

# A study on the influence of the dissolution test factors on *in vitro* release of ibuprofen from sustained release tablets

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## ABSTRACT

**Objectives.** The aim of this study was to investigate the influence of *in vitro* release test parameters on the release of ibuprofen from sustained release inert matrix tablets.

**Materials and methods.** Ibuprofen sustained release inert matrix tablets were manufactured at a laboratory scale using Kollidon® SR as matrix formator. The variables of *in vitro* release study were: dissolution media pH (7.2-6.8-5.4-1.2), apparatus type (rotative basket and rotative paddle) and stirring speed (50 rpm and 100 rpm).

**Outcomes.** An increase in ibuprofen solubility together with an increase on pH value was observed. Percentage drug release increases together with the increase of pH. Rotative paddle apparatus proved to generate much powerful hydrodynamic forces in comparison with rotative basket apparatus which leads to a rapid *in vitro* release. Increasing stirring speed will determine a faster release of ibuprofen from matrix tablets. Statistical comparison of release profiles was performed by means of similarity factor *f*<sub>2</sub>. Both statistical release profiles comparison (between apparatuses and between stirring speeds) showed no influences of apparatus type and stirring speed on *in vitro* release at pH 1.2 and 5.4. At pH 6.8 and 7.2 there are strong influences of both apparatus type and stirring speed on ibuprofen release from matrix tablets. Modeling of release kinetics showed a good fitting by Weibull and Korshmeier-Peppas equations (especially at pH 6.8 and 7.2) and a fair fitting by Higuchi equation (at pH 1.2 and 5.4).

**Conclusions.** *In vitro* release of ibuprofen from sustained release matrix tablets depends on dissolution media pH and release rate depends on judicious choice of dissolution test factors to made precise *in vitro/in vivo* correlations.

**Keywords:** *in vitro* release, dissolution test factors, drug-release models

## INTRODUCTION

Release rate of APIs from solid pharmaceutical dosage forms and also absorption rate is determined by dissolution so *in vitro* release plays an important role in predicting biopharmaceutical profile of a drug [1].

According to the Biopharmaceutical Classification System (BCS),

ibuprofen is included in class II (due to its high permeability and low solubility). Bioavailability of pharmaceutical dosage forms containing APIs included in BCS II is limited by dissolution rate [2].

Modified-release dosage forms are used in therapy for more than 50 years and are an important field for pharmaceutical companies (R&D)

and also for academics. An ideal MR dosage form can improve therapy and can offer the patient the following benefits: reduced administration frequency, adequate plasmatic concentrations, enhanced bioavailability and compliance [3]. Formulation of ibuprofen and the strategies applied to modulate its delivery, to acquire specific therapeutic

benefits, are still under research [4,5].

Oral bioavailability of a drug is dictated by physicochemical properties but also by physiological conditions [6].

In the manufacturing of sustained release matrix tablets, Kollidon® SR is often used due to its excellent pharmaceutical properties (flowability, compressibility etc.) [7].

There are a few studies describing the determination of critical parameters of drug substances that may influence the dissolution but also the comparison of different apparatuses and conditions (media, surfactants, stirring speed) [8,9].

## AIM

The aim of this paper was to investigate the influence of *in vitro* release test parameters on the release of ibuprofen from sustained release inert matrix tablets.

## MATERIALS AND METHODS

### Materials

Ibuprofen was supplied by Hubei Biocause Pharmaceutical Company Ltd., China. As diluent, directly compressible lactose (lactose DC) (Supertab 14 SD) from DMV-Fonterra Excipients GmbH&Co, Germany, was used. Kollidon® SR, from BASF-Germany, was chosen as matrix-forming excipient. To ensure free flow of powder blends and also

as anticaking agent, hydrophilic fumed silica (Aerosil® 200), from Degussa AG – Germany, was used. Lubricant (magnesium stearate) was produced by UNDESA, Spain.

### Reagents

Monopotassium phosphate, sodium acetate and potassium chloride were supplied by Chemical Company, Romania. Sodium hydroxide, glacial acetic acid and concentrated hydrochloric acid were manufactured by Merck – Germany, Sigma Aldrich – Germany and Nordic Invest – Romania, respectively. All reagents were analytical grade. In all experiments distilled water was used.

