STUDY OF DIFFERENT TECHNIQUES ON DISSOLUTION ENHANCEMENT OF AMBRISENTAN FROM IMMEDIATE RELEASE TABLET

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ABSTRACT:

In present study tablets were prepared with different techniques like direct compression and wet granulation and were evaluated for drug release. The drug release profile was compared with marketed product. Saturation solubility studies were performed for dissolution media selection. Tables with direct compression showed compression issues due to poor flow nature of blend. Tablets prepared with wet granulation process showed significant improvement in drug release when compare with marketed product. Full factorial design of experiments was conducted to find out effect of significant factors influencing the drug release. The characteristic 2Theta peaks of Ambrisentan API were observed at 8.898 (94.16% Relative Intensity) and 12.320 (100 % Relative Intensity), while in formulation the characteristic 2Theta peaks of Ambrisentan were observed at 8.971 (2.90 % Relative Intensity) and 12.376 (3.35 % Relative Intensity). This indicates that the cystallinity of drug is decreased in formulation.

KEYWORDS: Poor flow, wet granulation, drug release, stability, particle size, Ambrisentan.

INTRODUCTION

Oral route of drug delivery is the widely preferred route with respect to ease of administration and patient compliance. Majority of the discovered new chemical molecules are either poorly aqueous soluble or poorly permeable or both. The formulation development of these poorly soluble drugs or poorly permeable drugs is very challenging [1, 2]. More specifically developing immediate release dosage forms for these poorly soluble molecules is still more difficult task to perform. Among the various pharmaceutical formulations, solid dispersion is known to be one of the most effective strategies to improve the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs Solid dispersion shows a reduction in particle size and an increase in surface area of poorly water-soluble drugs, resulting in improved solubility, dissolution rate, and oral bioavailability [3, 4]. Solid dispersions are produced by co-evaporation, co-grinding methods and other methods [5,6].These methods produce very poor physical properties, such as flowability, mixing properties,

and compressibility, due to the semi-solid excipients used together in dosage form preparations which makes them unsuitable for producing commercial products[7]. In the present study, conventional wet granulation technique with different hydrophilic polymers to form a tablet which shows increased dissolution when compared with marketed product. The model drug selected for dissolution enhancement is Ambrisentan.

Ambrisentan tablets are indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. Ambrisentan is BCS Class II drug having poor solubility in water and therefore release of the drug is the rate limiting step [8.9]. Hence the objective of this study is to develop an immediate release tables of Ambrisentan using by different techniques which shows higher drug release profile when compared to marketed product in selected dissolution medium[10,11].

MATERIAL AND METHODS:

Materials

Ambrisentan was obtained as a gift sample from Glenmark Pharmaceuticals Limited, Mumbai. Microcrystalline cellulose was obtained as gift sample from DuPont. Lactose monohydrate and sodium starch glycollate were obtained as gift sample from DFE Pharma. Polyethylene glycol 6000 was obtained as gift sample from BASF. Hydroxypropyl cellulose was obtained as gift sample from Ashland. Magnesium stearate and Colloidal Silicon Dioxide were obtained as gift samples from Roquette and Evonik respectively.

Saturation solubility studies:

Saturation solubility studies of Ambrisentan were carried out in different aqueous media (Water, 0.1 NHCL, 4.5 Acetate buffer and 6.8 phosphate buffer)

In vitro drug release studies:

In-vitro dissolution studies of Ambrisentan tablets were carried out in 900 mL of Hydrochloric acid as dissolution medium using USP Type-II at 50 RPM. The temperature was maintained at 37 ± 0.5°C. 5mL aliquots were withdrawn at 10, 20, 30, 45 and 60 minutes and filtered using a 0.45µ filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 260 nm using HPLC UV detector using C18 column. Dissolution experiments were conducted in triplicate.

Dissolution of Marketed Product

Ambrisentan tablets manufactured by GSK Pharma was purchased and evaluated for dissolution profile in 900 mL of Hydrochloric acid pH 1.2 using USP Type-II at 50 RPM.

