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FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF MUSCARINIC RECEPTOR ANTAGONIST USING VARIOUS GRADES OF LACTOSE MONOHYDRATE AND API PSD TO STUDY IMPACT ON FLOW PROPERTIES AND DISSOLUTION OF DRUG PRODUCT

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ABSTRACT

Solifenacin succinate is a competitive muscarinic receptor antagonist. Solifenacin succinate is used to treat overactive bladder by relaxing the muscles in the bladder which improves the ability control the urination urge, urinary incontinence and increased urinary frequency in elderly patients. Solifenacin succinate belongs to the class of drug known as antispasmodics. Solifenacin succinate 10mg immediate release tablet formulation is prepared by direct compression strategy using the suitable excipients. During formulation development study, three different grades of lactose monohydrate and two lots of drug substances having different particle size distribution have been evaluated. Different grades of lactose monohydrate and PSD of drug substance ranging from d_{90} – 40 µm to 110 µm have been evaluated to check the impact on flow ability of the blend and dissolution characteristics of drug product respectively. During formulation development study, pre-compression or lubricated blend parameters such as bulk density, tapped density, PSD by sieve analysis, compressibility index, Hausner's ratio etc. have been evaluated. Post-compression in-process parameters such as weight of tablet, tablet dimensions, hardness, friability, disintegration time etc. have also been evaluated. Dissolution profile all the test formulations was evaluated and compared with the dissolution profile of reference product. Based on formulation development studies conducted for development of oral; immediate release tablet formulation Solifenacin Succinate Tablets, 10 mg using direct compression strategy, SuperTab 14 SD a grade of lactose monohydrate and PSD of drug substance less than 40 µm has been finalized

for better flow of lubricated blend and distribution of drug substance throughout blend which further ensured better physical and in-process properties, c and dissolution of drug product.

Keywords: Solifenacin Succinate, Lactose Monohydrate Grade, Particle Size Distribution, Immediate Release Tablet, Drug Release Kinetic, Dissolution, BCS

INTRODUCTION

The oral drug delivery system is the most widely utilized route of administration for the systemic effect due to ease of administration, pain avoidance and patient compliance. The immediate release tablet is highly accepted and rapidly growing drug delivery system because of rapid onset action, improved solubility and thus bioavailability. Solifenacin succinate is a competitive muscarinic receptor antagonist used in the overactive bladder. M3 receptor appears to be most important for bladder contractibility. Solifenacin binds to muscarinic receptors which modulates cholinergically medicated function as the contraction of smooth muscle and in particular, relaxes smooth muscle tone in the urinary bladder **[1]**.

Solifenacin succinate was approved for the treatment of overactive bladder in 2004. Solifenacin succinate is a BCS Class I drug (High Solubility, High permeable). It is a white to off white crystals and soluble in water, ethanol and glacial acetic acid in room temperature. The absolute bioavailability of the drug is approximately 90% and plasma concentrations of solifenacin succinate are proportional to the dose administration. Total clearance is upto 7-14 l/h, elimination half-life is 33-85 hours **[2]**.

The formulation is solid oral dosage form of solifenacin succinate 10mg tablet immediate release tablet prepared by direct compression method by varying the different grades of lactose monohydrate and particle size distribution method used. In which pre-compression study checked all micromeritics properties of the blend. Post-compression parameter such as thickness of tablet, hardness, friability, disintegration time and dissolution profile **[3]**.

This formulation is same as the innovator product of VESICARE 10mg tablet. The objective of this research is to develop for the patient compliance and cost effective in this formulation use the same excipeints to achieve the same pharmacokinetic and bioequivalence **[1]**.

MATERIALS

Solifenacin succinate was obtained as a gift sample from Enaltec Pharma Research Pvt. Ltd. Mumbai and other excipeints used in the formulation study such as varying different grades of lactose monohydrate, corn starch, Hypromellose, Magnesium Stearate, Opadry pink 03F540018.