### Tablets preparation

All powders were weighed on a three decimal places balance (Sartorius, Germany), passed through an 800 µm sieve and mixed in Mixer Y5, Y-shaped mixing vessel (Erweka, Germany). Due to excellent properties of powder blends (flowability and compressibility - data not shown) tablets were prepared by means of direct compression method using an eccentric tablet press Korsch EK-0 (Korsch, Germany) equipped with a 9 mm die, with flat punch. Also crushing strength, friability and disintegration time were within the European Pharmacopoeia requirements (data not shown). Qualitative and quantitative composition of tablets is presented in Table 1.

**TABLE 1. Qualitative and quantitative composition of the tablets**

Raw material – type	Supplier	Composition (mg/tablet)	Percentage	Laboratory batch (for 75 g)
Ibuprofen – API	Hubei Biocause	400.00	53.33	40.00
Supertab 14 SD - filler	DMV-Fonterra	203.75	27.17	20.38
Kollidon® SR – matrix-formator	BASF	135.00	18.00	13.50
Aerosil 200 – anticaking agent	Degussa AG	3.75	0.50	0.38
Magnesium stearate - lubricant	UNDESA	7.50	1.00	0.75
<b>Total core</b>		<b>750.00</b>	<b>100.00</b>	<b>75.00</b>

*Ibuprofen solubility determination*

The solubility of ibuprofen in different dissolution media was determined: phosphate buffers pH 7.2 (40 mM), phosphate buffers pH 6.8 (40 mM), acetate buffers pH 5.4 (40 mM), hydrochloric acid – potassium chloride (0.1 M). pH measurement was performed on an MP 225 pH-meter (Mettler Toledo, USA). Solubilities were determined in dissolution vessels at 37°C under stirring. Samples were extracted after 24 hours, filtered and after appropriate dilutions with dissolution media the absorbance was measured at 221 nm by means of Specord 200 Plus spectrophotometer (Analytik Jena, Germany). In all cases corresponding buffer was used as blank.

*In vitro release of ibuprofen from sustained release tablets*

*In vitro* release was tested by means of an PT-DT7 dissolution tester (PharmaTest, Germany) equipped with rotative basket (No. 1) and on PT-WS 100 dissolution tester (PharmaTest, Germany) equipped with rotative paddle (No. 2). Dissolution media (900 ml)

were the buffers solution described in the section Ibuprofen solubility determination. In all cases USP/EP Borosilicate glass vessel were used. Stirring speeds of 50 and 100 rpm were studied. Experimental design of this study is presented in Table 2.

Each time, 4 ml of dissolution samples were extracted and replaced with fresh dissolution media in order to keep constant the dissolution media volume (900 ml). Sampling times were: 0.5-1-1.5-2-2.5-3-4-5-6-8-10-12-24 hours. After filtering, appropriate dilutions of samples were performed (with mLine semi-automatic pipettes from Sartorius). The absorbance was measured at 221 nm by means of Specord 200 Plus spectrophotometer (Analytik Jena, Germany). In all cases corresponding buffer was used as blank.

*Release kinetics and statistical comparison of in vitro release profiles*

Modeling and comparison of dissolution profiles was performed by means of DDSolver (a freeware software working on Microsoft Excel platform) [10].

**TABLE 2. Experimental design of *in vitro* release study**

pH	Apparatus type	Stirring speed (rpm)	Symbol
7.2	1	50	7.2 50 B
6.8	1	50	6.8 50 B
5.4	1	50	5.4 50 B
1.2	1	50	1.2 50 B
7.2	2	50	7.2 50 P
6.8	2	50	6.8 50 P
5.4	2	50	5.4 50 P
1.2	2	50	1.2 50 P
7.2	1	100	7.2 100 B
6.8	1	100	6.8 100 B
5.4	1	100	5.4 100 B
1.2	1	100	1.2 100 B
7.2	2	100	7.2 100 P
6.8	2	100	6.8 100 P
5.4	2	100	5.4 100 P
1.2	2	100	1.2 100 P

Similarity factor  $f_2$  was used to statistically compare *in vitro* release profiles. This factor (indicating the closeness between two release profiles) is defined by the following equation (1).

$$f_2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

Where:  $R_t$  and  $T_t$  are the percentage of reference and test profile, at time  $t$  and  $n$  is the number of sampling points.

