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Formulation, Design and Evaluation of Immediate-Release Tablets of Spironolactone

Anwar Khan[1,2], Kamran Javed Naquvi[1*], Abdul Wadood Siddiqui[1], Mohsin Ali Khan[3]

[1]Department of Pharmacy, Institute of Biomedical Education and Research, Mangalayatan University, India.
[2]Department of Pharmaceutics, ERA College of Pharmacy, ERA University, India.
[3]Department of Biotechnology, Era's Lucknow Medical College and Hospital, Era University, India
Email: kjnaquvi@gmail.com

Abstract-

The aim of the current investigation is to design an immediate-release oral dosage form of Spironolactone 100 mg tablet which is indicated for the treatment of increased amounts of sodium and water to be excreted, while potassium to be retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. The objective to develop a pharmaceutically equivalent, stable, cost-effective and quality-improved formulation of immediate-release spironolactone 100 mg Tablet was established using the Qbd approach, having all the critical quality attributes within the specified limit. Spironolactone immediate-release tablet was systematically optimized using no of trial by changing the concentration of binder, disintegrant and lubricant which where the most influencing factor to impact on % drug release and disintegration time.

Mathematical modelling was performed using f1 and f2 similarity factor to check the closeness of innovator aldactone with the given generic product in all multimedia. The optimized formulation SPN1-03 was found to be of high quality following the critical quality attributes within the specified limit % drug release was found to be 95.00% in 60 min and disintegration time of 3-4 min, it was clearly observed that there is a significant impact of all three critical material attributes (disintegrant, binder, lubricant) on the quality evaluation of the product, batch no SPN1-03 was physicochemical stable when kept at stability chamber at (30ºC and 75%RH) long term for 3 month and 40ºC and 75% for 3 month.

Key words- Immediate release, Disintegrant, f1-f2 similarity factor, Lubricant, Qbd.

Introduction-

Formulation development began with QbD approach to identify the key performance attributes as well as the QTPP[1, 2]. From this quality target product profile, an initial list of critical quality attributes was identified. A risk assessment, in accordance with ICH Q9, was undertaken to identify the variables and unit operations which are most likely to impact the CQA. The development activities were then focused on these potential high risk areas. The risk assessment was starting with the physico-chemical characteristics of the API's and accompanying excipients, led to the identification of a viable formulation and manufacturing process[3,4,5].

Spironolactone belongs to the class of medications known as oral Aldosterone antagonist. It is used to increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents that act more proximally in the renal tubule [6, 7].

The development of an immediate-release (IR) formulation of spironolactone has the potential to address these challenges by enabling faster drug absorption, quicker onset of therapeutic effects, and improved flexibility in clinical use. Immediate-release tablets can also enhance patient compliance by providing a more predictable pharmacokinetic profile and simplifying dose adjustments.

This research paper aims to investigate the formulation, pharmacokinetics, and therapeutic potential of spironolactone immediate-release tablets. By addressing the limitations of existing spironolactone delivery methods, this study seeks to advance the application of this important drug, improve treatment outcomes, and expand its accessibility to a wider range of patient populations[8,9,10].

Aldosterone antagonist activity: Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy[11, 12].

Spironolactone, a potassium-sparing diuretic and aldosterone antagonist, has been widely used in clinical practice for its multifaceted therapeutic applications. Initially developed for the management of hypertension and edematous conditions such as congestive heart failure and cirrhosis, spironolactone has also gained prominence in the treatment of hyperaldosteronism, acne, hirsutism, and other off-label uses. Its mechanism of action involves competitive inhibition of aldosterone at mineralocorticoid receptors, leading to sodium excretion and potassium retention, which makes it a critical agent in conditions associated with excess aldosterone activity [13, 14, 15, 16].

Materials & Methods- Spironolactone was obtained as a free sample from Zhejiang Langhua Pharmaceutical co., ltd, China, gifted from Ind-swift Ltd Chandigarh. Calcium sulfate dihydrate was obtained from Canton Laboratories Pvt Ltd, Vadodara; Povidone was obtained from G C Chemie Pharmie Ltd. Magnesium stearate was obtained from JR Drug Chem, Gujrat, Corn starch were obtained from Ingredion Incorporated, Maharashtra. Opadry was obtained as a free sample from Colorcon, Goa.

