Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2016, 6(3), 399-406
doi: 10.15171/apb.2016.052
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Research Article

Improvement of Meloxicam Solubility Using a β-Cyclodextrin Complex Prepared via the Kneading Method and Incorporated into an Orally Disintegrating Tablet

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Article info

Article History:
Received: 2 October 2015
Revised: 2 July 2016
Accepted: 22 August 2016
ePublished: 25 September 2016

Keywords:
· Meloxicam
· β-cyclodextrin
· Kneading
· Orally disintegrating tablet
· Quality by design

Abstract

Purpose: The aim of this research was to formulate and develop an orally disintegrating tablet (ODT) that incorporated a MEL/β-CD complex, using a quality by design (QbD) approach to enhance solubility and drug release.

Methods: Multiple regression linear analysis was conducted to develop the kneading process and ODT formulation. Mixing time and amount of solvent were used as independent variables in kneading process optimisation, while the superdisintegrants were used to obtain the desired formulation. Fourier transform infrared spectroscopy and differential scanning calorimetry were performed for complex characterization.

Results: MEL/β-CD complexation was successful in enhancing MEL solubility. The results suggest that increasing the amount of solvent and mixing time enhances drug loading and drug release. However, increased solvent amounts present the problem of removing the solvent. Primojel and Polyplasdone had a significant effect on the water wicking and tablet disintegration process ($p<0.05$), although Polyplasdone negatively affected tablet hardness. Both an optimized KN process and ODT formulation were obtained using a QbD approach.

Conclusion: Incorporation of the MEL/β-CD complex during ODT formulation using the QbD approach serves as a model for ODT product development, with optimal product performance based on the specification of quality target product profiles. To understand more specific phenomena, one point in the middle of the design for each factor should be added to more powerfully estimate this effect and avoid the lack of estimate due to an inadequate equation.

Introduction

Drugs with poor water solubility present the challenge of low bioavailability. Furthermore, the rate limiting step in the absorption of a poorly water-soluble drug depends on its solubility.[1] Several methods have been developed to enhance the solubility of poorly water-soluble drugs, e.g. addition of solubilizing agents, dispersion of amorphous solids,[2] cyclodextrin complexation,[3] co-crystal formulation,[4] nano crystal formulation,[5] lipid formulation,[6] etc.

Cyclodextrin (CD) complexation is feasible method that has been used in the pharmaceutical industry to enhance solubility, drug release, and drug stability. Depending on the glucopyranose units, CD is divided into three types, i.e. α, β, and γ-CD, and to enhance their water solubility, modification of functional groups and substitution have been used.[7,8] In CD complexation, many preparation methods have been utilized, e.g. grinding, kneading, co-precipitation, spray drying, freeze drying, microwave radiation, etc.[3,9,10] These methods give different results in terms of yield, complexation efficiency, and input energy required.

The kneading (KN) method is a feasible, economic, less time consuming, and simple preparation method, obtains higher complexation yields, and is easier and more reproducible than the other methods.[10,11] Studies on the kneading process have been reported that interaction between guest molecules and CD occur during solidification of the paste.[9,10] Enhancement of dissolution using kneading was also observed for diclofenac sodium and CD with better results than their physical mixtures.[12] Some process parameters of kneading using carvedilol and β-CD, i.e. mixing time, amount added and frequency of solvent addition, affected the complex.[13] The result of complex formation is related to the level of interaction between drug and β-CD in aqueous solution and in solid state; therefore, it depends on the kneading process.[10]

Quality by design (QbD) is a development approach that uses statistical and multivariate analyses to assess and investigate the influence of each factor/critical process

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parameter (CCP) on critical quality attributes (CQAs) based on a quality target product profile (QTPP). Design experimentation (DoE) based on the QbD approach can minimize the number of runs and help obtain product knowledge.[14] The purpose of this study was to formulate and develop an orally disintegrating tablet (ODT) that incorporated meloxicam (MEL)/β-cyclodextrin (β-CD) to enhance its solubility and drug release, using the QbD approach to assess the factors studied.

Materials and Methods

Materials

Meloxicam (MEL, Lot No. 400240798) was obtained from Dexa Medica (Palembang, Indonesia), Avicel PH 102 was obtained from FMC Biopolymer (NJ, USA), Polyplasdone was obtained from ISP Pharmaceuticals (NJ, USA), and β-Cyclodextrin (β-CD, Kleptose) was obtained from Roquette (France). Sodium starch glycolate (Primojel), mannitol (Pearlitol 400DC) and sodium stearyl fumarate (Pruv) were obtained from DFE Pharma (Foxhol, the Netherlands), Roquette (Lestrem, France) and JRS Pharma (Rosenberg, Germany), respectively. All of the APIs and excipients were used as received.

