DOI: https://doi.org/10.31351/vol33iss1pp137-145

Assessment of Two-Phase Dissolution System as a Guide in Drug Formulation: The Furosemide Case

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Abstract

The performance and the quality control of a drug may be evaluated using different approaches. Dissolution test is a corner stone in these processes. However, many issues appeared when using monophasic dissolution system like keeping the sink condition and/or described the in-vivo performance for II and IV drugs. Therefore, this study was to evaluate the biphasic dissolution system as discriminatory tool to differentiate between manufacture process and different excipient use for Class IV drug. Furosemide was prepared by two different methods: direct compression and wet granulation. Different excipients (acid and base) were used for each method. Furthermore, two commercially available products (Lasix® and generic product FA) were used for comparison with the prepared formulation. All formulations were evaluated for physical properties like hardness, friability and disintegration. Monophasic and biphasic dissolution tests were carried out for all formulas. All physical properties of the prepared tablets were within acceptable values. The dissolution rates brand, generic, and prepared formulation were identical under monophasic conditions. The similarity factor was more than 50 and difference factor less than 15. On the other hand, the biphasic dissolution profiles (aqueous phase, organic phase and overall dissolution media) showed significant differences between all prepared formulations and the brand product. Moreover, the two phase system still had the ability to show the similarity between brand and generic product. Furthermore, the direct compression method showed lower release than wet granulation method. Similarly, the acid excipients showed higher release than the basic one. As a conclusion, the biphasic dissolution system showed an excellent discriminatory power. Moreover, this approach was superior over conventional dissolution system regarding identifying variations in production processes and excipients content.

Keywords Dissolution, biphasic, Difference factor, Monophasic, Similarity factor

تقييم نظام الانحلال ذي المرحلتين كدليل في صياغة الأدوية: حالة الفوروسيميد

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الخلاصة

يمكن تقييم أداء الدواء ومراقبة جودته باستخدام مناهج مختلفة. اختبار الانحلال هو حجر زاوية في هذه العمليات. ومع ذلك، ظهرت العديد من المشاكل عند استخدام نظام الذوبان الأحادي مثل الحفاظ على حالة الحوض و/أو وصف الأداء داخل الجسم الحي لأدوية الفئة الثانية والرابعة. لذلك، كانت هذه الدراسة لتقييم نظام الانحلال ثنائي الطور كأداة تمييزية للتمييز بين عمليات التصنيع واستخدام السواغ المختلفة للعقار من الفئة الرابعة. تم إعداد الفوروسيميد بطريقتين مختلفتين: الضغط المباشر والتحبيب الرطب. تم استخدام سواغ مختلفة (حمض وقاعدة) لكل طريقة. علاوة على ذلك، تم استخدام منتجين متاحين محليا Lasix ® و FA المنتج التجاري للمقارنة مع التركيبات المعدة. تم تقييم جميع التركيبات للخصائص الفيزيائية مثل الصلابة والتفتت والتفكك. تم إجراء اختبارات الانحلال الأحادي والذوبان ثنائي الطور لجميع الصيغ. كانت جميع الخصائص الفيزيائية للأقراص المعدة ضمن القيم المقبولة. كانت معدلات الذوبان لجميع أنواع الصيغ الثلاثة (العلامة التجارية، والصيغة العامة، والصياغة المعدة) متطابقة في ظل ظروف أحادية الانحلال. كان عامل التشابه أكثر من ٥٠ وعامل الاختلاف أقل من ١٥. من ناحية أخرى، أظهرت ملامح الانحلال ثنائي الطور (المرحلة المائية والمرحلة العضوية ووسائط الانحلال الشاملة) اختلافات كبيرة بين جميع التركيبات المعدة ومنتج العلامة التجارية. علاوة على ذلك، لا يزال نظام المرحلتين لديه القدرة على إظهار التشابه بين العلامة التجارية والمنتج التجاري. علاوة على ذلك، أظهرت طريقة الضغط المباشر إطلاقًا أقل من طريقة التحبيب الرطب. وبالمثل، أظهر السواغ الحمضي إطلاقًا أعلى من الإطلاق القاعدي. وكنتيجة لذلك، أظهر نظام التفكك ثنائي الطور قوة تمييزية ممتازة. علاوة على ذلك، كان هذا النهج متفوقًا على نظام الذوبان التقليدي فيما يتعلق بتحديد الاختلافات في عمليات الإنتاج ومحتوى السواغ.