Method- Spironolactone is BCS class II drug having low solubility. Spironolactone is having poor flow in nature due to its particle size. As the level of Spironolactone was to be kept 15.77% of total weight of core tablet similar to Innovator, and active is not free flowing, hence direct compression is not a suitable choice for manufacturing method.

To achieve better wettability leading to more dissolution, preferred manufacturing process was wet granulation process.

1. Spironolactone, Calcium sulfate dihydrate, maize starch were cosifted through sieve no 20. Sifted materials were mixed in high shear mixture.
2. Binder solution was prepared by dissolving Plasdone K29/32 in Purified water and kept aside till clear solution was prepared.
3. Binder solution and extra purified water was added to the dry mix of step no. 1 at slow impeller speed and granulated at fast speed of impeller and chopper.
4. Wet granules were dried in fluid bed dryer at inlet temperature set point 60ºC and high set point 65°C till target loss on drying was achieved.
5. The semi dried granules were passed through 10 ASTM and dried in fluid bed dryer at inlet temperature set point 60ºC and high set point 65°C till target loss on drying was achieved.
6. Dried granules were passed through sieve no. 22.
7. Peppermint flavour, dried corn starch were sifted through sieve no. 60.
8. Magnesium stearate was sifted through sieve no 60.
9. Dried and sized granules were blended with sifted peppermint flavour and dried corn starch.
10. Lubricate the above blend with sifted magnesium stearate.
11. Lubricated blend was compressed in a rotary press using round shaped concave punch

Table 1- prototype formulation of spironolactone tablet 100mg B.No (SPN1-01-03)-

Batch No & Batch Size		SPN1-01A	SPN1-01B	SPN1-01C	SPN1-02A	SPN1-02B	SPN1-02C	SPN1-03
S. No	Ingredients	mg/tab						
Intragranular Ingredients								
1	Spironolactone	100	100	100	100	100	100	100
2	Maize starch	25	25	25	50	50	50	50
3	Calcium sulphate dihydrate	436	436	436	411	411	411	411
Binder								
4	Plasdone K 29/32	20	20	20	20	20	20	20
5	Purified Water	q.s						
Extragranular Ingredients								
6	Peppermint flavour	3	3	3	3	3	3	_
7	Dried corn starch	25	0	12.5	50	18	30	50
8	Magnesium stearate	6	6	6	6	6	6	3
Total core weight		**615**	**590**	**602.5**	**640**	**608**	**620**	**634**

Difference and Similarity Factor-

Similarity factors of the various batches compared to standard. Difference and similarity factors are modelindependent approach used to estimate the dissimilarity factor (f1) and similarity factor (f2) to compare the dissolution profile of optimized formulation (F5) with innovator product. The difference between the reference and test curve at each time point and is a measurement of the relative error between two curves. The FDA suggested that two dissolution profiles were declared similar if f2 value between 50-100 and f1 was 0-15.

$f1 = \{(\sum t=\ln |Rt-Tt|) / (\sum t=\ln Rt]) \times 100$ -- Equation (1)

$f2=50 \cdot \log \{(1+\ln \sum t=\ln (Rt-Tt)\ 2)-0.5\times 100\}$ -- Equation (2)

Where, f1: Difference factor; f2: Similarity factor; n: time points; Rt: cumulative percentage dissolved at time t for the reference; Tt: cumulative percentage dissolved at time t for the test.

Micrometrics properties of drug substance-

Bulk Density and Tapped Density. Both bulk density (BD) and tapped density (TD) including compressibility index were determined as prescribed in USP42NF37. The compressibility index of the powder blend was determined by Carr's index. This can be used to predict flow properties based on density measurement. The formula for Carr's index is shown below-Hausner's Ratio (H). This expresses the flow properties of the powder and is measured by the ratio of tapped density (TD) to bulk density (BD). The powder blend was evaluated for bulk density and tapped density, compressibility index, and Hausner's ratio as described above.

