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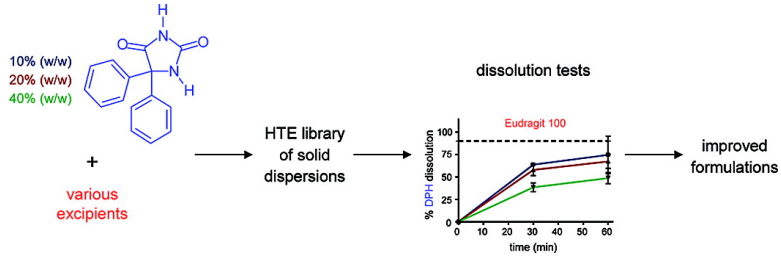

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High-Throughput Study of Phenytoin Solid Dispersions: Formulation Using an Automated Solvent Casting Method, Dissolution Testing, and Scaling-Up

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A high-throughput experimentation method for studying the dissolution of phenytoin, a poorly water soluble drug, was developed and validated. Solid dispersions with 12 excipients (7 polymers and 5 surfactants) were prepared and tested. Each excipient was screened with three drug loadings: 10, 20, and 40% (w/w). Each solid dispersion was prepared in triplicate, for a total of 108 samples. The drug dissolution was studied in simulated gastric fluid without pepsin plus 1% sodium laurylsulfate. This study led to the identification of three improved formulations, exhibiting an extent of dissolution higher than 90% after both 30 and 60 min. The HTE results could be reproduced at a larger scale using a conventional solvent evaporating method, proving the reliability of the HTE protocol.

1. Introduction

Phenytoin (diphenylhydantoin, DPH) is a well-known antiepileptic drug that is extensively used in epilepsy therapy. This drug shows both erratic and poor oral bioavailability, which may lead to pharmacokinetic and safety problems.[1,2] This fact is certainly a consequence of its poor water solubility and its insufficient dissolution rate. To overcome this issue, several formulation strategies have been applied. Some authors combined DPH with cyclodextrins, and the produced inclusion complexes exhibited a higher dissolution rate and anticonvulsivant activity.[3–5] An alternative to cyclodextrins is the use of solid dispersions (SD). Solid dispersions were used for many years to increase the drug dissolution rate. They consist of a mixture of a drug and an excipient and are obtained by evaporating a drug/excipient solution (solvent evaporation method) or by cooling a homogeneous mixture of a drug/excipient melt (melt extrusion). In the final product, the drug is dispersed at the molecular or at a nanoscale level in a matrix generally made of a water soluble polymer.[6] Different combinations of DPH and water-soluble carriers have been investigated: polyethylene-glycol 6000 (PEG 6000),[7] polyvinylpyrrolidone-sodium deoxycholate (PVP-DC Na),[8] and PVP-K30.[9]

To the best of our knowledge, published work dealing with the increase in the dissolution rate of DPH report the combination of the drug with only a limited number of excipients. Indeed, preparing and analyzing formulations at a laboratory scale is highly compound- and time-consuming. As a consequence, finding the optimal combination of a drug and an excipient can turn out to be very difficult. Therefore, there is a need to develop strategies for the rapid identification of formulations that can be used for preclinical studies where an adequate exposure in an animal model should be achieved in order to characterize the efficacy, toxicity, and side-effects of a drug. This is essential when formulating a drug candidate at an early stage.[10] For this purpose, the application of high-throughput experimentation (HTE) techniques is highly promising. HTE techniques enable the rapid preparation and screening of large libraries of samples by means of automated workstations and, therefore, are considered as one of the most powerful experimental methods in many fields of chemical and pharmaceutical research.[11–14] For these reasons, HTE methods are receiving growing attention in the field of drug formulation and delivery.[15–18] Suitable HTE protocols would allow the rapid screening of a vast number of formulations with a limited amount of lead compound, in order to identify a formulation that could provide the target solubility for evaluation in a preclinical study. Recently, some papers dealing with the application of HTE to drug formulation have been published: their topics include the formulation development of a Cremophor-EL-free intravenous solution of paclitaxel,[19] of an improved