Preparation of tablets:

The tablets were manufactured with two different techniques i.e. direct compression and wet granulation techniques

Direct compression:

The compositions of formulations used in direct compression in shown in table 1. Ambrisentan has very poor flow and compressibility properties. In order to improve the flow and compressibility properties, different combinations of diluents were used.

Table 1: Formulation compositions with direct compression technique.

Ingredient	AP 1 (mg/tab)	AP 2 (mg/tab)	AP 5 (mg/tab)	AP 9 (mg/tab)
Ambrisentan	5.0	5.0	5.0	5.0
Mannitol	276.5	199.1	199.1	-
Microcrystalline cellulose	-	77.4	-	138.2
Lactose Monohydrate	-	-	77.4	138.2
Hydroxy Propyl Cellulose	3.0	3.0	3.0	3.0
Sodium starch glycollate	10.0	10.0	10.0	10.0
Magnesium stearate	2.5	2.5	2.5	2.5
Colloidal Silicon Dioxide	3.0	3.0	3.0	3.0
Total	300.0	300.0	300.0	300.0

Manufacturing process:

As per the respective compositions, ambrisentan and all the excipients except Magnesium Stearate and Colloidal Silicon Dioxide were sifted through ASTM # 40 sieve These blends were mixed for 10 minutes. To the above blend colloidal silicon dioxide sifted through ASTM #60 was added and mixed for 5 minutes. Magnesium stearate sifted through ASTM #60 sieve was then added & mixed for 3 minutes. The lubricated blend was compressed into a tablet using suitable punches and dies on a rotary tableting machine.

Wet granulation:

The compositions of formulations manufactured by wet granulation technique are shown in table 2.

Table 2: Formulation compositions with wet granulation technique

S. No.	Ingredients	AP16 mg/tab
Stage-A (Blending)		
1	Lactose Monohydrate	85.00
2	Maize starch	38.00
3	Cellulose, Microcrystalline	10.28
Stage-B (Granulation)		
4	Ambrisentan	5.0
5	Hydroxypropylcellulose	3.50
7	Isopropyl alcohol	qs
Stage-C (Blending)		
8	Sodium Starch Glycolate	7.50
9	Silica, Colloidal Anhydrous.	0.20
Stage-D (Lubrication)		
10	Magnesium Stearate	0.50
Weight of tablet		150.0

Manufacturing process:

Lactose Monohydrate, Maize Starch and Microcrystalline cellulose are sifted through ASTM 40 mesh. Hydroxypropyl Cellulose and Ambrisentan was added to Isopropyl alcohol and stirred to form a clear solution. The sifted materials (Lactose Monohydrate, Maize Starch and Microcrystalline cellulose) are loaded into GPCG 1.1 and preheated at a inlet temperature of 55°C ± 10°C till the product temperature 40°C ± 10°C is achieved. Top spray granulation was performed by using the API Solution on the preheated materials. The wet granules were dried at inlet temperature at 60°C ± 10°C and product temperature at 50°C ± 10°C. The dried granules were sifted through # 40 ASTM mesh. Sifted extra-granular Sodium Starch Glycolate and colloidal silicon dioxide are added to dried granules and blended for 10 minutes. Magnesium Stearate sifted through 60 # ASTM mesh was added to the prelubricated granules and blended for 10 minutes. The Lubricated blend was compressed into tablets.

Design of Experiments

The goal of formulation development study (DoE) was to select the optimum level of formulation variables such as Cellulose, Microcrystalline, Hydroxypropylcellulose and Sodium starch glycolate (Control variables) and to understand the effect of these variables on drug product dissolution (Response factor). All the experiments were executed at lab scale by keeping the process and the batch size constant during the study.The experimental design selected was the Central Composite Design with 2 center points to screen the variables and to establish the design space. The software employed is Design Expert 8.0.7.1 (Stat Ease Inc., MN). The total tablet weight was kept constant in all the experiments.

Table 3: Details of the central composite design to evaluate the effect of formulation variables on drug product dissolution

Factors: Control Variables		Levels (mg)	
		-1 (low)	+1 (high)
A	Microcrystalline cellulose	5.0	15.0
B	Sodium starch glycolate	3.5	11.5
C	Hydroxypropyl cellulose	1.5	5.5

Physical evaluation of blend and tablets

Tablet blend was evaluated for bulk density, tapped density, hausner ratio, and compressibility index and particle size distribution.