Selection of dissolution media conditions- As per Guidance Dissolution Testing Of Immediate Release Solid Oral Dosage Forms, formulation should be evaluated in vitro under three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), apparatus, agitation, etc. We had selected three different dissolution media 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 for multimedia dissolution to cover whole physiological pH range.

Dissolution Apparatus- During development, Apparatus II: Paddle apparatus was selected as paddle is first choice of tablet formulation and also as per US Pharmacopoeia drug product monograph, recommended dissolution condition is USP. Apparatus II (Paddle)/1000ml/75rpm in pH 1.2 buffers (0.1N HCl) with 0.1% Sodium lauryl sulphate (w/v). Volume of Dissolution media- As per United State Pharmacopoeia drug product monograph, recommended dissolution volume 1000ml in buffer pH 1.2 buffers (0.1N HCl) with 0.1% Sodium lauryl sulphate (w/v).

Stability- As per ICH (International Council on Harmonisation) guidance, is a committee that provides the pharmaceutical stability guidelines. ICH stability guidelines for stability conditions and testing are followed throughout the world for product quality. Following is the list of ICH guidelines for stability testing- Q1A (R2) - Stability Testing of New Drug Substances and Products: This guidance is for analysis of the product for its stability in different environmental conditions. Q1C - Stability Testing for New Dosage Forms: Annex to the ICH Harmonised Tripartite Guideline on Stability Testing for New Drugs and Products.The climate is different in all the countries in the world. Stability studies of the pharmaceutical drug should be done according to the climatic conditions of the country. According to the ICH guidelines for stability studies, the climate of the world is divided into five different zones.

The whole world is divided into 5 groups according to their climatic conditions. In which india previously comes in, IV which is revised to IVb. Means for long term 30ºC ± 2ºC and 65% RH ±

5% has been updated to 30ºC ± 2ºC and 75%RH ± 5%. These stability studies zones are created due to the difference in temperature and humidity in different parts of the world. These zones have different ICH stability conditions for pharmaceutical products. Following are ICH stability conditions for these zones.Batch no-SPN1-03 was charged on stability chamber to access its shelf life for Accelerated and Long term stability analysis-

Results and Discussion-

Table 2- Physico-chemical characteristics of blend and tablet of B. No. SPN1-01A,01B, 01C, 02A, 02B, 02C, 03.

Granules-SPN1-01A				**Granules SPN1-02A**			**Granules SPN1-03**		
(at 105°C for till constant weight is achieved)		1.75% w/w		1.81% w/w			1.95% w/w		
BD		0.48 g/ml		0.62 g/ml			0.66 g/ml		
TD		0.63 g/ml		0.76 g/ml			0.815 g/ml		
CI		23.80%		18.42%			19.02%		
HR		1.31		1.23			1.23		
PSD of granules									
% cumulative									
Seive		5		11			0		
30 ASTM		14		27			17		
40 ASTM		23		43			50		
60 ASTM		29		55			64		
80 ASTM		34		60			70		
100 ASTM		100		100			100		
Uncoated Tablets									
Batch no	SPN1-01A	SPN1-01B	SPN1-01C	SPN1-02A	SPN1-02B	SPN1-02C	SPN1-03		
Appearance	White to off white colored, biconvex uncoated tablets. .								
Average weight (mg)	615.00 mg	590.00 mg	602.50 mg	640.00 mg	608.00 mg	620.00 mg	634.00 mg		
Hardness (N)	110-130 N	110-130 N	110-130 N	140-160 N	140-160 N	140-160 N	110-130 N	140-160 N	160-180 N
Friability (%)	0.1% w/w	0.1% w/w	0.1% w/w	0.1% w/w	0.1% w/w	0.1% w/w	0.1% w/w	0.12% w/w	0.1% w/w
Thickness (mm)	5.17 – 5.18 mm	4.98 – 5.01 mm	5.08 - 5.10 mm	5.16 – 5.18 mm	4.94 – 4.98 mm	5.09 - 5.12 mm	5.20 – 5.23 mm	5.10 – 5.18 mm	5.07 - 5.10 mm

