RESEARCH ARTICLE

Experimental Design for the Formulation and Optimization of Phloroglucinol Mouth Dissolving Tablets

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ABSTRACT

The purpose of the present study was to prepare and evaluate Phlorogluinol mouth dissolving tablets using experimental mixture design. Ten different formulations were generated based on three types of disintegrants (croscarmellose sodium, crospovidone and microcrystalline cellulose) by using simplex lattice design with Minitab 1.6® software. Tablets were prepared by direct compression technique. The percentage of drug release at 5min, 30 min and the disintegration time were statistically analyzed to get the optimized formulation. Drug content, hardness, friability and mass uniformity were carried out on the optimum formulation as further experiments. Tablets containing the mixture of the three disintegrants provided the best release profile and the fast disintegration. The results of the quality control tests for the optimized formulation complied with the requirements of the European Pharmacopoeia 9.2.

Keywords: Phlorogluinol, mouth dissolving tablets, experimental mixture design, disintegrant

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INTRODUCTION

Phloroglucinol (PHL) is a nonatropinic derivative with marked antispasmodic properties. It is devoted to treat the acute pain associated to functional troubles of the digestive tract or the bile duct.[1] Other studies have demonstrated that phloroglucinol has anti-inflammatory and antioxidant properties.[2,3] It undergoes extensive presystemic metabolism, which results in poor bioavailability after oral administration. Moreover, it has a short elimination half-life which makes repeated injections at short time intervals necessary and causes poor patient compliance.[4] Thus, development of an appropriate and more effective dosage form of this drug is needed.

During the last decades, several technologies have been developed to solve such problems.[5,6] Mouth dissolving tablets (MDTs) have been proposed as a novel approach to avoid the first pass effect and enhance the bioavailability of drugs.[7–9] As demonstrated by different authors, MDTs are widely recommended due to their substantial benefits including (1) accuracy of dosage, (2) easy portability, (3) ideal for pediatric and geriatric patients, (4) alternative to liquid dosage forms, (5) rapid onset of action and (6) better patient compliance.[10–13] MDTs are known by several names like quick disintegrating tablets, fast disintegrating tablets, oral disintegrating tablets, orodispersible tablets, rapid dissolving tablets and porous tablets. They can disintegrate or dissolve in the oral cavity without any additional water intake.[14]

Among the several methods used for manufacturing MDTs, the direct compression seems to be preferable one due to the limited number of processing steps, the low manufacturing cost and the conventional equipment used.[13,15,16] Similar to conventional tablets, MDTs generally contain water-soluble excipients and effervescent agents to ensure quick disintegration and dissolution, especially when direct compression method was applied. Superdisintegrants, a new class of disintegrant, are more effective at lower concentration with greater mechanical strength and disintegrating efficiency. On contact with water, this type of disintegrants swell, hydrate, change form or volume and lead to a disruptive change in the tablet.[17–19] According to previous studies, the association of superdisintegrants is more efficient than the use of superdisintegrant alone.[20] In this context, the association of two types of superdisintegrants (croscarmellose sodium (CCS) and crospovidone (PVP)) and microcrystalline cellulose (MCC), widely used as filler and disintegrant, has been considered in the present work to formulate PHL-MDTs.

Mixture plan design is a broadly practiced approach used to investigate relative proportions of constituents in pharmaceutical formulation. It is recommended as the suitable design, when two or more components are changing, but the total amount of these ingredients is fixed and constant. furthermore, it requires fewer experiments and less time and thus provides a more cost effective technique than the conventional process of formulating and optimizing dosage forms.[21]

The aim of the present work was to develop and optimize PHL-MDTs by using mixture experimental design. The amount of MCC, CCS and PVP was optimized to achieve the desired dissolution profile and disintegration time of tablets.

MATERIALS

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Table 1: Variables in the mixture design

Factors	Level	
	Low	High
X_1= fraction of MCC	0.37	1
X_2= fraction of CCS	0	0.63
X_3= fraction of PVP	0	0.63
Responses	Constrains	
Y_t= disintegration time	$6s \leq Y_t \leq 10s$	
$Y_{\%5min}$= percent drug released at 5min	$80\% \leq Y_{\%5min} \leq 90\%$	
$Y_{\%30min}$=percent drug released at 30min	$95\% \leq Y_{\%30min} \leq 103\%$	

Phloroglucinol dehydrate (PHL), crospovidone (PVP), croscarmellose sodium (CCS), microcrystalline cellulose (MCC), mannitol and magnesium stearate were supplied as gift samples from LDM company, Constantine, Algeria.

