



FORMULATION AND EVALUATION OF FAST DISSOLVING CHLOROTHALIDONE TABLETS

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ABSTRACT

An attempt has been made for the development of rapidly disintegrating oral tablets by direct compression using co-grinding and solid dispersion methods by using chlorthalidone as a model drug. Chlorthalidone is a well known diuretic used in the treatment of hypertension and oedema. The half life of chlorthalidone is 40 hours. The major problem with this drug is erratic absorption from GIT, limited aqueous solubility and a high melting point, which may hinder dissolution causing decreased bioavailability of the drug. Therefore the solid dispersions and co-grinding method were followed with a view to increase solubility and bioavailability. The tablet formulation containing polyvinyl pyrrolidone K-12 solid dispersion showed maximum drug release than the chlorthalidone polyvinyl pyrrolidone K-12 co-grinding method. The dissolution profile of best solid dispersion formulation (P3) was compared with co-grinding method formulation (F3). The prepared tablets were evaluated for hardness, friability, wetting time, disintegration time and *in vitro* drug release. DSC and FTIR studies revealed that no chemical interaction between the drug and the carrier. The stability studies were conducted as per the ICH guidelines and the formulations were found to be stable with insignificant change in the hardness, and disintegration time. Present study revealed that, using solid dispersion of the drug with the hydrophilic carrier Poly Vinyl Pyrrolidone can enhance the dissolution rate of chlorthalidone tablets.

Keywords: Chlorthalidone, Fast Dissolving Tablet, Superdisintegrant, Solid Dispersion, Co-grinding.

INTRODUCTION

The concept of Fast dissolving drug delivery system emerged from the desire to provide the patients with more conventional means of taking their medication. It is difficult for many patients to swallow tablets (hard gelatin capsules particularly in pediatric and geriatric patients.) Such problems can be resolved by means of Fast dissolving tablets. Chlorthalidone is a well known diuretic used in the treatment of hypertension and oedema¹. The major problem with this drug is that it is erratically absorbed from GIT, limited aqueous solubility and a high melting point. The half life of drug is 40 hrs, which may hinder dissolution and decrease bioavailability of the drug. The rate and extent of dissolution of the drug from any solid dosage form, determines the rate and

extent of absorption of the drug. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°), due to erratic or incomplete absorption from GIT². The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly water-soluble drugs. A number of drugs have shown to improve their dissolution character when converted to solid dispersions³⁻⁸ and also in the preparation of the powdered products, co-grinding is generally used for reducing the particle size. It has been reported that a strong force (such as grinding) may increase the surface energy and cause the

distortion of the crystallite resulting in the reduction of particle size.

Solid dispersion (SD), which was introduced in the early 1970s⁹, is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability¹⁰. Chiou and Riegelman defined the term SD as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method. When SD is exposed to aqueous media, the carrier dissolves and the drug release as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. Hence, in present study we attempted to improve the dissolution of chlorthalidone through the formulation of tablets containing solid dispersion and co-grinding method using PVP K-12 as carrier and croscarmellose sodium as superdisintegrant.

MATERIALS AND METHODS

Materials

Chlorthalidone was procured as a gift sample from IPCA Laboratories, Mumbai. Croscarmellose sodium (CP) was obtained as a gift sample from Maruthi chemicals Ahmedabad. Microcrystalline cellulose, magnesium stearate and talc were purchased from S.D. Fine Chemicals, Mumbai. All other materials used were of pharmaceutical grade.

Methods

Formulation of chlorthalidone tablets

Preparation of Solid Dispersions of chlorthalidone

Chlorthalidone solid dispersions in the ratios 1:1, 1:2, 1:4 and 2:1 were prepared employing hydrophilic carrier PVP by solvent evaporation technique. Accurately weighed

quantity of drug was dissolved in methanol to get clear solution. Carrier PVP K-12 was added to this solution and mixed thoroughly. The dispersions were initially dried at room temperature for 1 h to evaporate all the solvent with continuous stirring, followed by drying at 65^o for 6h in a hot air oven. The dried mass was crushed, pulverized and sifted through 80 mesh.

Preparation of co grinding of chlorthalidone

The 1:1, 1:2 1:4 and 2:1 (w/w) ratio physical mixture of chlorthalidone and PVP K-12 were mixed uniformly through a 100 mesh sieve screen with care to avoid any grinding action. The mixture was prepared by cogrinding in a glass mortar and pestle.

