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FORMULATION AND OPTIMISATION OF FAST-DISSOLVING ORAL FILMS OF ONDANSETRON USING BOX-BEHNKEN DESIGN

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1. INTRODUCTION

Swallowing a tablet sounds trivial until it is not. Children, older adults, people with dysphagia and anyone who is nauseous or without ready access to water may struggle with conventional oral solid forms, and those difficulties lead to missed doses and poor adherence [1, 2, 3]. Orodispersible films were developed in response. A film is a thin sheet of polymer carrying the drug, placed on the tongue where it hydrates and disintegrates within seconds to a minute or so, releasing drug into saliva, which is then swallowed or in part absorbed through the oral mucosa [1, 4, 5, 6]. Compared with orally disintegrating

Abstract

Fast-dissolving oral films are attractive for patients who cannot swallow tablets easily, including people who are nauseous. Ondansetron, a 5-HT₃ antagonist given in small doses, is a natural candidate. This narrative review summarises published work on formulating such films and on using a Box-Behnken design to optimise them. It covers drug and patient factors, film formers, plasticisers and casting, the construction and analysis of the design, film characterisation, and quality by design context. It reports no new experimental data and proposes no optimised composition. The literature shows that designed experiments are efficient, but studies are mostly single-laboratory, in vitro and weakly replicated, so findings should be treated as method illustrations.

tablets, films are thinner, can be dosed from small cut areas, and often feel less gritty in the mouth.

Ondansetron is a natural candidate for such a platform. It is a selective 5-HT₃ receptor antagonist used to prevent and treat nausea and vomiting after chemotherapy, radiotherapy and surgery, and the people who take it are, by definition, nauseous at the moment of dosing [7, 8, 9]. The dose is small, usually a few milligrams, the hydrochloride is water-soluble, and a rapid onset is clinically valued. Formulating it as a fast-dissolving film therefore combines a clear clinical need with a favourable physicochemical profile. The question for the formulation scientist is how to find a combination of polymer, plasticiser and other additives that gives films strong enough to handle and yet quick enough to dissolve, without trial and error that consumes weeks of laboratory time.

Statistical experimental design offers a more economical route. A Box-Behnken design varies several formulation factors together across three levels in a small number of runs and fits a quadratic model that describes how each response, such as disintegration time or tensile strength, depends on the factors and their interactions [10, 11, 12]. The model can then be used to locate a region where all the responses are acceptable at once. This review summarises the published literature on that approach as it applies to fast-dissolving oral films, using ondansetron as the worked example. It reports no experiments of its own, gives no new formulation results and offers no optimised composition. The aim is to make clear what the method can and cannot deliver, and what a careful reader should look for when a paper claims an optimum.

The article is organised around the questions that a formulation team would ask in order. Why ondansetron, and why films? Which polymers, plasticisers and processes are available? How is a Box-Behnken design built, analysed and checked? Which attributes of a film matter, and how are they measured? How does a design-space approach fit with regulatory expectations [13, 14, 15]? Evidence is drawn from reviews, original formulation papers, statistical texts and regulatory guidance. Because several of the formulation papers cited concern other drugs, the transferability of their findings to ondansetron is discussed where it is not

obvious. Limitations of the evidence base are set out at the end, together with suggestions for the kind of data that would strengthen it.

Oral film technology has roots in the confectionery and breath-freshening industries, and its move into pharmaceuticals was gradual. The first products were small strips of hydrophilic polymer carrying flavours, and drug-containing films followed once manufacturers could control dose uniformity across the cast sheet [1, 4]. Regulatory attention has increased in step, with pharmacopoeial descriptions of orodispersible films and discussion of requirements specific to this form [13]. The history is a reminder that the dosage form is still young, and many of the practical lessons in the literature come from a small number of research groups.

2. ONDANSETRON AND THE CASE FOR FILMS

Ondansetron blocks 5-HT₃ receptors on vagal afferents in the gut and in the chemoreceptor trigger zone and nucleus tractus solitarius of the brainstem, and in this way interrupts the emetic reflex triggered by serotonin released from enterochromaffin cells after cytotoxic therapy [7, 8]. Antiemetic guidelines place a 5-HT₃ antagonist in the standard prophylaxis of chemotherapy-induced nausea and vomiting, usually combined with dexamethasone and, for highly emetogenic regimens, an NK1 antagonist [8, 16]. Consensus guidelines for postoperative nausea and vomiting likewise list 5-HT₃ antagonists among first-line options [9]. The clinical position of the drug is secure, so formulation work focuses on convenience and speed of onset, not on altering the pharmacology.