Disintegration time (mins)	3 – 4.10 min	More than 15 min	12 -16 min	5.40min to 6.40min	More than 15 min	4-5.10 min	2.40 min to 3.20min	3.20min to4min	4.30min-4.40 min

Table3- Comparitive dissolution profile of Aldactone with inhouse Spironolactone Tablets USP 100mg B.No- SPN02-03

Dissolution; 0.1N HCl + 0.1% SLS 1000 ml, 75 rpm, USP II					
Time Points	% Release, PrAldactone*, B.No- W40914	% Release, SPN1-02A (Uncoated)	% Release, SPN1-02A (Coated)	B.No. SPN1-03 (Uncoated Tablet)	B.No. SPN1-03 (Coated tablet)
0	0	0	0	0	0
15	66	63	77	67	68
20	75	73	83	77	78
30	85	80	94	84	87
45	90	89	96	90	93
60	94	92	95	92	95
F2	-	75.44	55.26	88.07	79.85
F1	-	3.17	8.54	1.46	2.68

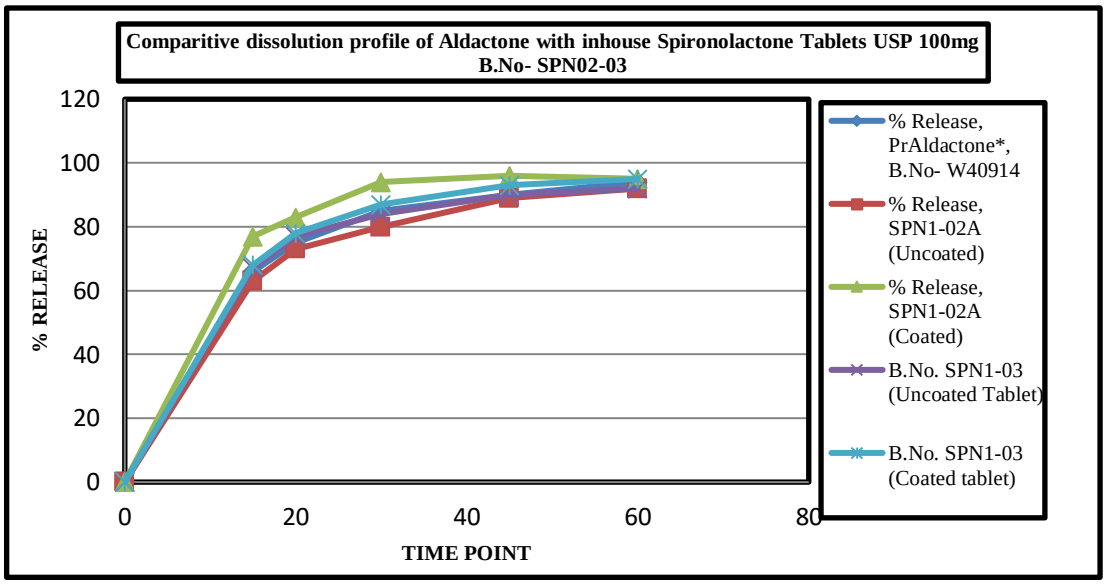

Figure1- comparitive dissolution profile of aldactone with inhouse spironolactone tablets usp 100mg b.no- spn02-03

Discussion- Physical parameters were unsatisfactory in trial SPN1-01B & SPN1-01C. Disintegration time was more than 15 min. So Next trial was planned with increased quantity of maize starch intragranularly to improve disintegration time of spironolactone tablet. All physical parameters of SPN1-02 A and SPN1-02C were satisfactory in trial. Dissolution of Uncoated and coated tablet of batch no SPN1-02 A was ok. But disintegration time of batch SPN1-02B was more than 15 min so in next trial magnesium stearate quantity will be optimized. All physical parameters of batch no SPN1-03 was satisfactory in trial. Multimedia Dissolution of coated tablet SPN1-03 vs innovator (PrAldactone* 100) was ok and were comparable.