Methods

MEL/β-CD complex preparation

Preparation of the MEL/β-CD complex was performed by the kneading method. Optimization of the kneading method was conducted to obtain an optimized complex that would be incorporated into the ODT formulations. A 2^2 factorial design was applied to optimize the KN process. Mixing time and the amount of solvent were used as independent variables, while the dependent variables were drug release (dissolution efficiency over 30 min; DE_{30min}) and entrapment efficiency (%EE) of the complex. The experimental design of the KN process is presented in Table 1 (in the KN Process section).

The drug release of the complex was determined via a dissolution test using the USP apparatus II model. A 500 ml of deionized water was used as a dissolution medium at a stirring rate of 100 rpm, and temperature was kept constant at 37±0.5°C. A MEL/β-CD complex equivalent to 5 mg MEL was used as the sample. 5 ml aliquots were withdrawn at 10, 15, 30, 45, and 60 min, with replacement of fresh medium at the same temperature. All the samples were analysed spectrophotometrically at λ_{max} 361 nm. Dissolution efficiency (DE) was calculated using following equation:

$$DE = \frac{\int_0^{30} y\delta t}{100T} \times 100\% \qquad (1)$$

Where *y* is the amount of drug released over time *t* and T is total time. DE was calculated for drug release over 30 min (DE_{30min}).

Entrapment efficiency (%EE)/drug loading was calculated based on the free amount of MEL in the MEL/β-CD complex. 100 mg of complex was washed with a small amount of 0.1 mol/L sodium hydroxide in methanol followed by methanol, and the amount of MEL in treated complex was determined spectrophotometrically at 361 nm. %EE was calculated using following equation:

$$\%EE = \frac{A-B}{A} \text{ x } 100\% \qquad (2)$$

Where A is the theoretical amount of MEL in the MEL/β-CD complex and B is the amount of MEL after washing.

The optimized complex was obtained based on the desirability function of DE_{30min} and %EE using factorial design as an experimental design.

Table 1. Design of experiments of KN process and ODT formulation

Run	Coded level			
	KN Process		ODT formulation*	
	A	B	C	D
1	-1	-1	-1	-1
2	+1	-1	+1	-1
3	-1	+1	-1	+1
4	+1	+1	+1	+1
Coded level			-1	+1
A : Mixing time (min)			20	40
B ; Amount of solvent (ml)			4	12
C ; Primojel (mg)			2	18
D ; Polyplasdone (mg)			2	18

*center point was added triplicates to estimate the curvature

Characterization of optimized complex

The optimized complex was characterized using spectroscopic analysis, thermal analysis, and solubility.

Solubility characterization for MEL and the MEL/β-CD complex was performed. Briefly, 50 mg of MEL or optimized complex was added to 5 ml double distilled water and sonicated for 15 min, followed by stirring for 48 h at ambient temperature. The saturated solubility of MEL in pure MEL and in complex was measured spectrophotometrically using UV spectroscopy at 361 nm.

In spectroscopic analysis, Fourier transform infrared spectroscopy Shimadzu 8400S (Kyoto, Japan) was utilized to identify the interaction between MEL and β-CD using potassium bromide pellets. 1% of the sample was dispersed on potassium bromide and compressed with 6 kN of compression force for 5 min. The pellet was scanned at wavenumber of 4000 – 400 cm^{-1} with resolution of 2 cm^{-1} and 10 iterations.

In thermal analysis, LINSEIS PT1600 (NJ, USA) differential scanning calorimetry was performed using 10 mg samples at 20°C/min under nitrogen atmosphere.

Tablet preparation

The direct compression method was used for tablet preparation. The optimized complex equivalent to 7.5 mg MEL was used in tablet formulation. The weight of the tablet for all formulations was kept constant at 200 mg and contained 30 mg Avicel PH102, 2 mg Pruv, and variable mounts of Pearlitol 400DC depending on

Primojel and Polyplasdone concentrations. The proportions of Primojel and Polyplasdone as independent variables in tablet formulation are presented in Table 1 (in the ODT Formulation section). All of the components in the formulation, except for lubricant, were passed through a 60 mesh sieve and blended in a cube mixer for 15 min at 25 rpm. Pruv was passed through a 100 mesh sieve, added to the blend and mixed for 2 min at 25 rpm. The final blends were compressed using a Korsch XP-1 single punch tablet (flat-face punch, diameter 8 mm).

Post-compression evaluation

Post-compression evaluation of the tablets looked at weight variation (n = 20 tablets), friability testing (n = 20 tablets) using a Gouming friability tester, and tablet hardness (n = 10 tablets) using a Gouming YD-1 hardness tester.

Water wicking was assessed based on tablet wetting time. The wetting time evaluation was performed using a petri dish and filter paper. Briefly, two pieces of paper filter were placed in the petri dish (diameter 10 cm) and 5 ml of 0.1% (w/v) dye solution was used. Wetting time was reported as the time required for the dye to reach the entire surface of the tablet.