After oral administration ondansetron is well absorbed but subject to first-pass metabolism, and bioavailability is around 60 per cent in healthy adults, with an elimination half-life of about three to four hours [7, 17]. Metabolism involves several cytochrome P450 enzymes, notably CYP3A4, CYP1A2 and CYP2D6, so several pathways contribute and inhibition of any single enzyme has a limited effect [7, 17]. Elderly patients show a longer half-life and higher exposure, which is why dosing

recommendations differ with age and hepatic function [17]. For a fast-dissolving film the main consequences are that the dose required is low and that absorption of drug swallowed in saliva is generally assumed to follow a profile similar to that of a tablet.

The physicochemical properties of ondansetron favour a film. The hydrochloride dihydrate is soluble in water, and a dose of 4 to 8 mg can be carried by a film of modest area and thickness without crowding the polymer matrix [18]. Taste is the practical difficulty. Ondansetron has a bitter taste, and in a product held in the mouth taste masking is a design requirement rather than a luxury. Sweeteners, flavours and, in some formulations, ion-exchange resin complexes or cyclodextrins have been used, and sensory panels or electronic tongue devices assess the result [5, 19]. A film that dissolves quickly but tastes unpleasant will be rejected by exactly the patients it is meant to help.

Regulators have shown interest in dosage forms that suit the people who use them. The EMA guideline on pharmaceutical development of medicines for paediatric use accepts orodispersible forms as suitable for children who can cooperate in use, though it asks for evidence of acceptability [20]. Reviews of formulations for children and older adults note that films avoid the choking risk some parents associate with tablets and offer flexible dosing by cutting [2, 3]. Dose flexibility cuts both ways, because cutting a film in the pharmacy or at home introduces variability in the dose, so pre-cut unit films are favoured for a narrow dose range [3, 13]. Patient-reported acceptability studies of films are still few.

Cancer patients present extra needs. Mouth sores from chemotherapy, dry mouth and changes in taste can all influence whether a film is tolerated, and a film that adheres strongly to inflamed mucosa could be uncomfortable [8, 16]. Postoperative patients in recovery cannot always drink water. These situations describe specific use cases that may differ from the healthy-volunteer settings in which many films are tested for disintegration and taste. Formulation scientists seldom have access to such patients early in development, and the literature offers little guidance on how

a film behaves in a dry, sore or inflamed mouth.

3. FILM COMPONENTS AND MANUFACTURE

The film-forming polymer is the structural component, and the range of polymers that have been tried is wide. Hypromellose (HPMC) in low-viscosity grades is the most commonly used, and pullulan, polyvinyl alcohol, hydroxypropyl cellulose, maltodextrin, sodium alginate and chitosan feature in the literature [5, 21, 22]. A comparison of several polymers for fast-dissolving films found marked differences in mechanical properties and disintegration, with some polymers giving films that were too brittle or too sticky to handle [22]. Maltodextrin films with plasticisers have been shown to dissolve quickly [21]. The chosen polymer determines the viscosity of the casting solution, the clarity of the film, its tensile behaviour and the speed of hydration.

Plasticisers are needed because many film-forming polymers dry to a stiff, brittle sheet. Glycerol, propylene glycol, polyethylene glycols, sorbitol and triacetin are widely used, and they act by inserting between polymer chains, reducing intermolecular forces and lowering the glass transition temperature [23, 24]. Increasing the plasticiser level raises elongation and flexibility and lowers tensile strength, and beyond some level the film turns tacky and difficult to peel from the liner [24, 25]. The effect depends on the polymer, the plasticiser and the moisture content, so the optimum level cannot be copied from one system to another. Because plasticiser level strongly affects both strength and disintegration, it features in most reported experimental designs.

Casting solution rheology links composition to process. Polymer concentration and viscosity grade set the viscosity, which must be low enough to degas and spread and high enough to hold a uniform wet layer on the liner [5, 22, 26]. Very viscous solutions trap bubbles and leave streaks, while thin ones run off or give films too thin to handle. The drug and plasticiser alter viscosity in turn, and so

does temperature. For this reason film formulation papers usually report the casting solution viscosity, or at least the grade and concentration of polymer, and the best of them state how long solutions were left to stand for air to escape. Such details are small, but they decide whether a design point can be repeated by another laboratory.

