FORMULATION AND EVALUATION OF SOLIFENACIN SUCCINATE IMMEDIATE RELEASE TABLETS USING VARIOUS SUPERDISINTEGRANTS

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ABSTRACT

Objectives: The aim of present work was to formulate and evaluate immediate release tablets of Solifenacin succinate and to achieve commercial availability of Solifenacin which has great market potential. Solifenacin succinate is an anticholinergic drugs, which is highly soluble and highly permeable (BCS Class I). Methods: The tablets were prepared by direct compression using Lactose anhydrous, HPMC E5, Sodium starch glycolate, Croscarmellose sodium and crospovidone with different concentration, Silicon colloidal dioxide as glidant and magnesium stearate as lubricants. The pre-formulation studies like XRD, FTIR & API and excipients ratio were carried out. The pre-compression parameters were evaluated for bulk density, tapped density, Carr’s index, Hausner ratio, angle of repose and particle size analysis. The post compression parameters were evaluated for weight variation, thickness, hardness, disintegration time and friability. The in-vitro drug release studies were conducted by USP type II dissolution apparatus. Result and discussion: The pre-formulation study shown the API and excipients were compatible. All the formulation passes the accepted limited for pre-compression and post compression parameters. Among the all formulation, F9 showed the higher drug release 98.12% containing 10% crospovidone (17mg) and having less disintegration time 3 min 30 sec.
Conclusion: The Solifenacin succinate immediate release tablets were prepared by the direct compression methods.

KEYWORDS: AOB, Solifenacin succinate, superdisintegrants, direct compression and BCS class.

INTRODUCTION
The immediate release tablets are highly accepted fast growing drug delivery system so an attempt was made to improve the onset of action of drug. The oral administration is the most popular route for the systemic effect due to ease of ingestion, pain avoidance and patient compliance.[1]

Immediate release tablets having the increased demand and become a rapidly growing area in the pharmaceutical industry because as they readily dissolve and disintegrates.[2] The superdisintegrants played pivotal role in immediate release drug delivery system, as they added to drug formulation. They act by breaking the crosslink between the drug and polymer as the tablets brake up into the small particle, hence it increases the dissolution rate and decrease the disintegration time.[3]

The formulations were designed to disintegrate in the stomach followed by their dissolution in the fluid of gastrointestinal tract.[4] The immediate release tablets were prepared by the direct compression method using lactose anhydrous as diluents, HPMC E5 as binder, SSG, CCS & crospovidone as superdisintegrants, Colloidal silicon dioxide as glidant and magnesium stearate as lubricants.[5]

The Solifenacin succinate is a competitive acetylcholine receptor antagonist for the treatment of overactive bladder and with symptoms of urge urinary incontinence, urgency and urinary frequency.[6] The Solifenacin succinate is a BCS class I drug, having high solubility and high permeability.

MATERIALS AND METHODS
Materials
Solifenacin succinate was a gift sample from Dr. Reddy’s Laboratory, Hyderabad. Lactose anhydrous, Croscarmellose sodium, crospovidone and sodium starch glycolate were gifted from Gland Pharma Ltd., Mumbai. Magnesium stearate, microcrystalline cellulose and
Aerosil were procured from S. D. Fine chemicals Pvt. Ltd, Mumbai. All other reagents used were of analytical grade.

**Formulation of immediate release tablets of Solifenacin succinate**

*Direct compression method*[^3]

The Solifenacin succinate tablets were prepared by direct compression methods. The superdisintegrants such as sodium starch glycolate, croscarmellose sodium, crospovidone were used in varying concentration (6-10% w/w) to get optimized formulation. The drug, diluents, binding agent and superdisintegrants were passed through sieve no. 40 and mixed together in a poly bags for 15min. The Aerosil were passed through sieve no. 40 and magnesium stearate was through sieve no. 60. Above all the excipients were mixed thoroughly in a poly bag and lubricated blend were compressed by RIMEK 12 station rotary compression machine.

**Table 1: Formulation for Immediate release tablets of Solifenacin succinate**

<table>
<thead>
<tr>
<th>Ingredients (mg/tab)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin succinate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Lactose anhydrous</td>
<td>141.3</td>
<td>137.9</td>
<td>134.9</td>
<td>141.3</td>
<td>137.9</td>
<td>141.3</td>
<td>141.3</td>
<td>137.9</td>
<td>137.9</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>10.2</td>
<td>13.6</td>
<td>17.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.2</td>
<td>13.6</td>
<td>17.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10.2</td>
<td>13.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Aerosil</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Total weight</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
</tr>
</tbody>
</table>

**Fourier transforms infrared spectroscopy**

The drug-excipients studies were studied by FTIR Spectrophotometric. The spectrum was recorded between wave ranges 400-4000cm⁻¹ using Bruker-α Opus software by KBr pellet method. The IR- spectrum of pure API, F3, F6 and best formulation F9 were recorded.