METHODS

Experimental Design

In order to evaluate the influence of CCS/ PVP/ MCC mixture in MDTs, the Simplex-Centroid Augmented mixture experimental design was used to develop PHL-MDTs with three independent variables. Selected dependent and independent variables are demonstrated in Table 1. The fraction of MCC (X_1) in a range from 0.37 to 1, the fraction of CCS (X_2) and PVP (X_3) both in a range from 0 to 0.63, in the total amount of disintegrants were independent variables, as shown in Figure 1. The disintegration time (Y_t), the cumulative percent of drug released in 5 min ($Y_{\%5min}$) and 30 min ($Y_{\%30min}$) were considered to be the dependent variables. The amount of total disintegrants was fixed at 270 mg, the amount of PHL at 80 mg and the total tablet weight at 450mg.Ten formulations were randomly arranged by Minitab software (version 1.6), as demonstrated in Table 2.

Preparation of Mouth Dissolving Tablets

Mouth dissolving tablets were prepared by direct compression method. All tablets contained: 80 mg PHL, 270 mg of total disintegrant mixture according to experimental design, 80 mg of mannitol, used as sweetener, and 20mg of magnesium stearate, used as lubricant. All the ingredients were passed through 40 mesh sieve separately to attain uniformity and mixed thoroughly. The lubricated blends were directly compressed into tablets with 10 mm punches using an alternative tablet press (Deltalab, Single punch machine).

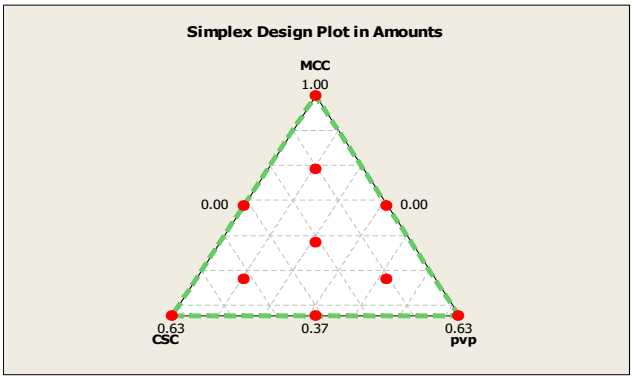

Figure 1: Augmented Simplex-Centroid Design

Table 2a: Experimental plan for mixture design

Run	Variable factor		
	MCC	CCS	PVP
1	1.000	0.000	0.000
2	0.370	0.630	0.000
3	0.370	0.000	0.630
4	0.685	0.315	0.000
5	0.685	0.000	0.315
6	0.370	0.315	0.315
7	0.580	0.210	0.210
8	0.790	0.105	0.105
9	0.475	0.420	0.105
10	0.475	0.105	0.420

Table 2b: Results of disintegration time and percentage drug release at 5 and 30min.

Run	Variable factor			Responses		
	MCC	CCS	PVP	$Y_{\%5min}$	$Y_{\%30min}$	Y_t
1	1.000	0.000	0.000	27.30	62.19	25
2	0.370	0.630	0.000	92.96	101.61	15
3	0.370	0.000	0.630	76.66	93.15	12
4	0.685	0.315	0.000	73.23	84.66	11
5	0.685	0.000	0.315	70.76	85.54	13
6	0.370	0.315	0.315	82.45	100.71	6
7	0.580	0.210	0.210	87.15	99.57	8
8	0.790	0.105	0.105	84.14	95.00	6
9	0.475	0.420	0.105	87.87	95.77	7
10	0.475	0.105	0.420	87.97	103.81	8

Evaluation of Mouth Dissolving Tablets

The optimized MDT was evaluated for different parameters like weight variation, hardness, friability, drug content, disintegration time and *in vitro* drug release.

Weight Variation

Twenty tablets were selected randomly and weighed individually using an electronic balance. The individual weights were then compared with the average weight.

Hardness

The crushing strength of 10 tablets was measured by using Monsanto hardness tester (CALEVA/THT10).

Friability

The friability of 20 tablets was measured in a Roche friabilator (CALEVA/FT2). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and the percentage friability was calculated from loss in weight as given in equation below:

$$\%\ Friability = \frac{loss\ in\ weight}{Initial\ weight} \times 100 \qquad (1)$$

% Friability of tablets less than 1% is considered acceptable

Drug Content

Ten tablets were randomly selected and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate, dissolved in suitable quantity of water. The solution was filtered through 0.45 mm membrane filter and drug content was analyzed using UV Spectrophotometer (Perkin Elmer) at a wavelength of 267 nm.

