RESEARCH ARTICLE

Formulation and evaluation of immediate release tablet using response surface methodology

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The purpose of the present work was to develop an optimized immediate release tablet for hypertensive patients using amlodipine besylate as a model drug candidate by optimization technique to produce the intended benefits. A 3^2 factorial design was employed in formulating immediate release tablet. The independent variables selected were superdisintegrants such as sodium starch glycolate and in addition to that, effect of microcrystalline cellulose was studied. The dependent variables considered for study was DT and DP_{60}. The tablets prepared were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, *in vitro* disintegration time, and *in vitro* drug release study. The response surface plots differentiate the results between the independent and dependent variables. Apart from fulfilling all official and other specifications, the tablets exhibited higher rate of release.

Key words: *Amlodipine besylate, factorial design, immediate release tablet*

INTRODUCTION

Amlodipine is a prototype second-generation dihydropyridine calcium channel blocker. They have a longer duration of action and can be given once daily. Amlodipine is used in the treatment of mild to moderate hypertension, chronic stable angina pectoris, or vasopastic angina (prinzmetal's or variant). In these conditions, it may be employed as monotherapy or in combination with other antihypertensives or antianginals. Amlodipine can be safely combined with ß blockers, ACE inhibitors, thiazides, and nitrates. It has a half-life of 40 hours and the initial effects are cumulative over many days.[1-3]

Various techniques can be used to formulate immediate release tablets; direct compression is one of the techniques that require the incorporation of a superdisintegrants into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and is very sensitive to changes in the type and proportion of excipients and the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics.[4,5]

The present work carried out for development of immediate release tablet amlodipine besylate by using the 3^2 factorial design method and studying the effect of independent variable on dependent variable to produce an effective formulation. The 3^2 factorial designs were applied for the effect of independent variable such as sodium starch glycolate and microcrystalline cellulose on the dependent response such as DT and DP_{60}, respectively.

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MATERIAL AND METHODS

Material

Amlodipine besylate was received as a gift sample from Concept Pharmaceutical Pvt. Ltd., Aurangabad, India. Microcrystalline cellulose was received as a gift sample from Colorcorn Asia Pvt. Ltd., Goa, India. Starch 1500, sodium starch glycolate was received as a gift sample from Concept Pharmaceutical Pvt. Ltd., Aurangabad, India. All other chemicals and reagents are of analytical grades.

Methods

Preparation of immediate release tablet of amlodipine besylate

The super disintegrants (sodium starch glycolate and

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microcrystalline cellulose PH102) were used to formulate the tablets. All the ingredients, as shown in Table 1, were co-ground in a pestle and motor and then aerosil and magnesium stearate were added and mixed for 10 minutes. The mixed blend of drug-excipient was compressed using a LABPRESS compression machine (Cadmach, Machineries Ltd. Ahmadabad, Gujarat, India) to produce tablets with 2.75-mm thickness and 9.28 mm in diameter. The tablet press setting was kept constant across all formulations. Details are mentioned in Table 1.

Optimization by 3^2 factorial design[1,6-8]

A 3^2 randomized full factorial design was used in the present study. In the design, two factors each were evaluated at three levels and experimental trials were performed. Details are mentioned in Tables 2 and 3. The amount of superdisintegrant, sodium starch glycolate (A), and microcrystalline cellulose (B) were selected as independent variables. *In vitro* DT and DP_{60} were selected as dependent variables.

Table 1: Generalized formulation of amlodipine besylate immediate release tablets

S. no	Ingredients	Quantity (mg)
1.	Amlodipine besylate	13.87
2.	Sodium starch glycolate	8.0
3.	Microcrystalline cellulose	90.00
4.	Starch 1500	70.00
5.	Mannitol	15.13
6.	Aerosol	1.0
7.	Magnesium stearate	2.0

Table 2: 3^2 Factorial design batches

Formulation code	Coded value		Total Weight of Tablet (mg)
	A	B	
A6	+1	-1	200
A7	0	-1	200
A8	-1	-1	200
A9	0	+1	200
A10	+1	+1	200
A11	+1	0	200
A12	0	0	200
A13	-1	+1	200
A14	-1	0	200
Coded values	Actual values (%)		
	A		B
-1	4		80
0	6		90
+1	8		100

Evaluation of blend[7-12]

The prepared blends were evaluated for parameters like bulk density, tap density, Carr index, Angle of repose, and Hausner ratio.

