# Enhancement of dissolution rate of Spironolactone by inclusion complex with β-cyclodextrin: formulation, characterisation, and evaluation

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**Abstract:**

The study was aimed to formulate immediate release tablets of poorly water soluble drug (Spironolactone) by using solubility enhancement technique (Cyclodextrine Complex). The prepared tablets were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies and in-vitro release studies. From the results,it was clear that immediate release solid dosage form showed improved dissolution rate than marketed product. The tablets compressed were evaluated for its physical parameters like thickness, hardness, weight variation, friability, drug content and disintegration tests. The dissolution profile of formulated tablet was compared with the marketed product and the formulated tablet showed better release profile than the marketed product.

**Keywords:** Cyclodextrine Complex, Differential scanning calorimetric studies, immediaterelease, Dissolution.

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## INTRODUCTION:

The oral route of drug administration is the most convenient and commonly used method of drug delivery[3]. due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability. Although salt formation, solublization, particle size reduction have commonly used to increase dissolution rate and thereby oral absorption and bioavailability of low water solubledrugs there is practical limitation to these techniques.Among numerous ways of enhancing drug dissolution Hydroxy Propyl Beta Cyclodextrin ( HP-β- CD) Complex formation along with drug is one of the promising technique[1].

Cyclodextrins(CDs), cyclicoligosaccharide with a hydrophilic outer surface and hydrophobic central cavity, can form a stable complex with a variety of drugs. CD complexation has been established as an effective method for the improvement of solubility and bioavailability of the many hydrophobic drug molecules[2].Indeed, the most significant characteristic of cyclodextrins is their ability to form inclusion complexes with variousmolecules through host–guest interactions

.These inclusion complexes have been revealed to improve the apparent stability, solubility, dissolution rate, and bioavailability of the guest bioactive molecules. Among various cyclodextrins, β-CD is the most frequently used in pharmaceutical excipient due to its wide availability, low cost, excellent biocompatibility, preferred cavitydimension, and wide regulatoryacceptance[4].

Spironolactone is an diuretic drug which is Practically insoluble in water.Spironolactone is used primarily to treat heart failure, edematous conditions such as nephrotic syndrome or ascites in people with liver disease, essential hypertension, low blood levels of potassium, secondary hyperaldosteronism. Spironolactone is recommended as a fourth line antihypertensive drug by current hypertension guidelines. However, data about its long-term efficacy and safety is limited[11].

Spironolactone is approved by the US Food and Drug Administration for treatingedema in pregnant women, though it has been classified pregnancy category C. In a systematic review of cases of male animals and humans exposed to spironolactone in utero, it was found that feminization of exposed males in animals was observed when spironolactone was administered at high doses (200 mg per day), and at doses less than 100 mg. In studies of humans treated with spironolactone for renal disease, there was no evidence of offspring feminization at doses as high as 400 mg a day[10].

## MATERIALS AND METHODS

### Materials

Hydroxy Propyl Beta Cyclodextrin ( HP-β-CD) is purchased from GangwalChemicals PVT LTD (West Mumbai, INDIA), Crospovidone XL is obtained from Anusha life science Limited (Maharashtra, INDIA), Lactose monohydrate is procured from DFE Pharma (Bangalore, INDIA), Mannitol, Aerosil and Magnesium stearate from Signet Chemical Corporation (Maharashtra, INDIA).

## Methods

### Preformulation study

Preformulation study is one of the important pre-requisite in development of any drug delivery system. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies on the obtained sample of drug are required.

### Confirmation of drug

Confirmation of drug was carried out by melting point determination, differential scanning calorimetry, infrared spectroscopy and uv- spectroscopy.

### Identification of drug

### Melting point determination

Melting point determination is prime requirement for the confirmation of drug D (spironolactone). Melting point isdetermined by Capillary method.

### Differential scanning calorimetry (DSC)

Preapared a sample for ready to DSC, the drug D (spironolactone) was filled or sealed in perforated aluminium pans and placed in to DSC chamber, then started heat to provide heating to chamber at constant rate 10 ºc to per minute , simultaneously or before starting maintain the flow of nitrogen 30-400. If sample testing get complited then the DSC show agreen signal and finally observed and record the reading with the help of graph.