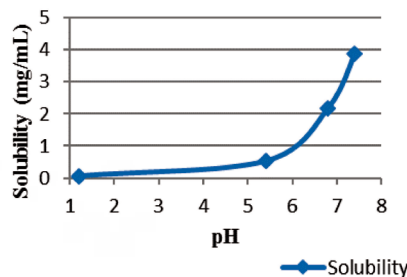
According to European Medicines Agency, values of  $f_2$  between 50 and 100 indicate the sameness of two *in vitro* release profiles. Evaluation of the goodness of fit of a model includes the calculation of coefficient of determination ( $R^2$ ) and of adjusted coefficient of determination ( $R^2_{adj}$ ) [11,12].

## RESULTS AND DISCUSSION

Solubility determination of ibuprofen showed an increase in solubility (fig. 1) together with an increase in pH value (pH = 1.2 – S = 0.05 mg/ml; pH = 5.4 – S = 0.52 mg/ml; pH = 6.8 – S = 2.18 mg/ml; pH = 7.4 – S = 3.89 mg/ml).

*In vitro* release profiles of ibuprofen in different dissolution condition are presented in Figure 2.

*Influence of the dissolution media pH on in vitro release of ibuprofen*  
In both cases (rotative basket



**FIGURE 1. Ibuprofen solubility variation versus pH**

apparatus and rotative paddle apparatus) percentage drug release increases together with the increase of pH due to higher ibuprofen solubility in phosphate buffers in comparison with its solubility in acetate and hydrochloric buffers (fig. 2).

*Influence of dissolution apparatus type on in vitro release of ibuprofen*  
Dissolution apparatus type has a significant influence on *in vitro* release of ibuprofen. Hydrodynamic forces are much powerful in case of rotative paddle apparatus in comparison with rotative basket apparatus and consequently *in vitro* release is more rapid (fig. 3). Also, some excipients may remain on the sieve of the basket, somehow explaining why release on rotative basket apparatus is lower.

Similarity factors for release profiles (tested at the same pH and the same stirring speed but on different apparatus type) were calculated (Table 3).

**TABLE 3. Statistical release profiles comparison (between apparatuses)**

Release profiles comparison	Similarity factor $f_2$
7.2 50 B and 7.2 50 P	41.59
7.2 100 B and 7.2 100 P	38.84
6.8 50 B and 6.8 50 P	34.34
6.8 100 B and 6.8 100 P	17.92
5.4 50 B and 5.4 50 P	85.19
5.4 100 B and 5.4 100 P	94.48
1.2 50 B and 1.2 50 P	96.79
1.2 100 B and 1.2 100 P	84.79

As stated in table 3, apparatus type does not influence release profiles at pH 1.2 and 5.4 ( $50 < f_2 < 100$ ). Release profiles corresponding to pH 6.8 and pH 7.2 are under a strong influence of apparatus type ( $f_2 < 50$ ).

