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Research Article

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Formulation and development of Atorvastatin Calcium and Ramipril bilayer tablet

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ABSTRACT

The present investigation deals with preparation of bi-layer tablets of model drug atorvastatin calcium(ATC) and ramipril (RA) and to determine the influence of the certain excipients on physical properties of the tablet. Wet granulation technique was used because of its ease of access and contains limited number of unit operations. Ac-disol and PVP K30 were used as disintegrant and binder respectively. Employing a 3² factorial design, the joint influence of two formulation variables like disintegration time and percent drug release were determined. The drug excipient compatibility studies were performed by physical observation and DSC. The multiple linear regression analysis was used to find the effect of these variables on physical properties of final formulation. Finally, a checkpoint batch is prepared to prove the validity of evolved method. Using the contour plot, effect of the independent variables on the responses was represented graphically. The stability studies of the optimized formula were carried as per ICH guidelines.

Keywords: Atorvastatin Calcium, Ramipril, bilayer tablet

INTRODUCTION

The aim of the proposed research was development of the bi-layered tablet containing atorvastatin calcium (ATC) and ramipril (RA) as model drug for cardiac patients. Atorvastatin (ATC), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, is a plasma lipid-regulating agent. ATC has therapeutic application in hyperlipidemia and cardiovascular events(1). Ramipril is chemically (2S,3aS,6aS)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2yl] amino}propanoyl octahydrocyclopenta [b] pyrrole -2-carboxylic acid. lowers the production of angiotensin II mainly used for the hypertension, Congestive heart failure, following myocardial infarction in patients with clinical evidence of heart failure (2). Bi- layered tablet refer to tablet containing subunits that may be either the same (homogenous) or different (heterogeneous). Bi-layered tablet allows for designing and modulating the dissolution and release characteristics. Bi-layered tablets are prepared with one layer of drug for immediate release wile second layer designed to release drug, later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential for release of two drugs in combination, separate two incompatible substances. Bilayered tablets are preferred when profiles of the drug are different from one another (3). The study was intended to select the best possible diluents, disintegrants and the binder combination to formulate the bi-layer tablets among all the diluents, disintegrants and binder used. Finally the impact of the binder ratio and disintegrant on various properties of the tablet were also determined by using 3^2 full factorial design method (4). The basic approach in the development of the bi-layer tablet is the use of disintegrant croscarmellose sodium (Ac-Di-Sol, Asahi Kasei Co., Ltd., Japan), is disintegrant used globally (5) and PVP K30 as the effect of binding agent on the physical characteristics i.e. granule size, bulk density and angle of repose etc (6). In this study, the above mentioned disintegrant and binder are selected and best combination was selected for further studies. The wet granulation technique was decided to adopt to prepare bi-layer tablets in an easy and comfortable way although it requires a series of unit operations (7).

EXPERIMENTAL SECTION

Materials

Atorvastatin calcium, butylated hydroxyl anisole, was obtained as a gift sample from Dr. Reddys Laboratory (Hyderabad, India). Ramipril was obtained as a gift sample from Lupin Laboratory (Pune, India). Crosspovidone, SSG, crosspovidone, crosscarmellose sodium, PVP K30, aerosil, microcrystalline cellulose, magnesium stearate, Iron oxide red. All reagents used in these experiments were analytical grades available from commercial sources and all solutions were prepared with the purified water.

Experimental design

The face centered, central composite design contains an imbedded factorial design with centre points. It is used to find the best set of values, for a set of factors, giving an optimal response. In this mathematical approach the design helps in exploring quadratic surface responses where each experimental response (Y) can be represented. A polynomial model developed based on the regression analysis of the statistically significant variables enables the study of the effects of each factor (X) and their interaction over the considered responses (Y) and hence can be used to predict responses of disintegration time (Y₁) and percent drug release (Y₂) values for bi-layer tablets. Comparison of predicted values for Y1, and Y2 with experimental data was used to test validity of the models. The independent factors, their levels and the analysed dependent responses are shown in Table 1 to 4. The matrix of the face-centred central composite design (CCD) is outlined in Table 3. Each row in the matrix represents an experiment and each experiment presents a set of results, which include the 2 responses or dependant variables studied. The selected levels are within practical use and were chosen to have a measurable effect on the responses. The amount of disintegrating agent (ac-di-sol, X₁) and the binding agent (PVPK30, X₂) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses (8).