Evaluation of chlorthalidone tablets

After the preparations of solid dispersion and cogrinding all the ingredients were added and mixed for 10minutes (Table 1) and was compressed using a single punch tablet machine to produce convex faced tablets weighing 150 mg and the prepared tablets were evaluated for various official specifications.

Weight variation

Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

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 Pfizer hardness tester. The hardness was measured in terms of kg/cm².

Friability¹¹

The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Six tablets were tested from each formulation.

Disintegration time¹²

Tablet was put into 100 ml distilled water at $37 \pm 2^\circ$. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus.

Content uniformity

One tablet was crushed and 30ml of distilled water was mixed and shaken for 15 minutes. Sufficient water was added to produce 50 ml and then centrifuged. To the clear supernatant liquid (5ml), add sufficient water to produce 100 ml and the absorbance maxima of the resulting solution was recorded as 275 nm.

***In vitro* drug release study of tablets^{13,14}**

In vitro release of the tablets (Table-3) was conducted using USP dissolution apparatus II (UV-1700 Shimadzu Corporation, Japan) at 75 rpm, using distilled water as a dissolution media maintained at $37 \pm 0.5^\circ$. Samples were withdrawn at various time intervals, filtered through a 0.45 micron membrane filter, diluted and assayed at 275 nm, using an UV/VIS spectrophotometer. All the results were performed in triplicate.

Characterization of chlorthalidone tablets

FTIR Studies

IR spectra for drug, and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies

DSC scans of about 10mg of drug and a powdered tablet was carried out using an automatic thermal analyzer system. (Mettler

Toledo, USA) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of $10^\circ/\text{min}$ from $50-300^\circ$.

Stability studies

The stability study of the tablets was carried out according to ICH guidelines at $40 \pm 2^\circ / 75 \pm 5 \% \text{RH}$ for 4 weeks by storing the samples in stability chamber (Lab-Care, Mumbai).

RESULTS AND DISCUSSION

The tablet formulations were evaluated for hardness, disintegration time, and wetting time and *in vitro* dissolution studies. Table 2 shows the hardness of tablet formulations F2, F3 was higher than the tablet formulations P2, P3. This may be due to the increase in the contact area among powder particles¹⁵ which may lead to late disintegration and wetting time of the P2, P3 formulations. The tablets prepared by the solid dispersion method disintegrated rapidly compared to the PVP cogrinding method, because of increased solubility and wettability of the tablets. The friability of all the formulations was $\leq 0.75\%$ indicating tablets ability to withstand abrasion in handling, packaging and shipment. The disintegration times of the tablets prepared by solid dispersion ranged between 13.3 to 18.7 seconds where as for the tablets prepared by cogrinding method were found to be 23.8 to 361.8 seconds.

Table 3 shows *in vitro* drug release data. Among all formulations the P3 formulation was indicating rapid drug release (Figure 1) than the other formulations, this may be due to improved wettability by the carrier. Where

Table 1: Formulation of fast dissolving tablets of Chlorthalidone

Ingredients	P1	P2	P3	P4	F1	F2	F3	F4
Amount of solid dispersion equivalent to 25 mg of drug (PVP)	56.42	79.26	116.0	36.26	-	-	-	-
PVP Co-grinding	-	-	-	-	25	50	75	12.5
Micro crystalline cellulose	85.78	64.74	28.00	107.74	116	91	66	128.5
Cross povidone	3	3	3	3	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5	3	3	3	3
Talc	1.5	1.5	1.5	1.5	3	3	3	3
Tablet weight	150	150	150	150	150	150	150	150

PVP - Poly Vinyl Pyrolidone.

Table 2: Evaluation of fast dissolving tablets

Formulation	Hardness (Kg/cm ²)	%Friability	Disintegration Time (Sec)	Wetting Time (sec)
P1	4.03 ±(0.25)	0.33 ± (0.01)	18.70 ±(0.30)	14.60 ±(0.52)
P2	3.42 ±(0.38)	0.49 ±(0.03)	15.72 ± (1.15)	14.52 ±(1.98)
P3	4.13 ±(0.25)	0.44 ± (0.10)	13.33 ± (1.55)	9.54 ±(1.62)
P4	3.42 ± (0.38)	0.41 ± (0.04)	28.00 ±(1.28)	18.33 ±(0.57)
F1	3.42 ± (0.15)	0.52 ± (0.01)	23.87 ±(1.25)	15.66 ± (0.57)
F2	4.25 ± (0.52)	0.59 ±(0.03)	181.29 ±(1.57)	173.31 ±(1.50)
F3	4.50 ±(0.41)	0.54 ±(0.02)	361.22 ± (1.92)	343.32 ±(1.94)
F4	3.33 ± (0.28)	0.33 ±(0.02)	28.33 ± (0.57)	18.66 ±(0.57)

