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Design of fast dissolving tablets of Chlorthalidone using novel co-processed superdisintegrants

N. G. Raghavendra Rao[1]*, K. Ravi Kumar[2]

[1]P. G. Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga, Karnataka, India
[2]Mallareddy Institute of Pharmaceutical Sciences, Hyderabad, Andhra Pradesh, India

ABSTRACT

In the present work, fast dissolving tablets of Chlorthalidone were prepared using novel co-processed superdisintegrants consisting of crospovidone and croscarmellose sodium in the different ratios (1:1, 1:2 and 1:3). Chlorthalidone is widely accepted for its excellent antihypertensive and anti-diuretic effect. Effect of co-processed superdisintegrants on wetting time, disintegrating time, drug content, and in-vitro release have been studied. Drug compatibility with excipients was checked by FTIR and DSC studies. Stability studies were carried out as per ICH guidelines for three months. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. In all the formulations, hardness test indicated good mechanical strength results were ranges from 2.96 to 3.24 kg/cm^2, friability is less than 1%, indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 2.11 to 2.21 mm. Drug content was found to be in the range of 98.10 to 99.88 %. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 24 to 124 sec. Among all the designed formulations, formulation CP1 was found to be promising and was displayed an in-vitro dispersion time of 19 sec, which facilitates its faster dispersion in the mouth. Among all the formulations CP1 containing 4% w/w of co-processed superdisintegrants was found to be promising and has shown an in-vitro dispersion time of 19 sec, wetting time of 24 sec. Stability studies on promising formulation indicated that there were no significant changes in drug content and in-vitro dispersion time ($p<0.05$). From this study, it can be concluded that dissolution rate of Chlorthalidone could be enhanced by tablets containing co-processed superdisintegrant.

Key words: Co-processed superdisintegrants, chlorthalidone, croscarmellose sodium, and crospovidone.

INTRODUCTION

Chlorthalidone is a phthalamide derivative of benzene sulphonamide and is designated as 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulphanilamide. Chlorthalidone is used in the present study and widely accepted for its excellent antihypertensive and anti-diuretic effect [1]. For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets. Because, faster disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug [2]. Solid oral dosage forms, especially tablets, remain one of the most popular because of advantages like patient convenience, ease of storage and dispensing, dose accuracy and easy manufacturability.

Major challenge for tablets manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug [3]. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately [4]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability [5]. Excipients with improved functionality can be obtained by developing new chemical excipients, new grade of existing materials and new combination of existing materials [6]. New combinations of existing excipients are an interesting option for improving excipients functionality because all formulations contain multiple excipients. One such approach for improving the functionality of excipients is co-processing of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual [7]. Co-processing excipients lead to the formulation of excipients granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity [8]. Several co-processed superdisintegrants are commercially available: Ludipress (lactose monohydrate, polyvinylpyrrolidone and crospovidone), Starlac (lactose and maize starch), Starcap 1500 (corn starch and pregelatinized starch), Ran Explo-C (microcrystalline cellulose, silica and crospovidone), Ran Explo-S (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G (microcrystalline cellulose, hydroxy propyl methyl cellulose and crospovidone) [9]. The widely used superdisintegrants are crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG). In the present investigation, the preparation and evaluation of fast dissolving tablets by using co-processed superdisintegrants containing CP and CCS was studied. The reasons for selection of CP are high capillary activity, pronounced hydration capacity and little tendency to form gels [10]. The concept of formulating fast dissolving tablets (FDT) of Chlorthalidone (excellent antihypertensive and anti-diuretic effect) using co-processed superdisintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [11]. The compositions of which are given in **(Table 1)**.

Table 1: Formulations of Chlorthalidone FDT Prepared by Direct Compression Method

Formulation code	CP0	PM1	PM2	PM3	CP1	CP2	CP3
Chlorthalidone	25	25	25	25	25	25	25
Superdisintegrants (CP+CCS)	--	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3
Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3
Pine apple flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Microcrystalline cellulose (Avicel PH-102)	30	30	30	30	30	30	30
Mannitol (Pearlitol SD 200)	86	80	100	80	80	80	80
Total weight in mg/tab	150	150	150	150	150	150	150

PM - Physical Mixture of crospovidone and croscarmellose sodium in different ratios (1:1, 1:2, 1:3), CP - Co-processed Superdisintegrants of crospovidone and croscarmellose sodium in different ratios (1:1, 1:2, 1:3), CP0 - Control formulation (without superdisintegrants), CP - Crospovidone, CCS- Croscarmellose sodium.