Results and discussions

Saturation solubility studies:

The saturation solubility studies showed low solubility of Ambrisentan across pH range of 1.2 to 7.4. The solubility increases with increase in pH

Table 4: Saturation solubility of Ambrisentan in different media.

Medium	Saturation solubility (mg/ml)
Hydrochloric acid media pH 1.2	0.021±0.05
Acetate Buffer Solution pH 4.5	0.022±0.04
Phosphate buffer solution pH 6.8	1.200 ±0.21
Phosphate buffer solution pH 7.4	10.98±0.14
Water, Purified	0.017±0.04

Selection of dissolution medium.

The dissolution medium selected is 900 ml of Hydrochloric acid media pH 1.2,Type II at sampling times of 10, 20, 30, 45 and 60 minutes. This medium is selected based on the pharmacokinetics data (T_{max}) of the marketed products.

Table 5 : Flow properties of formulation compositions

Parameter	AP 1	AP 2	AP 5	AP 9
Bulk Density (g/ml)	0.39	0.41	0.39	0.38
Tapped density (g/ml)	0.55	0.57	0.56	0.52
Hausner ratio	1.49	1.46	1.51	1.37
Compressibility Index	41.0	39.0	43.6	36.8
Physical observations	Poor flow, Capping and sticking to lower punch observed	Poor flow, Sticking observed	Poor flow; Improper die filling, and Sticking observed	Poor flow; Sticking observed

As per USP general chapter ⟨1174⟩ Powder flow, Haunser ratio between 1.35 to 1.45 exhibits poor flow and 1.46 to 1.59 shows very poor flow and for compressibility index between 32 to 32 exhibits poor flow and compressibility index greater than 38 shows very very poor flow. The results obtained for directly compressed formulations indicate that the blend shows poor flow and sticking issue.

Table 6: Physicochemical properties of formulation compositions

Physical Parameter	AP 16
Bulk Density (g/ml)	0.54
Tapped density (g/ml)	0.68
Hausner ratio (g/ml)	1.26
Compressibility Index (%)	25.9

Table 7: Dissolution profile in 0.1 N Hydrochloric acid, 50 RPM, Paddle 900 ml.

Time point (minutes)	% Drug release	
	Marketed Product	AP 16
5	18	25
10	52	61
15	79	87
20	85	94
30	98	98
45	99	99
60	99	99

The drug release from the test product was found to be higher than the marketed product The following table summarizes the experimental results the design of experiment batches.

Table-8: Experimental results of DoE Trials

Batch No	Run	Factor 1	Factor 2	Factor 3	Mean cumulative %
					Response
		Microcrystalline cellulose (mg)	Hydroxypropyl cellulose (mg)	Sodium starch glycolate(mg)	Dissolution at 10 minutes
AP20	1	10.00	3.50	7.50	57.0
AP21	2	15.00	1.50	11.50	96.0
AP22	3	15.00	1.50	3.50	91.0
AP23	4	5.00	1.50	3.50	89.0
AP24	5	5.00	5.50	3.50	23.0
AP25	6	15.00	5.50	3.50	33.0
AP26	7	5.00	1.50	11.50	89.0
AP27	8	15.00	5.50	11.50	48.0
AP28	9	5.00	5.50	11.50	33.0
AP29	10	10.00	3.50	7.50	63.0
AP30	11	1.59	3.50	7.50	41.0
AP31	12	10.00	3.50	0.77	43.0
AP32	13	18.41	3.50	7.50	75.0
AP33	14	10.00	0.14	7.50	88.0
AP34	15	10.00	6.86	7.50	35.0
AP35	16	10.00	3.50	14.23	65.0

Effect of variables on dissolution at 10 minutes:

The drug release at 10 minutes time point for all the batches were in the range from 23 to 96%. The mean cumulative amount of drug released was 23% at 10 minutes when the amount of Microcrystalline Cellulose, Hydroxypropylcellulose and Sodium Starch Glycolate used 5.00 mg, 5.50 mg and 3.50 mg respectively. Whereas, the drug release was 96% when the amount of Microcrystalline Cellulose, Hydroxypropylcellulose and Sodium Starch Glycolate used 15.00 mg, 1.50 mg and 11.50 mg respectively.

