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RESEARCH ARTICLE

Identification of Critical Factors Influencing the *In-Vitro* Dissolution o f Bicalutamide Tablets Prepared Using MADG Technique

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ABSTRACT

Purpose: This study was aimed to utilize the Moisture Activated Dry Granulation (MADG) technique to formulate Bicalutamide tablet and identify critical factors influencing its dissolution. **Methods:** The Bicalutamide inclusion complex was formed using the kneading method. Aeroperl 300 was selected as an adsorbent, polyvinylpyrrolidone (PVP) K30 as a binder, Microcrystalline Cellulose (MCC) and Lactose Monohydrate (LMH) in1:1 ratio as fillers. Croscarmellose sodium (CCS) and neusilin were used as disintegrating agents, as they did not affect the disintegration time when hardness and compression force increased. Box Behnken experimental design was used to optimize formulations and was evaluated for pre and post-compression parameters. The optimized formulation was compared with the marketed and wet granulation formulation. In addition, the short term stability testing of the optimized batch was performed. **Results:** The optimized inclusioncomplex of hydroxypropyl beta-cyclodextrin (HP-ß-CD) was selected based on a phase solubility study in 1:1 ratio with drug toimprove solubility. The optimized batch was prepared by MADG at granulator speed of 540rpm, using 4.30 % PVPK30, and 1.5 % Aeroperl 300. It showed a disintegration time of 208.33 sec.Percentage drug release was 95.02 % in 30 mins, and hardness 5.4 kg/cm^2. The stability study results confirmed the stability of the tablets. **Conclusion:** The Bicalutamide tablet was successfully formulated using the MADG technique. The parameters affecting the in-vitro dissolution were identified and optimized, leading to better bioavailability.

Keywords: Bicalutamide; Moisture Activated Dry Granulation technology (MADG); hydroxypropyl beta-cyclodextrin (HP-β-CD); Box Behnken design (BBD); Croscarmellose sodium

INTRODUCTION

MADG process involves the formation of granules by moisture. Instead of using heat for drying, added moisture absorbents absorb and distribute moisture, which results in uniform, free-flowing and compactable granules.[1] The major stages in the MADG process are Agglomeration – a uniform mixture is formed by mixing the drug with filler, and simultaneously water is sprayed to moisten the binder, resulting in the formation of spherical agglomerates, andmoisture distribution/absorption on addition of absorbents with continuous mixing which absorbs moisture from the moistened agglomerates, resulting in moisture distribution/absorption in the mixture, and the obtained mixture is relatively dry.[2–4] This technique is advantageous as it is simple, the processing time is short, drying and milling steps are excluded, and less energy is required.[5]

This technology does not demand new equipment or significant changes in processing techniques.[2] Thus the selection of granulators for the MADG process involves usinga simple planetary blender, high shear, low shear, or fluid bed granulation equipment in both laboratory and production scale settings.[6]

Bicalutamide (BCL) a poorly water-soluble drug, is a non-steroidal anti-androgen, newly developed for treating patients suffering from prostate cancer.[7] When BCL is given along with an agent LHRH-A which has the property to lower the level of serum testosterone in a combination, a 50 mg dose daily is sufficient.[8,9] However, it belongs to the BCS Class II category; hence it is a poorly water-soluble drug.[10]

The novel MADG technique for the formulation of Bicalutamide (BCS Class II drug) tablet involves sequential use of solubilization effort along with HP-βCD as one of the excipients to prepare inclusion complex in MADG process and along with that use of Neusilin US 2 with Croscarmellose sodium for optimizing disintegration time, has not been reported in the literature thus shows the novelty of the work.

METHODS

Preparation and Characterization of Bicalutamide: ß-Cd/HP- ß-CD Inclusion Complex

Physical Mixture[9,10]

A suitable quantity of Bicalutamide and ß-cyclodextrin or HP- ß -CD of different ratios were mixed in mortar and pestle, and then sieving was done through a #60 sieve.

Kneading method

Inclusion complex of Bicalutamide and ß-cyclodextrin or HP- ß -CD in 1:1, 1:1.5, and 1:2 ratios were prepared by kneading method. The ß -CD or HP- ß -CD was kneaded like paste with a small amount of water, with continuous trituration and slurry-like consistency. The drug was included in slurry, and further triturated continuously for 1 hour until the powder was obtained. The powder was sieved in a #40 sieve and stored in a desiccator.

Solubility study of Inclusion complex

An excess amount of inclusion complex was added to 10 ml vials containing 5 ml of 1%Sodium Lauryl Sulphate (SLS). The vials were sealed and placed in an orbital shaker for 48 hours at room temperature. The samples were filtered, diluted and analyzed spectrophotometrically at 272 nm.[11]

Selection and screening of excipients for the MADG process

Various excipients were selected according to the literature search, and screening was done as per their inactive ingredient guide (IIG) limits.[12] Different binders like hydroxypropyl cellulose, starch, and PVP K30 in 2.5%,5% and 7.5%amount were screened. The fillers like Avicel 102, LMHandmannitol were screened alone and in a 1:1 ratio while keeping the amount of binder PVP K30 constant. The moisture absorbents (Avicel PH 200, Avicel PH 102, Aerosil 200, Aeroperl 300, and Neusilin US2) were also screened.[11] Sodium starch glycolate (SSG) in 4%, 6% and 8%,Croscarmellose sodium (CCS) in 2%, 3% and 4% and neusilin in 1.5% and 3% amount were screened as disintegrants. The preliminary screening was optimized with the design of experiments.