Bulk density

The bulk density was calculated using the equation,
Bulk density = Weight of sample/Bulk volume

Tap density

The tap density was calculated by the following equation,
Tap density = Weight of drug sample/Tapped volume

Carr index

It is calculated by the formula,
C = VT-VB/VT
Where, *VB* is the freely settled volume of a given mass of powder, and *VT* is the tapped density of the same mass of powder.

Angle of repose

The angle of repose is calculated by,
Tan θ = h/r
Where, h is height of the pile and r is the radius of the pile.

Hausner ratio

It is calculated by the formula,

$$H = \frac{\rho_T}{\rho_B}$$

Where, ρ_B is the freely settled bulk density of the powder and ρ_T is the tapped density of the powder.

Evaluation of tablets[13-21]

Thickness and diameter

Thickness and diameter of tablets were determined using vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Table 3: Formulation design of amlodipine besylate immediate release layer tablet per design (3^2) layout

Tablet Ingredients	Formulation code/Ingredients (mg)								
	A6	A7	A8	A9	A0	A11	A12	A13	A14
Amlodipine besylate	13.87	13.87	13.87	13.87	13.87	13.87	13.87	13.87	13.87
SSG	4	4	4	6	6	6	8	8	8
MCC PH 102	80	90	100	80	90	100	80	90	100
Starch 1500	70	70	70	70	70	70	70	70	70
Mannitol	29.13	19.13	9.13	27.13	17.13	7.13	25.13	15.13	5.13
Aerosil	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total Weight	200	200	200	200	200	200	200	200	200

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability

Ten tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 minutes. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was measured as per the following formula:

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation

Randomly, 20 tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±4.5% (USP XX).

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of amlodipine besylate was dissolved in 50 ml of 0.1N HCl, filtered, diluted suitably, and analyzed for drug content at 240.80 nm using UV-visible spectrophotometer (UV 1600-Shimadzu, Japan).

Wetting time

A piece of tissue paper (12 × 10.75 cm) folded twice was placed in a Petri dish (Internal diameter = 9 cm) containing 10 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

Water absorption ratio

The procedure of water absorption ratio without Rosaline dye powder was followed for determining the water absorption ratio (R) which was determined according to the following equation:

$$R = [(Wa - Wb)/Wb] \times 100$$

Where, Wb and Wa were the weights of the tablet before and after use.

Disintegration time

Disintegration time for fast dissolving tablet (FDTs) was determined using united state pharmacopoeia (USP) disintegration apparatus with simulated gastric fluid (SSF) (pH 6.8, 900 ml at 37°C) as the disintegrating medium. To comply the test, all tablets should disintegrate within 3 minutes.

In vitro dissolution studies

In vitro drug release studies were carried out using USP dissolution rate test apparatus (apparatus 2, 50 rpm, 37±0.5°C) for 2 hours in 0.1N HCl (900 ml). At the different time interval, 5 ml of the sample was withdrawn and replaced with 5 ml of the 0.1N HCl. The dissolution samples were obtained at different time interval replacing with drug-free dissolution medium. The samples withdrawn were analyzed by a UV spectrophotometer at 240.80 nm.

RESULT AND DISCUSSION

Evaluation of prepared blend of amlodipine besylate

Before formulation, blends of API and excipients were prepared and evaluated for various parameters, as explained earlier. Bulk density was found in the range of 0.2941 to 0.3846 g/cm^3 and tapped density between 0.3773 and 0.4347 g/cm^3. Using the above two density data, Hausner ratio and compressibility index were calculated. The powder blends of all formulations with Hausner ratio <1.25 indicated better flow properties. The compressibility index was found to be between 7.68 and 22.05% and the compressibility-flowability correlation data indicated an excellent flowability of all powder blends. The better flowability of all powder blends was also evidenced from the angle of repose (in the range of 31.75-34.16°), which is below 40°, indicating good flowability. Details are mentioned in Table 4.