In vitro Disintegration Time

The *in vitro* disintegration test was carried out on six tablets using USP disintegration test apparatus (PHARMA

Table 3: Factor-proportion, predicted and obtained responses for the optimized MDT.

Factor	Proportion	Response	Actual response	Predicted response	P-value
X1	0.46	$Y_{\%5\ min}$(%)	93.96	89.08	0.02
X2	0.34	$Y_{\%30\ min}$ (%)	102.91	101.79	
X3	0.20	Y_t (sec)	6.83	6.00	

TEST/PTZS). Distilled water at 37±0.5ºC was used as a disintegration media. The time taken for complete disintegration of the tablet with no palpable residue in the apparatus was measured in seconds.

In vitro Drug Release

Dissolution rate was studied by using USP apparatus type II (paddle stirrer), in 900 ml of water at (37±0.5) °C at 50 rpm. Aliquots of dissolution medium (10 ml) were withdrawn at regular time intervals and replaced with pre-warmed (37±0.5) °C fresh dissolution medium at 5, 10, 15, 20 and 30 min. The samples were filtered through a 0.45 µm membrane filter and analyzed for drug content by UV/Vis spectrophotometer at 267 nm.

Statistical Analysis

The influence of variables on the responses was evaluated by experimental design analyses. The following third order polynomial equation was applied as a tool of mathematical modeling.

$$Y=b_1X_1+b_2X_2+ b_3X_3 + b_{12}X_1 X_2+b_{13}X_1 X_3 +b_{23}X_2 X_3 + b_{123}X_1 X_2 X_3 \quad (2)$$

Where, Y is the dependent variable and b_1, b_2, b_3, b_{12}, b_{13}, b_{23} and b_{123} are the estimated coefficients for corresponding factor X_1, X_2, X_3, X_{12}, X_{13}, X_{23} and X_{123}, respectively.

The single term (X) represents the average results of changing one factor at a time from its low to high value. The interaction term depicts the changes in the response when two or three factors are simultaneously changed.

The values of the coefficients were calculated to find out if the variables had some effects. The quality of the model provided by the data analysis (ANOVA) can be estimated by the magnitude R-squared (R^2) which expresses the percentage variability of the response explained by the model. A high R-squared, between 85 and 100%, indicates the stock or fund's performance moves relatively in line with the index; closer it is to 100%, the more predictive model is. Then, numerical optimization was applied to define and obtain formulation with desired drug release profile and disintegration time.

RESULTS AND DISCUSSION

The results of percentage drug release and disintegration time of all the experimental runs are listed in Table 2. Tablets containing only MCC as disintegrant (run 1) show a high disintegration time (Y_t = 25s) and a slow drug release at 5 and 30 min ($Y_{\%5min}$ = 27.3%, $Y_{\%30min}$ = 62.19%) as compared to the other formulations. However, an enhancement in drug release and disintegration time was observed in the presence of other disintegrant (CCS and PVP) for tablets of run 2, 3 and 6 where they contain the same amount of MCC with variation of the other disintegrants. Similar results were noticed earlier.[22] This may be explained by the fact that MCC, usually used as filler in tablet dosage forms, is not considered to be a superdisintegrant, thus it is unable to disaggregate the tablets and release the drug quickly in the absence of the other disintegrants. Several works have been investigated in the literature to demonstrate the disintegartion mechanism using MCC, CCS and PVP. Moreton found that MCC, upon contact with water, shows good wicking properties and hydrogen bonds between adjacent matchstick-like bundles resulting in breaking the tablet.[23] Wicking is a "whipping" action where material-material or air-material interface is replaced by water-material interface which lead to maintain capillary flow.[24] Concerning CCS, Goel et al. reported that its effectiveness has been claimed to be due to its rapid swelling and wicking upon exposure to water.[25] With respect to PVP, it is reported that it aids disintegration by