الكلمات المفتاحية : الانحلال، أحادي الطور ، ثنائي الطور ، عامل التشابه ، عامل الاختلاف .

Introduction

The Biopharmaceutics Classification System (BCS) and the corresponding guidance issued by the Food and Drug Administration (FDA) categorize drug substances into four groups based on aqueous solubility and intestinal membrane permeability [(1)]. This classification captures the two most significant factors influencing oral drug absorption; solubility and intestinal permeability.

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Received: 8/ 2/ 2023
Accepted: 19/ 4/2023

This system has proven to be a very useful and a widely accepted starting point for drug product development and drug product regulation[2]. Moreover, the dissolution test is a corner stone in all pharmaceutical research fields and industries [3,4]. However, many issues appeared when using monophasic dissolution system like keeping the sink condition and/or describe the in-vivo performance for Class II and IV drugs. Furthermore, in quality control and manufacturing of drug product, there is a need for a sensitive approach to capture any difference or similarity from the innovated product or preparation issues.

Biphasic system was firstly proposed to maintain sink conditions in 1961[5]. Previous studies have reported the development of a biphasic dissolution system and their correlation to in vivo absorption for different dosage forms including immediate release[6], modified release [7], lipid [8] and amorphous formulations [(5)]. Additionally, the biphasic system is greatly dependent on the partition coefficients of drugs between the aqueous medium and the organic solvent, so it is particularly useful for Class II and IV drugs as an absorptive sink [(9)]. Till now, the biphasic dissolution approach not approved by FDA or other authorities due to the paucity in the literature regarding its practical used in quality control and/or manufacturing process. Hence, the aim of this study was to evaluate the biphasic dissolution system as discriminatory tool to differentiate between manufacture processes and different excipient use for Class IV drug (furosemide)

Materials and Methods

Materials

Different materials were used in this project. Lasix® was a gift from the innovative global healthcare business Sanofi (Sanofi, France). Furosemide pure powder and Avicel PH102 (microcrystalline cellulose) were a gift from Awamedica Company for Drug Industries (Awa, Erbil, Iraq) and Pioneer Co. pharmaceutical industry (Sulaymaniyah, Iraq), respectively. Other materials were purchased from the corresponding suppliers. Sodium croscarmellose NF from (JRS Pharma, Rosenberg, Germany). Magnesium stearate and Starch 1500 from H.L. Blachford Ltd. (Mississauga, Canada) and Colorcon (Indianapolis, USA), respectively. 1-Octanol from (Sigma Aldrich Chemie GmbH, Steinheim, Germany). Ethanol 99% and Ethanol 70% (v/v) (EtOH) (Chemie GmbH, Steinheim, Germany). HCL (hydrochloric acid) from (CHD (P) LTD). Sodium dihydrogen phosphate (NaH2PO4.2H2O) and disodium hydrogen phosphate (Na2HPO4.2H2O) are both available from (Thomas Baker (Chemicals) Pvt. Ltd. in India). Sodium lauryl sulfate (SLS) and sodium hydroxide (NaOH) from (Carl Roth GmbH & Co., Karlsruhe, Germany).

Methods

Calibration curve of furosemide

Calibration curves for the model drug, furosemide, were generated in different media (phosphate buffer 50 mM, pH 6.8 plus sodium lauryl sulfate (SLS) and 1-Octanol). UV-spectrophotometer (Shimadzu, Japan) was used to measure the absorbance at ʎmax 276nm [10].