Values in parenthesis are standard deviation (±SD), n=3

Table 3: *In vitro* drug release and drug content of tablet formulations

Formulation	Time (Min)	%Drug Release	%Drug Content
P1	15	98.74 ± (0.38)	103.32 ± (0.54)
P2	10	99.00 ± (0.57)	99.97 ± (0.94)
P3	8	98.5 ± (0.98)	96.66 ± (1.25)
P4	20	98.23 ± (0.22)	100.00 ± (1.54)
F1	25	99.97 ± (0.82)	100.90 ± (0.81)
F2	30	101.15 ± (1.52)	99.97 ± (1.24)
F3	45	100.54 ± (0.98)	101.33 ± (0.24)
F4	25	99.36 ± (0.52)	102.10 ± (0.98)

Values in parenthesis are standard deviation (±SD), n=3

Table 4: Results of stability study

Formulation	Disintegration Time (sec)	% Drug Content
P1	17.50 ± (0.30)	101.33 ± (0.54)
P2	14.84 ± (1.15)	98.97 ± (0.94)
P3	13.35 ± (1.55)	95.66 ± (1.25)
P4	27.00 ±(1.28)	99.97 ± (1.54)
F1	22.57 ±(1.25)	101.33 ± (0.81)
F2	179.29 ±(1.57)	99.97 ± (1.24)
F3	360.57 ± (1.92)	101.54 ± (0.24)
F4	28.59 ± (0.57)	102.10 ± (0.98)