Experimental Design

The Box–Behnken design was selected for optimization of the formulation. The dependent and independent variables selected are shown in Table 1. Level of the variables low, medium and high were selected based on the results from preliminary screening methods.[11,13] In addition, second-order polynomial models with Design Expert® (Stat-Ease.v11.0.4.x64) were obtained.[12,13]

EVALUATION PARAMETERS

Characterizations of granules (Pre compressional parameters)

Flow properties of prepared MADG granules were evaluated by measuring the Angle of Repose, Bulk Density, Tapped Density, Carr's Index and Hausner's Ratio (HR) according to the US Pharmacopoeia methods and equations.[14]

Characterizations of Tablet (Post compressional parameters)[15,16]

All prepared batches were evaluated for characteristics like Weight variation, Content uniformity, hardness, stability, dissolution, and disintegration time.[17] *In-vitro* dissolution study was performed for 30 minutes in a USP type II dissolution test apparatus (Electro lab, Mumbai, India) operated at 50 RPM and maintained at 37°C. Five ml samples were collected every 5 minutes for 35 minutes and replacing with fresh dissolution media (0.1 MHCl containing 1% SLS).[18] *In-vitro* parameters of optimized batch like % drug release, disintegration time and hardness were compared with the marketed formulation prepared using the wet granulation method.[19]

Short term stability study of the optimized batch

Stability studies were carried out as per ICH stability testing guidelines.[20] For one month, the optimized formulation was stored at 40±2°C/75±5% relative humidity (RH).[21,22] The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets evaluated immediately after manufacturing.

RESULTS

Solubility study of Bicalutamide inclusion complex

Bicalutamide solubility in water was 0.0061±0.000152 mg/ml. As seen in Figure 1, both HP-ß-CD and ß-CD increases solubility by 40 folds approximately, but ß-CD was in ratio of 1:2 while HP-ß-CD 1:1. The formulation became more bulky if ß-CD was used. Additionally, ß-CD in higher concentration may cause nephrotoxicity thus HP-ß-CD was selected for further studies.

Table 1: Variables in Box Behnken design

Independent variables	Level					
	Coded value			Transformed value		
	Low	Medium	High	Low	Medium	high
X1= speed of granulator (rpm)	-1	0	1	200	400	600
X2= concentration of binder, PVP K 30 (%)	-1	0	1	2.5	5	7.5
X2= concentration of moisture absorbent, Aeroperl 300 (%)	-1	0	1	1	1.5	2
Dependent variables						
Y_1 = Disintegration time (min) Y_2 = % drug release (%) Y_3 = Hardness (Kg/cm^2)						

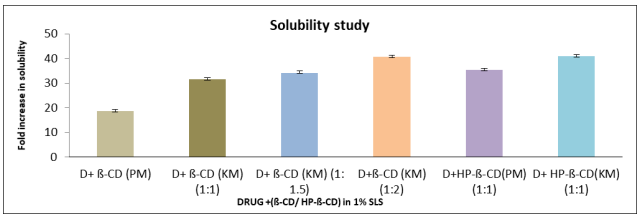

Fig. 1: Fold increase in solubility of drug– (ß-CD/ HP-ß-CD) complex(Phase solubility of Bicalutamide: Beta-cyclodextrin /HP Beta-cyclodextrincomplex

Selection and screening of excipients

According to pharmacopoeia, the hardness of the immediate release tablet must be 3.4 to 4.8 kg/cm^2, and friability must be less than 1%[14]. Based on hardness and friability data in preliminary trials, PVP K30 (2.5%, 5% and 7.5%) as a binder, Avicel 102 and LMH in (1:1) ratio as fillers were selected for further studies. Based on powders' flow property, Aeroperl 300 was selected as an adsorbent. Neusilin US2 (3%) and the cross-linking of CCS (4%) act synergistically, allowing the tablet to swell and absorb many times its weight in water leading to quick disintegration. Neusilin US2 acts as an adsorbent and improves flow ability, hardness, and tablet DT. However, Neusilin US2 and CCS did not affect the disintegration time when hardness and compression force increased. Therefore, all the screened excipients were used for further studies.

Optimization using Box Behnken Design

A three-level, three-factorial Box Behnken experimental design was used to evaluate the effects of selected independent variables on the responses, to maximize the hardness while controlling drug release and disintegration time. The speed of granulator (rpm) (X1), the concentration of binder, PVP K30 (%) (X2) and concentration of moisture absorbent, Aeroperl 300 (%)(X3) were independent variables to prepare each of the 17 formulations. The seventeen formulations with their responses are shown in Table 2. All responses were best fitted to the quadratic model.