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Table 1. Excipients

trade name	composition	supplier
Kollidon 12PF	polyvinylpyrrolidone, Mw = 2500 g·mol^{-1}	BASF
Kollidon 17PF	polyvinylpyrrolidone, Mw = 10000 g·mol^{-1}	BASF
Kollidon-VA 64	vinylpyrrolidone-vinyl acetate copolymer	BASF
PEG 6000	polyethyleneglycol Mw = 7300−8300 g·mol^{-1}	Acros
Lutrol F68	polyethylene-polypropylene glycol, Mw = 7680−9510 g·mol^{-1}	BASF
Lutrol F127	polyethylene-polypropylene glycol, Mw = 9840−14600 g·mol^{-1}	BASF
Eudragit E100	copolymer of 2-dimethylaminoethyl methacrylate, methyl methacrylate, and *n*-butyl methacrylate	Röhm GmbH
Solutol HS15	macrogol 15 hydroxystearate	BASF
Gelucire 44/14	PEG-32 glyceryl laurate	Gattefossé
Brij 35	polyoxyl 23 lauryl ether	Croda
Brij 58	polyoxyl 20 cetyl ether	Croda
Myrj 49	polyethyleneglycol 1000 monostearate	Croda

lipid-free formulation of propofol,[20] and of solutions of poorly water soluble drugs in an early stage.[21,22]

The aim of our work is to accelerate the systematic investigations of drug formulation with the desired dissolution rate. For this purpose, an HTE method was developed and validated. The method was successfully applied to improve the dissolution rate of DPH. In a second step, the hit combinations of the drug and the identified excipients were studied at a laboratory scale to check the validity of the HTE results.

2. Materials and Methods

2.1. Materials. Phenytoin (Eur.Ph. 5.8) was purchased from Fagron (Waregem, Belgium). Table 1 reports the excipients that were used. All other reagents were of analytical grade. Pharmaceutically acceptable, nonionic excipients were used. Two classes of excipients were employed: polymers and surfactants. The polymers include acrylate-based compounds (Eudragit E100), copolymers of polyoxyethylene−polypropylene (Lutrol F68 and Lutro F127), polymer of ethyleneglycol (PEG 6000), polymers of vinylpyrrolidone (PVP 12PF; PVP 17PF), and copolymer of vinylpyrrolidone and vinylacetate (Kollidon-VA-64). The surfactants are polyethyleneglycol alkyl ethers (Brij 35, Brij 58); polyethylene glycol fatty acid esters (Myrj49); and glycerol ester of fatty acids (Gelucire 44/14).

2.2. Equipment. A Tecan Genesis RSP 100 liquid-handling robotic workstation was used for dispensing all the liquids. Two configurations were used to prepare the formulation libraries.

In configuration 1 (preformulation configuration, see Figure 1), two sample racks were used: a source rack suitable for holding 21 drug and excipients solutions (3 positions for 100 mL vials and 18 for 25 mL vials) and a dispense rack consisting of a block with 60 positions for 10.0 mL glass vials and allowing one to heat up the vials and to mix the samples by means of individual magnetic stirring.

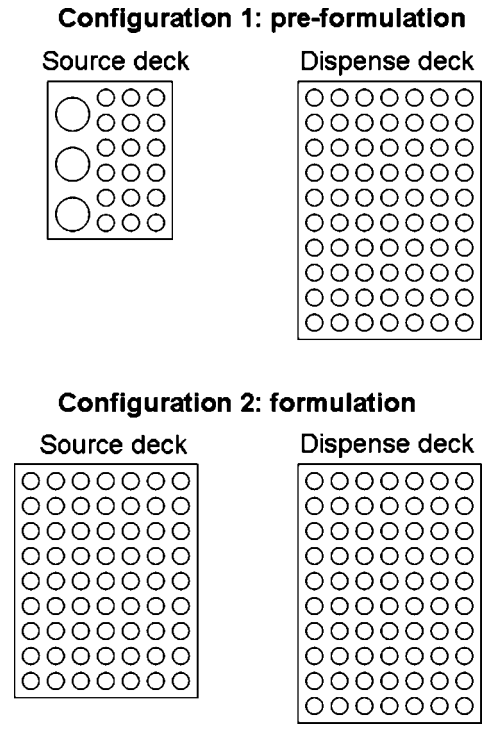

Figure 1. Layout of the source and dispense decks in configuration 1 (preformulation) and 2 (formulation).

In the second configuration (formulation configuration, see Figure 1), the source rack was substituted with a transfer rack with 54 positions for 10 mL glass vials, and the dispense rack was the same as described above.

The robotic arm of the Tecan dispenser makes use of two separate disposable tips (800 μL) made of conductive polymer composite in order to enable liquid level detection and to avoid cross-contamination. It dispenses the solution from the source rack to the selected position in the dispensing rack. Scripts were written in the Tecan-specific Gemini software for the liquid handling steps such as aspiration and dispensing.