Values in parenthesis are standard deviation (±SD), n=3

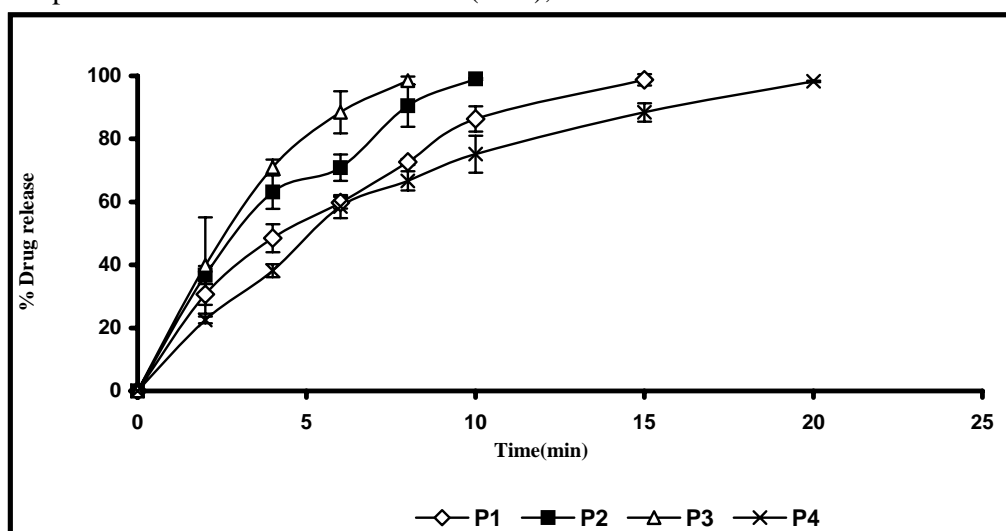


Fig. 1: *In vitro* release profiles of solid dispersions with PVP

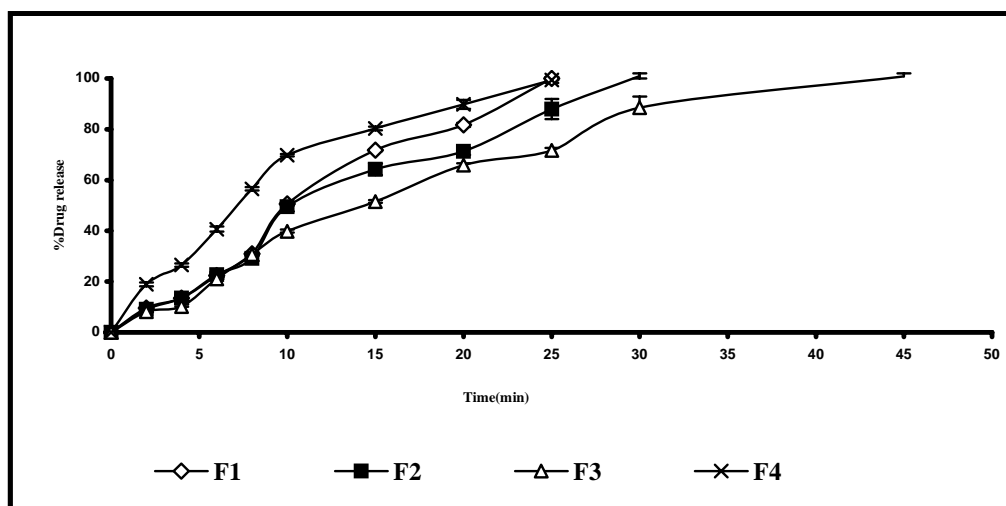


Fig. 2: *In vitro* release profiles of cogrinding with PVP

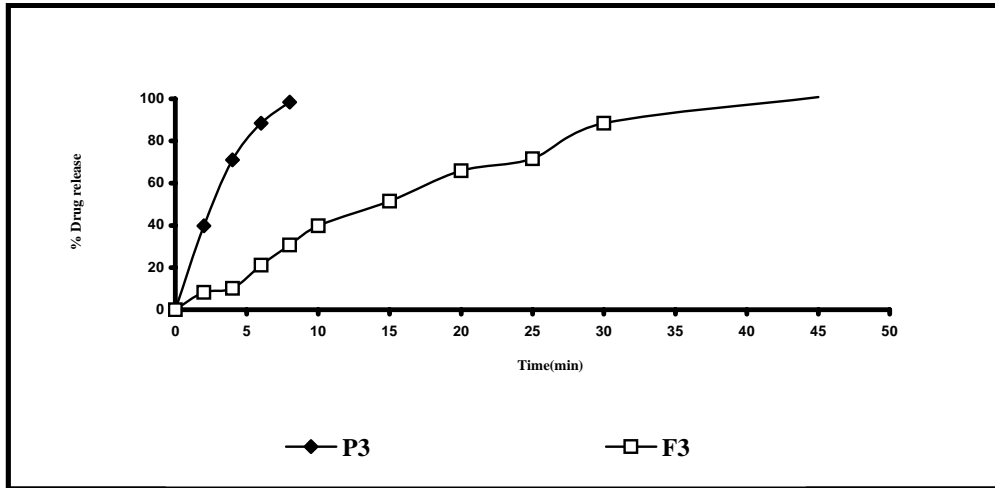
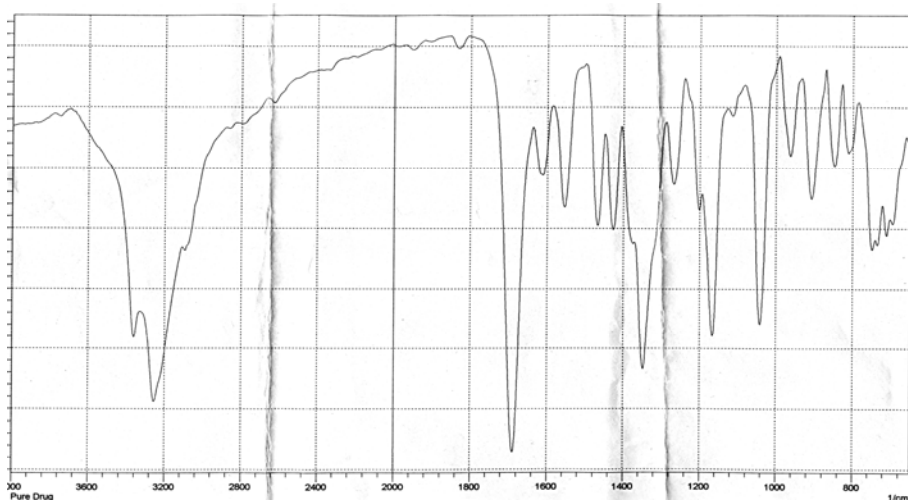
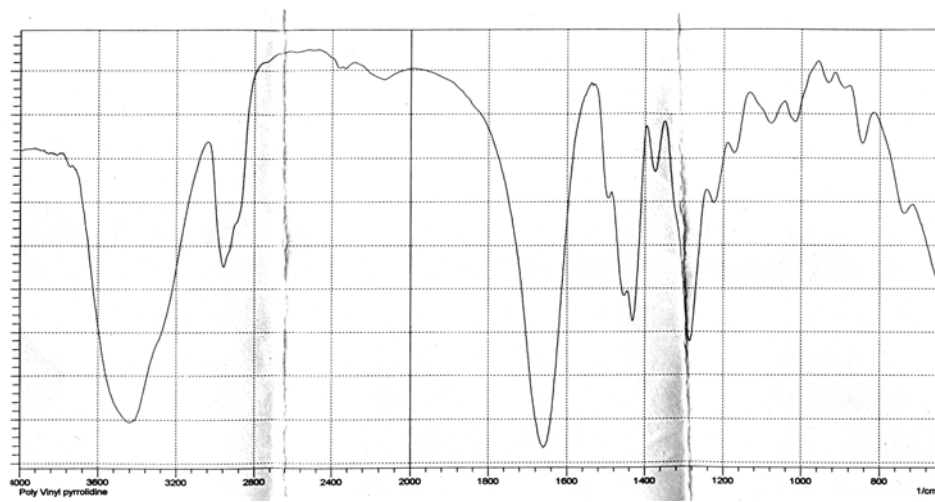