**X-Ray Diffraction Studies**

The X-Ray diffraction studies were performed for the API and best formulation. The XRD studies were performed to find out the changes in the crystallinity and amorphization in the formulation. The XRD was performed using P Analytical X pert pro X-ray diffract meter. Measurements were taken from 3⁰ to 50⁰ on the 20. API and best formulation F9 was analyzed to detect the any physical changes.
Differential scanning calorimetry

The DSC study was performed to find out the any changes in the melting point of API and various formulations. The DSC was studied using Mettler Toledo -822e model with 120 thermocouples which guarantees unchanged sensitivity.

Pre compression parameters

**Bulk density**[^7,^8]

Bulk density is also known as apparent bulk density (\(\rho_b\)). It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by the following formula.

\[
Db = \frac{M}{Vb}
\]

Where,
- \(M\) = mass of powder.
- \(Vb\) = bulk volume of the powder

**Tapped Density[^7]**

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted. The tapped density was calculated by following formula

\[
Dt = \frac{M}{Vt}
\]

Where,
- \(M\) = mass of powder
- \(Vt\) = tapped volume of the powder

**Angle of Repose[^8]**

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested By Newman, and free standing cone method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just
touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

Therefore \( \theta = \tan^{-1} \frac{h}{r} \)

Where,
\( \theta \) = Angle of repose
\( h \) = height of the cone
\( r \) = Radius of the cone base.

**Compressibility Index** \(^8\)

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

\[ \text{Compressibility index (\%)} = \frac{D_t - D_b}{D_t} \times 100 \]

Where,
\( D_t \) = tapped density
\( D_b \) = bulk density

**Hausner ratio** \(^8\)

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

\[ \text{Hausner ratio} = \frac{D_t}{D_b} \]

Where,
\( D_t \) = tapped density
\( D_b \) = bulk density

**Post compression Parameters**

**Tablet thickness test**

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Vernier caliper.
Weight variation test\textsuperscript{[9]}

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness\textsuperscript{[10]}

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm\textsuperscript{2} is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test\textsuperscript{[11]}

It is the measurement of mechanical strength of tablets. The Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolve at 25 rpm. After 100 revolutions, tablets were removed, deducted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

\[
\% \text{ Friability} = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100
\]

% Friability of the tablets less than 1% was considered acceptable.

Drug content\textsuperscript{[12]}

Ten tablets were powdered, and 10 mg equivalent weight of Solifenacin tablet powder was accurately weighed and transferred into a 100 ml with 0.1N HCL. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 220 nm.

Disintegration time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test was carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieves. The basket is raised and lowered about 28 to 32 times per minute in a medium maintained at 37± 2\textdegree C. Six tablets were placed in each of the tube and the time
required for complete passage of tablet fragment through the mesh # 10 was considered as the disintegration time of the tablet.

**In-vitro dissolution study of formulated tablets**

The *in-vitro* drug release studies were performed using USP rotating paddle (USP Type II) by using 900ml of 0.1N HCl at paddle speed of 75 rpm and at temperature 37±0.2°C. The 5 ml samples were withdrawn at time interval of 10, 20, 30, 40, 50 and 60 min. The sample volume was immediately replaced with the same volume of fresh media as when a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically at 220 nm. The cumulative amount of the drug released at each interval was calculated by using standard graph of Solifenacin succinate.

**RESULTS AND DISCUSSION**

**FT-IR study**

![Fig. 1: IR spectra of Solifenacin succinate API](image1)

![Fig. 2: IR spectra of F3 blend powder](image2)
The FTIR study concluded that the absorption present in solifenacin succinate were 3300±100, 3000±100, 2200±100, 1900±100, 1700±100, 1600±50, 1500±50, 1200±50, 1400±50. These all absorption band were present on the formulation. So this clearly suggests that the drug remains in the same form even in its formulations indicating that there is no interaction between the drug and polymer used for the study.

**Differential scanning calorimetry study**

The DSC study showed the following:

- **Endothermic peak at 120°C** indicating melting of solifenacin succinate.
- **Exothermic peak at 170°C** indicating recrystallization.

These observations suggest that solifenacin succinate undergoes a phase transformation during heating.

**Fig. 5: DSC thermogram of solifenacin succinate**
DSC of API in figure 4 exhibits characteristic sharp endothermic peak at 151.59°C, which due to the decomposition of drug associated with its melting point and indicate its crystalline nature. DSC of API with crospovidone figure 5 shows sharp peak at 202.71°C corresponds to the melting point of crospovidone. The excipients mixture showed peak at 202.13°C and the drug endothermic peak was at 130.62°C. This slight shift of endothermic peak of API towards low temperature and its broadening is due to change in the physical state and also results of physical interaction. There by conformed the no interaction between drug and excipients used.