MATERIALS AND METHODS

Chlorthalidone was procured as a gift sample from IPCA Laboratories, Mumbai. Superdisintegrants (Maruti Chem. Ahmadabad), Aspartame, Directly compressible mannitol (Pe arlitol SD 200), microcrystalline cellulose (MCC, PH-102), and sodium stearyl fumerate (Aan Pharma Pvt Ltd., Rakanpur-Gujarat). Talc and Magnesium stearate purchased from SD. fine chem., Mumbai. All other materials used were of pharmaceutical grade.

Preparation of Co-processed Superdisintegrants [12]: The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of CP and CCS (in the ratio of 1:1, 1:2 and 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44- mesh sieve and stored in airtight container till further use.

Preparation of fast dissolving tablets by direct compression method [13]: Fast dissolving tablets of chlorthalidone were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg by direct compression method using 7 mm bi concave punches on a 'Rimek mini press 1' a 10 station rotary compression machine.

Evaluation of Chlorthalidone tablets: The prepared tablets were evaluated for hardness, thickness and diameter, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies, and stability studies. Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. The thickness and diameter of 4 tablets (2 tablets from each batch) were recorded during the process of compression using calipers (Mitotoyo; Japan). The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Two tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula.

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test. Six tablets were tested from each formulation. In the disintegration time [14] study tablet was put into 100 ml distilled water at 37 ± 2^0C. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus and in wetting time [15] study a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5 cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. For the determination of drug content tablets were weighed individually, pulverized, and diluted to 250ml with sufficient amount of distilled water. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700 Shimadzu Corporation, Japan) at 276 nm.

The *in-vitro* dissolution study [16, 17] was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (distilled water) was taken in vessel and the temperature was maintained at 37 ± 0.5^0C. The speed of the paddle was set at 75 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with distilled water prior to analysis in the UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 276 nm. The stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^0C/75±5%RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai). The stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^0C/ 75 ± 5%RH for three months by storing the samples in stability chamber (Lab-Care, Mumbai).

Characterization of chlorthalidone tablets:

FTIR Studies: IR spectra for drug, tablets CP1 and PM1 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

DSC Studies: DSC scan of about 5mg, accurately weighed chlorthalidone and CP1 formulation were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) Sealed and perforated aluminum 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 for the sample was used as a reference. The entire samples were run at a scanning rate of 10 ^{o}C/min from 50-300°C.

RESULTS AND DISCUSSION

Co-processed superdisintegrants were prepared by solvent evaporation using CP and CCS in different ratios (1:1, 1:2, and 1:3). The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The angle of repose of co-processed superdisintegrants was found to be <30^0 which indicate excellent flow in comparison to Physical mixture of superdisintegrants (<30^0) due to granule formation, Carr's index in the range of 15.12 to 16.74 % and Hausner's ratio in the range of 1.16 to 1.26 **(Table 2).** Fast dissolving tablets of chlorthalidone were prepared using above co-processed superdisintegrants and physical mixtures of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of six formulations and control formulation CP0 (without superdisintegrant) were designed.

Table 2: Pre-compression parameters of co-processed superdisintegrants and physical mixture of superdisintegrants

Formulation code	Angle of Repose (θ) (±SD), n=3	Compressibility (%) (±SD), n=3	Hausner's Ratio (±SD), n=3
PM1	29.22 (1.44)	16.74 (0.24)	1.26 (0.05)
PM2	28.46 (2.26)	16.35 (0.14)	1.25 (0.04)
PM3	26.42 (1.22)	15.22 (0.24)	1.23 (0.04)
CP1	24.66 (1.42)	16.44 (0.34)	1.16 (0.03)
CP2	22.98 (0.86)	15.12 (0.52)	1.18 (0.02)
CP3	22.26 (0.64)	15.62 (0.28)	1.20 (0.03)