The disintegration test was carried out using a USP model disintegration tester, with 900 ml of distilled water as the medium. Six tablets were used as samples and the disintegration time was measured semi-automatically until the tablet passed through the sieve.

In vitro drug release

Drug release was determined using an Electrolab TDT 08L dissolution tester type apparatus II (paddle method), with 900 ml of phosphate buffer (pH 7.5) as the dissolution medium, temperature maintained at 37±0.5°C, and a stirring rate of 50 rpm. 5 ml aliquots were withdrawn at 0.5, 1, 2, 3, 5, 7, and 10 min, with replacement of 5 ml of the fresh medium. All samples were analysed spectrophotometrically at λ_{max} 361 nm. The amount of drug released at 1 minute (Q_{1min}) and DE_{30min} (calculated based on Equation 1) were used as drug release parameters to determine the optimized formulation.

Statistical analysis and optimization

The data obtained were analysed using Design Expert® software version 7.1.5 (Stat-Ease Inc., Minneapolis, MN, USA). Factorial models, including the intercept, main effect, and interactions, were generated for all the response variables using multiple linear regression analysis (MLRA). The models were evaluated based on several statistical parameters, including the determination coefficient (R^2), adjusted determination coefficient (Adj. R^2), predicted determination coefficient (Pred. R^2) and adequate precision (adeq. precision).

The significance of a factor's effect on the response was determined by F test or p-value of analysis of variance (ANOVA), with a confidence interval of 95% (p=0.05). These were calculated using the Design Expert® software. Contour plots were constructed based on the equations of the responses; such plots are useful for elucidating the interaction effects of factors on the response. The optimal formulation, was obtained by superimposing the contour plots for each parameter.[15]

Results and Discussion

Complex preparation and optimization

Enhancing the solubility of poorly water soluble drugs can be achieved via β-CD complexation.[7,8] The greater the solubility, the faster the drug release. The drug release profiles of MEL from the MEL/β-CD complex are presented in Figure 1. Almost all of the drug was released by 60 min, indicating that the complexation of MEL and β-CD enhanced drug release compared to MEL alone (about 40% of MEL was released at 60 min; data not shown). Differences in process parameters, i.e. the amount of solvent and mixing time, lead to different amounts of drug released. Therefore, to estimate the effects of the amount of solvent and mixing time on drug release and drug loading, and to obtain the optimized process parameters for kneading, the QbD paradigm using factorial design was employed.

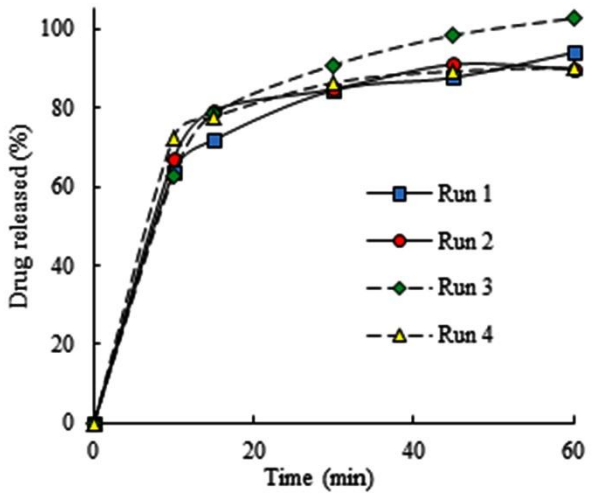

Figure 1. MEL released from MEL/β-CD complexes using kneading method

Since the DE_{30min} shows the drug release profiles from point to point,[15] the DE_{30min} was used to assess drug release. Based on a factorial design approach for DE_{30min}, the mathematical function for MLRA of DE_{30min} is presented in Table 2. In the equation for DE_{30min}, the intercept was 63.93, and is obtained in the centre point combination of each level. The amount of solvent (regression coefficient of 1.54) significantly affected DE_{30min} ($p < 0.05$) while mixing time did not (regression coefficient of 0.79; $p > 0.05$). An increase in solvent increased the dissolved β-CD and thus increased the possibility interaction between MEL and β-CD more so than β-CD in solid state, where interaction occurs only on the surface of the solid[9]. Interaction between the amount of solvent and mixing time (regression coefficient of -0.54) did not significantly decrease

DE_{30min} ($p > 0.05$). Figure 2a shows the influence of the amount of solvent and mixing time on DE_{30min}. At low mixing times, an increase in solvent increased the DE_{30min} higher than at high mixing times. The lowest DE_{30min} values were obtained with low mixing time and amount of solvent, while the highest DE_{30min} values were obtained with high mixing time and amount of solvent. Thus, increasing the mixing time and amount of solvent increased the drug release.