Characterization of batches prepared according to experimental design

Various pre and post compression parameters characterized the IR tablets. The results are summarized in Table 3 and Table 4.

Post-compression evaluation parameters

Post-compression parameters suggested that increased Aeroperl 300 at high concentration form high-density granules, which increased hardness. Increased concentration of PVP K30 affected DT, hardness and friability. Ata very high concentration, PVP K30 formed avery hard tablet, which affected DT time. An increase in granulator speed (rpm) decreased granule size and increased hardness; thus, the cumulative effect of granulator speed, binder concentration, PVP K 30 and moisture absorbent, Aeroperl 300, is shown in Table 4.

In-vitro drug release of prepared batches using MADG technique after applying experimental design

In-vitro drug release of prepared batches using MADG technique after applying experimental design is shown in figure 2 which depicts that percent drug release of pure drug at 30 mins is 15 % while for batch F1- F12 its 58.87%, 79.75%, 69.52%, 81.73%, 71.72%, 83.13%,79.34%, 83.18%, 79.32%, 91.22%, 59.74%, 79.78%, 78.30%, 78.91%, 98.89%,94.99%, 95.69% and 91.96% respectively. These results reflect that with varying the processing parameters changed the drug release.

Data analysis and optimization of formula

The causal factor and response variables were related using a polynomial equation with statistical analysis through Design-Expert® software. The quadratic model's approximations of response values (Disintegration, % of drug release in 30 min, hardness) were most suitable because its PRESS value was the smallest.

Table 2: Composition of tablet batches as per Box–Behnken design *

Batch	X_1 Speed of granulator (rpm)	X_2 The concentration of binder, PVP K 30 (%)	X_3 Concentration of moisture absorbent, Aeroperl 300 (%)	Y_1 Disintegration Time (DT) (Sec)	Y_2 % DrugRelease (%)	Y_3 Hardness (Kg/cm^2)
F1	200	2.5	1.5	393.6	58.87	2.8
F2	600	2.5	1.5	394.6	79.77	3.2
F3	200	7.5	1.5	418.3	69.52	4.8
F4	600	7.5	1.5	301	81.73	5.8
F5	200	5	1	401.3	71.72	3.4
F6	600	5	1	314	83.18	4.6
F7	200	5	2	300.3	79.34	4.4
F8	600	5	2	219.6	91.22	4.8
F9	400	2.5	1	404.3	59.75	2.9
F10	400	7.5	1	317.6	79.78	4.9
F11	400	2.5	2	315	78.3	3
F12	400	7.5	2	214.3	78.91	5.99
F13	400	5	1.5	194.3	92.74	5.1
F14	400	5	1.5	189.6	93.85	5.2
F15	400	5	1.5	158.3	94.99	4.99
F16	400	5	1.5	203.6	95.53	5
F17	400	5	1.5	226.3	91.9	5.3

* Talc and Mg. Stearate was added at 2mg and 1mg per tablet, respectively. The total weight of the tablet was 300 mg. Bicalutamide has added 50 mg per tablet.

Table 3: Pre-Compression parameters for the characterization of prepared batches according to experimental design *

Batch	Bulk density (gm./cc)	Tapped density (gm./cc)	Hausner's ratio	Carr'sIndex (%)	Angle of Repose (θ)
F1	0.30 ±0.01	0.36 ±0.02	1.220 ±0.04	18.028±0.32	31.20±0.24
F2	0.31 ±0.02	0.34 ±0.01	1.078 ±0.09	8.248±0.76	30.17±0.14
F3	0.32 ±0.01	0.36 ±0.01	1.139 ±0.04	12.236 ±0.27	28.17±0.21
F4	0.31 ±0.04	0.33 ±0.01	1.070 ±0.07	8.509±0.68	27.67±0.62
F5	0.30 ±0.06	0.35 ±0.02	1.197 ±0.03	16.408±1.18	31.08±0.32
F6	0.31 ±0.04	0.35 ±0.01	1.149 ±0.08	12.939 ±1.45	29.78±0.10
F7	0.30 ±0.02	0.35 ±0.03	1.163 ±0.08	13.961±1.39	28.98±0.35
F8	0.31 ±0.02	0.34 ±0.05	1.089 ±0.09	8.181 ±1.58	25.98±0.10
F9	0.31 ±0.04	0.35 ±0.02	1.138 ±0.01	12.131±0.87	29.00±0.22
F10	0.30 ±0.07	0.36 ±0.01	1.176 ±0.08	14.935±2.24	30.98±0.07
F11	0.30 ±0.04	0.34 ±0.09	1.108 ±0.09	9.708±1.56	25.23±0.21
F12	0.32 ±0.03	0.34 ±0.02	1.058 ±0.09	7.497 ±1.67	25.58±0.16
F13	0.31 ±0.02	0.34 ±0.02	1.087 ±0.01	7.971 ±1.22	27.70±0.22
F14	0.30 ±0.01	0.32 ±0.02	1.079 ±0.05	7.335 ±0.39	27.30±0.86
F15	0.30 ±0.01	0.32 ±0.02	1.079 ±0.05	7.335 ±0.39	27.21±0.09
F16	0.30 ±0.01	0.32 ±0.04	1.077 ±0.03	7.128 ±1.16	27.93±0.57
F17	0.32 ±0.09	0.34 ±0.03	1.061 ±0.02	7.681 ±1.88	27.85±0.15