Note: *Values in parenthesis are standard deviation (±SD)*

The data obtained from post-compression parameters such as hardness, friability, thickness, drug content, wetting time, and *in-vitro* disintegration time. The results are shown in **(Table 3)**. In all the formulations, hardness test indicated good mechanical strength results were ranges from 2.96 to 3.24 kg/cm^2, friability is less than 1%, indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 2.11 to 2.21 mm. Drug content was found to be in the range of 98.10 to 99.88 %, which is within acceptable limits. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 24 to 124 sec. Among all the designed formulations, formulation CP1 was found to be promising and was displayed an *in-vitro* dispersion time of 19 sec, which facilitates its faster dispersion in the mouth. Among all the formulations CP1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of CP and CCS) was found to be promising and has shown an *in-vitro* dispersion time of 19 sec, wetting time of 24 sec when compared to the formulation PM1 containing 4% w/w of physical mixture of superdisintegrants (1:1 mixture of CP and CCS) which shows *in-vitro* dispersion time of 36 sec, wetting time of 44 sec and control formulation (CPO) which shows 121 sec, 124 sec values respectively for the above parameters **(Table 3).**

Table 3: Evaluation of Felodipine FDT Formulations

FC	Hardness test (kg/cm^2) (±SD), n=6	Friability (%) (±SD), n=10	Thickness (mm) (±SD), n=4	Drug content (%) (±SD), n=6	Wetting time (sec) (±SD), n=6	Disintegration time (sec) (±SD), n=6
CP0	2.96 (0.26)	0.42 (0.02)	2.17 (0.03)	99.14 (1.20)	124 (2.62)	121 (1.16)
PM1	3.08 (0.12)	0.52 (0.06)	2.19 (0.04)	98.22 (1.10)	44 (1.22)	36 (2.12)
PM2	3.12 (0.14)	0.61 (0.04)	2.21 (0.02)	98.10 (1.90)	61 (2.24)	44 (2.16)
PM3	3.24 (0.22)	0.46(0.02)	2.21 (0.05)	99.20 (1.20)	72 (2.12)	52 (1.64)
CP1	3.32 (0.22)	0.51 (0.04)	2.11 (0.05)	98.78 (1.30)	24 (2.12)	19 (2.12)
CP2	3.06 (0.24)	0.48 (0.03)	2.13 (0.01)	99.74 (0.90)	38 (1.42)	32 (1.16)
CP3	3.24 (0.26)	0.46 (0.02)	2.16 (0.02)	99.88 (1.30)	46(2.02)	41 (1.24)

Note: *Values in parenthesis are standard deviation (±SD).*
FC- *Formulation code.*

The dissolution of chlorthalidone from the tablets is shown in **Fig 1**. *In-vitro* dissolution studies on the promising formulation CP1, PM1 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, and CP0 control formulations were carried out in distilled water,

and the various dissolution parameter values viz., percent drug dissolved in 4 min, 8 min, 12 min and 16 min (D_4, D_8 $D_{12,}$ and D_{16}), $t_{50\%}$, and $t_{90\%}$ are shown in **Table 4**. This data reveals that among all the formulation CP1 shows nearly faster drug release. The formulations CP1 50 % of drug released in 4.25 min, and 90 % of drug released in 14 min, CP0 control formulations 50 % and 90 % of drug released were more than 20 min.