Prepare furosemide immediate release formulationS

Two variables were assessed namely; manufacturing processes and excipients used. Therefore, 4 formulations were prepared to accomplish this objective. Two manufacturing methods; direct compression (D) and wet granulation method (G); and two types of ; Dextrose (acidic) and CaHPO4 (basic) were used. These formulas named by its variables: F1 (dextrose and D); F2 (dextrose and G); F3 ($CaHPO_4$ and D); F4 ($CaHPO_4$ and G). Dextrose and $CaHPO_4$ were chosen according to their acidic and basic properties, respectively. Each formula was listed in Table 1. In addition, these formulas were compared with a brand product (Lasix® Sanofi, France) and furosemide generic product (FA).

The physical properties of furosemide immediate release tablets.

Drug content, Hardness test, friability test and disintegration test were conducted as previously reported [11,14].

In-vitro dissolution tests

Monophasic dissolution test under sink condition

A type II dissolution apparatus (Cosmo lab. Equipment, India) was used in this study. The dissolution media was a (900 ml phosphate buffer 50 mM pH 6.8 with 0.5% w/v SLS) to maintain sink conditions. The apparatus was set at 100 rpm and 37 °C[15]. A 0.45 µm syringe filter was used to withdraw a five ml samples at a predetermined time intervals and a fresh dissolution media was replaced. Drug concentrations were analyzed using UV- spectrophotometer (Shimadzu , Japan)[(16)].

Table 1. Furosemide formulations with different excipient and preparation method. Formulas were named according to their diluent and preparation methods.

Components	Dex D (F1)	Dex G (F2)	$CaHPO_4$ D (F3)	$CaHPO_4$ G (F4)
Furosemide	40mg	40mg	40mg	40mg
MCC AvicelPH102 (disintegrant)	48% (125mg)	42% (110mg)	48% (125mg)	42% (110mg)
Mg Stearate (lubricant)	2% (5mg)	1% (2.5mg)	2% (5mg)	1% (2.5mg)
$CaHPO_4$ (diluent)	---	---	50% (130mg)	44% (115mg)
Dextrose (diluent)	50% (130mg)	42% (115mg)	---	---
CS (binder)	1% (2.5mg)	3% (7.5mg)	1% (2.5mg)	3% (7.5mg
Starch 1500(Disintegrant)	---	10% (25mg)	---	10% (25mg)

MCC: microcrystalline cellulose , CS: croscarmellose sodium , Dex: dextrose, $CaHPO_4$: dicalcium phosphate dihydrate ,D: direct compression, G: wet granulation,Overall weight of tablet is 300mg.

Biphasic dissolution test

A biphasic dissolution experiments were conducted in 250 ml glass beakers. The temperature was set at 37 °C and the paddle rotation at 100 rpm (comparable variables to monophasic dissolution test). Different volumes and ratio of the biphasic dissolution medium was used. These media as follows: 100 ml phosphate buffer and 20 ml 1-octanol (ratio of 10:2); 100 ml phosphate buffer and 50 ml 1-octanol (ratio of 10:5); and 100 ml phosphate buffer and 80 ml 1-octanol (ratio of 10:8) [17]. Samples were withdrawn from aqueous and organic media and the concentration of furosemide concentration was analyzed as previously mentioned in monophasic dissolution experiment.

Statistical Analysis

All experiments were done in triplicate. Several statistical approaches were used in this study. One-way ANOVA, paired t-test and repeated measurements ANOVA were used when appropriate. Moreover, the dissolution profiles' similarity, dissimilarity, and 90% confidence interval of difference were calculated using DDSolver software [(18)].

Results and Discussion

Calibration curve of furosemide

The regression analysis revealed high correlation coefficient (R^2 0.9994, R^2 0.9989) in phosphate buffer plus SLS and 1-octanol, respectively.

Furosemide immediate release tablets characterization

The prepared formulas showed comparable hardness (between 5.35 and 6.25 kg/cm^2) and friability (<1%) to Lasix® tablets. Moreover, those formulas showed an acceptable disintegration time (between 5.30 and 7.54 minutes). Statistical analysis revealed insignificant differences in hardness test for all formulations compared to marketed product (Lasix®). In addition, there were insignificant differences in friability test for all formulations against (Lasix®) except for F2 (P = 0.018). Nonetheless, all formulas showed significant difference indisintegration time values. As showed in Table 2. Moreover, there were insignificant differences in furosemide content between all formulas and Lasix® (P<0.05).