2.3. HTE Protocol. The formulation screening procedure consists of the following steps: (1) Setting up the Tecan workstation to configuration 1 and preparing the solutions of both drug and excipients in an organic solvent; (2) dispensing the stock solutions in the desired combinations to 10.0 mL vials containing a magnetic stirring bar; (3) homogenizing the samples using magnetic stirring; (4) changing the configuration of the Tecan workstation to configuration 2 and moving the vials to the source rack; (5) dispensing a chosen aliquot of the liquid to the dispense rack; and (6) heating up the solution to 40 °C to evaporate the solvent.

In steps 1 and 2, solvent casting was used for the preparation of the library of formulations. Solutions containing either drug or excipient were prepared in acetone. Drug and excipient solutions in acetone and pure acetone were dispensed into the desired location into 10.0 mL vials by the Tecan robot following specific Gemini programs. In step 3, each solution in the library was homogenized by magnetic stirring for 2 min. In step 4, the configuration of the Tecan workstation was changed to configuration 2, and the vials containing the preformulation solutions were placed in the

Table 2. Matrix Used to Prepare the Sample for the Validation of The HTE Method

series	% drug (w/w)	drug solution[a] (μL)	excipient solution[b] (μL)	acetone (μL)
1	33%	200	200	800
2	11%	200	800	200

[a] The drug concentration is 2.5% (w/v). [b] The excipient concentration is 5% (w/v).

Table 3. Matrix Used to Prepare the Library of HTE Formulations

% drug (w/w)	drug solution[a] (μL)	excipient solution[b] (μL)	acetone (μL)
10	150	675	675
20	150	300	1050
40	150	150	1200

[a] The drug concentration is 2% (w/v). [b] The excipient concentration is 4% (w/v).

source rack. In step 5, an aliquot of each preformulation solution was withdrawn and transferred to new 10.0 mL vials in the dispense rack. In the final step, the solvent was removed by heating the sample library at 40 °C overnight. This procedure allows for the automated, rapid preparation of solid dispersions. The use of the transfer step (5) improves the homogeneity of the solid dispersion film obtained after solvent evaporation (which would be reduced by the presence of a magnetic stirrer).

2.4. Validation of the HTE Method. For the validation of the HTE method, combinations of DPH and Kollidon-VA-64 were investigated. Two drug loadings were arbitrarily used: 11 and 33% (w/w, drug/total formulation). Ten independent replicates for these two series were prepared. Both drug and excipient solutions in acetone and pure acetone were mixed as described in Table 2 to prepare the preformulation solutions (preformulation step). Then, 600 μL of each solution were withdrawn and transferred to the final vials, and the solvent was evaporated to dryness (formulation step). The final expected DPH content in each formulation is 2.5 mg.

2.5. Preparation of the Formulations. 2.5.1. Preparation of the Library of Formulations Using HTE Techniques: Experimental Design. Drug and excipient solutions in acetone and pure acetone were mixed as described in Table 3 to prepare the preformulation solutions (preformulation step). Then, 500 μL of each solution were withdrawn and transferred to the final vials, and the solvent was finally evaporated to dryness (formulation step). The final expected DPH content in each formulation is 1 mg. Twelve excipients (see Table 1), 3 drug concentrations (10, 20 and 40%), and 3 replicates were investigated resulting in a total of 108 samples. Since the equipment allows the preparation of 60 samples, 2 batches were needed to prepare the 108 formulations.

2.5.2. Preparation of the Physical Mixtures. The physical mixtures were prepared by gently grinding in a mortar with a pestle the exactly weighed amounts of DPH and Kollidon-VA 64 in order to obtain a final concentration of 11% and 33% of DPH (w/w).

2.5.3. Scaling-Up of the Preparation of Formulations Using the Coevaporation Method. Conventional laboratory scale formulations were prepared by the coevaporation method, which requires a lager amount of drug (since the process volume is higher) and which is also more time-consuming (each solution has to be prepared independently). Coevaporated systems containing 10, 20, and 40% DPH were prepared by dissolving the drug and either Kollidon 12PF, Kollidon-VA 64, or Myrj 49 in 50.0 mL of acetone in a 250 mL round-bottom flask. The solvent was removed under vacuum at 40 °C using a Büchi R210 rotavapor (Flawil, Switzerland). The dispersions were stored under vacuum at 40 °C for 48 h. Finally, the solids were ground in a mortar with a pestle and passed through a 355 μm sieve.