The regression equation obtained for the response dissolution at 10 minutes was found to be high R-squared, adjusted R-Squared values and predicted R-squared values. The "Pred R-squared" of 0.7676 is in reasonable agreement with the "Adj R-Squared" of 0.8733. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The obtained Adequate Precision value of 15.422 indicates an adequate signal.

Table 9: Details of different statistical terms for selected model

(Response Surface Linear Model)

Parameter	Value
Standard Deviation	9.28
Mean	60.94
C.V. %	15.23
PRESS	2211.08
R-Squared	0.9004
Adjusted R-Squared	0.8733

Predicted R-Squared	0.7676
Adequate Precision	15.422

The contour plots and respective 3-D plots were shown below. The dissolution at 10 min was found to be influenced with the level of factors tested. The concentration HPC-ELF has negative effect on the dissolution at 10 minutes whereas SSG and MCC PH 101 has positive effect.

Figure 1: Contour plot for effect of MCC PH 101 and HPC ELF on dissolution at 10 minutes

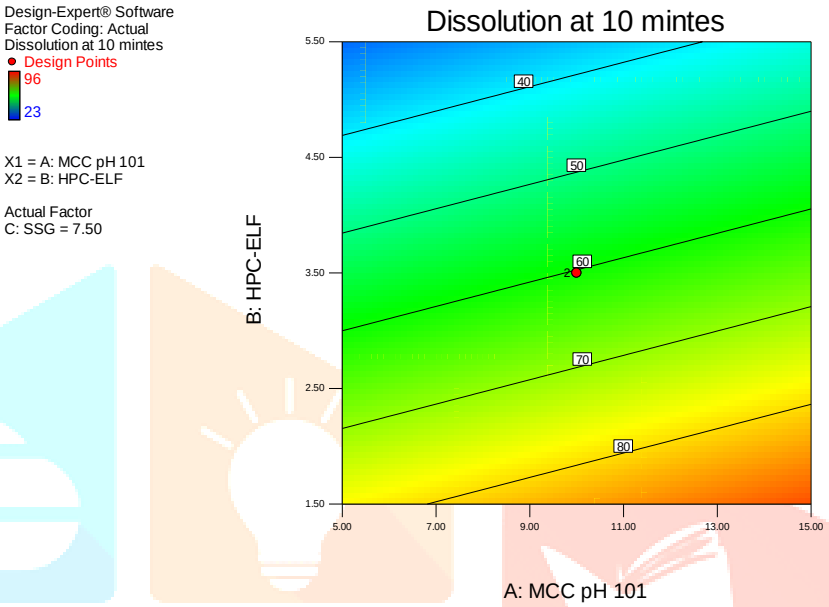


Figure 2: Model 3D graph for effect of MCC PH 101 and HPC ELF on dissolution at 10 minutes