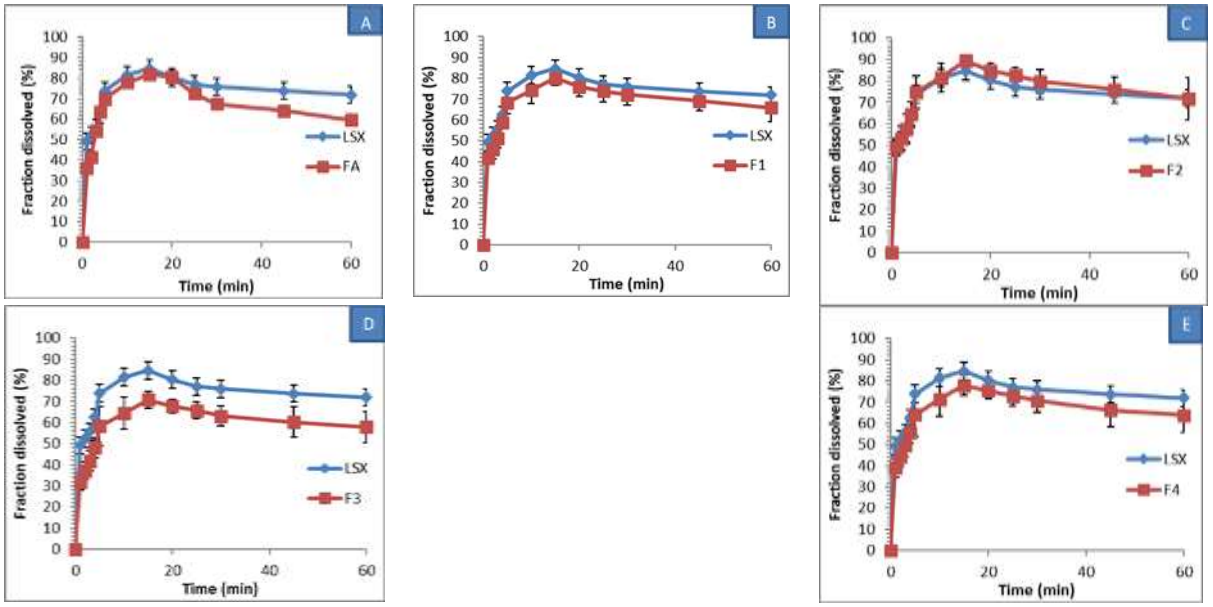
Table 2. Physical properties of furosemide Immediate Release Tablets (mean± standard deviation).

Formulas	Hardness (kg/cm^2)	Friability (%)	Disintegration Time(min)
F1	5.45±0.35	0.72±0.01	6.38±0.05**
F2	6.10±0.28	0.59±0.02*	5.30±0.21**
F3	5.35±0.07	0.700±.01	6.52±0.35**
F4	6.25±0.35	0.59±0.07	5.53±0.45**
Lasix®	6.15±0.63	0.74±0.04	7.54±0.37**

* *P<0.05;* ** *P<0.01*; P>0.05; Formulas: F1: Dextrose (acidic excipients, direct compression),F2: Dextrose (acidic excipients, wet granulation) F3: CaHPO4 (basic excipient, direct 8compression),F4: CaHPO4 (basic excipient, wet granulation),Lasix® (control): (marketed product**).**

In-vitro dissolution tests (Monophasic)

The dissolution profiles of prepared formulas and the marketed products were shown in Figure 1. More than 70% of API was released within 15 minutes for all preparations. Furthermore, the release time ($t_{25\%}$, $t_{50\%}$, and $t_{75\%}$) showed insignificant differences (P>0.05) between the prepared formulas and the products (Table 3).