Other excipients carry out supporting roles. Saliva-stimulating agents such as citric acid speed wetting, surfactants such as polysorbate help to disperse poorly wetted drug, sweeteners and flavours cover taste, and colorants or opacifiers give a recognisable appearance [5, 23]. Superdisintegrants are used less often than in tablets because the polymer itself dissolves, but some groups report faster disintegration when croscarmellose or sodium starch glycolate is included, at the cost of a more opaque and rougher film [26, 27]. Each addition changes the casting solution and the dry film, and the interactions are what a designed experiment is meant to reveal. A long list of additives raises the number of factors beyond what a three-level design can handle comfortably.

Solvent casting remains the dominant laboratory and industrial method. The polymer is dissolved in water or a water–alcohol mixture, plasticiser and drug are added, the solution is deaerated, cast with a blade at a set wet thickness onto a liner and dried in warm air, then cut to size [1, 4, 26]. Each step has quality implications: air bubbles leave holes, rapid drying produces a skin that traps solvent and can curl the film, and uneven casting thickness causes dose variation between cut units. Alternatives include hot-melt extrusion, semisolid casting and printing, the last of which offers tailored dosing but remains mainly experimental [5, 28]. Continuous manufacturing of films has been demonstrated at laboratory scale with analytical control [28].

Drug loading sets a ceiling on what can be done. A film of a few square centimetres can carry only a limited mass of drug before mechanical properties or disintegration deteriorate, and the upper limit is usually a few tens of milligrams at most [1, 4]. For a low-dose, soluble drug such as ondansetron the ceiling is not a problem. For poorly

soluble drugs, nanoparticles of drug dispersed in the polymer solution have been used to raise dissolution rate and loading, and polymer films containing stable nanoparticles of BCS class II drugs have been described [29, 30]. These studies show what is possible when drug properties are less favourable than those of ondansetron, and they widen the scope of the film platform.

Packaging and stability are needed for films as for any dosage form, and they are more demanding than for tablets because thin hydrophilic sheets take up moisture rapidly. Water uptake plasticises the polymer, softening the film and sometimes making it sticky, while loss of moisture in dry climates can make it brittle [5, 26]. Individual sachets made of aluminium laminate are the standard protection. Stability programmes follow the usual international conditions, with attention to disintegration time, tensile properties and drug content, and some films also need protection from light [5, 13]. These practical issues receive less space in the formulation literature than they merit.

4. BOX-BEHNKEN DESIGN

The Box-Behnken family of designs, introduced by Box and Behnken in 1960, is described in standard texts on response surface methodology as an economical way to fit second-order response surfaces [10]. Each factor is set at three coded levels, low, middle and high, written as -1 , 0 and $+1$. The design points lie at the midpoints of the edges of the factor space, together with replicated centre points, and no run combines the extreme levels of all factors at once. For three factors this gives twelve edge runs plus a few centre points, commonly fifteen runs in total, and for four factors twenty-four plus centre points [11, 31]. The designs and the methods that surround them are brought together in table 1, which lists the main elements discussed in this article.

A central composite design, the usual alternative, needs more runs for the same number of factors and adds axial points beyond the chosen range, which may be impractical when, for instance, a polymer concentration above the top level gives an unmanageable solution viscosity [12, 31].

The Box-Behnken design stays within the stated range, which is attractive for films whose casting behaviour changes abruptly outside a narrow window. Its drawbacks are that it cannot be built up sequentially from a factorial experiment and that it gives no information at the corners of the cube, where combinations of extreme levels may in practice be the most interesting [11, 32]. The distribution of the entries in table 1 by group is shown in fig. 1.

Table 1: Elements of designed optimisation of fast-dissolving films described in the literature

Element	Reported feature	Ref.
Box-Behnken design	Three-level design without corner runs; fifteen runs for three factors with centre points.	[10, 11]
Response surface methodology	Quadratic models fitted; contour plots and desirability used to locate an optimum.	[12, 31]
Pharmaceutical design of experiments	Screening followed by optimisation; confirmation runs check the model.	[32, 33]
Quality by design	Quality attributes, process parameters and a design space are defined.	[14, 15, 34]
Film characterisation	Thickness, strength, disintegration and taste methods differ between laboratories.	[5, 19]
Hypromellose films Polymer comparison	Polymer type strongly affects film strength and disintegration.	[22, 25]
Maltodextrin films	Plasticised maltodextrin gives quickly dissolving films.	[21]
Plasticiser effect	Glycerol and polyethylene glycol levels shape flexibility and tensile strength.	[24, 25]
Ondansetron sublingual films	Additives influenced in vitro release and mucosal permeation.	[18]
Ondansetron pharmacokinetics	First-pass metabolism limits oral bioavailability; elderly have higher exposure.	[7, 17]
Drug nanoparticles in films	Raise loading and dissolution rate for poorly soluble drugs.	[29, 30]