Table 4- Dissolution profile of Spironolactone Tablets USP 100mg B.No. SPN1-03 vs Innovator (PrAldactone*) in pH 4.5 Acetate buffer using Apparatus USP II.

Dissolution; pH 4.5 acetate buffer, 1000 ml, 75 rpm, USP II		
Time Points (min)	W40914 (^{Pr}Aldactone*) % Release	B.No. SPN1-03 (Coated tablet) % Release
15	22	27
20	26	30
30	30	32
45	32	33
60	34	34
F2	-	74.78

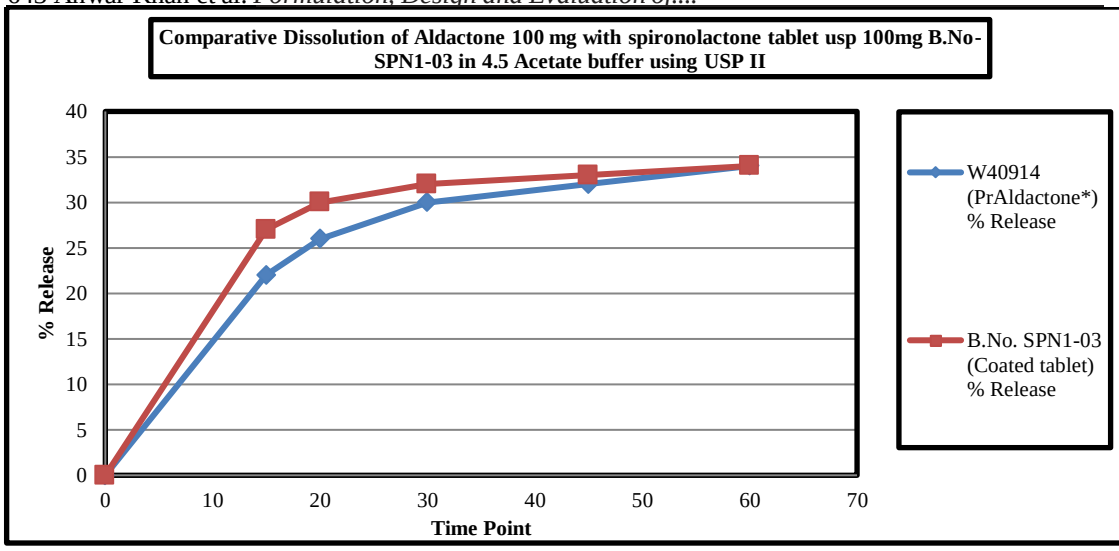

Figure 2- Graph of Comparative Dissolution profile of ^{Pr}Aldactone* 100 mg, B. No.W40913 with Spironolactone tablet USP 100mg, B. No. SPN 1-03 in pH 4.5 Acetate buffer using Apparatus USP II.

Table 5- Dissolution profile of Spironolactone Tablets USP 100mg B.No. SPN1-03 vs Innovator (^{Pr}Aldactone*) in pH 6.8 phosphate buffer using apparatus USP II.

Dissolution; pH 6.8 phosphate buffer, 1000 ml, 75 rpm, USP II		
Time Points (min)	W40914 (^{Pr}Aldactone*) % Release	B.No. SPN1-03 (Coated tablet) % Release
15	16	20
20	21	24
30	24	26
45	28	29
60	29	29
F2	-	**78.87**