A: FA: finished marketed product; LSX: Lasix®; B: F1: Dextrose (acidic excipients, direct compression); C: F2: Dextrose (acidic excipients, wet granulation); D: F3:CaHPO4 (basic excipient, direct compression); E: F4:CaHPO4 (basic excipient, wet granulation)

Figure 1. monophasic dissolution of Lasix® (LSX) and (finished products and formulas) in buffer phosphate buffer (pH 6.8, 900ml).

Table 3. Finished products and formulas of furosemide release time (Mean amount released ± SD).

parameter	Release time					
	F1	F2	F3	F4	FA	Lasix®
$T_{25\%}$	0.942±0.92	0.898±0.91	0.995±0.89	0.951±0.93	0.993±1.09	0.885±1.12
$T_{50\%}$	1.623±0.97	1.061±0.97	1.790±0.95	1.584±0.99	1.238±1.13	1.070±0.98
$T_{75\%}$	25.659±1.32	22.345±1.17	27.395±1.43	25.078±1.40	21.640±0.98	21.108±0.95

FA: finished marketed product , F1: Dextrose (acidic excipients, direct compression), F2: Dextrose (acidic excipients, wet granulation), F3:CaHPO4 (basic excipient, direct compression), F4:CaHPO4 (basic excipient, wet granulation)

Additionally, the results showed that all preparations were similar (similarity factor more than 50) and the difference factor less than 15 (Table 4). Moreover, all preparations follow the Weibull model using the previous reported criteria (Table 5) [18]. These results revealed that even though the formulas prepared with different excipients and or preparation methods, it was still similar using conventional USP II dissolution test with no discriminatory power.

Hence, the monophasic dissolution method discloses a low discriminatory power in differentiating between formulas.

Table 4. Similarity and difference factors between furosemide formulas

comparison	$\int_1$ ± SE	$\int_2$ ± SE
Lasix®×FA	8.56 ± 2.21	57.09 ± 4.30
Lasix®×F1	7.31 ± 1.09	64.86 ± 1.19
Lasix®×F2	3.02 ± 0.48	75.47 ± 1.14
Lasix®×F3	14.27 ± 5.54	51.15 ± 5.31
Lasix®× F4	10.43 ± 3.98	57.17 ± 5.98

$\int_1$: difference factor, $\int_2$: similarity factor, SE : standard error

Table 5. Mathematical release model of furosemide formulations.

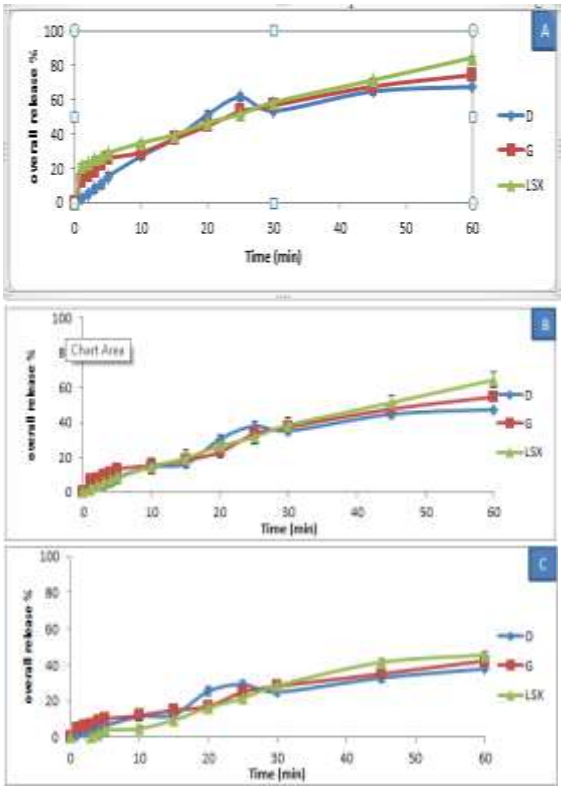
Model	Statistics	Formulas				
		F1	**F2**	**F3**	**F4**	**Lasix®**
Zero order	R^2-adj	-3.19	-2.96	-3.24	-2.51	-2.91
	AIC	135.75	133.28	136.22	128.82	132.76
	MSC	-2.72	-2.56	-2.75	-2.27	-2.53
First order	R^2-adj	0.64	0.34	0.68	-0.38	0.26
	AIC	103.67	109.91	102.23	116.69	110.99
	MSC	-0.26	-0.77	-0.14	-1.33	-0.85
Higuchi	R^2-adj	-0.66	-0.54	-0.68	-0.33	-0.52
	AIC	123.74	121.07	124.24	116.24	120.51
	MSC	-1.80	-1.62	-1.83	-1.30	-1.59
Weibull	R^2-adj	0.91	0.89	0.91	0.86	0.89
	AIC	86.49	87.12	86.32	87.75	87.21
	MSC	1.06	0.98	1.07	0.88	0.96
Korsmeyer-Peppas	R^2-adj	0.88	0.86	0.88	0.82	0.86
	AIC	89.98	90.13	89.96	90.41	90.16
	MSC	0.79	0.75	0.79	0.68	0.74