METHODS

Oral; immediate release tablet of solifenacin succinate was prepared by using direct compression method. The detailed manufacturing steps are as follows **[11]**:

1. All the ingredients were dispensed individually in polybag using calibrated balance.
2. Drug substance, lactose monohydrate and Hypromellose 2910 were sifted through ASTM sieve #40 geometrically and collected in a polybag.
3. The blend of step 2 was re-sifted through ASTM sieve #40 and collected in a polybag.
4. Magnesium stearate of step 1 was sifted through ASTM sieve #60 and collected in a polybag.
5. Blend of step 3 was added in a double cone blender and mixed for 30 minutes at 12 RPM.
6. Magnesium stearate of step 4 was added to the step 5 and mixed for 5 minutes at 12 RPM.
7. The lubricated blend of step 6 was compressed into tablets using 8 mm, biconvex, round shaped punches debossed 'S10' on upper punch and 'N' on lower punch fitted to single rotary tablet press.
8. 10% coating dispersion was prepared by adding required quantity of Opadry Pink 03F540018 in purified water under stirring. Stirring was performed until a homogenous coating dispersion was obtained.
9. Compressed tablets of step 7 were loaded in a auto coater (coating machine) and coating dispersion of step 8 was sprayed onto the tablets to achieve 3% weight gain.
10. After completion of coating process, tablets were dried at 40°C for 15 minutes.

Table No. 1: Formulation of immediate release of solifenacin succinate tablet

Batch No.	F1	F2	F3	F4	F5
Batch details	Lactose grade – SuperTab 11SD	Lactose grade – SuperTab 14SD	Lactose grade – SuperTab 30GR	Finer drug substance (D_{90} –110µm)	Coarse drug substance (D_{90} – 40µm)
Ingredients	mg/tablet				
Solifenacin succinate	10.00	10.00	10.00	10.00	10.00
Lactose monohydrate (SuperTab 11SD)	125.00	-	-	-	-
Lactose monohydrate (SuperTab 14SD)	-	125.00	-	125.00	125.00
Lactose monohydrate (SuperTab 30GR)	-	-	125.00	-	-
Corn starch	7.50	7.50	7.50	7.50	7.50
Hypromellose 2910	6.00	6.00	6.00	6.00	6.00
Magnesium stearate	1.50	1.50	1.50	1.50	1.50
Opadry Pink 03F540018	3.75	3.75	3.75	3.75	3.75
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight of tablet	153.75	153.75	153.75	153.75	153.75

Melting point determination: The melting point determine by introducing small amount and the capillary attached to graduated thermometer.

Determination of solubility: Qualitative solubility analysis of drugs was done by dissolving 5mg of drug in 5ml soluble in organic solvent such as Ethanol, Methanol, Water and Dimethyl formamide.

UV Spectrophotometer determination: 50mg of solifenacin succinate was weighed accurately and transferred it into 50ml volumetric flask with 50ml ethanol (1000ug/ml). It was sonicated for 5minutes, and then 5ml pipette out from first stock and transferred into 50ml volumetric flask the volume was made upto the mar with distilled water to get the stock solution (100ug/ml). This solution is further dilution were made by using this stock solution and Standard solution will be prepared at five concentrations. Further calibration curve of Solifenacin Succinate was plotted by measuring absorbance of 5µg/ml, 10 µg/ml,15 µg/ml,20 µg/ml and 25µg/ml solutions scanned in the range of 400-200nm using U.V. visible Spectrophotometric (SHIMADZU 1800). Spectrophotometric data for the estimation of solifenacin succinate at 215nm **[4, 6]**.

Compability study: The compatibility of solifenacin succinate with excipient was studied by FTIR spectroscopy. The method used for study is pressed KBR pellet method and the ratio of sample is should be 1:100, where 1 is a part of drug sample and 100 is a part of KBr. The scanning range was 4000-400cm^{-1} at ambient temperature (Perkin Elmer spectrum-65) **[7]**.

Physicochemical characterization of the Immediate Releases Tablet

Pre-compression study:(R.K.V. Naga Sudha, 2015)

Loss on drying: carried out by using halogen moisture analyzer at 105°C.