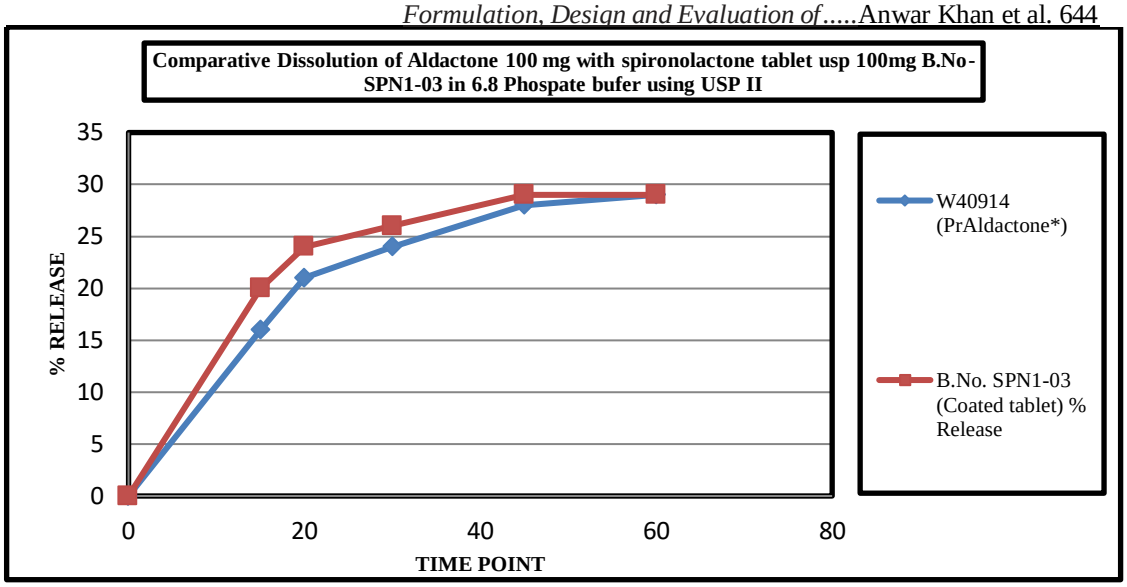

Figure 3- Graph of Comparative Dissolution profile of PrAldactone* 100 mg, B. No.W40913 with Spironolactone tablet USP 100mg, B. No. SPN 1-03 in pH 6.8 phosphate buffer using Apparatus USP II.

Table 6- Accelerated stability data of SPN1-03-

Batch no		SPN1-03-	
Storage Condition		Initial	40°C/75% RH
Time Period			3 Months
Parameters	Limit	Results	
Description	Beige colored, round shaped, film coated tablets	Beige colored, round shaped, film coated tablets	Complies
Average weight	655.02 mg ± 3% of average weight	654.6mg	657.4 mg
Resistance to crushing f tablets	For information (Target: NLT 100 N)	170-200N (5 tablet)	187, 192, 176, 184, 188 N
Disintegration Time	Not more than 30 minutes	7.30-8.20 min	6.20-7.50 min
LOD	Not more than 7% w/w	4.08% w/w	4.22% w/w
Assay* Each Film coated tablet contains: Spironolactone USP-100mg	Not less than 95.00 mg and not more than 105 mg per tablet of average mass. (95.0 % – 105.0 % of the labeled claim)	100.5%	98.8%
Dissolution Test 0.1N Hydrochloric acid+	Not less than 75 % (Q) of the labeled amount is	Time Point / % Release	% Release

0.1% SLS	dissolved in 60 minutes.	15	68	66
		20	78	75
		30	87	84
		45	93	89
		60	95	91

Table 7– Long term stability data of SPN1-03-

Batch no		SPN1-03-		
Storage Condition		Initial		30°C/75% RH
Time Period				3 Months
Parameters	Limit	Results		
Description	Beige colored, round shaped, film coated tablets	Beige colored, round shaped, film coated tablets		Complies
Average weight	655.02 mg ± 3% of average weight	654.6mg		658.4 mg
Resistance to crushing of tablets	For information (Target: NLT 100 N)	170-200N (5 tablet)		175, 186, 184, 189, 196N
Disintegration Time	Not more than 30 minutes	7.30-8.20 min		7.40-8.50min
LOD	Not more than 7% w/w	4.08% w/w		5.03% w/w
Assay* Each Film coated tablet contains: Spironolactone USP-100mg	Not less than 95.00 mg and not more than 105 mg per tablet of average mass. (95.0 % – 105.0 % of the labeled claim)	100.5%		101.05%
Dissolution Test 0.1N Hydrochloric acid+ 0.1% SLS	Not less than 75 % (Q) of the labeled amount is dissolved in 60 minutes.	Time Point	% Release	% Release
		15	68	70
		20	78	77
		30	87	85
		45	93	89
		60	95	97