2.6. Analysis of the Formulations. 2.6.1. HPLC Analysis. The DPH was assayed by HPLC.[23] The HPLC system consists of a Waters 1525 binary HPLC pump, a Waters 717*plus* autosampler, and a Waters 2487 dual λ absorbance detector (Milford, Massachusetts, USA). The HPLC system is controlled by a computer running the Waters Breeze v.3.30 SPA acquisition software. The HPLC separations were performed at room temperature on a Lichrocart column (125 × 4 mm id) packed with a Lichrospher 60 RP-8 select B 5 μm stationary phase (Merck, Darmstadt, Germany). The mobile phase was a mixture of methanol (HPLC grade) and water (55/45; v/v). The flow rate was 1 mL/min. The detection was conducted at 225 nm, and the injected sample volume was 20 μL. This method was validated, and the results showed good linearity, accuracy, and reproducibility between 1 and 100 μg/mL. The limit of detection and the limit of quantification were found to be 0.12 μg/mL and 0.20 μg/mL, respectively.

2.6.2. Drug Content Analysis. The DPH content in the samples produced by HTE was assayed by dissolving the film with 5.0 mL acetone. The concentration of DPH was determined by HPLC after appropriate dilution.

2.6.3. Drug Dissolution Test: HTE Formulations. Drug dissolution was performed by adding simulated gastric fluid (SGF) without pepsin plus sodium lauryl sulfate at a concentration of 1.0% (w/v) to the vials containing the formulations. For validation purposes, since the DPH content in the samples (produced by HTE or the physical mixtures) was 2.5 mg, the medium volume was 10.0 mL (see section 2.2.3.). For the samples produced by standard HTE (screening of excipient), since the DPH content was 1.0 mg, the medium volume was 4.0 mL (see section 2.2.4.). The experiments were conducted at room temperature, and the vials were shaken at 180 rpm using a Köttermann plate shaker (Köttermann Gmbh & Co, Uetze/Hänigsen, Germany). After 30 and 60 min, 1.0 mL of dissolution medium was withdrawn and replaced by fresh medium. The drug concentration was determined by HPLC after appropriate dilution. During the dissolution tests of the HTE samples, the solid films gradually dissolved without being released from the vessel wall. For samples that showed poor dissolution performance, some solid was still present on the vessel wall after the dissolution test.

2.6.4. Drug Dissolution Test: Laboratory-Scale Formulations. The dissolution tests were conducted on a Hanson SR8plus dissolution apparatus (Chatsworth, CA, USA) according to the paddle method (USP 24 method 2). The

Table 4. Determination of the DPH Content in the Formulations Prepared by HTE[a]

series	DPH loading (%, w/w)	DPH content (mg, mean ± s.d.)	rsd (%)	yield (%)
1	33%	2.40 ± 0.06	2.50	96.0
2	11%	2.39 ± 0.10	4.02	95.6

[a] Experiments conducted in triplicate (n = 3). s.d. = standard deviation; r.s.d. = relative standard deviation.

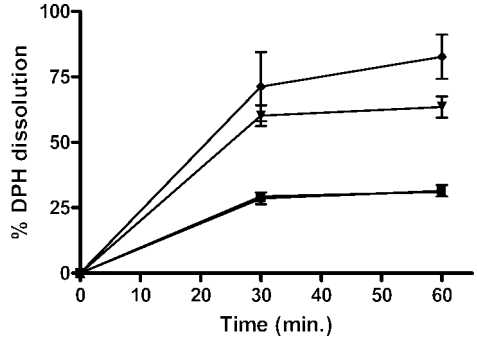

Figure 2. Dissolution profiles of phenytoin/Kollidon-VA-64 formulations: 33% physical mixture (▲); 11% physical mixture (■); series 1, 33% formulation (▼); series 2, 11% formulation (♦) (mean ± s.d., n = 7 for HTE formulation, n = 2 for physical mixtures).

dissolution medium was 500 mL of simulated gastric fluid without pepsin (USP 24) containing 1% of sodium lauryl sulfate and thermostatized at 37 °C. The paddle speed was set at 100 rpm. Samples containing 125 mg pure DPH were put into the dissolution medium. Then 2.0 mL samples were withdrawn at 0, 5, 10, 15, 30, and 60 min and immediately replaced by fresh medium. The samples were filtered using a 0.45 μm PTFE filter (Mancherey-Nagel, Düren, Germany). The first part of the samples was discarded, and the filtrates were analyzed by HPLC after appropriate dilution with methanol to avoid precipitation.