The fitted model is a quadratic polynomial. A response is described by a constant, linear terms for each factor, squared terms that

capture curvature and cross-product terms for pairs of factors [11, 31]. The coefficients are estimated by multiple regression and tested by analysis of variance. Useful diagnostics include the significance of each term, the lack-of-fit test against pure error from the replicated centre points, the coefficient of determination, its adjusted form, and a predicted value derived from cross-validation [12, 31]. A high R^2 alone is not enough, since the model may be over-fitted to a small data set, which is why the gap between the adjusted and predicted values is read carefully.

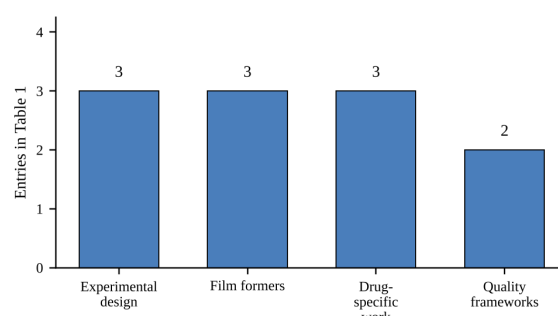


Fig. 1: Number of entries in table 1 by group

Choosing factors and levels is the scientific part of the work. For a fast-dissolving film the usual candidates are polymer concentration, plasticiser concentration and a third variable such as the level of a disintegrant or saliva-stimulating agent, with the active at a fixed dose per film [32, 33]. Screening designs, such as fractional factorials, are often used first to decide which of many candidate factors deserve the three-level treatment [32, 33]. Levels should span a range in which films can still be cast and peeled, otherwise runs fail and the design collapses. Prior knowledge from the polymer and plasticiser literature, and a few exploratory casts, guide the choice, and the rationale for the ranges should be reported because it affects what the model can say [22, 34].

Responses are the measured attributes that define product quality. Typical choices are disintegration time, tensile strength, percentage elongation or folding endurance, and the percentage of drug dissolved at a short time such as five or ten minutes [5, 19, 34]. Each response gets its own regression model, and the models are then combined. Responses that pull in opposite directions create the central tension in film

development, since stronger films tend to disintegrate more slowly. Plotting measured values and coded factor levels as contour maps and three-dimensional response surfaces helps show where compromises lie [12, 31]. The models describe only the region studied, and extrapolating beyond it is not supported by the design.

Optimisation then seeks settings at which all responses are acceptable. Numerical optimisation by the desirability function transforms each response to a scale from zero to one according to whether it should be minimised, maximised or held on target, and combines them into a composite desirability that is maximised [12, 31]. Overlaid contour plots serve the same purpose graphically. The predicted optimum should be confirmed by preparing the formulation, measuring the responses and comparing the observed values with the predicted ones, ideally within the prediction interval [11, 33]. Publications that stop at the prediction, or that present a single confirmation batch as proof, offer weaker evidence than those with replicated check points.

Software has made these designs accessible, and it has also made it easy to produce a model without understanding it. Commercial packages generate the run table, perform the regression and draw the surfaces within minutes, and the user must still judge whether the residuals are random, whether assumptions are met and whether the result is chemically sensible [31, 33]. Randomising the order of runs protects against drift in conditions such as ambient humidity during casting. Blocking is useful if the experiment must be spread over several days. These basic principles are well known to statisticians and are sometimes missed in formulation papers.

Confirmation is the step that turns a fitted surface into a usable claim. Once the model points to a promising region, extra batches are prepared at the predicted settings and their measured responses are compared with the prediction intervals, not with the point estimate alone [12, 31]. If the observed values fall inside the interval, the model has earned some trust. If they fall outside, the surface may be missing a term, or the process may have drifted between working sessions.