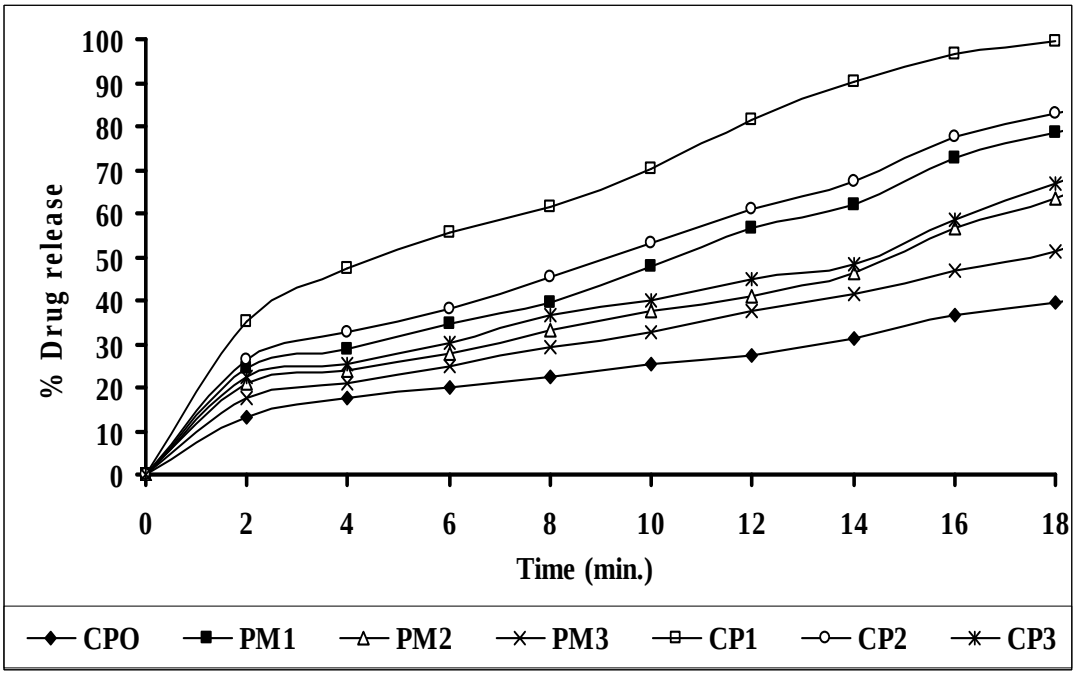

Fig 1: Dissolution studies of the Chlorthalidone FDT formulations.

Table 4: *In- vitro* Dissolution parameters of different fast dissolving tablet formulations

Formulation Code	Parameters					
	D_4	D_8	D_{12}	D_{16}	$T_{50\%}$	$T_{90\%}$
CP 0	17.68	22.41	27.34	36.39	> 20 min	> 20 min
CP1	47.08	61.54	81.36	96.64	4.25 min	14 min
PM1	28.70	39.65	56.58	72.48	10.48 min	> 20 min

CP0 is control formulation, CP1 is promising fast dissolving tablet formulation, PM1 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, D_4 is percent drug released in 4 min, D_8 is percent drug release in 8 min, D_{12} is percent drug release in 12 min, D_{16} is percent drug release in 16 min $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

Table 5: Tablet parameters after stability studies

Formulation	Period	Drug content (%)	Wetting time(sec) (± SD), n=6	Dispersion time (sec) (± SD), n=6
CP1	1 Month	98.78 (1.30)	24 (2.12)	19 (2.12)
	2 Month	98.71 (1.40)	25 (2.10)	18 (2.14)
	3 Month	98.64 (1.20)	25 (1.16)	18 (1.12)
PM1	1 Month	98.22 (1.10)	44 (1.22)	36 (2.12)
	2 Month	98.11 (1.24)	43 (1.12)	36 (1.14)
	3 Month	98.06 (1.22)	42 (1.14)	36 (2.12)

The stability study for all the formulations were carried according to ICH guidelines by storing the tablets in a stability chamber (Lab care, Mumbai) at $40^0 \pm 2^0$ C/ 75 ± 5% RH for three

months. There was no significant change in *in-vitro* dispersion time, wetting time and drug content of the formulation CP1 and PM1 **(Table 5).**

In **Fig 2** shows the IR spectrum of the pure drug and formulations CP1. As there is no variation and shift in the position of characteristic absorption bands in the IR spectrum of the formulation it can be justified that there is no interaction between pure drug and polymers used for the formulation.