3. Results

3.1. Validation of the HTE Method. 3.1.1. Determination of Drug Content. Before analyzing the drug dissolution performance, drug content was determined in the final formulations. Three out of the 10 samples were randomly chosen; the results are summarized in Table 4. Since the measured amount of DPH in both series 1 (2.40 mg) and series 2 (2.39 mg) is close to the target amount (2.50 mg), and since the relative standard deviations are below 5%, it can be concluded that the method used to dispense the drug is accurate and reproducible.

3.1.2. Drug Dissolution Test. Dissolution tests were performed on the samples produced during the validation step. The results are shown in Figure 2. The dissolution performances of the 11% and 33% physical mixtures are the same. The formulations produced by HTE show evidence of improved dissolution properties compared to the physical mixtures. A film consisting of the DPH and of the polymer was formed using the HTE method, and no crystallization was visually observed. It is concluded that the close contact between the drug and the polymer promotes the dissolution of DPH.[24] The dissolution rate of the HTE solid dispersion with a drug loading of 11% was the highest among these formulations. The inverse proportionality between the dissolution rate of DPH and its concentration in the solid dispersion is in agreement with what was observed at a conventional scale.[9]

3.2. HTE Screening. Finding both an optimal carrier and an optimal drug−carrier ratio are key elements in the field of solid dispersions technology in order to achieve the desired dissolution properties. Therefore, these two parameters were investigated by means of HTE. The screening results for the library of formulations of DPH solid dispersions are shown in Figure 3. The results are presented as the percentage of DPH which is dissolved in function of time. Relative standard deviations are below 10% for 66% of the tested formulations, indicating that the procedure has a good level of reproducibility, as was observed during the validation step. Seventeen percent of the tested formulations present a relative standard deviation between 15% and 28% (Table 5).

First of all, hit combinations can be identified. Hit combinations are defined as formulations that show a dissolution performance higher than 90% DPH dissolved after both 30 and 60 min. This limit is represented by a dashed line on each dissolution test depicted in Figure 3. Three DPH formulations meet this requirement: DPH/Kollidon 12PF, DPH/Kollidon 17PF, and DPH/Kollidon-VA-64. Their release extent is complete or almost complete after 30 min, and no precipitation occurs until 60 min regardless of drug content. For the nonhit formulations containing polymers (Lutrol F68, Lutrol F127, Eudragit E100, and PEG 6000) and surfactants (Myrj 49, Brij 35, Brij 58, Solutol HS15, and Gelucire 44/14), the dissolution performances are lower and lie between 80% (DPH/Brij 35, 10% DPH) and 23% (DPH/Myrj 49, 10% DPH) after 60 min. In all formulations, there is a relationship between drug loading and the release profile, similar to what is described in section 3.1.2 and in agreement with the results of a previous study: when the drug loading decreases, the dissolution performance is improved.[25] However, for the hit combinations the influence of the concentration of DPH in the solid dispersions is minor, and the samples with a drug loading of 10%, 20%, and 40% (w/w) show similar release characteristics. This feature is very important if the drug has to be dosed at a high level.

Finally, by comparison with the results obtained with the dissolution of DPH/Kollidon-VA-64 physical mixtures (which give a release of about 25%), it can be concluded that all of the formulations produced by HTE promote the dissolution rate of DPH and that this improvement is a function of the DPH/excipient combination and/or of the DPH loading in the formulation.

3.3. In-Vitro Dissolution Test of Laboratory-Scale Formulations. As described above, HTE allowed us to identify three hit formulations. To confirm the validity of these results, two of these formulations were prepared again at a laboratory scale: DPH/Kollidon 12PF and DPH/Kollidon-VA-64. The worst formulation identified by means of HTE, DPH/Myrj49, was also prepared on a laboratory scale and was considered as a negative control. For each formulation, three drug contents were prepared: 10, 20, and 40%. The 10% DPH/Myrj49 solid dispersion was not