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2,$$
(1)

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1 . The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed (9).

Preparation of bi-layer Tablets

For the drugs atorvastatin calcium (ATC) and ramipril (RA), disintegrant and binder were added in different percentage concentrations. The bi-layer tablets were prepared by wet granulation method. Firstly Sifted lactose monohydrate and microcrystalline cellulose, ac-di-sol and drug one after another sieve of mesh size 30 and mixed them. PVP K30 was dissolved in purified water. The bulk of above mixture was granulated with the binder solution of PVP (K30). Then passed the wet mass through mesh size 16 and dried the wet granules in fluidized bed dryer at 60-65°C. After that passed the dried granules through were passed through mesh size 22 and then 40. Finally the granules were mixed with the sifted aerosil, magnesium stearate and remaining quantity of ac-di-sol. The tablets were compressed at poor hardness (1-2 Kg) for the first layer of tablet then granules of another layer were compressed later on to produce the final hardness (approx.10 Kg) in order to form a bi-layer tablet.

am
l

<i>S</i> .	Formulation	ATC-1	ATC-2	ATC-3	ATC-4	ATC-5	ATC-6	ATC-7	ATC-8	ATC-9
No.	Ingredient	(<i>mg</i>)	(mg)	(mg)	(m g)	(m g)	(mg)	(mg)	(mg)	(m g)
1	Atorvastatin Calcium	10	10	10	10	10	10	10	10	10
2	Lactose Monohydrate	q.s.								
3	Dibasic Calcium Phosphate	10	10	10	10	10	10	10	10	10
4	Ac di sol	4	4	4	5	5	5	6	6	6
5	PVP K30	2	3	4	2	3	4	2	3	4
6	Aerosil	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
7	Magnesium Stearate	1	1	1	1	1	1	1	1	1
8	B.H.A.	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
9	Water	q.s.								
	TOTAL	100	100	100	100	100	100	100	100	100

(3)

S. No.	Ingredient	RAMI- 1 (mg)	RAMI- 2 (mg)	RAMI- 3 (mg)	RAMI- 4 (mg)	RAMI- 5 (mg)	RAMI- 6 (mg)	RAMI- 7 (mg)	RAMI- 8 (mg)	RAMI- 9 (mg)
1	Ramipril	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Microcrystalline Cellulose pH 102	q.s.								
3	Ac di sol	4	4	4	5	5	5	6	6	6
4	PVP K30	2	3	4	2	3	4	2	3	4
5	Sunset Yellow Supra	0.15	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
6	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Magnesium Stearate	1	1	1	1	1	1	1	1	1
8	Water	q.s.								
	TOTAL	100	100	100	100	100	100	100	100	100

Table: 2 Formulation trials of ramipril

Table: 3 Factorial design studies:	3 ² Full factorial design lay out
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	Variable Level	in Coded Form	Digintegration Time	% Drug Release± SD		
Datah anda	variable Level	In Coded Form	Disintegration Time			
Batch code	$X_1^{a}(mg)$ $X_2^{b}(mg)$		DT ± SD (Min)	Atorvastatin	Ramipril	
AR ₁	-1	-1	13.77±0.07	83.75	80.68	
AR_2	-1	0	15.75±0.03	80.83	74.32	
AR ₃	-1	1	18.48±0.07	77.31	71.58	
AR_4	0	-1	9.81±0.05	90.37	85.42	
AR ₅	0	0	10.44±0.12	87.49	81.1	
AR ₆	0	1	12.15±0.15	84.03	79.31	
AR ₇	1	-1	9.33±0.09	98.26	92.14	
AR ₈	1	0	10.14±0.17	95.43	88.58	
AR ₉	1	1	10.53±0.08	92.02	86.89	
Check Point	-0.2	0.8				

 $^{{}^{}a}X_{1}$ and ${}^{b}X_{2}$ are independent variable representing the concentration of binder and disintegrant in the coded values. Y_{1} and Y_{2} are the dependent variables representing the responses like Disintegration time and % drug release. All the values of Y_{1} and Y_{2} are the taken from the following table.