Bulk Density: 20gm of lubricated blend containing the API and excipients was weighed and transferred into a measuring cylinder. Bulk volume was noted and bulk density calculated by using the formula:

$$\textbf{Bulk density} = \frac{\textbf{Mass}}{\textbf{Volume}}$$

Tapped density: 20gm of blend transfer into the measuring cylinder place on the tapped density apparatus (Electro lab USP II) according to USP set the 10, 500, 1250 count and after completing taps calculate the tapped density.

Carr's index: As per standard formula the Carr's index is calculate.

$$\textbf{Carr's index} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times 100$$

Hausner's Ratio: Calculate by using the

$$\textbf{formula} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

Particle Size Determination: The main objective of particle size determination is determining different size of particles. Take sieve No. #20, #40, #60, #80, #110 take

empty weight of sieve. Arrange the sieve number in ascending order all the sieve stacked one above the other. Then place the solifenacin succinate blend in upper sieve and place all sieves on Electromagnetic sieve shaker and calculate the particle size. The particle size distribution directly influences on blend properties such as flow ability, porosity, reactivity or dissolution rate, packaging density.

Post-compression study [2]:

Weight of tablet: Twenty tablet randomly selected from each batch and individual weighed. The average weight and standard deviation of 20 tablets was calculated.

Tablet dimension: Thickness and diameter of the tablets were measure using a Vernier caliper. It is expressed in nm.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shock while handling, transportation and storage of tablets. Hardness of tablets measured by using Dr. Schleuniger hardness tester expressed in N.

Friability: Take 650mg weight of tablet. Place the tablet in Roche friabilator. The friability was operated at 25rpm at 100 revaluation then removes loose duct from then weights them accurately. The % friability was calculated by using following equation **[4]**.

$$\textbf{\% Friability} = \frac{\textbf{Initial weight} - \textbf{final weigth}}{\textbf{Initial weight}} \times 100$$

Disintegration time: In vitro disintegration time of tablets from each formulation was determined by using Disintegration Apparatus USP (Electro lab). In vitro Disintegration test was carried out at 37±5°C in 900ml by using disintegration media. The times taken for complete disintegration were observed.

In-vitro Drug Dissolution Studies: In vitro drug release was study for the solifenacin succinate immediate release tablets were carried out in USP II (Paddle) apparatus with 900ml of degassed dissolution medium maintained at 37±5°C for 45min at 50rpm. 5ml of the samples were withdrawn at 10, 15, 30, 45 min each internal was replaced with the same quantity of fresh dissolution medium collected sample were analyzed by HPLC method and calculate the percentage drug release **[7]**.

RESULTS AND DISCUSSION

1. **Solubility and Melting point determination (Table 2)**.
2. **Calibration curve by U.V. visible spectrophotometer:** The samples of different concentration were analyzed at215 nm **(Figure 1, 2)**.
3. **Compatibility study: (Figure 3, 4)**.
4. **Pre-compression study:** All micromeretics property was checked such as Bulk Density, Tapped Density, Hausner'sRatio,

Compressibility Index and Particle Size Distribution parameters were done. All parameters are measure the porosity or void fraction of substance it has directly influence for the flow of blend at the time of tablet compression **(Table 3)**.

5. **Particle size analysis:** sieve analysis of Optimized F4 Batch of Lubricated Blend **(Table 4)**.
6. **Post-compression study:** The prepared tablets were evaluated for weight uniformity, Thickness of tablet, hardness, friability, disintegration time. All test value are shown in **Table 5**.
7. **Evaluation of Coated Tablet:** After tablet coating 3% weight achieved and evaluated the parameter such as thickness, diameter and disintegration time **(Table 6)**.
8. **In-vitro dissolution study:** Comparative dissolution profiles of Reference product and Test products of Solifenacin Succinate Tablets, 10 mg in Water **(Table 7)**.
9. **Dissolution profile**: Graphical representation of comparative dissolution profile of Reference product and Test products of Solifenacin Succinate 10 mg tablet **(Figure 5)**.
10. **Drug release kinetic profile:** The release kinetics of immediate release table to optimize batch F4 was found to be following first order and kors-peppas kinetic as the value for $R^2$is (0.9845 and 0.9895) 'n' values show less than 1.0000 mean non-fickian release **(Table 8, Figure 6) [5, 6]**.

