphate powder

*Pot. Chloride powder

*Hcl concentrated (prep aired 0.1N Hcl)

3-primary data [6]

No.	company	drug	Result of dissolution test
1- 2- 3-	France Jordan India	Clopidegrol	(93.2 , 103, 110, 98, 101.8, 101.4)% (95, 94.8, 94.5, 96.2,95.4,97.5)% (69.4,36.8,47.3,66.3,62.8,81.7)%

Table-1: For clopidegrol tablet; Comparison in dissolution test was done for three company limit N.L.T.80%Q

No.	company	drug	Result of dissolution test
1- 2- 3- 4-	Germeny Jordan India Greek	Simvastatin	(84.2, 85.5, 83.8,89.6, 90.6 , 91.2)% (101.8,113,104,105.8,101.5,112)% (94.8,95.8,97.4,96.8,93.5,90.4)% (46.7,40.8,59.5,61.5,37.6,74)%

Table-2: For simvastatin tablet; Comparison in dissolution test was done for four company limit N.L.T.75%Q.

No.	company	drug	Result of dissolution test
1- 2-	Syria Lebanon	chlorpromazine Hcl tablet	(97,98.5,96.7,100.2,105.9,102)% (34,40.8,55.6,50.8,47.6,42.1)%

Table-3: For chlorpromazine Hcl tablet; Comparison in dissolution test was done for two company limit N.L.T.80%Q

4- Descriptive statistics:

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.
						Lower Bound	Upper Bound		
Clopidegrol	**France**	6	101.233	5.573	2.275	95.384	107.082	93.2	110
	Jordan	6	95.567	1.115	0.455	94.397	96.737	94.5	97.5
	India	6	60.717	16.145	6.591	43.774	77.659	36.8	81.7
Simvastatin	**Germany**	6	87.483	3.355	1.37	83.962	91.004	83.8	91.2
	Jordan	6	106.35	5.024	2.051	101.078	111.622	101.5	113
	India	6	94.783	2.562	1.046	92.095	97.472	90.4	97.4
	Greek	6	53.35	14.003	5.717	38.654	68.046	37.6	74
	Total	24	85.492	21.414	4.371	76.449	94.534	37.6	113
chlorpromazine	**Syria**	6	87.483	3.355	1.37	83.962	91.004	83.8	91.2
	Lebanon	6	106.35	5.024	2.051	101.078	111.622	101.8	113

Table-4: Descriptive Statistics for Dissolution test mean values were done to different companies by using Clopidegrol &Simvastatin Drugs

Multiple Comparisons			Sig.	C.S.	
ANOVA BY LSD	France	Jordan	0.336	NS	P>0.05
		India	0.000	HS	P< 0.01
	Jordan	India	0.000	HS	P< 0.01
	Germany	Jordan	0.000	HS	P< 0.01
		India	0.118	NS	P>0.05
		Greek	0.000	HS	P< 0.01
	Jordan	India	0.017	S	P< 0.05
		Greek	0.000	HS	P< 0.01
	India	Greek	0.000	HS	P< 0.01
T-TEST	Syria	Lebanon	0.000	HS	P< 0.01

Table- 5: Inferential Statistics for Dissolution test mean values were done to each pairs different companies by using Clopidegrol, Simvastatin and chlorpromazine Drugs.