Table 2. Statistical parameter and regression coefficient of equation of DE_{30min} and %EE in KN process optimization

Parameters	β_0	A	B	AB	Model (p-value)	R^2	Adj.R^2	Pred R^2	AP
DE_{30min} (p-value)	63.93	0.79** (0.073)	1.54* (0.009)	-0.58** (0.150)	0.0235*	0.886	0.800	0.543	7.11
%EE (p-value)	83.39	1.64* (0.027)	3.41* (0.002)	-0.27** (0.598)	0.0066*	0.940	0.895	0.761	10.55

β_0 = intercept; A,B, and AB = regression coefficient of (A), (B), and (A) (B); AP = adequate precision; * = significant term ($p < 0.05$); ** = not significant term ($p > 0.05$)

Efficiency of complexation can be assessed using drug loading/MEL trapped on β-CD (%EE). This function is based on free MEL after the KN process. Based on the factorial design approach for %EE, the mathematical function of the MRLA of %EE is presented in Table 2. From this equation, an intercept of 83.39 was obtained. While the amount of solvent (regression coefficient of 3.41) was a more dominant factor in terms of increasing the %EE than mixing time (regression coefficient of 1.64), both of factors were statistically significant ($p < 0.05$). However, the interaction of both was not statistically significant ($p > 0.05$). An increase in the amount of solvent enhanced MEL and β-CD dissolution, therefore increasing the interaction between MEL and β-CD, and MEL was incorporated into the β-CD cavity, but not completely. The contour plot of %EE is presented in Figure 2b, and shows a similar pattern to the DE_{30min} contour plot. To obtain the optimal process conditions for both DE_{30min} and %EE, the contour plots were combined to create desirability function and are presented in Figure 2c. A high mixing time (40 min) and amount of solvent (12 ml) were chosen as the optimized KN process and incorporated into the ODT formulations based on their giving the highest desirability value.