### UV spectrophotometer:

The stock solution of 100µg/ml was prepared by dissolving 10 mg of drug in 100ml of methanol. The UV spectrum of drug D (spironolactone) in methanol was scanned at 400 nm to 200 nm and observed the spectrum, and determined theλ max for identification of drug When the UV spectrum of drug D (spironolactone) in methanol was scanned at 400 nm to 200 nm, maximum absorbance was observed at 238 nm.

**Fourier transform infrared spectroscopy (FTIR) studies**

The IR spectrum of drug D, HPBCD,physical mixture of drug D and HPBCD, inclusion complex, and the presence of additional peaks corresponding to the functional groups was noted.

Marketed product sample was evaluated and parameter as below

**Table No.1: Marketed drug product characterization**

| **Sr.No** | | **Description** |
|---|---|---|
| 1. | Company name | RPG Life sciences Pvt. Ltd. |
| 2. | Brand Name | Pfizer |
| 3 | Description | White coloured round shape tablet |
| 4 | Label claim | Each uncoated tablets contain 25 mg of Spironolactone |
| 5 | Dosage form | Tablet |
| 6 | Shape | Round |
| 7 | Colour | White |
| 8 | Hardness(kp) | 2-5 |
| 9 | Thickness(mm) | 2.45 |
| 10 | Disintegration | 1 min 30 sec. |

# METHODS

**Preparation of Drug inclusion complex**

Inclusion complexes were prepared by kneading method by wetting the physical mixture of Spironolactone:HPβCD in different ratios in a mortar with methanol and water mixture (1:1). The wet mass was then kneaded thoroughly with a pestle to obtain a paste-like consistency. The mass was then dried at room temperature and the dry sample was passed through sieve #80 and stored in a desiccator until further use[5].

**Preparation of immediate release tablet**

Drug inclusion complex (160 mg), superdisintegrant in different ratios and excipients were blended using mortar and pestle. The drug inclusion and the superdisintegrant were sieved through

mesh #40 before blending. The mixture was mixed with magnesium stearate, aslubricant and aerosil as glidant and dispersing agent. they are priviosly sieved through mesh # 60. The above lubricated blend was compressed into tablet on a station rotary punch tablet machine using 9.5mm punch. The hardness was adjustedto 2-4 kg/cm$^2$[4,8]. The formulation design were given in Table 2.

**Table no. 02 Preparation of Immediate Release tablets of Batch No. F01- F09**

| Sr. no | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | SP-HP-B-CD | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 |
| 2 | Mannitol | 69 | 99 | 84 | 84 | 84 | 84 | 84 | 84 | 84 |
| 3 | Crospovidone XL | 15 | 15 | 9 | 21 | 15 | 15 | 15 | 15 | 15 |
| 4 | Lactose monohydrate | 50 | 20 | 41 | 29 | 36.5 | 33.5 | 36.5 | 33.5 | 35 |
| 5 | Aerosil | 3 | 3 | 3 | 3 | 1.5 | 4.5 | 3 | 3 | 3 |
| 6 | Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 1.5 | 4.5 | 3 |
| | Total | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Evaluation of lubricated blend and formulated tablet:Precompression parameters**

**Angle of repose**

The angle of repose gives the measurement of the maximum possible angle between the surface of the pile of powder and the horizontal plane. A simple funnel methodwas used to determine the angle of repose. For this, an accurately weighed powder blend was poured through a funnel that can be raised vertically. The funnel height was adjusted in such a way that the tip of the funnel just touched the apex of the powder heap. The powder was subjected to flow freely through the funnel onto the horizontal surface. After that, the diameter of the powder cone was determined and then its radius (*r*). The height of the pile (*h*) was also calculated accurately. Finally, the angle of repose was calculated using equation 1[6,9].

$$\text{Angle of repose} = \tan^{-1}(h/r) \text{ ----------> eq. (1)}$$

**Bulk Density and Tapped Density**

The bulk and tapped density of precompression powder was calculated by equations (2) and (3)[6]

**Carr's index**

The flow characteristics of precompression powder were determined by measuring compressibility index/Carr's index. Compressibility is the simplest way of measuring the flow property of powders. It is an indication of the ease with which materials can be induced to flow and is given by Carr's index (CI), which can be calculated from equation (4)

**Hausner's ratio**

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material[6].