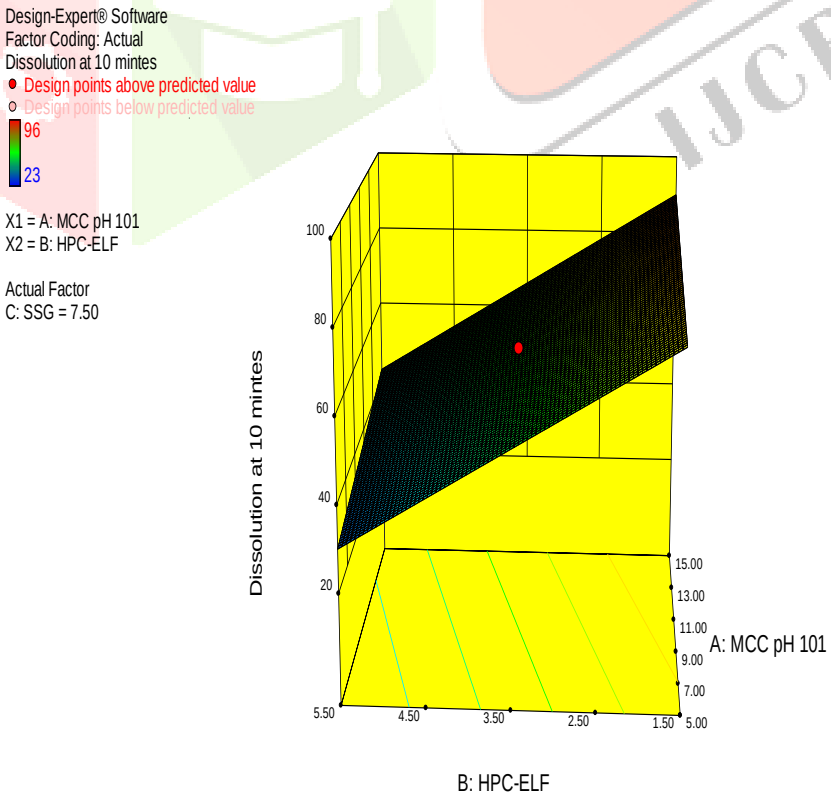


Figure 3 : Contour plot for effect of SSG and HPC ELF on dissolution at 10 minutes

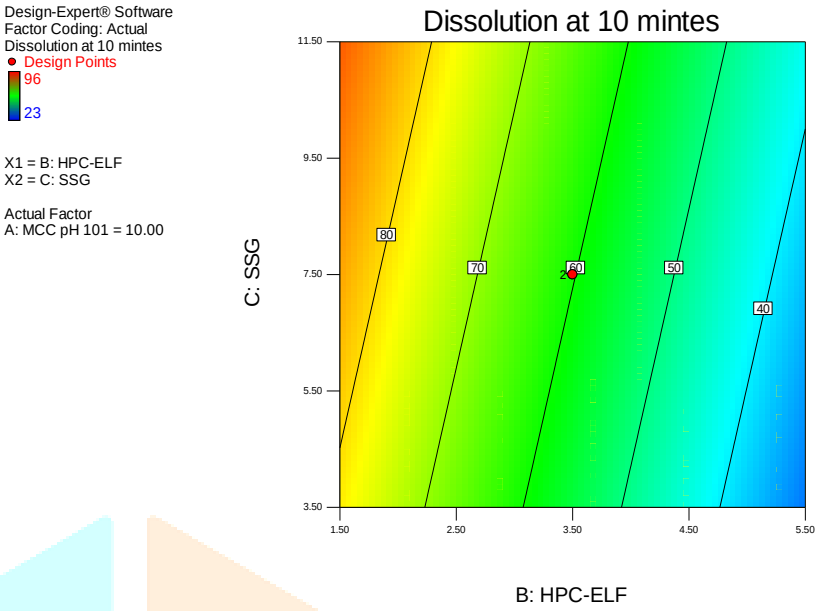


Figure 4: Model 3D graph for effect of SSG and HPC ELF on dissolution at 10 minutes

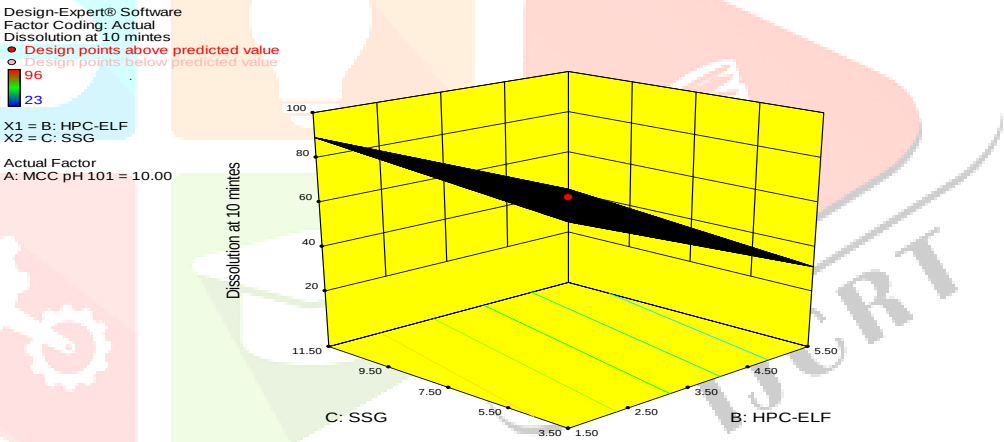


Figure 5: Contour plot for effect of SSG and MCC PH 101 on dissolution at 10 minutes