Bold color font represents the best model , F1; Dextrose (acidic excipients, direct compression),F2; Dextrose (acidic excipients, wet granulation) F3; CaHPO4 (basic excipient, direct compression),F4; CaHPO4 (basic excipient, wet granulation), R^2 Adjusted correlation coefficient , AIC, Akaike Information Criterion, MSC, Model Selection Criterion

Biphasic dissolution parameters for furosemide

The impact of biphasic dissolution media was assessed using Lasix® tablets. Previously reported article showed that using different volume ratio had an impact on the overall dissolution profile. Deng et al, proposed volume ratio of 10:8, 10:5 and 10:2 and set the highest release % as a criteria to choose the suitable volume ratio[17]. The overall release results showed that the highest release % for Lasix® occurred within volume ratio of 10:2 and more than 80% of furosemide was released within 60 minutes (Figure 2). Therefore, 10:2 volume ratio was chosen as appropriate media volume for the subsequent experiments. The most common methods to prepare immediate release tablets are direct compression (D) and wet granulation (G). They were also considered as variables in choosing the suitable volume ratio of dissolution media. The release profiles were shown in Figure 2.

The overall release percent were ranked as follow: Brand products > wet granulation tablet formulas > direct compression tablet formulas. Based on volume ratio, the release percent were ranked as follow: 10:2>10:5>10:8. This volume ratio created apparent differences in the release % for two immediate release tablets formulas (D and G) of furosemide. These imply a good discriminative capacity. Hence, the rotation speed of 100 revolutions per minute and the volume ratio of 10:2 were chosen for the biphasic test in subsequent experiments



D: furosemide with microcrystalline cellulose (neutral excipients, direct compression) G: frusemide with microcrystalline cellulose (neutral excipients, wet granulation) LSX: finished formula (Lasix®)

Figure 2. The overall dissolution profiles of furosemide formulas (neutral excipients). Volume ratio :(A) 10:2, (B) 10:5 and (C) 10:.

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Biphasic dissolution for furosemide formulas

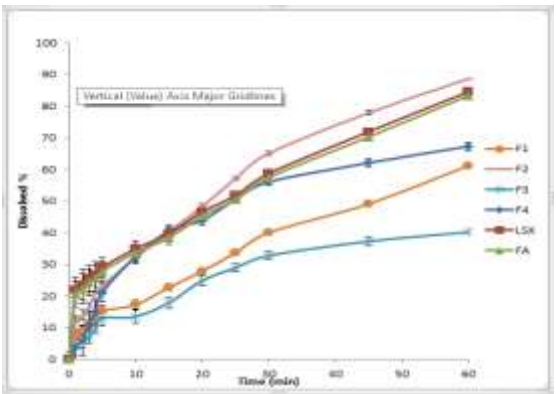
The releases for all preparations were analyzed using 90% confidence interval difference. The results showed that all prepared formulas were unsuccessfully to be similar to Lasix®. Moreover, marketed generic product (FA) was still similar to Lasix® (Table 6).