*(n=3, data are shown as mean±SD)

Table 4: Post-Compression parameters for characterization of prepared batches according to experimental design *

Batch	Hardness(kg/cm^2)	Friability (%)	DT (sec)	Weight variation (no. of tablets = 20)	Drug content (%)
F1	2.8±0.08	0.363±0.05	393.6±2.6	300.02±0.15	94±0.6
F2	3.2±0.08	0.290±0.04	394.6±1.2	299.85±0.33	96±0.3
F3	4.8±0.04	0.054±0.02	418.3±3.9	299.90±0.39	95±0.5
F4	5.8±0.08	0.011±0.04	301±2.6	299.92±0.42	97±0.32
F5	3.4±0.08	0.105±0.04	401.3±0.9	300.05±0.09	94±0.18
F6	4.6±0.08	0.076±0.03	314±0.8	299.77±0.53	95±0.4
F7	4.4±0.04	0.090±0.04	300.3±1.4	299.92±0.39	95±0.6
F8	4.8±0.08	0.072±0.03	219.6±0.8	300.01±0.28	96±0.24
F9	2.9±0.02	0.290±0.02	404.3±1.7	300.08±0.32	96±0.81
F10	4.9±0.08	0.032±0.01	317.6±1.4	299.87±0.66	97±0.6
F11	3.0±0.04	0.254±0.011	315±0.0.8	299.90±0.62	97±0.11
F12	5.99±0.08	0.011±0.04	214.3±0.7	299.99±0.50	96±0.19
F13	5.1±0.15	0.014±0.07	194.3±2.5	299.96±0.41	97±0.12
F14	5.2±0.08	0.021±0.08	189.6±0.9	299.77±0.69	97±0.18
F15	4.99±0.08	0.029±0.02	158.3±1.4	300.21±0.30	96±0.16
F16	5.0±0.04	0.014±0.07	203.6±2.5	300.28±0.36	96±0.14
F17	5.3±0.08	0.014±0.07	226.3±2.5	300.01±0.23	97±0.16

*(n=3, data are shown as mean±SD)

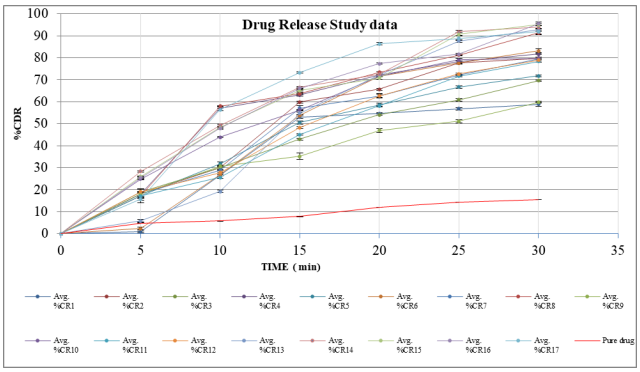

Fig. 2: *In-vitro* drug release study data

Effect on Response Y_1 (Disintegration Time)

The design expert software suggested a quadratic model with an R^2 value equal to 0.9637 (p=0.0003). A high value of the correlation coefficient (0.9637) indicates a good fit between the independent variables and the first dependent variable (Disintegration time). The model is significant, with a P-value of 0.0003 (table 5). The evolved mathematical model is

Y_1 (Disintegration Time) = 194.42 -35.53X_1 -32.03X_2 -48.50X_3 -29.57X_1X_2 +1.65X_1X_3 -3.50 X_2X_3 + 89.22X_1 X_1+ 93.22X_2 X_2+ 25.15X_3 X_3……..equation 4

The contour plot for the Disintegration time is shown in Figure 3. The 2D and 3D response surface plot derives that as the speed of granulator, the concentration of binder, PVP K 30 and concentration of moisture absorbent, Aeroperl 300 increases, DT time decreases. The contour lines are concentric in the contour plot (Figure 3a) since the interactions of terms (X_1, X_2) were found significant for DT as the acceptable region is in a full circle. While the interaction of X1 and X3 (Figure 3b) has a positive value, thus they will increase DT. Thus utilizing these interactions, DT can be adjusted according to the factor's value.