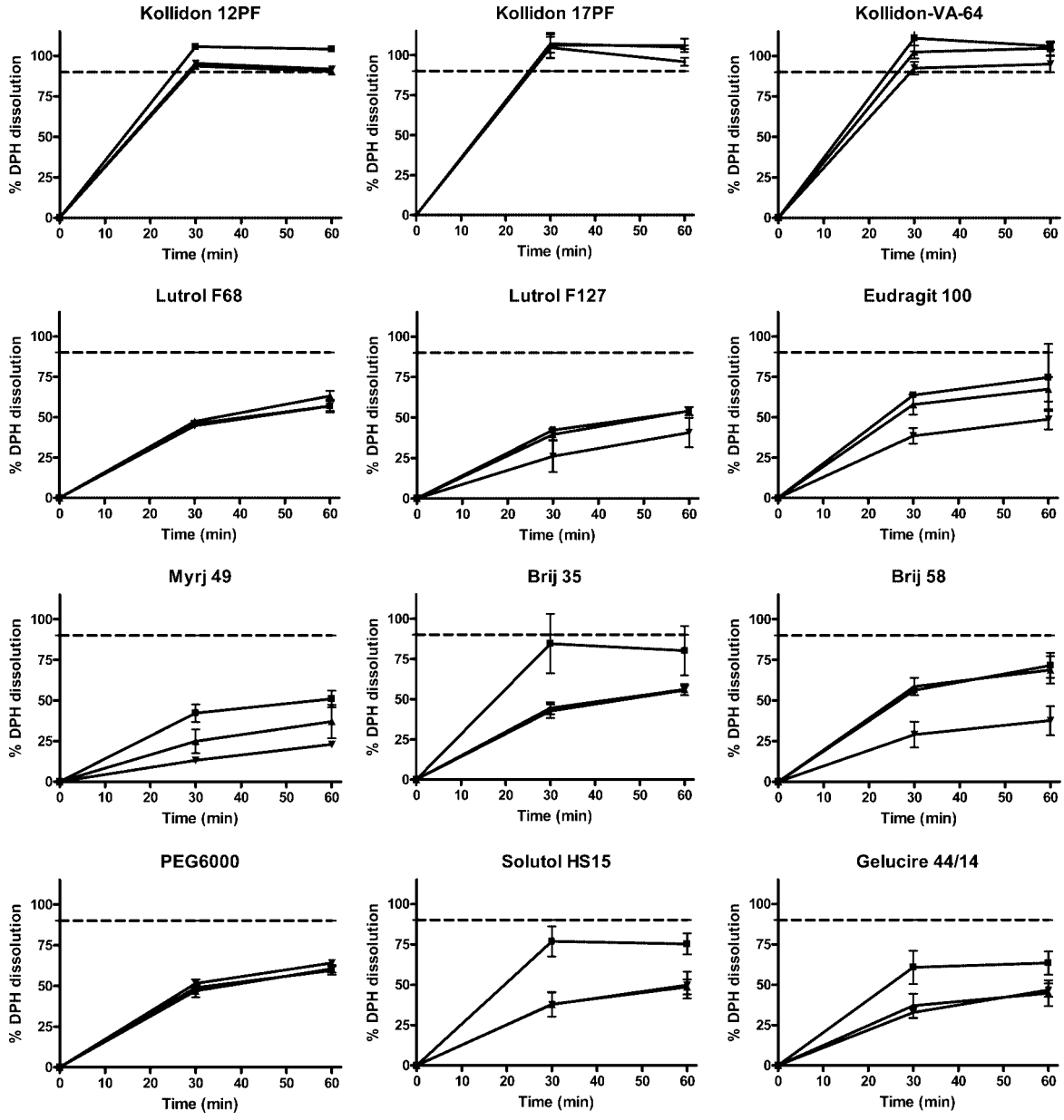

Figure 3. Release profile of DPH formulation prepared by HTE in simulated gastric fluid with 1% SLS. Key: (■) 10%; (▲) 20%; and (▼) 40% DPH (w/w) formulations. Data are reported as the mean of three replicates, and the error bars represent the standard deviation.

Table 5. Relative standard deviation values determined during the dissolution tests of the HTE formulations at the 60 minutes time point

rsd (%)	formulations
<10%	Kollidon 12PF (10; 20; 40%); Kollidon 17PF (10; 20; 40%); Kollidon-VA-64 (10; 20; 40%); Solutol HS15 (10; 20%); PEG 600 (10; 20; 40%); Lutrol F68 (10; 20; 40%); Lutrol F127 (10; 20%); Brij 35 (20; 40%); Myrj 49 (10; 40%) Gelucire 44/14 (40%)
10−15%	Brij 58 (10; 20%); Eudragit E100 (20; 40%); Gelucire 44/14 (10%)
>15%	Solutol HS15 (40%); Lutrol F127 (40%); Brij 35 (10%); Brij 58 (40%); Eudragit E100 (10%); Myrj 49 (20%); Gelucire 44/14 (20%)

