FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLET CONTAINING SPIRONOLACTONE HYDROXYPROPYL: β- CYCLODEXTRIN BINARY SYSTEM

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ABSTRACT
Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablet. In the present study, an attempt has been made to prepare fast dissolving tablets of the drug Spironolactone using superdisintegrants crosspovidone, crosscarmellose sodium and sodium starch glycolate by direct compression technique. The prepared tablets were evaluated for pre and post compression parameters i.e. angle of repose, car’s index, hausner’s ratio, hardness, friability, wetting time, weight variation, in vitro disintegration time and in vitro dissolution study. The hardness of the tablets was in the range of 3.0 - 4.70 Kg/cm². The percentage friability of the tablets was less than one. Weight variation test results showed that the tablets were deviating from the average weight within the permissible limits of ±7.5 %. Drug content uniformity study results showed that uniform dispersion of the drug throughout the formulation i.e. 96.0% to 102.0%. Tablets containing crosspovidone showed better disintegrating character along with the rapid release.

Keywords: Fast-dissolving tablets, Spironolactone, Superdisintegrants, Hydroxypropyl-β-cyclodextrin.

INTRODUCTION
There are many patients of different age groups complaint of some solid conventional dosage forms such as tablets and capsules due to difficulty in swallowing. In order to overcome this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration. The dissolution rate is a key parameter that determines the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug. The basic approach to the development of ODTs is the use of superdisintegrants such as Crosscarmellose sodium, Crosspovidone and Sodium starch glycolate. Spironolactone is 7α-(acetyl)sulfonyl)-3’, 4’-dihydrospiro [androst-4-ene-17, 2’ (5’H)-furans]-3, 5’-dione, calculated with reference to the dried substance. The drug is a renal competitive aldosterone antagonist in a class of pharmaceuticals called potassium-sparing diuretics, used primarily to treat heart failure, ascites in patients with liver disease, low-renin hypertension, hyperkalemia, secondary hyperaldosteronism (such as occurs with hepatic cirrhosis), and Conn’s syndrome (primary hyperaldosteronism). Spironolactone contains not less than 95.0 per cent and not more than 105.0 per cent of C₂₃H₃₃O₅S, calculated on the dried basis. A white to light tan powder. (B.P, I.P.)

Plentiful approaches have been reported for masking the bitter taste of the drugs such as (1) use of flavors and sweeteners, (2) use of polymeric carriers, (3) drug resin complexes, (4) formation of inclusion complexes with β-cyclodextrin, etc. Among all the possibilities, the β-cyclodextrin approach is of particular interest. β-cyclodextrins are ‘bucket like’ molecules, with a rigid structure and a central cavity. The internal surface of the cavity is hydrophobic and the outer is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This good thing permits the cyclodextrin to put up a guest molecule within the cavity, forming an inclusion complex. In this study, investigations were performed on the possibility of complexation of Spironolactone with hydroxypropyl-β-cyclodextrin for improving the solubility and dissolution rate, thereby increasing the bioavailability and therapeutic efficacy of Spironolactone. The complexes of Spironolactone with β-cyclodextrin were prepared by using kneading methods. Selective physicochemical determinations based on Fourier transform infrared spectra (FTIR), and powder X-ray diffractometry (PXRD) were used to characterize the complexes. This Spironolactone-β-cyclodextrin complex system was formulated into Orodispersible tablets by direct compression method. The ODT formulations were evaluated for their physical, disintegration and dissolution properties. An accelerated stability study on selected ODT formulation was also conducted to assess the formulation shelf life and determine any possible degradation.

MATERIALS AND METHODS

Materials
Spironolactone pure powder drug gifted from Ind-Swift Ltd. Sodium starch Glycolate (SSG), Crosspovidone, Crosscarmellose Sodium, Mannitol, Hydroxypropyl-β-cyclodextrin, Talc, Magnesium stearate and Aspartame were gifted by Mankind pharmaceutical industry. All other ingredients used were of pharmaceutical grade.