Table 6. Confidence interval (90%) difference of biphasic dissolution profiles for different formulas of furosemide.

Formulas or Finished products	Lasix®	
	Aqueous phase	Organic phase
FA	A	A
F1	R	R
F2	R	R
F3	R	R
F4	R	R

R; Reject or A; Accept. FA: finished products F1; Dextrose (acidic excipients, direct compression) F2; Dextrose (acidic excipients, wet granulation) F3; CaHPO4 (basic excipient, direct compression) F4; CaHPO4 (basic excipient, wet granulation)

In addition to the above statistical method (90% CI of difference), a repeated measures analysis of variance (ANOVA) was used as it is considered the most appropriate method as previously reported [19-24]. The overall dissolution releases (Figure 3) were analyzed using repeated measures analysis of variance (ANOVA). The release of the brand product was more than 80%, while, the release of the prepared formulas was ranked as follow: F2 (>80%) > F4 (>65%) > F1 (>60%) > F3 (>40%). The results showed insignificant differences (P > 0.05) between the overall release profiles of the finished furosemide products (Lasix® and FA). However, the results showed a highly significant difference between prepared formulas (F1 to F4) and Lasix®.

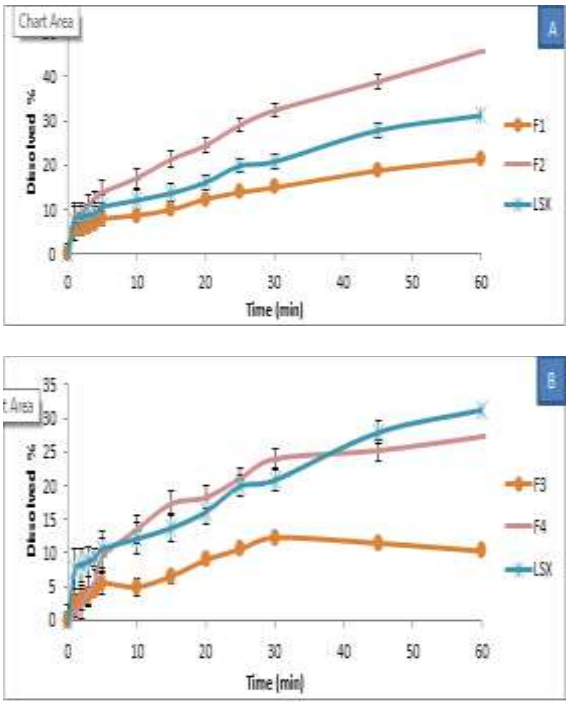


F1; Dextrose (acidic excipients, direct compression) F2; Dextrose (acidic excipients, wet granulation) F3; CaHPO4 (basic excipient, direct compression) F4; CaHPO4 (basic excipient, wet granulation) LSX: Lasix®
FA: finished product

Figure 3. Overall dissolution profiles of furosemide finished and prepared formulas.

Manufacture processes effect

Only the release in the aqueous phase was evaluated as it is the first phase that the drug dissolved in it. Each pair of prepared formulas was compared to Lasix®. These pairs as follows: (F1 and F2; direct compression) and (F3 and F4; wet granulation). The wet granulation method higher and significant (P<0.001) release compared to direct compression method as shown in Figure 4.



LSX: Lasix® F1; Dextrose (acidic excipients, direct compression) F2; Dextrose (acidic excipients, wet granulation) F3; CaHPO4 (basic excipient, direct compression) F4; CaHPO4 (basic excipient, wet granulation)

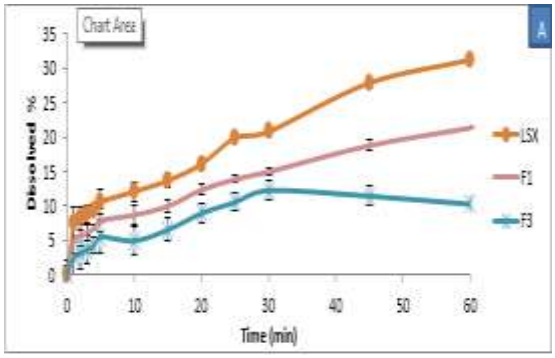
Figure 4. Furosemide aqueous phase dissolution profiles with different manufacturing processes (A: F1 and F2; acid excipients), (B: F3 and F4; base excipients) compared to Lasix® (LSX).