Table: 4 Coded values and actual values of X1 and X2 variables

Coded Volues	Actual Values			
Could values	X ₁	X ₂		
-1	4	2		
0	5	3		
1	6	4		

Compatibility studies of drugs with formulation excipients

Based on the literature search and the scientific knowledge it was decided to use the following excipients (as listed in table) for compatibility studies. The drug was triturated with each excipient in specific ratio in a glass vial (with and without addition of 20% moisture i.e. water). Vials containing pure drug and pure excipient (sample code-P) were also prepared to be studied as reference. These vials were subjected to accelerated storage of 50° C for three weeks and were observed for any significant physical change. Description test was carried out for initial as well as three week samples kept at 50° C (10).

Pre-compression parameters(11)

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula

$$tan \theta = h/r$$
 (2)
Therefore

 $\theta = tan^{-1} h/r$

Where, θ is Angle of repose h = height of cone r = radius of cone

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Bulk Density

Density is defined as mass per unit volume.

Bulk density, ρb , is defined as the mass of the powder divided by the bulk volume and is expressed as g/cm³. It depends upon particle size distribution; particle shape and the particle adhere together.

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk density was calculated using the formula

$$\rho b = M / V b \tag{4}$$

Where, Vb is bulk volume, M is the weight of the powder.

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. Data are shown in table 4.25 & 4.26. The tapped density (Vt) was calculated using the formula.

$$\rho t = M / V t$$

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows. $I = (\rho t - \rho b) / \rho t \times 100$ (6)

Where ρt = Tapped density, ρb = bulk density.

The value below 15% indicates a powder which usually gives good flow characteristics; where above 25% indicates poor flowability.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner ratio = $\rho t - \rho b$

Where pt is tapped density and pb is bulk density.

Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25)

LOD

The LOD of the granules was determined using an IR moisture analyzer. The granules were loaded into an aluminum sampling pan. Approximately 1 gram of sample was loaded in each case. The sample was heated at 105°C for 10 minutes. The percentage LOD was recorded for each batch.

Post-compression parameters include (12)

Thickness

The thickness of a tablet was the only dimensional variable related to the process. At a constant compressive load, tablet thickness varies with changes of die fill, particle size distribution, mixing, size of granules and the tablet weight. Tablet thickness was tested for batch-to-batch consistency. Twenty tablets were selected in a batch for the determination of thickness variation with vernier caliper. All readings should be taken in triplicate and determine its average.

Hardness

Adequate hardness is necessary to withstand the mechanical shock of manufacturing packaging and shipping, and to ensure consumer acceptance. Hardness of tablet relates to both disintegration and drug dissolution. Some tablets which are intended to dissolve slowly are made hard whereas others intended to dissolve rapidly are made of low hardness. Hardness of tablet was determined using ewereka hardness tester. The tablet was compressed between a holding ansil and a piston, and digital screen showed result.

(5)

(7)

Friability

Hardness of tablet is not a suitable indicator of strength because some formulations when composed into very hard tablets tend to 'Cap' on attrition, losing their crown portions. Friability of the tablets was determined using an Electrolab friabilator. This device subjects that tablet to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed twenty tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets were de-dusted using a soft muslin cloth and reweighed. The difference in weight before and after the run provides a measure of tablets friability and was calculated as follows:

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% Friability = (Initial weight - Final Weight)/(Initial Weight) X100 (8)
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Conventional tablets more than 0.5 - 1.0 % of their weight is generally considered acceptable.

Weight Variation

The weight of the tablet was measured with the help of digital electronic balance for confirming that tablet contained the specific amount of drugs. For determination of weight variation of tablets, twenty tablets were selected randomly from a batch and average weight was determined. The weight of tablet was 200 mg (100 mg + 100 mg). The individual tablets were weighed and was compared with average weight.