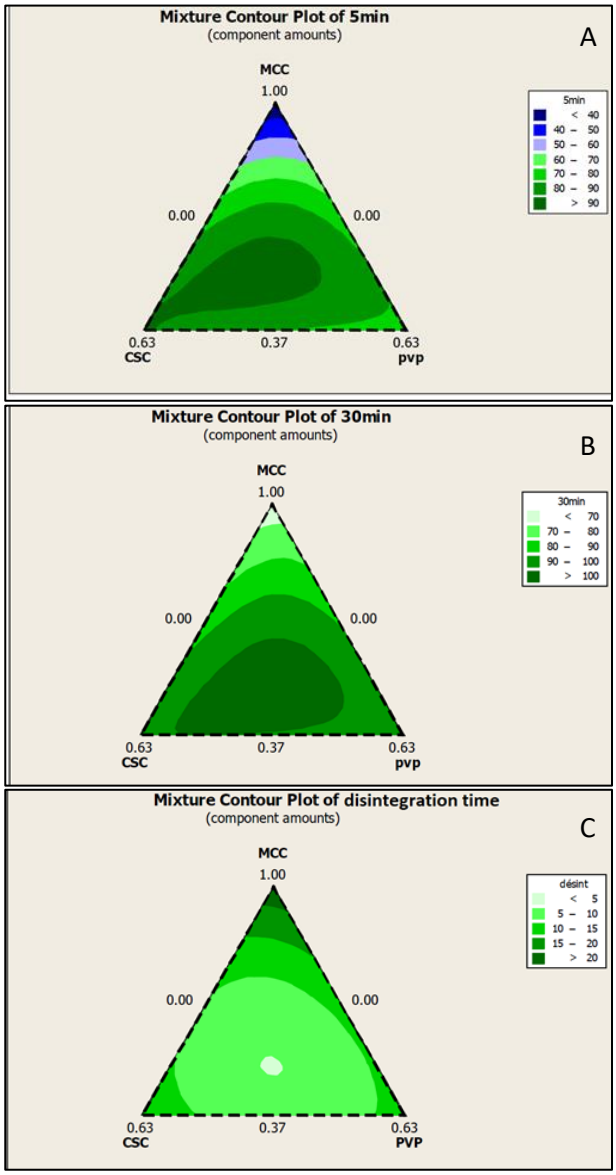

Figure 2: Contour plot of all the responses: A (Percentage drug released at 5 min), B (Percentage drug released at 30 min) and C (Disintegration time)

Table 4: Evaluation of the optimized formulation

Hardness (Kp)[a]	Friability (%)[b]	Drug content (%)[c]	Weight variation (mg)[d]
12.06 ± 0.54	0.19	99 ± 2.2	434.12 ± 2.78

[a] mean of 10 tablets
[b,c,d] mean of 20 tablets

high capillary activity through wicking with little swelling action.[26]

The Functionality of PVP and CCS was confirmed by the results of run 2 and 3 where the tablets contain the same amount of MCC with presence and absence of CCS and PVP. It is clear that tablets containing CCS give a higher release rate of PHL but disintegrate slowly as compared to those containing PVP. The amount of drug released in 5min, 30 min and the disintegration time were equal to 92.96%, 101.61%, 15s and 76.66%, 93.15%, 12s using CCS and PVP respectively.

One may conclude that CCS acts mainly on the release of PHL (by the swelling effect) whereas PVP acts mainly on the disintegration time (by the capillary effect).

Table 2 demonstrates also that the mixture of the three disintegrants was better than using one or two disintegrants (run 6, 7, 8, 9 and 10). This was in accordance with the results of Desai et al. where they reported a synergistic effect between mixtures of disintegrants and an enhanced disintegration of tablets containing different active ingredients with different water solubilities.[24]

Contour Plots Analysis

To elucidate the interaction effects of all the factors on the responses, contour plots were drawn and are illustrated in Figure 2.

Response 1 ($Y_{\%5min}$): effect on drug release at 5 min

The contour plots (Figure 2.A) showed the effect of different independent variables on cumulative drug released at 5min. A great increase in drug release was noticed using high amount of CCS (63%) or in the case of ternary mixture having the following compositions CCS [21%-63%], PVP [0%- 42%] and MCC [37%-68%].

The amounts of CCS had a marked effect on the release throughout the study. The Figure 2.A demonstrates that the release rate increased as the amount of CCS increased. This is related to the swelling property of this disintegrant; when incorporated in the tablet, CCS swells upon contact with water ensuring the break-up of the tablet. Similar result proved the effectiveness of CCS over other disintegrants.[27] Low drug release was obtained when the tablet contain only MCC ($Y_{\%5min}$<40%), which is in agreement with the results obtained by Surmey and his coworkers.[22]

Response 2 ($Y_{\%30min}$): effect on drug release at 30 min

The effects of different independent variables on cumulative drug released at 30min are shown in Figure 2.B. High drug release was noticed in the case of ternary mixture of CCS [16-47] %, PVP [16-40] % and MCC [37-68] %. These results confirm the effectiveness of the disintegrants mixture on PHL release which is linked to the capillary effect of PVP and the swelling property of CCS. Figure 2.B demonstrates also that the MCC is less efficient in enhancing drug release than the two other disintegrants which further confirms the efficiency of the mixture.