Table 2: Solubility and Melting point of solifenacin succinate

Sr. No.	Parameters	Observation
1.	Melting Point	147°C – 149°C
2.	Solubility	1. Completely soluble in Water. 2. Very soluble in Methanol. 3. Slightly soluble in Ethanol.

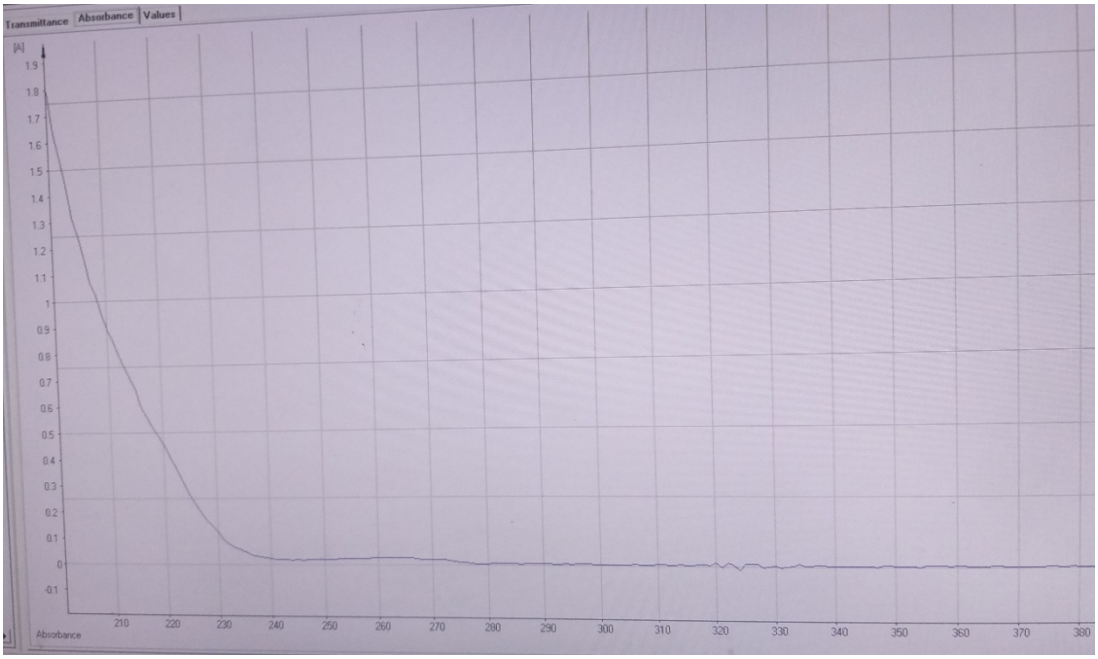

Figure 1: Absorbance maxima of solifenacin succinate

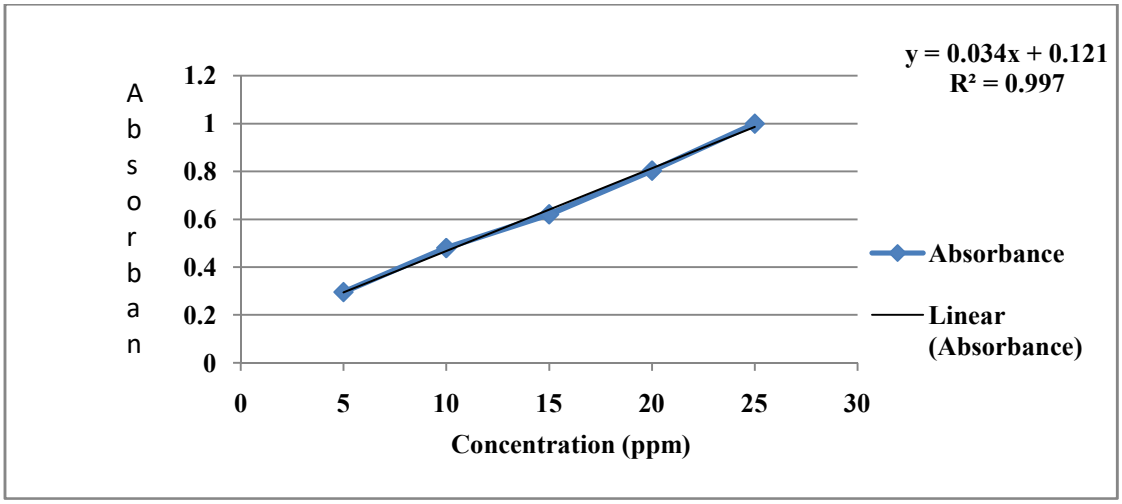

Figure 2: Calibration Curve of Solifenacin Succinate

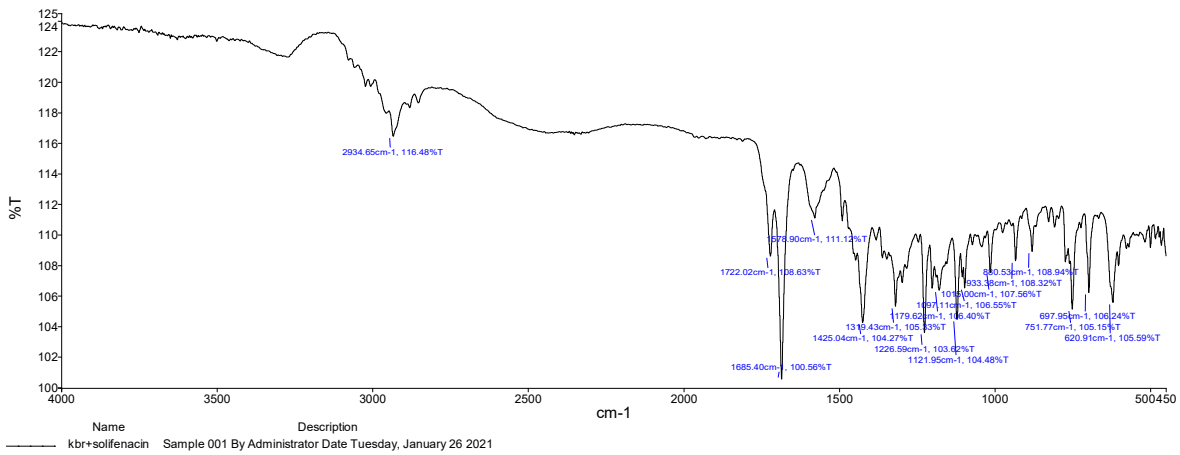

Figure 3: FTIR Spectra of Solifenacin Succinate

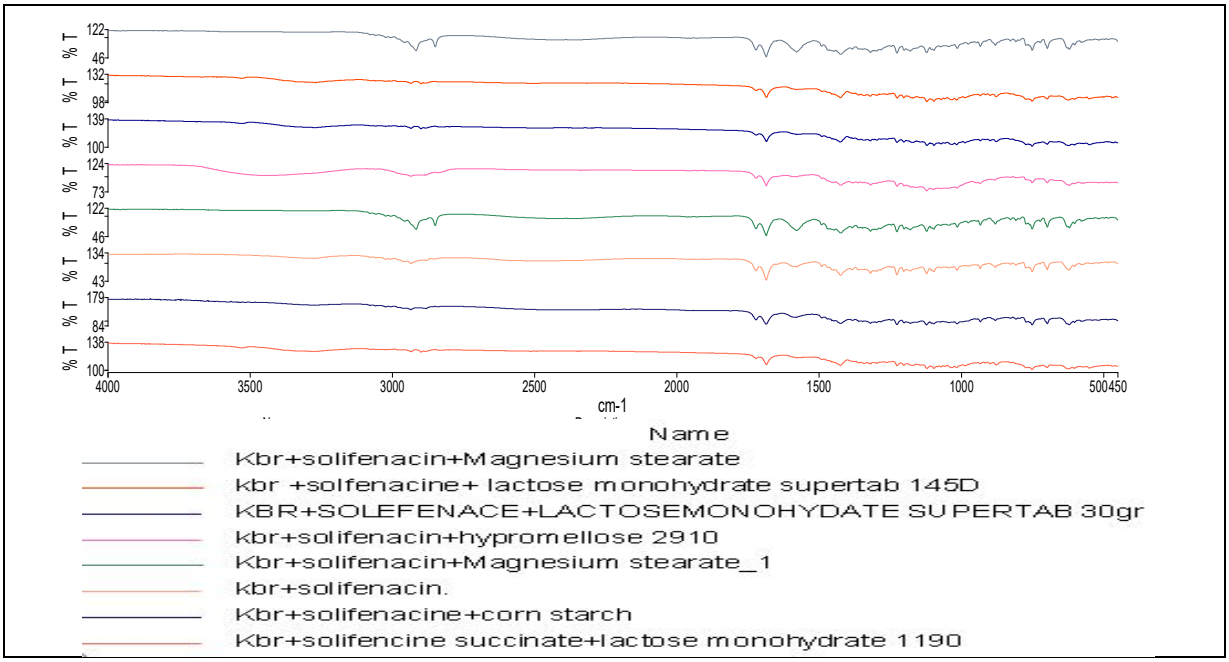