$$\text{Bulk density( gm/ml)} = \frac{\text{Mass of Powder}}{\text{Bulk Volume of powder in measuring cylinder (mL)}} \text{ ----------> eq.(2)}$$

$$\text{Tapped density( gm/ml)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of powder in measuring cylinder (mL)}} \text{ ----------> eq. (3)}$$

$$\text{Carr's index} = 100\ \frac{(V_0 - V_f)}{V_0} \text{ ---------> eq. (4)}$$

$$\text{Hausner's ratio} = V_0/V_f \text{ ----------> eq. (5)}$$

**Post compression parameters**

**Thickness**

Arbitrarily, five tablets from each formulation were taken, and their thicknesses were measured using the Vernier caliper. -en, the mean thicknessand SD were calculated[6].

**Hardness**

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The values are recorded and noted[9].

**Friability**

About 10 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated using the following formula[9],

Percentage friability = (initial weight-final weight/initial weight × 100).

**Weight variation**

The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. First, the total weight of 20 tablets from each formulation is determined, andthe average is calculated. The individual weight of the each tablet is also determined to find out the weight variation[9].

% wt variation = (average weight of tablet - weight of each tablet/average of tablet).

**Disintegration time**

In the disintegration timestudy, for each batch, three tablets were introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker containing 900mL of distilled water. Then, the time of disintegration wasrecorded at 37 ± 2°C. Finally, the mean disintegration time and SD were calculated[6].

**In-vitro dissolution study**

*In vitro* dissolution study is performed using USP type 2 apparatus (paddle) at 75 rpm. 0.1 N HCl 900 ml is used as dissolution medium which maintained at 37 ± 0.5°C. At definite time intervals, 5 mlof the fluid was withdrawn. Filtered through 0.45 μm membrane filter and again 5 ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid, and the samples were analyzed spectrophotometrically at 238nm [9].

**Drug content uniformity**

For the assay of the newly formulated tablets, random 20 tablets were weighed and powdered. The powder, equivalent to 50 mg, was weighed accurately and dissolved in 100mL of methanol. The solution was shaken thoroughly and sonicated for 15 minutes. The undissolved matters were removed by filtration through Whatman No.41 filter paper. The filtrate was diluted appropriately to prepare a final solution of 2 $\mu$g/mL. The absorbance of the diluted solutions was measured at 238 nm using a UV spectrophotometer. The concentration of the drug was determined from the standard calibration curve of Spironolactone. For each batch, the assay was calculated in triplicate. Then, the mean assay and SD were calculated[6].

**RESULTS AND DISCUSSION**

**Melting point determination**

The melting point of drug D was measured by using glass capillary method indicate the melting point of drug D (spironolactone) at 205 $^{o}$C . It was confirmed with the reported melting point of drug D in between 200-210 $^{o}$C.

**Differential scanning calorimetry (DSC)**

The thermal behavior of Spironolactone was determined using Mettler Toledodifferential scanning calorimeter. Samples were placed in aluminum crucible and the DSC thermograms were recorded at heating rate of 10 $^{\circ}$C/ min in the range 40 to 300 $^{\circ}$C under nitrogen atmosphere. The melting point of Spironolactone e by DSC was found to be 210 $^{\circ}$C. The reported melting point of DSC was 210-211 $^{0}$C. From this result we can confirms that the drug was Spironolactone.

**DSC thermogram of drug D (Spironolactone)**

The melting point of Spironolactone e by DSC was found to be 210 $^{o}$C. The reported melting point of DSC was 210-211$^{0}$C. From this results we can confirms that the drug was Spironolactone.

**UV Spectroscopy**

From spectrophotometric analysis $\lambda_{max}$ of Spironolactone was found to be 238 nm. The reported $\lambda_{max}$ Spironolactone was 238- 242 nm. From the spectroscopic analysis of Spironolactone the wavelength was found in the range of reported value here we confirms the drug was Spironolactone.

**Fourier Transform Infra-red (FTIR) Spectroscopy**

Fourier Transform Infrared spectra ofdrug D, HPBCD, physical mixture of drug D and HPBCD, inclusion complex
. physical mixture of, HPBCD with drug D and inclusion complex is shown in figure and its interpretation in table. From interpretation can conclude thatthere is no drug–polymer interaction. Pure drug D spectra showed sharp characteristic peaks and there are interpretive assignments of characteristic absorbance bands.