*Influence of stirring speed on in vitro release of ibuprofen*

As presented in figure 4, a bigger stirring speed will determine a

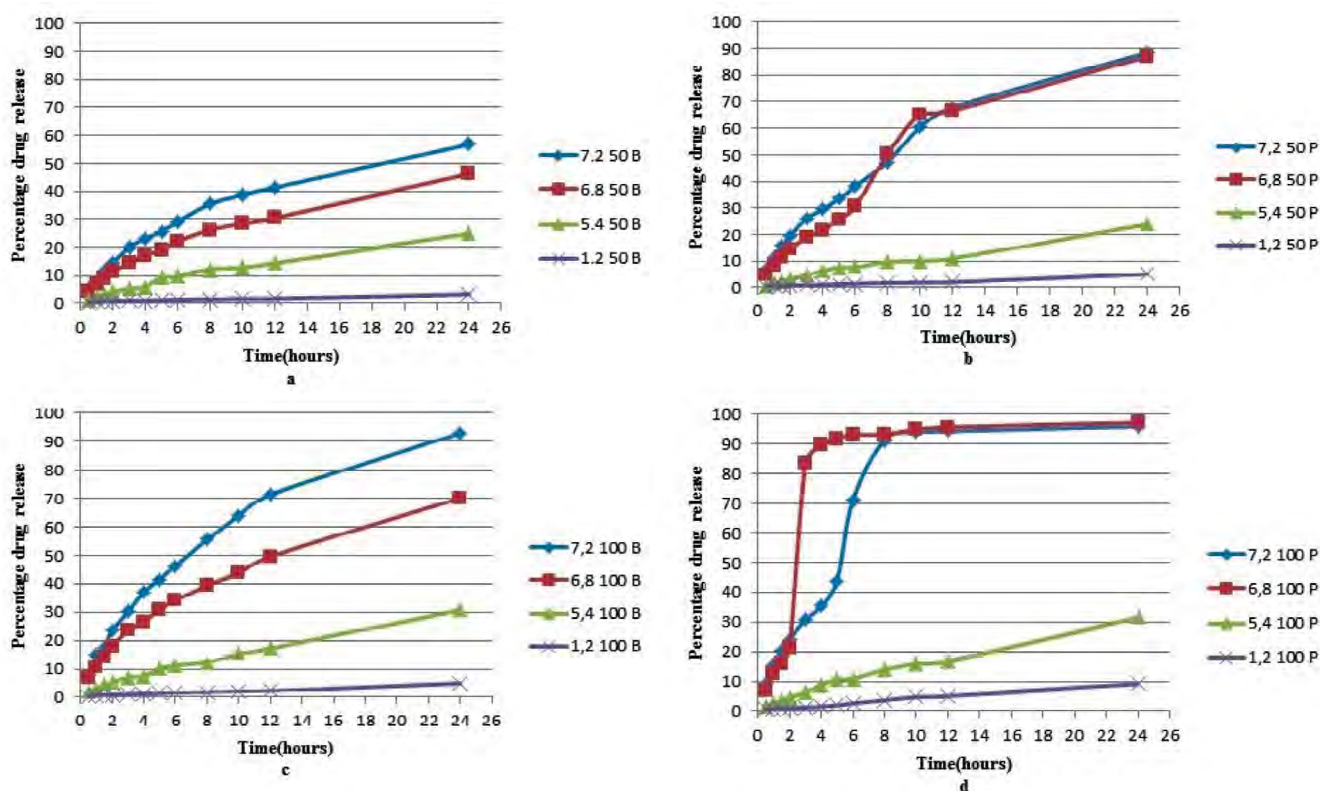


FIGURE 2. Drug release profiles for rotative basket apparatus (50 rpm – a; 100 rpm – c) and for rotative paddle apparatus (50 rpm – b; 100 rpm – d)

faster *in vitro* release of ibuprofen from sustained release tablets. Again, hydrodynamics plays an important role on dissolution.

Similarity factors for release profiles (tested at the same pH and on the same apparatus type but using different stirring speed) were calculated (Table 4).

TABLE 4. Statistical release profiles comparison (between stirring speeds)

Release profiles compared	Similarity factor $f_2$
7.2 50 B and 7.2 100 B	36.26
7.2 50 P and 7.2 100 P	34,25
6.8 50 B and 6.8 100 B	45.03
6.8 50 P and 6.8 100 P	19.08
5.4 50 B and 5.4 100 B	80.19
5.4 50 P and 5.4 100 P	69.76
1.2 50 B and 1.2 100 B	96.38
1.2 50 P and 1.2 100 P	84.05

As stated in table 4, stirring speed does not influence release profiles at pH 1.2 and 5.4 ( $50 < f_2 < 100$ ). Release profiles corresponding to pH