Figure 4: FTIR spectra of solifenacin succinate along with excipients

Table 3: Pre -compression evaluation of lubricated blend

Sr. No.	Parameter	F_1	F_2	F_3	F_4	F_5
1.	Bulk Density (g/ml)	0.57	0.54	0.61	0.58	0.56
2.	Tapped Density (g/ml)	0.77	0.70	0.79	0.72	0.76
3.	Compressibility index	25.97	22.86	22.78	19.44	26.32
4.	Hausner's Ratio	1.35	1.30	1.30	1.24	1.36
5.	LOD (w/w)	2.07	1.76	2.45	2.03	2.16

Table 4: Particle size Analysis

Sr. No.	Sieve Size	% Retained	Cumulative %retained
1.	#20	0	0
2.	#40	0	1.5
3.	#60	1.5	1.5
4.	#80	0.5	2.0
5.	#100	11.0	11.5
6.	#110	8.0	21.0
7.	Pan	79	100
Total		100.0	NA

Table 5: Evaluation of uncoated tablet

Sr. No.	Parameters	F_1	F_2	F_3	F_4	F_5
1.	Appearance	White to off white colored, round, biconvex tablets, de-bossed "S 10" on one side and "N" on another side.				
2.	Tablet weight (mg)	147.3 – 156.2	146.9 – 158.1	147.5 – 153.4	145.2 – 154.4	144.5 – 154.8
3.	Hardness (N)	37-52	45 – 58	33 - 49	42 – 54	44 – 53
4.	Thickness (mm)	3.29-3.33	3.28 – 3.34	3.31 – 3.35	3.26 – 3.34	3.26 – 3.33
5.	Diameter (mm)	7.51-7.53	7.49 - 7.52	7.51 – 7.54	7.51 – 7.53	7.51 – 7.53
6.	Friability %	0.14	0.09	0.22	0.06	0.11
6.	Disintegration time (min)	5 – 5	4 - 5	5 – 7	4 – 5	3 – 5