Response 3 (Y_t): effect on disintegration time

From the Figure 2.C, the disintegration time decreased as the amount of PVP and CCS was increased in the mixture. Owing to its high capillary effect, PVP when incorporated into the tablets increases its permeability by increasing the number of pores upon dissolution, allowing a high imbibition of water and disintegration of tablets. Similar results were already documented.[28,29] However, at very high levels of PVP or CCS, an increase in disintegration time has

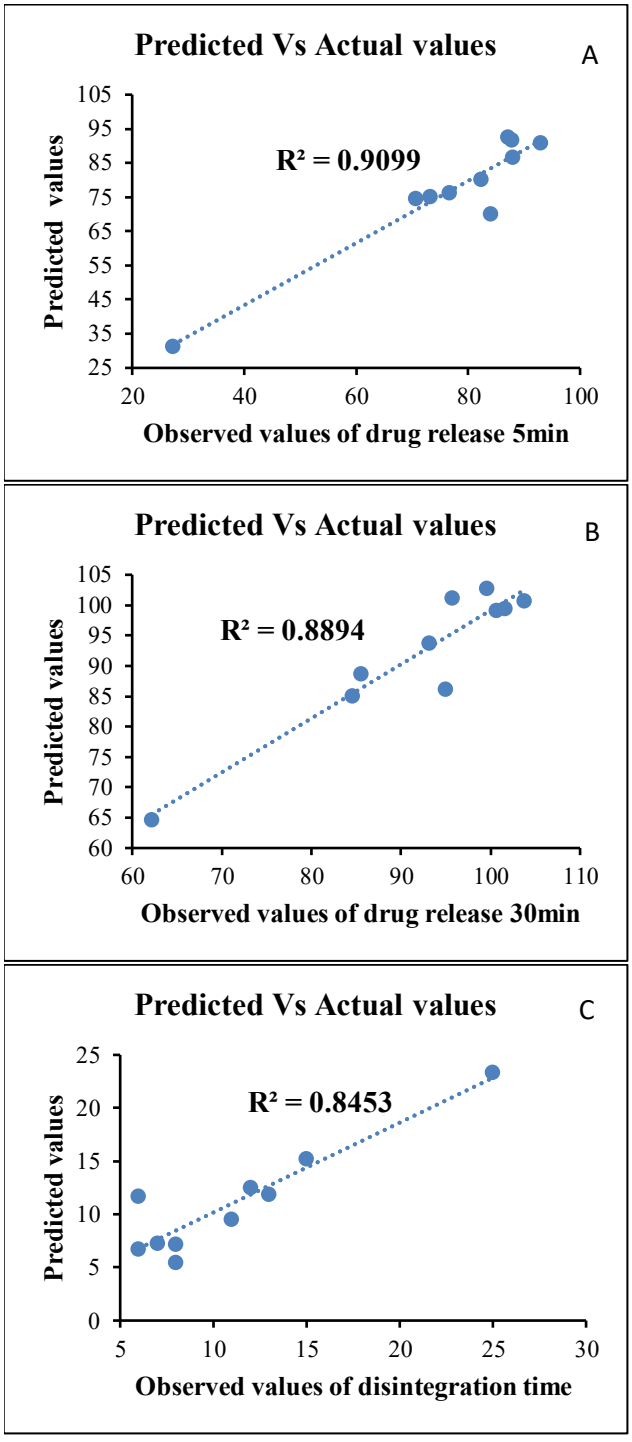

Figure 3: Linear correlation plots between actual and predicted values: A (Percentage drug released at 5 min), B (Percentage drug released at 30in) and C (Disintegration time)