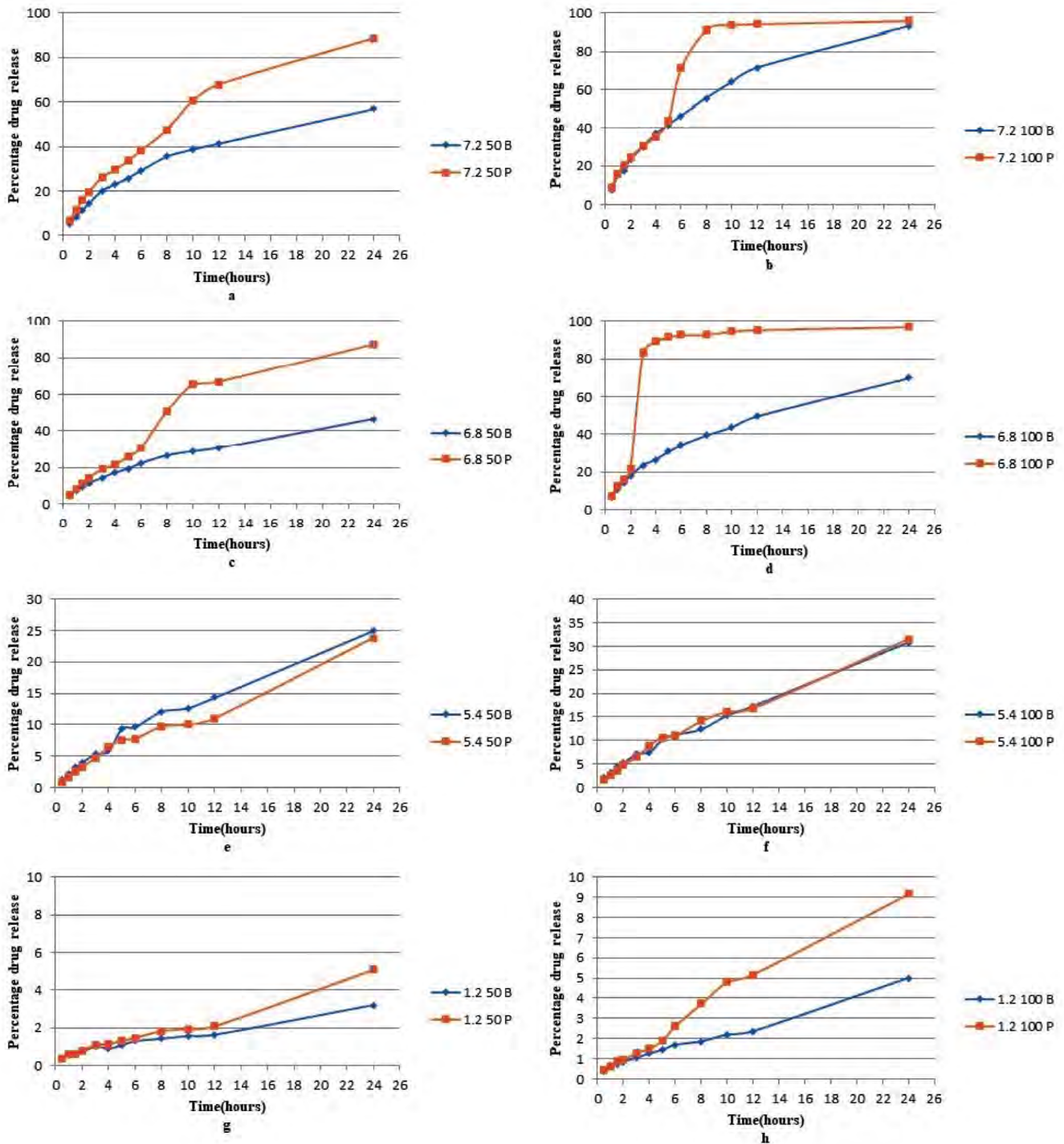
6.8 and pH 7.2 are under a strong influence of stirring speed ( $f_2 < 50$ ).

*In vitro* release profiles modeling  
All dissolution profiles were fitted

by means of Weibull, Korsmeyer-Peppas and Higuchi models (Table 5).