In vitro dissolution studies: *In vitro* dissolution studies for fabricated bi-layer tablet is carried out by using USPXX III Type II (Electro Lab dissolution tester) dissolution apparatus at 50 rpm in 900 ml of phosphate buffer pH 6.8 as dissolution media, maintained at 37 ± 0.5 °C. Bi-layer tablet of desired formulation were taken and placed in the vessels of dissolution apparatus. Sample of 10 ml were collected from the vessels at specified time intervals 5, 10, 15, 30, 45 and 60 min filtered and determined by simultaneous estimation in UV spectroscopy as described in the following procedure. Drug concentration was calculated from the standard and expressed as percentage of drug dissolved or released (13).

Stability Studies

These studies were performed for 1, 2, and 3 month's duration. The selected formulations were subjected to accelerated temp and humidity (40°C and 75%RH) in HDPE bottles. After each month dissolution profile, drug assay, and physical changes like colour, and aggregation were recorded. This will show the physical as well as chemical stability of the prepared formulation (ICH guidelines) (14).

RESULTS AND DISCUSSION

Drug excipient Compatibility studies: The endothermic peak of API was well retained in the DSC thermogram. From this it can be conclude that atorvastatin calcium and ramipril were found to compatible with excipients.

DSC

mW





Thermal Analysis Result

Figure: 1 DSC of (a) ATC, (b)-ac-di-sol, (c)- ATC and ac-di-sol





Figure: 3 DSC of (a) Ramipril, (b)-PVPK30, (c) Ramipril and PVPK30



Figure: 4 DSC of (a) Ramipril, (b)-AcDiSol, (c)- Ramipril and acdi-sol

Pre-compression study

The blend of ATC before compression were evaluated for angle of repose, bulk density, hausner's ratio, carr's index and %LOD as observed in table 5. The angle of repose was found to be in the range 21.80° to 33.13° which indicates good flow property. The hausner's ratio (1.08 to 1.24) and carr's index (8.24 to 17.56) were calculated and indicated the excellent flowability.

Table: 5 Pre-compression parameters of the preliminary bat	tches of atorvastatin calcium
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Formulation	Angle of Repose (°)	Bulk density (mg/ml)	Hausner's ratio	Carr's index	% LOD
ATC-1	25.35±0.21	0.428±0.12	1.09±0.2	8.74±0.24	1.05±0.15
ATC-2	26.80±0.22	0.447±0.15	1.16±0.26	13.70±0.6	1.06 ± 0.31
ATC-3	27.76±0.14	0.468 ± 0.26	1.16±0.3	14.28 ± 0.45	1.26±0.22
ATC-4	30.50±0.22	0.416±0.18	1.21±0.25	17.46±0.51	1.50±0.15
ATC-5	33.13±0.25	0.383±0.22	1.24±0.15	11.21±0.9	1.32±0.18
ATC-6	30.50±0.23	0.356±0.3	1.21±0.4	17.40±0.28	1.02±0.2
ATC-7	30.07±0.11	0.324±0.2	1.21±0.23	17.56±0.31	1.03±0.35
ATC-8	22.83±0.28	0.447 ± 0.18	1.10±0.25	9.15±0.85	1.2 ±0.26
ATC-9	21.80±0.21	0.412±0.35	1.08±0.51	8.24±0.35	1.09±0.19

Data are presented as mean \pm S.D. (n =3)

The blend of ramipril before compression were evaluated for angle of repose, bulk density, hausner's ratio, carr's index and %LOD as observed in table 6. The angle of repose was found to be in the range 21.13° to 30.50° which indicates good flow property. The hausner's ratio (1.04 to 1.21) and carr's index (8.24 to 17.56) were calculated and indicated the excellent flowability.

Table: 6 Pre-compression	parameters of	the preliminary	batches of	ramipril
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Formulation	Angle of Repose (°)	Bulk density (mg/ml)	Hausner's ratio	Carr's index	% LOD
RAMI-1	25.35±0.21	0.428±0.11	1.09±0.12	8.74±0.24	1.05±0.1
RAMI-2	26.80±0.22	0.447±0.15	1.16±0.16	13.70±0.60	1.06±0.12
RAMI-3	27.76±0.14	0.468±0.21	1.16±0.3	14.28±0.42	1.26±0.23
RAMI-4	30.50±0.22	0.416 ± 0.17	1.21±0.22	17.46±0.52	1.50±0.11
RAMI-5	21.13±0.25	0.383±0.24	1.04±0.15	12.21±0.19	1.32±0.13
RAMI-6	30.50±0.23	0.356 ± 0.35	1.21±0.43	17.40±0.28	1.02±0.15
RAMI-7	30.07±0.10	0.324±0.22	1.21±0.28	17.56±0.11	1.03±0.35
RAMI-8	22.83±0.28	0.447±0.35	1.10±0.15	9.15±0.80	1.20±0.29
RAMI-9	24.80±0.21	0.412±0.39	1.08±0.22	8.24±0.30	1.09 ±0.18