Preparation of inclusion complexes
Spironolactone hydroxypropyl-β-cyclodextrin complexes were prepared in a molar ratio of 1:2 by kneading method. The solid drug and hydroxypropyl-β-cyclodextrin complex of...
molar ratio of 1:2 prepared using Kneading method (KM). The hydroxypropyl-β-cyclodextrin of specific quantity according to molar ratio was dissolved in water and then drug was added to it and has been triturated with pestle for 2 h and then the complex prepared was placed in desiccators or 48 h to ensure proper drying9.

Phase solubility studies
Phase solubility measurements were performed according to the following method. An excess amount of drug complex was added to 10 mL 6.8 phosphate buffer solutions in volumetric flask and shaken on rotary flask shaker at constant temperature of 37 ± 0.5°C for 24 h. In order to reach equilibrium stands the solution for another 6 h. After equilibration the suspensions were filtered through 0.45 μm membrane filter and analyzed by UV10.

Preparation of tablets
Fast dispersible tablets containing 25mg of Spironolactone were prepared by direct compression method and the various formula used in the study are shown in [Table 1]. All the ingredients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc. Super disintegrants like sodium starch glycolate, crosspovidone and croscarmellose sodium were used in different ratios and finally the effects of combination of super disintegrants were studied. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner’s ratio. After evaluation of powder blend the tablets were compressed with single station tablet punching machine using 8 mm flat punches set.

Master formula given in table1
EVALUATION OF POWDER BLENDS 11, 12, 13, 14.

Bulk density
Bulk density (ρb) was determined by placing pre sieved drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M) “as it is”.

ρb = M/Vb

Tapped density
The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using following formula.

ρt = M/Vt

Angle of repose
Angle of repose (α) 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. The radius of the heap (r) was measured and angle of repose was calculated as follow.

α = tan -1 (h/r)

Compressibility index
The simplest way of measurement of free flow property of powder is compressibility. It is expressed in percentage, which is calculated as follows:

C = (Initial volume – Final volume) / Final volume * 100

Hausner’s ratio
Hausner’s ratio is an index of ease of powder flow; it is calculated by following formula.

Hausner’s ratio = ρt/ρb

ρt - Tapped density, ρb - Untapped bulk density.

Data given in table-2

POST COMPRESSION PARAMETERS

Tablet hardness
The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in terms of Kg/cm²15.

Weight variation
Twenty tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and was compared with average weight16.

Friability
The friability of a sample of 20 tablets was measured using a Roche Friabilator. Twenty pre-weighted tablets were rotated with speed of 25 rpm for 4 min. The tablets were then dedusted and reweighed, and the percentage of weight loss was calculated17.

Wetting time
Cylindrical tissue papers (10 cm diameter) were put in artificial saliva (pH—6.8) to pretend the tongue conditions in a Petri dish. Amaranth, a water soluble dye, was added. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time17.

Disintegration time (DT)
In vitro DT for ODT was determined using USP method. Each individual tablet was dropped in each of six tubes of apparatus and one disk was added to each tube. The time required for complete tablet disintegration was observed visually and recorded using a stopwatch17.

In vitro dissolution
In vitro dissolution studies of Spironolactone ODT formulated tablets were studied using USP dissolution Apparatus II. The dissolution medium was phosphate buffer (pH 6.8), the volume being 900 mL. The temperature was maintained at 37 ± 0.5°C. The rotation speed was 100 rpm. Five milliliters of aliquot were withdrawn at predetermined time of intervals. The medium was refilled with 5 mL of fresh buffer each time. Sample was analyzed by using UV at242 nm. The study was performed in triplicate17.

Graph shown in Fig-1

Drug content estimation
Twenty tablets were weighed and powdered. An amount of powder equivalent to 25 mg of Spironolactone was dissolved in 100ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 242 nm using UV-Visible spectrophotometer16.

Thickness
The thickness of tablets was determined by using vernier caliper18.