Effect on Response Y_2 (% Drug release NLT 85% in 30 min)

The design expert software suggested a quadratic model with an R^2 value equal to 0.9860 (p <0.0001). A high value of correlation coefficient (0.9860) indicates a good fit between the independent variables and the dependent variable (% drug release). The model is significant, with a P-value of <0.0001 (Table 5). The evolved mathematical model is

Y_2 (% drug release) = 93.80 +7.06 X_1 + 4.16 X_2 + 4.17X_3 -2.17X_1 X_2+0.1050X_1 X_3 -4.86 X_2X_3 -7.07X_1X_1-14.25X_2X_2-5.36X_3X_3 ……equation 5

Significant effect on % drug release of the tablet was shown by the speed of granulator, the concentration of binder, PVP K 30 and concentration of moisture absorbent, Aeroperl 300, as they have a positive effect on drug release. The contour plot for the % drug release is shown in Figure 4. The desired value of % drug release is NLT 85% in 30 mins. The acceptable region is shown in green, yellow and red regions. The 2D and 3D response surface plot shows the interaction effect of parameters where the interaction effect of X_1X_2 and X_2X_3 are negative while that of X_1X_3 is positive; thus, utilizing these interactions, drug release can be tailored according to the values of factors. The contour plots show

Table 5: ANOVA analysis

Response	Source	Sum of squares	Df	Mean square	F value	P-value	
R1 (Disintegration Time)	Model	1.200E+05	6	13330.46	20.67	0.0003	significant
	Residual	4514.23	7	644.89			
	Lack of fit	2085.46	3	695.15	1.14	0.4326	Not significant
	Core total	1.245E+05	16				
R2 (% Drug release)	Model	2005.47	9	222.83	17.49	0.0005	Significant
	Residual	89.18	7	12.74			
	Lack of fit	35.74	3	11.91	0.8915	0.5183	Not significant
	Core total	2094.66	16				
R3 (Hardness)	Model	16.75	9	1.86	137.85	< 0.0001	Significant
	Residual	0.0945	7	0.0135			
	Lack of fit	0.0240	3	0.0080	0.4545	0.7284	Not significant
	Core total	16.84	16				

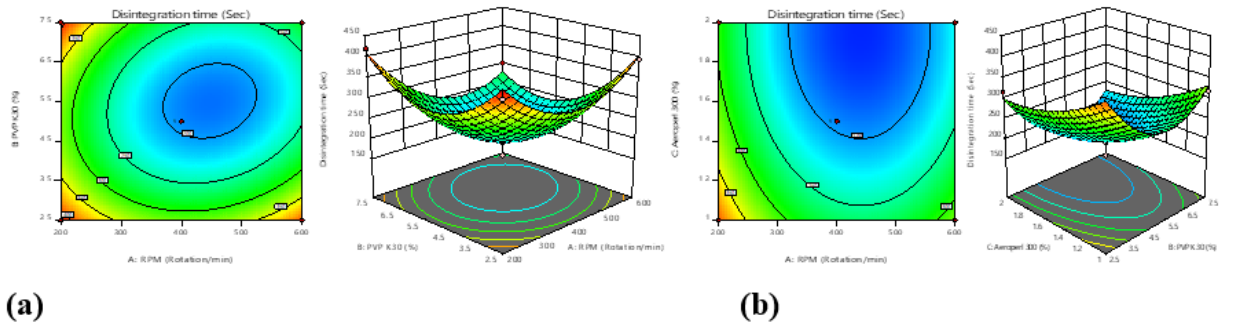

Fig. 3: (a) X1 and X2 interaction on 2D and 3D contour plot of Response Y1(DT), (b) X1 and X3 interaction on 2D and 3D contour plot of Response Y1 (DT)

that PVP K 30 in the range of 3.5-6.5, Aeroperl 300 in the concentration range of 1.2-2 and RPM in the range of 300-600maximized the % drug release.

Effect on Response Y_3 (Hardness)

The design expert software suggested a quadratic model with an R^2 value equal to 0.9944, with (< 0.0001). A high value of correlation coefficient (0.9944) indicates a good fit between the independent variables and the dependent variable (Hardness). The model is significant, with a P-value of <0.0001 (Table 5). The evolved mathematical model is

Y_3 (Hardness) = 5.12 +0.3750 X_1 + 1.20 X_2 + 0.2988 X_3 +0.1500X_1 X_2 -0.2000X_1 X_3 +0.24756 X_2X_3 -0.4328X_1X_1-0.5353X_2X_2-0.3852X_3X_3……..equation 6

Significant effect on hardness of the tablet was shown by the speed of granulator, the concentration of binder, PVP K30 and concentration of moisture absorbent, Aeroperl 300, as they all offer a positive effect, i.e. with an increase of these parameters, hardness will be maximized. The contour plot for the hardness is shown in figure 5. The desired value of hardness is 3-6 kg/cm^2. The acceptable region is shown in the green, yellow and red regions. The 2D and 3D response surface plot shows the interaction effect of parameters, and from the contour plots, we found that X_1X_2 and X_2X_3 show positive interaction. In contrast, X_1X_3 shows negative interaction; thus, utilizing these interactions, hardness can be tailored according to the values of factors.

Overlay plot

The overlay plot is generated by superimposing the contour plots of all the regions,[23] as shown in Figure 6. The range selected for the overlay plot was ± 10 as per USFDA criteria.The relative error should not be more than 5% as per USP.

$$\frac{\text{Predicted value} - \text{Observed value}}{\text{Predicted value}} \times 100 \text{.....equation 7}$$

The optimized batch was selected based on the following criteria:

Disintegration time (180-300), % CDR at 30 min should >85%, and hardness should be 4-6.