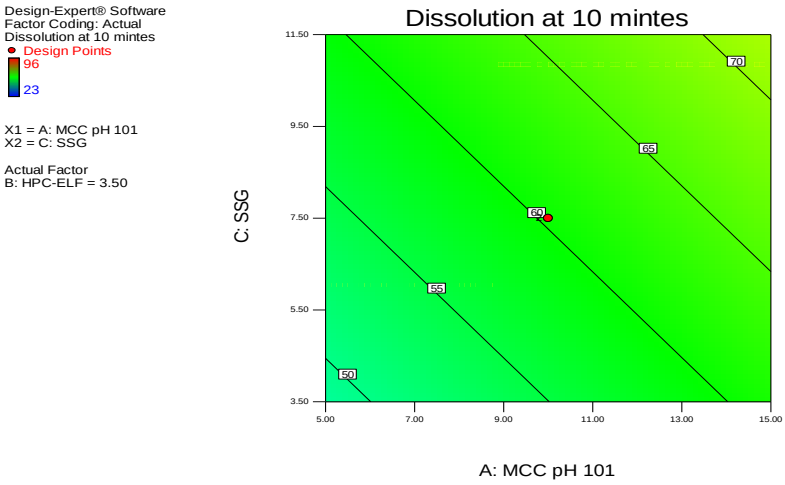
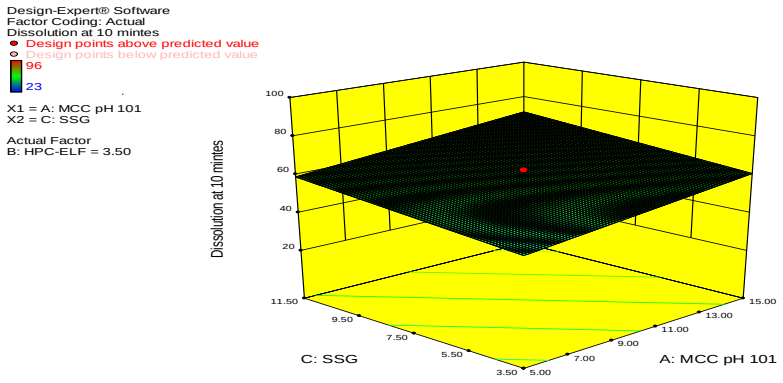


Figure 6: Model 3D graph for effect of SSG and MCC PH 101 on dissolution at 10 minutes



Final Formulation:

Based on the dissolution results from the design of experiments, the following composition was finalized.