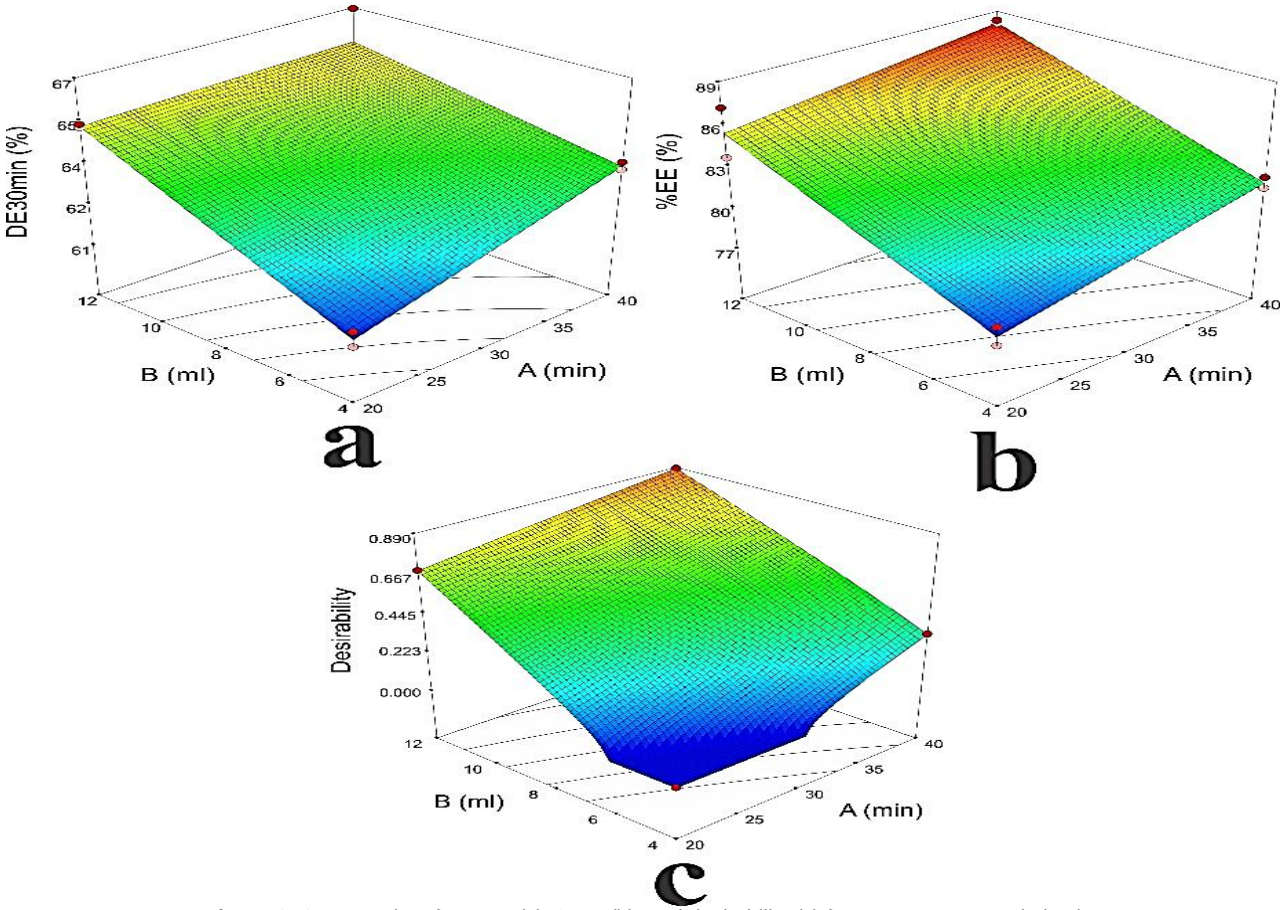

Figure 2. Contour plot of DE_{30min} (a), %EE (b), and desirability (c) from KN process optimization

Complex characterization

Characterization of the optimized KN MEL/β-CD complex was conducted, including evaluation of solubility enhancement, spectroscopic analysis using FTIR and thermal analysis using DSC. The solubility study showed that the MEL solubility and optimized KN in water (pH 6.7) were 10.57±1.11 and 58.68±4.00 µg/ml (measured at 27±1°C; ambient temperature), respectively. Therefore, complexation of MEL and β-CD increased the solubility of MEL 5.55-fold. The FTIR study was done to characterize the interaction between MEL and β-CD, and the results are presented in Figure 3. The MEL spectrum showed the vibration of N-H stretching at wavenumber 3300 cm^{-1}. The peaks at wavenumbers 1600 and 1150 cm^{-1} are due to C=N and S=O stretching vibrations, respectively. The spectrum FTIR of β-CD was assigned with peaks at wavenumbers 3300 (OH stretching vibration; broad peak) and 1000 cm^{-1} (OH bending vibration). Moreover, the FTIR spectrum of the physical mixture was the combination of both peaks of MEL and β-CD. Overall, in the KN complex, all of the MEL peaks appeared, and the KN and MEL spectra showed decreased intensity, especially at wavenumber 1200 to 1600 cm^{-1}. Therefore, the FTIR spectra confirmed that MEL was not completely loaded into the β-CD. The DSC thermogram (Figure 4) of MEL showed an endothermic peak with an onset at 259°C due to melting point. The β-CD and optimized KN thermograms showed a broad spectrum from 90–150°C (onset around 140°C) due to loss of water crystals from the structure lattice. An endothermic peak at around 259°C was not observed in the KN complex, although a small endothermic peak with low intensity was observed at 257°C due to peak shifting. The shifting to a lower melting point corresponded to an increase in solubility, and a decrease in intensity corresponded to the amount of unloaded MEL.

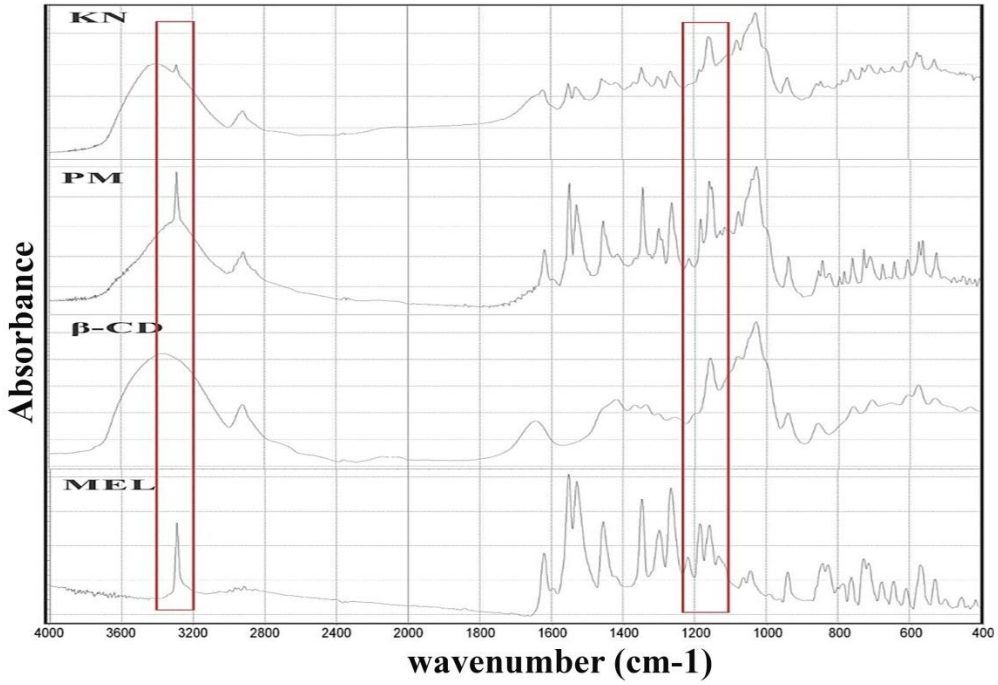

Figure 3. FTIR spectra of MEL, β-CD, their physical mixture (PM), and optimized KN complex (KN)