All the characteristic peaks of drug appear in the spectra of physical mixtures at the wave number indicating no modification or interaction between drug and the polymers. IR spectra recorded for drug D, hydroxypopyl-β- cyclodextrin, physical mixture and inclusion complex are shown in Figure.4-6. Pure drug D spectra showed sharp characteristic peaks at 2951.19 $cm^{-1}$ assigned to alkane C-H stretch group. The peak at 1760.85 $cm^{-1}$ can be assignedto aromatic compound C-H stretch group. The characteristic peak at
1674.27 $cm^{-1}$ can be assigned to imine/oxime C=N Stretch usually weak. The characteristics peak at 1188.19. $cm^{-1}$ revealed presence of sulfonate S=O Stretch groups, while peaks at 1249.91 cm-1 can be assigned to alkene C-C Stretch group respectively. The characteristics peak at
638.46 cm-1 revealed the presence of halo compound C-Br stetch group. All the above characteristic peaks of drug appears in the spectra of physical mixture at the same wave number indicating no modification or interaction between drug and the polymer while some diminution and disappearance of some peaks in inclusion complex may be due to encapsulation of drug into the polymer.

**Pre-compression parameters**

About 9 formulations were prepared with different ratios addition of different ingredients. For each designed formulations powder mixed blend of drug and excipients were prepared and evaluated for various parameters.

Blend were prepared and subjected to precompression evaluation like tapped density, bulk density, carr's index, hausners ratio and angle of repose (Table no.04).Tapped density of the formulations was good and in the range of 0.51-0.68±0.04gm/ml , where as the bulk density was in the range of 0.41-
0.54 gm/ml. The compressibility valueswere in the range of 15%- 20.33.From these values, it was evident that theseblends had good flow properties.