Evaluation of prepared tablets of amlodipine besylate

The prepared tablets of amlodipine besylate were evaluated for appearance, weight variation (±%), hardness (kg/cm^2), thickness (mm), friability (%), drug content (%), water absorption ratio, content uniformity (%), and wetting time (sec). The results were acceptable and within limits. The cumulative drug release was shown. Details are mentioned in Figure 1 and Table 5.

Factorial design

A 2-factor, 3-level factorial experimental design technique was employed to investigate the dependent variables like disintegration time and percent drug dissolved using the Design Expert Software (Version 7.1.4). The responses given by the software are expressed in terms of the quadratic polynomial equations which are given below

Final equations in terms of coded factors (Disintegration time)

$$DT = 22.25 + 3.76\,A + 1.48\,B - 0.305\,AB + 8.05\,A^2 - 0.44\,B^2$$

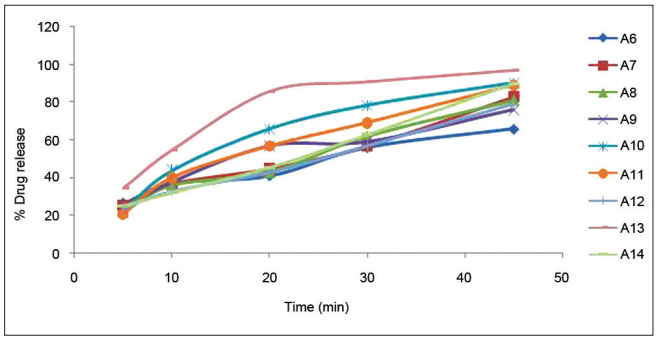

Figure 1: Cumulative percentage of drug release data

Table 4: Evaluation of physical characterization of blends

Formulation code	Bulk density (gm/cm³)	Tap density (gm/cm³)	Carr's index (%)	Angle of repose	Hausner ratio
A6	0.3846±0.012	0.4166±0.005	7.6812±0.04	33.69±1.34	1.0832±0.55
A7	0.3703±0.010	0.4347±0.003	14.81±0.02	32.38±1.20	1.1739±0.76
A8	0.3571±0.032	0.4347±0.010	17.85±0.07	34.99±1.08	1.2173±1.05
A9	0.3333±0.005	0.40±0.006	16.67±0.09	34.16±1.44	1.2001±0.30
A10	0.3225±0.016	0.40±0.021	19.37±0.021	36.59±1.32	1.2547±0.90
A11	0.3125±0.011	0.3921±0.004	20.30±0.05	32.38±1.26	1.2547±0.78
A12	0.2941±0.013	0.3773±0.007	22.05±0.03	31.75±1.08	1.2828±0.44
A13	0.3571±0.023	0.4347±0.015	17.85±0.05	35.39±1.10	1.2173±1.03
A14	0.3571±0.021	0.4347±0.020	17.85±0.07	26.88±1.22	1.2173±1.42