Data given in table-3

CHARACTERIZATIONS OF COMPLEXES

Fourier transform infrared spectroscopy (FTIR)
The study was carried out to determine the molecular structure serving as an identification test to ascertain the purity of the molecule. The spectra were recorded for pure drug, drug complex and drug complex with excipients. IR spectroscopy was obtained by a FTIR spectrophotometer (SHIMADZU, Japan) using NaCl pellets. The scanning range used was 400–4,000 cm-1. The IR Spectra of pure Spironolactone and its complex with hydroxypropyl-β-cyclodextrin shows no significant changes in peaks. Hence it concluded that the drug, its physical mixture and excipients are compatible with each other.
The FTIR spectra is shown in figure- 2-4

**Powder X ray diffraction (PXRD)**

The XRD patterns of drug powder and of complexes of hydroxypropyl-β-cyclodextrin were recorded. X-ray diffraction patterns of Spironolactone revealed highly crystalline nature. The X-ray diffractogram of Spironolactone showed number of sharp and intense peaks at 2θ of 9°, 11.2°, 12.2°, 16.2°, 17°, 18° and 20°. The XRD Spectra of above formulation shows no significant changes in peaks. Hence it concluded that the drug complex and excipients was compatible with each other.

The X-RAY diffraction pattern is shown in figure- 5-8

**STABILITY STUDIES**

Stability of drug has been defined as the ability of a particular formulation, in a specific container, to remain within physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with the time under the influence of variety of environmental factors such as temperature, light and humidity, and enables recommended storage conditions, retest periods and shelf-lives to be established. New selected batch (F) of Spironolactone ODT was packed in HDPE bottle, sealed and kept at 40°C and 75% relative humidity, and enables recommended storage conditions, retest periods and shelf-life to be established. Samples withdrawn were analyzed for drug content, hardness, and disintegration time.

Data given in Table -4

**CONCLUSION**

Phase solubility studies showed a higher solubility of spironolactone when hydroxypropyl- β-cyclodextrin was used in combination. Analysis of dissolution data showed a significant enhancement in dissolution rate with complexation using hydroxypropyl-β-cyclodextrin. Formulation with higher concentration of Crosspovidone (f) has satisfactory physical resistance, fast in vitro disintegration time, high dissolution rate and good stability. The formulations were subjected to stability studies as per ICH guidelines and were found to be stable after 1 months study. Rapid disintegration of tablets formulated in this investigation may possibly help in administration of Spironolactone in a more palatable form without water. Thus, the dosage form of various drugs, especially for pediatric, geriatric, bed ridden, and non-cooperative patients, can be successfully formulated using this technology.

**REFERENCES**


**TABLE 1 COMPOSITION OF SPIRONOLACTONE ODT**

<table>
<thead>
<tr>
<th>Components</th>
<th>A(mg)</th>
<th>B(mg)</th>
<th>C(mg)</th>
<th>D(mg)</th>
<th>E(mg)</th>
<th>F(mg)</th>
<th>G(mg)</th>
<th>H(mg)</th>
<th>I(mg)</th>
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<td>SSG</td>
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<td>Crosscarmellose Sodium</td>
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<td>Magnesium Stearate</td>
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<td>Mannitol QS</td>
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<td>Total</td>
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### TABLE 2 Evaluation of powder blends