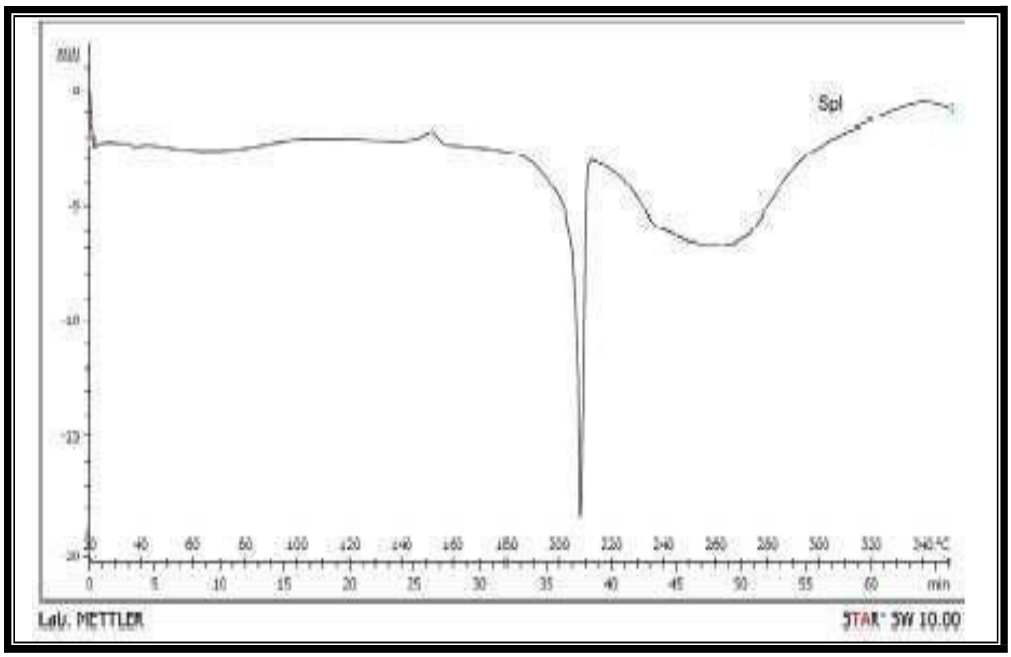


**Figure 01. DSC spectra of Drug D.**

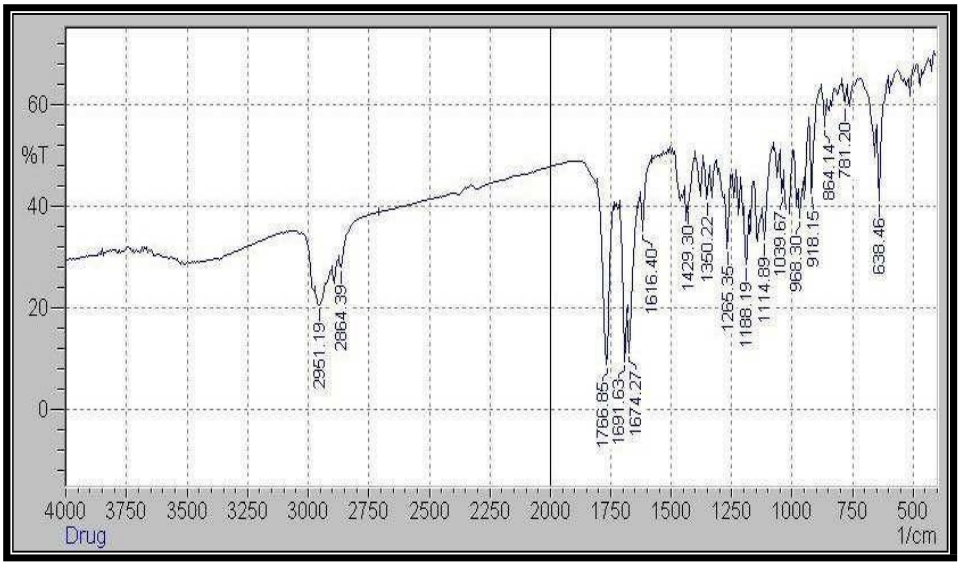


**Figure 02. IR Spectra of Drug D (Spironolactone).**

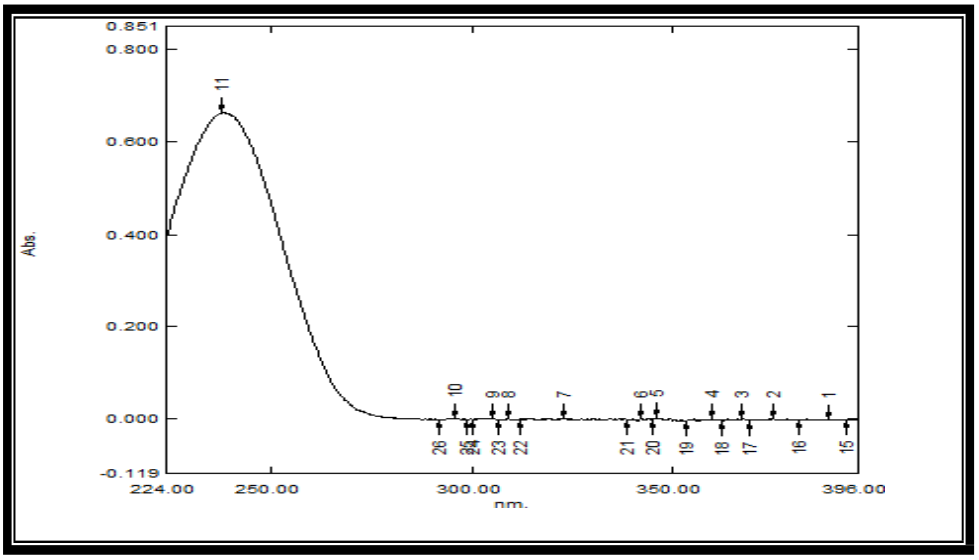


**Figure 03. UV Spectrum of drug D (Spironolactone)**

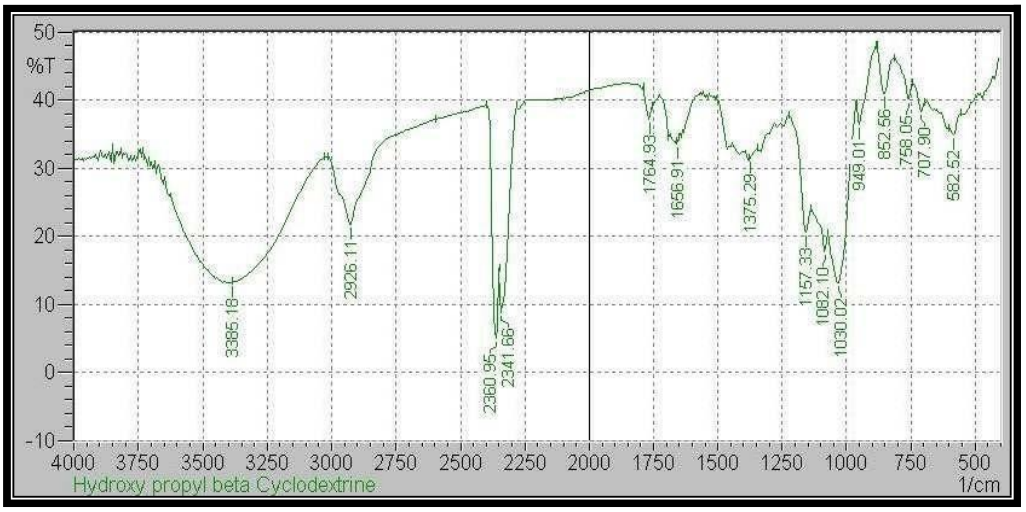


**Figure 04. IR spectra of HPβCD.**

In the above mentioned infrared spectrum of HPBCD ranges such as (3385.18,2926.11,2360.95,2341.66,1764.93,1656.91,1656.11,1375.29,1157.33,1030.02,948.01,582.52,707.90) are