Table 10: Final composition based on design of experiment trails

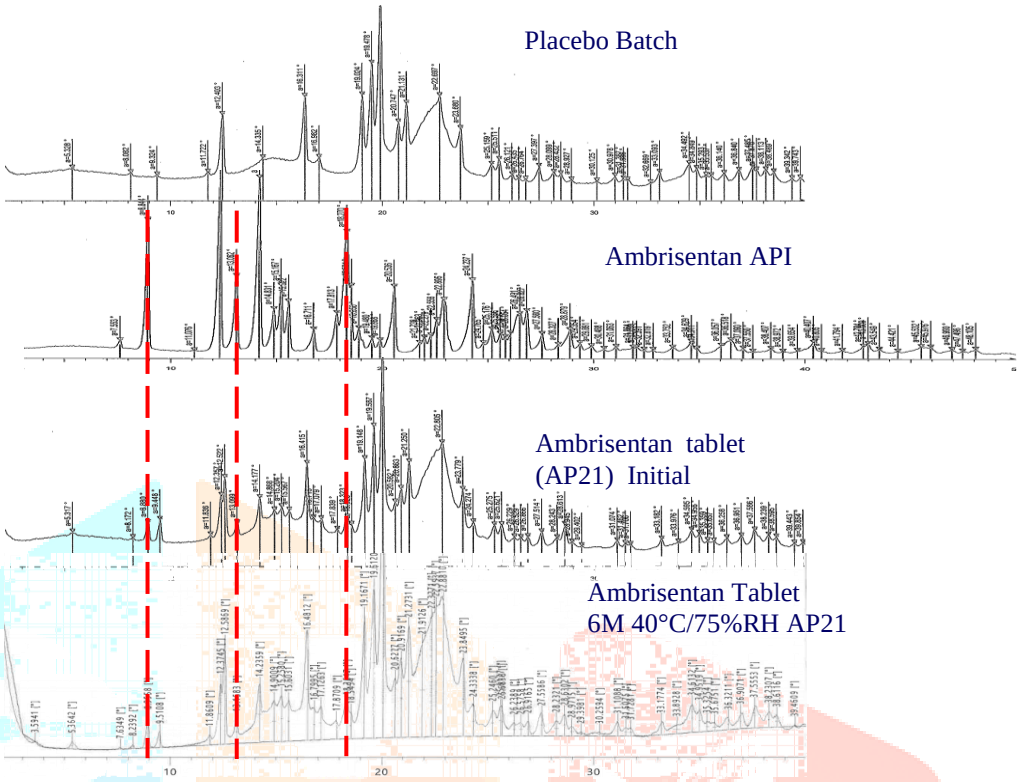
S. No.	Ingredients	AP 21 mg/tab
Stage-A (Blending)		
1	Lactose Monohydrate	92.00
2	Maize starch	38.00
3	Cellulose, Microcrystalline	15.00
Stage-B (Granulation)		
4	Ambrisentan	5.0
5	Hydroxypropylcellulose	1.50
7	Isopropyl alcohol	q.s
Stage-C (Blending)		
8	Sodium Starch Glycolate	11.50
9	Silica, Colloidal Anhydrous.	0.20
Stage-D (Lubrication)		
10	Magnesium Stearate	0.50
Weight of tablet		150.0

Table 11: Dissolution profile in 4.5 Acetate buffer, 50 RPM, Paddle 900 ml.

Time point (minutes)	% Drug release	
	Marketed Product	AP 21
5	14	21
10	45	56
15	64	69
20	76	86
30	81	94
45	89	99
60	99	99

The dissolution of the final formulation was also found to increase in 4.5 acetate buffer, when compared with marketed product.

Figure 7: Diffractogram of Placebo batch, Ambrisentan API and Ambrisentan tablets



The diffractogram of Ambresentan Tablet complies with Ambrisentan API at both Initial and on Stability and exhibits Ambrisentan API characteristic reflexes at 9.0°, 13.1° & 18.4° 2θ.

CONCLUSION:

In present study, it was found the direct compression with the studied compositions was not suitable to make tablets due to manufacturing process issues. A simple wet granulation process was tried with varying amounts of polymers and dissolution rate was found to be significantly enhanced when compared with marketed product. All the physical properties were satisfactory. Design of experiments indicate that the mean cumulative amount of drug released was 23% at 10 minutes when the amount of Microcrystalline Cellulose, Hydroxypropylcellulose and Sodium Starch Glycolate used 5.00 mg, 5.50 mg and 3.50 mg respectively. Whereas, the drug release was 96% when the amount of Microcrystalline Cellulose, Hydroxypropylcellulose and Sodium Starch Glycolate used 15.00 mg, 1.50 mg and 11.50 mg respectively. The concentration HPC-ELF has negative effect on the dissolution at 10 minutes whereas SSG and MCC PH 101 has positive effect. pXRD studies reveled that the characteristic 2theta values of ambrisentan were found in decreased intensity when compared with pure drug. This indicates that the cystallinity of drug is decreased in formulation which is contributing to get higher drug release.

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