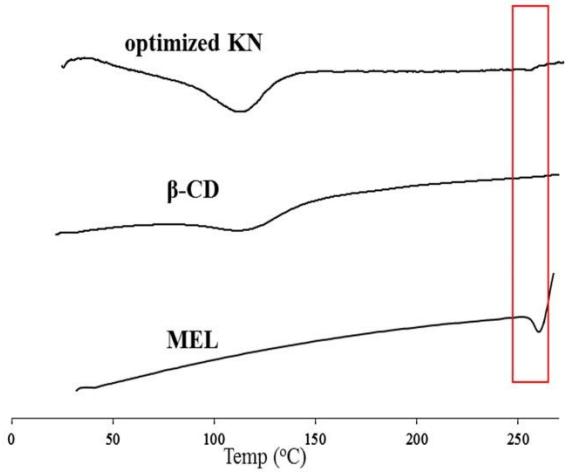

Figure 4. DSC thermogram of MEL, β-CD, and optimized KN complex

Tablet formulation and optimization

The optimal KN process to obtain an optimized complex with the highest DE_{30min} and %EE was incorporated into ODT formulations. Development of ODT formulations was conducted via the QbD approach, using factorial design. A preliminary study found a unique effect of the combination of crospovidone (Polyplasdone) and sodium starch glycolate (Primojel) on water wicking and disintegration process (data not shown). Thus, the effect of these factors on tablet physical properties (hardness, friability, wetting time (WT), disintegration time (DT) and drug release) was determined using the QbD approach to obtain the preferred design space or control strategy. Based on a factorial design approach, a mathematical model that describes the influence of Primojel and Polyplasdone was developed and is presented in Table 3.

Table 3. Statistical parameter and regression coefficient of ODT optimization

Statistic		Hardness	Friability	WT	DT	DE_{20min}
Regression coefficient	Intercept	31.13	0.55	26.21	18.99	73.06
	C	0.025**	-0.049*	-4.51*	-0.88*	-0.28**
	(p-value)	(0.9383)	(0.0176)	(<0.0001)	(0.0424)	(0.5549)
	D	-3.93*	-0.087*	-6.79*	-3.47*	1.39*
	(p-value)	(<0.0001)	(0.0005)	(<0.0001)	(<0.0001)	(0.0123)
	CD	3.78*	-0.033**	6.77*	4.51*	2.05*
	(p-value)	(<0.0001)	(0.0818)	(<0.0001)	(<0.0001)	(0.0012)
p-value	Curvature	0.3493**	0.6048**	0.1313**	0.2205**	0.0168*
	Model	<0.0001*	0.0010*	<0.0001*	<0.0001*	0.0024*
Fitting equation	R^2	0.9676	0.7883	0.9789	0.9590	0.7489
	Adj. R^2	0.9579	0.7248	0.9725	0.9467	0.6736
	Pred. R^2	0.9272	0.5237	0.9524	0.9078	0.4351
	AP	24.45	7.88	27.53	21.20	7.54

* = significant term ($p < 0.05$); ** = not significant term ($p > 0.05$); AP = adequate precision

ODT formulations must have sufficient strength to maintain their physical properties;[16] thus, hardness and friability as CQAs were used to determine the tablet strength. Hardness of all ODT formulations ranged from 22.9 to 39.4 N, with similar compression pressures and friability varying from 0.366 to 0.701%. The factorial design approach was applied to assess the effects of Primojel and Polyplasdone on the hardness and friability of ODT formulations, and the results are presented in Table 3.