observed peak equal to reported peak.

**FTIR Spectroscopy of physical mixture**

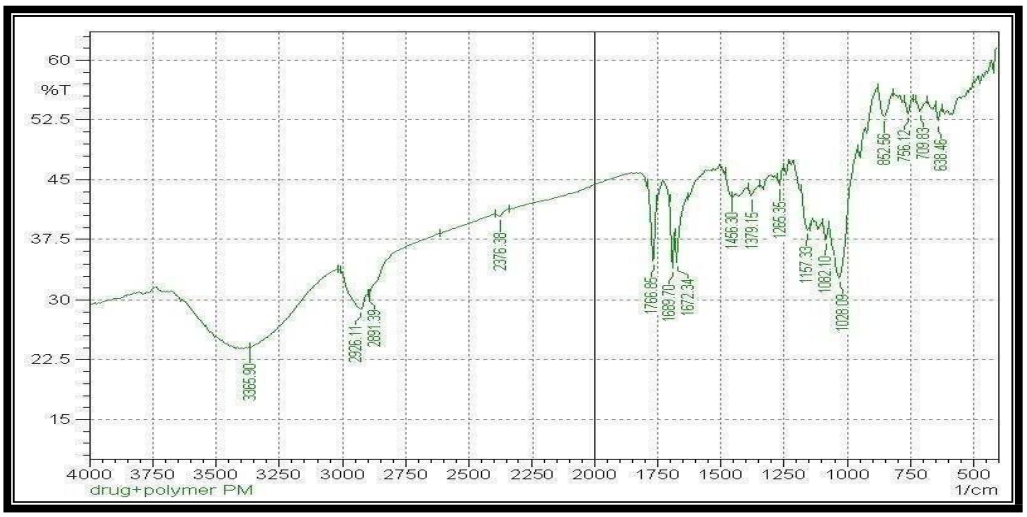


**Figure 05. IR spectra of physical mixture (drug D+polymer)**

In the above mentioned infrared spectrum of drug D ranges such as (3365.90,2926.11,2891.39,2376.38,1766.85,1639.70,1689.70,1672.34,1436.30,1379.15,1265.35,1157.33,1082.10,1026.09,852.56,756.12,709.83,638.46) are observed and are not interacted with spectra**.**