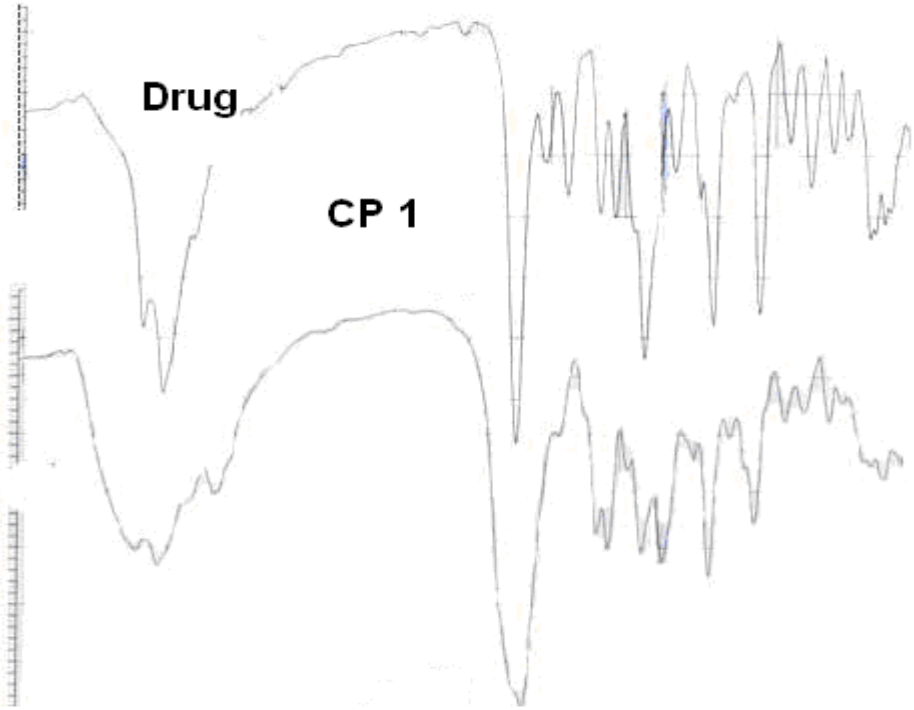

FIG 2: FTIR spectrum of pure drug Chlorthalidone (PD), spectrum of formulation CP1

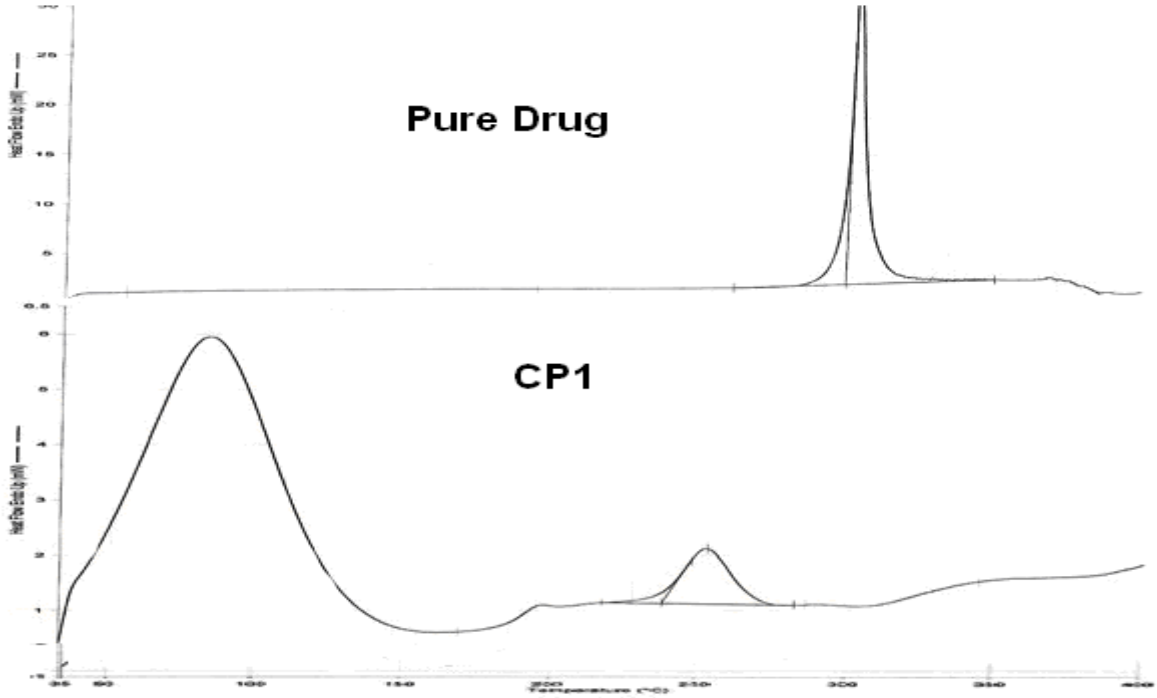

Fig 3: DSC thermogram of pure drug Chlorthalidone, DSC Thermogram of CP1 tablet.

In **Fig 3** shows the thermogram obtained by the thermal analysis of the pure drug has shown exothermic nature and the melting point of the compound appears to be around 225^0C. The DSC thermogram of the CP1 formulation obtained from its thermal analysis reveals that there is no marked change in the melting point of the pure drug and formulation. The melting point is in the range of 222^oC which is in the permissible range

CONCLUSION

Chlorthalidone tablets containing co-processed superdisintegrants exhibit quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed superdisintegrants of CP and CCS are superior to physical mixtures of CP and CCS used in chlorthalidone fast dissolving tablets.

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