Based on the hardness equation, the model was significant, with an intercept of 31.13 for the centre point of design and no significant difference with the curvature ($p > 0.05$). Polyplasdone (regression coefficient of -3.93) significantly decreased hardness ($p < 0.05$), while Primojel (regression coefficient of 0.025) had no significant affect on ODT hardness ($p > 0.05$). This indicates that Primojel is more compactible than Polyplasdone. Sodium starch glycolate is a more plastic, deformable material than crospovidone, and this characteristic therefore significantly affected hardness.[17,18] The interaction of Primojel and Polyplasdone significantly increased hardness due to recovery by Primojel's plastic deformation characteristic ($p < 0.05$). The friability equation was significant ($p < 0.05$), while the curvature was not ($p > 0.05$), and the intercept was 0.55. Polyplasdone (regression coefficient of -0.087) had a preferable effect on the friability, reducing it to a greater extent than Primojel (regression coefficient of -0.049) and was statistically significant ($p < 0.05$). Although Primojel did not reduce the hardness of the ODT formulation, lower interparticle bonding of Primojel increased friability; a similar result was reported in which an increased concentration of Primojel increased tablet friability.[17] The contour plots of tablet hardness and friability were used to elucidate the effects of Primojel and Polyplasdone on hardness and friability in the range of the design space. The lowest and highest hardness values were obtained at a low level of Primojel/high level of Polyplasdone and a low level of each factor, respectively. This indicates that increased superdisintegrant concentration reduces the hardness. With Primojel at a low concentration, an increase in Polyplasdone reduced the hardness to a greater extent than with Primojel at a high concentration. The greatest hardness value does not necessarily mean the lowest friability, as the lowest friability was obtained at a high level of each factor, and friability proportionally decreased with an increase in concentration of both superdisintegrants.

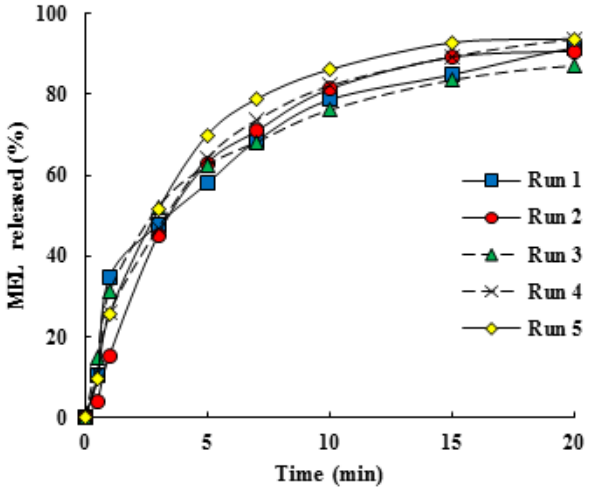

Figure 5. MEL released profiles from ODT MEL/β-CD complex

Rapid disintegration time was the desirable characteristic for the ODT formulations. In this phenomenon, the water wicking process and swelling mechanism is followed by interparticular breaking. The water wicking process was evaluated by WT. The WT and DT varied from 17.34 to 46.79 s and 10.63 to 28.88 s, respectively. Factorial design was applied to assess and elucidate the effects of Primojel and Polyplasdone on WT and DT, and the results are presented in Table 3. The WT and DT equations were significant ($p < 0.05$ for both) and the

curvatures did not have a significant difference from intercept ($p > 0.05$ for both). The intercepts for WT and DT were 26.21 and 18.99, respectively. Primojel, Polyplasdone, and the interaction of both had significant effects on WT and DT ($p < 0.05$ for all). Polyplasdone (WT and DT regression coefficients of -6.79 and -3.47, respectively) reduced WT and DT to a greater extent than Primojel (WT and DT regression coefficients of -4.51 and -0.88, respectively). This effect was induced by the disintegration mechanism of the superdisintegrant. Polyplasdone is dominant in water wicking through water capillary action, although Primojel has a swelling mechanism.[16,17,19] The combination of both had an undesirable effect, increasing the WT and DT based on the factorial design approach. This phenomenon involved an increase in the distance of water wicking due to the swelling action of Primojel and Primojel's gelling characteristic at high concentrations.

Drug release was depicted by the drug release profiles of the ODT formulations, which are presented in Figure 5. The drug release profiles for all runs showed a similar drug release pattern; for all drug runs, almost all of the MEL was released by 20 min. Therefore, DE_{20min} was used to compare the drug release profiles, and factorial design was applied to assess the drug release. The DE_{20min} equation was significant, but undesirable fitting of the curvature was found to be statistically significant ($p < 0.05$). This indicated that the fit of model was not appropriate to fit the model at the centre point of design space. Primojel (regression coefficient of -0.28) had not statistically significant effect on DE_{20min} ($p > 0.05$), but Polyplasdone and the interaction of both (regression coefficient of 1.39 and 2.05, respectively) significantly increased DE_{20min}. Although Primojel did not significantly affect drug release, the coefficient of regression had a negative sign, indicating the gelling properties of Primojel at high concentrations.

The desired model required a significant model term to indicate that the model could be used to describe the CQAs and that curvature was not significant. Therefore, the factorial model is adequate for estimating the pure error. The fitting model was used to characterize an appropriate and adequate equation for describing the CPPs on CQAs, i.e. the R^2 should be sufficiently high (more than 0.7), the difference between Adj. R^2 and Pred. R^2 should not more than 0.2, and AP should be more than 4. The inability to obtain an estimate occurs due to an inadequate or inappropriate equation.