TABLE 5. Goodness of fit for kinetic release models for ibuprofen

Kinetic model Profile symbol	Weibull		Korsmeyer-Peppas		Higuchi		
	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>	n	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
7.2 50 B	0.9979	0.9975	0.55	0.9542	0.9496	0.9833	0.9833
6.8 50 B	0.9954	0.9943	0.61	0.9894	0.9883	0.9844	0.9844
5.4 50 B	0.9882	0.9856	0.78	0.9825	0.9807	0.9090	0.9090
1.2 50 B	0.9083	0.8879	0.52	0.9344	0.9279	0.9303	0.9303
7.2 50 P	0.9762	0.9710	0.56	0.9755	0.9730	0.9534	0.9534
6.8 50 P	0.9507	0.9397	0.80	0.9235	0.9158	0.8716	0.8716
5.4 50 P	0.9649	0.9571	0.81	0.9761	0.9737	0.8554	0.8554
1.2 50 P	0.8799	0.8532	0.51	0.8720	0.8592	0.8094	0.8094
7.2 100 B	0.9889	0.9864	0.56	0.9607	0.9568	0.9791	0.9791
6.8 100 B	0.9925	0.9908	0.56	0.9940	0.9934	0.9898	0.9898
5.4 100 B	0.9752	0.9697	0.68	0.9886	0.9875	0.9058	0.9058
1.2 100 B	0.8859	0.8605	0.60	0.9213	0.9135	0.8695	0.8695
7.2 100 P	0.9208	0.9032	0.69	0.7334	0.7067	0.8250	0.8250
6.8 100 P	0.9246	0.9079	0.39	0.2592	0.1851	0.5966	0.5966
5.4 100 P	0.9815	0.9773	0.76	0.9928	0.9921	0.8993	0.8993
1.2 100 P	0.9843	0.9809	0.81	0.9708	0.9679	0.8171	0.8171



**FIGURE 3.** Influence of dissolution apparatus type on *in vitro* release of ibuprofen (pH 7.2 – a and b; pH 6.8 c and d; pH 5.4 e and f; pH 1.2 g and h)

Good fitting was achieved by using Weibull and Korsmeyer-Peppas models (especially at pH 6.8 and 7.2). Trying to explain release data with Higuchi equation resulted in a fair goodness of fit but somehow poorer (especially at low pH and high stirring speed) than the one

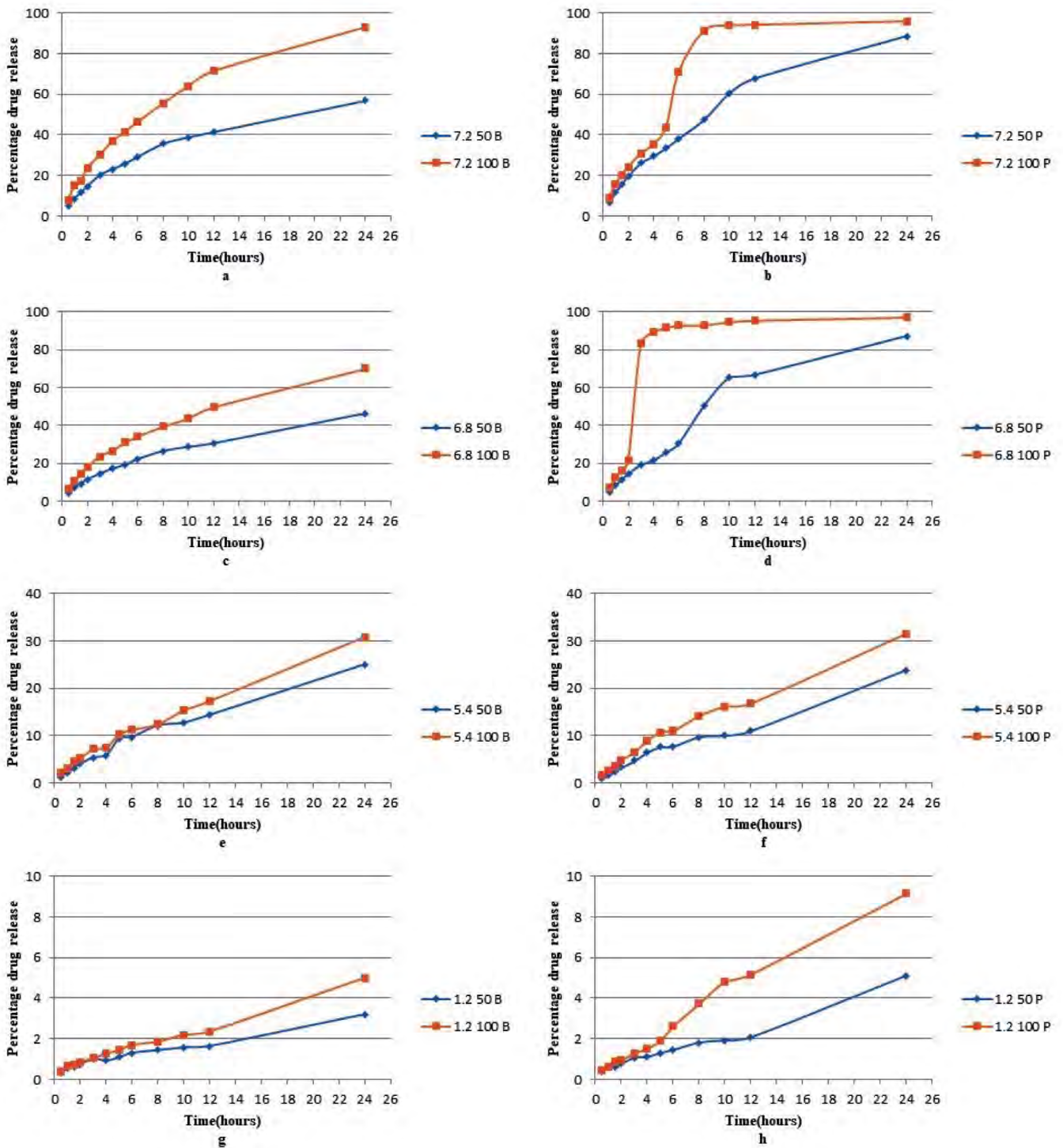
obtained by means of Weibull and Korsmeyer-Peppas models.