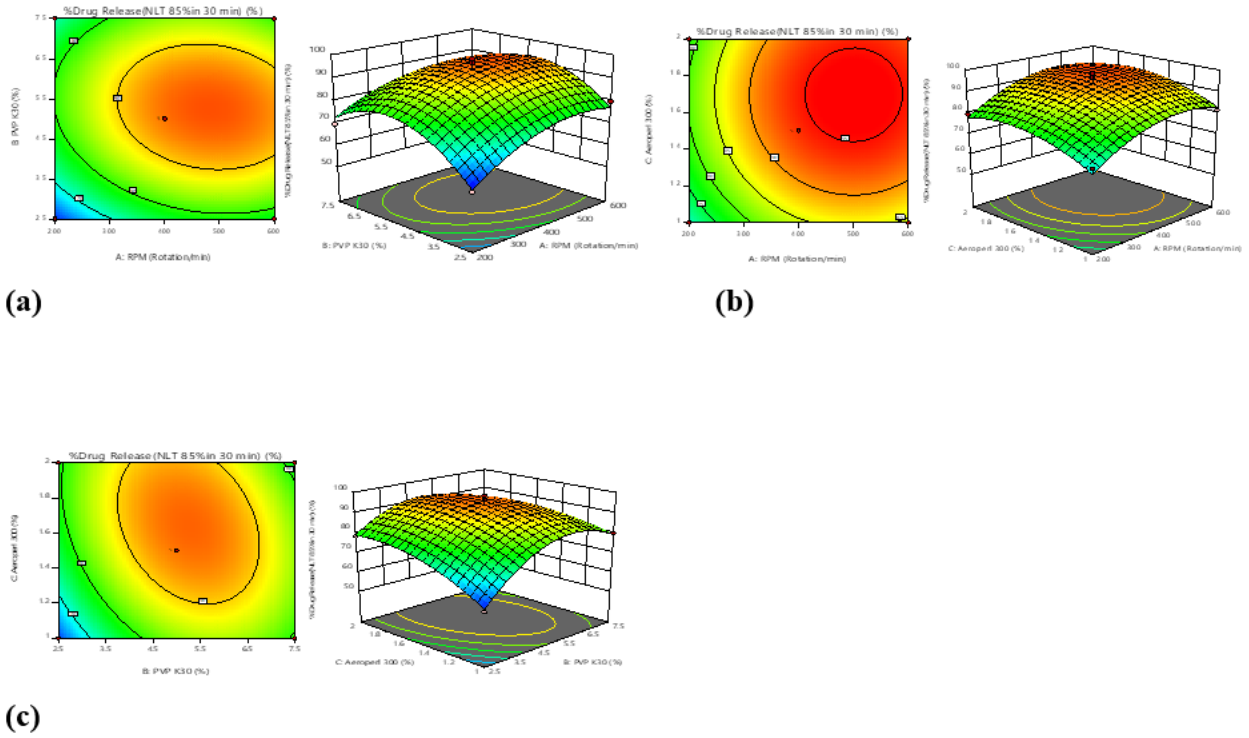

Fig. 4: (a) X1 and X2 interaction on 2D and 3D contour plot of Response Y2 (% CDR), (b) X2 and X3 interaction on 2D and 3D contour plot of Response Y2 (% CDR), (c) X1 and X3 interaction on 2D and 3D contour plot of Response Y2 (% CDR)