Table 6: Evaluation of coated tablet

Sr. No.	Parameters	F_1	F_2	F_3	F_4	F_5
1.	Appearance	Light pink colored, round, biconvex tablets, de-bossed "S 10" on one side and "N" on another side.				
2.	Tablet weight (mg)	151.3 -157.9	149.9 – 154.6	147.6 – 156.2	148.1 – 155.5	149.5 – 156.3
4.	Thickness (mm)	3.44 – 3.49	3.42 – 3.48	3.43 – 3.51	3.42 – 3.49	3.44 – 3.49
5.	Diameter (mm)	7.56 – 7.59	7.58 – 7.60	7.59 – 7.51	7.57 – 7.59	7.57 – 7.59
6.	Disintegration time (min)	6 - 7	6 - 7	7 - 8	6 - 7	6 -7

Table 7: In-vitro dissolution study of Solifenacin succinate

Dissolution (%)						
Batch No.	**C1700270**	**F1**	**F2**	**F3**	**F4**	**F5**
Batch details	**Reference product**	**Test products**				
Dissolution condition	***USP II (Paddle) / 900 mL degassed Water / 50 RPM***					
Time (min.)	**% Drug release**					
10	**60**	**45**	**62**	**48**	**59**	**66**
15	**81**	**78**	**85**	**82**	**83**	**88**
30	**94**	**95**	**96**	**94**	**95**	**97**
45	**93**	**97**	**98**	**97**	**98**	**99**
F2 value	**-**	**54.89**	**71.94**	**59.61**	**76.45**	**61.87**

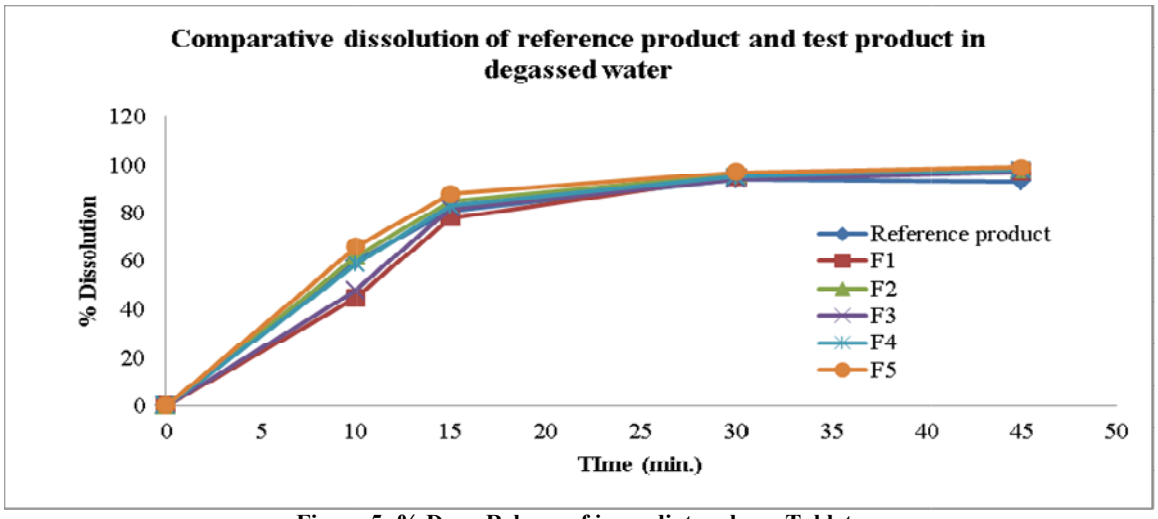

Figure 5: % Drug Release of immediate release Tablet.

Table 8: Drug release kinetic of solifenacin succinate

Time (min)	**0**	**10**	**15**	**30**	**45**
Cumulative % drug released	**0**	**59**	**53**	**95**	**98**
% drug remaining	**100**	**41**	**17**	**5**	**2**
Square root time	**0.000**	**3.162**	**3.873**	**5.477**	**6.708**
log Cumu % drug remaining	**2.000**	**1.613**	**1.230**	**0.699**	**0.301**
log time	**0.000**	**1.000**	**1.176**	**1.477**	**1.653**
log Cumu % drug released	**0.000**	**1771**	**1.919**	**1.978**	**1.991**
% Drug released	**100**	**59**	**24**	**12**	**3**
CubeRoot of % drug Remaining(Wt.)	**4.642**	**3.448**	**2.571**	**1.710**	**1.260**
Wo-Wt.	**0.000**	**1.194**	**2.071**	**2.932**	**3.382**