Fig. 3: Comparative *in vitro* release profiles of P3 and F3



A



B

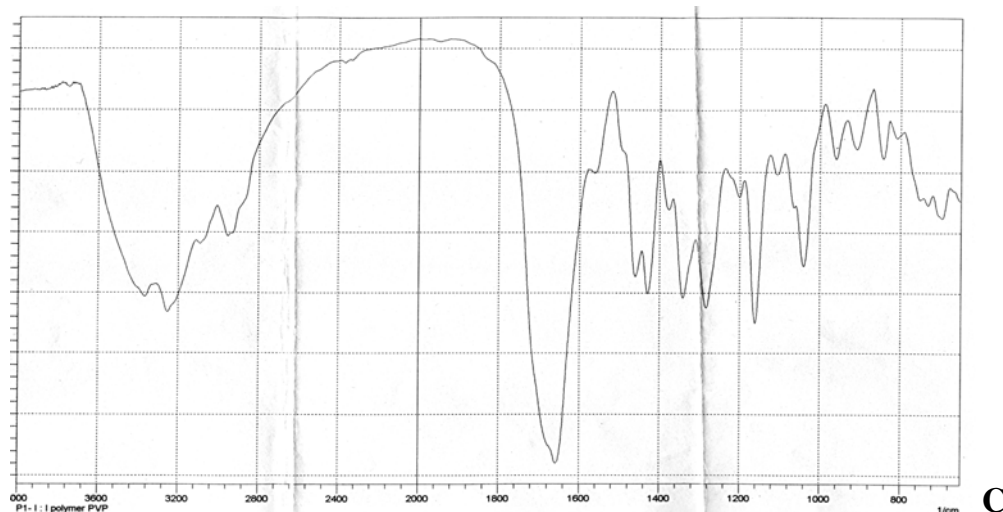


Fig. 4: FTIR spectra of pure Drug (A), Pure PVP (B) and Solid dispersion (P3)