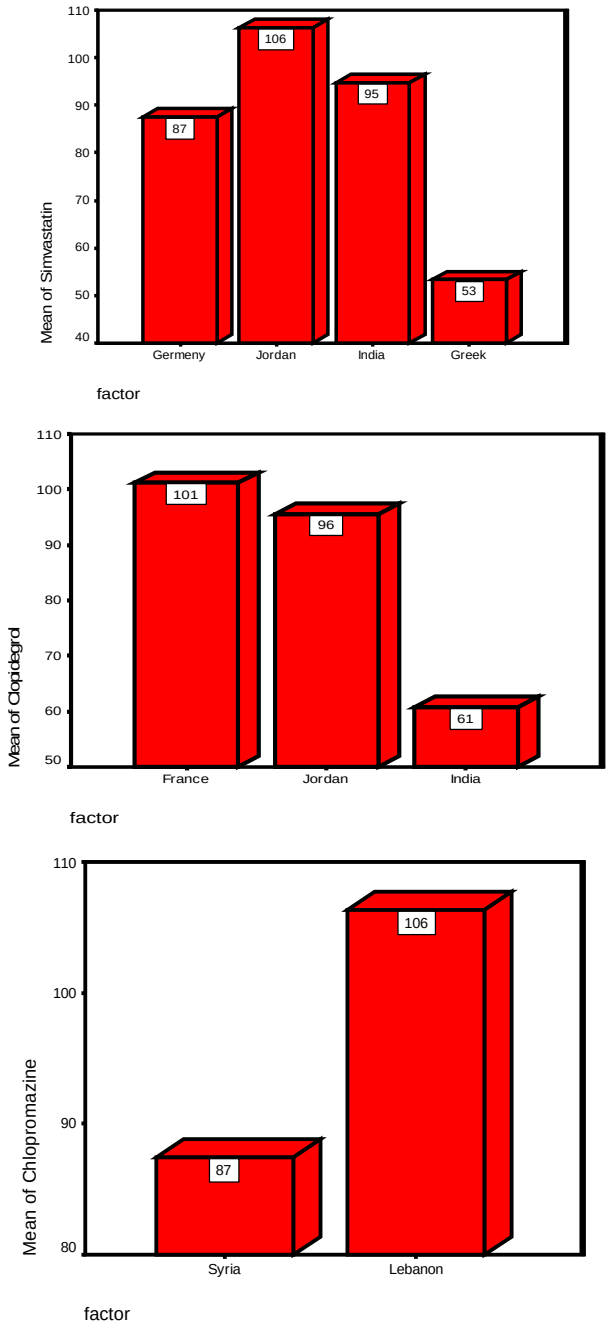

Figure-1: Bar–Charts for Dissolution test mean values were done to different companies by using Clopidegrol Simvastatin and chlorpromazine Drugs

Discussion:

Dissolution is defined as the process by which a solid substance enters in solvent to yield a solution and it is controlled by the affinity between the solid substances and the solvent, the equation of no yes – wintry is described the rate of solid dissolution

$$\frac{dw}{dt} = \frac{DA}{\sigma}(Cs-C)$$

Where $\frac{dw}{dt}$ = is the rate dissolution

Cs = is the solution solubility of the drug
C = is the concentration of the drug in the bulk solution
A = is the area of the solvent particles
σ = is thickness of the diffusion layer
D = is the diffusion coefficient of the dissolvent solute [3]
And there are factors which may affect dissolution rate and this different result can be contributed to it.

Factors affecting the rate of dissolution:

A - Factors related to the physicochemical properties of the drug.
B - Factors related to drug product formulation.
C - Effect of manufacturer process.
D - Factors related to test parameters on dissolution rate.

Factors related to the physicochemical properties of the drug:

A- Effect of solubility on dissolution: Aqueous solubility of the drug is the major factor that determines its dissolution rate. Some studies show that drug solubility data could be used as rough predictor of the Possibility of any future problems with bioavailability, A factor that should be taken into consideration in the Formulation design. [4]

B- Effect of particle size on dissolution: The dissolution rate is directly proportional to the surface area increases with the decreasing particle size, higher dissolution rate may be achieved through the reduction of the particle size. Physical properties of the drug particles other than size also affect indirectly the effective surface area by modifying the shear rate of the fresh solvent that's come in contact with the solid; these properties include the particles shape and the density. The mechanism by which the reduction in particles size improves dissolution is usually through the enhancement of the drug solubility. [4]

C- Effect of solid phase characteristics of the drug on dissolution: Amorphicity and crystallinity, the two important solid-phase characteristics Of drugs affect their dissolution profile. Amorphous form of drug usually exhibits greater solubility and higher dissolution rate as compared to that exhibited by the crystalline form. For example the amorphous form of novobiocin has greater solubility and higher dissolution rate than crystalline form. Blood

level studies confirmed such findings where administration of the amorphous form yielded about three to four times the concentration compared to the administration of crystalline form. Similar differences were demonstrated for griseofulvin, Phenobarbital, Cortisone acetate and chlorramphenicol. Chlorramphenicol palmitate is one example that exists in at least two polymorphs. The polymorph B is apparently more bioavailability .the recommendation might be that Manufacturers should use polymorph B for maximum absorption.