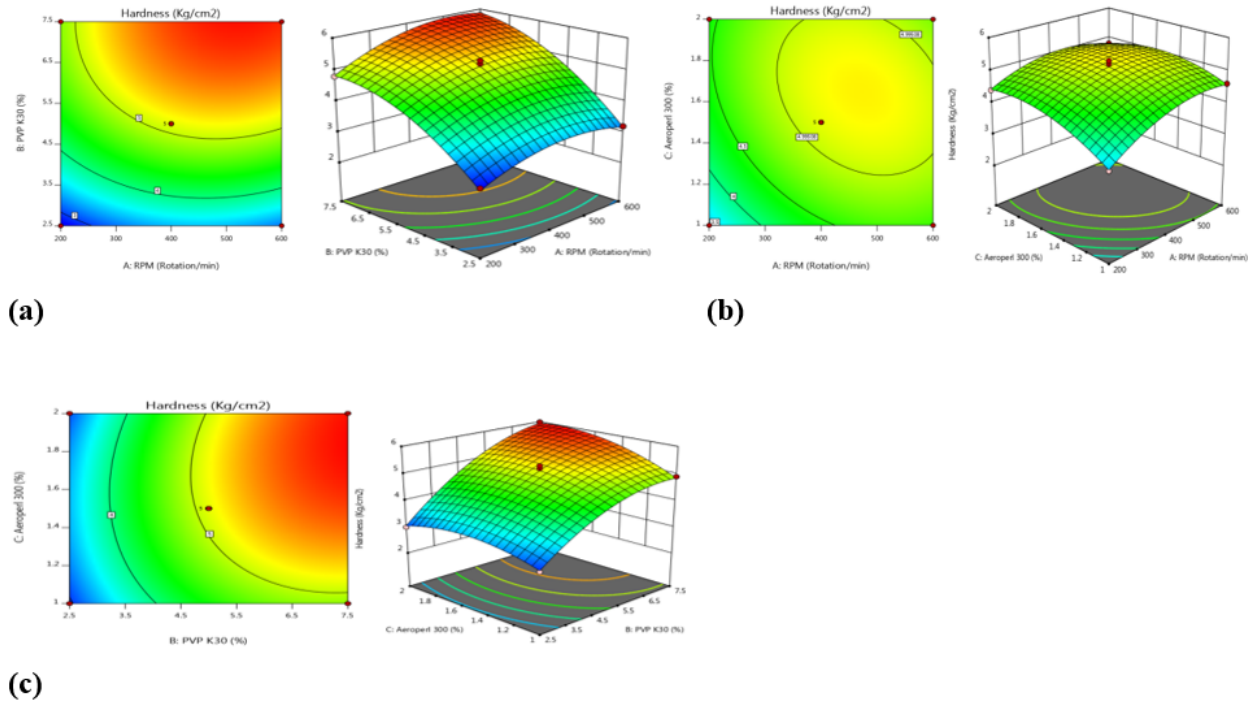

Fig. 5: (a) X1 and X2 interaction on2D and 3D contour plot of Response Y3 (hardness), (b) X1 and X2 interaction on 2D and 3D contour plot of Response Y3 (hardness), (c) X1 and X2 interaction on 2D and 3D contour plot of Response Y3 (hardness)

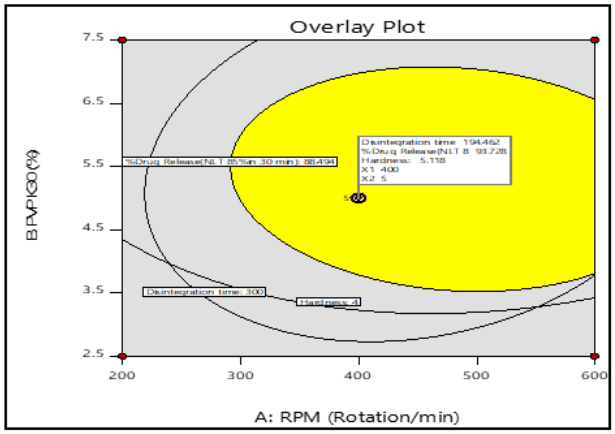

Fig. 6: Overlay plot

Validation of model

To verify the evolved models, the optimum formulation was prepared according to values of the factors and subjected to Disintegration time, % Drug release and hardness, as shown in Table 6. It demonstrates that the observed value of a new batch was relatively closer to the predicted value. The prediction error was less than 5%, which validated the model applied.[24,25] All batches were evaluated for different evaluation parameters, and they all are within the desired range, as shown in Table 7.

In-vitro comparison of optimized batch with marketed formulation and tablet prepared by wet granulation

An *in-vitro* comparison of the optimized batch with the marketed formulation is shown in Table 8. *In-vitro* comparison of optimized batch prepared using MADG with marketed formulation and tablet designed with wet granulation is shown in Table 9.

Disintegration time, % Drug release and hardness of optimized batch showed better results than marketed formulation and wet granulation.In-vitro comparison of an optimized batch with marketed formulation and tablet prepared with wet granulation demonstrates that the optimized MADG formulation shows considerably similar drug release, disintegration time and hardness as that of marketed formulation and has significantly better drug release and disintegration time and hardness compared to tablet prepared via wet granulation.

Stability study

The stability study of the optimized batch showed (Table 10) no significant changes in Disintegrating time, % Drug release and hardness. The DT and hardness were slightly increased while drug release was decreased somewhat, but the changes are not significant.

DISCUSSION

MADG approach increase content uniformity, which was critical parameter of the study as the selected drug was having very low dose. Energy and time were also saved in this process. As per the literature search, very less work has been done on MADG till date.In present research work Bicalutamide: HP-ß-CD complex (1: 1) has been prepared to enhance the solubility of Bicalutamide due to partial conversion of crystalline to amorphous state.The kneading method and physical mixture both were employed for solubility enhancement.[11,26] TheΔG°tr values were negative at the treated concentrations of the polymers, which reflect the spontaneous nature of the Bicalutamide solubilization. Screening of excipients results in selection of PVP K30 (5%) as binder, Avicel102 and LMH(1:1) as diluent, Aeroperl 300 (1.5%) as absorbent, Neusilin US2 (3%) along with Croscarmellose sodium (4%) as disintegrate. NeusilinUS2 showed synergistic effect with Croscarmellose sodium and helps in achieving target disintegration time.