Table 5: Evaluation of prepared tablets

Evaluation parameters	Formulation code								
	A6	A7	A8	A9	A0	A11	A12	A13	A14
Appearance	200 mg, white colored, 10 mm, round convex faced								
Weight variation (%)	201± 2.539	201± 2.661	199± 2.615	199± 2.412	201± 2.856	202± 2.149	201± 2.433	201± 1.954	199± 2.536
Hardness (kg/cm2)	4.35± 0.057	4.32± 0.057	4.02± 0.057	4.13± 0.100	4.20± 0.054	4.16± 0.056	4.26± 0.055	4.28± 0.053	4.31± 0.054
Thickness (mm)	3.23± 0.065	3.45± 0.030	3.63± 0.037	3.98± 0.017	3.93± 0.015	3.37± 0.015	3.43± 0.032	3.48± 0.060	3.52± 0.036
Friability (%)	0.27± 0.007	0.19± 0.005	0.36± 0.003	0.27± 0.037	0.35± 0.015	0.35± 0.001	0.34± 0.02	0.38± 0.01	0.32± 0.02
Drug content (%)	101.58± 0.89	100.14± 1.43	100.10± 1.92	100.08± 1.57	101.04± 1.56	101.75± 0.86	100.21± 1.27	101.54± 0.61	100.19± 1.02
Content uniformity (%)	100.58± 1.39	101.45± 1.34	100.52± 1.35	102.06± 1.07	100.08± 1.24	101.10± 1.02	101.13± 1.17	100.20± 1.28	100.14± 1.07
Water absorption ratio (%)	98.01± 0.25	92.0± 0.09	99.2± 0.07	113± 1.26	111± 0.65	101.59± 0.35	80.7± 0.02	110.29± 0.66	113.19± 0.38
Wetting time (sec)	10.1± 0.117	6.5± 0.604	8.5± 0.105	8.51± 0.525	9.52± 0.384	12.0± 0.172	9.51± 0.642	5.5± 0.374	6.5± 0.140
In vitro DT (sec)	32.6± 0.091	20.3± 0.045	24.1± 0.078	23.3± 0.317	35.0± 0.240	33.6± 0.155	22.2± 0.168	27.6± 0.130	27.0± 0.358
DP (%)	89.1± 0.156	102± 0.542	95.4± 0.129	95.7± 0.634	84.5± 0.432	85.6± 0.276	97.8± 0.467	90.1± 0.623	91.4± 0.854

The r^2 (0.9976) was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of coefficient and the mathematical sign it carries, that is, positive or negative. The positive coefficient of variable A, that is, sodium starch glycolate in case of response i.e. disintegration time indicates that as the sodium starch glycolate concentration was increased, the DT was increased. The relationship between the variables was further elucidated by using the response surface plot shown in Figure 2. A high level of factor A gave a least disintegration time. The "Pred R-Squared" of 0.9703 is reasonable agreement with "Adj R-Squared" of 0.9935. This may indicate a good fitting of the model. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 40.059 indicates an adequate signal. This model can be used to navigate the design space. The PRESS value shows 6.8025. The Model F value of 245.14 implies that the model is significant. The VIF value is 1. Details are mentioned in Table 6.

Final equations in terms of coded factors (percent drug dissolved)

$$DP = 97.9589 - 2.9116A - 2.8466B + 0.155AB - 9.3879\ A^2 + 1.2766\ B^2$$

The r^2 (0.9937) was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of coefficient and the mathematical sign it carries, that is, positive or negative. The negative coefficient of variable A, that is, sodium starch glycolate in case of response % drug dissolved indicates that as the sodium starch glycolate concentration was increased, the percent drug dissolved value was also decreased. The relationship between the variables was further elucidated by using the response surface plot shown in Figure 3. A high level of factor A gave a low value of % drug dissolved at all the levels of factor B, which indicated that the factor A has a significant negative effect on % drug dissolved. The "Pred