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<th>Parameters</th>
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<th>B</th>
<th>C</th>
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<th>F</th>
<th>G</th>
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<tbody>
<tr>
<td>Bulk Density gm/cm³</td>
<td>0.499±0.03</td>
<td>0.516±0.05</td>
<td>0.519±0.02</td>
<td>0.523±0.04</td>
<td>0.517±0.02</td>
<td>0.509±0.02</td>
<td>0.516±0.03</td>
<td>0.529±0.05</td>
<td>0.517±0.05</td>
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<tr>
<td>Tapped Density gm/cm³</td>
<td>0.599±0.05</td>
<td>0.600±0.02</td>
<td>0.612±0.04</td>
<td>0.607±0.03</td>
<td>0.624±0.04</td>
<td>0.610±0.02</td>
<td>0.621±0.02</td>
<td>0.614±0.03</td>
<td>0.612±0.02</td>
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<tr>
<td>Angle of Repose</td>
<td>26.21±0.05</td>
<td>25.04±0.02</td>
<td>32.02±0.03</td>
<td>29.03±0.04</td>
<td>31.02±0.06</td>
<td>32.02±0.01</td>
<td>28.06±0.03</td>
<td>29.08±0.05</td>
<td>28.57±0.08</td>
</tr>
<tr>
<td>% Compressibility</td>
<td>15.55</td>
<td>14.96</td>
<td>14.99</td>
<td>15.77</td>
<td>15.19</td>
<td>14.34</td>
<td>12.5</td>
<td>12.9</td>
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<tr>
<td>Hausners ratio</td>
<td>1.2</td>
<td>1.16</td>
<td>1.17</td>
<td>1.16</td>
<td>1.2</td>
<td>1.19</td>
<td>1.2</td>
<td>1.16</td>
<td>1.18</td>
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### TABLE 3 EVALUATION OF ODT SPIRONOLACTONE (mean ± SD, n= 3, n* =10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
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</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>8.02±0.04</td>
<td>8.01±0.02</td>
<td>8.00±0.03</td>
<td>8.02±0.01</td>
<td>8.03±0.01</td>
<td>8.04±0.02</td>
<td>8.02±0.03</td>
<td>8.02±0.01</td>
<td>8.03±0.02</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>33±0.05</td>
<td>4.30±0.02</td>
<td>4.32±0.07</td>
<td>4.30±0.04</td>
<td>4.32±0.06</td>
<td>4.41±0.07</td>
<td>4.36±0.04</td>
<td>4.40±0.05</td>
<td>4.36±0.04</td>
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<tr>
<td>Hardness (kg/cm²)</td>
<td>4.4±0.25</td>
<td>4.56±0.31</td>
<td>3.92±0.17</td>
<td>4.2±0.28</td>
<td>3.85±0.15</td>
<td>4.15±0.31</td>
<td>4.42±0.20</td>
<td>4.25±0.16</td>
<td>4.08±0.23</td>
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<tr>
<td>Friability (%)</td>
<td>0.451</td>
<td>0.57</td>
<td>0.486</td>
<td>0.752</td>
<td>0.645</td>
<td>0.802</td>
<td>0.735</td>
<td>0.539</td>
<td>0.634</td>
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<tr>
<td>Drug Content %</td>
<td>96±0.57</td>
<td>97±0.89</td>
<td>98.8±0.86</td>
<td>102±0.43</td>
<td>100±1.02</td>
<td>98.0±0.90</td>
<td>98.8±0.943</td>
<td>102±0.56</td>
<td>96±0.1.42</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>58±5</td>
<td>53±2</td>
<td>51±4</td>
<td>40±2</td>
<td>38±6</td>
<td>36±3</td>
<td>70±3</td>
<td>69±2</td>
<td>66±2</td>
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<tr>
<td>Weight Variation *(mg)</td>
<td>250±2.59</td>
<td>251.3±2.04</td>
<td>250.9±3.24</td>
<td>248.6±2.32</td>
<td>251.8±2.96</td>
<td>253.2±2.08</td>
<td>249.4±3.61</td>
<td>254.1±1.89</td>
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<tr>
<td>Wetting Time (sec)</td>
<td>79±4</td>
<td>74±3</td>
<td>72±2</td>
<td>52±4</td>
<td>47±2</td>
<td>45±1</td>
<td>90±2</td>
<td>87±3</td>
<td>80±2</td>
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Table 4 - Accelerated Stability study data of selected batch (F) of SPIRONOLACTONE ODT at 40°C /75% RH (mean ± SD, n = 3)

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<thead>
<tr>
<th>Parameters</th>
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<tr>
<td>Drug content</td>
<td>97.73±0.35</td>
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<tr>
<td>Hardness (Kg/cm³)</td>
<td>4.30±0.57</td>
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<tr>
<td>Disintegration time</td>
<td>38±3</td>
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<tr>
<td>Dissolution profile</td>
<td>95.15±1.30</td>
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</tbody>
</table>

**FIGURE-1 DISSOLUTION DATA GRAPH (pH-6.8)**
FIGURE 2  FTIR REPORT

Spironolactone

FIGURE 3

FTIR report with Excipients

FIGURE 4

Spironolactone complex with Hydroxypropyl-β-Cyclodextrine.
XRD REPORT: FIGURE-5

Spiranolactone pure drug

FIGURE-6

Spiranolactone complex with hydroxypropyl-β-cyclodextrine

FIGURE-7

Spiran lactone complex+SSG+MCC+Aspartame+Mag Stearate+Talc+Mannitol

FIGURE-8

Spiran lactone complex+Crospovidone+MCC+Aspartame+Mag Stearate+Talc+Mannitol