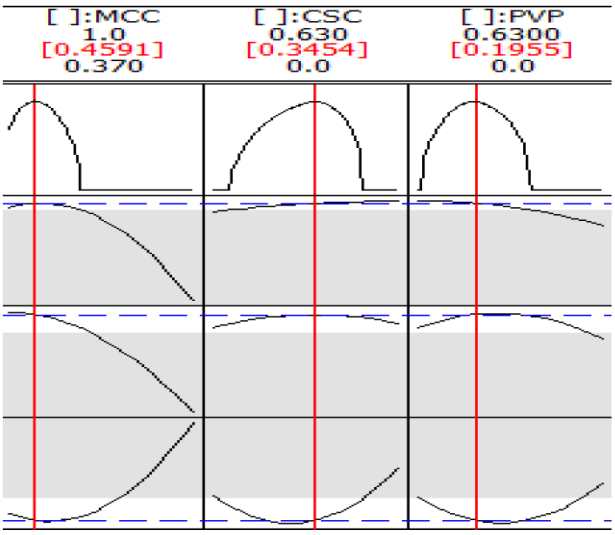

Figure 4: Representation of the optimal formula on minitab

been observed (Y_t is between 5 and 10s). Similar results were found by Pandya et al., Where PVP, at high concentrations, hindered tablet disintegration and subsequently decreased Celecoxib release.[29] Hu et al, have translated this phenomenon by the formation of a viscous gel layer that block the pores which makes the inside of the tablet inaccessible to water.[30] Shirwalker and his coworkers stated that CCS 8% w/w is the optimum level; any further increase in this level lead to the formation of a viscous gel layer acting as a barrier for disintegration.[31]

Validation of Experimental Design

Linear regression plots between the actual and predicted values of the response were illustrated in Figure 3. The linear correlation plots demonstrated high values of R-squared for all the three responses drawn between the predicted and experimental values indicating good correlation between independent and dependent variable.

The R-squared values of Y%5min, Y%30min and Yt were found to be 0.9099, 0.8894 and 0.8453, respectively. So the model is valid. The model proposes the following polynomial equations for the different responses:

$Y_{\%5min}=31.35X_1+73.28X_2+25.78X_3+142.56X_1X_2+208.47X_3X_1-534.67X_3X_2+1350.43X_1X_2X_3$

$Y_{\%30min}=64.75X_1+108.81X_2+75.50X_3+29.66X_1X_2+95.74X_3X_1-377.24X_3X_2+1089.92X_1X_2\ X_3$

$Y_t=23.38X_1+46.60X_2\ +28.68X_3-97.84X_3X_1-60.74X_2X_1-13.76X_3X_2-156.68X_1\ X_2\ X_3$

The values of the coefficients are related to the effect of variables (X_1, X_2 and X_3) on the responses. A positive value represents an effect that favors the response, whereas a negative value indicates an inverse relationship between the factor and the response. Basing on the values of the coefficients, the second and third term interactions have the largest influence on drug release and tablet time disintegration, the effect of the principal factors is less pronounced as compared to the mixture, and this may confirm the potential effect of associating disintegrants to formulate MDTs. The amount of MCC was found to be less significant on drug release and time disintegration. The negative sign of the interaction X_2X_3 in $Y_{\%5\ min}$ and $Y_{\%30min}$ indicates that as concentration of CCS and PVP increases in the tablet, drug release decreases due to the gel formation. Whereas, the negative sign of the interactions in Y_t indicates that as concentration of disintegrants increases, tablets disintegrate rapidely.

Selection of the Optimized Formulation

The constraints listed in Table 1 were used for numerical optimization of PHL-MDTs to achieve the desired responses by using the design expert program. The mixture containing 46% MCC, 34% CCS and 20% PVP shows the high PHL release and the fast tablet disintegration., as demonstrated in Figure 4.

Table 3 shows that there is no significant difference (p-value <0.05) between the predicted and obtained values of the considered responses which confirm the validity of the design.

Evaluation of the Optimized Formulation

The results of weight variation, hardness, friability and drug content assessed on the optimized formulation were listed in Table 4. The weight variation of all the optimized formulation complied with the pharmacopeial limits. Their hardness was within the acceptable range indicated the mechanical strength of the tablet. The percent friability was less than 1% revealing the physical integrity of the tablet. The percent of drug content in all the formulated tablets was in the range of 96.8 to 101.2%, ensuring the uniformity of drug content.

CONCLUSION

In summary, it was shown that Simplex-centroid Augmented Mixture Experimental Design can be successfully employed for designing a mouth dissolving tablet with desirable properties and evaluating the influence of CCS, PVP and MCC combination on the release behavior of PHL and the disintegration time of MDTs. It appears that the use of superdisintegrant combination results in faster disintegration of the tablets with enhanced drug release. The optimized formulation exhibited a reduced disintegration time (6s) and high drug release (94 and 103% at 5 and 30min, respectively).

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