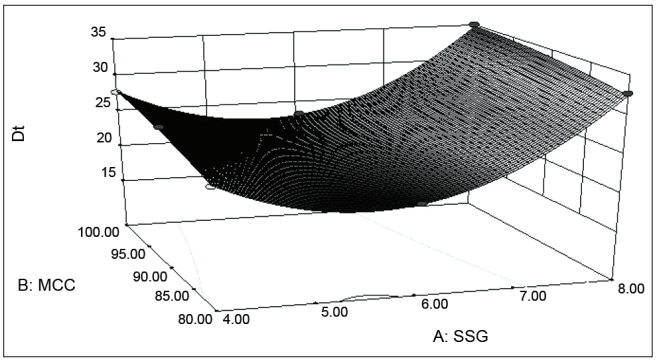

Figure 2: Response surface plot for Dt

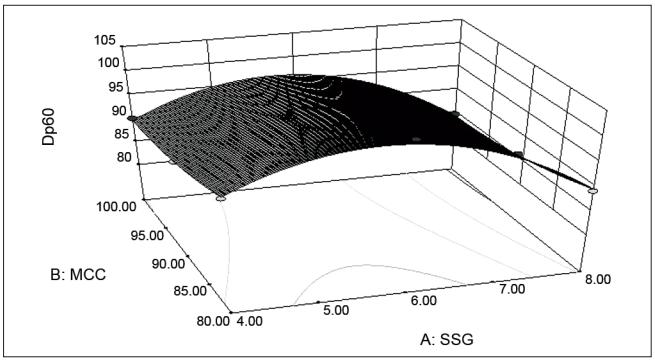

Figure 3: Response surface plot for Dp 60

Table 6: ANOVAs for DT

Source	Model	A-SSG	B-MCC	AB	A^2	B^2	Residual	Core Total
Sum of squares	228.61	84.8256	13.2016	0.3721	129.8198	0.3930	0.5595	229.1718
Degrees of freedom	5	1	1	1	1	1	3	8
Mean squares	45.7224	84.8356	13.2016	0.3721	129.8198	0.3930	0.1865	-
F value	245.1411	454.7928	70.7809	1.9950	696.0292	2.1075	-	-
P value	0.0004	0.0002	0.0035	0.2527	0.0001	0.2425	-	-
Coefficient estimates	22.2522	3.76	1.4833	-0.305	8.0566	-0.4433	-	-
Standard error	0.3219	0.1763	0.2159	0.2159	0.3053	0.3053	-	-
95% CI low	21.2277	3.1988	0.9222	-0.9922	7.0848	-1.4151	-	-
95% CI high	23.2766	4.3211	2.0444	0.3822	9.0285	0.5285	-	-
Std. Dev.	0.7667	C.V.%	0.8283	R-Squared 0.9937		Pred. R-Squared 0.9242		
Mean	92.5577	PRESS	21.2629	Adj. R-Squared 0.98323		Adeq-Precision 28.4789		

Table 7: ANOVAs for Dp 60

Source	Model	A-SSG	B-MCC	AB	A^2	B^2	Residual	Core Total
Sum of squares	278.75	50.8668	48.6210	0.0961	175.9063	3.2597	1.7635	280.5136
Degrees of freedom	5	1	1	1	1	1	3	8
Mean squares	55.75	50.8668	48.6219	0.0961	175.9063	3.2597	0.5878	-
F value	94.8374	86.5305	82.7102	0.1634	299.2376	5.5452	-	-
P value	0.0017	0.0026	0.0028	0.7131	0.0004	0.0999	-	-
Coefficient estimates	97.9588	-2.9116	-2.8466	0.155	-9.3783	1.2766	-	-
Standard error	0.5714	0.3130	0.3130	3.833	0.5421	0.5421	-	-
95% CI low	96.1402	-3.9078	-3.8428	-1.065	-11.1037	-0.448	-	-
95% CI high	99.7777	-1.9155	-1.8505	1.3705	-7.6529	3.0020	-	-
Std. Dev.	0.7667	C.V.%	0.8283	R-Squared 0.9937		Pred. R-Squared 0.9242		
Mean	92.5577	PRESS	21.2629	Adj.R-Squared 0.98323		Adeq-Precision 28.4789		

R-Squared" of 0.9242 is in reasonable agreement with the "Adj R-Squared" of 0.9832. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 41.007 indicates an adequate signal. This model can be used to navigate the design space. The PRESS value is 21.2629. The Model F value of 94.84 implies the model is significant. The VIF value is 1. Details are mentioned in Table 7.

CONCLUSION

In the present study, amlodipine besylate 10 mg tablets have been formulated and developed using direct compression technique, to provide a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects. The results suggest that suitably formulated immediate release tablets of amlodipine besylate with a superdisintegrants (sodium starch glycolate and microcrystalline cellulose) can be achieved by factorial design method.

The independent variables exhibited a good response on the dependent variables to produce an effective formulation. Thus, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy, and patient compliance.

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