Data are presented as mean \pm S.D. (n =3)

The blends were compressed and tablets were evaluated for weight variation, diameter, thickness, hardness, % friability and disintegration time as observed in table 7. The weight variation was found to be within the range of 0% to 5%. The diameter and thickness were found to be uniform. Hardness was found to be in the range of 10.05 to 11.09 kg/cm². The % friability was found to be in the range of 0.19% to 70%. The disintegration time was observed

with in the 18.48 minutes. The results indicate good correlation with the pharmacopoeial limits for all the atorvastatin calcium-ramipril (AR) combination.

Formulations	weight variation	Diameter	Thickness	Hardness	Friability	Disintegration
Formulations	(200mg)	(mm)	(mm)	(kg/cm ²)	(%)	Time(min)
AR_1	197.97±1.57	8.01±0.02	3.03±0.06	10.05±0.72	0.60 ± 0.07	13.77±0.07
AR_2	198.98±1.65	8.03±0.03	3.06±0.01	11.09±0.75	0.19±0.09	15.75±0.03
AR 3	198.59±1.85	8.05±0.01	3.02±0.03	10.39±1.36	0.67±0.15	18.48±0.07
AR_4	198.18±1.74	8.05±0.04	3.04±0.07	10.28±1.25	0.70 ± 0.05	9.81±0.05
AR 5	197.96±1.54	8.04 ± 0.05	3.08±0.06	10.35±1.20	0.61±0.04	10.44±0.12
AR ₆	199.18±1.41	8.02±0.01	3.10±0.09	10.45±1.09	0.41 ± 0.09	12.15±0.15
AR ₇	197.99±2.45	8.03±0.03	3.08 ± 0.08	10.28 ± 1.12	0.67 ± 0.05	9.33±0.09
AR ₈	199.46±1.45	8.04±0.03	3.05±0.08	10.15±2.06	0.34 ± 0.07	10.14±0.17
AR ₉	198.89±1.55	8.01±0.02	3.16±0.08	10.05±2.02	0.25 ± 0.09	10.53±0.08

Table 7: Post-compression parameters of the preliminary batches of formulation

Data are presented as mean \pm S.D. (n =3)

In-vitro drug release studies:

The dissolution data obtained for all formulations at pH 6.8 were plotted in accordance with the zero-order equation i.e. percent dissolved as a function of time (Figure 5-8). An ideal formulation should contain polymers and diluents at amounts as little as possible, as well as releasing its content release profile over a reasonable length of time, preferably with zero-order kinetics. Release kinetics was determined by multiple coefficients (R²) for individual formulation (Table 8 and 9). It is evident from Figure 2 and Table 3 that a linear relationship was obtained with r value close to unity for all formulations showing that drug release mechanism was mainly zero-order since it had a higher "R²" value for the whole release process. The zero-order rate describes systems where drug release rate is independent of drug concentration. The diffusional exponent of batches A1 and A9 imply that the drug release was case II or zero-order transport. Formulation A7 is following zero order as well as first order kinetics. For systems exhibiting case II transport, the dominant mechanism for drug transport is due to polymer matrix relaxation. The diffusional exponent of batches A1, to A9 indicates non-Fickian type of release mechanism, meaning that drug release couples Fickian diffusion with polymer matrix relaxation - so-called anomalous diffusion - and may indicate that drug release is controlled by more than one process.