### CONCLUSIONS

Sustained release matrix tablets with ibuprofen were manufactured. Factors related to experimental design of *in vitro* release testing

were dissolution media pH, apparatus type and stirring speed.

Solubility of ibuprofen and percentage drug release proved to increase together with the increase of pH.



**FIGURE 4. Influence of stirring speed on *in vitro* release of ibuprofen (pH 7.2 a – rotative basket and b – rotative paddle; pH 6.8 c – rotative basket and d – rotative paddle; pH 5.4 e – rotative basket and f – rotative paddle; pH 1.2 g – rotative basket and h – rotative paddle)**

Stirring speed can influence the release of ibuprofen from matrix tablets. At 100 rpm, because of much higher hydrodynamic forces, more active substance is released in comparison with 50 rpm. Also, a

faster *in vitro* released was proved at 100 rpm. Release profiles generated in hydrochloric and acetic buffers are comparable ( $50 < f_2 < 100$ ) but the sameness is not achieved in phosphate buffers ( $f_2 < 50$ ).

Apparatus type is another factor that can influence the release of ibuprofen. *In vitro* release using paddle apparatus is faster in comparison with rotative basket apparatus. Sometimes excipients

may get stuck on the sieve of the basket altering the release. Again, release profiles generated in hydrochloric and acetic buffers are comparable ( $50 < f_2 < 100$ ) but the sameness is not achieved in phosphate buffers ( $f_2 < 50$ ).

The modeling of release kinetics was performed by means of Weibull, Korsmeyer-Peppas and Higuchi equations. Higuchi model resulted in a fair goodness of fit (sometimes poor especially at 100 rpm). On the other hand, good fitting was achieved by using

Weibull and Korsmeyer-Peppas (except kinetic model 6.8 100 P). All kinetic model seemed to have a better goodness of fit in phosphate buffers and 50 rpm (both apparatuses) in comparison with hydrochloric and acetate (with the exceptions presented in Table 5).

*In vitro* release of ibuprofen from sustained release matrix tablets depends on dissolution media pH and release rate depends on judicious choice of dissolution test factors to made precise *in vitro/in vivo* correlations.

*Conflict of interest:* none declared  
*Financial support:* none declared

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