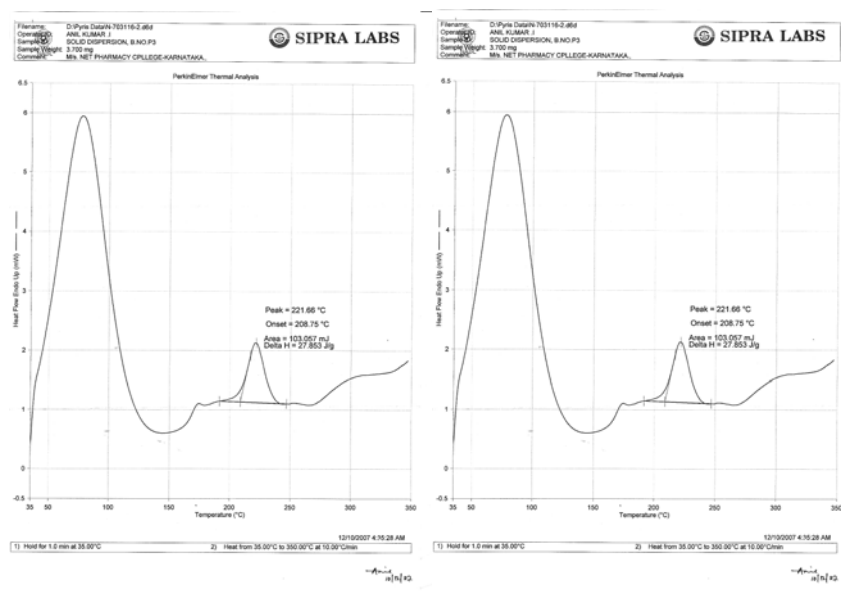


Fig. 5: DSC thermograms of pure drug (A), solid dispersion P3 (B)

as F3 formulation shows slow release (Figure 2) when compared to P3 formulation, this may be due to formation of viscous boundary layer around the drug particles, leading to decrease in the dissolution rate and increased accumulation of carrier molecule in the bulk causing saturation, thus retarding chlorthalidone release. Mechanism for the burst effect may be attributed to the rapid

disintegration and dissolution of a tablet, due to the use of super disintegrant together with the hydrophilic carrier in the formulations. Superdisintegrant CP has a known mechanism of capillary action which allows rapid swelling by creating uniform pressure on the surface of the tablet, allowing faster wettability and disintegration. And hydrophilic carrier on contact with water

solublize leaving drug in finer state which subsequently solublize rapidly showing burst release. The drug content of all the tablet formulations was found between 98 to 101%. In Figure 3 the comparative *in vitro* release profiles of the solid dispersions and co-grinding methods of P3 and F3 formulations respectively are shown. Among all the formulations P3 showed the faster dissolution ($\leq 98.5\%$ in 8 minutes) compared to F3 ($\leq 100.54\%$ in 45 minutes). Hence P3 can be considered as the best formulation for rapid release of drug.

IR spectra of chlorthalidone, PVP and solid dispersion are shown in Figure 4. Pure drug showed characteristic absorption bands at 3280-3400 cm^{-1} and the solid dispersion of PVP showed similar characteristic absorption bands in the same range without significant change in the wave number indicating no chemical interaction between drug and the polymer.

Thermograms of pure drug and the solid dispersion were depicted in Figure 5. DSC reports reveal that there is a sharp endothermic peak at 225°C for pure drug which is in agreement with the theoretical m.p of the drug. The formulation P3 (1:4 PVP) is showing two endothermic peaks at 225.5°C (drug) and 70°C. The second endotherm at 70°C appears for the carrier PVP which is in agreement the theoretical m.p of pure PVP. The peak height of drug is reduced and has become broader in nature which may be attributed to the change in the physical state of the pure drug from crystalline form to amorphous form due to molecular dispersion.

Stability studies were carried out at 45° for 4 weeks in order to determine the change in *in*

vitro release profile on storage. No appreciable change in physical characteristics was observed at the end of 4 weeks (Table 4). Disintegration time and drug content was almost same, before and after storage for 4 weeks at 45°.

CONCLUSION

The major problem of chlorthalidone that it is erratically absorbed from GIT, its limited aqueous solubility and a high melting point, which may hinder dissolution and decrease bioavailability. Results revealed that it is possible to enhance dissolution rate and bioavailability by using solid dispersion and co-grinding of the drug with the hydrophilic carriers poly vinyl pyrrolidone and cross povidone. Finally it can be concluded that using solid dispersion of the drug with the hydrophilic carrier poly vinyl pyrrolidone can enhance the dissolution rate of chlorthalidone tablets.

ACKNOWLEDGEMENTS

Authors thanks to IPCA laboratories Ltd Mumbai for providing a gift sample of chlorthalidone and Maruthi chemicals for providing a gift sample of superdisintegrant. The authors are also thankful to **Dr. R. H. Udupi**, Professor, N.E.T. Pharmacy College, for his valuable suggestions in carrying out this research work. The authors are also thankful to Principal and Management, N.E.T. Pharmacy College, Raichur for providing the facilities.

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