Authors often suggest two or three independent check batches, ideally made on a different day with a fresh polymer solution [33]. Reporting those results beside the model diagnostics lets readers judge an optimum for themselves [32]. Without them, a desirability score is only a calculation.

5. CHARACTERISATION OF FILMS

Thickness and weight uniformity are the first checks. Thickness is measured with a micrometer or similar gauge at several points, and variation across a cast sheet directly produces variation in drug content when units are cut to size [5, 19]. Orodispersible films are typically well under half a millimetre thick. Weight variation of cut units, and ideally drug content uniformity by an assay such as ultraviolet spectrophotometry or liquid chromatography, confirm that the casting step gives reproducible doses. Surface appearance, clarity, tackiness and ease of peeling are noted qualitatively. These simple measures often explain why a formulation that looked promising in a small trial gave erratic results in a larger one.

Mechanical properties determine whether a film survives handling and packaging. Tensile strength, elongation at break and Young's modulus are measured with a texture analyser or universal testing machine by pulling a strip of defined size until it fails, and folding endurance, the number of times a film can be folded at the same place before breaking, offers a simple alternative [19, 27]. Films that are too stiff break when peeled from the liner or bent in the blister, while those that are too soft deform and stick. A useful balance is described in different ways by different authors, and targets rarely match across papers, which limits the comparison of one study with another [5, 19].

Disintegration and dissolution are the performance tests. For films, disintegration is often measured in a Petri dish with a small volume of water or simulated saliva, the time being recorded when the film breaks or dissolves, and sometimes with a modified apparatus that holds the film in a basket [5, 19]. Pharmacopoeial and regulatory expectations for orodispersible forms are in the order of minutes, typically three or less

[13, 19]. Dissolution testing uses compendial apparatus with small volumes of medium, sampled at short intervals. Results depend strongly on method details, such as how the film is held and how much liquid is available, which is why published times from different laboratories should not be compared directly [13, 19].

Moisture content, surface pH and taste are further quality attributes. Moisture content, measured by loss on drying or Karl Fischer titration, affects mechanical properties and stability. Surface pH close to neutral is preferred to avoid irritation of the oral mucosa [5, 26]. Taste is assessed with human panels where ethical approval allows, and with animal behavioural models or electronic tongue devices as alternatives [5, 19]. Mouthfeel and the sense of the film adhering to the tongue or palate matter to patients in ways that standard tests do not capture. Where the drug is bitter, as with ondansetron, taste scores can decide whether a technically successful film is a viable product.

Findings from ondansetron films illustrate the way in which these tests are applied. Fast-dissolving sublingual films of ondansetron hydrochloride were prepared with hydrophilic polymers and various additives, and their *in vitro* release and mucosal permeation were compared, showing that the choice of additive influenced both [18]. Studies of other drugs report similar findings: salbutamol sulphate films examined polymer type and level [25], verapamil strips explored polymer and plasticiser choices [35], and triclosan films for the oral cavity addressed mechanical and release characteristics [36]. Seen together, the papers describe a consistent pattern in which polymer concentration governs strength, plasticiser governs flexibility and soluble additives govern the speed of break-up.

In vitro permeation work deserves a brief note. Some ondansetron film studies measured passage of drug across animal buccal or sublingual mucosa in diffusion cells to explore whether any absorption occurs through the oral mucosa itself [18]. Mucosal permeation can in principle give a faster onset than swallowing, but the contact time of a fast-dissolving film is short, and most drug is

likely to be swallowed with saliva. The relative contributions have not been well quantified, and animal mucosa differs from human tissue in thickness and permeability [26]. For this reason claims about sublingual absorption from a film that dissolves in seconds deserve scepticism until pharmacokinetic data support them.

6. OPTIMISATION AND CONTROL

A Box-Behnken experiment is more useful when set inside a quality by design (QbD) framework. Under quality by design principles the starting point is a quality target product profile, from which the critical quality attributes (CQAs), such as disintegration time, tensile strength and content uniformity, are derived [14, 15]. Risk assessment identifies the formulation and process variables most likely to affect them [37], and designed experiments then quantify those relationships. The result is a design space, a region of factor settings within which quality is assured and movement is not regarded as a change [14, 15]. The approach moves the emphasis from testing a final product to understanding the process that makes it.