X-ray diffraction study

Fig. 7: X-ray diffractogram of Solifenacin succinate

Fig. 8: X-ray diffractogram of lubricated granules of Solifenacin succinate tablets
The X-Ray Powder Diffraction pattern of Solifinacin succinate tablets exhibit the diffraction peaks at 2-theta values, which are characteristic of Solifinacin succinate drug substance. This indicates that the Polymorphic Form of Solifinacin succinate drug substance remains unchanged during the process of Tablet Formulation.

Pre-compression parameter

Table 2: Pre-compression parameter for all formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose (x± SD; n=3)</th>
<th>Bulk density (x±SD; n=3)</th>
<th>Tapped density (x± SD; n=3)</th>
<th>Hausner ratio (x± SD; n=3)</th>
<th>Carr’s index (x± SD; n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>22.51±0.11</td>
<td>0.457±0.15</td>
<td>0.482±0.25</td>
<td>1.121±0.52</td>
<td>5.18±0.12</td>
</tr>
<tr>
<td>F2</td>
<td>24.16±0.51</td>
<td>0.445±0.14</td>
<td>0.499±0.45</td>
<td>1.114±0.45</td>
<td>10.82±0.45</td>
</tr>
<tr>
<td>F3</td>
<td>27.40±0.18</td>
<td>0.445±0.45</td>
<td>0.502±0.12</td>
<td>1.116±0.52</td>
<td>11.35±0.25</td>
</tr>
<tr>
<td>F4</td>
<td>25.21±0.45</td>
<td>0.463±0.23</td>
<td>0.514±0.23</td>
<td>1.084±0.14</td>
<td>9.9±0.36</td>
</tr>
<tr>
<td>F5</td>
<td>29.25±0.58</td>
<td>0.457±0.13</td>
<td>0.499±0.56</td>
<td>1.142±0.13</td>
<td>8.41±0.52</td>
</tr>
<tr>
<td>F6</td>
<td>24.22±0.69</td>
<td>0.452±0.52</td>
<td>0.529±0.25</td>
<td>1.121±0.25</td>
<td>14.5±0.14</td>
</tr>
<tr>
<td>F7</td>
<td>26.56±0.23</td>
<td>0.445±0.14</td>
<td>0.514±0.36</td>
<td>1.114±0.36</td>
<td>13.4±0.23</td>
</tr>
<tr>
<td>F8</td>
<td>26.02±0.52</td>
<td>0.457±0.45</td>
<td>0.499±0.33</td>
<td>1.188±0.58</td>
<td>8.41±0.15</td>
</tr>
<tr>
<td>F9</td>
<td>22.01±0.11</td>
<td>0.456±0.14</td>
<td>0.481±0.24</td>
<td>1.120±0.52</td>
<td>5.17±0.12</td>
</tr>
</tbody>
</table>

The flow properties for all formulations were performed by measuring various parameters. The angle of repose for powder blend was in the range of 22.01 to 29.25°. The bulk density was in range of 0.445 to 0.463 gm/ml and tapped density was in range of 0.481 to 0.529 gm/ml. The Carr’s index was in the range 5.17 to 14.5 and Hausner’s ratios in the range of 1.084 to 1.188. The results confirmed that the powder blend possessed considerable flow properties for all the formulations.