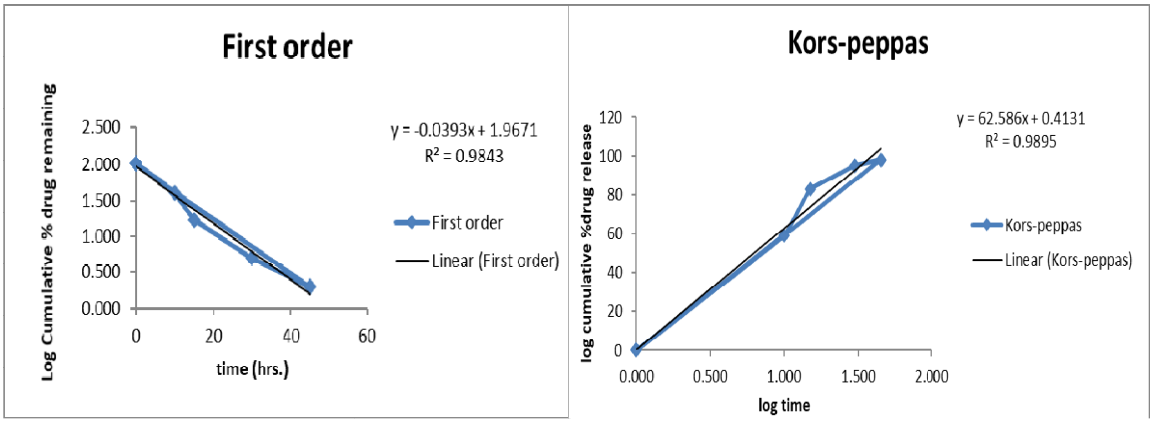

Figure 6: Drug release kinetic by first order and Kors-Peppas plot

CONCLUSION

In the presence study, olifenacin succinate 10mg immediate release film coating tablet formulation use Formulation of tablet was successfully done by using the direct compression method the five trail batches were taken. All the trail batches formulation was evaluated pre-compression and post-compression parameter shows the satisfactory results. Form five trail batches F4 batch was optimized batch in which use the fine particle size of API and Lactose Monohydrate super tab 14SD grade shows the better dissolution profile and match with the innovator product. The formulation development study demonstrated that F4 batch prepared by using SuperTab 14 SD has better flow properties and better in-process compression parameters compared to other formulations prepared with different diluents. Moreover, the F4 batch prepared with finer drug substance (d_{90}-40 µm) ensured better distribution of drug substance throughout the blend, thus better content uniformity considering low dose formulation and comparative dissolution properties of drug product compared to the reference product (VESIcare®). Therefore, lactose grade SuperTab 14SD has been finalized as a diluent which constitutes approximately 80% part of the formulation to ensure better flow properties and compatibility of the lubricated blend. Drug substance having PSD d_{90}-40 µm has been finalized to ensure comparable dissolution properties of drug product when compared to the dissolution profile of reference product (VESIcare®). Further, F4 batch has been considered as a final optimized batch on the basis of drug release kinetic model which shows first kinetic using Kors-Peppas kinetic method. The drug release kinetic shows first order kinetic and kors-peppas kinetic model as the value for $R^2$is (0.9845 and 0.9895) 'n' values show less than 1.0000 mean non-fickian release.

Abbreviations:

FTIR: Fourier Transform Infrared Spectroscopy.

USP: United State Pharmacopoeia.

UV: Ultra-Violet Spectroscopy.

HPLC: High Performance Liquid Chromatography.

API: Active Pharmaceutical Ingredient.

BCS: Biopharmaceutical Classification System.

KBr: Potassium Bromide.

IR: Immediate Release.

%: Percentage.

N: Newton.

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