**FTIR Spectroscopy of inclusion complex:**

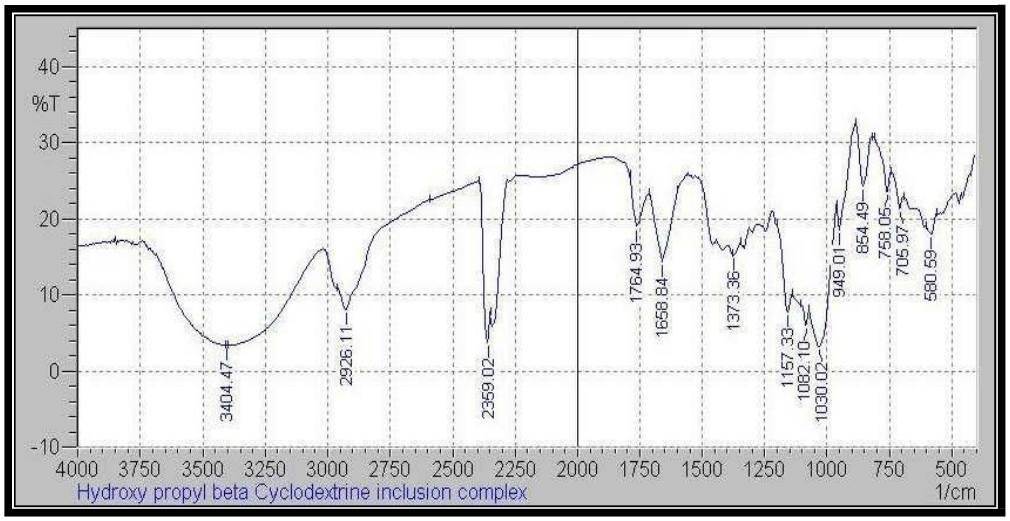


**Figure 06. IR spectra of inclusion complex (drug D+polymer).**

In the above mentioned infrared spectrum of drug D ranges such as (3404.47,2926.11,2356.02,1764.93,1658.84,1373.36,854.49,758.05,705.97,580.59) are observed and are not interacted with spectra**.**

**Table No. 03: Drug-polymer interaction studies through IR spectroscopy.**

| Polymer | Drug peak ($cm^{1}$) | Polymer peak ($cm^{-1}$) | Drug + Polymer (PM) peaks | Interactions |
|---|---|---|---|---|
| **HPBCD** | 2951.19,2864.39,1674.27,1616.40,1429.30,1350.22,638.46 | 3385.18,2926.11,1764.93,1157.33,852.56,758.05,707.90,582.52 | 3365.90,2926.11,1766.85,1689.70,1672.34,852.56,709.83 | No |

**Table No. 04: Precompression parameter**

| B.No | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Hausner's Ratio (HR) | Compressibility Index (%) |
|---|---|---|---|---|
| F1 | 0.51 ±0.02 | 0.60 ±0.03 | 1.17 | 15.090 |
| F2 | 0.44 ±0.02 | 0.53 ±0.02 | 1.22 | 18.18 |
| F3 | 0.41 ±0.03 | 0.51 ±0.04 | 1.26 | 20.80 |
| F4 | 0.38 ±0.03 | 0.48 ±0.03 | 1.26 | 20.59 |
| F5 | 0.40 ±0.05 | 0.49 ±0.01 | 1.22 | 18.33 |
| F6 | 0.54 ±0.02 | 0.68 ±0.02 | 1.24 | 17.85 |
| F7 | 0.54±0.02 | 0.67±0.04 | 1.24 | 17.80 |
| F8 | 0.51±0.02 | 0.62±0.04 | 1.2 | 15.77 |
| F9 | 0.50±0.02 | 0.61±0.04 | 1.19 | 16.55 |

**Post compression parameters**

Blend with good flow properties were subjected to compression to formulate immediate release tablets. Results of post compression evaluation is reported in(table no.05) Physical parameters such as color and weight variation was found within the specification of I.P 1996. Average weightof the all nine formulations were found in the range of 295-308 mg.

Thickness was found within the specification of I.P 1996 with average thickness of all nine formulations were found to be in the range of 3.50-4.50 mm.

Hardness of the F9 formulation was found to be 4-5 Kp which was similar to reference product. Average friability of all

nine formulations were found in the range of 0.9%-0.15%. which was within specification and disintegration time of

F9 formulation was found to be in range 1-2 min comparatively less than otherformulation.