analyzed since after solvent removal, a paste was obtained, which prevented subsequent sieving. Figure 4 depicts the dissolution test for all the formulations and also for pure DPH. The results show that the DPH dissolution rate is improved when it is formulated with Kollidon 12PF and Kollidon-VA-64. On the contrary, Myrj49, considered as a negative control, has little influence on the DPH dissolution rate, as was expected from the HTE results. Both 20% and 40% DPH/Myrj49 formulations exhibit a dissolution profile comparable to that of the pure drug. As can be seen in Figure 4, Kollidon 12PF improves the dissolution rate of DPH, and its performance is inversely proportional to drug loading (10% DPH/Kollidon 12PF SD > 20% DPH/Kollidon 12 PF SD > 40% DPH/Kollidon 12PF SD), although this difference is more pronounced after 10 min and becomes less marked after 30 and 60 min, in line with the HTE results. For all drug loadings, the maximum concentration is obtained after 10 min and, afterward, a precipitation occurs. If the 90% dissolution extent is once again taken as the target, only two DPH/Kollidon 12PF solid dispersions meet this requirement: 10% DPH SD and 20% DPH SD, while HTE also identified 40% DPH SD. Kollidon-VA-64 also enhances the DPH dissolution rate and, as has been observed for the Kollidon 12PF, the trend depends on drug content: 10% DPH/

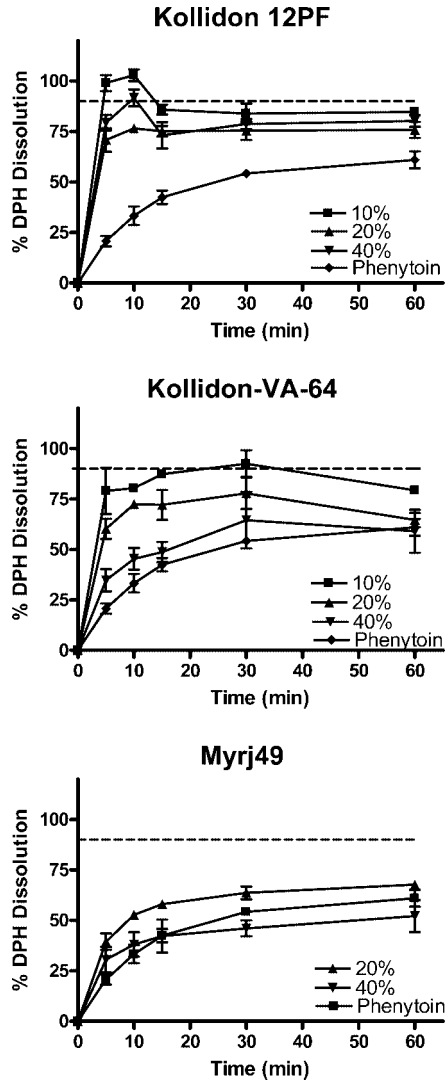

Figure 4. Release profile of laboratory-scale DPH formulation produced by solvent evaporation in simulated gastric fluid with 1% SLS. Key: (■) 10%; (▲) 20%; and (▼) 40% DPH (w/w) formulations; (♦) pure DPH. Data are reported as the mean of two replicates, and the error bars represent the standard deviation.

Kollidon-VA-64 SD > 20% DPH/Kollidon-VA-64 SD > 40% DPH/Kollidon-VA-64 SD. The latter presents a dissolution rate comparable to that of pure DPH. The maximum concentration of DPH/Kollidon-VA-64 SD is reached after 30 min, and only the concentration of the 10% DPH/Kollidon-VA-64 SD is higher than 90%.

4. Discussion

For the past few years, HTE has been increasingly involved in the investigation of the drug formulation process. However, most of the papers on this topic focus on the screening of the solubility of a drug in several excipients with the aim of preparing liquid formulations.[20–22] The formulation and evaluation of solid dispersions made by solvent casting using an HTE approach represent a new subject of research. In a very recent study, Shanbhag et al. used HTE to identify combinations of drug and excipients that give good results with respect to the dissolution rate.[26] Then, formulations were prepared at a laboratory scale followed by in vitro and in vivo evaluations. The last results showed an increase of the oral bioavailability of the drug when using a solid dispersion identified by HTE. In the same paper, the authors described the important factors required when using an HTE approach. To be considered efficient, the HTE protocol has to allow (1) the preparation of more formulations than would be possible at a laboratory scale; (2) the identification of systems that can easily be transposed to a laboratory scale; and (3) the use of a small amount of compounds with respect to traditional methods. The method presented here meets all of these requirements.