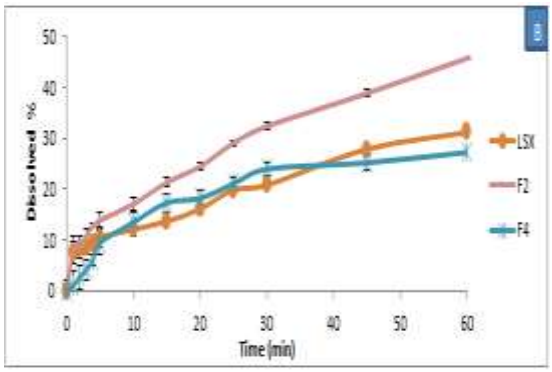
The results showed that the release patterns among the direct compressed formulations were significantly lower than other formulations. These results may be due to particle size reduction of the drug and the excipients in the formulations [25, 26]. Moreover, the higher release could be

contributed to the higher concentration of croscarmellose sodium (disintegrant) [27]. Another reason may be due to the presence of Starch 1500 in the wet granulation method which increase the wettability of the granules [28]. Furthermore, binders could improve wettability process. The hydrophobic drug was exposed on the surface of the granule made by direct compression, whereas diluents/binders partially coated the drug during wet granulation thus improving its wettability [17].

Excipients Effect

The following pairs of formulas were used to assess the excipient effect: direct compression formulas (F1 and F3; acidic and basic excipient, respectively) and wet granulation formulas (F2 and F4; acidic and basic excipient, respectively) Figure 5 shows that F1 and F2 (acidic excipient) had higher and significant (P<0.001) release profile than F3 and F4 (basic excipient).





F1; Dextrose (acidic excipients, direct ompression)
F3; CaHPO4 (basic excipient, direct compression)
F2; Dextrose (acidic excipients, wet granulation)
F4; CaHPO4 (basic excipient, wet granulation)
LSX: Lasix®

Figure 5. Furosemide aqueous phase dissolution profiles using different excipients (acid and base excipients; A: direct compression; B: Wet granulation) compared to Lasix® (LSX).

It is well known the microclimate pH effect of the excipient that formed around the drug will enhance or decrease the dissolution process of that particular drug. The acidic excipients will increase the dissolution of the basic drug and vice versa (29). However, this was not the case in this study as the acidic excipient formulation had higher release profile than basic excipient for acid drug (furosemide). It is known that surface of CaHPO4 particles behave as an alkaline (30). Moreover, it was reported that this surface behavior will lead to adsorb many acidic drugs (30-33). Therefore, the overall drug that available to be dissolved and released was less. As a final result, the biphasic dissolution system gave excellence discrimination between preparation method, as well as, different excipient use

Conclusion

Dissolution is a corner stone method for drug development. However, many issues could be raised during routine quality control processes or in-vitro-in-vivo correlations especially for class IV drugs. The present study showed an excellent discriminatory power of the biphasic dissolution system over monophasic dissolution approach. The results could easily evaluate the effect of changing between preparation method (direct compression and wet granulation) and changing excipient with different acidity properties. Furthermore, the system proved that bioequivalent marketed products are still similar to each other. Therefore, the biphasic dissolution system may be used as a benchmark for manufacturing before in-vivo testing, and its adaptation is necessary for the development of any product.

Funding

The authors did not receive any funds.

Ethics Statements

This study was performed in accordance with the ethical standards and protocols approved by the Committee of The College of Pharmacy, Mustansiriyah University and authorized the experimental techniques and protocols utilized in this work.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Author Contributions

Mohammed Abdulzahra Hussein and Mohanad Naji Sahib contributed equally: Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper.

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