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**Table No. 05: Post compression parameter**

| B.No | Average Hardness (kp) | Friability (%) | DT (min.) | Average Weight (mg) | Average Thickness (mm) |
|---|---|---|---|---|---|
| F1 | 6-7 | 0.9 | 8-9 | 295 | 3.50-4.50 |
| F2 | 4-5 | 0.9 | 8-9 | 300 | 3.50-4.50 |
| F3 | 4-5 | 0.1544 | 10-12 | 297 | 3.00-4.00 |
| F4 | 4-5 | 0.11 | 1-2 | 307 | 3.50-4.50 |
| F5 | 3-5 | 0.18 | 2-3 | 301 | 3.50-4.50 |
| F6 | 6-7 | 0.11 | 8-9 | 305 | 3.50-4.50 |
| F7 | 4-5 | 0.13 | 5-6 | 300 | 3.50-4.50 |
| F8 | 4-5 | 0.19 | 11-12 | 299 | 3.50-4.50 |
| F9 | 4-5 | 0.12 | 1-2 | 308 | 3.50-4.50 |

***In-vitro* drug release:**

For all Batch dissolution parameters and results of % drug release is shown inTable 6.

**Table No. 06 % Drug release of tablets in 01. N HCl at 75 rpm**

| Time | Reference product | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 30 | 33 | 34 | 28 | 38 | 33 | 20 | 36 | 25 | 65 |
| 10 | 45 | 59 | 68 | 52 | 55 | 49 | 36 | 50 | 36 | 80 |
| 15 | 63 | 67 | 73 | 60 | 64 | 63 | 51 | 64 | 46 | 89 |
| 20 | 67 | 86 | 81 | 74 | 75 | 72 | 62 | 71 | 52 | 93 |
| 30 | 80 | 91 | 94 | 77 | 82 | 83 | 70 | 78 | 63 | 97 |
| Infinity | 97 | 97 | 98 | 81 | 91 | 98 | 79 | 89 | 71 | 99 |

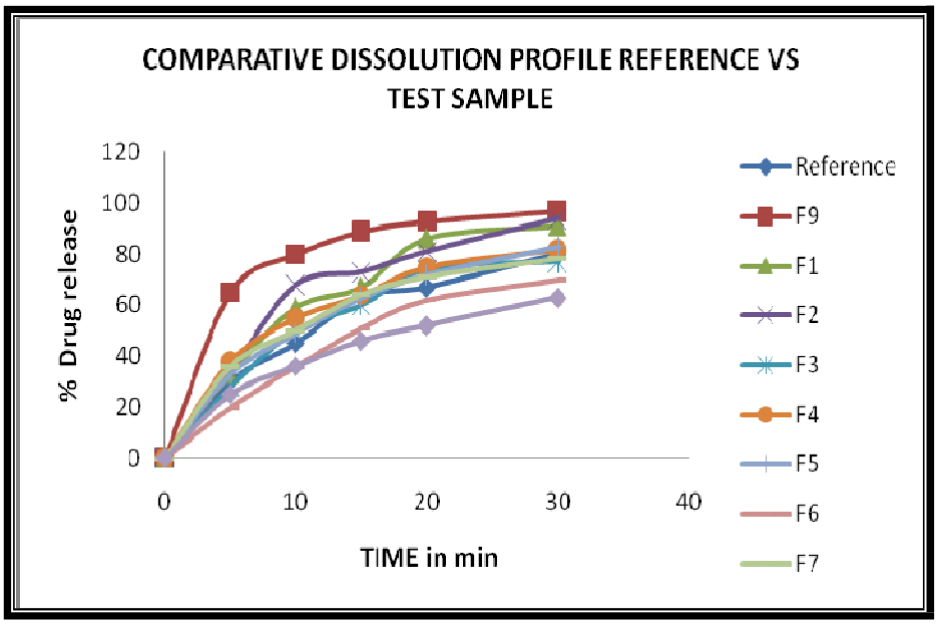


**Figure 07. Dissolution profile**

From precompression and compression parameter of drug D immediate release tablet shows that batch F9 was suitable as immediate release dosage form. Disintegration and dissolution test of all batches were performed in pH 1.2 buffer containing 0.1% SLS. It represent that crospovidone shows ideal disintegration which confirms the earlier report.

## CONCLUSION

From the present work, it may be concluded that the immediate releasing tablets drug D (Spironolactone) can beprepared by direct compression method was found to be good without any chipping, capping and sticking. Commercial formulations were evaluated using various tests including in vitrodissolution studies. The prepared formulations exhibited better dissolution profiles, drug release, drugcontent uniformity and less disintegration time compared to the commercial formulation. It can be concluded that the immediaterelease tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action with better dissolution compared to marketed formulation.

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