The CQA of prepared tablet were optimized by using Box Behnken design. The seventeen batches were prepared using different speed of granulator (rpm), concentration of binder, PVP K 30 (%) and concentration of moisture absorbent, Aeroperl 300 (%) were evaluated. The granules had good flow and compression strength while tablet had good hardness, DT and %CDR. For the preparation of granules lab scale mixer granulator was used.[19] Comparison of optimized formulation with marketed formulation and wet granulation showed that optimized formulation gave results similar to that of marketed formulation and better than that of wet granulation. Short term stability study was conducted at 40°±2° 75% ±5% RH for 1 month. Disintegration time, % CDR and Hardness were measured at frequent intervals and significant difference was not found.

CONCLUSION

MADG is a novel yet simple technique for granulation, which overcomes the downsides of highly used wet granulation method. The current research explored the MADG technique for preparation of tablets of a new non-steroidal anti-androgen drug Bicalutamide for treatment of prostate cancer. The combined effect of binder, moisture absorbent, and the optimized speed of granulator were reflected in the % Cumulative drug release (CDR), which showed better drug release than the conventional wet granulation method. Simplicity of technology and FDA approved excipients used in formulation can be taken further at industry level without complicated regulatory issues. If the aforementioned formulation will scaled-up to manufacturing level, the process will be easy by minimizing waste and saving time, energy and cost.

Table 6: Determination of % relative error through checkpoint batches

Batch code		Responses	Predicted value	Experimental value	% Relative Error
Optimized batch	X1= RPM	Y1=Disintegration time (sec)	212.22 sec	208.33 sec	2.4
	X2= PVPK 30	Y2= % Drug release (%)	92.68%	95.02%	1.15
	X3=Aeroperl 300	Y3= Hardness (kg/cm^2)	5.64 kg/cm^2	5.4 kg/cm^2	4.27
Check point batch 1	X1= RPM	Y1=Disintegration time (sec)	215.9sec	218.66 sec	1.32
	X2=PVPK 30	Y2= % Drug release (%)	91.017%	86.43 1%	5.1
	X3=Aeroperl 300	Y3= Hardness (kg/cm^2)	5.0675 kg/cm^2	4.86 kg/cm2	3.89
Check point batch 2	X1= RPM	Y1=Disintegration time (sec)	235.59sec	251.66 sec	5.56
	X2= PVPK 30	Y2= % Drug release (%)	92.68%	93.99 %	1.4
	X3=Aeroperl 300	Y3=Hardness (kg/cm^2)	4.76 kg/cm2	4.66 kg/cm2	2.54

Table 7: Evaluation parameters of Check Point Batches *

Parameters	Optimized Batch	Checkpoint Batch 1	Checkpoint Batch 2
Pre-compression parameters			
Bulk density (gm./cc)	0.31±0.02	0.31±0.02	0.30±0.04
Tapped density (gm./cc)	0.34±0.02	0.34±0.05	0.34±0.09
Hausner's ratio	1.087±0.04	1.089±0.09	1.108±0.09
Carr's Index (%)	7.971±1.20	8.181±1.58	9.708±1.51
The angle of repose (θ)	25.23±0.21	25.58±0.16	27.70±0.22
Post compression parameters			
Hardness (kg/cm^2)	5.4±0.16	4.86±0.14	4.66±0.14
Friability (%)	0.011±0.04	0.054±0.02	0.076±0.03
Disintegration time (sec)	208.3±0.94	218.66±1.24	248.66±2.05
Weight variation	299.923±0.48	300.015±0.28	299.769±0.53
Drug content (%)	97±0.12	97±0.18	97±0.12
Drug release (%)	95.02±0.52	86.43±0.95	93.99±0.31

*(n=3, data are shown as mean±SD)

Table 8: Comparison of optimized batch prepared using MADG with marketed formulation

Sum (Rt-Tt)	44.73	Rt = Cumulative percentage dissolved of Reference product at time t
Sum (Rt-Tt)^2	587.86	Tt = Cumulative percentage dissolved of Test product at time t
Sum Rt	368.05	
Difference Factor f1	12.15	Range: 0 > f1 < 15 It should be closed to "0"
Similarity Factor f2	55.58	Range: 50 > f2 < 100 It should be closed to "100"
Difference Test f1	PASS	
Similarity Test f2	PASS	

Table 9: Comparison of optimized batch prepared using MADG with marketed formulation and tablet prepared with wet granulation *

Sample	DT (sec)	% Drug release (%) (in 30 mins)	Hardness (kg/cm^2)
Optimized batch	208.3±0.94	95.02±0.52	5.4±0.13
Marketed	209.3±0.94	92.76±0.83	5.13±0.47
Wet granulation	245±0.86	85.03±0.33	4.7±0.82

*(n=3, data are shown as mean±SD)

Table 10: Stability study of optimized batch *

Sr.No.	Testing period	DT (sec)	% Drug release (%)	Hardness (Kg/cm^2)
1	Initial	208.3±0.94	95.02±0.52	5.4±0.63
2	10 days	207.6±1.24	94.99±0.69	5.4±0.82
3	20 days	208..6±1.24	95.03±0.33	5.43±0.14
4	30 days	208.6±1.70	94.84±0.36	5.46±0.47

*(n=3, data are shown as mean±SD)

CONFLICT OF INTERESTS

No conflict of interest.

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