Figure: 5 Zero Order % Release of ATC in Formulation AR₁-AR₄



Figure: 6 Zero Order % Release of ATC in Formulation AR5-AR9



Figure: 7 Zero Order % Release of Ramipril in Formulation AR₁-AR₄

 Table: 8 Release kinetics summary of various dissolution models: zero order, first order, Higuchi, Hixon-Crowel of ATC in formulation

 AR1-AR9

Essential diam Carla	R ² For						
Formulation Code	Zero Order	First Order	Higuchi	Hixson-Crowell			
ATC-1	0.993	0.964	0.757	0.980			
ATC-2	0.996	0.973	0.873	0.976			
ATC-3	0.997	0.983	0.920	0.975			
ATC-4	0.992	0.966	0.857	0.983			
ATC-5	0.992	0.972	0.918	0.982			
ATC-6	0.988	0.990	0.968	0.941			
ATC-7	0.987	0.995	0.984	0.942			
ATC-8	0.992	0.993	0.980	0.955			
ATC-9	0.989	0.995	0.995	0.951			



Figure: 8 Zero Order % Release of Ramipril in Formulation AR5-AR9

 Table: 9 Release kinetics summary of various dissolution models: zero order, first order, higuchi, hixon-crowel of ramipril in formulation AR1-AR9

Formulation Code	R ² For			
	Zero Order	First Order	Higuchi	Hixson-Crowell
RAMI-1	0.993	0.965	0.878	0.976
RAMI-2	0.990	0.951	0.826	0.992
RAMI-3	0.994	0.959	0.784	0.986
RAMI-4	0.990	0.991	0.991	0.969
RAMI-5	0.991	0.973	0.955	0.979
RAMI-6	0.994	0.975	0.935	0.981
RAMI-7	0.989	0.994	0.990	0.951
RAMI-8	0.995	0.994	0.989	0.964
RAMI-9	0.990	0.994	0.984	0.950





Figure: 9 Contour plot of disintegration time for formulation AR

Figure: 10 Surface plot of disintegration time for formulation AR

Experimental Design Analysis:

Three-dimensional (3D) plots and Contour plots for the measured responses were formed, based on the model polynomial functions to assess the change of the response surface. Also the relationship between the dependent and independent variables can be further understood by these plots. Since the model has two factors, one factor was held constant for each diagram; therefore, a total of 2 response surface diagrams was produced one for each response.

Response surface plots are presented using optimal levels of the factors studied. Considering the greatest difference in model polynomial functions response, the surface plots for responses Y_1 (Disintegration Time) and Y_2 (% Drug Release) are further presented (Figures 9-14). In Figure 10 (Right), response surface plots (3D) showing the effect of concentration of disintegrant (X_1) and ratio of binder (X_2) on the response Y_1 (Disintegration time of formulation AR) and in figure 12 and figure 14, response surface plots (3D) showing the effect of concentration of disintegrant (X_1) and ratio of binder (X_2) the response Y_2 , respectively are presented. The influence of concentration of disintegrant (X_1) and ratio of diluents (X_2) are presented.

As the concentration of disintegrant increased, the disintegration time is reduced and the percentage drug release was also increased the response where the disintegration time is least found that the tablets are dispersible and hence optimum disintregration time less than 15 min was chosen for further study. the other variable X_2 amount of binder had considerable interaction with disintegrant (X_1) was found significant (figure: 9-14) showing that as the amount of binder increased the disintegration time was also increased.





Figure: 11 Contour plot of % Drug Release of ATC in formulation AR

Figure: 12 Surface plot of % Drug Release of ATC in formulation AR



Figure: 13 Contour plot of % Drug Release of ramipril in formulation AR



Figure: 14 Surface plot of % Drug Release of ramipril in formulation AR

CONCLUSION

By the application of the 3^2 factorial design three-dimensional (3D) plots and contour plots for the measured responses it is confirmed that out of the 9 formulation prepared the batch AR₇ is showing the best with the drug release and the disintegration time as the dependent variable, Ac-di-sol and PVP K30 as the independent variable. Thus the ANOVA study of the linear regression model, response surface plot as well as contour plot confirms the predicted batch with the desirability of 0.992. This conclude that the use of Ac-di-sol with 6 mg as disintegrating agent and the PVP K30 as binder with 2 mg in formulation will give the best formula for the bi-layered tablet.

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