In the film setting, critical process parameters include casting thickness, drying temperature and time, and the rate of airflow in the dryer, besides the formulation factors. Visser and colleagues applied a quality by design approach to extemporaneously prepared orodispersible films and identified the factors that shaped physical properties, showing that the approach is feasible even at small scale [34]. Industrial production adds variables such as line speed and web tension. A design space established on a laboratory casting table may not hold on continuous equipment, and verification at larger scale is needed before the claims can be extended [28, 34].

Verification and control complete the picture. After the design space is defined, a control strategy specifies in-process checks such as thickness and weight of the cast sheet, moisture at the end of drying and release tests on finished units [15, 37]. Process analytical technology may help in principle, as continuous manufacturing studies have shown with inline analytical control [28]. Statistical

process control charts catch drift. Stability studies on the optimised formulation confirm that the attributes persist over shelf life. Papers on optimised films often stop at the optimum prediction and a short stability check, and the distance between that and a validated manufacturing process is considerable [13, 14].

7. LIMITATIONS AND FUTURE DIRECTIONS

The evidence on optimised fast-dissolving films has limits that readers should keep in view. Most studies are single-laboratory formulation papers with one batch per design point, little replication outside the centre points and a short stability follow-up [5, 38]. Models describe a narrow region and are often reported with differences between adjusted and predicted R^2 that go unremarked. Disintegration and dissolution methods differ, so optimum values are not portable. For ondansetron the published formulation work is largely in vitro, so claims of faster onset rest mostly on laboratory results and not on comparative human data [17, 18].

Some statistical caveats are specific to the design. With fifteen runs and ten coefficients in a three-factor quadratic model, few degrees of freedom remain for estimating error, and the replicated centre points describe variability only at the centre of the region, which may not represent the corners or edges [11, 31]. Disintegration times are often skewed and may need a logarithmic transformation before regression. When several responses are modelled, the chance of a spurious significant term rises. Categorical factors, such as polymer grade or plasticiser type, do not fit naturally into a response surface and are usually handled by running separate designs [31, 32]. Authors seldom discuss these points, and readers have to judge them from the tables supplied.

Several gaps stand out. Human taste panels, paediatric acceptability work and pharmacokinetic comparisons of films with tablets would show whether in vitro advantages matter to patients [2, 3, 20]. Methods for testing disintegration need standardising across laboratories, perhaps

through an agreed biorelevant protocol with a defined volume of liquid. Wider adoption of risk assessment and design-space language would bring academic work closer to the regulatory vocabulary [14, 15, 37]. Finally, replicated experiments reported in full, including failed runs and diagnostics, would let others judge whether a model is robust. Without those steps the literature may produce many optima and few transferable principles.

Commercial considerations influence the literature. Proprietary manufacturing know-how, patents on polymer systems and the cost of specialised casting lines mean that industrial films are rarely described in detail in the public domain [4, 28]. Academic reports, by contrast, use hand-cast laboratory films that are inexpensive to make and easy to vary. The resulting gap makes it difficult to say how well designed-experiment results translate into production, and it limits the usefulness of published optima as starting points for manufacture. Collaboration between universities and industry on openly published case studies would be valuable, because it would show which laboratory findings survive scale-up and which do not.

8. CONCLUSION

A Box-Behnken design is an efficient way to explore the formulation space of ondansetron fast-dissolving films, because three or four factors can be studied in fifteen to twenty-seven runs and the resulting quadratic models make trade-offs between strength and disintegration visible [10, 11, 12]. The method works best when factors and levels are chosen with knowledge of the polymers and plasticisers, when responses are measured by agreed methods and when predictions are confirmed with replicated check batches [5, 33, 34]. Used that way it saves materials, time and a good deal of guesswork.

Its results are limited by the quality of the experiment around it. Published optimisations are mostly single-laboratory, in vitro and lightly replicated, and they say little about taste acceptability, human exposure or large-scale production [17, 18, 28]. Placing designed experiments inside a quality by design framework, reporting diagnostics fully

and testing films in the patients who need them would turn promising laboratory optima into dependable products, and would give clinicians and regulators a firmer basis for trusting them [13, 14, 20].

9. ABBREVIATIONS

CQA-Critical quality attribute, CYP-Cytochrome P450, EMA-European Medicines Agency, HPMC-Hypromellose (hydroxypropyl methylcellulose), ICH-International Council for Harmonisation, NK1-Neurokinin-1, QbD-Quality by design, 5-HT₃-5-hydroxytryptamine type 3, BCS-Biopharmaceutics Classification System

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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