Table 8-Comparative dissolution profile of Aldactone 100 mg with spironolactone tablet USP 100 mg Batch no- SPN1-03 at initial, accelerated and long term stability studies-

Time Point	W40914 (^{Pr}Aldactone*)	SPN1-03 (initial)	SPN1-03 (30ºC and 75%RH 3 month)	SPN1-03 (40ºC and 75%RH 3 month)
0	0	0	0	0
15	67	68	66	70
20	77	78	75	77
30	84	87	84	85
45	90	93	89	89
60	92	95	91	97
f2 (Similarity Factor)		79.19	90.49	77.15
f1 (Difference Factor)		2.68	1.22	2.44

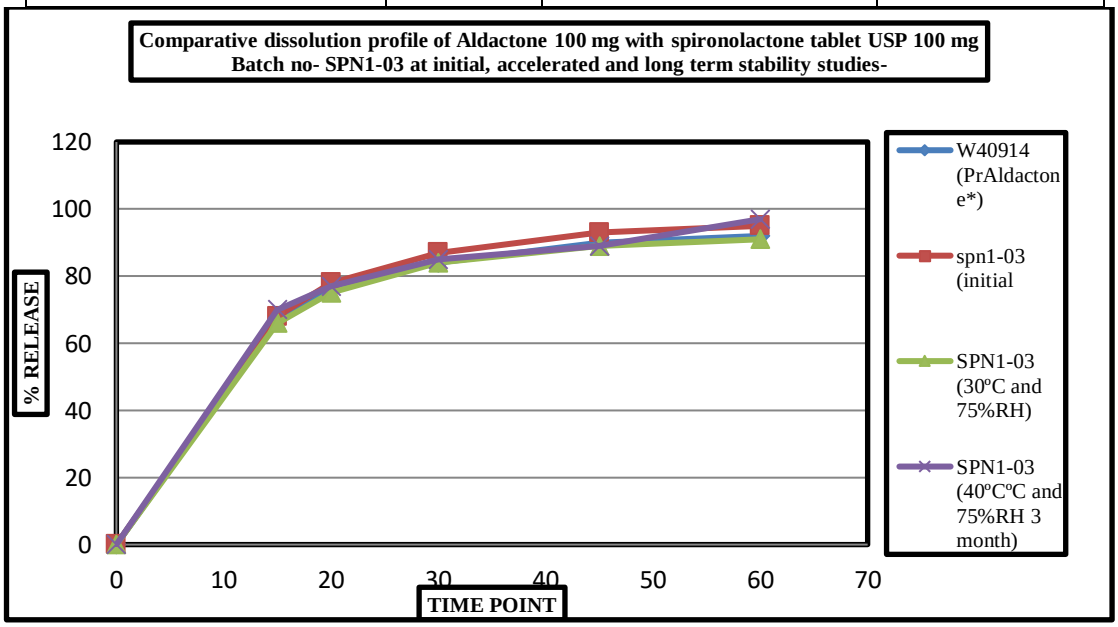

Figure 4- Comparative dissolution profile of aldactone 100mg with SPN1-03 at Initial accelerated and long term stability study.

Conclusion- All physical parameters of batch no SPN1-03 was satisfactory in trial. Multimedia Dissolution of coated tablet SPN1-03 vs innovator (PrAldactone* 100) was ok and were comparable.

All the initial testing of batch SPN1-03 showed that the formulation composition and manufacturing process were satisfactory. Results of complete finished product specifications were within limit & comparative multimedia dissolution profile was also comparable to PrAldactone* 100mg tablets. All the physico-chemical parameter of Batch no has been evaluated and are within limit, the batch no-SPN1-03 was also proof stable over (30ºC and 75%RH) long term for 3 month and 40ºC and 75% for 3 month.

The invitro dissolution profile is also matched with aldactone with similarity factor more than 50 and difference factor less than 15 in both long term and accelerated stability condition.

Conflict of Interest- The authors have no conflicts of interest regarding this investigation.

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