Post-compression parameter

Table 3: Post-compression parameter for all formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Average weight (mg) (x±SD; n=3)</th>
<th>Thickness(mm) (x±SD; n=3)</th>
<th>Hardness (x±SD; n=3)</th>
<th>Friability (%) (x±SD; n=3)</th>
<th>Disintegration time (min-sec) (x±SD; n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>170 ± 0.10</td>
<td>3.51±0.02</td>
<td>6.5±0.11</td>
<td>0.27±0.01</td>
<td>4 min 37 sec</td>
</tr>
<tr>
<td>F2</td>
<td>170 ± 0.12</td>
<td>3.52±0.05</td>
<td>6.2±0.12</td>
<td>0.23±0.02</td>
<td>4 min 25 sec</td>
</tr>
<tr>
<td>F3</td>
<td>171 ± 0.10</td>
<td>3.55±0.09</td>
<td>6.7±0.11</td>
<td>0.25±0.05</td>
<td>4 min 10 sec</td>
</tr>
<tr>
<td>F4</td>
<td>171 ± 0.13</td>
<td>3.49±0.07</td>
<td>6.5±0.17</td>
<td>0.21±0.02</td>
<td>4 min 30 sec</td>
</tr>
<tr>
<td>F5</td>
<td>169 ± 0.15</td>
<td>3.50±0.10</td>
<td>6.1±0.15</td>
<td>0.20±0.01</td>
<td>4 min 15 sec</td>
</tr>
<tr>
<td>F6</td>
<td>170 ± 0.18</td>
<td>3.48±0.04</td>
<td>6.2±0.11</td>
<td>0.23±0.01</td>
<td>3 min 56 sec</td>
</tr>
<tr>
<td>F7</td>
<td>171 ± 0.12</td>
<td>3.49±0.02</td>
<td>6.4±0.21</td>
<td>0.24±0.02</td>
<td>3 min 58 sec</td>
</tr>
<tr>
<td>F8</td>
<td>170 ± 0.11</td>
<td>3.45±0.04</td>
<td>6.2±0.14</td>
<td>0.22±0.02</td>
<td>3 min 49 sec</td>
</tr>
<tr>
<td>F9</td>
<td>170 ± 0.10</td>
<td>3.52±0.05</td>
<td>6.5 ±0.13</td>
<td>0.23±0.01</td>
<td>3 min 30 sec</td>
</tr>
</tbody>
</table>
The post compression parameters were evaluated for all the formulation. The hardness and friability for all formulation were in acceptable limits. The hardness of tablets prepared by direct compression was in range of 6.1 to 6.7 KP. The friability for all formulation was found to below 1% so tablets will not break during the handling on machines or shipping. The weight variation was found in the range of 169 ± 0.15 to 171 ± 0.13mg. The disintegration times for all formulations were in range of 4 min 37 sec to 3 min 30 sec. Hence, all formulation passed the accepted post compression parameter.

3.6. *In-vitro* drug release studies

![Drug release profile for F1, F4 and F7 containing 6% superdisintegrants](image1)

**Fig. 9:** Drug release profile for F1, F4 and F7 containing 6% superdisintegrants

![Drug release profile for F2, F5 and F8 containing 8% superdisintegrants](image2)

**Fig. 10:** Drug release profile for F2, F5 and F8 containing 8% superdisintegrants

![Drug release profile for F3, F6 and F9 containing 10% superdisintegrants](image3)

**Fig. 11:** Drug release profile for F3, F6 and F9 containing 10% superdisintegrants
The *in-vitro* drug release studies were performed for all formulation. All formulations contained the various superdisintegrants with different concentration. The formulation F9 revealed the 98.56% drug release containing 10% crospovidone (17 mg) in 0.1N HCl. The *in-vitro* drug releases for all the formulation were in the range of 67.79 to 98.12% at the end of 60 minutes. Out of the three superdisintegrants used Crospovidone shown the maximum drug release with decreased disintegration time.

**3.7. *In-vitro* release kinetic studies**

| Table 4: *In-vitro* release kinetics for all formulation |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Formulation** | **Correlation coefficient (r^2) of first order** | **Correlation coefficient (r^2) of zero order** | **DE_{30} (%)** | **Q_{20} (%)** | **T_{50} (min)** |
| F1 | 0.734 | 0.864 | 35.00 | 49.23 | 22 |
| F2 | 0.775 | 0.916 | 36.66 | 52.56 | 17 |
| F3 | 0.773 | 0.934 | 31.00 | 55.23 | 13 |
| F4 | 0.771 | 0.912 | 38.33 | 51.23 | 18 |
| F5 | 0.791 | 0.937 | 41.50 | 53.89 | 16 |
| F6 | 0.770 | 0.958 | 42.16 | 55.95 | 13 |
| F7 | 0.746 | 0.902 | 40.83 | 54.12 | 15 |
| F8 | 0.781 | 0.963 | 43.33 | 63.23 | 9 |
| F9 | 0.756 | 0.964 | 53.33 | 69.52 | 8 |

From the release kinetics studies all the formulation followed the first order kinetics as having greater r^2 values when compared with the Zero order. The dissolution efficiency was calculated and F9 formulation showed the dissolution efficiency at 30 min was found to be 40%, Q_{20} was 69.52% and T_{50} was 8 min. Hence, it is considered as the best formulation.

**CONCLUSION**

The disintegration time of the tablets prepared by using superdisintegrants was well within the limits. Crospovidone provided the immediate and highest release compared to other superdisintegrants. It was concluded that Solifenacin succinate immediate release tablets could be successfully prepared by direct compression technique. The Solifenacin succinate being a water-soluble drug would be readily available in a dissolved form for rapid oral uptake resulting in enhanced bioavailability. All the formulation passes the accepted limited for pre-compression and post compression parameters. Among the all formulation, F9 showed the higher drug release 98.12% containing 10% crospovidone (17mg) and having less disintegration time 3 min 30 sec comparing with all formulation. Hence, it is concluded that crospovidone superdisintegrants was successful in developing Solifenacin succinate immediate release tablets.
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