D- Effect of polymorphism on dissolution: Numerous reports have shown that polymorphism and the state of hydration, Solvation, and/or complexation markedly influence the dissolution Characteristics of the drug. [4]

Factors related to drug product formulation:

It has shown that the dissolution rate of a pure drug can be altered significantly when mixed with various excipients during manufacturing process of solid dosage forms.

These excipients are added to satisfy certain pharmaceutical functions such as diluents (fillers), dyes, binders, granulating agent, disintegrants, and lubricants.

A- Effect of granulating agents and binders: Phenobarbital tablets granulated with gelatin solution provide faster dissolution rate in gastric fliud than those prepared using sodium carboxymethylcellulose or polyethylene glycol 6000 as a binder. This observation was attributed to the fact that gelatin imparts hydrophilic characteristics to the hydrophobic drug surface, whereas PEG 6000 forms complex with poor solubility, and sodium carboxy-methylcellulose is converted to its less soluble acid from at low PH of gastric fluid [4].

B- Effect of disintegrate and diluents: The type and amount of disintegrating agent and even the method of addition before or after the granulation all these factor effect the formulation especially the dissolution rate of the dosage form. Copagel (low viscosity grade of sodium carboxy-methylcellulose) when added before granulation of Phenobarbital tablet will slow dissolution rate. However, when added after the granulation the dissolution rate will not be affected. Starch, the most commonly used diluent, the effect of increasing the content of the starch in the formulation of salicylic acid tablet lead to increasing in dissolution rate.

C- Effect of lubricants: The nature, quality and quantity of lubricants added can affect the dissolution rate.Magnesium stearate is a hydrophobic lubricant

tend to retard the dissolution rate of salicylic acid tablet, whereas sodium lauryl sulphate enhances the dissolution rate [4].

Factors related to the manufacturer process:

A- Method of granulation: Wet granulation has been shown to improve the dissolution rates of poorly soluble by imparting hydrophilic properties to the surface of the granules. The critical formulation and proper mixing sequence and time of adding the several ingredients are the main criteria that affect the dissolution rate. [4]

B- Effect of compression force on dissolution rate.

Factors related to test parameters:

Eccentricity of the stirring device, guiding the shaft, vibration, Agitation intensity, Surface tension of the dissolution medium, temperature, pH of the dissolution medium.[4]

6-interpretation:

In this study the physical and chemical characteristics solubility testing by using three types of drugs which are: (Clopidegrol tablet, Simvastatin tablet, Chlorpromazine tablet) from different sources (France, Jordan, India, Germany, Creek, Syria and Lebanon) according to American standard (U.S.P30) to obtain the results to the primary solubility testing data the result of the significant level comparison to analysis the variation for the test of equal means of the data of solubility as following:

1- The solubility of the French drug is the heights with significant level differences at:
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using chlorpromazine in similarly test for average reading of solubility by using t-test.

Conclusion:

Given the importance of the examination results of the test objectives give us an idea of the different pharmacological effectiveness of three types of drugs within the human body (bioavailability), especially in state companies failed for this examination. [5]

The difference in the result can be correlate to all factors which affect the dissolution rate from the raw material (purity) which can affect solubility, and all diluents which was use. [6]

Biopharmaceutical aspects are as important for stability concerns as they are for batch release after production, in vitro dissolution being of high relevance in quality control and quality assurance.

Pharmaceutical analysis today entails more than evaluation of active ingredients or formulated product, so we should understand the physic-chemical properties of drug molecules using advanced industrumental methods through studying of interactions between drug and excipients. [7]

With extensive role that had been played by analytical chemistry in development of pharmaceutical industry ,the sciences and technology utilized today have made pharmaceutical analysis more complicated compared to what it was years ago.

According to the statistical hypotheses testing , we can concludes the following results :

1 - The solubility of the French drug is the heights with significant level differences at:
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