The goal of this study was to identify formulations that are able to increase the dissolution rate of the drug, which is one of the most influential parameters for improving oral bioavailability.[27] Therefore, the only factor of response was the extent of dissolution. It is well known that solid dispersions are thermodynamically unstable systems that tend to convert into more stable ones by recrystallization, the occurrence of which leads to a decrease of the dissolution performance.[6] The approach presented here allows the evaluation of large numbers of novel formulations while extensive characterization of the solid dispersions can be done at a later stage on selected systems.

Solvent casting was used to prepare the formulations by HTE. The method allows for accurate and reproducible dosing of both drug and excipient. This has been proved by a validation test, showing that the drug content is equal to the theoretical content and that the same formulations present the same dissolution behavior. Such a validation step is an essential feature in order to check if the aspiration and dispensing operations performed with the HTE workstation have been correctly calibrated to allow the preparation of formulations with appropriate accuracy and reproducibility. Using the HTE protocol presented here, it is possible to test a library defined by the combination (in triplicate) of 12 excipients and 3 drug loadings in 1 day and with a minimum of materials. A classification was made on the basis of the dissolution performance of the HTE formulations. The chosen benchmark was a dissolution extent higher than 90% at the two sampling times: 30 and 60 min. Out of all formulations, 3 were identified as hit formulations. These solid dispersions are the results of the combination of DPH and Kollidon 12PF, Kollidon 17PF, and Kollidon-VA-64. The stabilization of solid dispersions using Kollidon-containing polymers is well described in the literature. It has been shown that the stabilization of an amorphous drug by Kollidon and Kollidon-VA-64 is mainly related to the interaction of the drug and the polymer by means of hydrogen bonding rather than to the polymer molecular weight and the glass transition temperature of the polymer.[28] The minor influence of the polymer molecular weight could account for the similar dissolution performances observed with the two different grades of Kollidon.

On the basis of the HTE results, 3 formulations were selected and prepared using a conventional solvent evaporating method at a laboratory scale: DPH/Kollidon 12PF, DPH/Kollidon-VA-64, and DPH/Myrj49. The two first formulations were screened as HTE hit combinations. The remaining HTE hit DPH/Kollidon 17PF was not scaled up because the behavior of Kollidon 17PF is expected to be very similar to

that of Kollidon 12PF, from which it differs only for the molecular weight.[28] The last formulation (DPH/Myrj49) was selected as the negative control since it presented the lowest increase in the dissolution rate in the HTE test. The up-scaled results show that there is a good correlation between the drug dissolution performance of the HTE formulation and the corresponding laboratory scale formulation. The formulations identified as hits in the HTE tests show improved dissolution also on a conventional laboratory scale, although the performance in the latter case is on average lower, in line with what is reported in the literature.[26] The discrepancy between the HTE and the conventional scale results can be attributed to the different types of vessels used with the two approaches: the shape of the vessel and the ratio between its surface and the sample amount influence the thickness of the solid dispersions and, thus, their dissolution behavior. Moreover, the poor dissolution performance of DPH/Myrj49 solid dispersions is also observed at a larger scale, attesting that negative results obtained by HTE are not due to false negatives. These results allow us to conclude that the method developed here is a very useful tool to rapidly identify formulations that enhance drug dissolution.

5. Conclusions

In the present study, a general and reliable HTE protocol for the rapid preparation of drug formulations was developed and validated. The method allows for the preparation of a library of 108 formulations in 1 day, with a minimum of materials. This protocol was successfully applied to identify binary solid dispersions that are able to increase the dissolution rate of DPH. The HTE method was used to study the combination of 3 different drug loadings of DPH with 12 excipients: 7 polymers and 5 surfactants. Three combinations provided dissolutions higher than 90% after 30 min. These solid dispersions were scaled up with the traditional co-evaporation method and showed a release extent analogous to the one obtained with the high-throughput approach. Moreover, a negative combination was also prepared at a larger scale and displayed dissolution properties comparable to those of the pure drug, in agreement with the high-throughput results. The developed HTE method has the flexibility and broad applicability to become a useful tool for accelerating research output in the field of drug formulation.

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