The design space for an optimal formulations could be determined by the QTPP of the ODT formulations, such as sufficient tablet strength (hardness greater than 25 N and friability less than 0.5%; in pharmaceutical development, friability less than 0.8 is preferable[20]), rapid water wicking (WT less than 30 s), rapid disintegration (DT less than 20 s) and high drug release (DE_{20min} greater than 75%). Based on these criteria, the non-linear optimal design space of the ODT formulation was achieved and is presented in Figure 6f. The non-linear combination is yellow in colour, and from it, the linear combination to obtain the optimum design space is shown to be Primojel 8.5-9% and Polyplasdone 8-9%, and the optimized ODT formulation was obtained at Primojel 8.5% and Polyplasdone 9%.

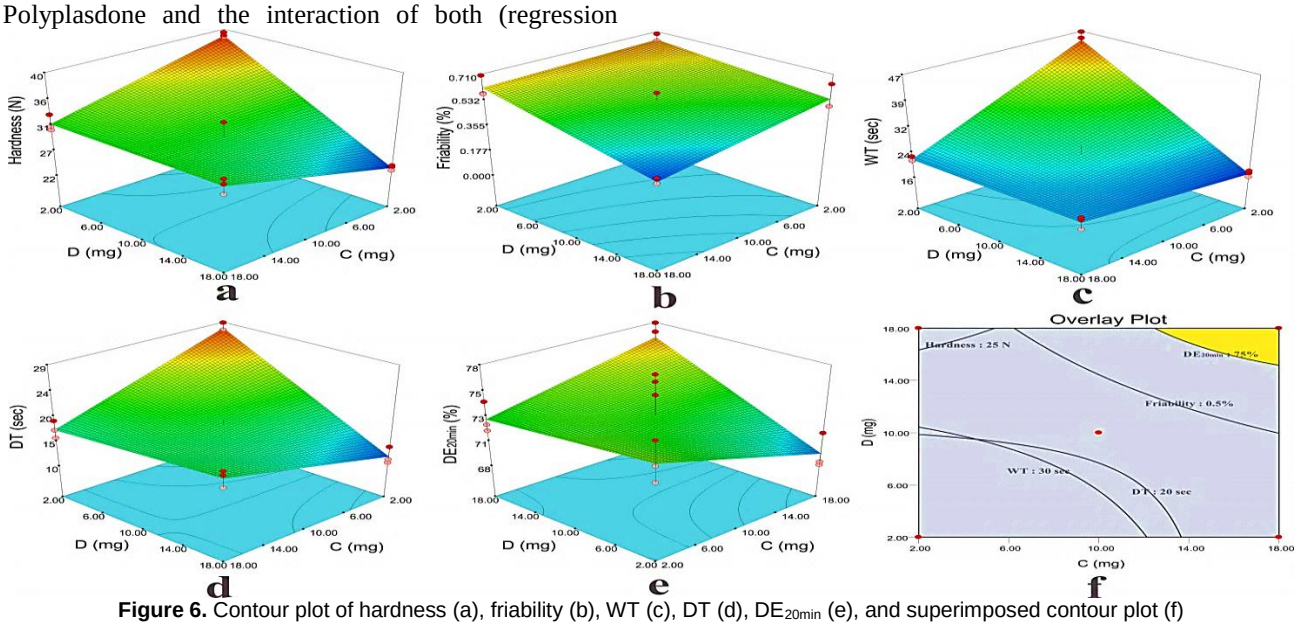

Figure 6. Contour plot of hardness (a), friability (b), WT (c), DT (d), DE_{20min} (e), and superimposed contour plot (f)

Conclusion

The QbD approach was successful for assessing and investigating the effect of mixing time and amount of solvent in the KN process and obtaining the optimized KN process conditions to be incorporated into ODT formulations. The results suggest that increasing the amount of solvent and mixing time enhances drug loading and drug release, although increasing the amount of solvent appears to have the problem of solvent removal. In the ODT formulation, Primojel and Polyplasdone had a significant effect on wicking properties, the disintegration process, and hardness. Incorporation of the MEL/β-CD complex into the ODT formulation using the QbD approach serves as a model for ODT product development

with optimal product performance based on the specifications of the QTPP. To understand more specific phenomena, one point in the middle of the design space for each factor called as curvature should be added into the 2^2 factorial design, providing a powerful equation to estimate the effects on drug release and drug loading, and to avoid the inability to obtain an estimate due to an inadequate equation.

Acknowledgments

Muhammad Ali Azhari, Chaterin R. Siagian, and Bambang R. Suryadi would like to thank the DIPA UNS for financial support. Syaiful Choiri also would like to thanks Dexa Medica (Palembang, Indonesia), Roquette (Lestrem, France), DFE Pharma (Foxhol, the Netherlands), JRS pharma (Rosenberg, Germany) for providing API and excipients. All authors declare that they have no conflict on interest.

Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest in this work.

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